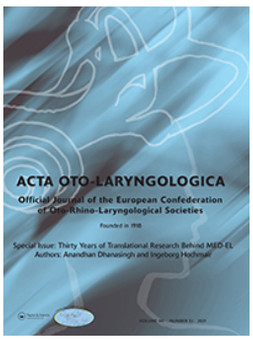

Acta Oto-Laryngologica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ioto20

Thirty Years of Translational Research Behind MED-EL

Anandhan Dhanasingh & Ingeborg Hochmair

To cite this article: Anandhan Dhanasingh & Ingeborg Hochmair (2021) Thirty Years of Translational Research Behind MED-EL, Acta Oto-Laryngologica, 141:sup1, (i)-(cxcvi), DOI: 10.1080/00016489.2021.1918399

To link to this article: https://doi.org/10.1080/00016489.2021.1918399

Published online: 16 Apr 2021.

ACTA OTO-LARYNGOLOGICA

VOLUME 141 NUMBER S1 2021 PAGES S1–S184

ACTA OTO-LARYNGOLOGICA

Official Journal of the European Confederation of Oto-Rhino-Laryngological Societies

Founded in 1918

Special Issue: Thirty Years of Translational Research Behind MED-EL
Authors: Anandhan Dhanasingh and Ingeborg Hochmair

Taylor & Francis
Taylor & Francis Group

VOLUME 141 NUMBER S1 2021

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Acta Oto-Laryngologica

Print ISSN 0001-6489, Online ISSN 1651-2251

Subscription information

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Airfreight and mailing in the USA by agent named WN Shipping USA, 156-15, 146th Avenue, 2nd Floor, Jamaica, NY 11434, USA.

Periodicals postage paid at Jamaica NY 11431.

US Postmaster: Please send address changes to *Acta Oto-Laryngologica*, WN Shipping USA, 156-15, 146th Avenue, 2nd Floor, Jamaica, NY 11434, USA.

Subscription records are maintained at Taylor & Francis Group, 4 Park Square, Milton Park, Abingdon, OX14 4RN, United Kingdom.

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2019 Impact Factor: 1.157
5-Year Impact Factor: 1.277
Ranking: 32/42 (Otorhinolaryngology)
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Thirty Years of Translational Research Behind MED-EL

Anandhan Dhanasingh

Ingeborg Hochmair

Edited by Dijana Mitrovic

This compendium is dedicated to Prof. Erwin Hochmair, co-founder of MED-EL, in honour of his 80th birthday in December 2020.

Quote from Mary Lasker:

If you think research is expensive, try disease.

Preface by Paul Van de Heyning

Severe to profound hearing loss affects the quality of life, disrupting the essential needs of communicating – and consequently, belonging and participating in society. For neonates, if not rehabilitated, it leads to reduced speech and language development and later effects on education. Adults faced with losing their hearing may experience social isolation, stigma, inability to perform their job, and even loss of independence. In older people, severe and profound hearing loss leads to an increase in cognitive decline and risk of dementia [1]. It is estimated that fifty million people worldwide are faced with some degree of hearing loss where hearing aids do not provide sufficient speech understanding. One out of 2000–4000 new-borns with hearing impairment cannot be rehabilitated with hearing aids to a degree that would allow them to follow mainstream education.

Cochlear implantation (CI) is the standard of care which (re)opens and (re)gains the world of hearing in the profoundly deaf population. CI has boosted a lot of otological and auditory neurocognitive research in all aspects, as it provides an aim, meaning, and applicability. It is estimated that worldwide, there are more than 700,000 cochlear implant users, and about 70,000 patients are implanted every year. However, not all severely to profoundly deaf and hard of hearing children worldwide have access to CI and only under 5% of adult candidates receive one. This emphasises the continuous need for awareness [2].

This compendium covers the highlights of thirty years of MED-EL's CI research that is led, guided and inspired in all its aspects by Ingeborg Hochmair. In particular, the focus of the issue is on the one hand on the translational science research aspects and the collaboration between clinicians, their teams and their patients, and on the other hand on MED-EL's engineers, researchers, product developers, statisticians, lawyers and administrators to achieve the innovations and the realisations in daily practice. It is the initiative of Ingeborg Hochmair for this compendium to pay tribute to all these clinical and technological collaborative efforts.

Already more than fifteen years before MED-EL's foundation, Ingeborg recognised the necessity of translational research avant la lettre. Indeed, to realise what she at the time called *an optimistic goal to provide the ability to understand some speech,* the collaboration with the late Prof. Kurt Burian from the Medical University of Vienna in Austria led to the first implantation of a micro-electronic multi-channel cochlear implant, developed by herself and her husband Erwin Hochmair in December 1977 [3]. Her mission to restore hearing and communication, and thereby to bring happiness among deaf and hard of hearing persons in this better world, will always remain her core passion. So, in the year 1990, she hired the first teammates at MED-EL on her path to provide an improved CI to the people in-need.

What I have witnessed at MED-EL over the many years of collaboration, is open communication, belief in people's insights and expertise, empowerment, unique attendance in conferences and symposiums, careful listening in the communications, and long-term support. As CEO, Ingeborg has the credentials and the gift to lead an extensive team with the same spirit and motivation as she dedicates to the restoration of hearing sense to patients. Her passion is clearly translated to the creation of a community with clinicians, researchers and other stakeholders of the public and private domain.

It has been thirty years since MED-EL's establishment. Meanwhile, the experimental CI surgeries have become the standard of care within a broader indication, for example, patients with severe hearing loss, residual hearing or single-sided deafness. Most of the deaf-born children with an early CI implantation may nowadays follow mainstream education, many adult CI users may use the telephone again, and numerous studies have demonstrated the improved quality of life (QOL) amongst many other beneficial effects. Importantly, CI has proved to be cost-effective. In 2013, the vast contributions of Ingeborg Hochmair in the CI field were rewarded with the Lasker-DeBakey Clinical Medical Research Award, received together with Prof. Graeme Clark and Prof. Blake Wilson.

The following seven chapters will focus on highlights and breakthroughs during the thirty years of CI research and achievements: (i) Bilateral Cochlear Implantation, (ii), Electric-Acoustic Stimulation in Partially Deaf Patients, (iii) Auditory Brainstem Implant (ABI), (iv) Cochlear Implantation in Single-sided Deafness, (v) Signal Processing and Audio Processors, (vi) Drug Delivery in Cochlear Implantation Application, and (vii) Special Electrodes for Demanding Cochlear Needs.

Every chapter will begin with a brief history timeline, acknowledging clinician(s) who proposed the initial idea(s), and which MED-EL further developed as a treatment option for specific indications. This is where it gets the most interesting to read these seven chapters, and at the same time, it is shown how much research effort is involved in bringing a concept to patients. It involves many rounds of experiments in the laboratory setup and discussions with clinicians before passing through the regulatory processes to the application to patients. Continuous high-end technological progress achieved by MED-EL was essential in all its product breakthroughs but remains outside of the scope of this overview.

Let me illustrate this attitude and efforts of collaboration, open-mindedness, flexibility, mission, commitment, perseverance, robustness, long-term planning, ethics and service to the society for severe to profound hearing loss.

Chapter 1 describes the restoration of a full soundscape. Convinced by research on the importance of binaural hearing and sound localisation, Prof. Helms and Prof. Joachim Müller from Würzburg in Germany were the first to perform a bilateral CI in 1996, by implanting MED-EL devices. Later, in 1998, they also performed the first bilateral CI in a 4-year-old

child (1st ear 1996, 2nd ear 1998) ear who was bilaterally profoundly deaf since birth. This has opened a wide door for research to understand how the brain processes electric stimulation coming from both ears, making a sense out of it. Through several years of research until this day, the benefits of a second CI are irrefutably proven with better speech in noise and directional capabilities. We now know that children with bilateral severe to profound hearing loss should be provided with bilateral CI as early as possible in their life, for optimal hearing development, directionality and language skills. Binaural hearing is an essential gift for them to perform well in school. All endeavours and efforts in this field have resulted in bilateral CIs becoming the standard of care for children in many countries.

Chapter 2 narrates how Prof. Christoph von Ilberg from Goethe University Frankfurt in Germany surprised and pieced together the CI world and the residual hearing world in 1996 by reporting that residual low tone hearing could be preserved after a CI procedure. Through careful observations and open-minded, out-of-the-box thinking, Prof. von Ilberg was determined to prove the advantages of combining electric stimulation in the high tones with acoustic amplification in low tones. At first – as it happens with many spectacular innovations – disbelief by many otologists and audiologists arose, but not MED-EL. MED-EL saw vast opportunities for many patients with low tone residual hearing but who had poor speech understanding. MED-EL and Ingeborg believed in Prof. von Ilberg's insights and observations, and supported the project by delivering new technologies, that is, dedicated highly flexible electrodes, unified audio processors and algorithms – and the EAS (electric acoustic stimulation) was born. Today, EAS has become the standard of care for patients with residual hearing. My team and I could participate in the development of surgical techniques and multicentre studies where I witnessed the impressive efforts done by clinicians and by the MED-EL team to improve, refine and evaluate the EAS meticulously, and also to disseminate and teach EAS to otologists and audiologists.

The concept of cochlear structure preservation surgery emerged from the EAS concept. For the successful CI treatment with hearing preservation – while bearing in mind the importance of optimal electrode choice – it is equally important to keep the cochlear structures intact. Evidence that structure preservation surgery also improved outcomes for patients without residual hearing became clear over the years.

Chapter 3 gives an insight into the development of MED-EL's auditory brainstem implant (ABI). It was Prof. Jan Helms from the Würzburg University in Germany who expressed a request to MED-EL to develop an ABI to rehabilitate hearing in bilaterally deaf neurofibromatosis type II (NF-II) patients who typically lose their acoustic nerve following the surgical resection of acoustic neuroma. A dedicated electrode paddle was designed and produced to link with the CI stimulator, aiming at the ventral cochlear nucleus stimulation in the Luschka's foramen of the brainstem. Prof. Robert Behr and Prof. Joachim Müller realised the first implantation. Numerous improvements followed as a result of experience gained and built up knowledge. Eventually, children born with acoustic nerve aplasia were also treated with ABI. The indications for ABI are scarce, and hence the number of patients is limited to a few hundred worldwide. As with other orphan disorders, R&D in such cases is not profitable. But MED-EL felt the duty to support patients and the surgeons, and to develop the latest technologies so that basic hearing can also be offered equally to these patients.

Chapter 4 on single-sided deafness (SSD) is the one I was most involved in. In 2002, we studied the effects of acquired single-sided deafness, among which incapacitating tinnitus was prevailing. I considered the possibility of implanting a CI in SSD patients with the aim to minimise the tinnitus and to improve the hearing capabilities. I discussed the medico-surgical experiment with Ingeborg, and I got her full support. After receiving permission from the UZA Institutional Review Board, I implanted the first SSD patient with CI in 2003. We observed a decrease in tinnitus and hearing restoration in that patient, and the following first month after fitting exceeded my expectations. The following cohort study confirmed these early results. Like EAS, this project also triggered several years of disbeliefs, but nowadays, almost all CI conferences have dedicated sessions on the topic of SSD. In 2013, MED-EL obtained CE marking for its CI to be used in SSD within the European Union followed by FDA approval in 2018. Ten to fifteen years needed for an idea to become a standard clinical therapy appears not to be unusual considering the condition and climate of a long-term scope. Results of CI in paediatric SSD are now appearing and will allow refining the patient selection.

Chapter 5 covers signal processing, which is the heartbeat of CI. It is the basis of the fitting algorithms. Knowledge on this topic among the CI surgeons and audiologists leads to better rehabilitation and hearing outcomes. Basic research and clinical and psychoacoustic experiments have increased insights into the electrophysiological functioning of the cochlea and prompted Prof. Blake Wilson from Duke University in the US to invent the continuous interleaved strategy (CIS). As mentioned above, his merit was awarded the Lasker–DeBakey Clinical Medical Research Award. Together with Erwin Hochmair and Prof. Clemens Zierhofer from the University of Innsbruck in Austria, Prof. Wilson played a significant role in establishing the signal processing within the MED-EL hearing system.

Chapter 6 on drug delivery found its first ideas in the work of Prof. Jan Kiefer from Goethe University Frankfurt in Germany in the early 2000s. Involved in the development of EAS and structure preservation surgery, he was one of the first CI surgeons to apply corticosteroids together with CI to the inner ear to reduce the inflammation reaction created by the implanted electrode and to preserve the residual hearing better. The comprehensive search for reliable and robust drug-eluting electrodes has entered the first clinical experimental phases, progressively releasing dexamethasone inside the cochlea.

In chapter 7, the flexibility of MED-EL to adapt to special needs is illustrated. The chapter describes the equally given importance to the special group of patients who have congenital abnormal inner ear malformations. These abnormal

cochleae vary a lot in size, shape and anatomy. A regular CI electrode may not be suitable in most cases; therefore, MED-EL has designed and produced many special electrodes to accommodate the individual special cochlear needs. Prof. Göran Bredberg, Prof. Millo Achille Beltrame, Prof. Levent Sennaroglu, Prof. Henryk Skarzynski, Prof. Thomas Lenarz, Prof. Joachim Müller, Prof. Luis Lassaletta, Prof. Javier Gavilan, Prof. Stefan Plontke and Prof. Hubert Löwenheim are all prominent CI surgeons in the field today. They have been highly instrumental in supporting MED-EL to develop electrode arrays to meet the needs of special cochlear conditions.

The path from an idea, a hope or an experiment to become a standard of care and to reach so many deaf and hard of hearing patients in thirty years of MED-EL's research, is explained in detail in chapters on the following pages. The future is certainly going to take the CI technology to the next levels, and MED-EL will continue to remain the main driver and generator of innovation. The **chapter 8** 'Translational Research around Five Categories of CI' by Dr. Ingeborg Hochmair is given at the end of this compendium where she shares her views on the overall goals, learnings and successes of translational research in the hearing loss treatment at MED-EL

My colleagues in the CI field and I, by being part of the translational science research, as described in the following chapters, have appreciated and still do the empowerment not only by providing innovative CI technology but very importantly, by the joint power, the trust and the belief in our insights and experiences by someone with a huge experience in the field. And this support is not aiming at short success but at the far horizon of providing new hearing and communicating capabilities and services to patients with hearing loss. With the same set of mind, 27 international comprehensive CI centres have united in an independent research consortium called HEARRING (www.hearring.com) to study, promote and educate on hearing loss by applying auditory implant technology. I invite all otologists, audiologists and researchers committed to hearing science to join the comprehensive and collaborative R&D project initiated by Ingeborg Hochmair.

This is a moment where we can proudly look back at the thirty years of MED-EL's CI research. Many of us have dedicated our whole professional carrier to helping deaf and hard-of-hearing patients, and so did Ingeborg and Erwin Hochmair and their MEDEL team, being convinced and committed to going further on this path.

Prof. Paul Van de Heyning, MD, PhD
Consultant Otology, Neurotology and Auditory Implants,
Former Dean of the Faculty of Medicine and Health Sciences,
Former Chairman - Dept. of ENT and Head and Neck Surgery,
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President of the XV Int. Conf. on Cochlear Implants and
other Implantable Auditory Technology CI2018

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Acta Oto-Laryngologica
Volume 141 Number S1 March 2021

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ACTA OTO-LARYNGOLOGICA
2021, VOL. 141, NO. S1, S1–S21
https://doi.org/10.1080/00016489.2021.1888193

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REVIEW ARTICLE

Bilateral cochlear implantation

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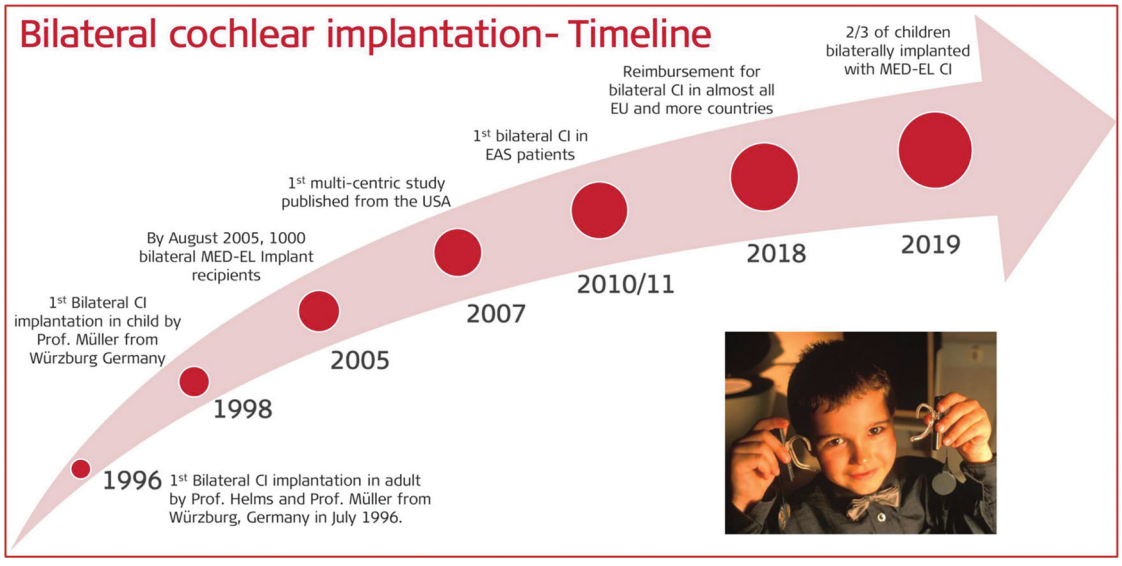
ABSTRACT

Binaural hearing has certain benefits while listening in noisy environments. It provides the listeners with access to time, level and spectral differences between sound signals, perceived by the two ears. However, single sided deaf (SSD) or unilateral cochlear implant (CI) users cannot experience these binaural benefits due to the acoustic input coming from a single ear. The translational research on bilateral CIs started in the year 1998, initiated by J. Müller and J. Helms from Würzburg, Germany in association with MED-EL. Since then, several clinical studies were conducted by different research groups from across the world either independently or in collaboration with MED-EL. As a result, the bilateral CI has become the standard of care in many countries along with reimbursement by the health care systems. Recent data shows that children particularly, are given high priority for the bilateral CI implantation, most often performed simultaneously in a single surgery, as the binaural hearing has a positive effect on their language development. This article covers the milestones of translational research from the first concept to the widespread clinical use of bilateral CI.

ARTICLE HISTORY
Received 13 December 2020
Accepted 6 January 2021

KEYWORDS
Binaural hearing; sound localization; simultaneous bilateral CI; sequential bilateral CI



1.1. Introduction

The ear transmits sound waves to the brain, and having an ear on each side of the head helps with localising the direction of the sound. The term *binaural hearing* refers to normal hearing with two ears. The hearing has two primary functions: communication (speech recognition) and warning (acoustic source localisation). The critical task for the central auditory pathways is to break down the auditory messages sent by the two ears into auditory objects. The segregation and localisation of auditory objects constitute an essential means of separating target signals from noise and competing sources. With asymmetric or single-sided deafness, or with a cochlear implant (CI) on one side, the monaural exploitation of sound messages significantly lessens the performance compared to what it should be in a binaural situation [1]. Binaural hearing in normal-hearing individuals offers speech intelligibility, sound source localisation, understanding the speech in a noisy environment, and hearing with enough loudness. Technically, the benefits or effects of

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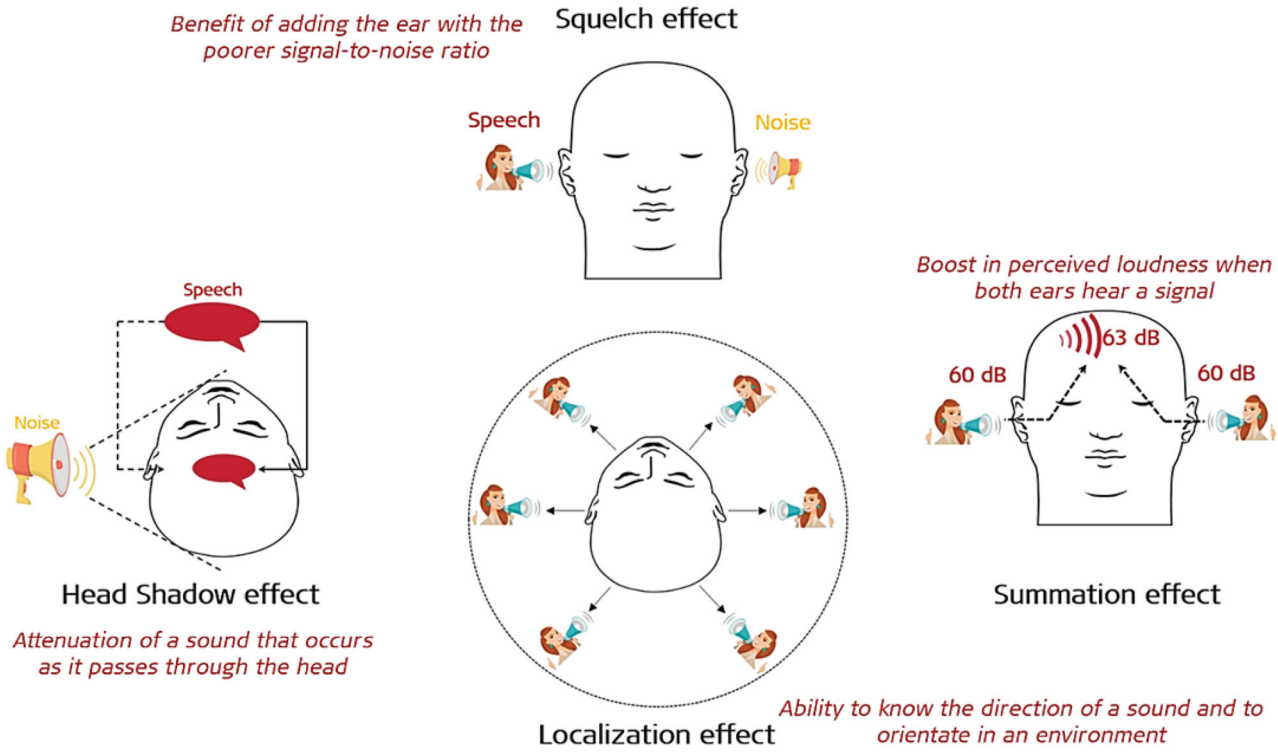


Figure 1. Illustrations of the various effects of binaural hearing (image courtesy of MED-EL).

binaural hearing can be brought under the terms *head-shadow*, *squelch, summation* and *localisation* (Figure 1). In brief, the *head-shadow* effect results from the physical placement of the head which acts as an acoustic barrier and attenuates sound (speech or noise) on one ear if that sound (speech or noise) comes from the other ear. *Squelch* effect corresponds to the brain's ability to suppress background noise and attend to a specific auditory signal that comes binaurally. *Summation* effect, also known as *loudness summation*, refers to the identical loudness perception due to balanced action potentials coming from both ears to the auditory brainstem. *Localisation* is the ability to perceive directions of where different sounds are coming from, and it helps with the orientation [2].

To sum up, most noise reduction and acoustical orientation abilities of the human auditory system rely on the listener having access to time, level and spectral differences between sound signals, perceived by the two ears [3]. However, single-side deaf (SSD) patients, asymmetric hearing loss (AHL) patients, and unilaterally implanted patients with CI cannot experience these binaural benefits due to the acoustic input coming from a single ear. Additionally, the real-world listening environment in which the signal and the unwanted competing sounds may overlap spectrally and temporally, as well as spatially, makes the listening worse. While the unilateral CI treatment in bilaterally deaf children offers significant benefit in terms of speech development, still the full binaural benefits are missing to a certain degree [4], and the bilateral CI is not a luxury but rather a right to experience it.

The incidence rate of bilaterally born deaf population is approximately 0.3–1 per 1,000 births [5], and the bilateral CI was not a topic of research and interest until 1995. Before that, bilateral CI was not a treatment option to restore binaural hearing – instead, it was used either as a technology upgrade in combination with an older, still functioning device with no wish of replacement or due to inadequate performance with the device in the ipsilateral ear. Early research in these accidental bilateral CI implantations showed that the auditory system has the potential to process and integrate additional information provided by two different devices [6].

MED-EL takes inspiration from nature by designing its technologies to mimic it, such as with the unique concept of long electrode array length to cover the entire frequency range, flexible electrode array design to preserve the intracochlear structures, frequency-specific group delays in the sound coding strategy to mimic the natural hearing and more. In that aspect, binaural hearing is also a natural phenomenon science which MED-EL made every effort to understand by sponsoring/supporting several clinical studies across the world, and before translating it to the concept of bilateral CI. Nowadays, as a result of all translational science efforts from MED-EL, bilateral CI is highly acknowledged in several countries and reimbursed for the entire treatment.

This article will review the history of how and when MED-EL started its journey of bilateral CI, summarise fundamental research studies that are either MED-EL sponsored/supported or that involved MED-EL CI device, and which demonstrated the benefits of bilateral CI. The article will also point out the critical studies that reported on the cost-utility with bilateral CI.

1.2. Beginning of MED-EL's bilateral CI journey

In July 1996, MED-EL's bilateral multichannel CI journey started with the first bilateral implantation in an adult to restore binaural hearing. The surgery was performed by Prof. Helms and Prof. Müller in Würzburg in Germany (Figure 2).

Figure 2. ENT surgeons from Julius-Maximilian University of Würzburg, Germany, who performed the first bilateral CI implantation with MED-EL's CI device (in 1996).

A brief history about the patient reveals that he already had a single-channel MED-EL CI device implanted in one ear and received a multichannel MED-EL CI in the second ear. The multichannel CI device in the second ear provided him with a superior hearing experience, compared to the single-channel CI in the first ear. The circumstance encouraged him to request the replacement of the latter with a multichannel CI device. The observed hearing benefits under binaural CI condition (Figure 4(A)) attracted the researchers from the Research Triangle Institute (Research Triangle Park, North Carolina, USA) to perform extensive series of audiological tests – which reconfirmed the gain in speech understanding and instilled confidence in the Würzburg ENT team to extend the bilateral CI treatment to the paediatric patient population.

Figure 3. Engineers and audiologists who designed and developed the HSM sentence test to evaluate the speech understanding of CI users in noise. [1]MED-EL and [2]University of Würzburg, Germany.

1.3. The German Hochmair-Schulz-Moser sentence test

In the mid-'90s, there was no practical audiological test available to evaluate speech understanding ability of CI users in noise. The German Hochmair-Schulz-Moser (HSM) sentence test was designed and developed by Dr Ingeborg Hochmair, Dr Eckard Schulz, DI Ludwig Moser and DI Markus Schmidt (Figure 3) with the desire to have enough test sentences for the repeated evaluation of speech understanding of CI users in noise.

The name HSM derives from the surnames Hochmair, Schulz and Moser. The test consists of thirty lists of twenty everyday sentences with the level of difficulty corresponding to sentences spoken in everyday life with background noise [7]. The whole test material was made available on compact disc (CD) and Comité Consultatif International Téléphonique et Télégraphique (CCITT) noise on the second channel of the CD to mimic the real-world background noise. Over time, this test became one of the gold standards in the evaluation of speech understanding of CI users in noise.

1.4. The first paediatric patient receives bilateral CI

In January 1998, the first bilaterally implanted paediatric patient (Max, a four-year-old boy from Germany) was operated on the second ear after he had received his first CI in 1996 at the age of 2 years, by the same ENT group from Würzburg. In the year 2000, Prof. Müller and his colleagues published their experience of understanding binaural benefits from their patients implanted with MED-EL CI devices (COMBI 40 or COMBI 40+) in combination with the continuous interleaved sampling (CIS) signal processing strategy [8]. Figure 4(A) shows the percentage of correct word results which were higher in the bilateral CI listening condition, compared to the monaural listening condition from the very first patient implanted bilaterally with MED-EL's COMBI 40 device in 1996. Figure 4(B) shows significantly higher sentence test scores of bilateral CI condition in comparison to the monaural CI listening condition from four patients bilaterally implanted with COMBI 40 device. These were the very first hearing performance results of bilaterally implanted CI users with MED-EL devices, and the authors concluded that all implanted patients showed significant

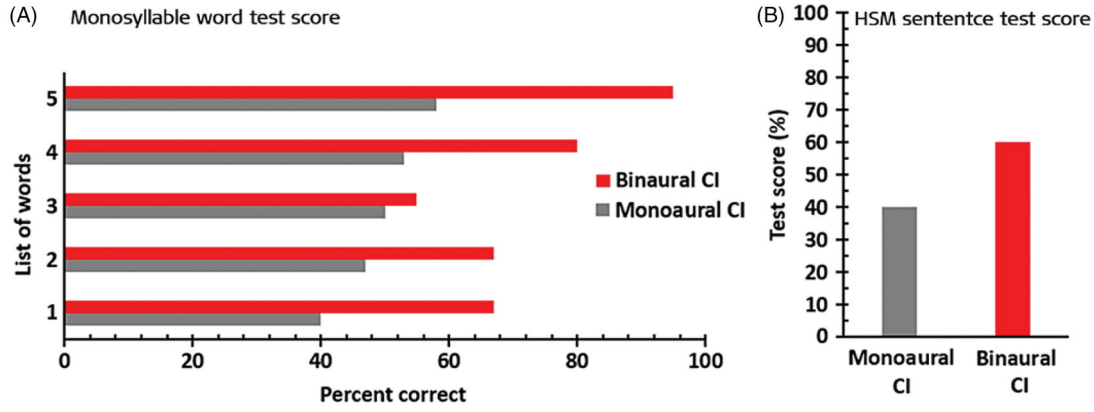


Figure 4. (A) Monosyllabic word scores at 80 dB sound pressure level (SPL) of the very first patient. (B) Test scores in noise (numbers, HSM sentences, monosyllabic words, S/N ratio 5-13 dB) for 4 bilaterally implanted adult patietns (n = 17 tests).

benefits from the second implant. Better hearing monoaural implant results (grey bars) compared to the binaural condition (red bars) (A). HSM sentence test scores in noise with S/N of 5–13dB for four bilaterally implanted adults (B). Histograms created from data given in Müller et al. [8].

1.5. Early evidence of binaural hearing benefits with CI

In 2002, the same ENT group studied the binaural benefits of bilateral CI in adult patients ($n = 8$) who were implanted before 2001 with COMBI 40 or COMBI 40+ devices that used CIS or CIS + sound coding strategy from MED-EL [9]. They quantified the gain in SNR at speech reception threshold (SRT) in a symmetrical test setup that largely minimised the interaural differences in SNR by positioning four loudspeakers at 45°, 135°, 225° and 315° azimuth, to eliminate any head shadow effects (Figure 5(A)).

Further in the year 2002, a multicentre study on bilateral CI took place between the ENT department of Ruhr University Bochum in Germany, the University of Würzburg in Germany, and the University of Bern in Switzerland [10] (Figure 7).

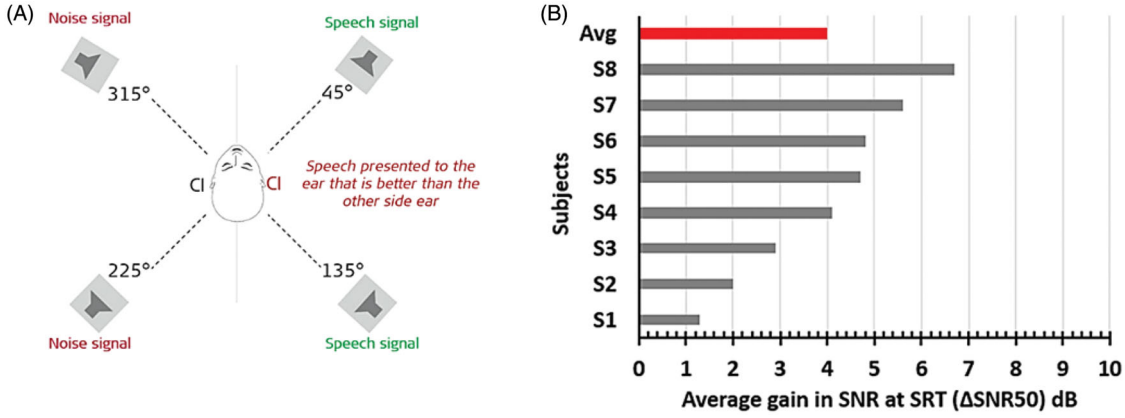


Figure 5. Symmetrical test setup to quantify the gain in SNR at the SRT (A). The average gain in the SNR overtime at the speech reception threshold (ΔSNR_{50}) of eight patients under bilateral CI condition (B). Test scheme and histogram created from data given in Schön et al. [9].

The CI hearing ear was evaluated based on unilateral monosyllable scores in quiet. In patients in whom the right CI ear was the better CI ear, the speech signal was presented simultaneously from 45° to 135° azimuth, and the noise signal simultaneously from 225° to 315° azimuth. If on the other hand, the left CI ear was the better CI ear, the speech and noise loudspeakers were switched. The test results showed that patients showed a gain in SNR_{50} when using both implants instead of the better CI ear alone, with a mean ΔSNR_{50} of 4 dB, translated into an average improvement in speech reception of 28% (Figure 5(B)). This remarkable bilateral benefit was achieved despite the largely absent head shadow SNR benefit, as a result of the symmetrical test setup. Therefore, the ΔSNR_{50} was achieved mainly due to the combination of bilateral summation and squelch effects.

In the same year, the same ENT group performed further series of audiological tests, including sentence and monosyllabic word tests in noise, to study the head shadow, squelch and summation effects that are associated with binaural hearing [3].

Figure 6(A) shows the audiological test results of comparing the monaural and bilateral CI condition. It was observed that with bilateral CI, the scores from all tests were significantly higher than in the monaural CI condition. Figure 6(B) shows the results of binaural effects. For each CI ear, the unilateral head shadow benefit was determined by subtracting the sentence test score with speech presented from the front and noise to the contralateral ear from the test score with a speech from the front and noise presented to the ipsilateral ear. From all patient results, the average head shadow showed a benefit of 20.4%. For a specific direction of noise presentation, the squelch effect contribution of 10.7% across all patients was observed by subtracting the score when listening with the better SNR ear alone from the scores when listening with both CIs. The contribution due to the bilateral summation effect was calculated for monosyllabic words in quiet by subtracting the score obtained with both CIs from the score obtained with one CI. The summation benefit accounted to 18.7% across all results.

Altogether, seventeen postlingually deaf patients were bilaterally implanted with MED-EL COMBI 40 or COMBI 40+ device which used CIS signal processing strategy. The two CIs were implanted either simultaneously as a one-stage or sequentially as a two-stage procedure. HSM sentence test at 70 dB hearing level and with a relatively low SNR, among all patients resulted in higher scores in the bilateral CI listening, in comparison with the monaural listening with their better CI ear (Figure 8). This was yet another evidence which demonstrated the binaural hearing benefits with bilateral CI.

Although these early reports on binaural hearing benefits with bilateral CI in adults were encouraging [3,8–10], the sequentially bilaterally implanted children had some challenges with getting used to the second CI at early stages of their bilateral CI journey, before reaching their plateau performance.

In 2002, Dr Kühn-Inacker suggested that preparing children psychologically for different hearing sensation and speech understanding with the second CI is essential [11] (Figure 9). To avoid any early disappointments with the second CI, it was recommended to have the first CI in use in combination with the second CI. Optimisation of the second CI speech processor

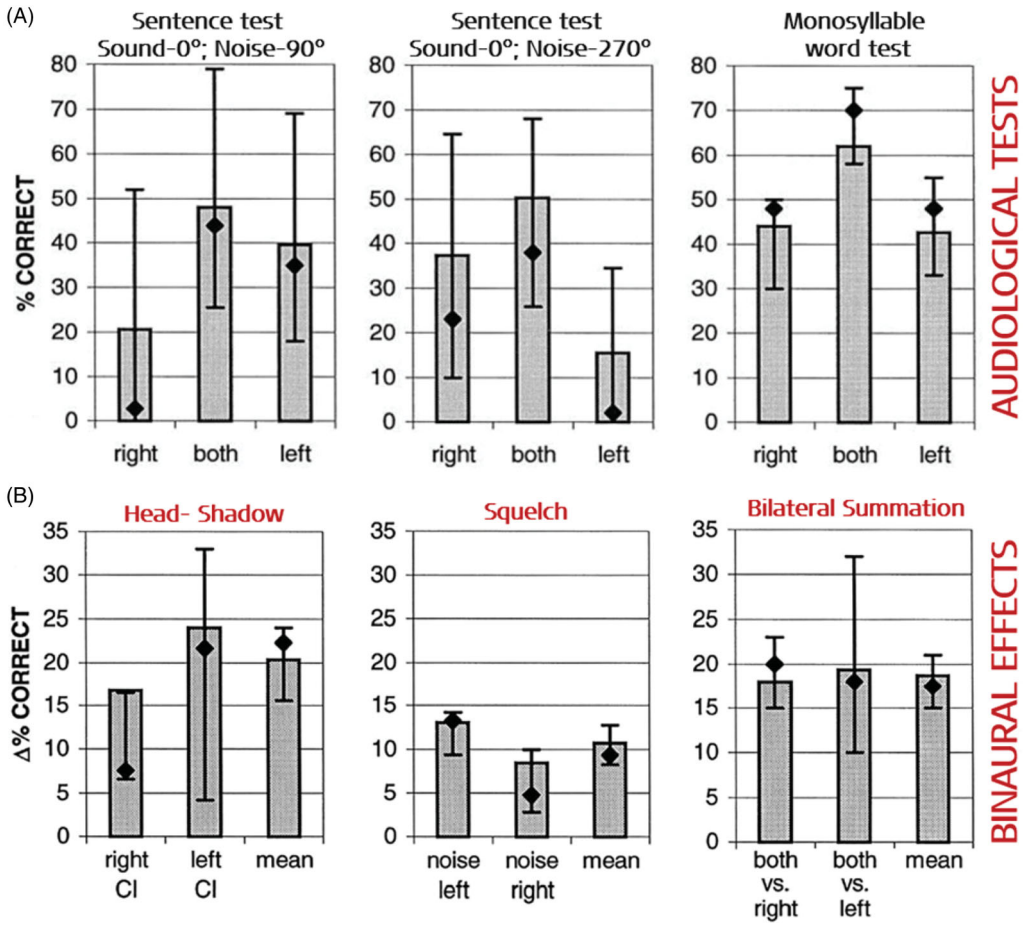


Figure 6. The first row showing audiological test results with mean, median and standard deviation at first and third quartile (A). The second row showing binaural advantage due to head shadow, squelch and the bilateral summation effects, calculated from the first-row results [3] (B). Statistical analysis: Two-tailed tests were used for all comparisons. Reproduced by permission of Wolters Kluwer Health, Inc.

Dr Thomas Stark [1]

Prof. Mattheus Vischer [2]

Prof. Pascal Senn [3]

Prof. Martin Kompis [2]

Figure 7. A collaboration between CI surgeons and audiologists from Germany ([1]Ruhr University Bochum, [2]University of Würzburg) and Switzerland ([3]University of Bern) who evaluated the effectiveness of bilateral CI in postlingually deaf patients.

should be performed with great care while keeping the first CI speech processor at constant settings. Moreover, a separate auditory training with the second CI might be necessary to align auditory competencies with both systems.

1.6. Bilateral CI in Asia

In 2003, the bilateral CI implantation with MED-EL CI device (COMBI 40+ and CIS strategy) extended to Hong Kong and that demonstrated the binaural hearing benefits in discriminating Cantonese (Chinese dialect) lexical tones in the background noise and quiet test condition by four Cantonese-speaking CI users [12] (Figure 10).

Cantonese, with its six contrastive tones, has a characteristic that different tones of the same phonemic segments carry a different meaning. The voice-contrastive pitch patterns produced by the vocal cord convey the lexical meanings of Cantonese tones, and these tonal changes are not detectable by lip-reading. The perception of these tones requires good temporal and spectral auditory abilities.

Speech was presented at 65 dB SPL in relation with speech weighted noise, at SNRs of +15, +10, +5, 0, −5, −10 and −15. Figure 11 shows the mean percentage of correct Cantonese lexical tone discrimination scores of the four patients in both monaural and bilateral listening conditions at various SNRs and in quiet. A score of 66.77% or above, was regarded as being significantly above the chance levels, as shown by the red horizontal line in Figure 11.

In the bilateral CI condition in quiet and at SNRs of +15, +10 and +5, the discrimination scores resulted above the set value of 66.77%, whereas in monaural CI condition,

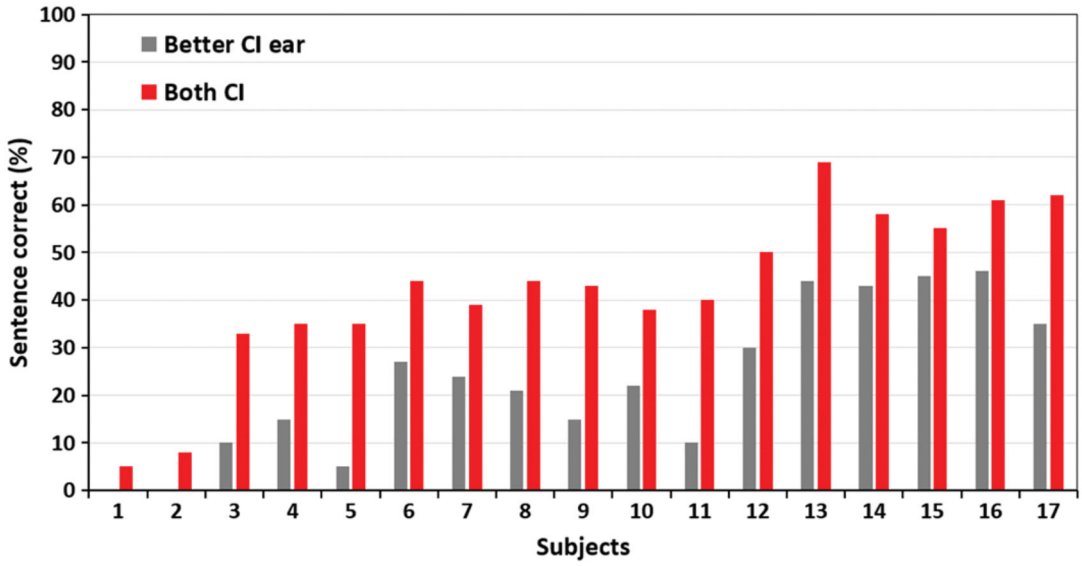


Figure 8. Scores of HSM sentence test at 70 dB hearing level and 10 dB signal-to-noise ratio (S/N). Histogram created from the data given in Stark et al. [10].

Figure 9. Dr phil. Heike Kühn-Inacker, Psychologist, Universitätsklinikum, Würzburg, Germany.

Dr Dennis Kin-Kwok Au (Audiologist)

Prof. Yau Hui (CI surgeon)

Prof. William Ignace Wei (CI surgeon)

Figure 10. Audiologist and CI surgeons from the University of Hong Kong Medical Centre, Queen Mary Hospital, Hong Kong.

the discrimination scores were correct only at SNRs of +15, +10. Only +5 dB SNR (speech stimuli 5 dB louder than the background noise) was needed for the bilateral listening condition, whereas +10dB SNR was needed for the monaural listening conditions to discriminate between Cantonese lexical tones. In the same year, another Chinese report on the binaural benefits with bilateral CI showed lower hearing thresholds and better speech discrimination scores under aided conditions, in comparison to the monaural CI condition from two patients implanted with MED-EL COMBI 40+ device [13].

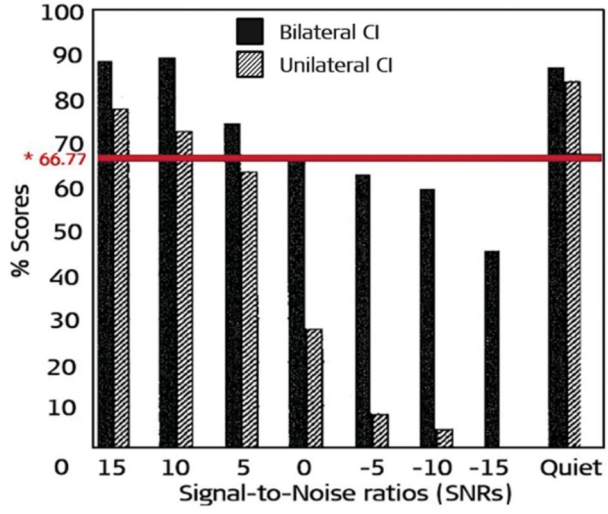


Figure 11. Mean percentage of correct Cantonese lexical tone discrimination scores, obtained from four bilaterally and eight unilaterally implanted CI patients at various SNRs and in quiet. * A score of ≥66.77% was regarded as being significantly above the chance level [12]. Reproduced by permission of Elsevier B.V.

1.7. MED-EL's involvement in evaluating bilaterally implanted CI patients

In 2004, MED-EL evaluated the sound localisation abilities in bilateral CI users [14] (Figure 12). Twenty postlingually deaf patients with an average age of forty-five years participated in the study. They were implanted either with MED-EL's COMBI 40 or COMBI 40+ device and used the CIS + strategy, and they had at least one month of bilateral CI hearing experience before being included in the study.

Localisation testing with both unilateral and bilateral CI listening was performed in an anechoic chamber with an array of nine loudspeakers, equally distributed throughout 180° in the frontal plane (Figure 13). Bursts of speech-shaped noise were used as stimuli presented at 60-, 70- or 80-dB SPL – values considered above the automatic gain


Dr Peter Schleich


Dr Patrick D'Haese

Figure 12. MED-EL specialists who were involved in evaluating the sound localisation abilities of bilateral MED-EL CI users in the year 2004.

control (AGC) compression onset. The responses from all twenty participants were brought under three main patterns, as shown in Figure 13. For the unilateral listening conditions, the pattern I (Figure 13, first row in red) resembled a pattern of guessing by the participants where responses were scattered over all presentation azimuth ϕ (x-axis), and the mean values for the response azimuth Ψ (y-axis) are close to 0 with high standard deviation. Pattern II (Figure 13, second row in blue) showed a pattern of guessing where

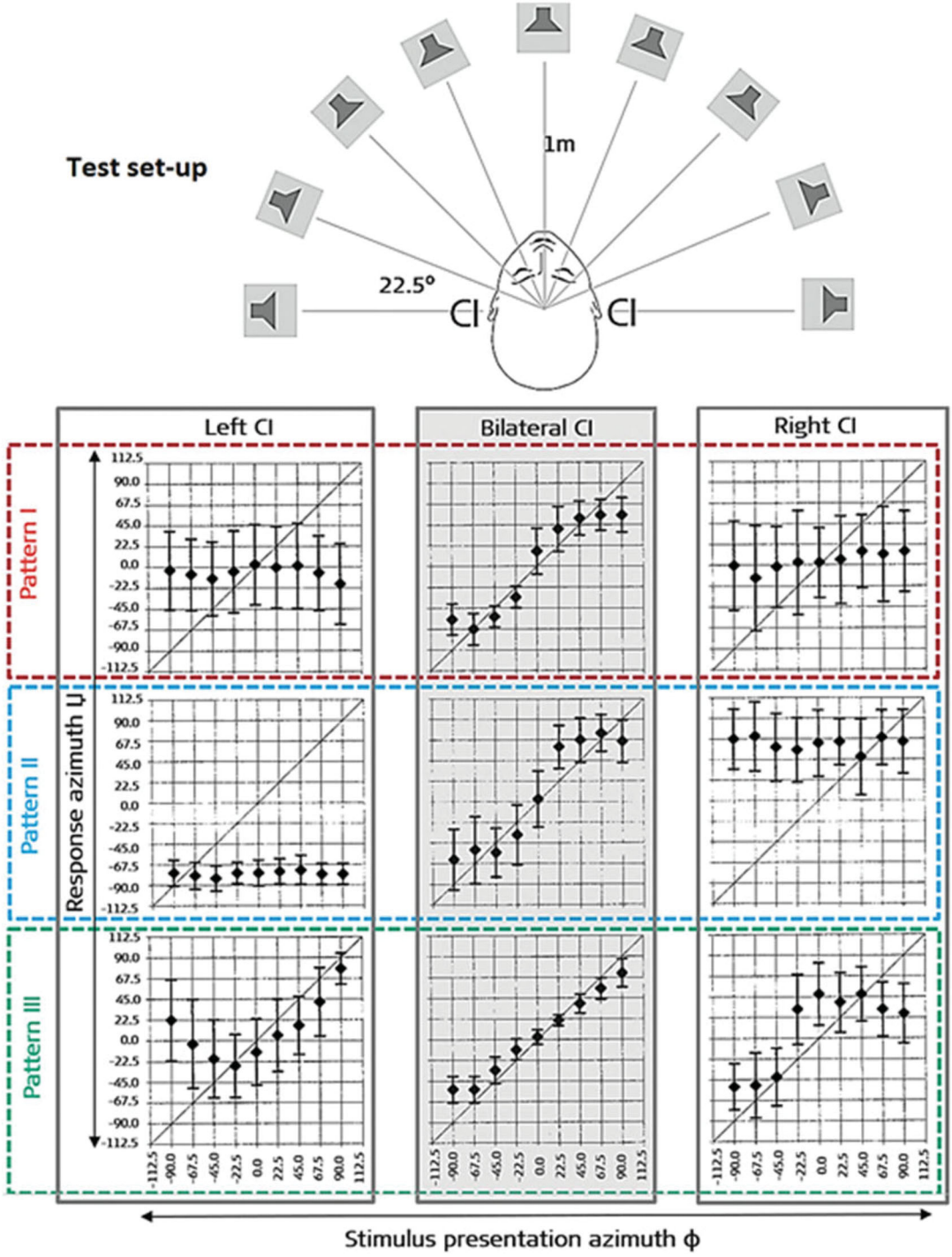


Figure 13. Sound localisation responses in 3 different patterns. The left column shows results for left CI only; middle column for both CIs; right column for the right CI only [14]. Statistical analysis: Post hoc analysis ($p \leq 0.05$). Reproduced by permission of Wolters Kluwer Health, Inc.

responses were scattered over loudspeaker positions (sound source) ϕ, ipsilateral to the implant only and leading to a marked bias in the mean values towards the side where the implant was used. Pattern III (Figure 13, third row in green) showed a relation between ILI and ϕ, somewhat even for the unilateral listening conditions. Authors pointed out that among these three patterns, all forms of hybrids existed.

Under bilateral listening conditions (grey shaded middle column), the sound localisation was significantly better than in the unilateral listening conditions in all three patterns of responses. The study evidenced a substantial benefit in sound localisation under bilateral CI listening conditions in late-deafened patients.

In 2004, another important report from Würzburg clinic was published, which demonstrated improved auditory skills in a group of children ($n = 18$) implanted bilaterally with a MED-EL CI. The time difference between the first and the second CI ranged from zero to four years. From the standard speech audiometry in quiet, the mean word discrimination scores tested with both CIs (86.4%) showed a tendency to be significantly higher than that reached with the left CI (75.1%) or the right CI alone (71.8%) (Figure 14). Based on results from the speech discrimination test, the influence of time delay between both implantations, as well as the influence of age at first CI implantation, did not affect the outcome. However, it was recommended to minimise the time before restoring hearing in the second ear, as well as before beginning with the rehabilitation program.

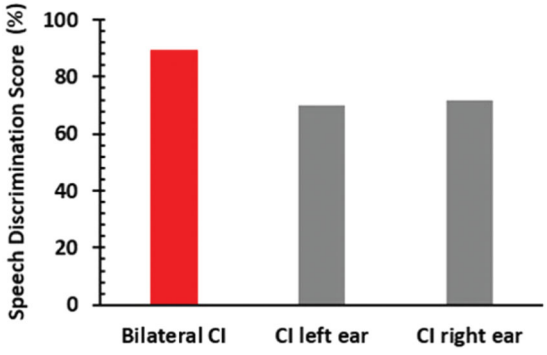


Figure 14. Mean of monosyllabic word discrimination scores tested in quiet with both CIs, as well as with the right CI and left CI separately. Statistical analysis: Wilcoxon test and paired *t*-test. Histogram created from data given in Kühn-Inacker et al. [].

In 2005, as more research works began to take place in evaluating the binaural benefits of bilateral CI, the year also marked more than one thousand bilateral MED-EL CI implantations across the world. This was an encouraging milestone for the scientific efforts led by MED-EL with the support of ENT professionals globally. The ability to detect an interaural level (loudness) difference and interaural time (lateralisation) difference combined – also known as a *binaural cue* – is another benefit of binaural hearing. In the same year, Dr Nopp, a signal processing engineer from MED-EL, together with clinicians from the Julius Maximilian University of Würzburg, evaluated the sensitivity of both, level and time differences, of bilaterally implanted CI patients [15]. For the level difference evaluation, tests were performed with each of the two audio processors' unbalanced loudness. The loudness unbalancing was performed by decreasing the volume on one side's audio processor while keeping the volume on the other side unchanged. The localisation bias ϕ_B in azimuth as obtained from the localisation experiment is shown as a function of the loudness difference for four different patients (Figure 15(A)). Loudness was rated on a linear scale, consisting of five categories (*very soft, soft, medium, loud,* and *very loud*) and where *one* corresponded to the lowest level and *fifty* to the highest level. The level difference was calculated by subtracting left-CI-only loudness judgements from the right-CI-only loudness judgements, obtained at the same presentation level. The findings showed an increase in the magnitude of localisation bias (ϕ_B) with increasing the loudness difference, and the linear regression amongst four patients is evidence of bilateral CI patient's ability to sense interaural level differences.

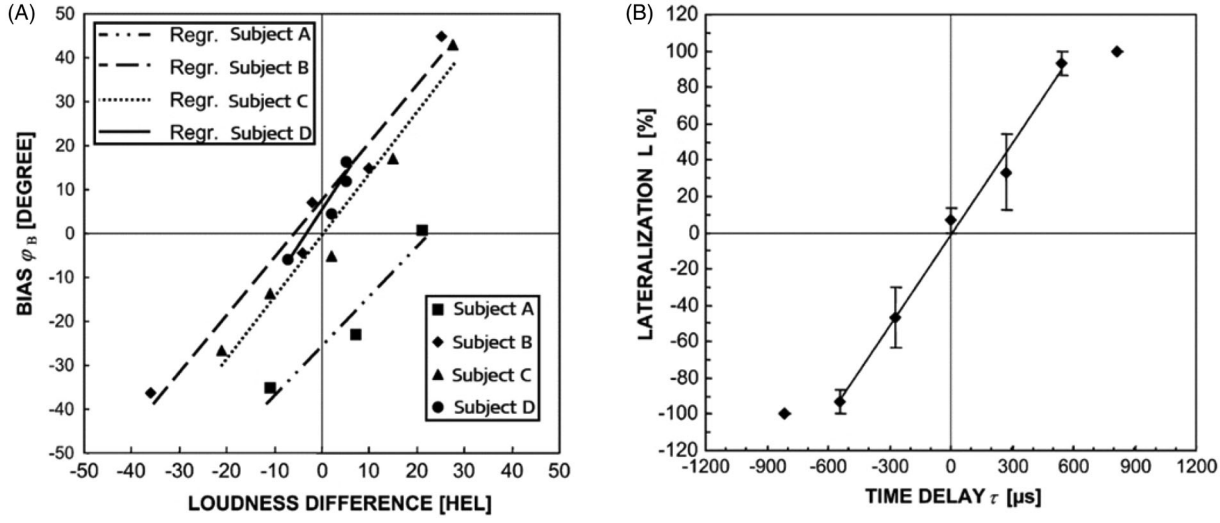


Figure 15. (A) Localisation bias ϕ_B as a function of loudness difference between right and left CI. (B) Mean values and standard deviation error values of lateralisation L as a function of interaural time difference τ for subject A from the previous experiment shown in graph A [15]. Reproduced by permission of Wolters Kluwer Health, Inc.

Lateralisation test results are shown in Figure 15(B) for the best performer with the mean values (diamond symbol) and standard error values (error bars) of lateralisation L (left ear: L = −100%; right ear: $L = 100\%$) as a function of interaural time difference τ (τ corresponds with the pulse on the right ear leading). For the time difference testing, a pair of pulses, separated by a specific time difference, was presented to the patients through their speech processors with one pulse directed to each side. The range of time differences used in the test was always symmetrical to 0μs, with the minimum time difference (left side pulse leading) ranging from −600 μs to −1,200 μs, and the maximum time difference (right side pulse leading) ranging from 600μs to 1,200μs. Between the minimum and maximum time difference, twelve pairs of seven equally spaced time differences, including 0μs, were tested. The patients' judgement on time difference was recorded on a linear scale with seven equally spaced units (corresponding to seven various time differences tested) with the centre of the scale referring to the centre of the head. In the range from −540μs to 540μs, the patients showed a relatively linear increase in L with τ increasing. Beyond and below this time difference range, sensitivity to L saturated. The results seen from these two experiments demonstrated that in principle, it was possible to have ILDs and ITDs in patients implanted bilaterally with CIs.

1.8. New measures of binaural benefits with bilateral CI

An alternative measure for spatial hearing is the minimum audible angle (MAA) test, with which the smallest angular separation of two sounds is perceived to come from distinct sources. MAA is an excellent measure which is consistent and reliable in discriminating left/right task and may be applied to infants as young as few months of age, as well as older patients. In normal-hearing children and infants, the MAA can reach 12° to 19° at six months of age – which decreases to between 4° to 6° by eighteen months of age – and 1° to 2° by five years of age, at which point they are not significantly different from an adult's MAA [16]. The MAA thresholds are worse in the absence of binaural cues, and this makes MAA an indicator of the emergence of binaural abilities in children who are fitted with CI. Prof. Senn and his colleagues from Switzerland showed that adult bilateral CI users express near-normal MAAs of 3°to 8° in front and back of the head, while at the sides, relatively poor MAAs of 30° to 45° (control group's normal hearing was 7° to 10°) were found [17]. The possible reason for the poor MAAs at the sides could be the audio processor's microphone position (positioned above pinna). In other aspects, the study pointed out the deficiency of envelope-based CIS speech coding strategy in not carrying fine structure cues. The importance of fine structure information in the coded sound signal in the modern sound coding strategy of "Fine Structure Processing" is given in article 5 within this compendium, under section 5.2.3.

In 2006, Dr Litovsky and her colleagues from the US studied binaural benefits using MAA as a measure in bilateral and bimodal listening conditions in two groups of children, with one group bilaterally implanted with CI and the other group unilaterally implanted with CI, including MED-EL devices, with the contralateral ear fitted with a hearing aid (HA) [16]. In the CI–CI group, MAA thresholds were lower (better) in the bilateral mode than in the monaural mode for all paediatric patients. In the CI–HA group, the results were similar, with most patients (six out of eight) showing bilateral benefit, compared to the monaural condition, but with no statistically significant differences (Figure 16). The presented results suggest that the ability of bilateral CI advancement in paediatric patients does not require prior binaural experience and may not be restricted to those who are implanted immediately after the onset of deafness. However, they cautioned that the extent to which a *critical period* exists during development for these abilities remains to be determined. Important recommendations, such as electrode channels distribution along the tonotopic axis of the cochlea equally in both ears, along with the speech processing strategy carrying fine structure information to specific channels along the two CI arrays matching spectrally and temporally, were made. A brand comparison results on the MAA is further given in section 1.10.

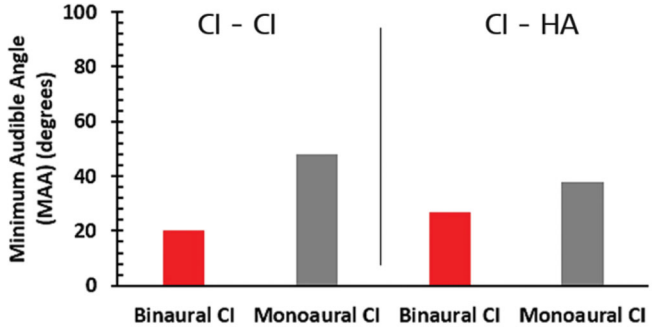


Figure 16. Group average MAA values for two groups of paediatric patients, both in bilateral and monaural CI listening condition. CI–CI = bilateral CI; CI–HA = CI on one ear and a hearing aid on the contralateral ear. Statistical analysis: Paired-sample *t*-tests ($p < .05$). Histogram created from data given in Litovsky et al. [16].

1.9. More evidence on binaural benefits with MED-EL's bilateral CI

In 2006, Prof. Ricketts and his colleagues from the Department of Hearing and Speech Sciences at Vanderbilt School of Medicine in the US, along with the support of MED-EL through a research grant, investigated the comparison of speech recognition in noise between bilateral and unilateral CI modes among postlingually deaf adult bilateral CI recipients [18]. Sixteen bilaterally implanted C40+ patients (TEMPO + audio processor with CIS + processing strategy) were recruited for this study. Both, the hearing in noise test (HINT) and speech recognition test at fixed SNRs were performed in a soundproof room with the patient sitting in the centre. Five uncorrelated, competing noise samples were played through loudspeakers placed at the 30°, 105°, 180°, 255°, and 330° azimuth relative to the position of the head. The test stimuli were presented from a

loudspeaker placed directly in front of the participant (0° azimuth; Figure 17(A)).

these experiments provide evidence of significant bilateral speech recognition in the noise of CI recipients in an envir-

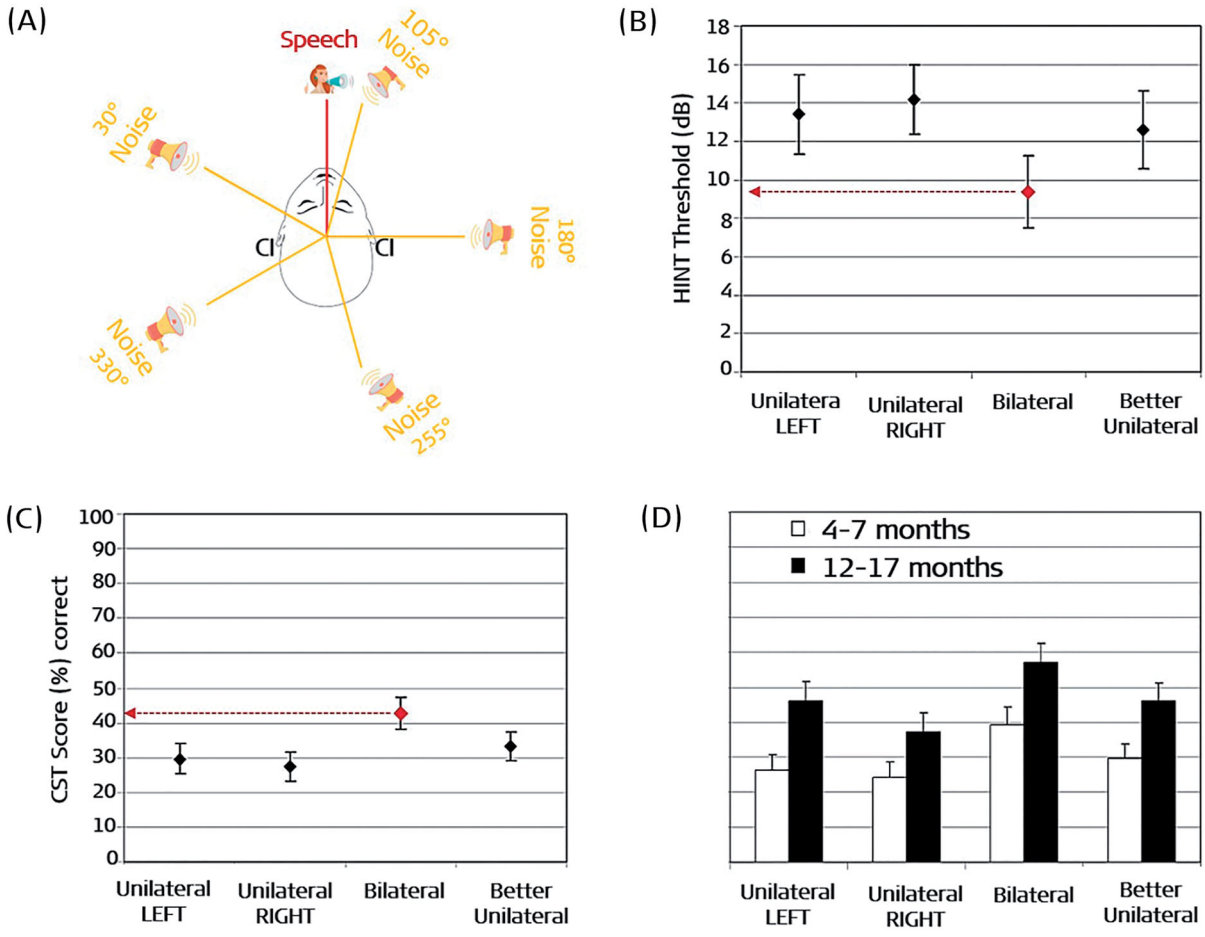


Figure 17. Audiological test setup (A). HINT test hearing threshold showing lower values for the bilateral CI listening condition (B). Speech recognition in noise evaluated using the CST showed higher values for bilateral CI listening condition even at long-term test period of seventeen months (C and D) [18]. Statistical analysis: ANOVA test ($p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

HINT test included two ten sentence lists that were randomly selected without replacement, and the hearing threshold was measured when the participants correctly identified at least 50% of the presented sentences. Speech recognition at fixed SNRs was evaluated using the connected speech test (CST), which is a test of intelligibility for everyday speech that consists of twenty-four pairs of speech passages produced conversationally by a female speaker. Participants' average speech-recognition in noise performance scores across the two unilateral conditions, the bilateral condition and the better unilateral condition as measured by the HINT and CST, are shown in Figures 17(B,C), respectively, with bilateral condition offering better scores compared to other listening conditions. Performance data for the two unilateral conditions, the bilateral condition and the better unilateral condition measured at 4–7 months and 12–17 months after activation is shown in Figure 17(D). Participants performed significantly better in the bilateral condition than in other listening conditions. The results of

onment with multiple noise sources. This advantage is presumed to be attributable to the combined effects of binaural squelch and summation.

In 2007, the first French report by Dr Polanski from Portmann Institute was published on the binaural benefits of bilateral listening with MED-EL CI devices in an elderly patient who was deaf for more than fifty years, as well as suffering from tinnitus [19]. The patient had been implanted in February 2004 on the left side with MED-EL's COMBI 40 device, with all twelve electrode channels fully intracochlearly. With the first activation of the device, the patient presented better conversational abilities without lip-reading and tinnitus disappeared. Two years later, the patient was implanted with the second implant on his right ear due to tinnitus complaints. Figure 18 shows the patient wearing both implants, and with such, his hearing scores were better than with unilateral listening condition tested at one-year post-operation, along with the complete absence of tinnitus when the device was switched on. Effects of long-term

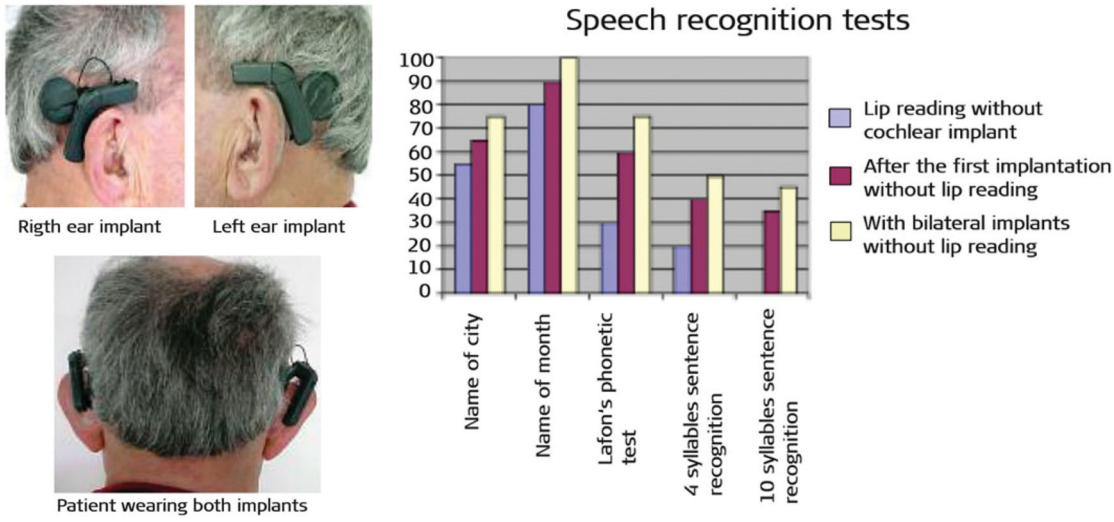


Figure 18. Patient wearing MED-EL CI device on both ears. Speech recognition test results showing better hearing in bilateral listening condition [19].

auditory deprivation were not seen on this patient whose hearing performance with CI was exceptional along with the tinnitus suppression.

2007 marked the tenth year of MED-EL's journey in bilateral CI, as well as it saw a review article from the UK which analysed all published evidence up to then, supporting the trend towards bilateral CI. It also added recommendation to CI manufacturers to develop future CI systems with binaural hearing enhancing features in mind, as well as with the reduction of costs in mind to ensure the hearing restoration is made widely available [20].

In the same year, the first multicentre study from the USA on MED-EL's bilateral CI reported the speech perception results at one-year postoperation from a total of twenty-six postlingually deaf patients with relatively short duration of deafness [21] (Figure 19).

Since different centres across the US were involved in this multicentre study, to create consistency in testing procedures, direct audio input (DAI) was used for the presentation of all test stimuli. The direct input was unattenuated but with microphone input attenuated by at least 30 dB, along with automatic gain control (AGC) circuit disabled. The results given in Figure 20 show the improvement in consonant-noun-consonant (CNC) scores over time (from one to twelve months test intervals), and superior hearing performance in the bilateral listening condition when compared with the better of the two unilateral conditions. In fact, this was the study that was used as a support at a later time, in the year 2018, when establishing the reimbursement of bilateral CI treatment in the US.

While the previous studies were involving standard audiological tests in laboratory conditions, in the year **2007** a team of specialists from the Washington University School of Medicine in the USA, along with the support of MED-EL through a research grant, demonstrated the binaural benefits in bilateral CI users of various CI brands under more challenging speech-perception tasks [22]. They included seven bilateral CI users to their study, with three implanted with MED-EL's COMBI 40+ device, two with Advanced Bionics

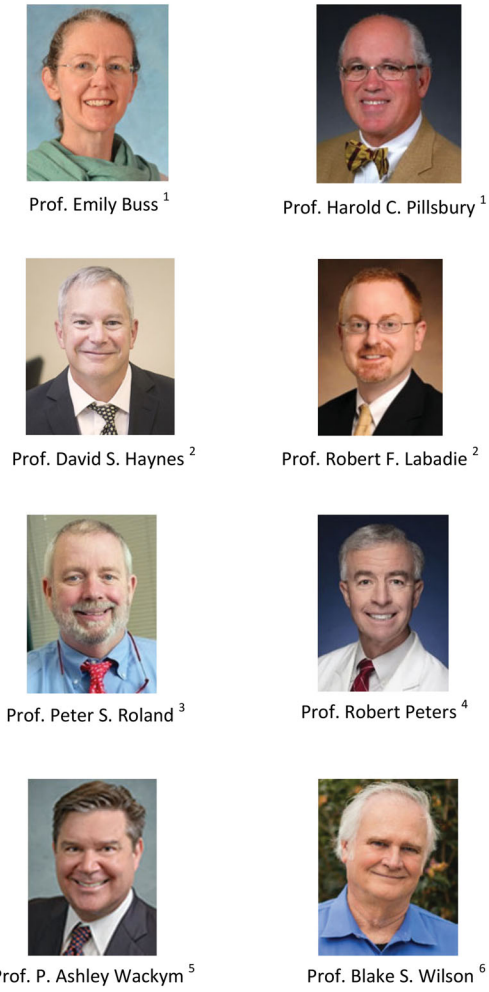


Figure 19. Clinicians from different centres in the USA evaluated the long-term effectiveness of bilateral CI in adults: [1]The University of North Carolina School of Medicine, [2]Vanderbilt University School of Medicine, [3]University of Texas Southwestern, [4]Dallas Otolaryngology Associates, [5]Medical College of Wisconsin, and [6]Research Triangle Institute.

HiRes 90 K device, and the remaining two with Cochlear™ Nucleus® device. The most challenging speech perception task for the CI patients was the SPIN (Speech Perception in

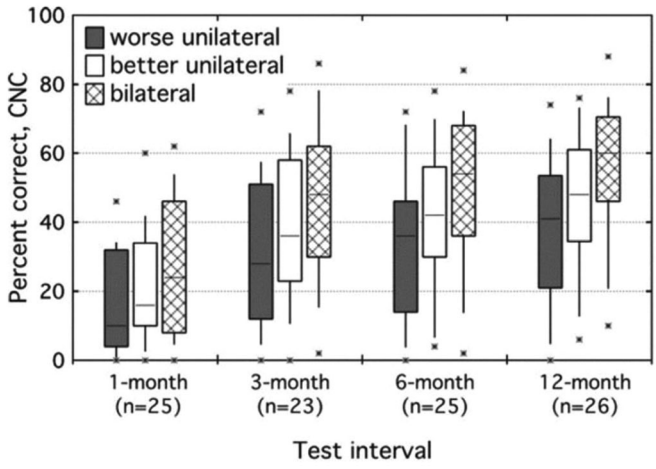


Figure 20. The distribution of CNC word scores in quiet (in %) is plotted as a function of the post-surgery test intervals. Horizontal lines indicate the median of each distribution, boxes span the 25th to 75th percentiles, vertical lines show the 10th to 90th percentile range, and stars indicate the minimum and maximum scores. Data for the worse of the two unilateral conditions are indicated with dark grey shading, those for the better unilateral condition with solid white shading, and those for the bilateral condition with grey and white hatching [21]—statistical analysis: ANOVA test (one-tailed, $p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

Noise) test with CNC test at 70 dB SPL in the presence of twelve-talker speech babble with +8 SNR. The results were compared between the best unilaterally listening ear against the bilateral listening condition. As expected, all patients showed better hearing in the bilaterally listening condition (Figure 21). The report suggested that with the technological advancements in the CI, it would make more sense to test the real binaural benefits of the bilateral CI under the most realistic and challenging test conditions.

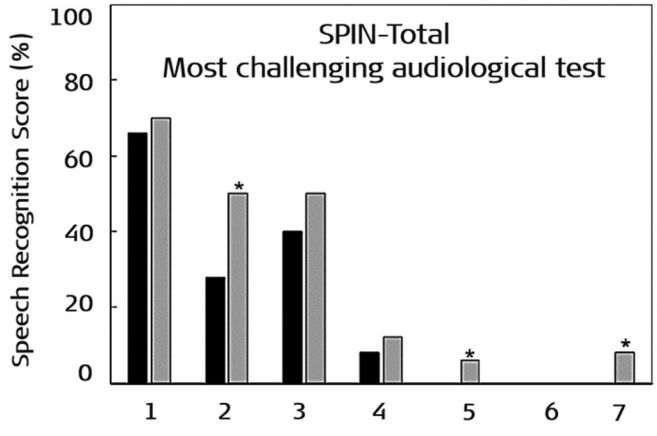


Figure 21. Speech recognition scores in percentage correct for the best unilateral (black) and bilateral (grey) ear conditions for individual patients implanted with various CI brands. Subject 1: MED-EL; Subject 2: HiRes 90 K; Subject 3: MED-EL; Subject 4: MED-EL; Subject 5: Nucleus; Subject 6: Nucleus; Subject 7: HiRes 90 K [22]. * indicates statistical significance between unilateral and bilateral CI condition. Reproduced by permission of Wolters Kluwer Health, Inc.

Between **2008 and 2011**, several reports from across the world added valuable evidence to binaural benefits with bilateral implantation with MED-EL CI devices in both, children and adults [23–33]. These well-designed studies in adults and children have documented significant auditory benefits for bilaterally implanted recipients when compared with monaural use and include improved speech perception in quiet and in noise, sound localisation, as well as subjective benefits.

Music appreciation by bilateral CI users is seen as another advantage of binaural hearing. A multicentre study from the UK, Germany and Switzerland showed that bilateral CI users with a MED-EL device enjoy significant advantages over unilaterally implanted CI users when it comes to appreciating, perceiving and accessing music for a variety of purposes [31] (Figure 22).

Kim Veekmans, MSc [1]

Prof. Joachim Müller [2]

Prof. Mattheus Vischer [3]

Dr Steffi J Brockmeier [4]

Figure 22. Clinicians from different centres who looked into the music perception of CI users: [1]Nottingham Cochlear Implant Programme, UK; [2]University of Würzburg (in 2009), Germany; [3]University of Bern, Switzerland; [4]University of Basel, Switzerland, and Technical University of Munich, Germany.

Dr Brockmeier developed the musical test that was sponsored by MED-EL. Figure 23 shows patient responses to questions on musical instrument identification, where bilateral CI users show superiority compared to the unilateral CI users in identifying the correct musical instruments. The difference between the unilateral and bilateral CI groups was not only in which instruments they reported recognising, but also in the number of instruments recognised correct by the bilateral CI group. All patients were postlingually deaf adults, familiar with musical genres mentioned in the questionnaire. Results from the study using the questionnaire indicate that bilateral CI users enjoy some significant advantages over unilateral users when it comes to appreciating, perceiving and accessing music.

1.10. Brand comparison on hearing quality and sound localisation with bilateral CI

Differences in CI technology, including electrode array length, number of stimulating channels, individual electrode contact separation distance, sound coding strategies, and other aspects amongst the CI brands, may result in differences with subjective experiences and benefits to the patient. Brand comparison in terms of superior hearing is a

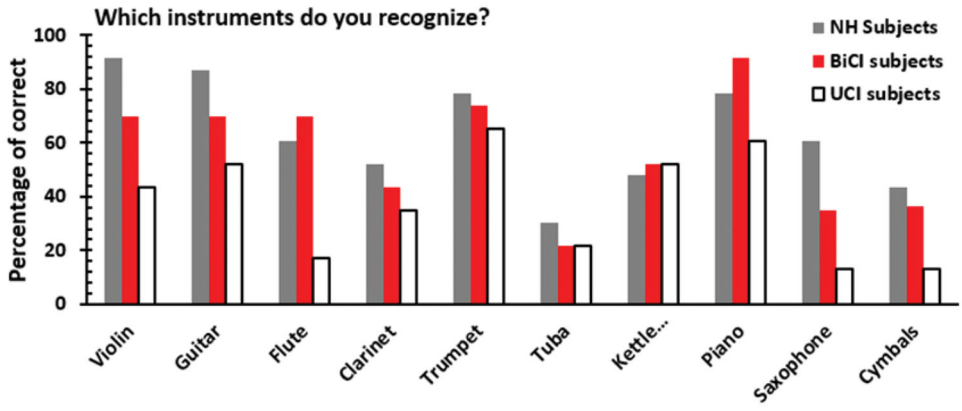
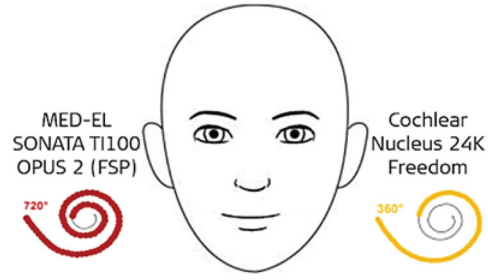


Figure 23. The x-axis describes the various instruments recognised in musical pieces; the y-axis is the percentage of *yes* answers for normal hearing, bilateral CI users, and unilateral CI users [31]. Histogram created from data given in Veekmans et al. [31].

challenging topic to address as there are several factors to be considered, including age, pathology of HL and resulting neuronal cell survival, quality of the test setup, patient's motivation on the day of testing – factors which may contribute to the variability in the test results. However, one of the best situations to study differences in hearing quality that arises from different CI brands is with bilaterally implanted CI patient with postlingual deafness, who is implanted with CIs from two different CI brands – preferably operated by the same surgeon to avoid any surgical technique factors. The postlingually deaf patients who have had the natural hearing in their past could better grade the quality of hearing through their CI by comparing it to their natural hearing experience.

In 2011, there were two scientific articles published from Australia (Royal Prince Alfred Hospital and Sydney Cochlear Implant Centre) which studied the difference in the quality of hearing between MED-EL CI and Cochlear™ CI, bilaterally implanted in postlingually profoundly deaf adult patients [34,35]. The first one was a case study from a sixty-three-year-old bilaterally deaf female who was implanted with CI devices from both abovementioned CI brands, one in each ear. After six weeks of activation, the patient described her experience with the first CI (Cochlear™) as being very mechanical: "Sounds are like two tins hitting together," whereas sounds with the second CI (MED-EL) were described as being quite natural (Figure 24).

In another study involving five bilaterally implanted participants with MED-EL and Cochlear™ CI device in each ear, the choice of going for MED-EL device in their second ear was due to expected music appreciation. Given this reason for choosing MED-EL, this study focused on any significant differences between devices in terms of music appreciation. The subjective assessment was made in the form of visual analogue scales (VAS), with evaluation results



"Ms. GD was interviewed 6 weeks after the insertion of the Med-El implant. *At this time, Ms GD described what she heard with her original Cochlear Corporation implant as being very mechanical 'sounds are like two tins hitting together'*. She said that she had enjoyed listening to music but found it 'quite microphone like'. *The difference she noticed with her Med-El (with the Nucleus switched off) was significant. She described the sounds as being quite natural.* Ms. GD believed that her voice had a more natural tone and that friends had commented that she was speaking more naturally."

	Subject 1		Subject 2		Subject 3		Subject 4		Subject 5	
Subjective assessment	MED-EL	Cochlear	MED-EL	Cochlear	MED-EL	Cochlear	MED-EL	Cochlear	MED-EL	Cochlear
Natural	7	4	7	5	9	7	8	5	8	8
Pleasant	6	3	9	8	10	7	9	6	8	8
Distinct	5	2	8	8	9	7	8	4	8	8
Tinny	8	3	3	0	9	7	7	2	8	8
Reverberant	5	3	6	5	10	7	7	3	8	8

*VAS 1 = 'unnatural', 'unpleasant', 'indistinct', 'more tinny' and 'less reverberant', VAS 10 = 'natural', 'pleasant', 'distinct', 'less tinny' and 'more reverberant'.

Figure 24. Participant's subjective assessment on hearing quality between MED-EL and other CI brand [34,35]. Reproduced by permission of Taylor and Francis Group.

ranging from 1–10 and assessing how natural, pleasant, distinct, tinny and reverberant music sounds, with each of their implants separately and with both implants together. Subjectively, four out of five thought their MED-EL device was *better, much better,* or *very much better* than their Cochlear™ device for music appreciation. Four out of five thought that music sounded *more natural, less tinny* and *more reverberant* with their MED-EL device, compared to their Cochlear™ device. However, the authors have cautioned that these participants received the Cochlear™ device first in their worse hearing ear, followed by MED-EL device in their better ear, and this could have contributed to subjectively favouring MED-EL device over the Cochlear™ device. Still, speech perception was also compared between the two ears, and it was not significantly different. What remains, none of the participants in this study subjectively favoured Cochlear™ device over MED-EL device [34].

In 2018, Prof. Raine and his colleagues from the University of Bradford in the UK studied the effect of inter-implant interval and the onset of profound deafness on sound localisation with devices from different CI manufacturers [36]. The study comprised of one hundred and twenty-seven bilaterally implanted children aged four years or older who were tested at least twelve months post-second implantation with various CI brands, both simultaneously and sequentially (Table 1).

Sound localisation testing was performed in a semi-circular array of loudspeakers at −60, −30, 0, +30, and +60 degrees azimuth, as shown in Figure 25.

The stimuli were pre-recorded female voices with the average presentation level of 70 dB. For each patient, sound-source localisation accuracy was measured *via* the root mean square error (RMSE) of thirty test trials. While the age at the onset of deafness and the inter-implant interval having a decreasing RMSE with increasing time are interesting findings, significant differences were obtained between the CI manufacturers as reported in this study, and these shall be given importance. On average, MED-EL systems were associated with more accurate sound localisation, with RMSE of 5.79° smaller than with Cochlear™, and 9.19° smaller than with Advanced Bionics, as calculated by the regression analysis. One of the reasons for more accurate sound localisation with MED-EL system, as reported in this article, is that maybe MED-EL's front-end sound processing applies less compression to sounds louder than 65 dB SPL compared to Cochlear™ or Advanced Bionics, better-preserving ILD cues as a result.

Table 1. Number of children implanted bilaterally, either simultaneously or sequentially, with different CI brands.

Manufacturer	Simultaneous implantation ($n = 65$)	Sequential implantation ($n = 62$)
MED-EL	27	38
Cochlear™	31	24
Advanced Bionics	1	48

The three studies mentioned above hint at the advantageous design of MED-EL CI devices in mimicking natural hearing [34–36]. This may be attributed to the two unique features in MED-EL's CI system which includes long and flexible electrode array, covering the entire frequency range electrically, and fine structure coding strategy that takes in both, place and time information along with no compression of the acoustic signal.

1.11. Bilateral CI in electric acoustic stimulation (EAS™)

With a profound acceptance of bilateral CI as a treatment option to restore binaural hearing in severely to profoundly deaf patients, the indication of bilateral CI with MED-EL devices was extended to patients with functional low-frequency residual hearing as well.

In 2010, Prof. Van de Heyning and his colleagues from the Antwerp Medical University in Belgium published a single-case study [32]. With their forty-eight months' study period, they concluded that with flexible electrodes, such as with the FLEXSOFT™, and with a nearly full intracochlear electrode insertion, the hearing preservation is feasible in bilateral CI condition (Figure 26).

In 2011, Prof. Usami and his colleagues from Shinshu University in Japan performed two bilateral CI surgeries in patients with functional low-frequency residual hearing, using a twenty-four-millimetre-long electrode array (FLEX24™) [37]. In both patients, the low frequency was well preserved even at twelve months postoperation and demonstrated excellent hearing scores in noisy conditions, along with improved sound localisation abilities.

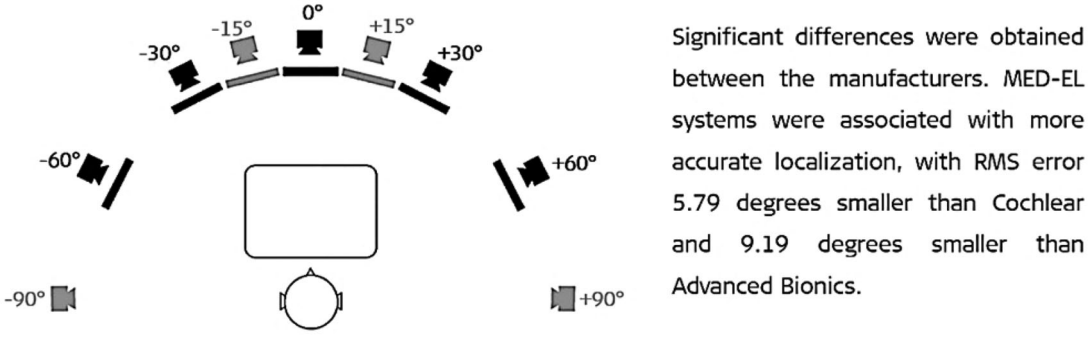


Figure 25. Sound localisation test setup with a child seated in front of the table and facing the centre of the arc of loudspeakers. Active (black) and inactive (grey) loudspeaker positions are shown in degrees azimuth; negative angles denote locations to the left, and positive angles denote locations to the right of the centre [36]—statistical analysis: Linear multivariable regression model.


Prof. Paul Van de Heyning


Prof. Shin-Ichi Usami

Figure 26. First bilateral CI treatment in an EAS patient by Prof. Paul Van de Heyning from Antwerp Medical University in Belgium in 2010, and Prof. Shin-Ichi Usami from Shinshu University in Japan in 2011.


Dr Eva Karltorp

Figure 27. Dr Eva Karltorp and her colleagues from Karolinska University Hospital, Stockholm, Sweden and University of Oslo, Norway, investigated the importance of early CI treatment in infants on their spoken language development.

Both abovementioned reports encouraged the extension of bilateral CI as a means of treatment to patients with partial deafness in the low-frequency region.

1.12. Simultaneous versus sequential CI implantation

In 2010, the question of the optimal time for bilateral CI implantation in children was still unanswered. The overall goal of bilateral CI is to achieve similar levels of hearing performance on both sides, thereby bringing the benefits of binaural hearing. With paediatric patients, language development relies on their hearing ability and providing them with binaural hearing benefits with bilateral CI would be a logical choice [38].

Unilaterally implanted children had mismatched timing of brainstem activity, resulting in a decrease in brainstem response latencies, which was not the case in children receiving bilateral CI simultaneously. Such unbalanced timing in unilaterally CI implanted children was resolved with the second implantation (nine months later), but the unbalanced timing issue persisted in patients with prolonged time of having only unilateral devices [27]. Dr Sharma and her colleagues from the US evaluated the sensitive period on central auditory development in children with unilateral and bilateral CIs [39]. Children who were implanted bilaterally early (<3.5 years of age) displayed rapid development in cortical auditory evoked potential (CAEP) waveform morphology, whereas late-implanted children (>7 years of age) showed aberrant waveform morphology. Children deprived of sound for more extended periods of time may have increased language learning difficulties when compared to those who were implanted within the critical period. As for the importance of language development, simultaneous bilateral implantation should be considered where possible – otherwise, as low as possible inter-implant interval between two CIs should be considered in children. As mentioned in the above section, a study by Prof. Raine and his colleagues showed that the RMS error was seen to increase with increasing inter-implant interval between the two CIs [36]. This was another study which pointed out to the importance of short inter-implant interval if simultaneous implantation cannot be accommodated.

In 2019, Dr Karltorp and her colleagues from Karolinska University Hospital in Stockholm in Sweden and University of Oslo in Norway published their findings that investigated whether providing CI at 5–11 months of age had a stronger positive influence on spoken language development and speech recognition than providing it at 12–29 months of age [40] (Figure 27).

Another aim was to examine whether the medical risks associated with surgery were greater in younger patients. One hundred and three children were implanted with CI, out of which ninety-five were implanted with MED-EL CI device. Out of one hundred and three children, ninety-eight received bilateral CIs: seventy underwent a two-stage sequential bilateral implantation and twenty-eight children underwent a one-stage simultaneous bilateral implantation. The language performances of the children at the age of six years were compared between children who were implanted between 5–11 months and 12–29 months at the time of surgery. Peabody test was used to check the receptive vocabulary and the six-year estimation revealed a significant negative correlation between the age at the time of the first CI and receptive vocabulary of −1.3. This suggested that a one-year delay in surgery, on average, caused a delay of 1.3 years delay in receptive vocabulary at six years of age, as shown in Figure 28.

The study concluded that fitting CI before a child's first birthday was crucial for spoken language development at six years of age. Infants who received their implants before nine months of age had an even more age-typical language profile. The medical risks associated with CI surgery under nine months were no greater than for children who were older when they had CI surgery.

In 2020, a multicenter study from France looked into the French national registry of cochlear implantations from January 2012 to December 2016 to assess the incidence rate of bilateral CI and the results of bilateral CI in adults and children [41]. They mainly looked at the results of CAP (category of auditory performance) and speech audiometry with monosyllabic and disyllabic word lists, before and after bilateral CI implantation. The database showed nine hundred and forty-two bilateral CIs out of which three hundred and fifty-four were implanted simultaneously, and five hundred and eighty-eight took place sequentially. Children and adults had an incidence rate of 59% and 41%, respectively. CAP scores are used to grade the hearing performance with their CI switched on by qualitatively grading their awareness and responses to various forms of sound and speech signals. Higher CAP scores relate to better hearing performance and vice versa. Within the simultaneously implanted group, the number of patients with CAP score <3 decreased after one year from 169 (85.8%) to 57 (58.8%), and the number of patients with CAP ≥5 (good understanding of speech)

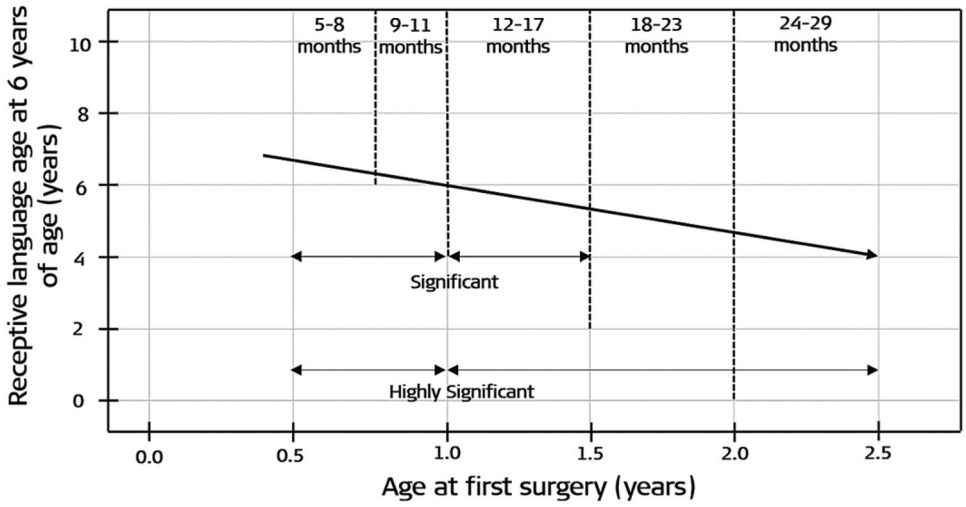


Figure 28. Mean slope and delay calculated from individual regressions on receptive vocabulary, according to Peabody test. Graph created from data given in Karltorp et al. [40].

increased from 10 (5.1%) to 74 (37.6%) after implantation. Within the sequential group, 16 patients (9.7%) had a CAP score of <3 before receiving the second implant, compared to 3 (1.8%) afterwards, and 102 (61.8%) had a CAP score ≥5 before, and 139 (84.2%) after receiving a second implant. With the sequential implantation, the number of patients with a higher CAP score saw significant improvement after receiving first CI and did again with the second implant. In terms of speech discrimination results, simultaneous implantation group had 0% to 65% and 0% to 70% with monosyllabic and dissyllabic word list correct scores, respectively, when presented at 60 dB in noise. With the sequential implantation group, the monosyllabic word list correct was 56 ± 27% with first CI, and it increased to 62 ± 21%, whilst with the dissyllabic word list, the first CI resulted to 70 ± 27%, and that increased to 77 ± 26% with the second implant.

The authors concluded that simultaneous bilateral CI significantly improved hearing. For sequential CI, at one year, when auditory results were already excellent from the first implant, the hearing scores further significantly improved under bimodal condition.

In 2020, a report was published by Prof. Gao and his colleagues from the Union Medical College Hospital in Beijing in China, which demonstrated the safety of simultaneous bilateral CI in children aged 12–18 months, with applying standard CI surgical techniques and using MED-EL CI devices [42] (Figure 29).

Twenty-one children aged between 12–18 months met the inclusion criteria and took part in this study. Ten patients received a unilateral CI. Nineteen patients received simultaneous bilateral CI and were operated with applying standard surgical technique (transmastoid facial recess approach with round window insertion). Safety was assessed *via* monitoring peri- and post-operative adverse events. No adverse events were reported in any of the patients and it was concluded that simultaneous bilateral CI can be performed using the same surgical technique as unilateral implantation, and poses no increased safety risk for children

Prof. Gao Zhiqiang

Figure 29. Prof. Gao Zhiqiang and his colleagues from Union Medical College Hospital, who demonstrated the safety of simultaneous bilateral CI in children aged 12–18 months.

aged 1–2 years. This study was fully sponsored by MED-EL, including the cost of the CI devices and external accessories.

In terms of incremental cost-effectiveness ratio (ICER) which takes into account the cost associated with the CI treatment and hearing benefits it brings to the patient, the simultaneous implantation of bilateral CI was established to be more effective and economical than the sequential bilateral CI – as reported by Pérez-Martín et al. in 2017. This cost-effectiveness report – originating from Spain – included retrospective data of two hundred and seventy-three children [43]. A similar finding was reported by Bond et al. from the UK in the year 2010, with including data of one hundred and thirty bilaterally implanted children [44]. The British Cochlear Implant Group (BCIG) reports annually on the number of bilaterally implanted children and adults, either simultaneously or sequentially (Figure 30) [45]. Between 2015–19, the simultaneously bilaterally implanted children represented a substantially larger group compared to sequentially and unilaterally implanted, which evidences a strong trend towards the former.

Considering the pieces of evidence from abovementioned research studies on simultaneous versus sequential bilateral CI, the former has proven as a valuable contribution to oral communication amongst its recipients, and with minimal surgical risk. Therefore, whenever the financial aspects and patient's medical condition accord, then simultaneous implantation is preferred, and especially so in children, as it could help them to have a more typical auditory cortex

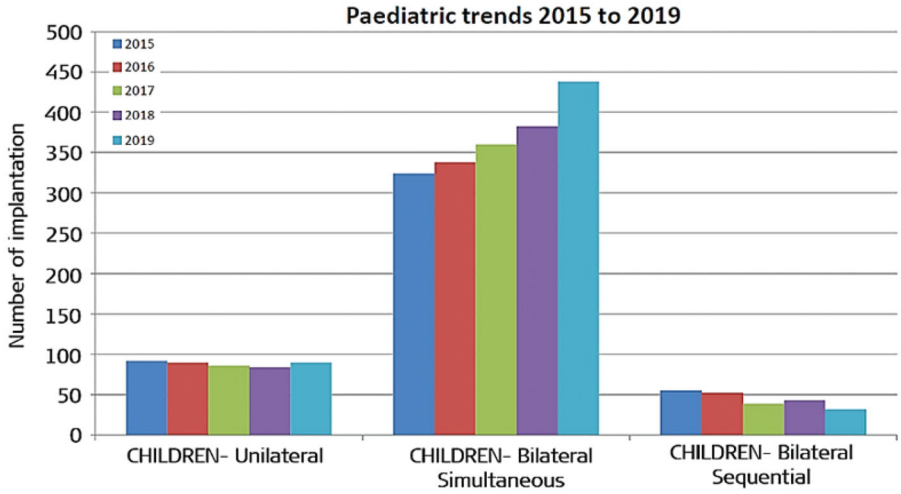


Figure 30. Data from BCIG showing the number of CI implantations in children unilaterally, simultaneously bilaterally, and sequentially bilaterally, which took place between 2015 and 2019 [45]. Histogram taken from British Cochlear Implant Group.

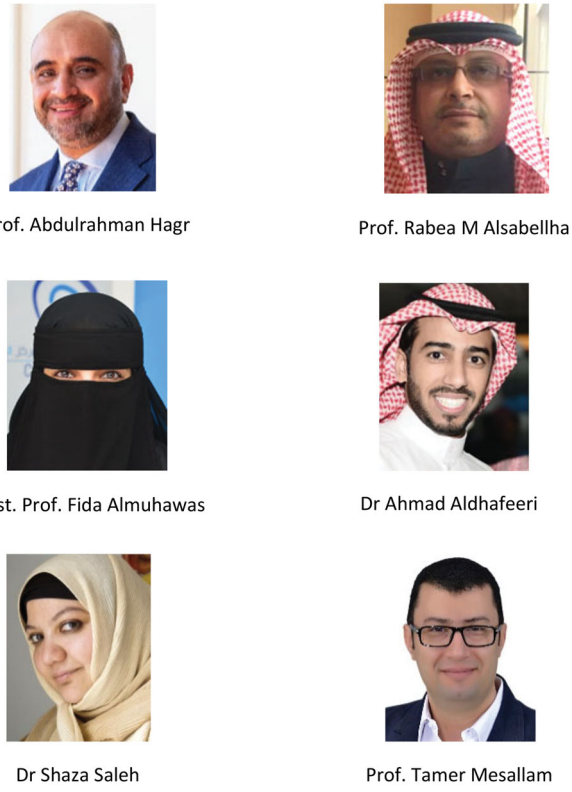


Figure 31. Clinicians from Saudi Arabia, who were all part of the early activation and CI surgery under local anaesthesia studies.

development, as well as it would avoid a second surgical procedure and the costs associated with it. Bilateral sequential implantation has shown better hearing benefits compared to unilateral implantation, and therefore when a situation does not allow for simultaneous bilateral implantation, then bilateral sequential implantation could be pursued.

Early activation of the CI audio processor is a technique that is being followed in some clinics with the aim of restoring hearing as soon as possible following the CI surgery, and as well to reduce the hospitalisation costs. CI surgery under local anaesthesia is another practice that is followed, especially in a group of patients who do not tolerate general anaesthesia. Group of clinicians from Saudi Arabia reported on the feasibility of audio processor activation one day after the CI surgery, including the group of patients that underwent CI surgery under local anaesthesia [46,47] (Figure 31). They concluded that early implant activation did not impact the healing process of the incision site, and also the evolution of electrode impedance and stimulation levels were consistent with the standard four weeks postoperative activation.

Early activation of the CI audio processor, although it is reported safe, depends on the individual clinic and operating surgeons' comfort of choosing such a technique or not. Nevertheless, this is one additional possibility of encouragement for bilateral CI either simultaneously or sequentially.

From all the evidences given in this section, is it clear that performing simultaneous CI implantation on both sides is safe from the surgical point of view, including in children. The trend is moving towards simultaneous rather than sequential implantation of bilateral CI and it adds cost-benefit for both, the healthcare system and the patients.

1.13. Reimbursement for bilateral CI from the healthcare systems

The therapeutic impact of CI has transformative effects on patients with severe-to-profound hearing impairment. How these benefits confer improvement in health-related quality of life, has been the focus of many clinical studies. Cost-utility is a term often used in medical device-related treatment, and it is expressed as a function of the net cost of treatment to the net effect in quality-adjusted life years. There were several studies (Table 2) performed which investigated the cost-utility ratio of the CI treatment, concluding that the cost associated with the CI treatment, including the bilateral CI, is highly effective for both, the patient as well as the healthcare system in the long run [48–50].

Originating from different parts of the world, all of the studies point towards overall cost-effectiveness of bilateral over unilateral and in particular, to the simultaneous bilateral implantation.

Table 2. Summary of studies that reported on the cost-effectiveness associated with bilateral CI treatment.

Study	Design	Population	Country	Conclusion
Perez-Martin et al. [43]	Retrospective cost-effectiveness model	273 children	Spain	BCI is cost-effective compared to UCI
Bond et al. [44]	A systematic review and pooled cost-effectiveness	130 children	United Kingdom	BCI is cost-effective when significant discounts are given for the second CI
Smulder et al. [48]	Randomised controlled trial	38 adults	Netherlands	BCI is cost-effective only after used for prolonged periods
Chen et al. [49]	Theoretical cost-utility analysis	142 adults	Canada	Sequential BCI is most cost-effective when greater discounts are given on second CI and used for more extended periods
Trinidade et al. [50]	Retrospective cost analysis	29 adults	USA	Simultaneous BCI is cheaper compared to sequential BCI when $n > 22.1\%$ UCI patients convert to BCI.

BCI: bilateral cochlear implant; CI: cochlear implant; ICER: incremental cost-effectiveness ratio; N/A: non applicable; QALY: quality-adjusted life years; UCI: unilateral CI.

Health Utility Index (HUI®) is another term that relates to the generic health-related quality of life measurement tool. HUI® is the perfect health-related quality of life score. In 2008, a group from Marion and Indianapolis, USA, evaluated the improvements in quality of life of twenty-three bilaterally implanted CI recipients, implanted with various CI brands, including MED-EL [51]. For all twenty-three participants from this study, HUI® showed a score of 0.33 on average before CI implantation, which increased to 0.69 after receiving their first CI. With the second CI, the HUI® score reached a mean of 0.81, which is close to 1.0 – the perfect health-related quality of life score.

The purpose of all mentioned research studies from this article is to demonstrate the benefits of binaural hearing with bilateral CI – which shall ultimately help convince the healthcare systems to reimburse the costs associated with the treatment.

Within Europe, Switzerland was the first country to reimburse the cost of bilateral CI and Prof. Mattheus Vischer was instrumental in convincing the healthcare system on the importance of bilateral CI, especially in children. In Germany, the social insurance code (SGBV) regulates adequate treatment of both ears individually. Legal counsel for early cases from the year 1997 on, lead to precedence cases and coverage of most second CIs by the health insurance before the year 2005. In Austria, it was never a problem for the patients to get the second CI cost reimbursed by the healthcare system.

In 2018, the healthcare system in the USA, Canada, and almost all of the European Union (EU) countries had agreed to reimburse the cost of bilateral CI treatment – either sequential or simultaneous – in children and adults, complimenting all the research efforts that took place since 1999.

1.14. Communicating science through gaming

Science should be easy to understand. However, concepts from the scientific community may get across as overly complicated sometimes. To simplify the context and the full benefits of bilateral CI, MED-EL has taken the challenge as an opportunity to come up with a gaming concept which is available for anyone to play and grasp. *Switch-On-Life* was created to help with understanding the importance of binaural hearing, what it means, and how it helps with benefiting our daily lives (Figure 32).

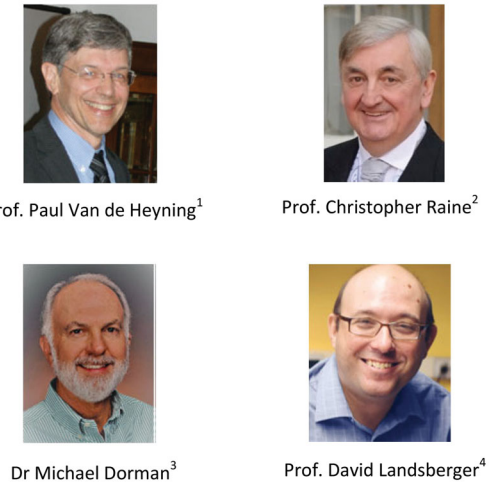


Figure 32. Experts from [1]Antwerp Medical University, Belgium, [2]Bradford Teaching Hospitals, UK, [3]Arizona State University, USA, and [4]NYU Grossman School of Medicine, USA, supported the development of Switch-On-Life web-platform.

In 2020, MED-EL launched an interactive web-platform (www.switch-on-life.com) which offers a playful experience on hearing, hearing loss and hearing implant technology, and which enables the user to discover the importance of hearing with two ears. Switch-On-Life – a project conceived and led by Dr Schleich from MED-EL – aims to provide the realisation of how basic scientific findings and observations are translated to MED-EL's CI technology and the clinical routine. Thanks to Prof. Van de Heyning, Prof. Raine, Dr Dorman and Dr Landsberger and their technical insights, this interactive web-platform was made possible.

1.15. Conclusion

In 2019, among MED-EL CI devices implanted bilaterally across the world, two-thirds were in children – this indicates the importance of bilateral CI treatment given to children as the binaural hearing helps them with success in their personal life and career at later stages. The best example is Mr Max Röder from Germany, who, in 1998, was the first child to receive bilateral CI (Figure 33). The binaural benefits offered by bilateral CI allowed him to speak and hear with capacities of an ordinary hearing person, which helped him throughout his journey to reach the successful academic

Figure 33. Max Röder, the first bilaterally implanted CI child in the year 1998, who is now a computer science graduate, living his life like every other normal-hearing person (Image courtesy of MED-EL).

graduation from his bachelor studies in computer sciences from the University of Würzburg in Germany in 2018. In the year 2020, Mr Röder found an employment opportunity at MED-EL and was appointed as a development engineer in the Research and Development department.

Just like Mr Röder, there are thousands of children across the world who would have benefitted from the bilateral CI, funded either by the national healthcare systems or privately. Considering the importance of binaural hearing, the bilateral CI treatment option should become the gold standard in treating bilaterally deaf patients, supported by the healthcare system in every county.

Bilateral CI restores binaural hearing in both, profoundly deaf and partially deaf patients. Scientific collaboration between clinicians from clinics across the world and researchers from MED-EL has brought the bilateral CI solution to the *state-of-the-art* with restoring binaural hearing. While every CI brand may claim to be technologically superior, it is the patient who uses the technology and can describe the actual CI hearing experience. The three mentioned studies which compared the CI hearing quality, saw a preference towards experiencing a naturally sounding hearing with their MED-EL CI device, over any mechanically sounding CI, as reported by the users implanted with other CI brands. Natural hearing that comes from MED-EL CI device is mainly due to its sound coding strategies, inspired from nature by mimicking both, time and place coding – the two top distinctive features of MED-EL – carrying fine structure information, as well as due to the electrode arrays with their tonotopic distribution over the entire cochlear length. While the device technology is one of the aspects for successful hearing through CI, another aspect would be the time at which it is provided to the patient. For paediatric patients, it is their first two to three years of life that plays the critical role with obtaining the optimal benefits through a CI technology, and the latter shall reach them during that time to provide them with the communication means through binaural hearing. This is exactly what happened with Mr Röder, who received his bilateral CI before the age of four in 1998, and which helped him to develop his communication means thoroughly. Today, he is as successful as anyone else with normal hearing. The journey of Mr Röder with his bilateral CI is one single success story that could well represent many other bilateral CI users' experience. Although the healthcare system is in great shape in the Western world, there is a space for improvement in the rest of the world, and more specifically, an immense potential lays in allowing the bilateral hearing to every single patient in need, and in advancing the necessary reimbursement systems which currently obstruct this.

Acknowledgments

The authors would gratefully like to acknowledge the key contributors to the development of the subject matter. Their contributions are outlined in this article. The authors further acknowledge Reinhold Schatzer from MED-EL for his valuable input and comments during several rounds of review meetings that contributed to the final version of this article.

Disclosure statement

This article is sponsored by MED-EL and has not undergone the regular peer-review process of Acta Oto-Laryngologica. Both the authors are affiliated with MED-EL.

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ACTA OTO-LARYNGOLOGICA
2021, VOL. 141, NO. S1, S22–S62
https://doi.org/10.1080/00016489.2021.1888477

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REVIEW ARTICLE

EAS-Combined electric and acoustic stimulation

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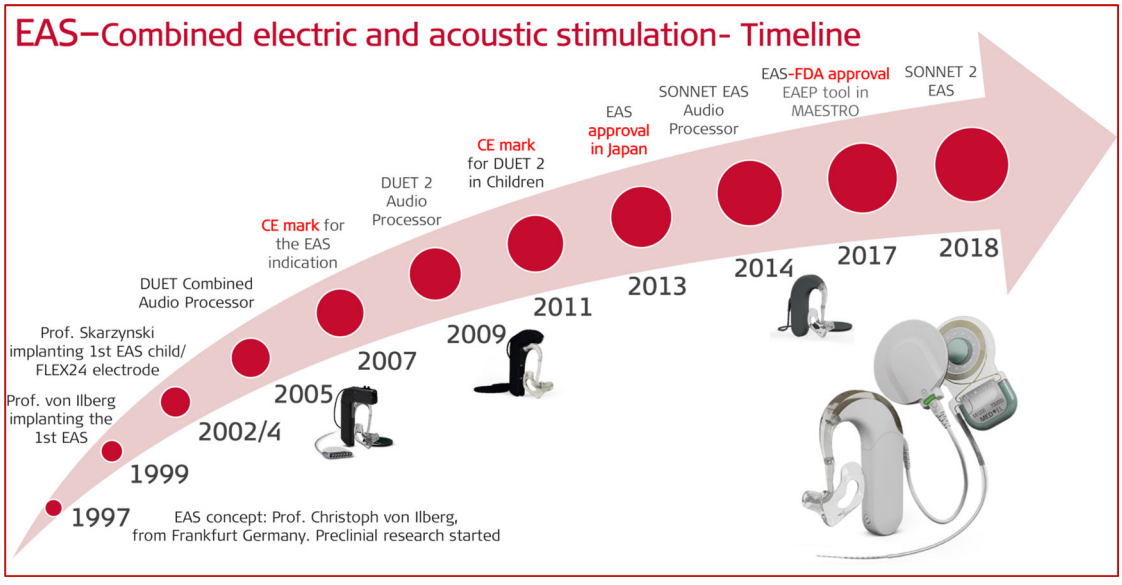
ABSTRACT

Electric-acoustic stimulation (EAS) is a special treatment modality for those patients who are profoundly deaf in the high-frequency (HF) region and retain usable hearing in the low-frequency (LF) region. Combining the electric stimulation with cochlear implant (CI) in the HF and acoustic amplification of residual hearing using a conventional hearing aid (HA) in the LF region defines EAS. The EAS concept was first proposed by C. von Ilberg from Frankfurt, Germany in the year 1997. In association with MED-EL, all the necessary safety studies were performed in non-human subjects before the first patient received it in 1997. In association with MED-EL, all the necessary safety studies were performed in non-human subjects before the first patient received it in 1999. For the patient to successfully use the EAS concept, the residual hearing needs to be preserved to a high extent and for several years. This requires a highly flexible electrode array in safeguarding the intra-cochlear structures during and after the CI electrode array insertion. Combining the HA unit with the audio processor unit of the CI was necessary for the convenient wearing of the unified audio processor. Fitting of the unified audio processor is another important factor that contributes to the overall success of the EAS treatment. The key translational research efforts at MED-EL were on the development of flexible electrodes, a unified audio processor, innovations in the fitting process, intra-operative monitoring of cochlear health during electrode insertion, pre-operative soft-ware tool to evaluate the cochlear size and electrode selection and some new innovations tried within EAS topic. This article covers the milestones of translational research from the first concept to the widespread clinical use of EAS.

ARTICLE HISTORY
Received 13 December 2020
Accepted 6 January 2021

KEYWORDS
Electric-acoustic stimulation; flexible electrode; unified audio processor; hearing preservation; Electro-cochleography



2.1. Introduction

The science behind human hearing is a fascinatingly complex process, and the last decades have seen outstanding achievements with mimicking nature to achieve more natural hearing in cochlear implant (CI) patients. To understand even a small portion of the sound's journey in human hearing, it is crucial to interrelate each of the journey's detailed properties. In this chapter, however, the focus will

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This article is a part of the compendium entitled 'Thirty years of Translational Research behind MED-EL' authored by Anandhan Dhanasingh (Director) (Anandhan.dhanasingh@medel.com) and Ingeborg Hochmair (CEO, CTO) (Ingeborg.hochmair@medel.com).
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lay on the portion between the oval window (OW) and the brainstem, and the relevant realised milestones.

It is now understood that once the sound hits the OW, it creates an intracochlear vibration, and more precisely, it causes a vibration of the basilar membrane (BM) – all the way from OW to its apical end, the helicotrema. The travelling wave namely passes through different frequencies which are logarithmically distributed along the BM – from high at the OW, to lower towards the apex. Now depending on the cochlear health, inner-hair cells on stimulated pitch regions during the BM vibration (Figure 1(A)) get excited and fulfil their function as mechanoreceptor cells by transforming the mechanical force received from the BM underneath them into electric signals. This mechanical force actuates the inner-hair cells to bend against the tectorial membrane, which is covering them. The bending opens small channels in the inner-hair cells, allowing ions in the surrounding fluid (endolymph of the scala media) to rush in and convert the physical movement to an electrochemical signal which excites the auditory nerve, and which then sends the electric signals to the brainstem – and after subsequent auditory functionalities, the patient eventually perceives a relevant sound [1]. The outer-hair cells are different group that mechanically amplify low-level sound that enters the cochlea and such amplification may be powered by the movement of their hair bundles.

In some patients, the high frequency (HF) responsible inner-hair cells are permanently damaged. This may occur due to variety of reasons, including ageing, noise-related hearing loss (HL), genetics, medication side effects and different diseases, causing severe to profound HL in the HF region (Figure 1(A)) [2]. However, the low frequency (LF) residual hearing with mild to moderate HL could still be utilised in such patients through a sound amplification device, like hearing aid (HA). The exact frequency range and the degree to which the HL occurs can be detected from the pure tone audiogram of the patient, tested in the quiet condition. Figure 1(B) is a typical audiogram of an extended indication (indication 2) of a partially deaf patient with severe to profound HL in the HF region which extends from 1,500–8,000Hz, and mild to moderate HL from LF to mid-frequencies in the range between 125–1,500Hz. A normal-hearing is referred to when the hearing threshold is within twenty-five decibels (dB) of HL across all frequencies.

In the late '90 s, according to Niskar et al., 14.9% of the US children had some degree of LF HL of at least sixteen decibels HL in one or both ears [3]. To accommodate this unique but relatively common partial deafness, the technology which combines both, electric stimulation of HF region and acoustic

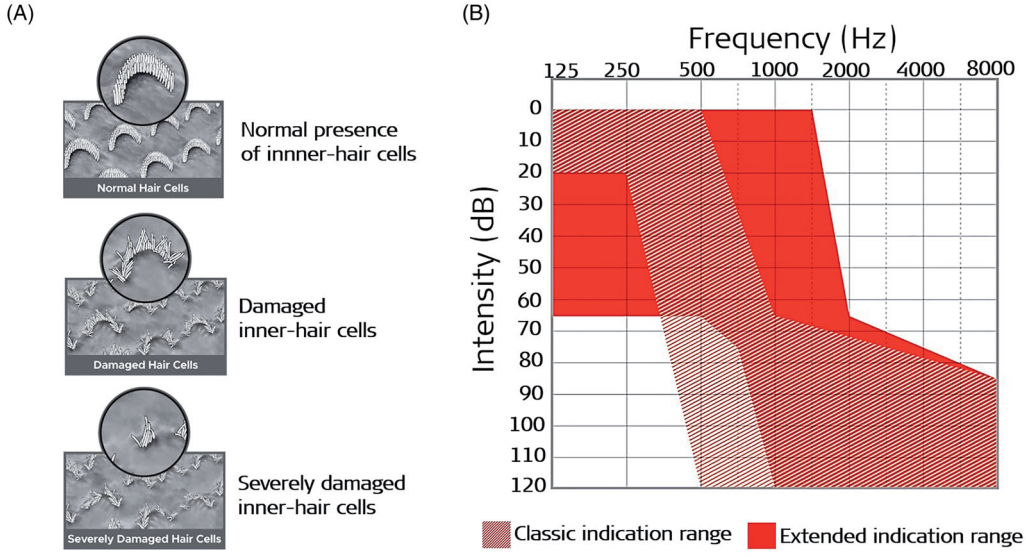


Figure 1. Morphology of inner-hair cells in three different conditions (A) [2]. Typical audiogram of a partially deaf patient with severe to profound HL in the HF region: indication from the earlier times when the functional LF residual hearing cut-off was kept at 500 Hz which was extended to 1,500Hz under expanded indication criteria (indication 2) (B). Image (A) reproduced by permission of www.davidsonhearingaids.com.

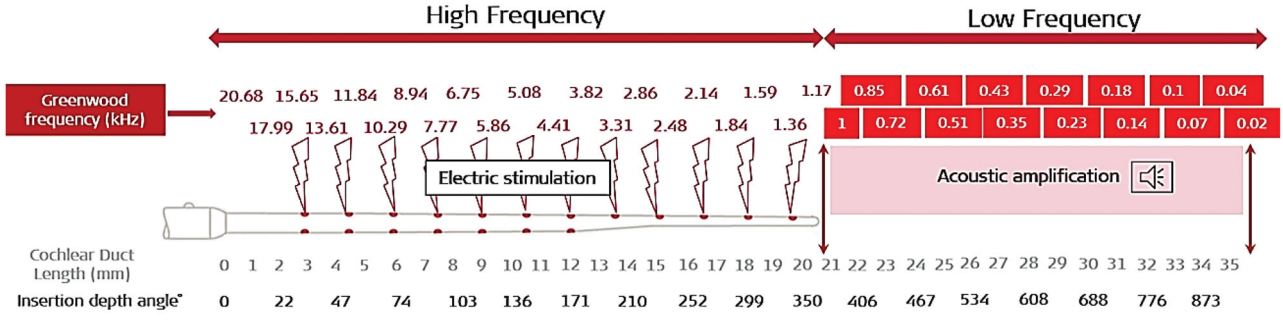


Figure 2. Schematic representation of electric stimulation in the HF region and acoustic amplification in the LF region in an average-sized cochlea (image courtesy of MED-EL).

amplification of LF region, was developed as the EAS™ (Electric Acoustic Stimulation Hearing Implant System). Figure 2 shows the electric stimulation provided by implanting the CI electrode array to cover the HF region and acoustic amplification of the LF region. Where the electric stimulation of the HF region and acoustic amplification of the LF region shall cross-over, depends on the patient's hearing condition and the history of progressiveness of the HL.

The successful implementation of this treatment modality in partially deaf (PD) patients requires consideration of the below points:

i. highly flexible CI electrode array design
ii. an extra safe surgical procedure in placing the CI electrode array with minimal, if not zero, damage to the intracochlear structures
iii. corticosteroids to minimise the inflammation reaction following the electrode array insertion
iv. an efficient audio processor that combines acoustic stimulation from the HA module with the electric stimulation from the CI electrode array
v. optimised fitting strategy

To address the above points, we will canvass through a brief history of MED-EL's electric acoustic stimulation (EAS) journey beginnings in the late '90s, followed by its early research works that supported the development of the first EAS™ system. This article covers the key clinical studies that evaluated the safety and effectiveness of unified EAS™ audio processors from the first generation until the most recent generation so far, along with patients' overall hearing performance with the system. This article will also address some EAS-relevant topics, such as the effective hearing preservation (HP) classification system in general, and how it may be mathematically calculated in a uniform manner. The article will walk us through the topic advancements, including identification of patient-specific LF cut-off region, effective preservation of residual hearing, long electrode arrays in EAS, and electrocochleography to monitor inner ear function during the electrode insertion process. Advancements in genetic testing to predict HP results will be discussed, as well as the current EAS indication criteria, and studies that supported MED-EL in obtaining its EAS™ device approval by the notified bodies in the USA, EU and Japan. Also, this article will give a short overview of the annually held Hearing and Structure Preservation (HSP) workshop.

2.2. Beginning of MED-EL's EAS journey

In 1997, MED-EL's EAS journey began with Prof. von Ilberg's (EAS inventor and patent holder) suggestion to create a concept which would combine electric and acoustic stimulation as a mode of treating partially deaf patients (Figure 3). EAS applies to patients with LF functional hearing, to patients who will undergo HP surgery, and postoperatively, to patients who would use both, electric stimulation and acoustic amplification. At the time, the below questions on the safety and efficacy of such treatment option were raised by Prof. von Ilberg himself, his colleagues, and MED-EL.

Figure 3. Prof. Christoph von Ilberg, Head of the ENT department, from Johann Wolfgang Goethe University Hospital Frankfurt, Germany, the inventor of the EAS concept. US patent number: 6231604B1.

i. Does the simultaneous EAS interfere with physiological discharge patterns of the auditory system?
ii. Is a chronic electric stimulation hazardous to residual hair cells?
iii. Is a simultaneous EAS beneficial to patients with severe high-frequency HL?

The physiological discharge patterns of the auditory system in response to EAS were explained through an experiment involving non-human subjects with acute electric stimulation in their normal-hearing ears [4]. Under anaesthesia, normal hearing adult subjects underwent nerve exposure through posterior fossa with a ball electrode, fixed at the RW for electric stimulation. Single-fibre action potentials were conventionally recorded from the auditory nerve in response to acoustic stimuli, delivered to the eardrum through a condenser microphone in a closed system. The response area of the single fibre was tested for acoustic stimuli, electric stimuli and combined EAS. Figure 4 demonstrates the effect on an HF fibre with acoustic tuning curve before (Figure 4(a)) and after (Figure 4(b)) simultaneous EAS. The random distribution of spikes in the subtraction plot presents no major differences compared to the original tuning curves (Figure 4(c)). With the simultaneous EAS (Figure 4(d–f)), there is an increase in the overall activity, but the shape of the tuning curve remains unchanged. By plotting the difference between acoustic stimulation (AS) vs EAS, it is apparent that the electric stimulation reduces the number of acoustically evoked spikes (Figure 4(e)). In the subtraction plot of EAS–AS (Figure 4(f)), a slight decrease in spike activity in the response area may be seen, and the electrically driven activity becomes apparent. This acute experiment demonstrates that the electric stimulation in a normal hearing ear does not substantially interfere with natural acoustic hearing.

To examine the effect of chronic electric stimulation on the hair cells, normal hearing adult non-human subjects were used for chronic experiments with gold ball electrodes bilaterally implanted at the RW [4]. The left side underwent a chronic stimulation, and the right side was kept unstimulated and served as a control ear. The stimulation was continuously running with biphasic charge-balanced pulses (30 Hz, 200μs/phase) at currents of approximately 100 μA for 24 h/day and compound action potential (CAP) audiograms were measured once a week on both ears by placing the subjects under sedation. Acoustic stimuli, using tone pips from 300–64,000Hz, were used for measuring the thresholds of acoustically evoked CAP, whilst the auditory brainstem response (ABR) and the threshold of electrically evoked auditory brainstem response (eABR) of the chronically stimulated side were both determined using the

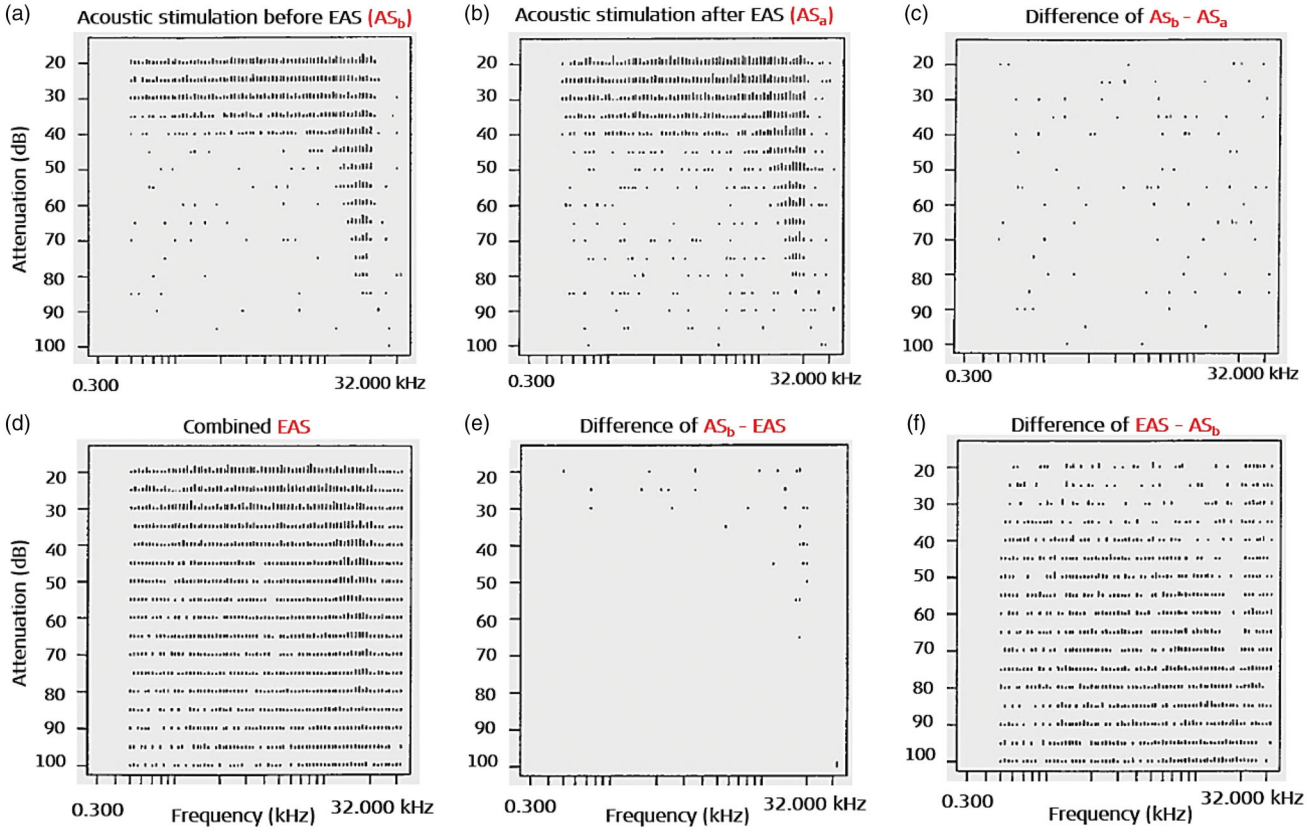


Figure 4. Responses of an HF single fibre (18.1 kHz) in a normal-hearing subject during different stimulation conditions. (a) Response areas evoked by acoustic stimulation, recorded before EAS (AS_b): 0 dB equals to approximately 110 dB sound pressure level (SPL). (b) Same stimulation after combined EAS (As_a). (C) Subtraction plot of acoustically evoked response areas (AS_b–As_a): no differences appear. (d) Response area evoked under EAS. (e) Subtraction plot of response areas (AS–EAS). (f) Subtraction plot of response areas (EAS–AS) [4]. Reproduced by permission of Karger AG, Basel.

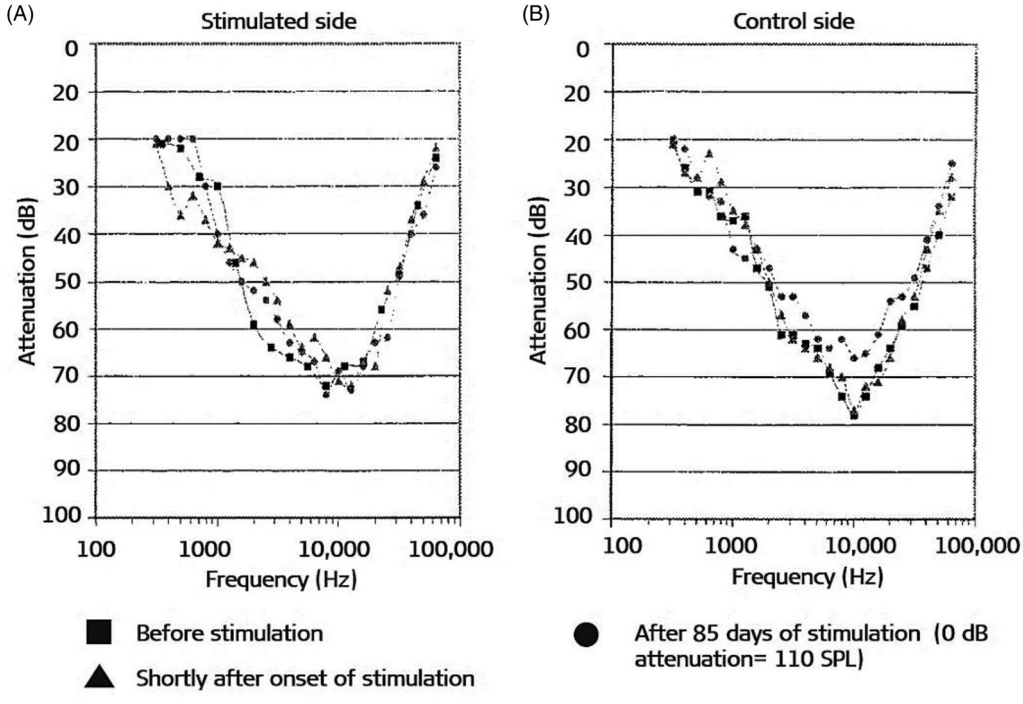


Figure 5. CAP audiograms in normal-hearing non-human subjects before and after chronic electric stimulation: square points refer to the time before stimulation, triangle points refer to the time shortly after the onset of stimulation, and circle points refer to 85 days after stimulation, for both stimulated and the control ear. No major differences were identified between the two ears [4]. Reproduced by permission of Karger AG, Basel.

standard averaging procedures and were compared with the prestimulation values.

Figure 5 compares CAP audiograms from subjects at three different time points, including before stimulation, shortly after the onset of stimulation, and after eighty-five days of electric stimulation in both, stimulated and the control ear. The results showed no significant differences between the two ears, suggesting that the hearing thresholds were not negatively affected by the continuous chronic suprathreshold extracochlear electric stimulation.

2.3. First EAS concept application in human

In 1999, the two experiments which showed no adverse effects of electric stimulation in normal hearing ears [4], inspired Prof. von Ilberg to apply the combined EAS treatment modality to a patient with a history of slowly progressive bilateral HL [4]. The patient was fitted with bilateral high-power HA from Phonak, and the CI was implanted when the patient was fifty years of age. The implanted system was MED-EL's COMBI 40+ with the STANDARD electrode array of 31.5 mm length, inserted only 20 mm intracochlearly and *via* cochleostomy surgical approach. This was to ensure electric coverage until 1,000Hz starting from the RW entrance, leaving the LFs from 1,000Hz towards the apex with acoustic amplification. Audiological tests were performed two months postoperatively, where the hearing scores from Göttingen sentence test showed an increase in hearing performance with CI alone and in the combined EAS mode, in comparison with the HA alone (control ear). Also, with an increased number of stimulating channels activated in the first/basal turn of the cochlea, the hearing performance was improving.

Table 1 summarises the acute results of speech understanding in a patient with LF residual hearing. With eight basal channels covering the centre frequency range from 300–5,500Hz, the speech scores resulted in 92% correct with combined EAS (HA + CI), and 88% with CI alone mode. The scores dropped to 22.9% and 0%, respectively, when only two stimulating channels were kept active.

This was the first study to evaluate the synergistic effect of combined EAS concept with MED-EL CI in an adult patient with severe-to-profound HF HL and preserved functional LF hearing. The utilisation of a separate HA unit and *behind-the-ear* (BTE) speech processor of CI posed some practical challenges to the patient in the ease of using two separate audio processors. This impelled the authors to recommend the development of a unified speech processor which would combine both, electric stimulation and acoustic amplification.

In 2002, the same team of specialists chose to apply the combined EAS treatment method to further eight patients [5]. Patients were included based on their pure-tone audiograms with a hearing threshold between 30–60dB in the frequency range between 0.25–1kHz and >60dB above 1 kHz in the ear to be implanted with MED-EL's COMBI 40+ device and TEMPO + BTE audio processor. The STANDARD CI electrode array was inserted intracochlearly through a 1 mm diameter cochleostomy. For amplification of the acoustic hearing on the ipsilateral ear, all patients used high power *in-the-ear* (ITE) HA from Resound®. The implantation of CI electrode preserved residual hearing to within 10 dB HL in four out of eight patients, which was considered as complete hearing preservation. In two further patients, it was preserved partially with up to 30 dB HL, while the remaining two patients lost their residual hearing after implantation. Figure 6 presents the pre- and post-operative results of the Freiburg monosyllable word test.

The preoperative performance of the individual optimal loudness in the best-aided condition with ipsilateral HA at 70 dB and in the best-aided condition did not exceed 15% correct answers, whereas with the CI alone mode, the hearing performance reached 53% correct answers and it increased to 78% with the addition of HA (Figure 6). This was a clear demonstration of the synergistic effect between electric and acoustic stimulation in the HF and LF regions, respectively. In terms of LF hearing preservation in these patients, complete preservation was possible in 50%, and at least partial preservation in 75% of those who were implanted with a partial insertion of the STANDARD electrode array. The insertion depth of approximately 22 mm out of the total 31.5 mm ensured at least eight channels intracochlearly for a fully functioning CI, as well as attempt to preserve residual hearing in the LF region.

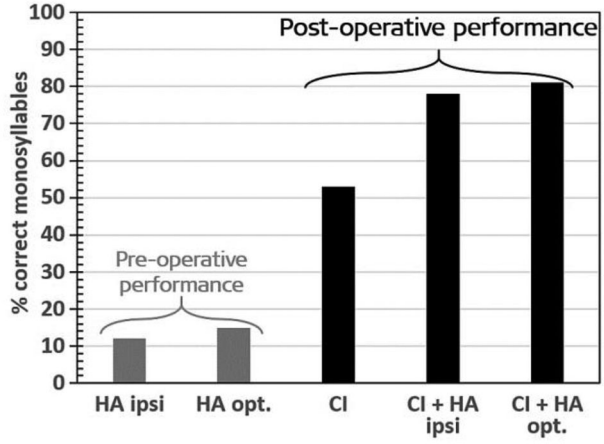


Figure 6. Preoperative Freiburg monosyllabic word scores, tested with the ipsilateral HA and in the best-aided condition at optimal loudness. Postoperative monosyllabic word score with CI alone at 70 dB presentation level, and with CI + HA in the ipsilateral ear ($n = 4$), as well as CI + HA in the optimal condition—either ipsi-, contra-, or bi-lateral at 70 dB. Histogram created from the data given in Kiefer et al. [5].

Table 1. Acute results of the speech understanding (Göttingen sentence test) in a single patient with LF residual hearing after CI implantation [4].

Basal channels (CI)		8 (C1–C8)		6 (C3–C8)		5 (C4–C8)		4 (C5–C8)		2 (C7–C8)	
Filter frequency (CI), Hz	Control	300–5,500		620–5,500		893–5,500		1,284–5,500		1,047–5,500	
Test condition	HA	CI	HA + CI	CI	HA + CI	CI	HA + CI	CI	HA + CI	CI	HA + CI
Göttingen sentences	0%	88%	92%	18.6%	88.2%	0%	58.3%	0%	38%	0%	22.9%

Scores with HA alone, CI alone, and ipsilateral combination of both, HA + CI under conditions of different numbers of active channels.

In the same year, the combined EAS concept extended to neighbouring Poland to reach a twenty-five-year-old prelingually HF deaf patient, who was fitted with HA at the age of four [6]. The patient was implanted with MED-EL's COMBI 40+ system with STANDARD electrode array, inserted 18–20mm intracochlearly through the RW entrance, ensuring angular insertion depth of 360° with eight stimulating channels inside the cochlea. Electrode insertion through the RW opening at that time was very special as Cochleostomy approach was the common practice among the surgeons. A postoperative pure-tone audiogram showed a decrease in hearing threshold sensitivity of 15 dB across the LF region, compared to the preoperative condition. Speech comprehension was performed using Pruszewicz monosyllabic word test (Figure 7). Before the CI surgery, with HA alone, the patient was able to score 23% and <5% in quiet and in noise, respectively. One week past the first fitting, the results increased slightly – to 30% and 5%, respectively – but at three weeks, the hearing performance improved significantly and reached 90% and 65% under the combined effect of both, electric and acoustic stimulations.


Prof. Henryk Skarzynski (CI/ABI surgeon)

Dr Artur Lorens (Audiologist)

Dr Anna Piotrowska-Lorens (Audiologist)

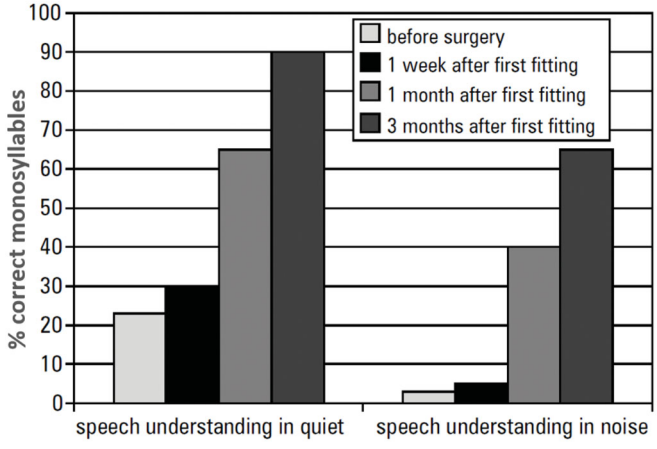


Figure 7. Clinicians from the Warsaw Institute of Physiology and Pathology of Hearing, Poland, treated the first Polish EAS-indicated patient with MED-EL device. Results of monosyllabic speech understanding after CI in quiet surroundings and noise [6].

This relatively rapid monosyllabic word test score increase, otherwise considered one of the most difficult in the standard audiological practice, is clear evidence of how the auditory system positively embraces the EAS. The results proved another favourable outcome of the EAS technique in providing the restoration of normal hearing in partially deaf patients.

In 2002, Prof. Skarzynski and his colleagues reported the first ever child patient with residual hearing implanted with MED-EL's COMBI 40+ device and was using EAS postoperatively with a HA for acoustic amplification and CI audio processor for the electric stimulation. This patient was implanted in the year 2000 at the age of 8 years.

In 2003, Prof. Skarzynski and his colleagues introduced the concept of treating partial deafness with cochlear implantation (PDCI). Many of these partially deaf (PD) patients would not have been considered as CI candidates in the past because their speech recognition was either borderline or better than the criteria for standard CI. However, children with PD display different speech development and language acquisition patterns when compared to normal-hearing children or children with severe-to-profound sensorineural hearing loss [7].

2.4. Dedicated electrode array design and surgical procedures, supporting the EAS

The year **2004** was quite a busy year for the clinicians from Frankfurt in Germany and Vienna in Austria in further exploring the combined EAS concept in more patients, and in parallel, trying to understand more about the intracochlear structure preservation with the placement of the CI electrode array through cochleostomy drilling. For MED-EL, it was an important year with the introduction of FLEX24™ electrode array, which offered a significant design change from its predecessor, the STANDARD electrode array (Figure 8).

In parallel, specialists from both, Goethe University Frankfurt in Germany and the Medical University of Vienna in Austria implanted fourteen patients who had residual hearing thresholds in the ear to be implanted at <60dB in at least two of the frequencies (125-, 250-, or 500-Hz), and at >60dB at ≥1kHz [8] (Figure 9).

All patients were implanted with MED-EL COMBI 40+ system with the limited electrode insertion depths of 19 mm, and up to eight channels of the STANDARD electrode array were placed inside the cochlea through a 1 mm diameter cochleostomy. The study aimed to understand how well the LF residual hearing can be preserved with the insertion of a CI electrode array to basal turn with only above-described

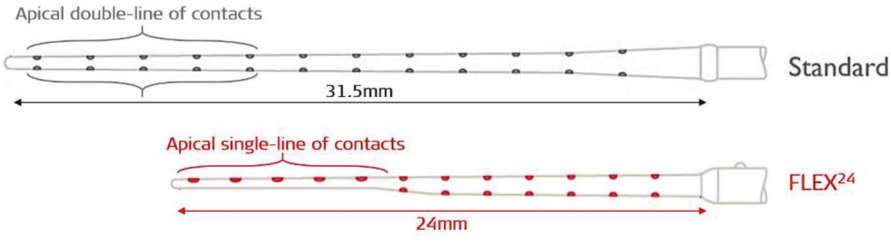
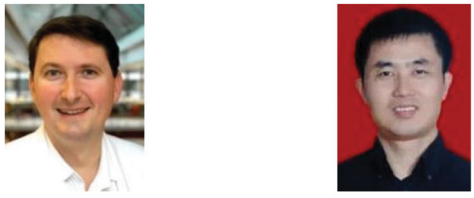


Figure 8. Illustration of STANDARD electrode array with apical double-lined channels and FLEX24™ electrode array with apical single-lined channels (image courtesy of MED-EL).

Prof. Wolfgang Gstöttner[1] Prof. Jan Kiefer[1]



Prof. Wolf-Dieter Baumgartner[2] Dr Qing Ye[1]

Figure 9. CI surgeons from [1] Johann Wolfgang Goethe University Hospital Frankfurt, Germany, and [2] Medical University of Vienna, Austria, who implanted MED-EL EAS™ device in patients with measurable LF residual hearing.

conditions [8]. Figure 10 shows pure tone audiogram of fourteen individual patients (13 adults, 1 paediatric) along with the average plot for both, preoperative and three months postoperative conditions. The average preoperative threshold in the frequency range between 125–1,000Hz was 60 dB, and it increased to 75 dB three weeks after the operation. A 15 dB drop in hearing after surgery with cochleostomy drilling was still considered good conservation of residual hearing by the authors of the study.

One of the critical factors in the EAS process is the preservation of intracochlear structures, which is directly related to the preservation of the LF residual hearing. Any disturbance to the intracochlear structures or the cochlear physiology would disrupt the residual hearing, and therefore both, the CI electrode and the surgical approach shall be as atraumatic as possible.

In 2004, by the same group of specialists from Frankfurt, another laboratory test was piloted on eight cadaveric temporal bones to understand the intracochlear level of trauma caused by each of the two surgical approaches with MED-EL's STANDARD electrode array – RW and cochleostomy approach. Histological evaluation unveiled basal cochlear trauma in almost 30% of the implanted human temporal bones, associated with the bony cochleostomy drilling. On the other hand, the RW approach revealed smoother insertion, consequently manifesting a deeper and more atraumatic introduction of the array to scala tympani (ST) [9]. The latter result was one of the key motivations going forward towards a gradual shift from the cochleostomy to RW approach.

In all previously combined EAS implantations, the STANDARD electrode was inserted to accommodate only eight channels intracochlearly, leaving the four basal channels extracochlearly and at the time, MED-EL CI device was used as an off-label device in EAS implantations. To have an ideal electrode array choice for the EAS solution, MED-EL developed FLEX24™ electrode array with 24 mm length, and with apical five channels in a single-channel configuration, as illustrated in Figure 8. In comparison – the STANDARD electrode array has all twelve channels in a double-lined configuration.

Prof. Adunka and his colleagues were instrumental in evaluating the FLEX24™ electrode array (in the year 2004), both in the laboratory and in the clinical setup (Figure 11). Inserting an electrode array exerts a certain force on the intracochlear structures, and any consequential trauma

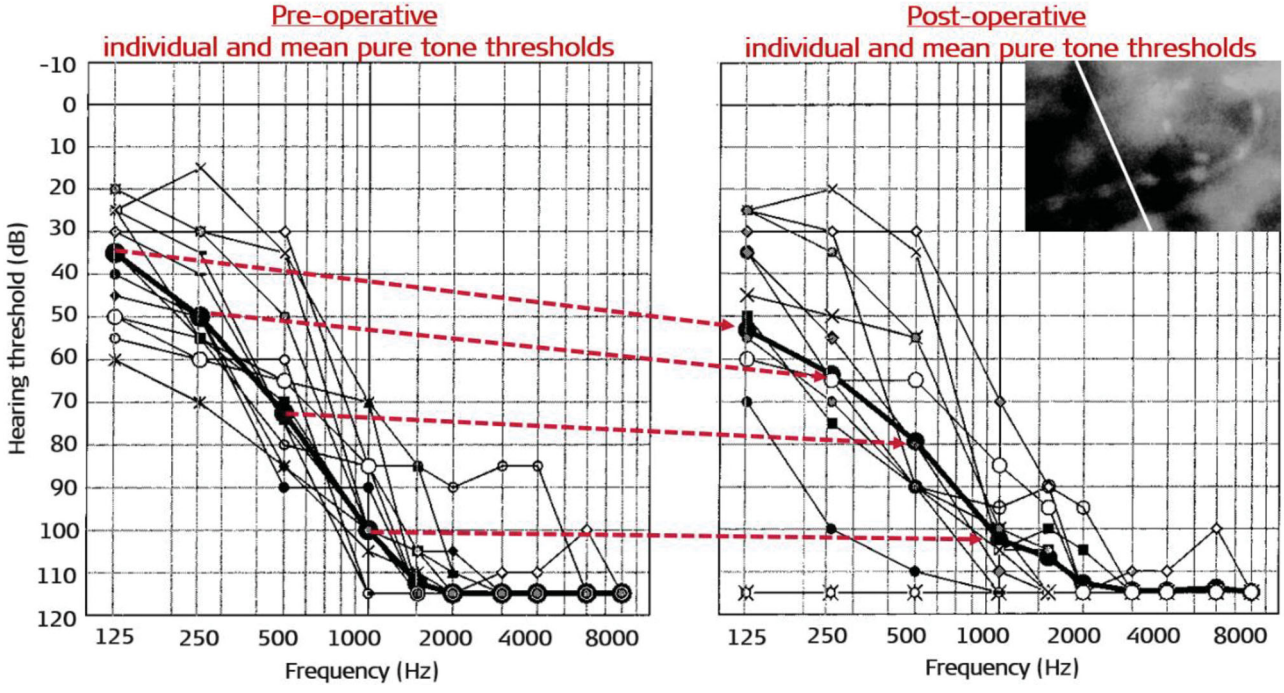


Figure 10. Individual audiograms and mean values (bold black line) with pre-op and three months post-op pure-tone thresholds in the ear chosen for implantation [8]. Reproduced by permission of Taylor and Francis Group.

Figure 11. Prof. Oliver Adunka from Johann Wolfgang Goethe University Hospital Frankfurt, Germany, performed an in-vitro evaluation of FLEX24™ electrode array in the year 2004.

depends mostly on the array stiffness [10]. In a laboratory setting and with a plastic ST model, the insertion force with FLEX24™ measured on average 22 mN, while with the STANDARD electrode array it increased to 35 mN on average, when reaching the intracochlear insertion depth of 24 mm with both (Figure 12(A)). Lower insertion force indicates the flexible nature of the electrode array. The volume of FLEX24™ electrode array, as measured from its 3 D computerised model, is 7mm^3, which is almost four times less than the volume of ST measured from RW entrance to the most apical point, the helicotrema (Figure 12(B)) – this was a later finding and reported in the year 2020 by Dr Dhanasingh from MED-EL [11]. In the same year (2004), Prof. Adunka and his colleagues from the Johann Wolfgang Goethe University Hospital Frankfurt showed the importance of round window membrane (RWM) approach of electrode insertion in achieving an atraumatic CI surgery. The superiority of the approach was proved in eight fresh human cadaveric temporal bones to which FLEX24™ electrode was inserted through RWM approach to reach an average insertion depth of 382.5° with no damage to the intracochlear structures. The histological analysis revealed that this electrode array was positioned entirely inside the ST with no deviation to scala vestibuli (SV), preserving the organ of Corti (Figure 12(C)) [9]. The authors concluded that a combination of the flexible electrode array with an ideal array length of 24 mm, along with the RW approach with surgical placement inside the ST, ensures the preservation of intracochlear structures, which is a prerequisite for the successful acoustical amplification of LF residual hearing.

2.5. Unified audio processor unit, combining acoustic and electric stimulation

A unified audio processor that technically combines HA unit to the CI audio processor is another important technological advancement which was needed at the time for complete acceptance of the EAS™ technology among the partially deaf patients. The challenges included practical handling of two separate devices with different types of batteries and battery life spans, insufficient amplification with ITE HA in the frequencies below 500 Hz, and posed challenges with the fitting of these two devices separately. Internally at MED-EL, Dipl. Ing. Schmidt and his colleagues were strongly engaged in the development of the DUET™ unified audio processor (Figure 13).

In 2005 November, as the world's first hearing implant company to combine HA with CI audio processor, MED-EL introduced DUET™ audio processor in order to overcome all the practical issues with having two separate devices as

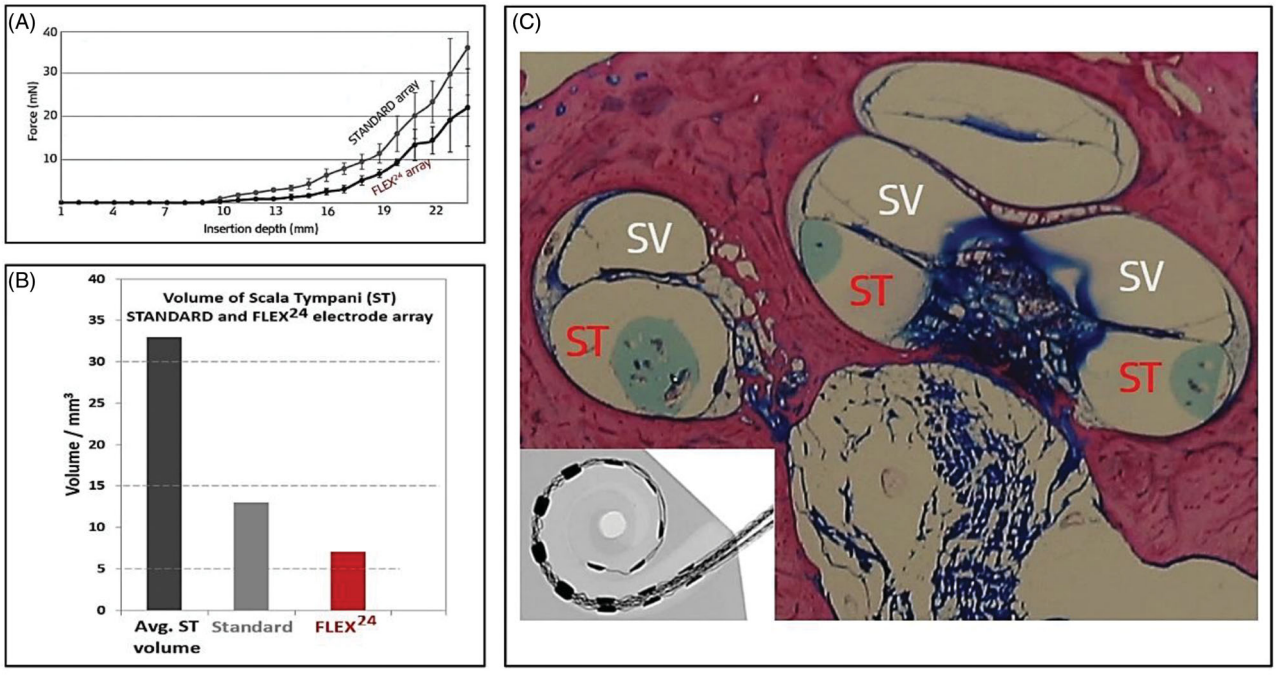


Figure 12. Force measurement data is showing 40% lower values for FLEX24™ electrode array in comparison with the STANDARD electrode array (A) (Courtesy of MED-EL). Mean ST volume compared against STANDARD and FLEX24™ electrode arrays—a later finding from the year 2020 (B) [11]. Histological evaluation of FLEX24™ in human cochlea, showing complete ST placement (C) [9]. Histological image—Courtesy of Freiburg Medical University, Germany, Study sponsored by MED-EL.

Dipl. Ing. Marcus Schmidt, M.Sc.

Dipl. Ing. Rene Zangerl
(Former employee of MED-EL)

Figure 13. Engineers from MED-EL who were part of the development of DUET™ unified audio processor.

mentioned above (Figure 14). The DUET™ audio processor featured a single microphone for the TEMPO + audio processor (using the continuous interleaved sampling (CIS+) strategy) and a two-channel HA, allowing 40 dB gain through 1,800Hz in one unit. The ear received the acoustic amplification through the ear mould positioned inside the external ear canal, receives an acoustic amplification from the processor. The processor unit controls both the HA and the CI speech processor, which is powered by a single battery pack. The DUET™ system was designed to amplify acoustic hearing between 125–1,500Hz and between 30–75dB.

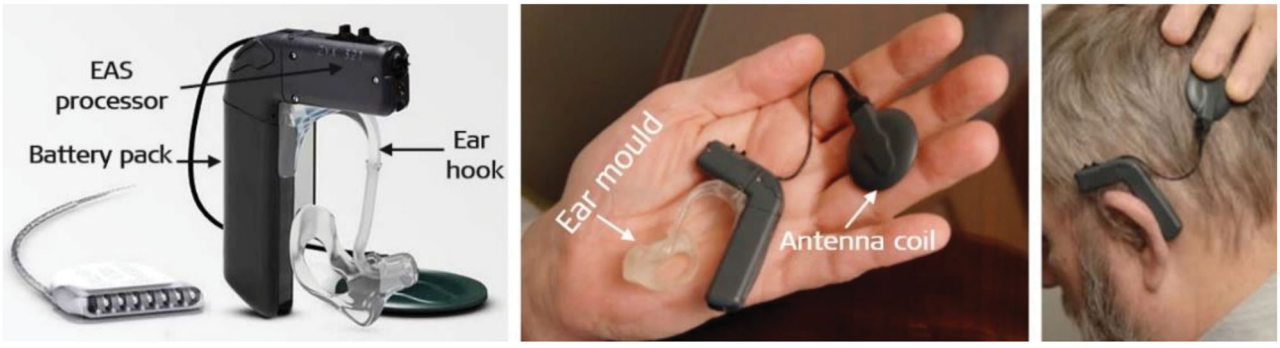


Figure 14. DUET™ unified audio processor (image courtesy of MED-EL).

Prof. Skarzynski and his colleagues from the Institute of Physiology and Pathology of Hearing in Warsaw in Poland, supported by Dr Polak from MED-EL, evaluated the effectiveness of DUET™ EAS™ audio processor for the first time in partially deaf patients [12]. The study comprised of eleven partially deaf adults, implanted with MED-EL COMBI 40+ device and STANDARD electrode array, inserted 18–22mm and with eight stimulating channels intracochlearly. After at least one year of CI use, these patients were fitted with DUET™ audio processor for at least one month before their hearing performance was analysed. The CI was fitted with a frequency range between 0.3–8.5 kHz. Control group comprised of twenty-two adult CI patients implanted with MED-EL COMBI 40+ in combination with STANDARD electrode array inserted to its full length of 31.5 mm and twenty normal-hearing adult patients participated for comparison of the hearing performance of partially deaf patients, treated with the EAS™ technology. The mean duration of CI and DUET™ use before audiological testing was 22.3 months and 3.4 months, respectively. Audiological tests, including pure-tone audiograms in three different listening conditions, Pruszewicz monosyllable (Polish) word tests in quiet at a signal-to-noise ratio (SNR) of 10- and 0-dB, and the Polish Hochmair-Schulz-Moser (HSM) sentence test at 10 dB SNR, were conducted across all patient groups. Figure 15(A) shows an almost complete return of normal hearing thresholds across all frequencies with the EAS™ hearing solution, which was not the case with only acoustic amplification of HA unit from DUET™ audio processor. The HA alone from the DUET™ audio processor certainly did help patients improve their hearing thresholds in the LF region, but that was not enough to bring back the HF hearing. The monosyllabic word test results in the partially deaf patient group tested in quiet, at 10- and 0-dB SNR, the condition DUET™ only and best-aided (plus contralateral HA), were significantly higher than in the CI only patient group. The significantly higher scores obtained with the conditions DUET™ only over the CI only condition suggests that the application of additional HA allows the utilisation of the LF hearing to a greater extent. For the best-aided condition, the patients scored 91.4% in quiet on average, and 78% at 10 dB SNR (Figure 15(B)). Although DUET™ processor was used only for a short duration of 3.4 months, the data given in Figure 15(B) placed the partially deaf patients treated with EAS™ and DUET™ in an intermediate position between CI only and NH group (Figure 15(C)).

Overall, the study showed the efficacy of EAS™ hearing solution with DUET™ processor in partially deaf patients. It had also revealed a hearing performance gap (red shaded area in Figure 15(C)) between prosthetic (EAS) patients and normal-hearing patients, and at the same time, EAS group showed better hearing performance compared to the CI group (grey shaded area in Figure 15(C)). An important factor to note is that those with good preoperative hearing reached better hearing on average than the CI patients.

In parallel to Prof. Skarzynski's study mentioned above, Priv.-Doz. Dr med. Helbig, Prof. Baumann and their colleagues (Figure 16), also evaluated the efficacy of MED-EL's DUET™ audio processor in nine partially deaf patients [13].

Before the study, patients were using MED-EL's TEMPO + audio processor unit, controlling the CI and during the study, they received an additional ITE HA to amplify the LF signal. The study also revealed the same practical

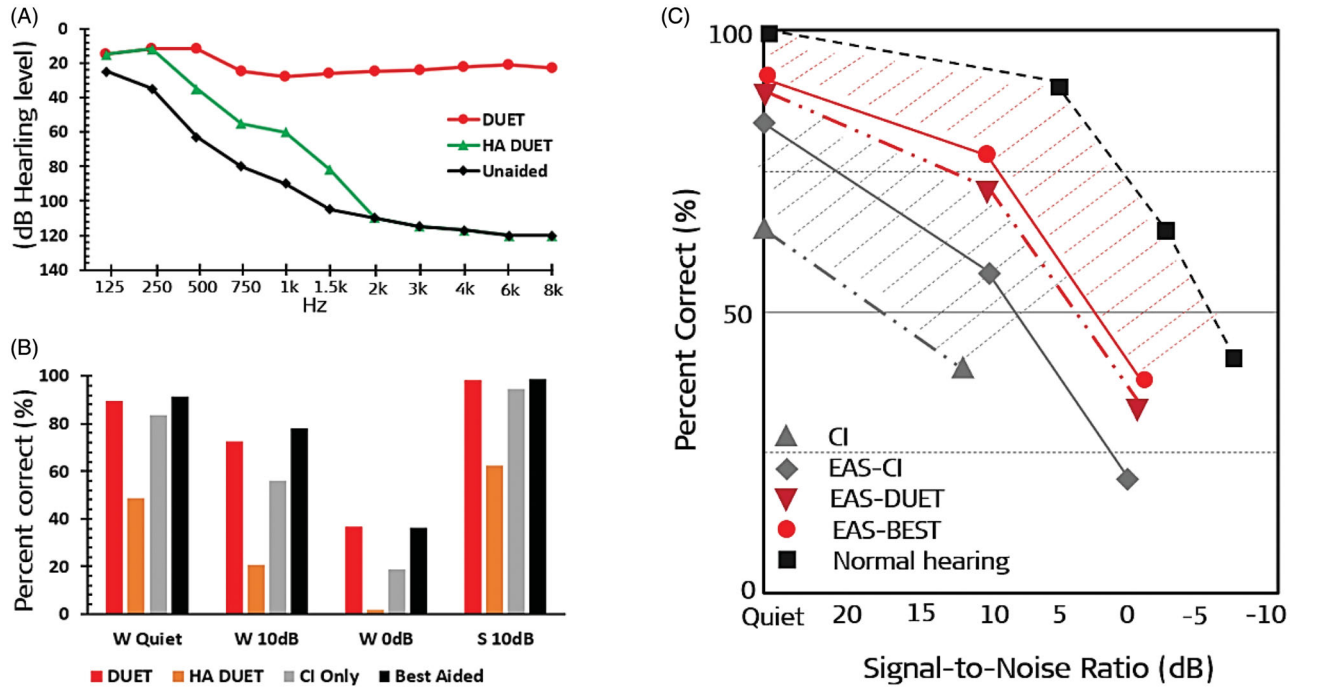


Figure 15. Mean audiograms for the implanted ear in three different listening conditions (unaided, HA alone from DUET™, and CI + HA) (A). Pruszewicz monosyllable test results in quiet at 10- and 0-dB SNR and Polish HSM sentence test results at 10 dB SNR for the group of partially deaf patients ($n = 11$). Mean values for the conditions DUET™ only (CI + HA), DUET™ HA only, CI only, and best-aided (plus contralateral ear) are shown with *W* (word test) and *S* (sentence test) (B). Comparison of Pruszewich monosyllable test results for three groups of patients: (1) CI patients ($n = 22$) tested with their CI (contralateral ear was unplugged), (2) partially deaf patients using the EAS™ ($n = 11$) (tested in three conditions: CI only (contralateral ear plugged), DUET™ only (contralateral ear plugged), and best-aided (plus contralateral ear)), and (3) NH group ($n = 20$) tested in both ears. The red shaded area shows the hearing performance gap between EAS™ and normal hearing, and the grey shaded area shows the hearing performance gap between the CI and EAS™ (C) [12]. Statistical analysis: ANOVA single-factor test was used to compare speech data between three groups ($p < .05$). Graphs and histogram created from raw data provided by Dr Polak (MED-EL) one of the authors of Lorens et al. [12].

Priv.-Doz. Dr med. Silke Helbig
(CI Surgeon)

Prof. Uwe Baumann (Audiologist)

Figure 16. A team of ENT surgeons and audiologist from Johann Wolfgang Goethe University Hospital Frankfurt, Germany, evaluated the effectiveness of DUET™ audio processor.

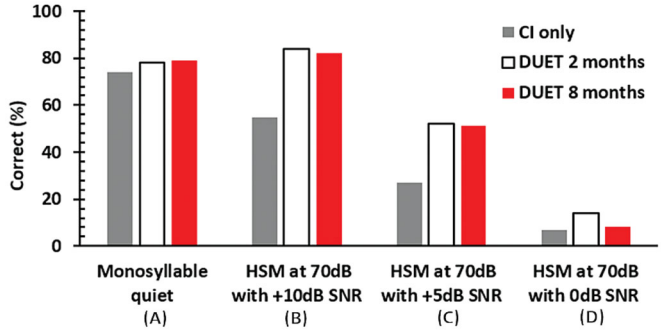


Figure 17. Mean results of Freiburg monosyllables in quiet at 70 dB (A), HSM sentences at 70 dB with + 10 dB SNR (B), HSM sentences at 70 dB with +5dB SNR (C), and HSM sentences at 70 dB with 0 dB SNR (D). Statistical analysis: Parametric Student's t-test was used to detect discrepancies between the test intervals ($p < .05$). Histogram created from data given in Helbig et al. [13].

challenges with the usage of two separate controlling devices. All patients underwent the Freiburg monosyllables speech perception test at 70 dB SPL, and the HSM sentence testing in quiet and in noise (+10dB, +5dB and 0 dB SNR) before switchover, and again at two and eight months after switching to the new EAS™ (Figure 17).

Testing for monosyllables with DUET™ system at both, two and eight months of EAS™ use, revealed a significant benefit with the mean values' increase of 14%, compared to before the switchover testing with CI only (Figure 17(A)). The cohort achieved a mean result of 77% correct answers after two months, and the result increased to 78% at eight months after moving to the new device. With the HSM sentence test, the patients achieved better results with the DUET™ system, compared to the CI only condition when tested in noise at the +10dB, +5dB, and 0 dB SNR. At +10dB SNR, the mean result increased from 55% to 84% after two months and kept a similar rate at eight months, with 81% correct answers (Figure 17(B)). Testing at the +5dB SNR increased from a mean value of 26% in the CI only condition to 53% after two months and resulted in 51% at eight months (Figure 17(C)). At difficult listening conditions at 0 dB SNR, the mean results increased from 5% to 14% after two months, and after eight months they resulted in 8% (Figure 17(D)).

Both of the abovementioned studies point out the major benefit of the unified audio processor for better speech understanding in quiet and noisy situations. This was

underlined with patients' high scores in difficult listening conditions, as well as with reported user comfort improvements, compared to the experience before switching [12,13].

In 2007, MED-EL became the world's first hearing implant company to CE-mark its EAS hearing system with indication criteria of at least 65 dB HL in LF frequencies at up to 750 Hz. The abovementioned studies from Germany/Austria [8], Poland [12] and Germany [13] were highly instrumental in demonstrating the value of MED-EL's EAS™ hearing system.

2.6. Acceptance of the unified audio processor by the patients

The success of any technology may be claimed by its wide user acceptance. For DUET™ audio processor, the patient acceptance depended mainly on the preservation and successful acoustic amplification of LF residual hearing, in combination with effective CI stimulation of HFs. Prof. Baumann and Priv.-Doz. Dr med. Helbig studied the acceptance of the HA part of the DUET™ device in fifteen patients who underwent EAS™ surgery at their clinic [14]. Eleven out of fifteen patients accepted DUET™ processor and were using it in their daily life, whereas four rejected acoustic amplification due to insufficient benefit and were using electric stimulation only. The mean pure tone audiometric thresholds of both groups are given in Figure 18(A). Within the frequency range of up to 500 Hz, the DUET™ audio processor users showed hearing thresholds of maximum 75 dB, while the nonusers of the device showed increased hearing thresholds of up to 105 dB. Both groups revealed a maximum HL at the maximum hearing threshold of 120 dB at frequencies above 500 Hz.

With electric stimulation only, the four patients who were not using DUET™ audio processor scored only 66% in monosyllable word testing (group's mean value, Figure 18(B)), and 62% in sentence testing at 10 dB SNR (Figure 18(C)). The study revealed that patients with preserved residual hearing and who had hearing thresholds better than 75 dB in the frequency region of ≤500Hz experienced optimised benefits offered by the EAS™. The conclusion also indicates the importance of atraumatic electrode array design and surgical technique in preserving the LF residual hearing. However, it shall be bared in mind that factors such as certain genetic predispositions, could still cause progressive HL over subsequent time, irrespectively of atraumatic electrode design and surgical techniques.

2.7. The second-generation unified audio processor

The year 2009 marked ten years of MED-EL's EAS™ hearing system research efforts that resulted in the second generation of DUET™ EAS™ audio processor, which was named as DUET-2™ (Figure 19). The DUET-2™ audio processor utilises dedicated parallel signal processing for both, acoustic and electric stimulation, using an omnidirectional microphone which allows each signal to be optimised for maximum efficiency. The acoustic amplification was raised to over 43 dB, and the acoustic frequency range was optimised to between 125–1,700Hz. DUET-2™ also features the *FineTuner*™ remote control, which allows adjustment of the settings without any hearing interruption. DUET-2™ applies automatic sound management (ASM), enabling users to experience optimal hearing by automatic adjustment of the audio processor setting based on the sound environment and background noise without removing the BTE speech processor for manual adjustment, based on the environment, background noise, or both. Safety features include continuous static electricity self-monitoring of the device (*SoundGuard*™) and relevant automatic stimulation stop. In terms of battery, the low battery alert feature was introduced as well. Overall, DUET-2™ weighs fourteen grams less than the DUET™ audio processor.

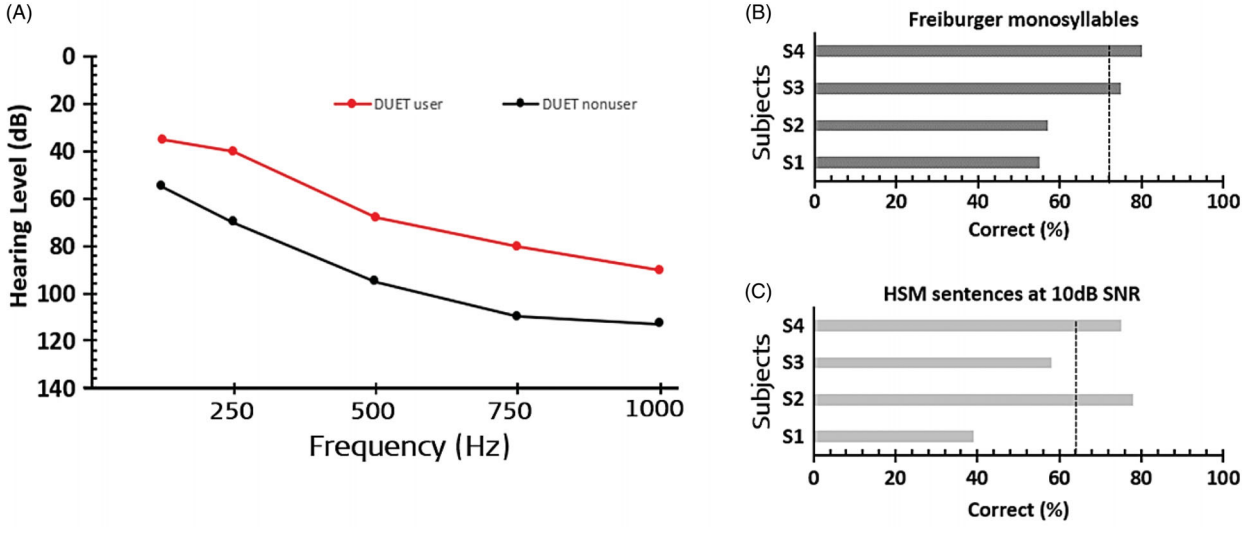


Figure 18. Mean pure-tone audiometric results of DUET™ users ($n = 11$) and DUET™ nonusers ($n = 4$) (A). Speech audiometry results of the four patients who rejected DUET™ and used the CI processor: the Freiburg monosyllable word test correct answers with 66% (mean) (B) and HSM sentence correct answers with 62% at 10 dB SNR (mean) (C). Graph and histograms created from data given in Helbig et al. [14].

Figure 19. DUET-2™ EAS™ audio processor with its remote control *FineTuner™* (image courtesy of MED-EL).

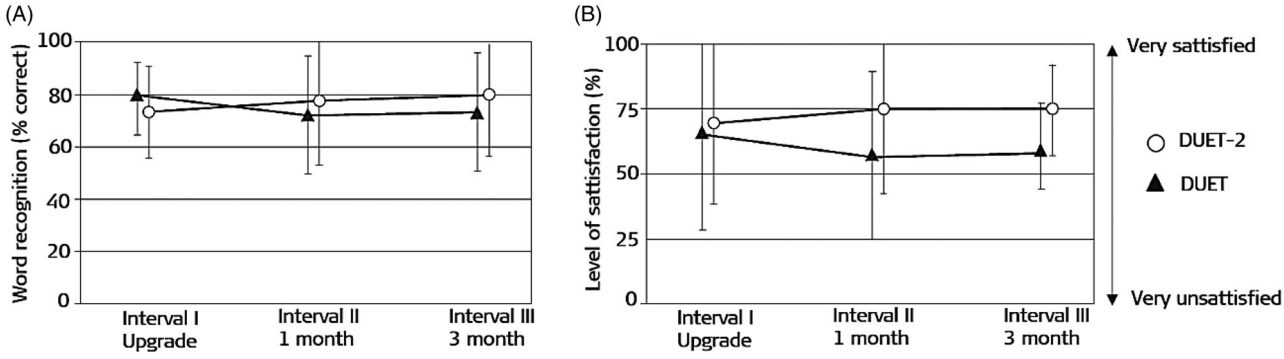


Figure 20. Mean Pruszewicz monosyllabic word recognition in background noise with an SNR of +10dB (A) and mean subjective report on sound quality satisfaction of music stimuli (B) [15]. Statistical tests: One-way repeated measures (RM) ANOVAs were used to assess the improvement of DUET™ and DUET-2™ and the level of user satisfaction across three-time intervals. Reproduced by permission of Taylor and Francis Group.

User acceptance of DUET-2™ audio processor was evaluated by Prof. Lorens and Prof. Skarzynski [15], involving ten just under forty-three years old on average, experienced DUET™ users who had been using the device twenty-five months on average. DUET-2™ was offered as part of the processor upgrade, and the fitting map from DUET™ was simply transferred to DUET-2™ to evaluate the overall benefits straight after the upgrade, and at one- and three-months intervals. Pruszewicz monosyllabic word testing and user questionnaire showed that DUET-2™ is either similar or slightly better than DUET™ in terms of hearing performance and general acceptance of the processor by the patients.

The monosyllabic word test result did not show any significant differences between DUET™ and DUET-2™ processors (Figure 20(A)). Visual analogue scale (VAS) satisfaction with the sound quality for speech and music stimuli was 69% for DUET-2™ at upgrade (interval I) which increased to 75% at the second interval and reached 80% at the third. These results revealed statistical superiority of the second generation with $p = .014$ (Figure 20(B)), and the study concluded that the conversion from DUET™ to DUET-2™ improved patient satisfaction and the subjective benefits.

In 2010, the focus expanded towards music perception by the EAS™ users, as assessed with the Music Sounds in Cochlear Implants (Mu.S.I.C) test by Dr Brockmeier from the Technical University of Munich in Germany and her colleagues from other CI centres in Europe [16]. Thirteen patients met the EAS inclusion criteria and underwent soft surgery to receive MED-EL COMBI 40+ CI with a STANDARD electrode and CIS + speech coding strategy. The Mu.S.I.C test battery consists of six objective subsets assessing aspects of pitch, rhythm, melody, harmony, chord and timbre perception. The patients were tested under EAS condition, and the results were compared with those of CI and normal hearing (NH) participants. The EAS patients performed better than the CI participants on pitch and melody discrimination, but poorer when compared to NH participants. No significant difference was found in the three groups with chord and rhythm discrimination. With instrument detection, both EAS and CI participants performed significantly lower on instrument detection than NH participants, but a positive trend was observed for EAS over CI participants in xylophone, soprano, flute and double bass instruments (Figure 21).

This was an encouraging preliminary result showing the added benefit of acoustic amplification when it comes to music perception.

In 2011, MED-EL CE-marked its EAS™ hearing system in combination with DUET-2™ audio processor as a treatment option for children with partial deafness. To restore

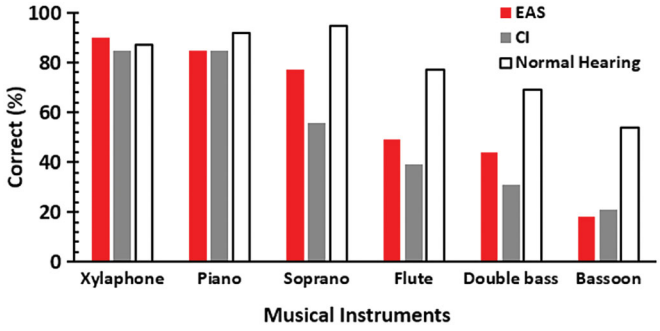


Figure 21. Instrument identification. Scores on instrument identification according to instruments for all three groups. Histogram created from data given in Brockmeier et al. [16].

hearing in the paediatric population with the named technology was another important milestone in MED-EL's EAS™ journey.

2.8. Evolution of surgical approaches in EAS

While technological advancements in optimising audio processors and implants were the focus at MED-EL, expert CI surgeons were focusing on fine-tuning the surgical procedure which is seen as an essential factor influencing the HP results in EAS patients. In the late '70 s, when Prof. Burian from the Medical University of Vienna, performed the first MED-EL CI implantation, the RW approach was used for accessing the cochlea for the electrode array insertion. Then the trend shifted to cochleostomy drilling on the cochlear promontory which was later adopted also in EAS surgery.

In 2003, Prof. Skarzynski performed successful HP surgery with RW approach, and the soft surgical techniques were later described in the year 2007 [17].

In 2004, Prof. Kiefer described the cochleostomy surgical technique, which was applied in the EAS cases at the time [8].

In 2009, the Hearing and Structure Preservation (HSP) consensus meeting that took place in Vienna in Austria, hosted by Prof. Baumgartner and Prof. Gstöttner, resulted in the recommendation of prioritising RW approach over the cochleostomy approach – not just in HP/EAS surgery but in every CI surgery in general. The expert CI surgeons who were the panellists approving this recommendation, were Prof. Baumgartner and Prof. Gstöttner from Medical Faculty of the University of Vienna in Austria, Prof. Lenarz from Hannover Medical School in Germany, Prof. Rask-Andersen from Uppsala University in Sweden, Prof. Skarzynski from the Institute of Physiology and Pathology of Hearing in Warsaw, Poland, and Prof. Van de Heyning from Antwerp University Hospital in Belgium.

In 2010, Prof. Skarzynski reported on the HP results obtained from fifteen EAS paediatric patients implanted with MED-EL CI device with STANDARD/FLEXSOFT™ electrode array, using RW approach [18]. These fifteen patients underwent HP surgery between the years **2004** and **2007** using RW technique to increase the likelihood of better HP results. Pure tone audiograms and Polish version of monosyllabic word test were performed at various time points, including before surgery and one, three, six and twelve months after surgery to follow up on the HP and the hearing performance results. HP immediately after surgery was achieved in all patients; however, three patients were considered as having non-functional partial preservation. The average hearing thresholds measured before surgery and one to four years thereafter showed no statistical significance across any of the frequencies measured, as demonstrated in Figure 22(A). The monosyllabic word testing under noisy conditions is shown in Figure 22(B). The post-implantation scores after one year of CI use exceeded the preimplant scores in all patients.

The results presented in this study indicate the possibility of preserving good LF hearing when using the RW approach with an insertion depth of between 20–30mm

With the introduction of EAS™, the intracochlear structure preservation became an important topic even in cases with no LF residual hearing. In order to make every CI surgery highly atraumatic to the intracochlear structures, MED-EL introduced FLEX28™ electrode array (Figure 23) in the year **2011**. It measures 28 mm in implantable length and belongs to the FLEX Series, which aims to preserve the intracochlear structures with deep insertion, especially in cases with expected progressive HL. The suggestion for this electrode came from Prof. Harold Pillsbury from the University of North Carolina as he thought that a slightly shorter than STANDARD electrode would be good for several US surgeons to achieve full insertion offering electric stimulation covering the entire frequency range.

In 2019, The first simultaneous bilateral EAS surgery in the world was performed by Prof. Usami and his colleagues

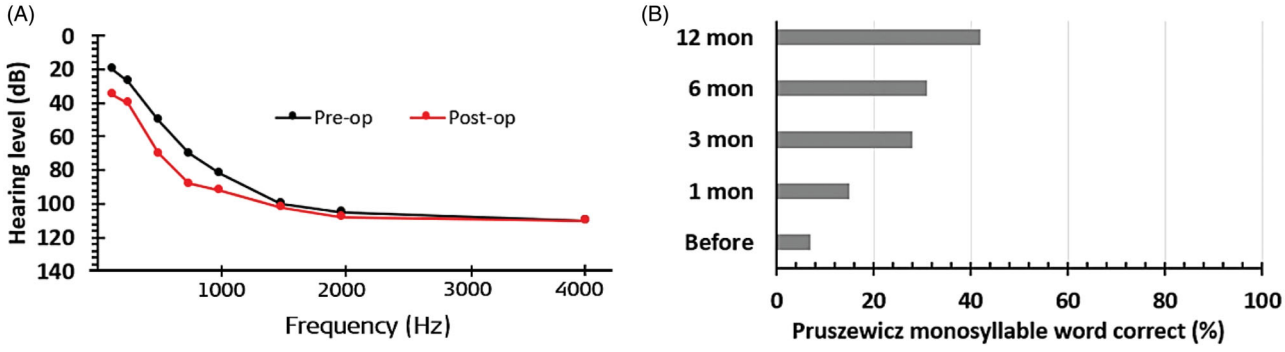


Figure 22. Preoperative and postoperative audiograms showing the mean hearing level for each frequency for the CI implanted group (A). Monosyllable scores overtime under the noisy condition for patients with PD. Graph and histogram created from data given in Skarzynski et al. [18].

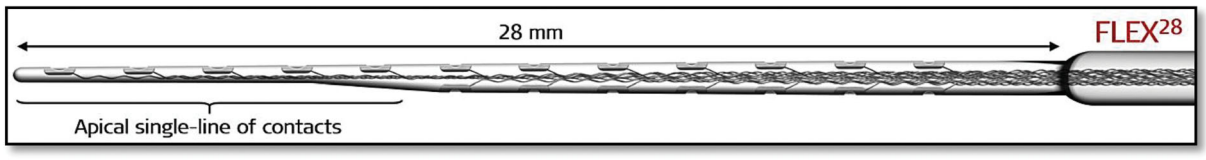


Figure 23. FLEX28™ electrode array with an implantable array length of 28 mm, along with five apical channels in a single line and extra slim configuration (Image courtesy of MED-EL).

from the Matsumoto University in Japan in an adult patient of age 31 who chose MED-EL EAS™ hearing system. FLEX28 electrode was chosen in this patient [19].

2.9. Reimplantation with EAS™ and residual hearing preservation

Reimplantation is an important CI topic in general, as device failure due to variety of reasons could potentially occur. If that shall happen in an EAS™ case, the explantation and subsequent reimplantation should avoid any trauma to the intracochlear structures to ensure successful application of the acoustic amplification of LF residual hearing through the HA unit of EAS™ audio processor – even after the revision surgery. The first report on achieved hearing preservation, following a reimplantation surgery in an EAS patient, was published in **2011** [20] by Dr Hoffman and his colleagues from New York Eye and Ear Infirmary in the US (Figure 24).

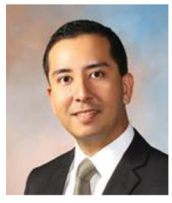
Figure 24. First report on hearing preservation after reimplantation by Dr Ronald Hoffman from New York Eye and Ear Infirmary, New York, USA.

The patient was a forty-three-year-old male who had a sensation of bilateral non-pulsatile tinnitus for many years and wearing HA with decreasing satisfaction. The patient was implanted with MED-EL's EAS™ hearing system in combination with the FLEX24™ electrode array, inserted *via* RW opening with ten channels intracochlearly. Three months postoperative unaided audiogram evaluation revealed good preservation of residual hearing, improvement in hearing thresholds and in aided consonant-nucleus-consonant (CNC) word scores. At six months postoperatively, the patient complained of air accumulation under the skin flap, which he tried to remove by rubbing the area with his knuckles, and that resulted in electrode lead's wire breakage. The CI was explanted ten months postoperatively and reimplanted with FLEX24™ once again. The follow-up audiometric evaluation at three months post-reimplantation revealed good preservation of auditory thresholds, and the patient reported wearing DUET™ audio processor approximately sixteen hours per day maximum, as well as he expressed general satisfaction with the reimplantation.

In 2012, an EAS™ reimplantation of two cases was reported from the University of Western Australia [21] (Figure 25).

The first case was a ten-year-old girl with bilateral severe-to-profound mid-to-high frequency sensorineural HL, who was implanted with FLEX24™ electrode array, with eleven out of twelve channels intracochlearly. At eighteen months postoperatively, a suspected device failure was reflected by fluctuating impedances found during the fitting and the patient was re-implanted with FLEX24™ with full cochlear insertion. The patient retained complete hearing preservation after reimplantation, as evident at the three months follow-up pure tone audiogram (Figure 26).

The second patient was a fifty-year-old man with a fifteen-year history of progressive bilateral moderate-to-severe downward sloping sensorineural HL who underwent the first implantation with FLEX24™ electrode array and with eleven contacts intracochlearly. Device failure was detected at thirteen months postoperatively with a subjective sensation of a: 'Double voice, crackling sound, and an echo.' The patient was re-implanted with the FLEX28™ electrode array, fully intracochlearly and with no noticeable insertion resistance, resulting in complete hearing preservation, as seen at post-reimplantation pure tone audiogram (Figure 26).



Asst. Prof. Jafri Kuthubutheen

Prof. Gunesh Rajan

Figure 25. CI surgeons from the University of Western Australia (in 2012) reported on hearing preservation after CI reimplantation surgery.

In 2013, a joint case report from three different centres, in which ENT surgeons shared their findings with hearing preservation during reimplantations, was published [22]. Demographic data of the three patients who had, on average, 23 mm of electrode array inserted intracochlearly during their first implantation, is given in Table 2.

Before the revision surgery, pure-tone audiogram average of all cases showed considerable LF residual hearing.

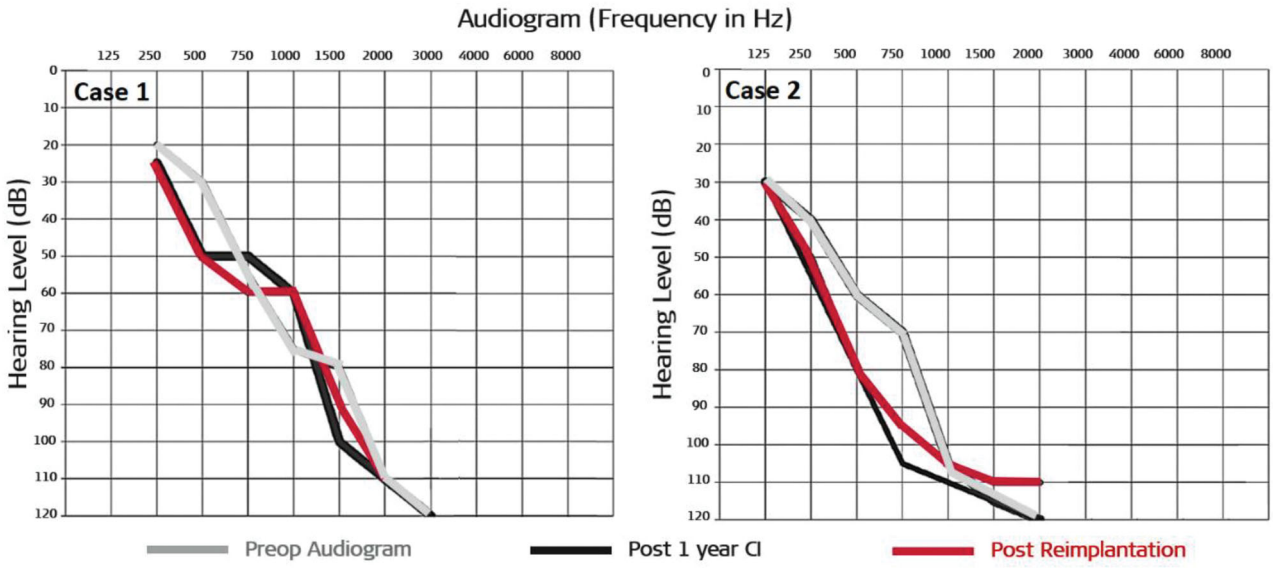


Figure 26. Pure-tone audiometry results of *case 1* (child) and *case 2* (adult) with pre-op (grey line), post-1-year CI (black line) and post-re-implantation (red line) audiogram results [21]. Reproduced by permission of Wolters Kluwer Health, Inc.

Table 2. Demographic data of the three patients with preserved residual hearing after undergoing reimplantation [22].

Patient—centre	Cause of hearing loss	Surgical approach	Implant	Insertion depth	Reason for revision	Surgical approach	Implant	Insertion depth
1—Perth	Progressive	RW	FLEXSOFT™ (31 mm)	10 channels (24 mm)	Extrusion/ infection	RW	FLEX28™ (28 mm)	Full insertion (28 mm)
2—Manchester	Progressive	Cochl.	FLEXSOFT™ (31 mm)	10 channels (24 mm)	Progressive device malfunction	Cochl.	FLEX20™ (20 mm)	11 channels (18 mm)
3—Frankfurt	Slight progression	Cochl.	FLEX24™ (24 mm)	12 channels (23 mm)	Implant failure after trauma	Cochl.	FLEX24™ (24 mm)	Full insertion (24 mm)

RW: Round Window; Cochl.: Cochleostomy.

Hearing thresholds were at least 65 dB at frequencies up to 250 Hz, 85 dB at 500 Hz, and 105 dB at 1,000Hz. Reasons for revision surgery were mainly infection and implant failure, and the patients were reimplanted with FLEX28™, FLEX20™ and FLEX24™ electrode arrays, respectively in three cases as given in Table 2. Post reimplantation, the residual hearing in all patients was preserved completely within frequencies up to 250 Hz. This was the first EAS™ patient group reimplantation report, operated by three different ENT surgeons from three different locations, which was, concurrently, concluded with complete hearing preservation (Figure 27).

In 2018, Prof. Brown and his colleagues from the University of North Carolina in the US demonstrated the HP in a single patient who underwent CI reimplantation surgery after nine years and with a MED-EL CI device, featuring FLEX24™ electrode array in both instances [23]. The patient had audiometric testing and speech perception test with CNC words in quiet and noise at various time points, including nine years after implantation after the first implanted device failed due to electrode wire breakage and three months after the reimplantation. Figure 28(A) shows postoperative audiometric test results at various time points, including at the time of device failure and three months

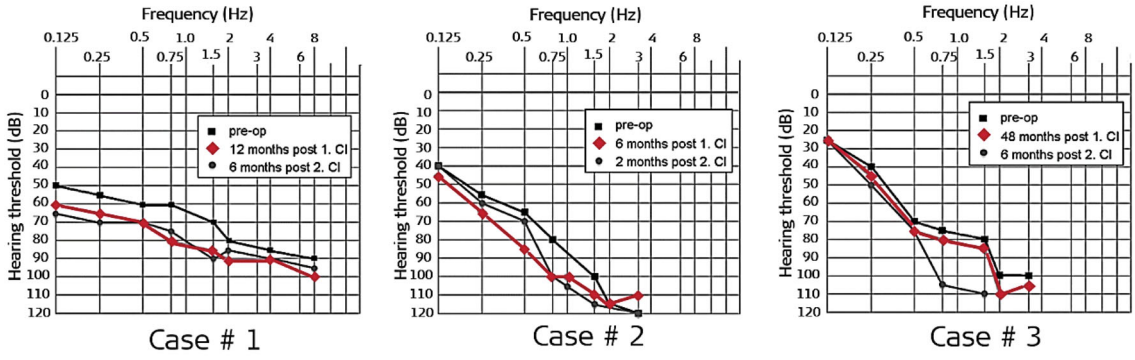


Figure 27. Pure-tone audiometric thresholds determined preoperatively and postoperatively in three patients, implanted with EAS™ [22]. Reproduced by permission of Wolters Kluwer Health, Inc.

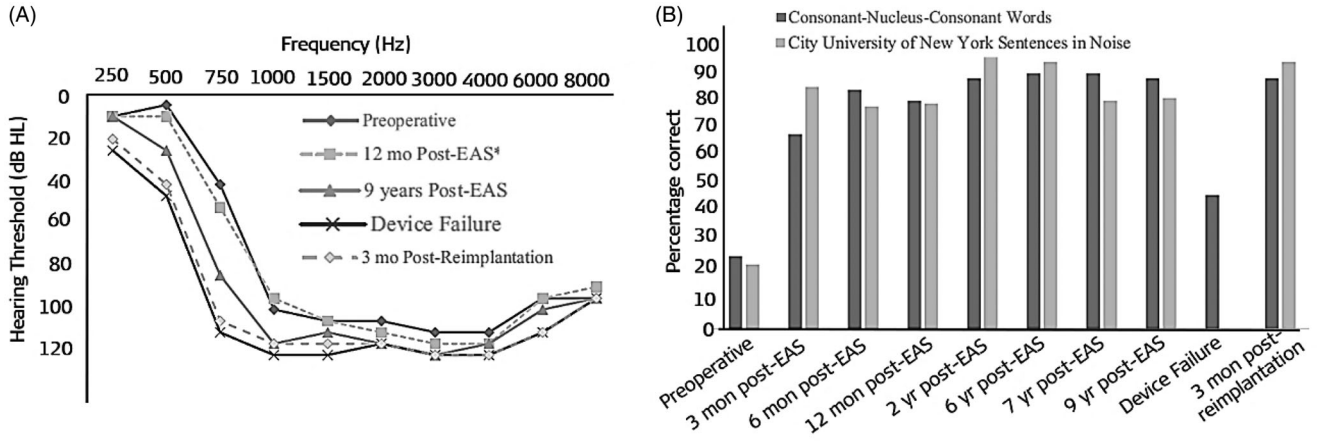


Figure 28. Unaided pure-tone audiometric hearing thresholds at various time points, including at the device failure time point, and three months post-reimplantation (A). Speech perception test results at various time points (B). Graph and histogram created from data given in Thompson et al. [23].

post-reimplantation with preservation of LF hearing with thresholds similar to the preoperative findings. Postoperative speech perception testing demonstrated improved performance with EAS as compared with the preoperative performance (Figure 28(B)). The patient reported a gradual change in sound quality and a significant decline in communication abilities at nine years after the first implantation, with aided speech perception decrease from 90% to 48% in CNC words. Audiometric testing was performed with three months follow-up intervals, and the patient's residual hearing was unchanged, which demonstrated restoration of aided speech perception performance that matched his best performance with the initial device. This was the first reported case to show normal LF HP after nearly ten years of EAS™ device use and two CI procedures in the same ear.

All these reports are supporting the fact that hearing preservation in EAS™ cases is possible even after CI reimplantation, helping the patients to benefit additionally from the acoustic amplification of their LF residual hearing.

2.10. Consensus on the method of hearing preservation classification

Until 2011, the method of calculating the rate of hearing preservation postoperatively in patients with measurable LF residual hearing was simply subtracting the preoperative hearing thresholds from the postoperative hearing thresholds. Typically, if the difference was within 10 dB HL, then the result was considered as complete hearing preservation. This may be making sense if the preoperative audiogram is in the normal to mild HL range in the LF. However, if the patient's preoperative hearing in LF is in the range of 80 dB or worse, then postoperatively, with the same 10 dB loss, the patient would have no hearing at all, but this could still be considered as complete hearing preservation, which may be misleading.

In 2013, the HEARRING group (www.hearring.com), an independent organisation formed by a group of expert CI surgeons and audiologists, came up with a new classification system in calculating the hearing preservation based on what the patients can actually *hear* postoperatively, rather than reporting on how much hearing was *lost* [24]. The HEARRING group proposed the following formula for the hearing preservation classification:

$$\text{Relative change} = \frac{(\text{PTA post} - \text{PTA pre})}{(\text{PTAmax} - \text{PTA pre})}$$

PTA post represents the pure-tone average measured postoperatively, *PTA pre* is a pure-tone average measured preoperatively, and *PTA max* is the limit of the audiometer. This equation is representing relative change as a percentage of HL and is applicable for all CI users with measurable preoperative residual hearing (PTA: 0–120dB) across the frequency range measurable with an audiometer. The HL is then converted to hearing preservation by calculating 100% minus the relative change in percent:

$$S = \left[1 - \left(\frac{(PTA\ post - PTA\ pre)}{(PTAmax - PTA\ pre)}\right) * 100\right]\%$$

S represents hearing preservation on a numerical scale. The numerical scale may be converted to a categorical scale for ease of reporting, as given in Table 3.

Table 3. Scale for the proposed hearing preservation classification system [24].

Percentage of residual hearing preserved	Classification
>75 %	Complete HP
>25–75%	Partial HP
0–25%	Minimal HP
No measurable hearing	Loss of hearing/no hearing

The authors of the report recommended the above formulas to be generally used by clinicians in their clinical practice and their scientific reports, with deciding on electrode array types, and for better evidence-based practice in the CI field (Table 4).

2.11. EAS™ in unilaterally deaf patients

CI surgery with preservation of LF residual hearing helps partially deaf patients to achieve more natural hearing as a

Table 4. Clinicians from the HEARRING group who were involved in establishing the method of HP classification.

Prof. H. Skarzynski (Poland)	Prof. P. Heyning (Belgium)	Asst. Prof. S. Agrawal (Canada)	Prof. S. Arauz (Argentina)
Prof. M. Atlas (Australia)	Prof. W-D. Baumgartner (Austria)	Prof. M. Caversaccio (Switzerland)	Prof. M. Bodt (Belgium)
Prof. J. Gavilan (Spain)	Prof. B. Godey (France)	Prof. K. Green (UK)	Prof. W. Gstöttner (Austria)
Prof. R. Hagen (Germany)	Prof. D.M. Han (China)	Prof. M. Kameswaran (India)	Prof. E. Karltorp (Sweden)
Prof. M. Kompis (Switzerland)	Prof. V. Kuzovkov (Russia)	Prof. L. Lassaletta (Spain)	Dr. F. Lefebvre (France)
Prof. Y. Li (China)	Dr M. Manikoth (India)	Dr J. Martin (UK)	Prof. R. Mlynski (Germany)
Prof. J. Müller (Germany)	Dr M. O'Driscoll (UK)	Prof. L. Parnes (Canada)	Dr S. Prentiss (USA)
Dr S. Pulibalathingal (India)	Prof. C. H. Raine (UK)	Prof. G. Rajan (Australia)	Dr. R. Rajeswaran (India)
Dr J. A. Rivas (Columbia)	Prof. A. Rivas (Columbia)	Prof. P. Skarzynski (Poland)	Prof. G. Sprinzl (Austria)
Prof. H. Staecker (USA)	Prof. K. Stephan (Austria)	Prof. S. Usami (Japan)	Dr Y. Yanov (Russia)
Dr M. E. Zernotti (Argentina)	Dr K. Zimmermann (Canada)	Prof. A. Lorens (Poland)	Prof. G. Mertens (Belgium)

result of combining acoustic amplification in the LF region and the electric stimulation in the HF region. Unilaterally implanted patients with preserved acoustic hearing at LF in the implanted ear will most likely be making use of bilateral LF acoustic amplification if the contralateral ear has sufficient acoustic hearing in the LF region. This is because the hearing preservation in the LF region helps the EAS patients to use their interaural time difference (ITD) and interaural level difference (ILD) cues to separate the target and noise when speech and noise originate from different spatial locations.

In 2013, a multicentric study from the USA and Poland demonstrated indirect benefits of binaural hearing by the preservation of LF residual hearing after CI treatment in unilateral deaf patients [25] (Figure 29).

Figure 29. Team of clinicians from USA ([1]Vanderbilt University, [2]Arizona State University, [3]Mayo Clinic, Rochester, [4]University of Texas Southwestern, [5]University of North Carolina), Poland ([6]International Center for Hearing and Speech) and [7]MED-EL demonstrated the benefits of binaural hearing by preserving the LF residual hearing during CI procedure in the ipsilateral ear.

Twenty-one native speakers of English and seventeen of Polish language participated in the named study. English speakers were unilaterally implanted with CI from various CI brands, whereas Polish speakers were unilaterally implanted with MED-EL's 31.5 mm long electrode array (STANDARD) in eleven, and 24 mm of the STANDARD's array in six patients. All Polish patients were implanted *via* RW surgical approach, while all English patients were implanted *via* cochleostomy. In order to understand the binaural benefits, including the squelch effect, head shadow effect and loudness summation effect, the speech recognition in noise experiments were conducted with patients surrounded by eight loudspeakers in a circular pattern. The speech stimuli always originated from the speaker placed at 0° azimuth and the noise was fixed at 72dBA (A is a type of calibration), originating from all eight loudspeakers, which would imitate noise occurring at a large gathering or a noisy restaurant. The speech stimuli in English and Polish language were presented to these two groups of patients at a fixed +6dB and +2dB SNR, as reported in this study. However, personal communication from the authors of the study declares that the Polish patients were actually tested at 0 dB SNR and not at +2dB SNR.

The speech recognition was assessed for all thirty-eight patients in the best-aided EAS condition (CI + binaural acoustic hearing), as well as in bimodal condition with the ipsilateral ear occluded with foam or earplug. The results of the fixed SNR testing at +6dB and +2dB SNR for both English and Polish speakers are given in Figure 30(A). For the English speakers implanted with various CI brands, the mean performance at +6dB SNR was 48.7% in bimodal, and 58.3% in the best-aided EAS conditions. At +2dB SNR, the mean performance dropped to 40% in bimodal, and to 50.2% in the best-aided EAS conditions. For the Polish speakers implanted with MED-EL CIs, the mean performance resulted in 79.4% in bimodal, and 85.1% in the best-aided

condition at +6dB SNR. At +2dB SNR (which is actually 0 dB SNR, according to the personal communication from the authors), the mean performance dropped to 64.7% in bimodal, and to 74.2% in the best-aided EAS condition. The results obtained from the Polish speakers at 0 dB SNR should be seen much superior compared to the English speaker results obtained at +2dB SNR (typically, +2dB SNR corresponds to approximately 6% of the mean speech recognition improvement). Figure 30(B) shows normalised benefit as a function of the LF PTA in dB HL for the implanted ear.

hypothesised that ILD cues were present and utilised by the unilaterally CI implanted listeners with binaural acoustic hearing. These data not only provide evidence of functional efficacy for hearing preservation in the implanted ear, but also for the expansion of the CI criteria to include individuals with LF thresholds in even normal to the near-normal hearing range. The study suggests that MED-EL's EAS™ users have better hearing in noisy situations.

The difference in hearing performance between English and Polish speaking group could have been caused either by the device or the unified audio processor fitting methods.

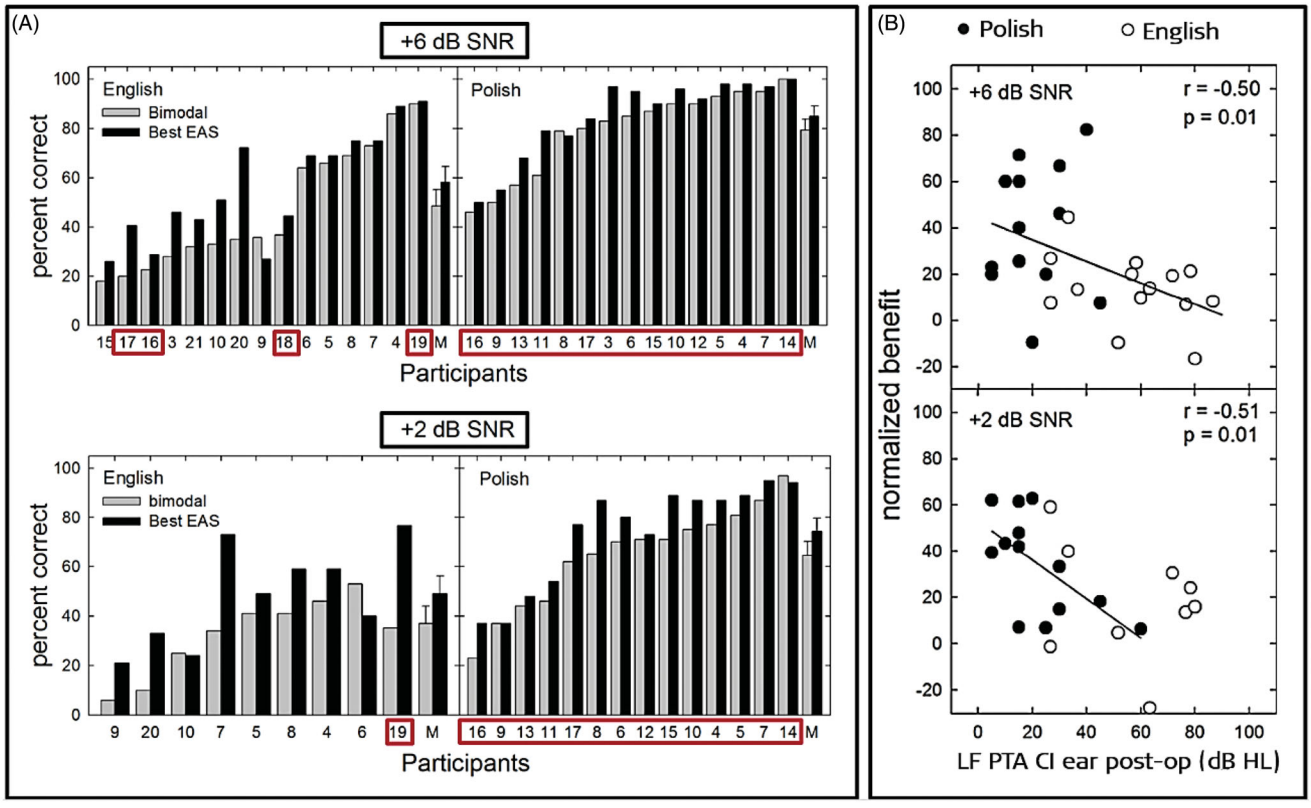


Figure 30. Individual and mean speech recognition scores (% correct) for fixed level SNR of +6dB and +2dB for both groups under two different listening conditions and the participant numbers inside the red boxes correspond to MED-EL implanted devices (A). The Polish group given under +2dB SNR was actually tested at 0 dB SNR as per the personal communication from the authors. Normalised EAS benefit for speech recognition at +6dB and +2dB SNR as a function of low-frequency pure-tone average in dB HL (note: Polish group was tested at 0 dB SNR and not at +2dB SNR as mentioned in this study, according to the personal communication from the authors) (B) [25]. Reproduced by permission of Wolters Kluwer, Inc.

An interesting twist of a tale was the finding showing CI insertion depth of >20mm being an effective treatment option for patients with considerable LF acoustic hearing in both ears. The amount of postoperative hearing preservation benefit was seen as the largest at the most difficult listening condition (speech recognition at +2dB SNR). The degree of normalised EAS benefit was also significantly correlated with postoperative LF PTA in the implanted ear, and it in part explains the preservation of ITD cues, responsible for better hearing scores. The advantage of the head shadow effect in the best-aided condition is another possible explanation for the better hearing scores. ILD cues are present for LF stimuli, generally in the range of 2 dB or less and considering the experiment performed in the study, it was

One of the key differences amongst the fitting methods was the selection of cut-off frequency between electric and acoustic stimulation. While MED-EL patients were fitted with cut-off frequency obtained from unaided audiogram at 65 dB HL, for Cochlear™ patients, the fitting method included a selection of cut-off frequency typically at 80 dB from unaided audiogram [26].

2.12. The third-generation unified audio processor

In 2014, MED-EL introduced SONNET®, the third generation EAS™ audio processor with new features, enabling users to enjoy close to natural hearing (Figure 31).

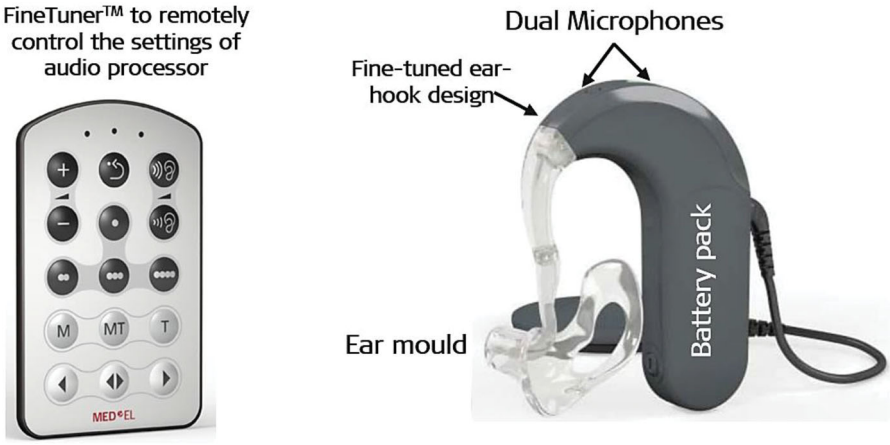


Figure 31. SONNET® EAS™ audio processor (image courtesy of MED-EL).

The acoustic gain from the HA unit of the audio processor was increased from 43 dB in DUET-2™ to 48 dB and maximum power output of 118 dB SPL across all frequencies in SONNET®. Battery life was increased to up to sixty hours, and the volume of acoustic amplification was made adjustable together with the electric stimulation *via* the same volume control in the *FineTuner™*. Directionality function of the dual microphones helps to focus on sounds that are coming from the front of the listener and attenuates the background noise. Wind noise reduction was another new feature which minimises the continuous wind noise for improved listening in outdoor environments.

2.13. Clinical trials in Japan and the USA

In the same year, an important clinical trial results published from Japan that was sponsored by MED-EL to evaluate hearing preservation results and speech discrimination outcomes of hearing preservation surgeries using medium electrodes in Japanese-speaking patients [27] (Figure 32). *The official clinical trial period was from 1st August 2010 till 1st April 2014. The first patient was implanted on 20th August 2010 and the last patient that was implanted was on 16th November 2012. FLEX^{24} electrode array was implanted in twenty-five patients.*

The results of the study were highly valuable for approval of MED-EL's EAS™ hearing system by the Japanese authority which is similar to Food and Drug Administration (FDA) in the USA. In the named study, the hearing preservation surgeries were performed in twenty-nine ears of twenty-seven patients whom all had late or postlingual onset of HF sensorineural HL with a very good functional LF hearing. All patients fulfilled the audiological criteria for EAS and were implanted with FLEX24™ electrode array. The audiometric evaluation in the range between 125–8,000Hz was performed preoperatively and at one, three, six and twelve months after the initial EAS™ stimulation. Pure-tone hearing was evaluated four weeks postoperatively, at the time of CI and EAS™ fitting, as well as at three, six and twelve months. The audiograms of twenty-nine ears are shown in Figure 33 with LF (250–1,000Hz). After the initial deterioration of the pure-tone thresholds at

Figure 32. Team of CI surgeons from Japan: [1]Shinshu University School of Medicine, [2]Toranomon Hospital, Tokyo, [3]Kobe City Medical Center General Hospital, [4]Nagasaki University Graduate School of Biomedical Sciences, and [5]Miyazaki University School of Medicine were involved in the clinical evaluation of EAS™ hearing system.

the first CI activation at one month postoperatively, it remained highly stable at the same level for an additional eleven months. Postoperative audiogram measured at twelve months from each of the operated ear is depicted in red color in Figure 33.

Improvement of speech discrimination and perception scores are given in Figure 34. The average monosyllable discrimination score in quiet was improved from 24.1% preoperatively with hearing aid (AS) to 67.4% with EAS 12-months after the first fitting. This postoperative

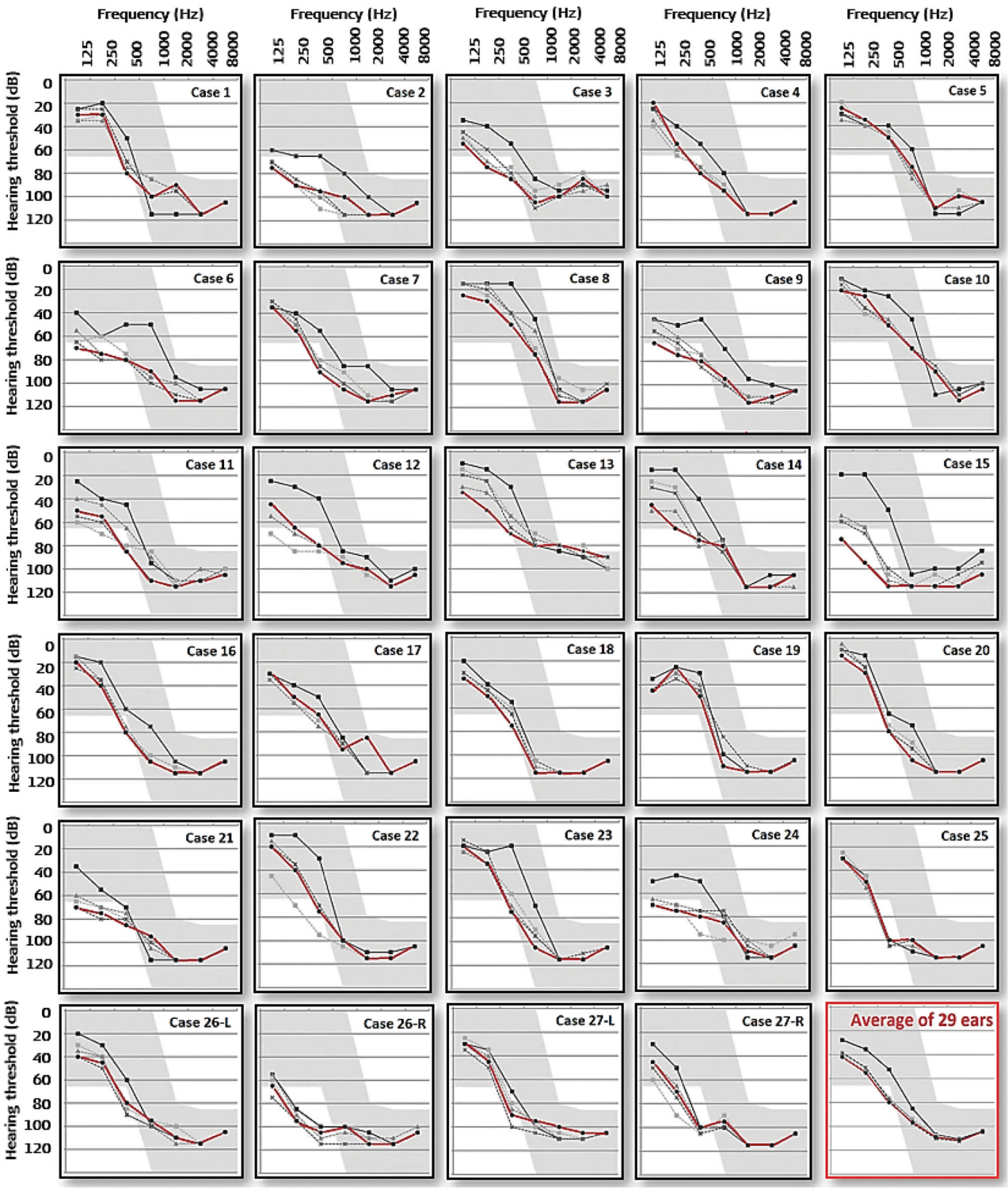


Figure 33. Pure-tone audiograms of each of the twenty-nine operated ears measured at various time points. Black continuous lines correspond to the preoperative time points and the red continuous lines correspond to the twelfth month post-surgery. Shadow indicates the audiological criteria for EAS clinical trial. The average audiogram of all ears is shown within the red outlined section [27]. Reproduced by permission of Taylor and Francis Group.

improvement occurred gradually from 48.4% at 1 month to 67.4% at 12 months and was mainly based on the adaptation of electric stimulation, because in a comparison of monosyllable discrimination scores in three conditions (acoustic stimulation only (AS only), electric stimulation only (ES only), and EAS), acoustic stimulation scores changed only slightly from 13.8% to 18.1% at 12 months after the first fitting, but electric stimulation improved from 35.0% to 55.4%. Also, the EAS condition showing the best performance for monosyllable discrimination revealed that acoustic stimulation combined with electric stimulation increases perception ability (EAS results were significantly better than ES only; $p < .001$) (Figure 34(A)). Similar results were observed in monosyllable, word, and sentence perception tests in noise.

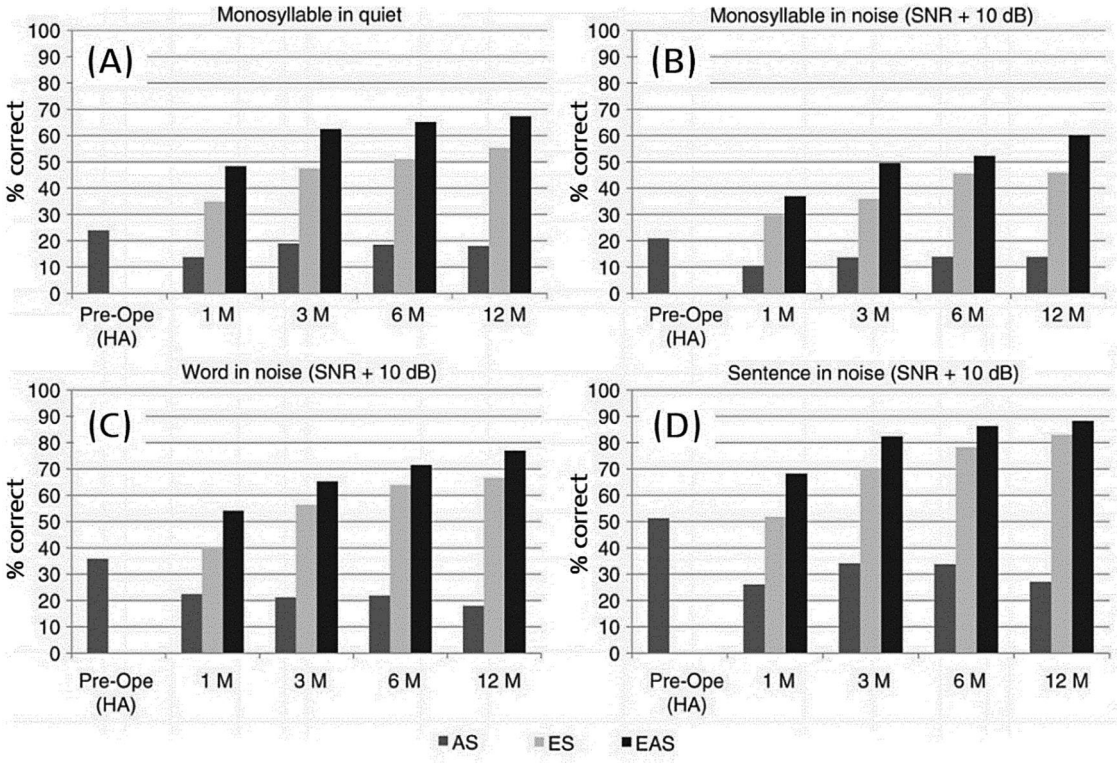


Figure 34. Mean values for speech discrimination and perception scores at different time points and under different listening conditions [27]. Monosyllable word test in quiet (A), in noise (+10dB SNR) (B), word test in noise (+10dB SNR) (C), and sentence test in noise (+10dB SNR) (D). Statistical analysis: paired *t*-test. Reproduced by permission of Taylor and Francis Group.

The results for monosyllable perception in noise were improved from 21.0% preoperatively with hearing aids to 60.2% with EAS 12-months after the first fitting. This postoperative improvement occurred gradually from 36.9% at 1 month to 60.2% at 12 months. Also, EAS results (60.2% correct) were significantly better than AS only (13.9% correct) and ES only (46.0% correct) results ($p < .001$ and $p = .009$) (Figure 34(B)). The average word and sentence perception test score in noise improved from 35.8%, and 51.3% to 77.0%, and 88.2%, respectively (Figure 34(C,D)). In both word and sentence perception tests, EAS showed the better results. EAS results were significantly better than the ES only results ($p = .002$ for word and $p = .01$ for sentence)

The study concluded that EAS™ is beneficial also for Japanese-speaking patients with less residual hearing at lower frequencies, indicating that the indication criteria could be expanded for EAS.

In 2018, a multicentric FDA clinical trial study, sponsored by MED-EL, was published (Figure 35). *The first and the last patient within this clinical trial was implanted in April 2007 and in December 2014 respectively. The study results were collected until February 2016.*

The study included sixteen different CI centres within USA to evaluate the safety and effectiveness of the EAS™ system in adults with residual LF hearing and severe-to-profound HL in the mid-high frequencies. Also, evaluating the speech perception in quiet and noise was part of the study objective [28]. Altogether, seventy-three patients who met the EAS inclusion criteria were part of the study, and they were implanted with the EAS™ system with FLEX24™ electrode array for an insertion depth of approximately 20 mm. Access to the cochlea was achieved *via* the RW approach in fifty-five (75.3%), and *via* the cochleostomy approach in seventeen (23.3%) patients, while the approach was unspecified in one patient (1.4%). Postoperatively, the patients were fitted with DUET audio processor, combining electric stimulation and acoustic amplification. In total, 67 of the 73 patients completed the audiometric testing and effectiveness outcome tested preoperatively and three, six and twelve months. Speech perception was assessed at these intervals using the City University of New York (CUNY) sentences in noise and CNC words in quiet.

An initial decrease in unaided thresholds was shown by 3 months post-activation, and thresholds remained stable (within 2 dB HL) through the 12-month interval (Figure 36(A)). Mean LF-PTA increased by 24.1 dB in sixty-seven patients who were tested at both, the preoperative and at the twelfth-month, post-activation intervals. Out of these, fifty-three patients (79.1%) experienced a LF-PTA shift of less than 30 dB HL. Eight patients (11.9%) had profound or total HL, as determined by a LF-PTA of >90dB HL. A total of sixty-five out of sixty-seven patients (97.0%) were able to use EAS through DUET™ audio processor at twelfth-month post-activation.

Table 5 summarizes the improvement in hearing scores as measured by CUNY sentences in noise and CND words between the preoperative and postactivation time points. Such an improvement was seen in both EAS and electric only mode.

Individual speech perception outcomes of CUNY sentences in noise and CNC words in quiet are shown in

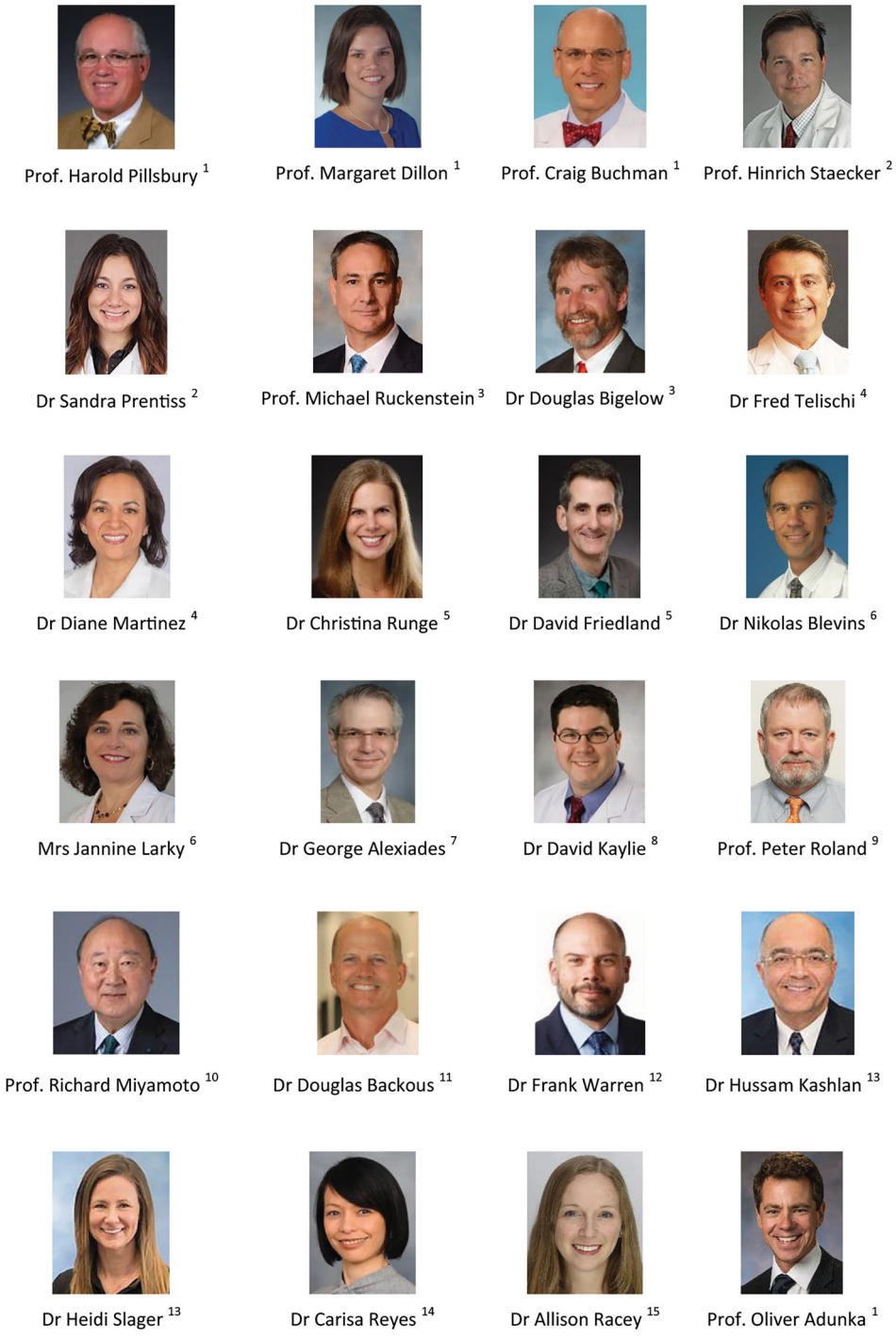


Figure 35. Clinicians from CI clinics across the USA who were involved in the FDA clinical trial study evaluating the safety and effectiveness of MED-EL EAS™ system. [1]University of North Carolina, [2]Kansas University Medical Center, [3]Hospital of the University of Pennsylvania, [4]Miller School of Medicine of the University of Miami, [5]Medical College of Wisconsin, [6]Stanford University, [7]New York Eye and Ear Infirmary, [8]Duke University, [9]University of Texas Southwestern Medical Center, [10]Indiana University, [11]Swedish Neuroscience Institute, [12]Oregon Health Sciences University, [13]Michigan University, [14]Boys Town National Research Hospital, Nebraska and [15]MED-EL.

Table 5. Summary of primary and secondary effectiveness endpoints.

	Acoustic hearing Preop (baseline) mean ± SD	EAS 12 months postactivation Mean ± SD		Electric Only 12 months postactivation Mean ± SD	
	N = 67	*N* = 66	Improvement from baseline	*N* = 67	Improvement from baseline
CUNY sentences in noise	30.9 ± 27.2	73.4 ± 23.9	+42.2 ± 29.8	55.6 ± 29.6	+24.6 ± 31.5
CNC words	30.4 ± 13.4	66.9 ± 18.5	+36.5 ± 23.5	48.4 ± 19.0	+18.0 ± 23.0

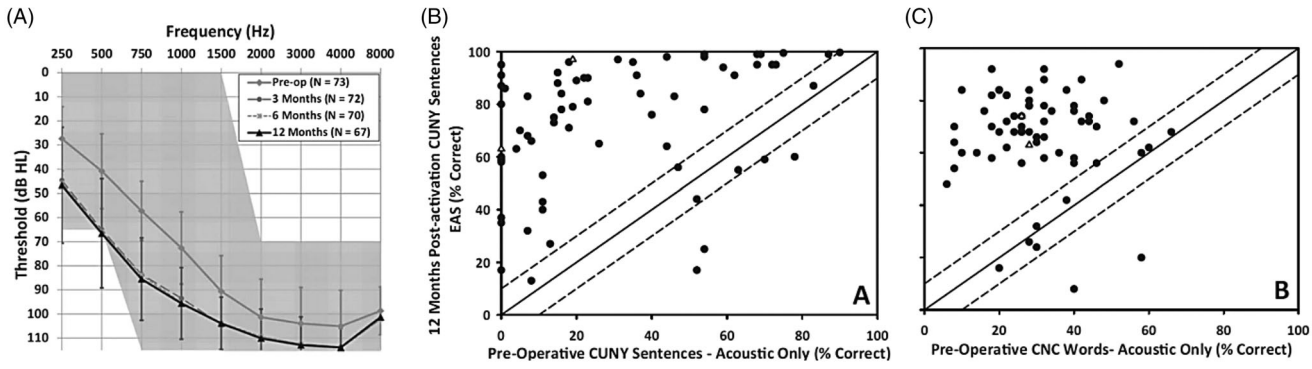


Figure 36. Average pure-tone unaided thresholds. Lines show mean audiograms obtained preoperatively (grey, solid line, diamonds), at three months (grey, long-dashed line, circles), at six months (grey, short-dash line, stars) and twelve months post-activation (black line, triangles). Error bars indicating standard deviation from the mean are shown for pre-op and twelve months interval (A). Speech recognition scores for all patients followed-up until the twelfth-month post-activation interval. Scores for CUNY sentences in noise (B) and CNC words in quiet (C) are represented by filled circles for patients using EAS and open triangles for those tested in CI alone condition. A solid reference line is shown on both figures, indicating no change in score from the preoperative to the twelfth-month post-activation interval. Dashed lines are shown at ±10% of the solid reference line to indicate scores that may fall within test-retest variability [28]. Statistical analysis: paired *t*-tests and Wilcoxon signed-rank test, with least-square means used to estimate change from the preoperative interval. Reproduced by permission of Wolter Kluwer Health, Inc.

Figure 36(B,C) respectively for all sixty-seven patients reaching the twelfth-month study endpoint, with percentage correct shown as a function of the preoperative score. Patients with speech perception scores greater than 10% above the reference line were classified as performing better. Scores within ±10% of the reference line were classified as results with similar performance, and scores >10% below the reference were classified as results with worse performance. With CUNY sentences in noise, fifty-seven out of sixty-seven patients (85.1%) performed better at twelfth-month in the EAS condition, compared with the preoperative aided condition, when tested in the implanted ear. With CNC words in quiet, fifty-nine out of sixty-seven patients (88.1%) performed similarly or better at twelfth-month in the CI alone condition (full-frequency electric map) compared with the preoperative aided condition. Four out of sixty-seven patients (6.0%) performed worse on both tests (CNC and CUNY) at twelfth-month with electric stimulation only.

This FDA clinical trial data illustrated a successful application of combined electric and acoustic stimulation in adult CI recipients with LF residual hearing. Patients experienced additional performance and subjective benefits from the EAS, beyond those of electric stimulation alone, reconfirming the advantages of the EAS, particularly in difficult listening conditions. The FDA approval for implantation with a thin, flexible long electrode and combined EAS provides an effective treatment option for individuals with low-frequency acoustic hearing who do not meet traditional CI candidacy.

In 2013 and 2017, MED-EL received approval in Japan and FDA approval in the USA for its EAS™ hearing system, which was a significant – and at the time unprecedented amongst all CI brands – milestone.

Cochlear Corporation, another CI manufacturer received FDA approval of its Hybrid hearing system in the year 2014 [29]. Cochlear recruited 50 patients in their clinical trial study and a 16 mm long electrode array was inserted through a small cochleostomy drilling inferior to the RW entrance. They evaluated the hearing benefits using CNC word test at six-month postactivation whereas MED-EL evaluated at 12-month postactivation. Table 6 compares the results of Cochlear Hybrid hearing system with MED-EL EAS hearing system.

While the word scores at the pre-operative acoustic only mode and postactivation are more or less similar in both the clinical trials, it is important to note the electrode array length, which is 20 mm with MED-EL EAS whereas it was 16 mm with Cochlear Hybrid. Within 6 months of postactivation, 22 out of 50 patients (44%) of the patients from the Cochlear Hybrid group lost the residual hearing while it was only 8 out of 67 patients (11.9%) from MED-EL EAS group at 12-months postactivation. This can only be explained for the flexible nature of MED-EL's electrode incorporating wavy wires conserving the intra-cochlear structures which would not have been the case with Cochlear's thin electrode that incorporates straightened metal wires bunched together giving the rigid property. The cochleostomy approach was predominantly used in all the patients in the Cochlear's clinical trial while it was mainly the RW approach in majority of the patients and cochleostomy approach in some patients in MED-EL's clinical trial.

Table 6. Summary of primary outcomes (CNC word scores) comparing MED-EL EAS and Cochlear Hybrid hearing system.

MED-EL EAS hearing system [28] (Electrode insertion depth ≈ 20mm)				Cochlear Hybrid hearing system [29] (Electrode insertion depth ≈ 16mm)			
Word scores (%)			% of patients with Profound/ total hearing loss postactivation	Word scores (%)			% of patients with Profound/ total hearing loss postactivation
Acoustic alone preoperative	12 months postactivation with EAS	Improvement from baseline		Acoustic alone preoperative	6 months postactivation with Hybrid	Improvement from baseline	
30.4 ± 13.4	66.9 ± 18.5	+36.5 ± 23.5	11.9	28.4 ± 14.7	64.2 ± 26.6	+35.8 ± 27.7	44

2.14. Long-term hearing preservation results from around the world

It is evident that the integration of residual acoustic hearing can increase speech perception in noise as well as music appreciation in candidates for electric stimulation with a CI [4–6,8,12–17]. Despite optimal electrode array design, surgical technique and corticosteroid treatment, long-term HL may occur due to intracochlear immunocompetent reactions to the electrode array, or due to blood components or other elements that lead to an inflammatory response. Furthermore, genetically driven HL progression is discussed as a potential cause. The question remains whether residual hearing can be preserved for a long time after HP surgery or not, and therefore, long-term results in the EAS patient population are of great importance. Over the years, several CI specialising groups around the world have reported on the long-term results observed from their centres, and this section will cover most of those pieces of evidence.

In 2010, Prof. Skarzynski and his colleagues shared their clinical experience in treating partially deaf (PD) patients [30].

i. Ten years of management of PD adults and children, with varying levels of preservation of residual hearing, using combined stimulation (EAS).
ii. Seven years of follow-up of PD adults who retained 93.2% of good low-frequency hearing after implantation, complemented electrically (EC).
iii. Nearly five years of follow-up of PD children, who retained 100% of good LF hearing after implantation, complemented electrically (EC).
iv. Seventeen years of experience using RW approach, gained since the initial stages of the Warsaw CI program already.

In 2011, Dr Helbig and her colleagues from Johann Wolfgang Goethe University Hospital Frankfurt in Germany reported on thirty-three months follow-up of HP results from twenty-two severely to profoundly deaf patients with measurable residual hearing preoperatively, implanted with MED-EL's FLEXSOFT™ electrode array using RW approach [31]. Pure tone audiograms were measured for these patients at three different time points, including at pre-operative stage, at thirty-three months post-surgery and one measurement was performed intermediately. Figure 37 shows the dimensions of FLEXSOFT™ electrode array and the mean pure-tone audiometric results of patients with preserved hearing at three time points. A statistically significant drop in the hearing was observed between preoperative and postoperative measurements, but not between intermediate and long-term measurements. The study demonstrated that postoperative residual hearing is stable in most cases in medium to long term (six to thirty-three months follow-up if implanted with a flexible electrode array).

In 2013, Prof. Atlas and his colleagues from the University of Western Australia studied the long-term HP rates (>24 months) in thirteen CI recipients implanted with MED-EL EAS™ and FLEX24™, who had measurable LF residual

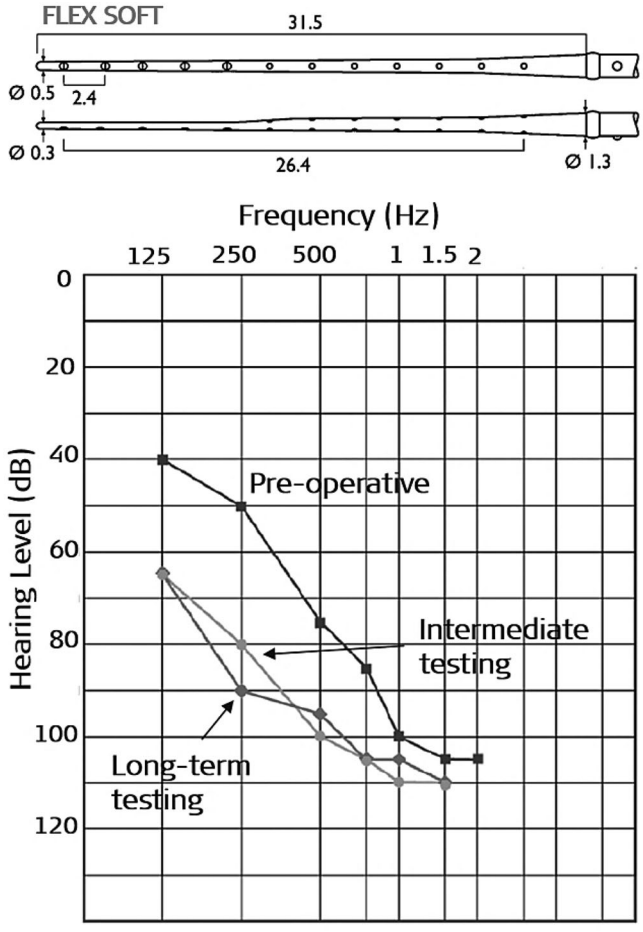


Figure 37. FLEXSOFT™ electrode array with its dimensions in millimetres (image courtesy of MED-EL). Mean pure-tone audiograms measured at three different time points [31]. Statistical analysis: Nonparametric Wilcoxon signed-rank test to look for the difference between test intervals ($p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

hearing before surgery [32]. Figure 38 depicts the HP rate, and at under three months post-operation time, complete HP was observed in 42.9%, partial HP in 50% and minimal HP in 7.1% of the patients. Between six and twelve months, complete HP reduced to 22.2% patients, partial HP was seen in 66.7% and minimal HP in 11.1% of the patients. Between twelve and twenty-four months, the complete HP slightly increased to 33.3%, partial HP to 22.2% and minimal HP to 44.4%. Until the twenty-fourth month, there was no case reported with complete loss of residual hearing. However, beyond twenty-four months of follow-up, 12.5% of patients had a complete loss of residual hearing, whereas 25% maintained complete HP. The study concluded that because of the electric stimulation from the long electrode array there was no difference in the quality of life witnessed between EAS and non-EAS users (not shown in Figure 38), and if the LF hearing is preserved, patients will enjoy the added benefits of EAS, including more natural hearing and music appreciation.

In 2014, the first long-term results on the HP in the range of ten years follow-up were reported by Prof. Van de Heyning and his colleagues from Antwerp University Hospital in Belgium, in which they studied nine post-lingually partially deaf EAS patients who underwent HP surgery [33]. HP rates were evaluated preoperatively and three,

Prof. Marcus Atlas

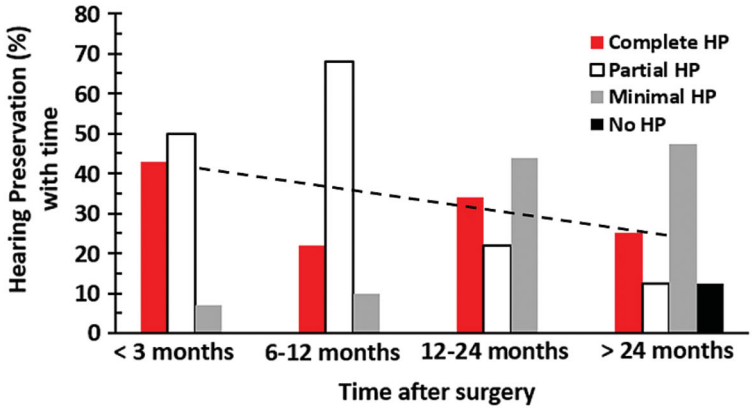


Figure 38. Prof. Marcus Atlas studied the long-term HP results from his patient population implanted with MED-EL EAS™ system. Results are summarised in the above graph: hearing preservation over time and the linear trendline summarises changes over time—statistical analysis: 1-way ANOVA test. Histogram created from the data given in Santa-Maria et al. [31].

six, twelve, eighteen and twenty-four months postoperatively, as well as annually after that. None of the patients had progressive HL, autoimmune disease, nor both. The electrode array types MEDIUM, FLEX28™ or FLEXSOFT™ were used, and HP formula proposed by the HEARRING group was applied for calculating the HP rates. Figure 39 quantifies the degrees of HP, showing complete HP obtained in 'subject 2′ (left ear, 85%) and 'subject 5′ (100%) up to six years postoperatively. Partial HP was achieved in 'subject 1′ (47%), 'subject 2′ (right ear, 56%), 'subject 4′ (left ear, 34%; right ear, 56%), and 'subject 6′ (44%) up to six years postoperatively. There was only minimal RH in 'subject 7′ (13%) and 'subject 3′ (19%) six years after surgery. In summary, the study conveys that long-term HP in EAS users after HP surgery is possible, although there is a small continuous decline of 3% HP per year. Not shown in Figure 39, the long-term speech perception results from the study showed a continuous statistically significant improvement for monosyllables in quiet, sentences in quiet, and sentences in noise. Also, the subjective benefit was found already three months after the implantation.

In 2016, Prof. Usami and his colleagues from Shinshu University School of Medicine and International University of Health and Welfare, both in Tokyo in Japan, evaluated the long-term threshold changes in the LF hearing region by comparing patient groups with stable hearing and progressive HL [34]. Altogether, seventeen individuals were enrolled and received MED-EL EAS™ implant with FLEX24™ electrode array through RW approach along with an intraoperative/systemic infusion of dexamethasone. Postoperative HP rates were calculated using the HEARRING HP numerical scale. Under the stable hearing group (Figure 40(A)), two patients had complete HP over the five years, whereas six patients had either partial or minimal HP. Within the progressive HL group (Figure 40(B)), four patients had complete HP until the second year after surgery, and after that, it migrated to partial HP. Within this group, another four patients who had partial HP until the second year shifted to mild HP after that. In short, the HP rates remained stable over time within the stable hearing group, whereas it declined over time in the progressive HL group (Figure 40). The authors concluded that EAS™ provided better speech perception scores (data not shown in Figure 40) in those patients with a larger degree of residual hearing compared with those who had at least minimal hearing preserved in the LF hearing region. Furthermore,

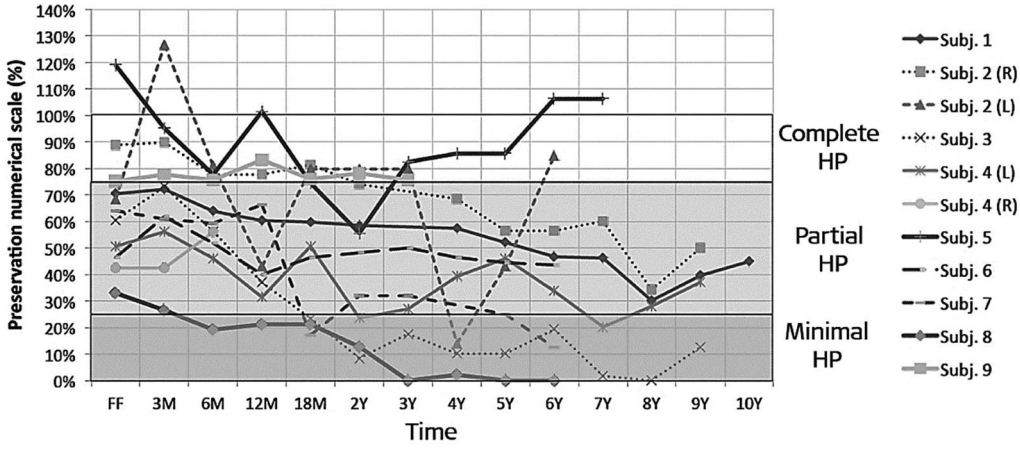


Figure 39. Hearing preservation for each patient using the HP numerical scale [33]. Reproduced by permission of Wolters Kluwer Health, Inc.

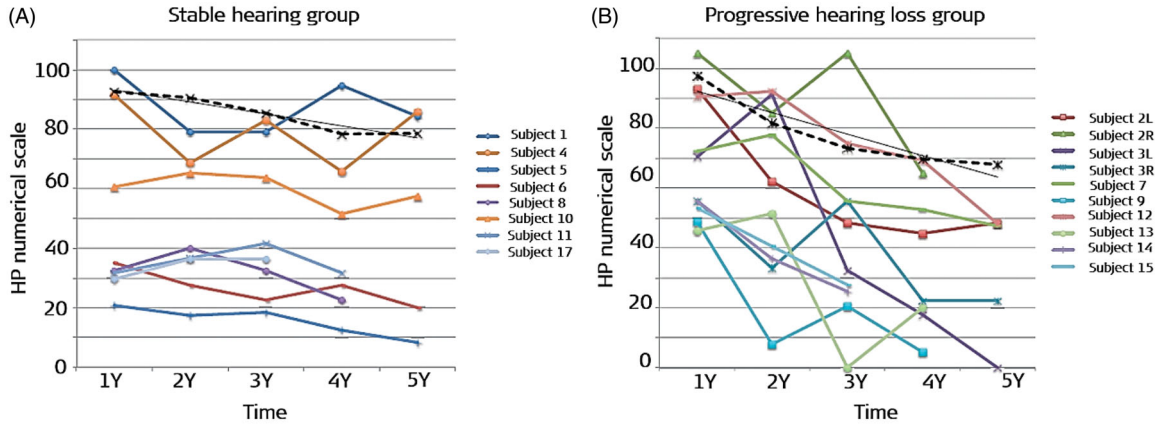


Figure 40. The linear regression coefficient for the decline in HP score of the stable hearing group, as categorised from the average linear regression coefficient of the decrease in hearing preservation score (A). The linear regression coefficient for the decline in HP score of the progressive HL group (B) [34]. The dotted line in black in both graphs, indicates the average for the contralateral ear. Reproduced by permission of Taylor and Francis Group.

the authors suggested that EAS™ can provide improvement in hearing ability over the long term even if the residual hearing is lost to some extent over time.

In 2016, another report on the long-term HP (up to twenty-four months) was published. Ninety-six EAS patients (one hundred and three ears) implanted with MED-EL EAS™ with FLEX24™ were included in the study in which the HP techniques were applied by Dr Helbig and her colleagues from the Johann Wolfgang Goethe University Hospital Frankfurt in Germany [35]. Forty-seven out of ninety-six patients had a history of progressive HL in the HF, and unknown aetiology was reported in twenty-four patients. The remaining patients had other aetiology, including sudden HL, viral infection, autoimmune disease and other. Immediate postoperative results showed that 25% of the patients had complete HP, and 60% partial HP. At twelve months after surgery, 27% had complete HP, and 55% maintained partial HP. At long-term follow-up (up to twenty-four months), the complete HP rate dropped to 12%, and partial HP was maintained in 53% of the patients. Regarding the complete loss of residual hearing, a slight inclination in the number of cases from the immediate post-operative stage (4%) to long-term (15%) was observed (Figure 41). The authors concluded that long-term residual LF HP is feasible in a subset of patients implanted with EAS™. From the residual hearing cohort, eighty-two out of ninety-five patients (85.3%) could utilise acoustic amplification post-operatively, fifty-eight out of sixty-six (87.9%) after twelve months, and thirty-eight out of forty (95.0%) in the long-term outcomes.

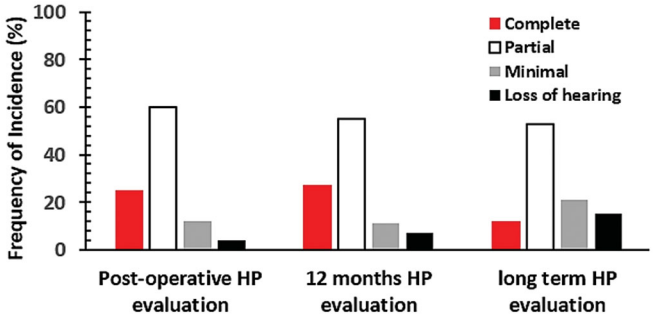


Figure 41. HP with regards to shifts of pure-tone averages in low frequencies (125-, 250- and 500-Hz). Results are shown for postoperative, 12 months, and long-term shifts (>24 months) from pre-operative measurement. Histogram created from data given in Helbig et al. [35].

In 2020, Prof. Sprinzl and his colleagues from the University Clinic St. Pölten in Austria studied the long-term HP results (>12 months) from eight patients (ten ears) implanted with MED-EL EAS™ and FLEX24™ at their centre [36] (Figure 42).

Prof. Georg M. Sprinzl

Priv. Doz. Dr Astrid Magele

Figure 42. Clinicians from University Clinic St. Pölten, Austria, who investigated the long-term HP in EAS™ CI users.

They reported that in the long-term, complete HP was achieved in 50% of the ears, partial HP in 40%, and minimal HP in 10% of the ears (Table 7). They further mentioned that none of the patients lost the residual hearing completely. They concluded that the combination of acoustic and electric stimulation *via* the EAS™ system is a safe, effective, and most importantly, stable treatment option for patients with normal-to-moderate HL in the LFs and severe-to-profound HL in the HFs.

All these pieces of scientific evidence show encouraging results, pointing to the direction of long-term HP possibility in the majority of the EAS patients implanted with a flexible electrode array. Inflammatory and immunocompetent reactions, as well as individual genetic background, are assumed to be the main influences of counteracting HP in some cases.

The University of North Carolina, USA is in the process of publishing (at the time of writing this chapter) their findings on long-term hearing preservation results from the patient population who were a part of MED-EL EAS FDA

Table 7. Eight patients (ten ears) with long-term follow-up data [36].

Long-term group	Electrode type/system	Benefit Freib. 65dB	Benefit Freib. 80dB	HP %	HP type
1 (R)	FLEX24™/EAS™	25	30	80.9	Complete
1 (L)	FLEX24™/EAS™	15	20	84.9	Complete
2 (L)	FLEX24™/EAS™	60	60	66.3	Partial
3 (L)	FLEX24™/EAS™	60	55	67.8	Partial
3 (R)	FLEX24™/EAS™	70	75	80.7	Complete
4 (L)	FLEX24™/EAS™	60	45	11.8	Minimal
5 (L)	FLEX24™/EAS™	30	20	46.2	Partial
6 (L)	FLEX24™/EAS™	65	40	88.6	Complete
7 (R)	FLEX24™/EAS™	50	45	77.3	Complete
8 (L)	FLEX24™/EAS™	45	75	41.0	Partial

clinical trial. FDA required a post-approval study following subjects from the original EAS clinical trial for at least five years post-implantation. Fifty subjects returned for follow-up in the post-approval study, with more than half of the subjects (68%) having six years or more of experience with their EAS device. At the long-term interval, all subjects continued to experience improvement over pre-operative speech perception scores on at least one measure. Of the 50 subjects in the long-term study, 43 maintained aidable low-frequency residual hearing (at least one threshold better than or equal to 80 dB between 125 and 1000 Hz). Further data analysis will be completed and published in the future.

2.15. Optimised fitting procedure in EAS patients

With the unified EAS™ audio processor that combines acoustic amplification and electric stimulation in one ear, there was a need to develop an optimised fitting strategy. Typically, the EAS candidates have much higher expectations of hearing performance after implantation in comparison to standard CI candidates. The EAS users usually reach the ceiling effect in speech test in quiet and expect greater improvements with the speech in noise test.

In 2002, Prof. Wilson (with his colleagues) from the Center for Auditory Prosthesis Research, Research Triangle Park in the US was the first person to find out that electric and acoustic overlap is beneficial [37].

In 2005, Prof. Kiefer and his colleagues from Johann Wolfgang Goethe University Hospital Frankfurt in Germany fitted thirteen EAS patients with CI processor and a HA on the implanted side and based on their findings they proposed that the acoustic amplification cut-off frequency be obtained from the unaided audiogram at 65 dB HL [38].

In 2008, Dr Vermeire and her colleagues from the Antwerp Medical University in Belgium fitted four EAS patients with CI processor and a HA on the implanted side and evaluated the HA amplification [39]. The authors reconfirmed that reduced electric and acoustic overlap is beneficial to reach better EAS benefit. However, questions remained on how much overlapping between electric stimulation and acoustic amplification in EAS patient is needed to reach the most optimised benefit and secondly, how with the combined audio processor, the acoustic and electric parameters interact.

In 2010, Dr Polak from MED-EL, together with clinicians from multiple centres, evaluated twenty-four EAS patients fitted with DUET™ audio processor that combined both acoustic amplification and electric stimulation [40]. The authors evaluated (i) when to fit electric and acoustic modality, (ii) important acoustic and electric parameters for DUET™, (iii) modified half gain rule by use of DUET™, (iv) optimal gain, (v) effect of cut-off frequency in EAS and electric-only mode, and (vi) they identified optimised benefit for EAS patients using the unified audio processor. DUET™ HA was fitted with half gain rule and compared with the individual gain adaptations. Electric stimulation was tested for full frequency range and minimum frequency obtained from unaided audiogram at 50-, 65- and 80-dB HL. Tested acoustic and electric parameters parameters included compression threshold (40–70dB), low cut slope (Th500-Th250)/2, 0, 18 dB/octave), compression threshold (1:1 – 1:2) and lower electric frequency (200 Hz from unaided audiogram – at 50, 65, and 80 dB HL) The experiments were performed at electric-only or EAS-only mode. For each test condition, patients were asked to switch their processor to the testing condition for either two hours or one day, depending on the test difficulty. The authors observed a difference in speech performance between both CI frequency ranges in Electric-only and EAS-only conditions. Therefore, it was proposed to fit both modalities (acoustic and electric) at the same time. Overall, the half gain rule was satisfactory; however, it was necessary to adjust the optimal gain for each patient. 81% of the patients reached the best score when the acoustic cut-off frequency was obtained at 65 dB HL from unaided audiogram. The cut-off frequency difference of 50 Hz from the optimised value influenced the outcomes. To reach optimised benefit, electric and acoustic overlap was needed. Selecting the correct cut-off frequency had the highest impact on the optimised benefit. For the tested group, single parameter changes from optimised value degraded the benefit by 32.3% in EAS mode. Other parameters influencing the EAS performance were low cut slope, compression threshold and compression rate. A single change in any of these parameters from the optimal value degraded the overall speech benefit from 20.5% (for low cut slope) to 23.0% (for compression). Figure 43 depicts optimised benefits of the tested groups. EAS improvement for monosyllable in quiet was 47%, while EAS benefit over electric-only mode varied from 10% to 15% depending on speech tests. Data showed a relatively small benefit for HA only condition. Immense synergistic benefits when adding CI to the acoustic hearing and when adding ipsilateral (implanted ear) HA to the CI was seen.

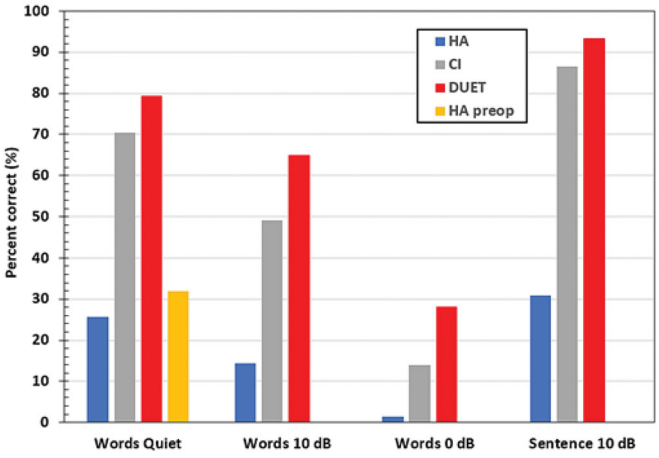


Figure 43. Speech results of all patients with the DUET™ fitting parameters [40]. CI = electric only; HA = acoustic only; DUET = EAS; (image courtesy of Dr Polak from MED-EL).

Together with the development of a surgical pre-planning tool for individualised electrode array selection, there was a need to develop an EAS fitting strategy with deep electrode array insertion. This was especially important with several clinics beginning to implant patients with better residual hearing and with long electrode arrays, such as with STANDARD, FLEX28™ or FLEXSOFT™ with full intracochlear insertion.

In 2016, at the XV Hearing and Structure Preservation Workshop, Oct 20–23, Paris, Dr Polak, Prof. Skarzynski and Prof. Lorens introduced the so-called Natural Based EAS fitting [41]. In patients utilising both, acoustic and electric modality, one of the important aspects is to find out how many electrodes are inserted in the region with the residual hearing, and in patients with the anatomical gap, to find out how many electrodes are missing to reach the identified acoustic region. Having such information, the electrodes residing in the acoustic region may be turned off, and the remaining electrodes may be fitted according to the frequency tonotopicity for electric stimulation. Acoustic amplification is performed for the low frequencies with the cut-off frequency obtained from the unaided audiogram, typically at 65 dB-HL. Another approach may propose to keep all electrodes residing in the acoustic region on and at the same time to keep the frequency tonotopicity for the remaining electrodes residing in the electric region. This notion is based on outcomes reported by Prof. Lorens and colleagues [42], showing no degradation in speech benefit if all electrodes are activated (including the electrodes in the acoustic region); the reason for this may be that the electric and acoustic stimulation provide a frequency match. If the electrodes residing in the acoustic region remain turned off, with ongoing hearing deterioration (i.e. from clinical observation at the Institute of Physiology and Pathology of Hearing in Warsaw, Poland, the natural drop of hearing in EAS users is 2–3dB per year), the electrode in the apical region may be turned on once the hearing in this region is not functional anymore. The advantage of such a fitting is that the electrodes responsible for the higher frequencies will not change their frequency allocation, so with possible acoustic hearing deterioration, no adjustments to any parameter changes are required.

Additionally, all EAS patients utilise their complete fine structure information. If patients can utilise only limited fine structure information *via* acoustic amplification, the remaining higher frequency fine structure information is supplied *via* fine structure channels (i.e. FS4 strategy, MED-EL). Therefore, the Natural Based EAS fitting may utilise both principles, the phase-locked temporal information for the low frequencies and the organised firing of groups of nerve fibres at higher frequencies.

This method of natural-based fitting was recently applied by Prof. Usami and his colleagues in EAS patients implanted with longer electrode arrays and found to be beneficial [43].

2.16. EAS in paediatric patients

Paediatric patients are a select group, as additional care needs to be taken during all phases of CI treatment. Children with partial deafness display different speech development and language acquisition patterns when compared to normal-hearing children or children with severe-to-profound sensorineural HL [44]. Not every CI surgeon is willing to perform the delicate surgery in children and especially in children with partial deafness, as any minor degree deviation from soft surgical techniques could compromise the LF residual hearing – which is crucial for speech and language development. This section will list the key surgeons who implanted EAS™ in paediatric patients and will also cover the consensus statement on the identification of paediatric EAS criteria.

In 2000, Prof. Kiefer and his colleagues performed the first surgery in a child who had a measurable residual hearing at 125-, 250-, 500- and 1,000-Hz. The patient was implanted with MED-EL CI for electric stimulation of the HF region starting at 1,000Hz, and acoustic amplification of LF below 1,000Hz was amplified with conventional HA. This was an important milestone in MED-EL's EAS journey.

In 2004, Prof. Skarzynski and his colleagues implanted the first PDCI paediatric patient in Poland by applying the HP techniques with MED-EL EAS™ CI device.

In 2012, the youngest child at the time to receive EAS™ with HP surgical technique was a thirteen months old infant, operated by Dr Kuthubutheen and Prof. Rajan from the University of Western Australia.

In 2018, Prof. Usami and his colleagues implanted an eleven months old infant – considered the youngest child to date at the time – with EAS™ and with HP technique.

In 2018, amongst the HEARRING members, a consensus was made for paediatric EAS patients, based on which criteria for identification of children with partial deafness was established – as in past experiences, the latter represented a challenge due to lack of verbal feedback in audiological assessment in children. Regarding the age-dependent language development, four groups of children were identified, and recommendation of an assessment tool based on age was proposed (Table 8).

Table 8. Recommended age-specific assessment tools. [44].

	0–3 years	3–6 years	1. years	>10 years
Electrophysiology	ABR, ASSR, or DPOAE	ABR, ASSR, or DPOAE	Yes	Yes
Behavioural audiometry	Yes, 2 tests with a minimum of 3 months' time difference	Yes, 2 tests with a minimum of 3 months' time difference	Yes	Yes
Speech pathology	Yes, 2 tests with a minimum of 3 months' time difference	Yes, 2 tests with a minimum of 3 months' time difference	Yes	Yes
Sound localization	Not possible	Yes, if possible	Yes	Yes
Hearing aid testing	Yes, up to 6 months	Yes, up to 6 months	Yes, up to 6 months	Yes, up to 6 months
Genetic testing	Investigational	investigational	investigational	investigational
Cortical evoked potentials	CAEP	CAEP		
Listening effort	Investigational	Investigational	Investigational	Investigational
Spectral modulation testing	Investigational	Investigational	Investigational	Investigational

ABR: auditory brainstem response; ASSR: steady-state auditory response; DPOAE: distortion product otoacoustic emissions; CAEP: cortical auditory evoked potential.

In summary, partial deafness in children is a hearing disability which needs to be identified early to avoid the risk of permanent speech and language deficits. The consensus included on strong recommendation that every child undergoing CI shall be implanted using the HP surgical technique, irrespective of the level of residual hearing.

2.17. Advancements in EAS

Like any other field, EAS has also been complemented with several advancements in terms of technological, surgical and audiological aspects in the last years, and this section will list the key published pieces of evidence in this regard.

2.17.1. Combination of cochlear duct length and Greenwood's frequency map

It is known since the 1930s from Dr Hardy's work that the cochlear duct length (CDL) varies among the human population, from a minimum of 25.26 mm to a maximum of 35.45 mm – facts established through histological assessment of cadaveric human cochleae [45]. The fundamental question of how the individual patient's CDL could be estimated from the preoperative radiographic images has been a great motivation for MED-EL to conduct extensive researches since 2010. The first research began with the collaboration between MED-EL engineers and Dr Alexiades, intending to establish mathematical equations which would estimate the CDL along the organ of Corti and the tonotopic insertion depths (Figure 44).

The reason for estimating the CDL along the organ of Corti is that the lateral wall electrodes, once placed inside the ST, would position precisely under the BM and therefore it is the most reasonable to establish the CDL along the organ of Corti. Moreover, Greenwood's frequency function may be further applied to estimate the patient-specific frequency map along the organ of Corti [46]. By combining the data from Dr Hardy [45] and Dr Escude [47], the resulting mathematical equations [48] would take a single cochlear measurement (the cochlear diameter, or so-called *A-value*) in the oblique coronal radiological plane as the only input from the preoperative computed tomography (CT) images, as given in Figure 45.

Dr George Alexiades
(Weill Cornell Medicine New York)

Dr Claude Jolly
(MED-EL)

Dr Anandhan Dhanasingh
(MED-EL)

Figure 44. ENT surgeon from New York, USA, and engineers from MED-EL established the mathematical function in the estimation of patient-specific CDL.

Combining CDL [48] and the Greenwood's function [46], as given in Figure 46, would present the picture to clinicians with cochlear insertion depth, including the identification of where the LF residual hearing starts – consequently helping in choosing the most suitable electrode array length. This opened a new door towards the even more individualised approach with taking into consideration each individual and unique cochlear anatomy, providing anatomy-based CI treatment to each patient [49]. This was a concept MED-EL proposed in the year 2011 and developed the research-based CDL software in 2014 (link to download).

In 2018, MED-EL joined hands for a specific project with CAScination AG, a Swiss company which developed a tablet-based otological planning software OTOPLAN® (www.otoplan.ch). With dedicated cooperation in this domain, the tool incorporated much of MED-EL's research efforts as shown in Figures 45 and 46, and further fine-tuned it to develop an even more sophisticated tool which utilises the cochlear parameters as an input to estimate the CDL, along with the corresponding frequency mapping and the visualisation of MED-EL's

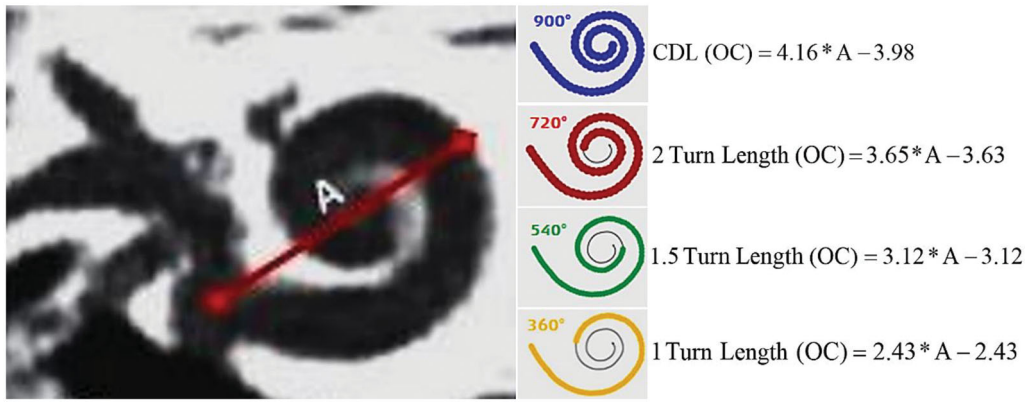


Figure 45. Mathematical equations to estimate the CDL along the organ of Corti (Image courtesy of MED-EL).

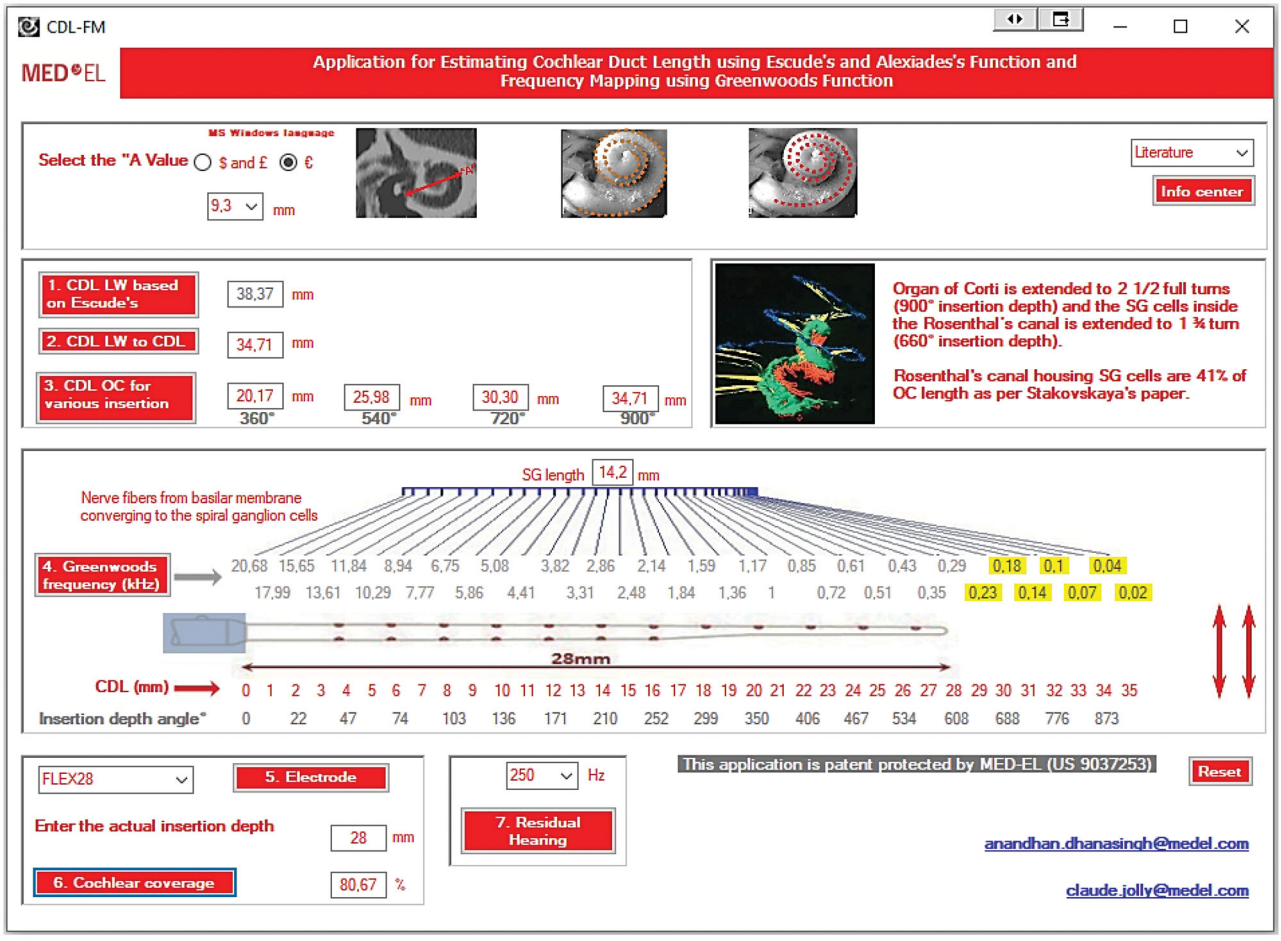


Figure 46. Applying the CDL value in Greenwood's frequency function would result in patient-individual frequency map. From this map, the starting point of LF residual hearing is possible to identify (image courtesy of MED-EL) [49].

electrode portfolio, tailored for specific patient anatomies. It also allows 3 D segmentation of delicate anatomical structures of the temporal bone, as well as it can precisely calculate safe trajectory, for either conventional or robotic surgery with its minimally invasive surgical system, HEARO®. Dr Zoka Assadi from MED-EL was highly instrumental logistically in the joint development of OTOPLAN® software.

To summarise, combining cochlear parameters measured from the preoperative radiological imaging with Greenwood's frequency function, it is possible to establish the exact location of the functional acoustic region towards the lower frequencies in a partially deaf cochlea. This also helps to choose the optimal electrode array length and to foresee different varieties in finding the tonotopic frequency match, as shown in Figure 47.

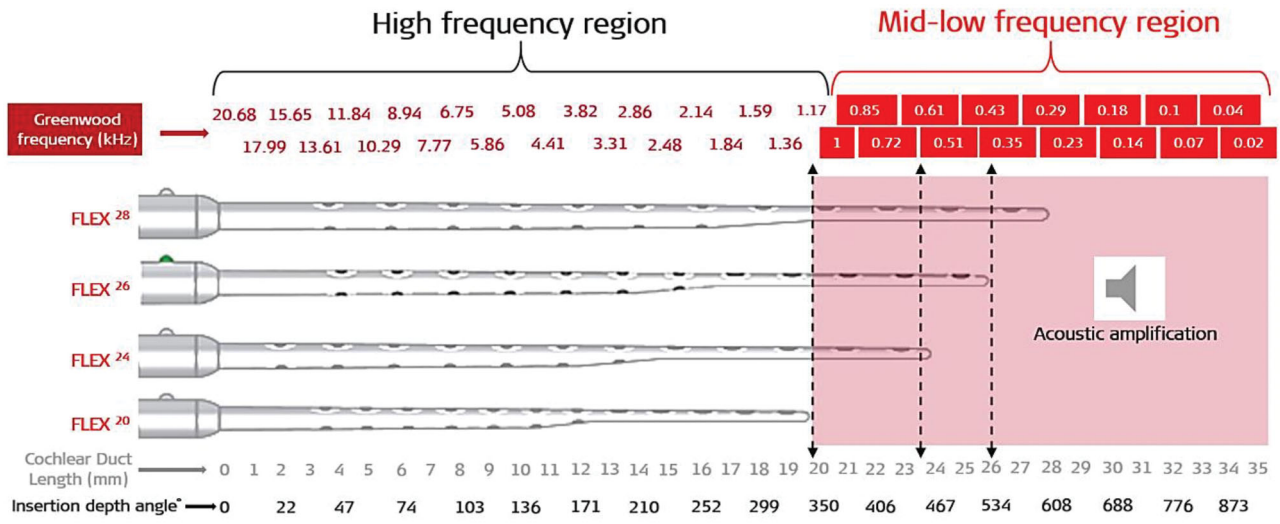


Figure 47. Illustration of Greenwood's frequency map for an average CDL of 35 mm with an assumption of low frequency functional residual hearing, starting at 1,000Hz. Visualisation of different electrode array lengths shows how many channels would be in the acoustic amplification zone (image courtesy of MED-EL).

2.17.2. Long electrode arrays in classic EAS candidates

It has become a trend to use short electrode arrays in EAS patients to preserve the LF residual hearing. The latter was reflected in literature until 2010, describing electrode insertion depth to up to 18–22mm as a standard in clinical practice amongst clinicians globally. An important question that accompanied the EAS topic was residual HL over time or during surgery, and more precisely, would a short electrode array suffice in providing full electric coverage in such situations. Clinicians believed that implanting a longer electrode array, which physically reaches well beyond the basal turn of the cochlea and still effectively preserves the LF residual hearing, would be the most desirable option. If the LF residual hearing deteriorates over time, a long electrode array will substitute it with electric coverage – with an eventual extension over the entire frequency range. Studies have shown that if EAS patients lose residual hearing over time and if they had symmetric hearing preoperatively, then the synergistic EAS effect is still preserved, i.e. if the contralateral ear retains residual hearing. In such a case, the healthy ear would still offer support to the implanted ear, despite its residual HL [12,24].

In 2010, Prof. Staecker and his colleagues from University of Kansas in the US moved forward with implanting a long electrode array in eighteen patients with measurable LF residual hearing – but not EAS candidates – and evaluated the effect of CI electrode array insertion depth on HP [50]. A total of eighteen patients were implanted with the soft surgical technique with either MEDIUM (24 mm electrode array length) or STANDARD (31.5 mm electrode array length). Electrode arrays reached intracochlear insertion depth in the range of 20–28mm with a near-complete cochlear frequency coverage. The LF residual hearing was well preserved, as shown in Figure 48(A), and the PTAs were calculated for the frequencies 250-, 500-, and 750-Hz, and plotted against the electrode

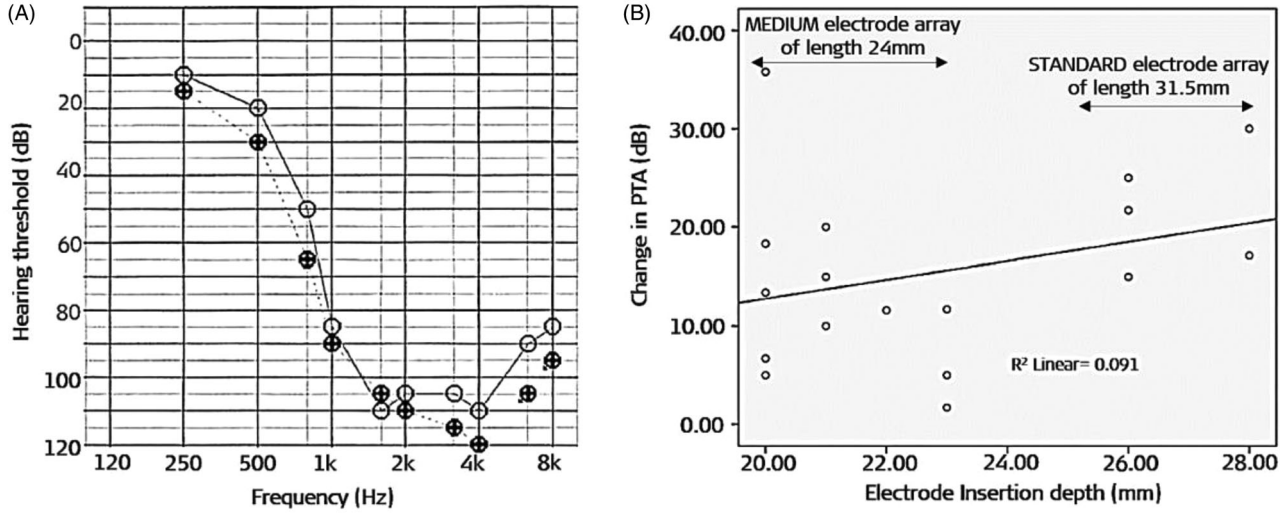


Figure 48. Example audiogram of pre-op (open-circle) and post-op (crossed circle) with the MEDIUM performed with a MED-EL STANDARD electrode array. The HP remained stable over eighteen months (A). Effect of electrode insertion depth on postoperative change in hearing (B). Using the RW approach, there was no clear relationship between implant insertion depth and post-operative PTA [50]. Reproduced by permission of Journal of American Academy of Audiology.

insertion depth. The graph in Figure 48(B) demonstrates no clear relationship between the electrode insertion depth and the amount of residual hearing preserved, indicating that the apical region of the cochlea may be reached without compromising hearing thresholds (r^2=.091). This was one of the early studies that demonstrated the possibility of implanting long electrode arrays in patients with functional LF residual hearing.

In 2011, Prof. Skarzynski and his colleagues reported on the possibility of LF hearing preservation with the deep insertion of MED-EL's electrodes (STANDARD and FLEXSOFT^{TM}), using the RW surgical approach [51]. The study included forty-two patients (implanted until the year 2008) with 85 dB HL or better at 500 Hz, and 80 dB or better at 125 Hz and 250 Hz. Pure tone audiograms were taken at different time points, including preoperatively and postoperatively at three, six and thirteen months. Three patients lost their residual hearing immediately after the surgery, and additional three patients lost their hearing progressively between three and thirteen months postoperatively. Figure 49 shows the mean audiograms for the implanted ear with significant differences between preoperative and postoperative thresholds for all measured audiometric thresholds.

In 2019, Prof. Lenarz reported on a new concept of partial insertion of a longer length flexible electrode with the aim of preserving LF residual hearing in potential EAS patients [54]. This was a conservative approach of minimizing the loss of residual hearing following EAS treatment. Six EAS patients were implanted with a partially inserted (FLEX^{24}, FLEX^{28}) electrode from MED-EL, with basal most two contacts left outside the cochlea. Median preoperative and postoperative air-conduction thresholds at six-month post-activation are shown in Figure 50. All patients had preserved functional residual hearing defined HL $\leq$ 80 dB HL at 250 Hz at first activation and 6 months post first activation. In no case a complete hearing loss (>30 dB) occurred.

Part of the partial electrode insertion concept is that there is no need for the overall implant replacement when the residual hearing losses over time, instead with a minor revision surgery, the partially inserted electrode array can be further pushed inside the cochlea. The justification for the partial electrode insertion is the high probability of hearing preservation, however the patients need to be informed about the possible revision surgery later.

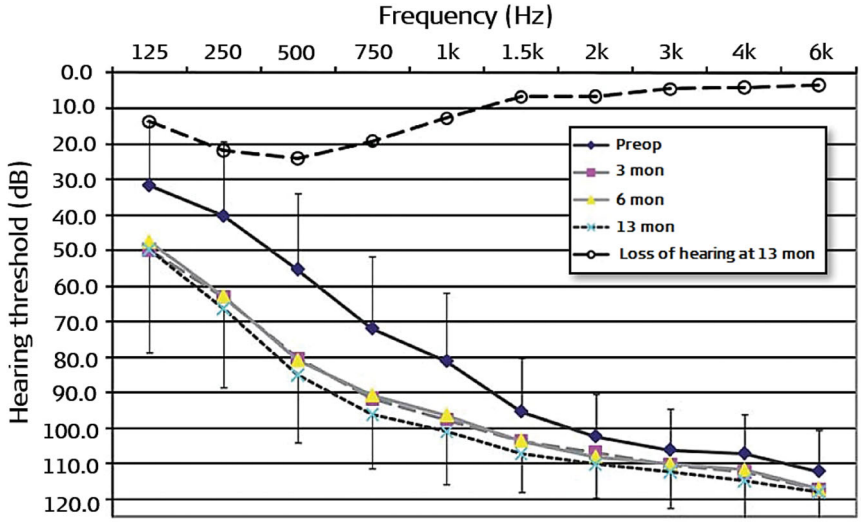


Figure 49. Mean audiograms of the implanted ear at four testing time points (pre-op and post-op at 3, 6, and 13 months). Error bars depict standard deviations [51]. Statistical test: ANOVA two-factor-without-replication test was used for comparison of hearing thresholds at various time points ($p < .05$). Reproduced by permission of Taylor and Francis Group.

In 2013, a similar report came from Dr Mick and his colleagues from Sunnybrook Health Sciences Centre at the University of Toronto in Canada, with which they proved a high degree of residual hearing preservation at two years postoperatively in patients with the history of progressive HL, implanted with FLEXSOFT^{TM} [52].

In 2014, another encouraging report was published, demonstrating the preservation of residual hearing in the LF in profoundly deaf patients who were implanted with FLEXSOFT^{TM} [53]. In the study conducted by Prof. Green and his colleagues from the University of Manchester in the UK, thirteen out of fourteen patients preserved their residual hearing in an average follow-up period of two years.

In 2020, Prof. Usami and his colleagues reported on their experiences with implanting FLEX28^{TM} in ten EAS-indicated patients [43]. The confidence for implanting FLEX28^{TM} in EAS-indicated patients came from their earlier experience that showed the possibility of HP with FLEXSOFT^{TM} and FLEX28^{TM} in non-EAS-indicated – but with measurable LF residual hearing – patients [55]. Figure 51 shows preoperative and six months postoperative audiogram with very minimal threshold shifts, as illustrated by the red dotted arrow marks. The argument for the longer length flexible electrode by the authors is that even if the residual hearing deteriorates over time, the electric stimulation covering the entire frequency range would continue offer good hearing benefit to the

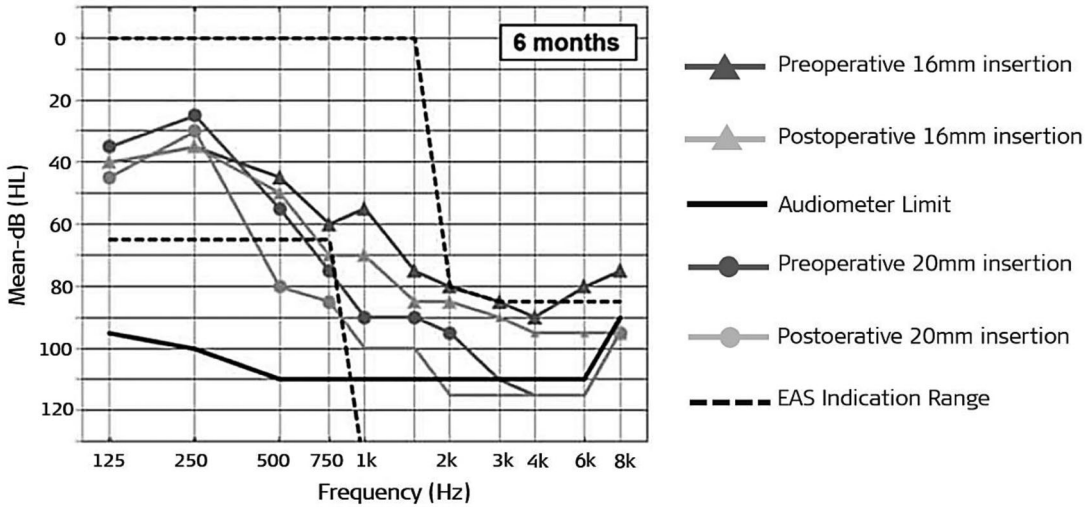


Figure 50. Air-conducted hearing thresholds at 6 months postactivation for 16 mm insertion ($n = 3$) and 20 mm insertion ($n = 3$) [54]. Reproduced by permission of Wolters Kluwer Health, Inc.

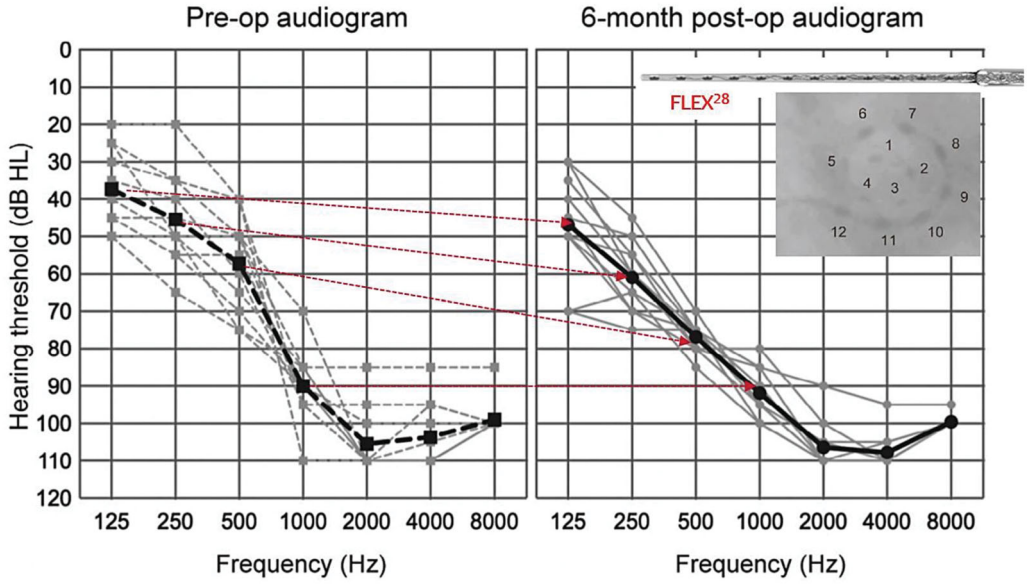


Figure 51. Average air-conduction hearing thresholds. The dashed and solid lines indicate pre-op and six months post-op, respectively. Grey and black lines show the individual and mean results [43]. Reproduced by permission of Taylor and Francis Group.

patients. They further recommended genetic testing in every patient to find out if there will be any deterioration of LF residual hearing over time.

All presented studies in this section show that the RW approach enables the reduction of electrode insertion trauma (EIT), thereby preserving the LF hearing, even with long electrode array insertion. An inherent factor with implanting long electrode arrays is that if the LF hearing is lost over time, then the electric coverage of most, if not all, of the frequencies is possible, helping patients in optimising their hearing potential. Patients with a good preoperative hearing level in the LF retain residual hearing postoperatively, even with long electrode arrays.

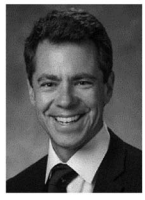
The hearing preservation rates with various length electrode arrays varies from clinic to clinic as it is evident from these published reports and it essential to have a detailed preoperative counselling with the candidates explaining them the probabilities of hearing preservation and outcomes with different lengths of electrode arrays and treatment concepts.

2.17.3. Electrocochleography in the monitoring of inner ear functions during and after surgery

Preservation of residual hearing is successful in many but not all cases. Online monitoring of hearing during CI

surgery is one way of ensuring the presence of residual hearing during and at the end of the surgery. Intracochlear recording of electric potentials from sensory cells in response to acoustic stimulation during CI electrode array insertion is also known as intracochlear electrocochleography (ECochG) [56]. ECochG recorded signals have several components, including compound action potential (CAP), summation potential, cochlear microphonics (CM), and auditory neurophonics (ANN). CMs are regarded to reflect the status of hair cells, indirectly measuring cochlear health. In case of a deterioration of CMs during the intraoperative ECochG measurement, the operating surgeon could immediately adapt the insertion, thus improving the preservation of residual hearing. Caution needs to be taken as the ECochG does not necessarily reflect the actual hearing of the patient as the pure-tone audiometry does. MED-EL recently came up with a concept of online biofeedback developed by Dr Polak (US patent numbers: 8862220 and 8170678).

In 2014/15, Prof. Adunka and his colleagues from the University of North Carolina in the US conducted several studies in human and non-human subjects to characterise the ECochG signals and to detect cochlear trauma during electrode insertion. A non-human subject proved that with normal hearing within its species, the CMs were more sensitive than the CAPs when detecting a cochlear trauma induced by electrode insertion [57]. The in-human study using external ECochG measurement system showed that it is possible to measure it extracochlearly at the RW membrane, and intracochlearly by placing a temporary, flexible electrode array inside the cochlea intraoperatively in patients with good functional/measurable LF residual hearing [58]. Figure 52 shows a sample response measurement recorded extracochlearly at the RW membrane, and intracochlearly.



Prof. Oliver Adunka

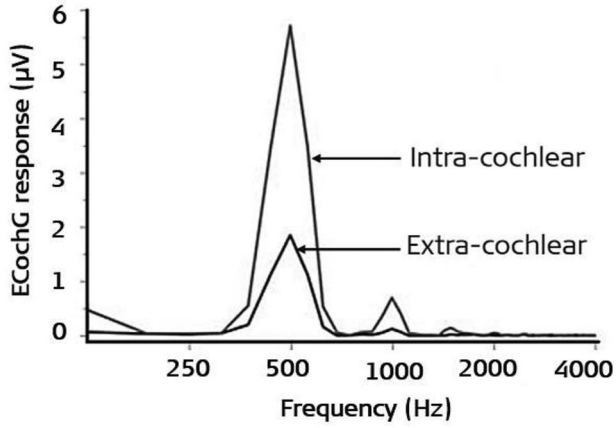
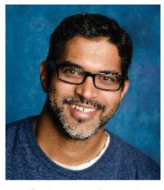


Figure 52. Prof. Oliver Adunka, who led the study in characterizing ECoghG signals. Example comparison of extracochlear (at the RW membrane) and intracochlear (just over the RW membrane) ECochG recordings [57]. Reproduced by permission of Wolters Kluwer Health, Inc.

system which measures the ECochG involving minimal manual steps by the surgeon during the CI electrode array insertion.

In 2012, under a research software platform from MED-EL, a novel concept of Electric and Acoustic Evoked Potential (EAEP) was introduced, allowing for acoustic-only and synchronous acoustic and electric stimulation. EAEP tool includes ECochG recordings. The recording methodology to determine the status of cochlear health was

In 2016, Prof. Rajan and his colleagues from the University of Western Australia were the first to measure the CM during cochlear implantation procedure using a MED-EL implant electrode array [59]. During the intraoperative monitoring, a prototype software algorithm was used to communicate with the standard implant interface and the CI *via* an external coil. The acoustic stimulus used was a 500 Hz tone pip, and the most apical electrode channel obtained the recordings in a millisecond time window. Figure 53 shows the results of CM



Prof. Gunesh Rajan

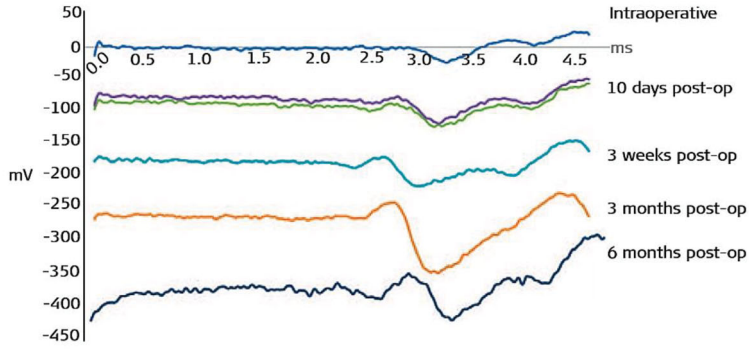


Figure 53. Prof. Gunesh Rajan was the first one to measure CM during CI procedure. Post-op CM measurements (from the top) at intra-op, and ten days, three weeks, three months, and six months post-op [59]. Reproduced by permission of Wolters Kluwer Health, Inc.

measurement from a patient who was implanted with FLEX24™ (full intracochlear electrode insertion) – the results are given intraoperatively, and ten days, three weeks, three months and six months postoperatively. Due to no intracochlear structural damage, postoperative responses are similar to the intraoperative, indicating preservation of hair cells function.

In 2019, Prof. Lorens and his colleagues from the Institute of Physiology and Pathology of Hearing in Poland recorded the CM directly from the CI in CI recipients with measurable residual hearing [56]. This was achieved in sixteen CI recipients implanted with MED-EL devices with different electrode arrays (FLEX20™, FLEX24™, MEDIUM, FLEX28™, FLEXSOFT™ or STANDARD). For the acoustic stimuli, either tone pips at frequencies 0.25-, 0.5-, 1-, 2- and 4-kHz, or 1 ms clicks were used. The duration of the tone pips was chosen to be sufficiently long to identify the CM in the response. A prototype software algorithm (Research Evoked Potentials Software from MED-EL) allowed the recording window to be increased to up to 20 ms and to communicate with the standard implant interface and the CI *via* an external coil. Figure 54 is an example CM measured from the first, third and fifth electrode channels in response to tone pips of 500 Hz acoustic stimulus. This study aimed to find the most sensitive stimuli to which ECochG can be recorded during intraoperative and postoperative monitoring. In the HP patients, the most sensitive stimuli were 500 Hz and 1 kHz tone pips and 1 ms click.

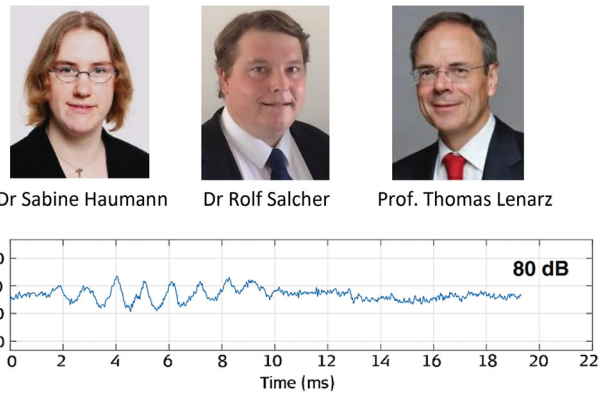


Figure 55. Clinicians from Hannover Medical School. Example of an intraoperative ECochG recording just after the electrode insertion process. Data is shown for 1,000Hz tone burst [59]. Image courtesy of Dr Sabine Haumann, Hannover, Germany.

However, the current status of ECochG research is at its early stages before it moves toward potentially becoming a part of a clinical routine with the EAS™ surgery, HP surgery, or both. EAEP offers the possibility to stimulate the cochlea electrically with the CI electrode array and with acoustic amplification with a short delay between the two stimuli. EAEP opens the door to several research possibilities, for example, to how the cochlea responds to electric stimulation if the acoustic amplification is masked and vice versa.

Prof. Artur Lorens

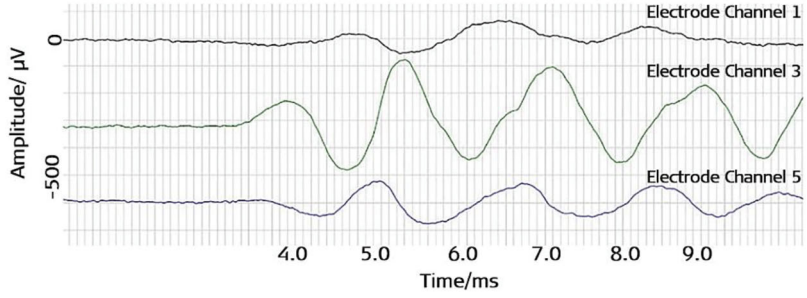


Figure 54. Prof. Artur Lorens led the study in measuring CM directly from the CI during CI surgery. Example of intracochlear ECochG recordings for tone pips and clicks from electrode channels 1, 3, and 5 [56].

In 2019, Prof. Lenarz and his colleagues from Hannover Medical School in Germany measured ECochGs using MED-EL's research software in combination with FLEX24™ and FLEX28™ electrode arrays, implanted in ten patients with identifiable residual hearing [60]. The ECochG recordings were performed both extracochlearly and intracochlearly with the acoustic stimulus of tone bursts at 250-, 500-, and 1,000-Hz. Figure 55 shows an example recording of ECochGs measured intracochlearly with a CI electrode array inserted 20–22mm with an acoustic stimulus of 1,000Hz at a loudness of 70 dB and 80 dB. The amplitudes of intracochlear ECochG were detected higher than the extracochlear.

All pieces of evidence seen in this section show encouraging results of the possibility of monitoring the cochlear health during and after CI electrode insertion.

In 2017, the EAEP tool was added to the MED-EL's fitting software MAESTRO and was CE-marked for official use in clinical practice.

2.17.4. Genetic screening in predicting hearing loss

Half of the congenital HL is genetic with more than four hundred known syndromes with HL as a feature and more than one hundred known genes that have HL as the only clinical manifestation. Most cases of congenital HL are identified soon after birth *via* newborn hearing screening (NBHS). However, many HL cases only become apparent later in life due to the expression of late-onset HL mutations or following an environmental insult, like antibiotic use or head trauma, in the genetically predisposed patient. A genetic screening panel that incorporates a population's

common HL genes could hence represent an effective adjunct test to newborn screening, improving time of diagnosis and treatment [61].

In 2020, Dr Yoshimura, Prof. Usami and their colleagues carried out genetic testing that has the potential to impact HP, following CI [19]. Forty-four patients (forty-one families) with age at implantation above six and with measurable residual hearing in the LF with a threshold less than 80 dB HL were implanted with FLEX24^{TM}, FLEX28^{TM} or FLEXSOFT^{TM}. To define the extent of hearing deterioration following CI, they measured auditory thresholds before surgery and six months after initial activation using the HEARRING HP scale. The aim of the study was to investigate the predictive factors, including the aetiology of HL as a patient-related factor, influencing residual HP after CI. Genetic testing was performed to identify the responsible genes for HL. They identified the cause of HL in twenty-one families, and nineteen patients out of those received a genetic diagnosis, with the CDH23 gene most frequently implicated, followed by ACTG1, mit1555A > G, MYO7A, MYO15A, SLC26A4, and TMPRSSS3. Additionally, two patients were diagnosed with otosclerosis and congenital diaphragmatic hernia (Figure 56(A)).

Prof. Pu Dai

(PLA General Hospital, Beijing)

Prof. De-Min Han

(Tongren Hospital, Beijing)

Figure 57. Clinicians from two biggest Hospital in Beijing, China, who undertook the concurrent hearing and genetic screening of 180,469 neonates with follow-up.

microarray platform to identify nine variants in four genes, GJB2, SLC26A4, mtDNA 12SrRNA, and GJB3. The important finding from this mega-study is that infants with pathogenic combinations of GJB2 variants and SLC26A4 variants may pass newborn hearing screening, and most of them will develop hearing loss at an early age (<5 years old).

These two recent studies show that newborn genetic screening clearly shortens time to diagnosis and intervention, reveals the aetiology of genetic deafness and ensures timely habilitation of infants and young children. Also, the genetic screening predicts the possibility of preserving residual hearing in patients with LF hearing following CI procedure.

Dr Hidekane Yoshimura

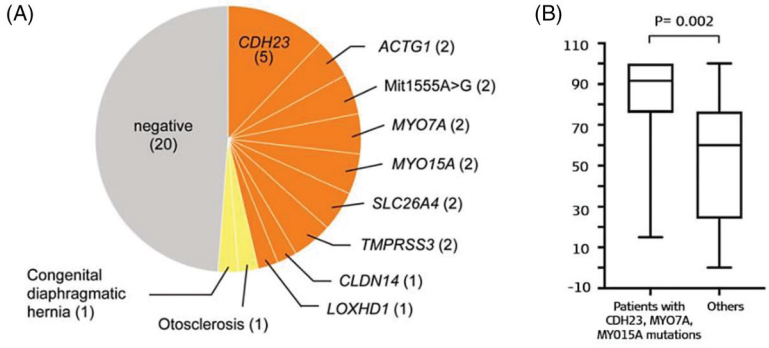


Figure 56. Aetiology of patients with residual acoustic hearing. (A) ($n = 41$): orange indicates genetic causes of HL; yellow indicates other causes; grey indicates unknown. (B): comparison of HP scores in each group [19]. Reproduced by permission of Taylor and Francis Group.

Out of all the abovementioned genes, they found that patients who had pathogenic variants in the CDH23, MYO7A, or MYO15A gene showed statistically better HP scores compared with patients with HL due to other causes (Figure 56(B)). Between these two groups, the age was comparable (33.5 vs 37.4 years). In summary, these results reveal that genetic testing facilitates not only the diagnosis of patients with HL but also the prediction of HP after CI.

In the same year, a report on concurrent hearing and genetic screening of neonates by Prof. Dai, Prof. Han and their colleagues from the two biggest hospitals in Beijing, China was published, showing the importance of genetic screening in the early identification of late development of hearing loss in children [62] (Figure 57).

The study included 180,469 infants born in Beijing between April 2013 and March 2014 with the last follow-up on February 24, 2018. Hearing screening was performed using Transiently evoked otoacoustic emission (TEOAE) and dried blood spots were collected for genetic screening using DNA

2.17.5. Electro-natural stimulation (ENS)

The EAS topic has come a long way since its introduction in the year 1997. It started with implanting patients with LF residual hearing from ~500Hz, which was then expanded to 1,500Hz with the advancements in the flexible electrode array design and soft surgical skills. Combination of acoustic amplification of LF region and electric stimulation in the HF region has shown to be highly beneficial for the patients. However, some patients who have natural or near-natural LF residual hearing with HL only in the HF region may not fall under the eligibility criteria for CI. These patients may become the candidates for CI in the future with the developing advancements in the EAS topic.

In 2019, Prof. Skarzynski and his colleagues published their findings on the long-term HP results in a select group of patients ($n = 12$) who had a natural hearing in the LF until 1,500Hz [63] (Figure 58).


Prof. Henryk Skarzynski Prof. Artur Lorens Prof. Piotr Skarzynski

Figure 58. Clinicians from the Institute of Physiology and Pathology of Hearing, Warsaw who introduced the Electro-Natural Stimulation in partial deafness treatment of adults CI users.

Nine out of twelve patients were implanted – with soft surgical HP technique – with MED-EL CI device in combination with MEDIUM or FLEX24^{TM} electrode array, partially inserted to reach an intracochlear depth of 20- and 21-mm. Figure 59 displays the average preoperative and postoperative air conduction hearing thresholds. The HP rate evaluated one month after the CI surgery indicated that seven out of nine patients maintained complete HP. In the long-term follow-up (thirty-six months), five out of nine patients still maintained complete HP, whereas the remaining four had partial HP. None of the patients experienced minimal HP or complete loss of hearing. The aetiology of all nine patients was unknown. Prof. Skarzynski is well known in the CI field for his outstanding soft surgical skills, and the excellent HP results reported in the study could be due to his surgical expertise – while the same outcomes may not be obtained for sure if the same surgeries would be performed with a less experienced surgeon. In conclusion, the authors reported that soft surgical technique could lead to excellent HP in patients who have normal hearing to up to 1,500Hz and HF HL.

2.17.6. Electrode selection based on pre-operative residual hearing level

There is some research work underway looking at the pre-operative level of residual hearing in predicting the likelihood of the patient to use the acoustic component of the EAS system post-operatively. Prof. Lenarz and his colleagues from Hannover Medical School in Germany are currently (in the year 2020) investigating the effect of pre-operative residual hearing level and predicting the likelihood of the patient using the acoustic component post-operatively and selecting the electrode array length accordingly.

2.18. Distinct HP surgical techniques

Soft surgical technique was originally proposed by Lehnhardt et al. [64], is one of the critical factors which affect the HP results. The proposed methods remain in clinical practice to this day with little change. This section lists some of the key surgical approaches in order to achieve optimal HP results [65]:

- route of electrode insertion through RW membrane opening whenever possible
- mild hypothermia
- avoidance of drilling directly over the cochlear promontory to prevent vibration-related trauma
- avoidance of blood entry into the scala tympani to minimise fibrosis formation
- avoidance of bone dust in the cochlea to prevent new bone formation
- application of steroid at the cochlear entrance and inside the cochlea to minimise foreign body inflammation and to heal intracochlear trauma (if any)
- avoidance of perilymph leakage and suctioning to prevent an abrupt change in cochlear pressure
- slow electrode insertion at a speed of 15mm of the electrode array length per minute to enable full electrode insertion, to minimise electrode insertion-related trauma, and cochlear pressure change [66]
- avoidance of filling the middle ear space with fascia to prevent impeding the ossicular chain movement.

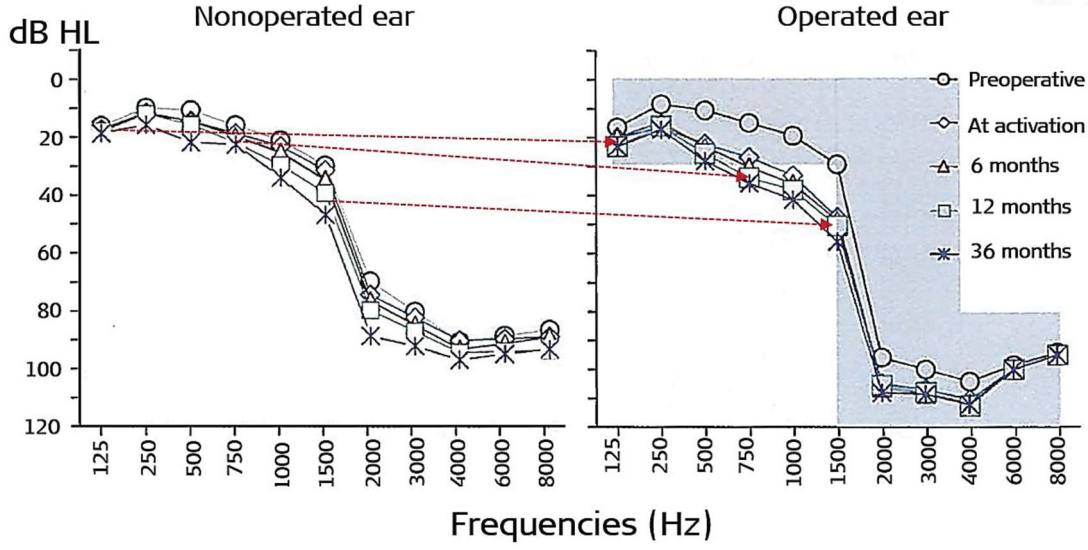


Figure 59. Average pre-op and post-op air conduction hearing thresholds for operated and non-operated ear [62]. Reproduced by permission of Karger AG, Basel.

2.19. Current (the year 2021) indication for EAS and its audiogram

The following conditions are considered safe for treatment with MED-EL EAS™ hearing system:

- no age restrictions
- air-bone gap ≤10dB for two or more frequencies (0.5-, 1-, 2- and 4-kHz) in each ear
- pre-operative CNC monosyllables score ≤60% in the best-aided condition
- radiologic evidence of bilateral patent cochleae
- no rapid hearing loss
- fulfilling the audiogram criteria as shown in Figure 1(B)

2.20. Reimbursement from the healthcare system

All the pieces of scientific evidence presented in this chapter have shown that MED-EL EAS™ hearing system is safe and effective in restoring both, HF and LF hearing in partially deaf patients. Also, it has been approved by the notified bodies from the EU, the USA, Japan, Canada and Australia for clinical use in patients, making it eligible for reimbursement of the treatment costs from the healthcare system.

2.21. Hearing and structure preservation workshop

The Hearing and Structure Preservation's (HSP) workshop came into existence with the initiative by the group of

Figure 60. Clinicians from around the world who have hosted the HSP meeting between 2002–19. [1]Indiana University, USA; [2]Johann Wolfgang Goethe University Hospital Frankfurt, Germany; [3]UT Southwestern Medical Center, USA; [4]Institute of Physiology and Pathology of Hearing, Poland; [5]University of North Carolina, USA; [6]Antwerp Medical University, Belgium; [7]Kansas University Medical Center, USA; [8]Medical University of Vienna, Austria; [9]University of Miami Ear Institute, USA; [10]St. Thomas Hospital, UK; [11]Sunnybrook Health Sciences Centre, Canada; [12]Heidelberg Medical University, Germany; [13]Shinshu University, Japan; [14]Vanderbilt University, USA; [15]University Hospital of North Paris, France; [16]University of Western Australia, Australia; [17]Uppsala University, Sweden; [18]New York Eye and Ear Infirmary, USA.

expert CI surgeons in hearing preservation (HP) and is supported logistically by MED-EL. Its primary focus/aim is on advancing the CI field in general, HP and EAS in particular, strengthening the scientific evidence base, and generating a platform for exchange between research groups. It was originally started as HP workshop in the year 2002 hosted by Prof. Miyamoto from Indiana University, USA, which changed to HSP in the year 2013. Figure 60 shows all the HSP meetings that took place so far (until the year 2019) along with the clinicians who have hosted it.

Although MED-EL has been supporting the logistical side of the workshops so far, it is the host clinician who is fully responsible for the scientific side of the workshop. It has been the tradition that the clinicians present their latest research findings related to HSP topic in this workshop before submitting it to any scientific journals for publication, making the workshop highly interesting for the participants. Internally at MED-EL, it is Dr Polak, the Head of Electrophysiology for Assessment, Research and Development, who is responsible for the whole scientific program and Dr Garnham for the life science part of the EAS and HP program (Figure 61).

Dr Marek Polak
Head of Electrophysiology for Assessment- R&D

Dr Carolyn Garnham
Director of Life Science Research- R&D

Figure 61. Experts from MED-EL, who are responsible for the HSP workshop, logistically supported by MED-EL.

2.22. Conclusion

The indication criteria for CI have expanded over the years from severe to profound HL over the entire frequency range to patients with near-normal hearing in the LF region. Thanks to the advancements in the CI electrode array design, soft surgical techniques, fitting techniques, as well as the audio processor advancements, combining the acoustic unit of HA to the CI became a treatment option for partially deaf patients with the EAS™ hearing system. Most importantly, the cochlear condition with its unique anatomy should be addressed in detail and individual manner from infants to geriatric patients. Preserving the LF residual hearing in the CI ear gives the possibility to use the natural ITD and ILD cues to enjoy the benefits of binaural hearing if the contralateral ear has a natural hearing or if it is aided with the HA for acoustic amplification of the LF hearing. With all these clinical evidences showing the added benefit of EAS in comparison to electric stimulation only, or acoustic stimulation only modes, the combined EAS should become the standard treatment option for patients who do not benefit enough with the HA alone. Good understanding of partially deaf patients' hearing history before surgery may help the surgeons to choose the optimal electrode array length. If the hearing history shows progressive HL, then choosing a long electrode array length with flexible feature would ensure electric stimulation over the entire frequency range. Genetic testing to understand the chances of progressive HL and the intraoperative ECochG method to monitor the electrode insertion related trauma are both considered to be the future trends in combined EAS treatment. Corticosteroid treatment of the inner ear is another key topic that supports the HP by suppressing the inflammation reaction caused by the introduction of a foreign body, which is the electrode array insertion trauma. This is addressed in detail in chapter 6 of this compendium.

Looking back, it is evident that a strong international scientific collaboration between clinicians and engineers from MED-EL made it possible to master every aspect in the advancements of the technological, surgical and fitting sides of the EAS™ system. Results of the several laboratory experiments and clinical trials helped MED-EL to develop the EAS™ hearing system and to make it commercially available as a product to treat partially deaf patients. EAS™ is yet another example of the translational science path MED-EL took to bring a unique concept from laboratory settings to patients.

Acknowledgments

The authors would gratefully like to acknowledge the key contributors to the development of the subject matter. Their contributions are outlined in this article. The authors further acknowledge Marek Polak from MED-EL for his valuable input and comments during several rounds of review meetings that contributed to the final version of this article.

Disclosure statement

This article is sponsored by MED-EL and has not undergone the regular peer-review process of Acta Oto-Laryngologica. Both the authors are affiliated with MED-EL.

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ACTA OTO-LARYNGOLOGICA
2021, VOL. 141, NO. S1, S63–S81
https://doi.org/10.1080/00016489.2021.1888486

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REVIEW ARTICLE

ABI-auditory brainstem implant

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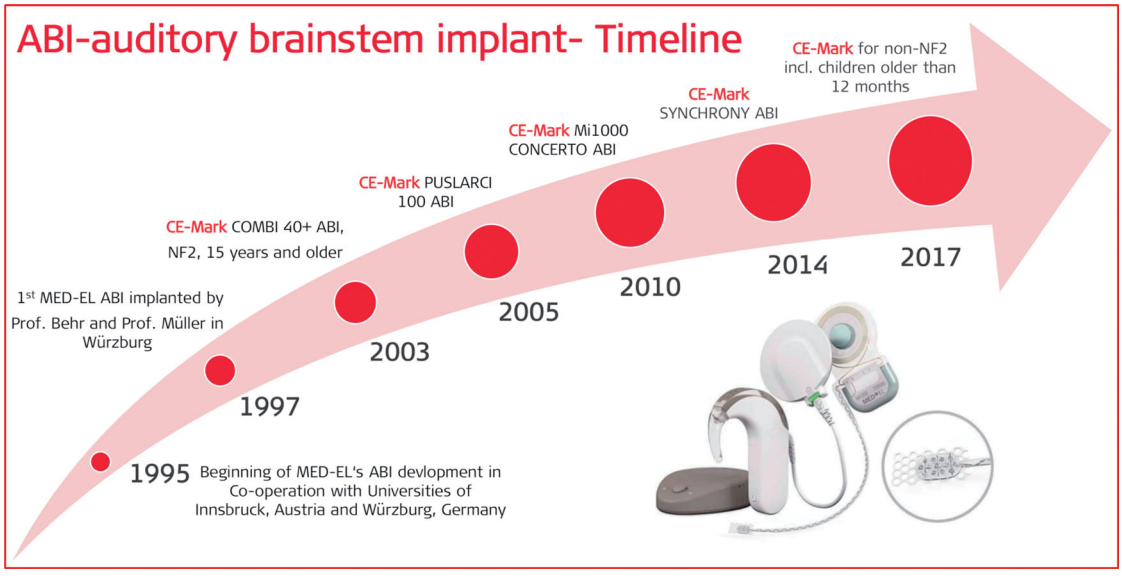
ABSTRACT

The Auditory Brainstem Implant (ABI) is based on the classic cochlear implant (CI) but uses a different stimulation electrode. At MED-EL, the early development activities on ABI started in the year 1994, with the suggestion coming from J. Helms and J. Müller from Würzburg, Germany in collaboration with the Univ. of Innsbruck Austria. The first ABI surgery in a neuro-fibromatosis (NF2) patient with the MED-EL device took place in the year 1997. Later, the indication of ABI was expanded to non-NF2 patients with severe inner-ear malformation, for whom a regular CI will not be beneficial. Key translational research activities at MED-EL in collaboration with numerous clinics investigating the factors that affect the hearing performance amongst ABI patients, importance of early ABI implantation in children, tools in pre-operative assessment of ABI candidates and new concepts that were pursued with the MED-EL ABI device. The CE-mark for the MED-EL ABI to be used in adults and children down to the age of 12 months without NF-2 was granted in 2017 mainly based on two long-term clinical studies in the pediatric population. This article covers the milestones of translational research from the first concept to the widespread clinical use of ABI in association with MED-EL.

ARTICLE HISTORY
Received 13 December 2020
Accepted 6 January 2021

KEYWORDS
Neuro-fibromatosis; non-tumor; cochlear nerve deficiency; non-auditory side effects



3.1. Introduction

Cochlear implants (CI) have been clinically proven to be effective in restoring hearing in sensorineural hearing loss (SNHL). The electric stimulation from the CI electrode is picked up by the peripheral neural fibres of the spiral ganglion cell bodies and transmitted to the cochlear nerve which then leads it to the cochlear nucleus (CN) of the auditory brainstem to reach the brain.

Conditions such as the absence or nonfunctional cochlear nerve or suspected to be rendered nonfunctional cochlear nerve due to tumour presence or its removal – all such conditions preclude CI to act as a connection between the inner ear and CN. CN being positioned anatomically in the near vicinity of the cochlear nerve and directly on the auditory brainstem has proven to be a surgically viable location for the application of direct electric stimulation.

This article will introduce the history of ABI at MED-EL and the translational science path it took from a university laboratory to the patients in restoring hearing. This article also covers the MED-EL sponsored/supported/site-initiated studies

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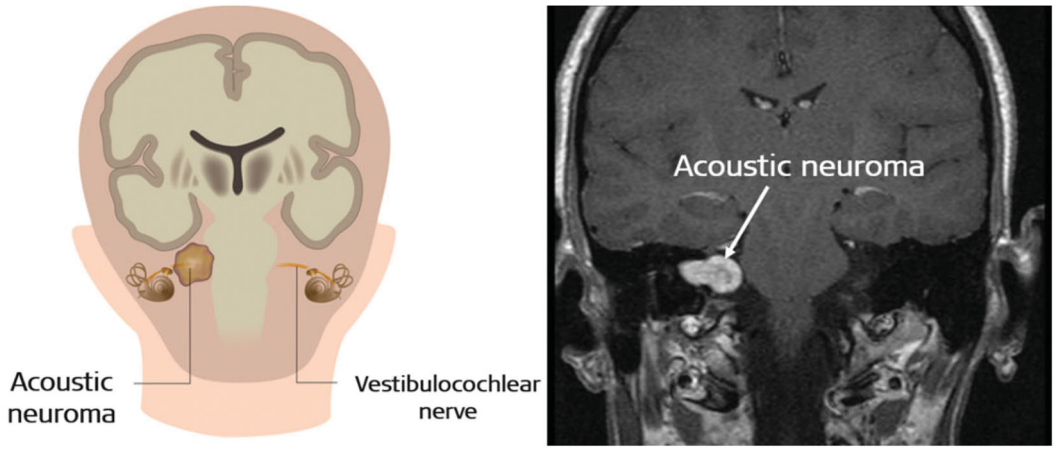


Figure 1. Scheme showing acoustic neuroma on the auditory nerve. (www.healthdirect.gov.au/acoustic-neuroma).

that reported on the hearing performance of the ABI implantees. Those studies were of great support to MED-EL with bringing forward its Auditory Brainstem Implant (ABI) approved by the notified bodies and consequently commercialising it within the European Union (EU) and other countries.

3.2. MED-EL's journey in the development of ABI

In 1994, the journey of ABI started at MED-EL. Prof. Helms and Prof. Müller who had heard about ABI activities in Los Angeles, suggested that MED-EL should develop an ABI system which would restore hearing in patients diagnosed with neurofibromatosis type 2 (NF2) and needing tumour removal surgery as these patients if deaf after the surgery did not have any possibility for hearing restoration. An excellent co-operation between the University clinics for ENT (Prof. Jan Helms) and neurosurgery (Prof. Klaus Roosen) proved helpful.

Acoustic neuromas in the internal auditory meatus (IAM) is a pathological signature in NF2 patients, as shown in Figure 1. These patients are bound to lose their natural hearing during their life as it causes severe damage to the cochlear nerve. NF2 is a genetic disorder characterised by the growth of non-cancerous Schwann cell tumours in the nervous system, with an estimated incidence rate of 1 in 40,000 people worldwide [1].

The most common tumours associated with NF2 are called vestibular schwannomas (VS) or acoustic neuromas (AN), and they develop along the auditory nerve, leading to SNHL and deafness. VS and AN may also cause brainstem compression resulting in neurologic morbidity and mortality that requires a surgical procedure for its removal [2]. The underlying reason for the neuromas to develop are the mutations in the NF2 gene. Schwann cells surround the neurons and act as supporting structure. NF2 gene, which is present in Schwann cells, provides instructions for making a protein called merlin that regulates the multiplication of the Schwann cells. The mutations in the NF2 gene lead to the production of a nonfunctional version of merlin protein that cannot regulate the growth and division of Schwann cells, resulting in the formation of tumours – a characteristic of NF2 [3,4].

In 1995, the first ABI paddle electrode research and development activities that resulted in MED-EL's ABI product with the scientific collaboration between the University of Innsbruck in Austria and the University of Würzburg in Germany. Mag. Mark and Dr Herzog who are now appointed at MED-EL in different roles – and at the time were MSc and PhD students, respectively – began their exploration on the development of ABI paddle electrode for human application (Figure 2).

Figure 2. Master- and PhD- students at the University of Innsbruck (Prof. Erwin Hochmair) involved in the early development of the ABI electrode.

The first version of the ABI electrode had penetrating needles made of Hysol (epoxy material) as a base, and platinum-iridium (90:10) wires of 75 µm thickness, which projected perpendicularly to the surface of the paddle as shown in Figure 3(A).

Prof. Steffen Rosahl from Hannover around 1995, supported evaluating the ABI electrode with penetrating needle contacts in non-human subjects. On the one hand, the penetrating needles may be suitable for self-anchoring on the CN, but on the other hand, no scientific evidence with regards to the traumatic effects in penetrating the CN directly with such needles existed at the time. That resulted in flatting the contacts decision, and distribution over the paddle surface along with a polyester mesh on the bottom side of the paddle for natural fixation over the CN (Figure 3(B)). ABI paddle electrode with flat contacts was mainly the work of Dr Kovacs – another PhD student at the time at the University of Innsbruck who was funded by MED-EL.

MED-EL's ABI system looks identical to the CI system in every aspect, other than in the design of the electrode array, which is placed close to the neural elements. Whilst the CI electrode array has the stimulating contacts distributed longitudinally along the array length, enabling the electrode to be placed inside the cochlear lumen to match the tonotopic frequency distribution (Figure 4(A)) closely, the ABI electrode has to be in a paddle format with the stimulating

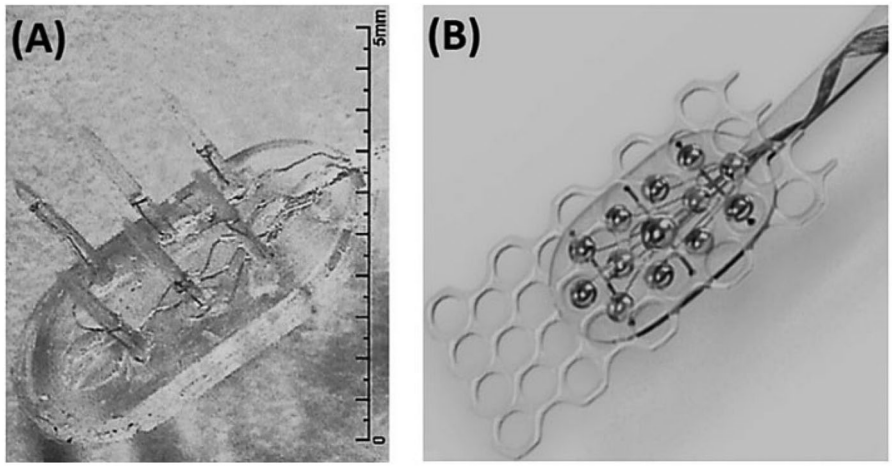


Figure 3. ABI paddle electrode with penetrating needle contacts (A) and flat contacts (B) (image courtesy of MED-EL).

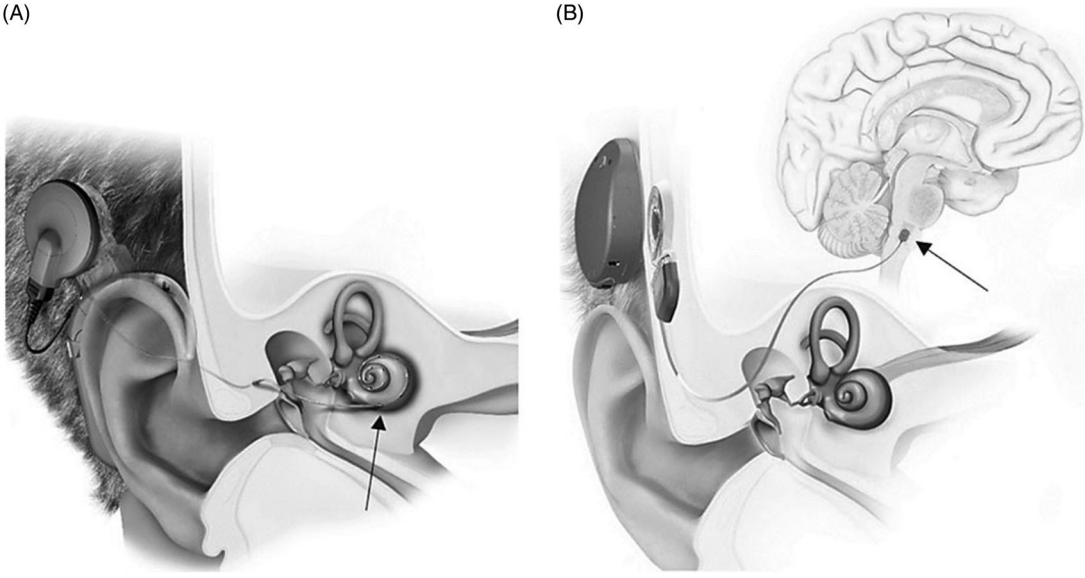


Figure 4. CI system, with a straight longitudinal electrode placed inside the cochlea (black arrow) (A). ABI system, with the pad electrode placed on the CN (black arrow) (B) (image courtesy of MED-EL).

contacts distributed within the paddle, enabling it to cover the rostral surface of the CN (Figure 4(B)).

3.3. Description of the first ABI system

MED-EL's first commercially available ABI system was developed with C40+ implant technology, a ceramic-based implant housing that measured 33.5 mm × 23.4 mm × 3.95 mm. The ABI implant electronics are identical to those of C40+ CI. They include twelve individual capacitors for every output, safeguarding the neuronal elements by blocking out any direct current components. ABI active electrode array is connected to the stimulator, and the array consists of twelve active platinum contacts which are partially embedded within a silicone paddle that measures 5.5 mm × 3.0 mm × 0.6 mm. A polyester mesh embedded in silicone exceeds the size of the paddle – allowing the fibrous tissue growth – which eventually stabilises the paddle over CN. The electrode lead diameter increases from 0.7 mm at the silicone paddle to 1.3 mm over the length of 10 cm up until its connection with the stimulator housing. The reference electrode for closing the electric circuit is in the shape of three-leaf clover, surgically positioned under the periosteum of temporalis muscle on the temporal bone. The telemetry measurements confirm the proper functioning of the implant. Implant's stimulator houses a magnet to attract the external antenna coil from the audio processor. The external components of MED-EL's first ABI system consist of TEMPO + BTE audio processor or the CIS PRO + body-worn device. Figure 5 shows MED-EL's first ABI system along with BTE audio processor.

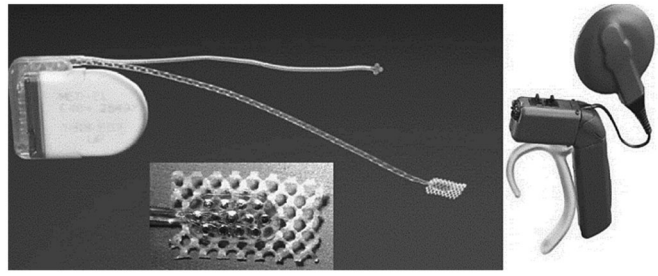


Figure 5. MED-EL's C40+ ABI system with paddle electrode and externally worn TEMPO + BTE speech processor (image courtesy of MED-EL).

3.4. MED-EL's first ABI implantation in patients

In 1997, on 10 June, the first MED-EL ABI implantation took place at the Julius Maximilian University of Würzburg in Germany as part of a clinical trial aiming at a CE-marked device. The ABI implantations were performed following the study protocol prepared by Mrs. Darcy Ochs from MED-EL together with surgeons. The surgery was performed by two doctors, Prof. Behr, the neurosurgeon and Prof. Müller, the otologic surgeon creating a milestone in MED-EL's journey with scientific exploration and development of the ABI system (Figure 6).

Prof. Robert Behr (Neurosurgeon) | Prof. Joachim Müller (Otologist) | Prof. Jan Helms (Otologist)

Figure 6. Surgeons from Julius-Maximilian University of Würzburg, Germany (in the year 1994) who suggested and supported MED-EL in developing the ABI system.

The placement of the ABI paddle electrode at the best anatomical location on the CN is essential in bringing effective hearing sensation to patients. Such landmark is identified by placing a temporary ABI placement electrode intraoperatively, which comprises four stimulating electrode channels to electrically stimulate the auditory brainstem (Figure 7, inner picture). If such electric stimulation is applied at the best anatomical location of the CN, then the response from the CN can be recorded by the recording electrodes which are fixed on the head's surface.

If recordings show waves as shown in Figure 7, then this is a proof that the CN is functional, and this way of electrically stimulating the auditory brainstem and recording its responses is known as electrically evoked auditory brainstem response (eABR). This method helps surgeons with placing the actual ABI paddle electrode at the anatomical location from where the satisfactory responses were recorded.

In 2001, there were already sixteen patients implanted with MED-EL's ABI system. Patients' age at the time of surgery ranged from eighteen and a half to 63 years, and all of them had NF2 clinical history of deafening. Patients' hearing performance was evaluated by the number and sentence tests, performed at different time points and in patients' mother tongue (Figure 8). In 2002, the audiological test results of patients implanted with MED-EL's ABI were published in the American Journal of Audiology by Prof. Behr and his colleagues [5]. There was another study that took place in parallel which evaluated the audiological performances of twenty patients implanted with MED-EL's ABI, although it was published at a later time, in the year 2007 [6].

Figure 8 summarises the audiological test results from both studies. Figure 8(A,B) show the hearing benefits in number and sentence test, respectively, with ABI in combination with

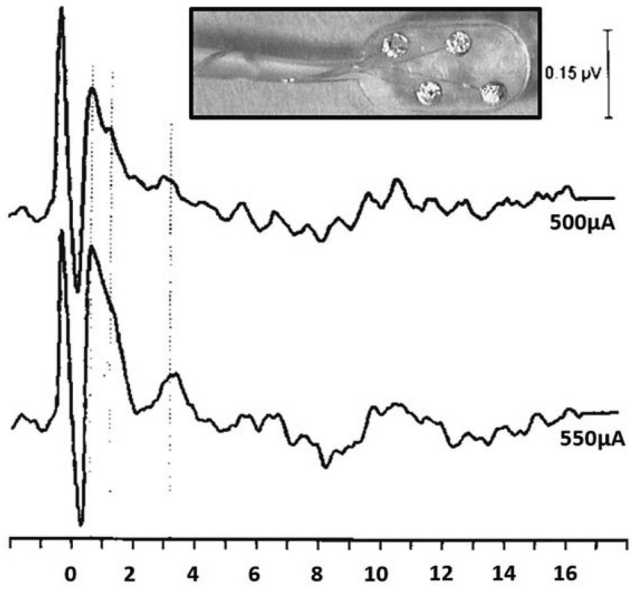


Figure 7. MED-EL's ABI placement/test electrode with four stimulating contacts and waves in eABR recording (image courtesy of Prof. Behr) [5].

lip-reading (LR). Also, some patients did exceptionally well with ABI only. Figure 8(C) shows the loudness scaling of ABI patients that are similar to normal hearing participants. Figure 8(D) compares the number, sentence and word test results at 1 and 2 years postoperatively where the results show a gradual increase in the hearing scores with time.

In 2003, MED-EL obtained the CE mark for its COMBI 40+ ABI system to be implanted in over 15-year-old NF2 patients. To include the COMBI 40+ ABI system to its hearing implant solution portfolio was a historic moment in MED-EL's journey. In 2005, MED-EL upgraded its ABI system to PULSARCI 100 implant type hardware, including the CE marking. The difference between COMBI 40+ and PULSARCI 100 is in the implant electronics and the mode of communication between the latter and the externally worn audio processor.

In 2007, September 26th, the first paediatric patient of age 3.5 years was implanted with MED-EL ABI system by Prof. Levent Sennaroglu from Hacettepe University, Ankara Turkey.

3.5. Nonauditory side effects with ABI stimulation

It is not unusual for NF2 patients with ABI to experience nonauditory sensations [6]. Typically, nonauditory side effects are produced *via* inadvertent stimulation of cerebellar flocculus, the cerebellar peduncle, the long sensory tracts, or the facial nerve. Up to 42% of ABI users experienced nonauditory sensations with electric stimulation which are benign but could cause considerable patient discomfort, and this was reported in 2007 [7]. In 2018, Dr Polak (MED-EL) and Prof Colletti reported a small incidence rate of nonauditory side effects with only 6 out of 17 patients [8]. Nonauditory side effects are generally minimised by deactivating/configuration of electrode channels.

In 2007, Prof. Behr and his colleagues published their experience with MED-EL's ABI system, especially with the nonauditory side effects and the number of deactivated

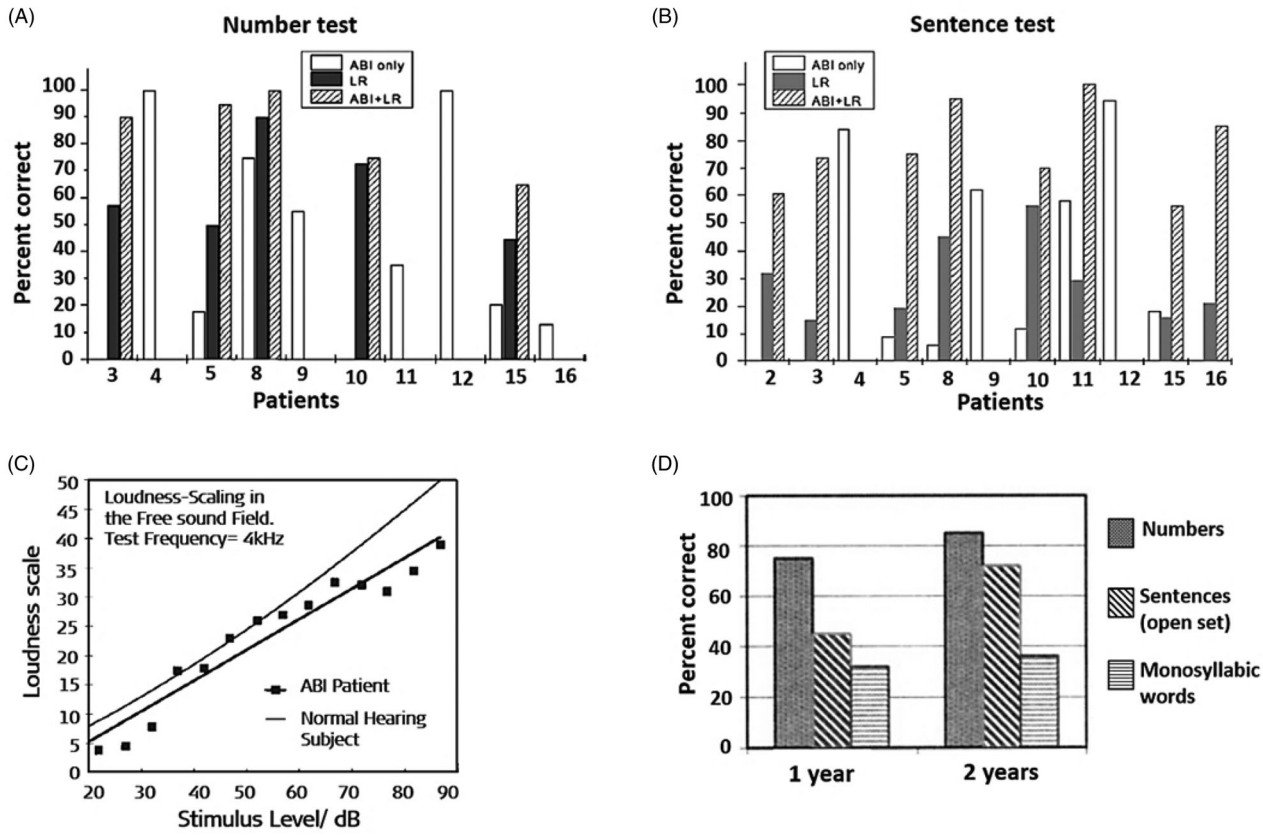


Figure 8. Number (A) and sentence test (B) under various conditions with ABI, LR and ABI + LR [5]. Loudness scaling of the ABI subjects is similar to the normal hearing subjects when tested in the free sound field at a test frequency of 4KHz (C). Number, sentence, and word test scores of ABI patients at 1 and 2 years post-operatively, showing an increase in scores with time (D) [6]. Reproduced by permission of Georg Thieme Verlag KG.

channels to minimise those, in a cohort of twenty patients [6]. Side effects included sensations such as twitching in the arm and abdomen, pressure in the ear, and diplopia (Figure 9).

All side effects were resolved with deactivating electrode channels randomly in a trial and error fashion. In terms of the number of individual electrodes used after the first fitting process by these patients ($n = 20$), an average of 70.2%

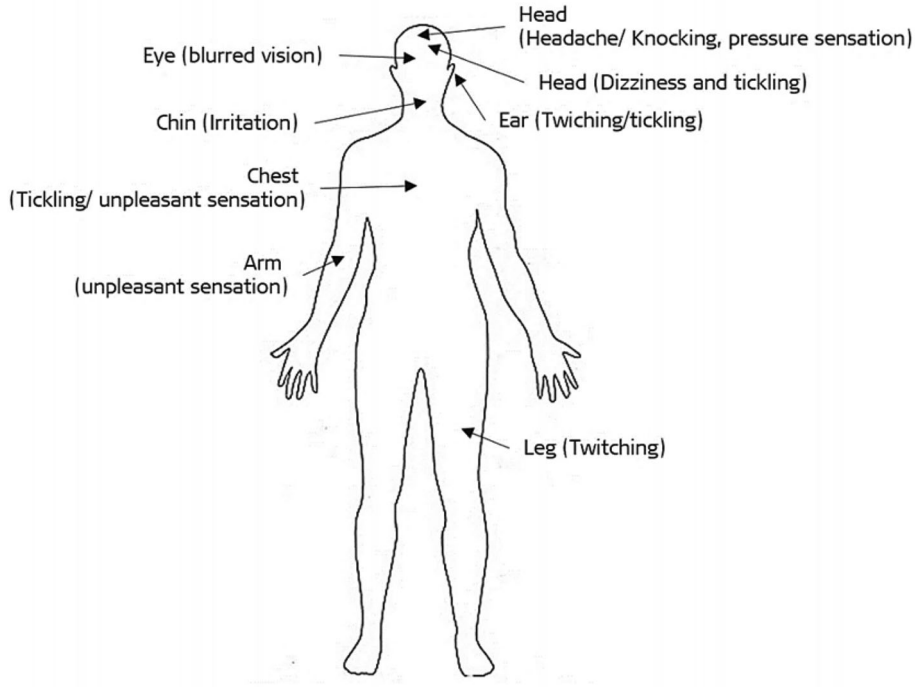


Figure 9. Nonauditory sensations on different parts of the body as felt by the ABI implanted patients (image courtesy of MED-EL).

Table 1. Number of patients and the auditory channels after the first fitting and used channels [6].

Number of patients	Auditory channels	Number of patients	Used channels
13	12	3	12
2	10	3	10
1	11	1	9
3	9	3	8
1	0	3	6
		4	5
		1	4
		1	3
		1	0

was used for sound sensation (Table 1), and the remainder relates to the abovementioned side effects. In comparison to this study, Dr Polak and his colleagues also reported on ABI side effects, but they used eABR to determine which channels are giving sound sensation and which are causing non-auditory side effects. An average of 79.7% of all electrode channels in their twenty patients was used for sound sensation, and showed eABR responses without any non-auditory sensations [8].

Table 2 presents the cumulative average of postoperative audiological results. Compared to ABI only mode, the audiological results were higher with the assistance of LR. Also, at 12 months, the results showed improvement from the sixth month.

Table 2. Postoperative audiological results in terms of LR improvements with the ABI device [6].

		6 months	12 months	2 years
LR + ABI	Sentences (%)	59.6 ($n = 9$)	79.3 ($n = 5$)	67.5 ($n = 9$)
	Numbers (%)	62.9 ($n = 9$)	87.5 ($n = 5$)	81.3 ($n = 5$)
ABI only	Sentences (%)	46.0 ($n = 4$)	48.4 ($n = 6$)	42.7 ($n = 8$)
	Numbers (%)	40.1 ($n = 8$)	69.5 ($n = 5$)	51.7 ($n = 9$)
Both groups	Sentences (%)	58.5 ($n = 12$)	81.3 ($n = 7$)	71.1 ($n = 12$)
	Numbers (%)	53.3 ($n = 9$)	84.3 ($n = 7$)	78.5 ($n = 11$)

The study demonstrated and reconfirmed that ABI in NF-2 patients is a safe and promising procedure for those who would otherwise remain deaf. Almost all patients were able to perceive environmental sounds, and for many patients, comprehension of open speech was restored to a useful level.

3.6. ABI in non-tumour cases

Although the ABI was initially developed as a solution for NF2 affected patients only, in **2002**, Prof. Colletti from the University of Verona in Italy and Prof. Shannon from the University of Southern California in the USA were keen on expanding it to indications other than the NF2 (Figure 10). The indications included patients with cochlear nerve aplasia (absence) – in such cases, a CI may not be beneficial – and patients with complete cochlear ossification – in such cases, the CI implantation may be challenging.

Prof. Colletti and his colleagues performed first ABI implantation in cochlear nerve aplasia patients [9], and one of the surgical challenges associated with such surgery is the validation of the presence or absence of CN. The only way

Prof. Vittorio Colletti Prof. Robert Shannon

Figure 10. Prof. Vittorio Colletti from the University of Verona and Prof. Robert Shannon from the University of Southern California, evaluated the effectiveness of ABI in non-NF2 patients.

to define the presence and functionality of CN is by electric stimulation on the area corresponding to CN upon surgical exposure of brainstem. Such electric stimulation may be effectively done by placing the temporary ABI placement electrode on the anatomical landmark of the CN, as established by the surgeon, followed by the recording of eABR responses [5].

In 2009, Prof. Colletti and his colleagues from Italy together with Prof. Shannon from the House Ear Institute in Los Angeles, USA published their 10-year experience of monitoring the hearing performance of NF2 and non-tumour patients implanted with ABI [10]. In the non-tumour patient population were included those with head-trauma, auditory neuropathy, cochlear malformations and altered cochlear patency. Sentence recognition score in auditory-only mode ranged from 10% to 100% (mean = 59%, median = 53%, $SD = 21.34$) in the non-tumour groups, compared to the NF2 patient group where the results ranged between 5% and 31% (mean = 10%, median = 16%, SD = 15.21). The authors of the study grouped their non-tumour patients to three cohorts based on the hearing scores.

Rapid improvement in performance was mainly associated with head trauma and severely altered cochlear patency while the patients with auditory neuropathy and neurologic disorders were the group with slow performance improvement as shown in Figure 11.

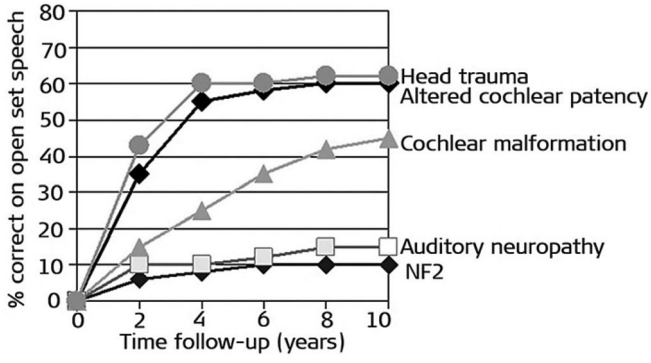


Figure 11. Open set speech per cent correct in NF2 and non-tumour patients [10]. Statistical analysis: 2-tailed paired Student's *t*-test. Reproduced by permission of Wolters Kluwer Health, Inc.

In 2010, MED-EL upgraded its ABI system from ceramic implant housing to titanium housing (Figure 12) and CE marked it under the name CONCERTO ABI system for 15-years and older NF2 patients.

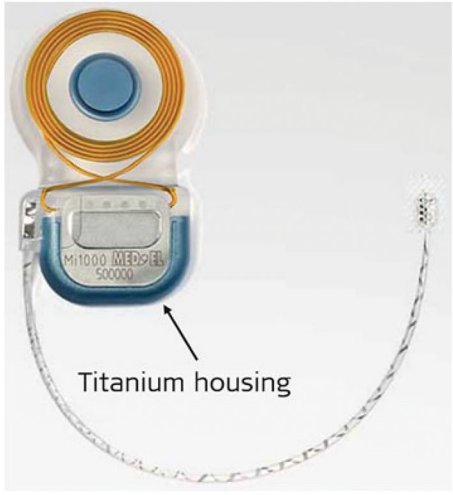


Figure 12. CONCERTO ABI implant system with titanium housing encasing the implant electronics (image courtesy of MED-EL).

3.7. Consensus on ABI for children and non-NF2 patients

Earlier studies that reported on excellent hearing benefits with ABI in non-NF2 patients [5–10] encouraged clinicians to widen the ABI indications to non-NF2 candidates officially. A consensus statement on indications, surgical procedure, electrophysiological tests and postoperative rehabilitation was established. Moreover, two consensus meetings took place in the years 2009 and 2013 to bring a unified message from the experienced clinicians (Figure 13) across the world [11,12].

(i) Which children and non-NF2 patients are candidates for ABI?

Prelingually deaf patients with inner ear malformation, cochlear nerve hypoplasia/aplasia and children with bilateral

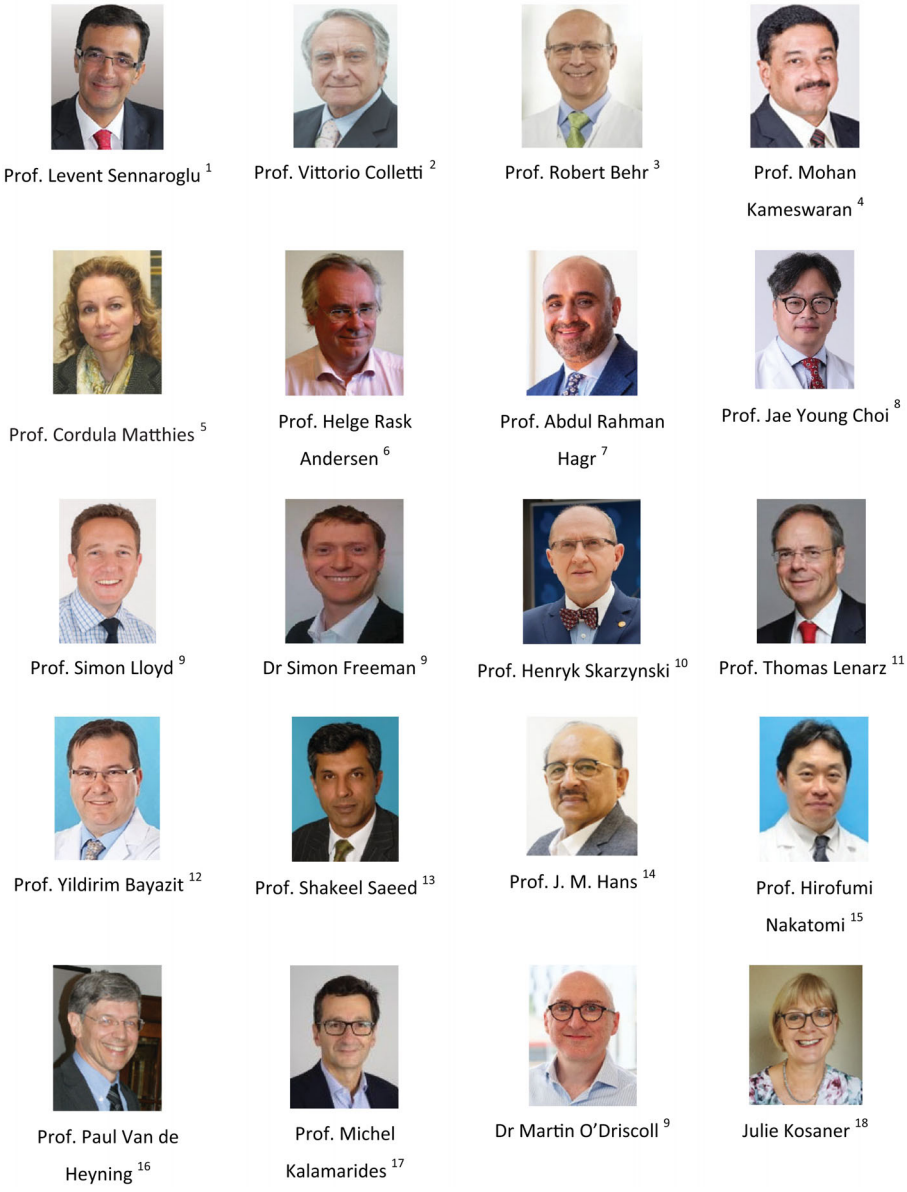


Figure 13. Experienced ABI clisnicians with MED-EL ABI system. [1] Hacettepe Medical University, Turkey; [2] University of Verona, Italy; [3] Klinikum Fulda, Germany; [4]Madras ENT Research Foundation, India; [5] University of Würzburg, Germany; [6] Uppsala University Hospital, Sweden; [7] King Saud University, Saudi Arabia; [8] Yonsei University Seoul, South Korea; [9] Central Manchester University Hospital, UK; [10] Institute of Physiology and Pathology of Hearing, Poland; [11] Hannover Medical School, Germany; [12] Medipol University, Turkey; [13] University College London Hospitals, UK; [14] ENT and Hearing Care New Delhi, India; [15] University of Tokyo, Japan; [16] Antwerp Medical University; [17] Pitie-Salpetriere Hospital, France; [18] MEDers Speech and Hearing Center, Turkey.

and total inner ear ossification shall be considered candidates. Also, individuals deafened postlingually due to meningitis, temporal bone fractures with cochlear nerve avulsion, otosclerosis with gross cochlear destruction, or unmanageable facial nerve stimulation with CI may be considered as ABI candidates.

(ii) Which healthcare team is the best to undertake the ABI intervention?

The team should comprise of otologist or neuro-otologist, radiologist, paediatric neurosurgeon, implantation-experienced audiologist, electrophysiologist, speech and language habilitation specialist, experienced neuroradiologist, and experienced paediatric anesthesiologist with intensive care unit facilities for children.

(iii) What are the radiological indications?

There are three patient categories under radiologic indications. Well defined congenital indications are Michel aplasia (absence of both, inner ear and auditory nerve), cochlear aplasia (absence of cochlea), cochlear nerve aplasia (absence of cochlear nerve), cochlear aperture aplasia (missing structure between IAC and the cochlea) as defined from the radiographs. Possible congenital indications include hypoplastic cochleae with cochlear aperture hypoplasia, common cavity and incomplete partition type-I cases with cochlear nerve aplasia and ears with CI that did not result in satisfactory outcomes in the first attempt. Acquired indications include postlingually deaf children with severe meningitis-related cochlear ossification – as viewed from computed tomography (CT) and magnetic resonance imaging (MRI). Other indications include bilateral temporal bone transverse fractures with cochlear nerve avulsion, cochlear otosclerosis with gross destruction of the cochlea, which is readily diagnosed in CT and MRI, and with facial nerve stimulation limiting the CI use.

(iv) Which ear side should be selected for ABI?

The side with better developed lateral recess for optimal placement of the ABI paddle electrode and which has an entrance to the lateral recess is more favourable as less cerebellar retraction is expected.

(v) ABI revision

The first ABI surgery shall be performed in an experienced centre that minimises or avoids revision surgery as it could involve excessive damage to the vascularisation and scarring around the implant paddle array.

(vi) What are the contraindications?

Auditory neuropathy is contraindicated with the ABI surgery.

(vii) What is the age limit for ABI in children?

Children younger than 1 year have less relative blood volume and cerebrospinal fluid in the posterior fossa, and there is a risk of brain swelling. Therefore, the optimum age for elective intracranial surgery in children is between 18 and 24 months. However, depending on the experience of the surgical team, the minimum age for ABI in children may be as early as 1 year.

(viii) Surgical approach

Retro-sigmoid approach is the preferred route to implant ABI in children and non-NF2 cases.

(ix) Importance of electrophysiologic tests before and after ABI activation

Electrophysiologic (EP) testing may provide two levels of guidance: firstly, the optimal electrode positioning during ABI surgery and secondly, it may be used to decide which electrode delivers sufficient auditory response levels. The preparation for activating the device should permit observation of the heart rhythm as the vagus nerve is potentially close to the intended location of the ABI array.

(x) Rehabilitation

Auditory verbal therapy, along with total communication and speech reading, should be encouraged to convey more linguistic and language information to these children.

3.8. MED-EL's ABI implantations across the world

Over time, treatment of NF2 patients with MED-EL's ABI system extended to many countries, including Poland, Japan, China, Philippines and South Africa.

In 2013, a multicentric international study reported on the nonauditory side effects and the number of deactivated channels from 32 patients implanted with MED-EL's ABI system [7] (Figure 14).

At the time of first fitting, 8.8 ± 2.2 out of 12 available electrode channels were activated to provide auditory stimuli to the patients. The reasons for deactivating the remaining contacts varied from no auditory sensation, unpleasant sound sensation (faint, scratchy or persistent), contacts with same pitch rank, electrode contacts with mixed auditory and nonauditory sensations, and electrode contacts with only nonauditory responses. Different pitch perceptions are generated by the electric stimulation of different electrode contacts from the ABI paddle electrode. Deactivation of electrode channels due to nonauditory sensations could be theoretically thought to affect the hearing performance of patients with ABI; however, there was no apparent existence in the correlation between the number of active electrodes and patient's hearing performance and this is given in section 3.11.

Figure 14. Expert ABI surgeons who implanted MED-EL's ABI implant systems: [1]University of Würzburg, Germany; [2]National Tokyo Medical Center, Japan; [3]NTT Medical Center Tokyo, Japan; [4]Toranomon Hospital Tokyo, Japan; [5]Institute of Physiology and Pathology of Hearing, Poland; [6]Free State University, South Africa; [7]University of Hong Kong Medical Centre, Hong Kong; [8]University of the Philippines Manila, Philippines.

3.9. ABI versus CI in patients with cochlear nerve deficiency

Children with cochlear nerve deficiency (CND) are a distinct patient population which generally performs below average amongst paediatric CI recipients, with some exceptions. This raises medical and ethical considerations when selecting a device and intervention that prove most beneficial. In the ABI consensus meetings that took place in 2009 and 2013, the ABI experts collectively agreed that ABI should be indicated for children with CND.

In 2014, Dr Liliana Colletti and her colleagues from the University of Verona in Italy evaluated the auditory perceptual ability of children ($n = 40$) with CND. The cohort was implanted with CI ($n = 20$) and ABI ($n = 20$) (either MED-EL or Cochlear®) and evaluated for auditory perceptual ability using Category of Auditory Performance (CAP) index [13]. Children with any degree of cochlear malformation and either absence/smaller cochlear nerve fitted with ABI demonstrated significantly earlier and better perceptual outcomes of CAP test than children implanted with CI (Figure 15).

In 2020, Prof. Hagr, Prof. Alsanosi, Prof. Alzhrani and their colleagues from King Saud University in Saudi Arabia and other centres in the Middle East, investigated CI outcomes in children with nerve deficiency [14] (Figure 16).

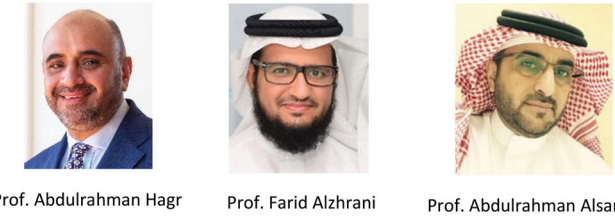


Figure 16. Clinicians from King Saud University, Saudi Arabia, investigated the CI outcomes in children with auditory nerve deficiency.

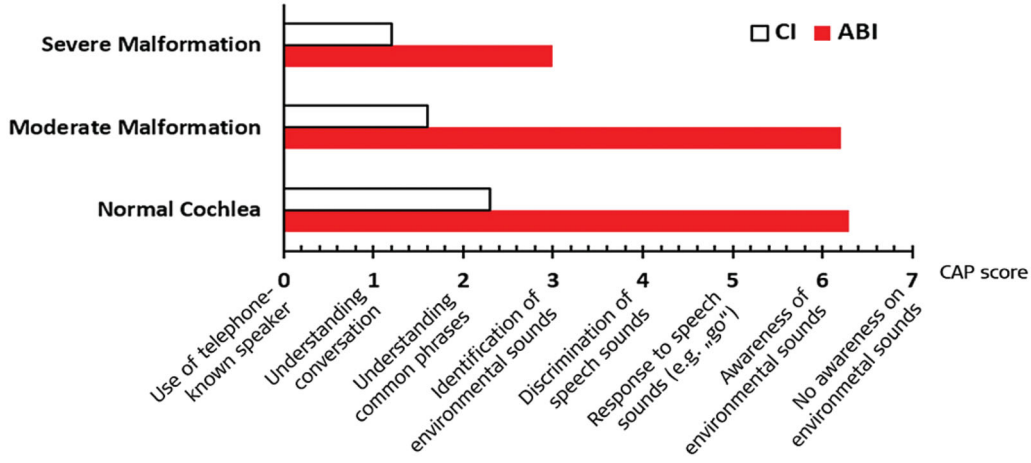


Figure 15. Categories of auditory perception scores of children with CND who were implanted with ABI/CI [13]s. Statistical analysis: Wilcoxon Mann-Whitney test ($p < .05$). Histogram created from data given in Colletti et al. [13].

A total of seven children with prelingual profound deafness with auditory nerve deficiency and a control group of ten children with no cochlear nerve anomalies were included in the study. Patients from both groups were implanted with MED-EL SYNCHRONY CI device. Speech skills ratings using Meaningful Auditory Integration Scale (MAIS) and Meaningful Use of Speech Scale (MUSS) were compared across the groups. In general, patients with auditory nerve deficiency performed poorer than those without nerve deficiency, as it is reflected in Figure 17. It was concluded that CI outcome in children with auditory nerve deficiency is poorer than those without nerve deficiency. This was a similar observation reported by Colletti et al., as mentioned above [14].

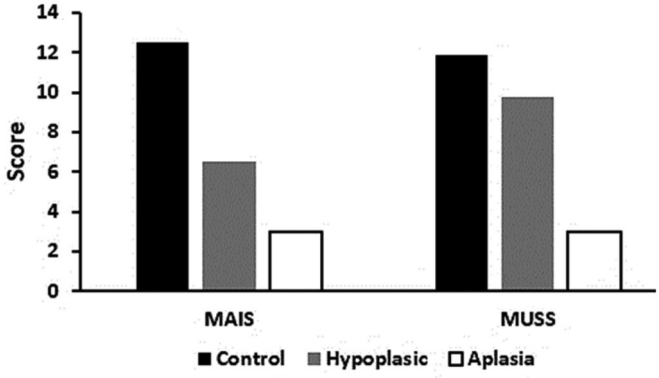


Figure 17. Average scores of MAIS and MUSS scales are compared for the three groups of patients. Histogram created from data given in Yousef et al. [14].

3.10. Importance of MRI compatible implant

NF2 patients, following the tumour removal and the ABI surgery, may need to undergo a follow-up MRI scans to check for any new tumour growths, and in such situation, MRI compatible hearing implant system prevails over the MRI non-compatible hearing implant systems.

In 2014, while the research community was committed to evaluating the hearing performance of ABI implanted patients and developing a consensus statement for ABI to be implanted in non-tumour cases, MED-EL continued its dedication of bringing the best implant solutions to patients. MED-EL further upgraded its ABI system to SYNCHRONY implant platform which is known for its unique diametrically magnetized magnet that self-aligns in response to the external magnetic field in the MRI machine (Figure 18(A,B)).

The SYNCHRONY ABI implant system enables patients to undergo a 1.5 tesla MRI without magnet removal. Also, the single unit audio processor (RONDO®) was made available in combination with the ABI hearing system. This upgraded system was CE marked for implantation in patients who are 12 years and older. It is of fundamental value to mention that Prof. Hochmair, Dr Zimmerling and Dr Jamnig from MED-EL invented the concept of diametric implant magnet that allows MRI scanning without the need for implant magnet removal (Figure 19). MED-EL was the first hearing implant company to have such implant magnet in its CI and ABI hearing systems (US patent numbers: 6348070 and 8634909 [15]).

Figure 19. Engineers from MED-EL who invented the diametric magnet for MRI compatible implant.

In 2017, a case study by Prof. Staecker and his colleagues from Kansas in the USA demonstrated the clinical importance of MRI compatible implant magnet in ABI patient [16]. The latter was a 27-year-old female with a bilateral

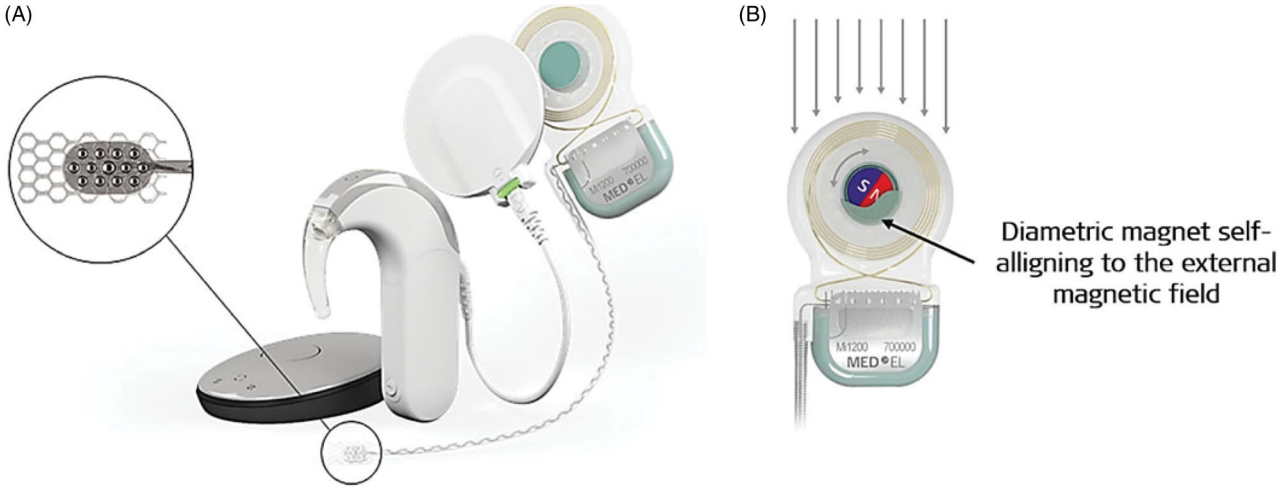


Figure 18. SYNCHRONY ABI system showing both single unit and BTE audio processor (A). The implant has a 1.5 T conditional MRI compatible magnet that self-aligns to the external magnetic field (B) (image courtesy of MED-EL).

vestibular schwannoma, and she was under observation for some time before opting for MED-EL's SYNCHRONY ABI implant system for her left side. After surgery, the patient underwent postoperative MRI scans for tumour growth observation on her right side. The MRI compatible implant magnet allowed the MRI scans without the need for implant magnet removal and attainment of clear and quality images of the contralateral side (Figure 20).

Prof. Hinrich Staecker

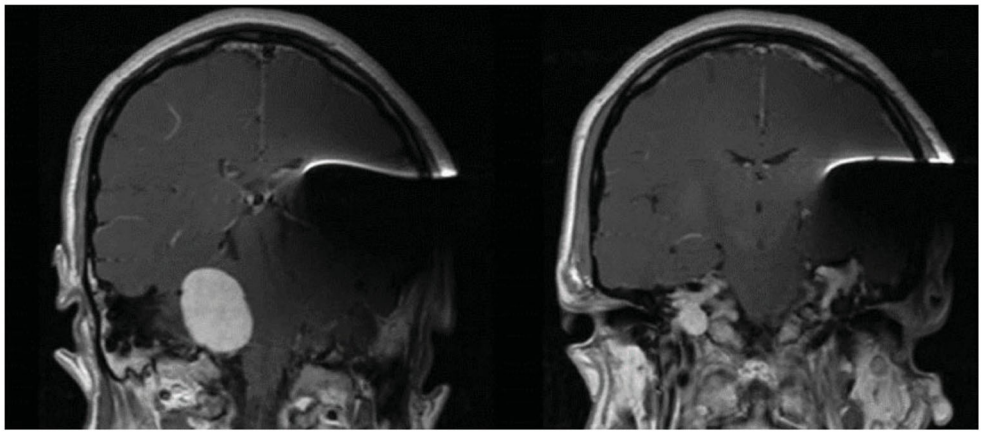


Figure 20. MRI with MED-EL's SYNCHRONY ABI implant demonstrated clear and quality images of the contralateral side. The ABI created moderate metallic artefact distortion that limits evaluation of the ipsilateral cerebral and cerebellar hemispheres. Image adapted from Shew et al. [16].

3.11. Factors which affect hearing performance amongst ABI patients [17–19]

The ABI has shown acceptable hearing outcomes in patients, including in children with both, NF2 and non-tumour conditions. Children implanted at 2–3 years of age have developed open-set speech recognition and have attended general education [17]. Although these results are encouraging for implantation of ABI for various indications, there is considerable variability in hearing outcomes, ranging from high levels in open-set speech recognition to only sound awareness and a supplement of lip-reading. The aforementioned makes it challenging for clinicians to discuss the benefits of ABI during preoperative patient counselling sessions. There could be several factors contributing to the variability in hearing outcomes. In order to have a clear understanding of these factors, Prof. Behr and clinicians from different centres across the world investigated the hearing outcomes on all patients implanted with MED-EL's ABI hearing system with open-set speech understanding scores included [18] (Figure 21). Open-set speech understanding is defined as speech understanding is $\geq$30% without lip-reading on sentence test. One-third of the NF2 patients implanted with MED-EL's ABI system reached open-set speech understanding.

1. *NF2 tumour size* of larger than 2–3 cm in diameter would impinge on the brainstem surface, and the surgical removal of the tumour would cause some damage on the brainstem. However, earlier reports on the analysis of hearing outcomes related to tumour size with excluding other factors have shown no correlation between tumour size and hearing outcomes [19]. The latter was further confirmed with a study conducted by Prof. Behr and his colleagues [18] in which they – based on the tumour size – grouped MED-EL's ABI implanted patients ($n = 26$) to one group with tumour size $\leq$3 cm and the second group with tumour size of >3 cm. The sentence recognition score did not show any significant difference between these two groups ($p = .83$, two-tailed t-test). Some patients with a tumour size of >4 cm were able to obtain >80% sentence recognition test scores correctly.
2. *Tumour stage* is another factor that was investigated, and it showed no difference in hearing outcomes between patients with tumour stage III or IV. Tumour stage IV corresponds to tumour size >5 cm, and which compresses the brainstem – this suggests that patients with large tumours (>5 cm) may reach open-set scores.
3. *Length of deafness* before ABI surgery is seen as another contributing factor towards variability in hearing outcomes amongst ABI patients. Group of patients who became deaf 1 year or less before implantation ($n = 18$) obtained significantly higher speech recognition scores (65% correct scores), compared to the group of patients whose deafness duration lasted more than 1 year before ABI surgery ($n = 7$; 45% correct scores; $p = .03$, two-tailed t-test).
4. *The surgical effect* on minimising the CN damage is another contributing factor to the hearing outcomes. Semi-sitting position showed better speech recognition scores compared to the lying position. In a semi-sitting position, the intraoperative bleeding is minimised due to reduced intracranial venous pressure. Bipolar electrocautery and associated excitotoxic effects on the neural elements in CN could be another explanation for the variations in hearing outcomes with ABI in general. Surgical techniques of exposing auditory brainstem (translabyrinthine (TL) vs retrosigmoid (RS) approach) could also contribute to a certain degree in the hearing outcomes, as it was reported by Prof. Behr and his colleagues [18] with findings that the RS

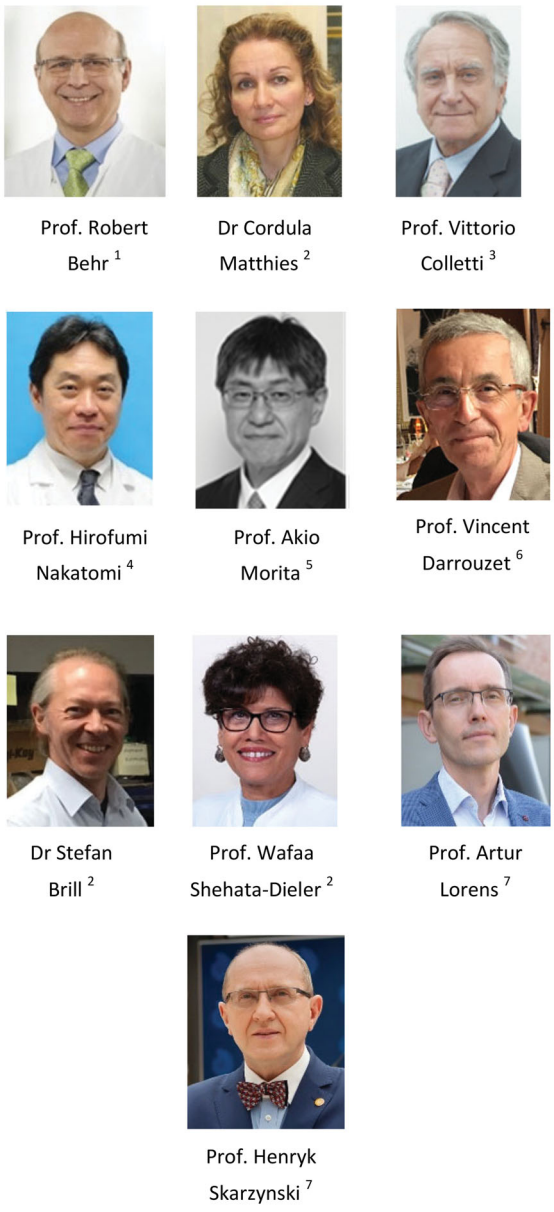


Figure 21. Clinicians from different centres investigated the factors contributing to variability in ABI outcomes: [1] Klinikum Fulda, Germany; [2] University of Würzburg, Germany; [3] University of Verona, Italy; [4] University of Tokyo, Japan; [5] NTT Medical Center Tokyo, Japan; [6] University of Bordeaux, France; [7] Institute of Physiology and Pathology, Poland.

approach results in 30% higher speech recognition scores in comparison with the TL approach. Nevertheless, such a comparison was not possible due to the small number of patients with open-set scores with the TL method.

5. Another factor that may be thought to influence hearing outcomes is the *number of stimulating channels* in the paddle electrode. MED-EL's ABI paddle has twelve active stimulating channels, whereas the ABI paddle from Cochlear® has twenty-two. If the number of active stimulating channels acts as the deciding factor in better hearing outcomes, then theoretically, all the Cochlear® ABI implantees should outperform MED-EL's ABI implanted patients. However, scientific facts reveal the opposite, according to the report from Prof. Colletti and his colleagues [17]. Prof. Behr and his colleagues have also obtained similar findings with MED-EL's ABI implanted patients [18]. They categorised patients into three groups based on the number of activated electrode contacts. Group I had five to seven active electrode contacts, group II had eight to nine, and group III had ten to twelve electrode contacts active. The corresponding mean sentence recognition scores were 52%, 70.3% and 54% correct, respectively. Two-tailed *t*-test comparisons revealed no significant differences amongst the three groups, with p values ranging from 0.08 to 0.90.
6. Not all activated channels produce *distinct pitch sensations*. During the ABI audio processor fitting, multiple channels with similar pitches may be included hoping that they will contribute to independent spectral information, even if they are perceived to be of similar pitch. Interestingly, with MED-EL's ABI device, none of the patients who had distinct pitch sensation on all 12 channels reached open-set speech understanding scores. Patients with better speech understanding ($\geq$60%) have a higher number of distinct pitch electrodes (9.1 contacts) than patients with poorer speech understanding ($<$60%) with 7.4 contacts. The minimum number of distinct pitch electrodes to reach the open set was found to be five.
7. *Maximum comfort level (MCL)* may be an indicator of distance between the electrode channel and stimulated nerve, and in that sense, higher current levels are required with increased distance. With MED-EL's ABI system, Prof. Behr and his colleagues [18] showed that the patient group with MCL $<$28 nC reached higher sentence recognition scores (67.1%) than patients with higher MCLs ($>$28 nC) and which are typically seen in CI patients. This result suggests that the ABI paddle electrodes placed proximal to neural structures positively relate to the hearing performance.
8. During ABI surgeries, *intraoperative recordings of eABR* would assist the surgeon in optimal placement of the paddle electrode on the CN. Auditory responses are peaks in the recorded responses with a latency of five to six milliseconds, and the amplitude of the peaks grows with increased stimulation level. In a typical hearing mechanism, the number of peaks in eABR ranges from one to five, corresponding to the mixture of responses from the auditory nerve and brainstem nucleus. With the ABI paddle electrode stimulating the brainstem nucleus by bypassing the auditory nerve, there is no auditory nerve response as a result, and the latency of peaks related to brainstem nucleus is shorter due to no mechanical delays of the cochlea or its nerve. The eABR recordings may be categorised by having one, two or three distinct peaks, depending on the optimal placement of the paddle electrode, as well as they relate to the health of neural elements in the brainstem nucleus. The study by Prof. Behr and his colleagues of using MED-EL's ABI device showed two peaks in most eABR recordings, and these recordings were obtained from patients who had good hearing outcomes. However, there was no significant correlation

between the number of peaks and the level of speech recognition [18]. This data is inconclusive due to the fact that not all ABI patients in this cohort had eABR measured from the implant directly as this was only possible after the year 2008.

9. *The rate of stimulation* on each electrode is related to the MCL levels, and the stimulation rate is determined by the number of stimulating electrode channels and the duration of each stimulation pulse. MED-EL's ABI device used either CIS + or HDCIS signal processing strategy until the year 2011, and the default programming mode of applying biphasic pulses had a minimum pulse width of 7μs, which allowed stimulation rate to up to 4225 pulses/second/electrode. For patients who required higher thresholds and current levels, the pulse duration was lengthened, and in patients with open set, the overall stimulation rate started as low as 377 pulses/second/electrode. However, grouping patients with stimulation pulses higher or lower than 1200 pulses/second/electrode, the speech recognition scores differed significantly (67.1% vs 45.7%; $p = .03$, two-tailed t-test) [18]. This suggests that higher stimulation rate positively influences speech performance. In contrast to the MED-EL's system, SPEAK strategy from Cochlear® that is typically used in ABI patients has the mean stimulation rate of only 250 pulses/second/electrode.

While these are the widely studied factors which contribute to the variability in hearing performances of ABI patients with NF2, the optimal identification of the CN, its size variations and the tonotopic arrangement of neural elements – which are hard to understand in patients in-situ – may also be other contributing factors.

3.12. The importance of early ABI implantation in children

Prelingually deaf children make remarkable advances in auditory perception following CI implantation, and this is mainly due to the supply of sensory information through CI to the developing brain while the developmental plasticity is still strong [20]. However, children with the absent auditory nerve – and therefore not CI candidates – are a more challenging patient population. If early CI implantation in children could bring better hearing outcomes, then this should also happen with ABI in children who are CI contraindicated.

In 2014, Prof. Colletti and his colleagues reported on hearing outcomes from a consecutive group of sixty-four children who they followed up for 12 years postimplantation with ABI. The children had a variety of aetiologies, including cochlear nerve aplasia, auditory neuropathy (AN), cochlear malformations with dysplasia of the eight nerve, and other cochlear abnormalities. The patients were initially fitted with a CI but with no sound detection outcomes [21]. Their findings revealed a positive trend toward better outcomes with a CAP score of seven in children implanted with an ABI at a very young age – at 2 years old (Figure 22(A)) – and particularly no other disorders (Figure 22(B)).

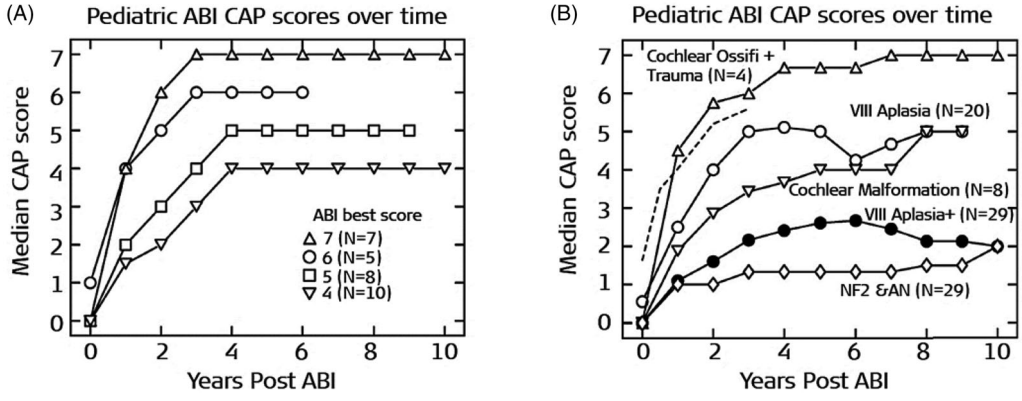


Figure 22. High CAP score of seven was recorded in patients implanted with ABI as young as two years of age (A). High CAP score was identified in patients with cochlear ossification and trauma, which is not considered as a disorder when compared with a condition like NF2 and AN (B) [21]. Reproduced by permission of Karger AG, Basel.

In 2015–2016, MED-EL sponsored a study to evaluate the safety and efficacy of ABI in children, and the study took place in Chennai in India, at the Madras ENT Research Foundation (MERF) [22], led by Prof. Kameswaran and Dr Rajeswaran (Figure 23).

Prof. Mohan Kameswaran[1] Dr Ranjith Rajeswaran[2]

Figure 23. Team of CI/ABI [1] surgeon and [2] audiologist from Madras ENT Foundation (MERF) evaluated the safety and effectiveness of MED-EL's ABI hearing system in young children with various forms of inner ear malformations.

Ten children were included in the study, with the mean age at implantation of 3.5 ± 1.3 years. Michel's aplasia, cochlear nerve hypoplasia and cochlear aplasia were the causes of their deafness, and all children received either MED-EL's

PULSAR ABI or CONCERTO ABI implant with OPUS 2 audio processor. As far as the safety of the device was concerned, there were no reports on device failure other than one adverse event related to device or surgical procedure. The hearing performance was measured through different assessment methods, including Listening Progress Profile (LiP), Meaningful Auditory Integration Scale (MAIS), Meaningful Use of Speech Scale (MUSS), Monosyllabic-Trochee-Polysyllabic (MTP), Categories of Auditory Perception (CAP), Speech Intelligibility Rating (SIR) scale, the LittlEARS Auditory Questionnaire (LEAQ), and the Checklist of Auditory Communication Skills. Tests were performed preoperatively and compared with the twelfth postoperative month results. Significant improvements in LiP ($p = .012$), MAIS ($p = .008$), MUSS ($p = .011$), MTP 3 ($p = .042$), CAP ($p = .011$), SIR ($p = .008$), LEAQ ($p = .008$) and in the Checklist of Auditory Communication Skills ($p = .012$) results were observed from preoperation to 12 months postoperatively. Performance from 12 months to 24 months after first fitting significantly improved or remained stable for every test. A significant improvement was reached for MAIS ($p = .028$), MUSS ($p = .041$), SIR ($p = .046$), LEAQ ($p = .019$), and the Checklist of Auditory Communication Skills ($p = .021$). Performance remained stable for LiP ($p = .090$), MTP 3 ($p = .0141$). The study concluded that ABI provision and use is safe and allows significant auditory development in children with cochlear (nerve) aplasia or hypoplasia and without NF2.

In 2017 September, MED-EL was finally granted the CE mark for its SYNCHRONY ABI system to be implanted in non-tumour children as young as 12 months and older. This was a significant milestone in MED-EL's journey with its ABI system, and the approval was obtained based on the two abovementioned studies along with an expert opinion that was given by Prof. Behr from Klinikum Fulda in Germany to the notified body.

3.13. New concepts tried with MED-EL ABI system

This section will describe the key novel concepts that were tried with the MED-EL ABI system.

3.13.1. Bilateral ABI with a single implant

It is known from the CI field that bilateral CI implantation brings binaural hearing benefits in patients with bilateral deafness. If bilateral CI bring binaural benefits, then bilateral ABI should result in the same. MED-EL thought that if two independent ABI electrode arrays could be implanted to Foraminae of Luschkae (Figure 24(A)) in one surgery bilaterally, that would be highly beneficial in terms of reducing the surgical complications, as well as of associated surgical costs. Under the Custom Made Device (CMD) council directive 93/42/European Economic Community (EEC) [24], a modified ABI implant with a SPLIT electrode lead with two branches of ABI paddle electrode was designed and developed by MED-EL to be implanted in a patient who suffered from tumours in the midline of the posterior fossa, and who was also expecting to undergo spinal cord surgery. Prof. Behr from Klinikum Fulda in Germany performed the surgery to implant this CMD ABI device in the year 2009, although its results were published only in 2018 [25]. The intraoperative eABR recordings and postoperative CT images confirmed the proper placement of the two ABI paddle electrodes (Figure 24(B)).

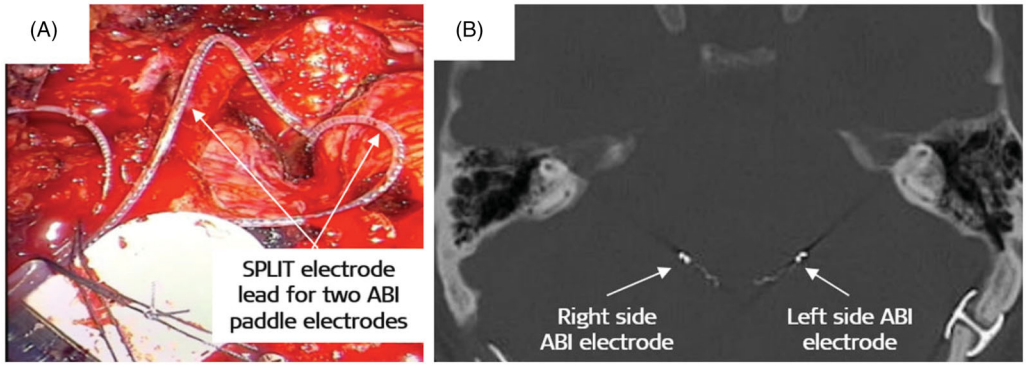


Figure 24. The surgical image of SPLIT ABI electrode showing two branches of electrode lead that goes into both Foraminae of Luschkae (A). Postoperative CT image showing the proper placement of ABI paddle electrodes bilaterally [23].

The left side paddle electrode had dislocated after 3 months, but due to patient's precondition, it was decided not to perform revision surgery to reposition it. The authors concluded that the special device design and the surgical experience of placing two paddle electrodes in a single surgical procedure is feasible and safe for the patient.

3.13.2. Midbrain implant

Depending on schwannoma size and the surgical procedure, some damage may be induced to the CN upon schwannoma removal. Prof. Colletti attempted to place MED-EL's ABI paddle electrode on the inferior colliculus (IC) as shown in Figure 25 – which is one step higher in the auditory pathway [25] – of a patient previously treated with ABI with the paddle electrode placed on the CN, but with limited speech recognition results.

The results of the first patient with IC implant showed substantial benefit from electric stimulation with no

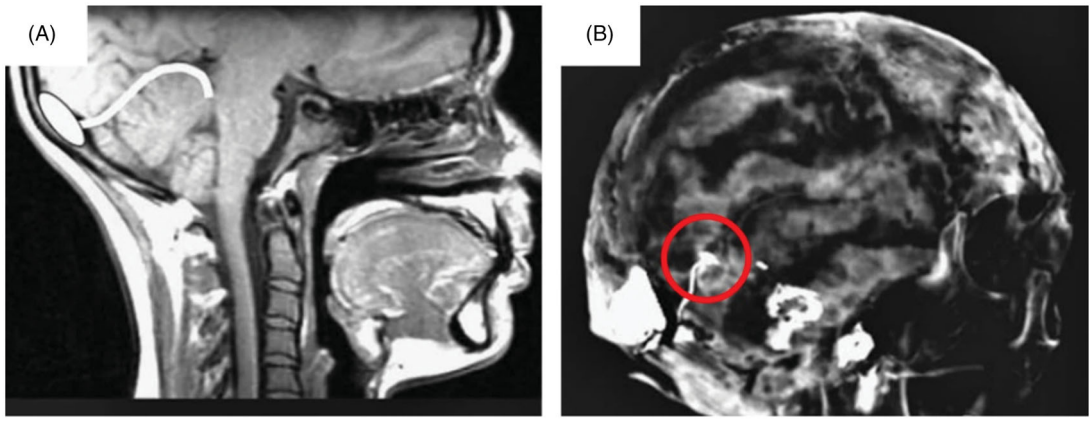


Figure 25. Schematic of the surgical approach and electrode placement on the IC (A). X-ray image of the implant placed on the IC taken at a slightly oblique angle. The red circle points to the ABI paddle electrode [26]. Reproduced by permission of Wolters Kluwer Health, Inc.

complications or side effects. All twelve electrodes produced auditory sensations with no non-auditory responses. The threshold levels were as low as 5nC, indicating the array in excellent position over auditory pathway structures. The patient was able to discriminate multisyllabic words at 80% correct in a five-choice test that was based on prosodic and syllabic cues. Face-to-face communication with the implant demonstrated a significant improvement in speech understanding over lip-reading alone. Recognition of words and sentences increased from 5% and 10% to 80% and 90%, respectively, after the revision surgery. These results indicate that the stimulation on the surface if the inferior colliculus in the auditory midbrain could provide an alternative possibility for auditory prosthetic devices.

3.13.3. A Novel method in the audio processor fitting of children with ABI

One of the main challenges in providing small children with an ABI is the fitting of their audio processor, as reliable subjective feedback from them is challenging to obtain. With the ABI indication criteria expanding in toddlers, there was a need to develop an easy and reliable method to perform the fitting of the audio processor. eABR is an established method and the gold standard in ABI, and it is commonly used during the ABI paddle electrode positioning on the CN during surgery. Until the end of the year 2008, eABR recording was only possible with the ABI placement electrode, which meant that immediately after selecting a location with the best response, the surgeon had to place the ABI paddle electrode precisely on such spot on the CN. The method represented a challenge to the operating surgeon, but at the beginning of 2009, MED-EL's ABI implant was enhanced with the eABR feature within the paddle electrode, which ensured validation of the best placement.

From literature, it is known that nonauditory sensation by some electrode contacts in the ABI paddle electrode is always present and therefore finding these specific electrode contacts is also challenging in small children. In the year 2018, Prof. Colletti from the University of Verona and Dr Polak from MED-EL developed a novel method of fitting the audio processor based on postoperative eABR [8]. From a group of children with a mean age of 2.4 years ($n = 17$), the postoperative eABR recordings showed differences in the number of waves. This is also the first study detailing the morphology of eABR responses in congenitally deaf children implanted with ABI. The most robust was the wave P2 that appeared from 1 ms to 2.5 ms, and which was present in all measured eABRs. Wave P3 occurred between 1.7 ms and 4.5 ms and wave P4 between 3.5 ms and 5 ms. Another key finding was that waves P3 and P4 were present only in the presence of P1 and P2, and the nonauditory responses that were confirmed by the observation, subjective responses, or both, were recordable only after 2.5 ms. These findings make the wave P2, which appeared between 1 ms and 2.5 ms, a prominent element and its presence in the postoperative eABR could be used during the ABI audio processor fitting in small children. This data suggests that postoperative eABR fitting could help toddlers implanted with ABI to achieve auditory perception and development quickly.

3.13.4. Tools in preoperative assessment

The goal of the preoperative assessment tools is to minimise the time of hearing deprivation in questionable candidates, who would typically not be implanted or implanted with a question mark, and to help the implant team to decide which implant is the best choice for each candidate. Both tools discussed below were developed for the MED-EL's MAESTRO 9.0 clinical system and required only a dedicated evoked potential measuring system [26].

In some instances, candidates show no response or a questionable response to sound whilst diagnostic imaging tests suggest normal or abnormal anatomy. This may occur in patients with a narrow internal auditory canal or patients with either malformed or patent cochlea. For such cases, the preoperative Promontory Stimulation System was developed. Its benefits were evidenced in initial studies with a success rate of 80–90% in CI implanted children. The system intends the transtympanic electrode to be placed on the round window niche, and biphasic electric pulses are delivered to the transtympanic electrodes. At the time of stimuli, the MAX interface triggers the

evoked potential device, and the eABR response is obtained from the surface electrodes, as shown in Figure 26. If the eABR shows a positive response, the implant team may decide to proceed with cochlear implantation. If no responses are obtained, the candidate may be considered for an ABI, or further tests may be required.

3.14. Star performance with ABI

It is known from the literature that NF2 patients implanted with ABI, their hearing performance may unfortunately not be reported as excellent mainly due to complications associated with the tumour itself and the surgical removal of it

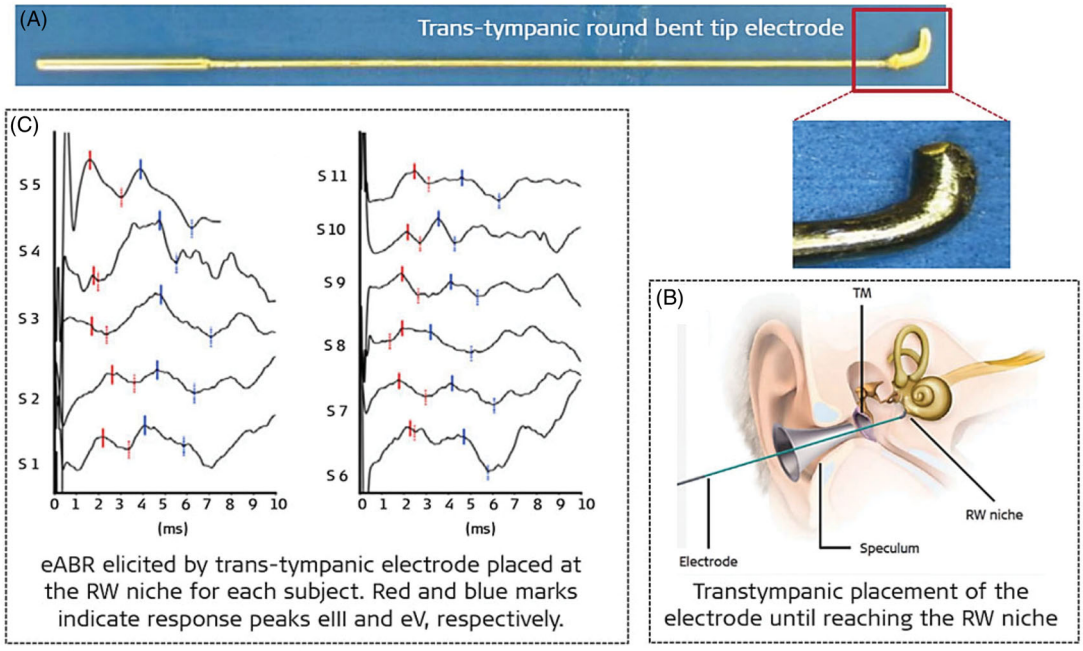


Figure 26. Transtympanic rounded-bent tip electrode that facilitates easy placement at the RW niche (A). Illustrative representation of the transtympanic electrode placement at the RW niche (B). PromStim eABR responses for all 11 patients (C) [27] (image courtesy of MED-EL).

In situations where an individual shows no response or is expected to have no response to the sound, and where imaging tests show normal or abnormal anatomy, or where the individual has already been selected for either a CI or an ABI, an intraoperative test of nerve functionality may be used. This test includes placement of the cochlear test electrode into the scala tympani (ST).

The intra-cochlear test electrode contains four electrode contacts. It is intended to be inserted into the ST during surgery. The length of the electrode is 18 mm, as indicated by the marker ring. Three of the electrode contacts are placed directly into the ST, and the fourth electrode contact is placed under the temporalis muscle. Biphasic pulses are generated using the MAX interface and delivered to the cochlea. At the time of stimulation, the MAX interface triggers the evoked potential, and eABR response is obtained from the surface electrode as depicted in Figure 27.

This tool is suitable for individuals with questionable functionality of the auditory nerve, individuals with a narrow internal auditory canal and patent or malformed cochlea, in tumour patients to monitor nerve functionality during the tumour removal, or in situations where any other tests/methods failed to show CI candidacy, including the use of eABR with the Promontory Stimulation System.

affecting the cochlear nucleus. This section showcases few NF2 subjects implanted with MED-EL ABI devices, who are star performers with their hearing abilities.

In 2000, Skarzynski et al. reported implanting MED-EL Combi40+ ABI device in a 28-year-old woman with bilateral deafness caused by NF2 [28]. This was the first ever ABI surgery in Poland. The surgery took place at the Institute of physiology and pathology of hearing, Warsaw, Poland with the support of neurosurgeons from the University of Würzburg. Limited migration of the ABI pad electrode was observed a few weeks after surgery and eight channels were finally stimulated using a CIS speech coding strategy. She was able to detect and identify most environmental sounds and was able to hear music. There was a continuous improvement of her auditory skills and very importantly, no changes in the stimulation parameters nor in the electrode placement. She continued her profession as a Polish to German language translator, was taking care of her children, speak over the telephone and was able to learn Italian as a third language using tapes and books simultaneously.

In 2009, Skarzynski et al. reported sequential bilateral ABI (MED-EL Combi40+) in a 27-year-old man with NF2 [29]. The first implantation took place on 4 April 2006 and the second implantation on 26 June 2008. Both surgeries were led by Prof. Robert Behr from the University of

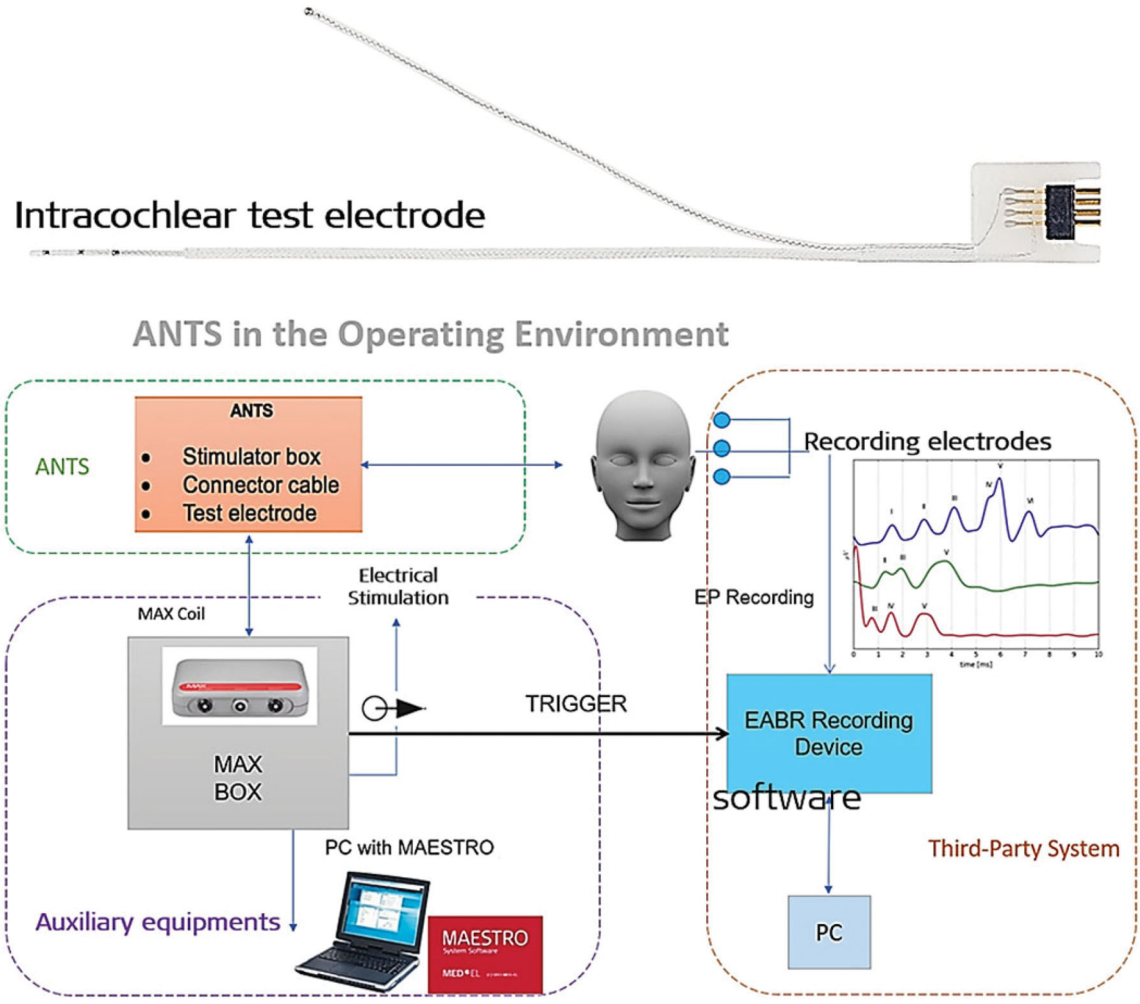


Figure 27. Intracochlear test electrode and test set-up in recording the eABR responses (image courtesy of MED-EL).

Würzburg, Germany. This patient continued his profession as a singer even after the ABI surgery, owned a business, and remained very active.

While these two studies are published evidences, there are a lot more ABI star performers who were implanted with MED-EL ABI device.

3.15. Current (the year 2021) eligibility criteria for MED-EL's SYNCHRONY ABI system

The following conditions are indicated safe for treatment with MED-EL's SYNCHRONY ABI system:

- Twelve months or older
- Cannot benefit from a cochlear implant
- Nonfunctional auditory nerve:
  - Auditory nerve aplasia
  - Auditory nerve hypoplasia
  - Head trauma
  - Non-NF2 tumour
  - Severe cochlear ossification
- Neurofibromatosis type 2 (NF2)
- Implantation concurrent with tumour removal surgery

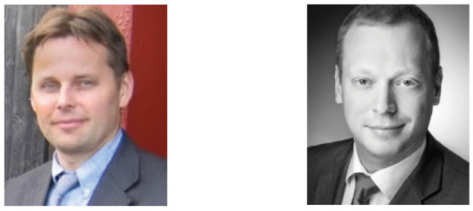
3.16. Reimbursement from the healthcare system

Reimbursement from the healthcare system is a topic of commercial importance, as well as it serves as a direct acknowledgement of the acceptance by the medical society. In 2020, Health Quality Ontario declared that compared with no intervention, ABI provides benefit for completely deaf adults with NF2 or severe inner ear abnormalities, contraindicated for CI [30]. Surprisingly, in well-developed countries like Australia, Belgium and the USA, ABI is not reimbursed by the healthcare systems in general. In contrast, in European countries such as in Austria, Denmark, Finland, France, Germany, Netherlands, Norway, Poland, Portugal, Russia, Slovakia, Spain, Sweden, Switzerland and in countries like Iran and Turkey, the cost of ABI is reimbursed.

By 2021, more than three-hundred and fifty non-NF2 children of age down to 1 year, were implanted with MED-EL ABI system in 30 countries world-wide involving 57 surgeons.

3.17. MED-EL's commitment towards ABI candidates

As ABI surgery involves certain complications and risks as discussed throughout this chapter, MED-EL has dedicated electrophysiological assessment experts to attend every ABI surgery as to ensure optimal placement of ABI paddle electrode over the CN and optimal eABR measurements. Also, MED-EL covers all financial costs associated with bringing in an expert paediatric electrophysiologist during ABI surgeries in countries where such experts are lacking. While these overhead costs are relatively high and, in many cases, exceed the break-even price of the device, MED-EL continues its mission of providing hearing to every individual, and especially to children. Up to date (2021), MED-EL has supported more than six hundred ABI cases worldwide, and this journey has just started as many more milestones are to be achieved in the years to come for MED-EL (Figure 28).



Dr Marek Polak Dr Jan Heusers

Figure 28. Electrophysiological experts from MED-EL who attend every MED-EL ABI surgery.

3.18. Conclusion

It is MED-EL's tradition to closely collaborate with clinicians globally and to strive to deliver the best hearing implant solutions for treating deaf and hard of hearing patients. The ABI device is an excellent example of strong collaboration between a medical device company and clinicians. With the experiences gained over the years, it is much clearer today that children under the age of two can be safely implanted with ABI. Audiological assessments from the ABI implanted patients suggest that the device offers useful hearing to non-tumour patients, with results comparable to CI patients. With NF2 patients, the hearing performance may unfortunately not be reported as excellent, mainly due to complications associated with medical conditions and surgical effects while removing the tumour/s. However, one-third of MED-EL implantees have shown to have more than 30% correct open-set speech scores. MED-EL continues with technologically advancing and further improving its ABI implant system, stimulation strategies and its fitting software by bringing in new features that could minimise or entirely remove the side effects of electric stimulation.

Preoperative assessment tools (ANTS and Stimulator Box supporting ANTS) developed by MED-EL were recently introduced at the 3rd ABI consensus online meeting (due to COVID19 pandemic) organised by Prof. Sennaroglu in 2020. The consensus of this meeting is yet to be published and the topics that were discussed were prelingual deafness indication, possible congenital ABI indications, ABI outcomes and surgical procedure in ABI reimplantation.

The translational science path with the ABI paddle electrode design originated in the laboratories of Innsbruck and Würzburg universities to later reach the patients in restoring hearing and has culminated in the regulatory approval of the MED-EL ABI, which is the only ABI system with CE mark and other regulatory approval for not only NF2 patients but for non-tumour patients including children down to 12 months of age.

Acknowledgments

The authors would gratefully like to acknowledge the key contributors to the development of the subject matter. Their contributions are outlined in this article. The authors further acknowledge Marek Polak from MED-EL for his valuable input and comments during several rounds of review meetings that contributed to the final version of this article.

Disclosure statement

This article is sponsored by MED-EL and has not undergone the regular peer-review process of Acta Oto-Laryngologica. Both the authors are affiliated with MED-EL.

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ACTA OTO-LARYNGOLOGICA
2021, VOL. 141, NO. S1, S82–S105
https://doi.org/10.1080/00016489.2021.1888496

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REVIEW ARTICLE

CI in single-sided deafness

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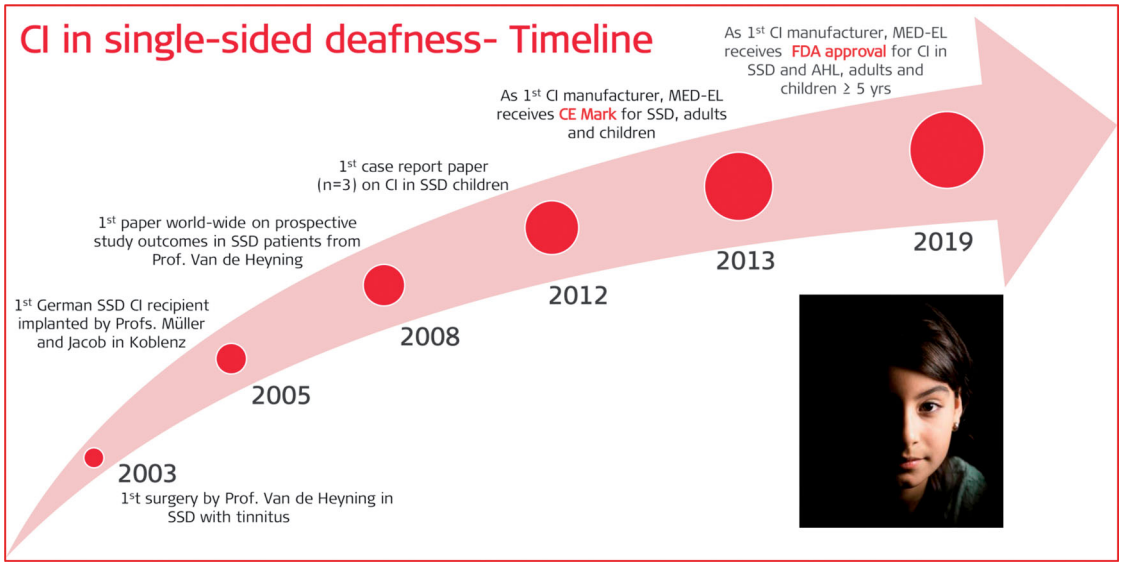
ABSTRACT

The cochlear implant (CI) as a treatment option for single-sided deafness (SSD) started with a clinical study looking in to the influence of cochlear implantation with a MED-EL device on incapacitating unilateral tinnitus in SSD. The study began in 2003 and was conducted by P. Van de Heyning and his team in Antwerp, Belgium. The first CI in SSD without tinnitus in Germany was implanted by J. Mueller and R. Jacob in Koblenz in 2005. Translational research activities took place since then to evaluate the CI as a treatment option for SSD not only in adults but also in children. They assessed the hearing performance of SSD patients implanted with CI, importance of long electrode arrays in SSD patients, degree of acceptance of CI by SSD children, importance of early CI implantation in SSD children in developing language skills, music enjoyment by hearing with two ears and evidence on spiral ganglion cell body distribution. In 2013, MED-EL was the first CI manufacturer to receive the CE mark for the indication of SSD and asymmetric hearing loss (AHL) in adults and children. In 2019, MED-EL was the first CI manufacturer to get its CI device approved for patients over the age of five with SSD and AHL, by the FDA in the USA. This article covers the milestones of translational research from the first concept to the widespread clinical use of CI in SSD.

ARTICLE HISTORY
Received 13 December 2020
Accepted 6 January 2021

KEYWORDS
Binaural hearing; tinnitus; sound localisation; music enjoyment



4.1. Introduction

The auditory pathway starts in the cochlea from the inner hair cells of the organ of Corti which send the signal to the spiral ganglion cell bodies (SGCB) through the peripheral neural fibres in response to the acoustic signal. The central axons of the SGCB form the cochlear nerve, and the vestibular nerve joins the cochlear nerve entering the internal auditory meatus (IAM) – commonly called as cochlear-vestibular nerve – which is a clinically relevant location, as any damage to it would normally affect both, auditory and vestibular functions. The nerve in the IAM travels a short distance of around 1cm to reach the surface of the brainstem at the ventral (anterior) cochlear nuclei (CN). Until CN, the neural fibres coming from each ear are kept separated on their own sides. The neural fibres from the ventral CN extend to the dorsal (posterior) CN, and from here most of the fibres cross

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This article is a part of the compendium entitled 'Thirty years of Translational Research behind MED-EL' authored by Anandhan Dhanasingh (Director) (Anandhan.dhanasingh@medel.com) and Ingeborg Hochmair (CEO, CTO) (Ingeborg.hochmair@medel.com).
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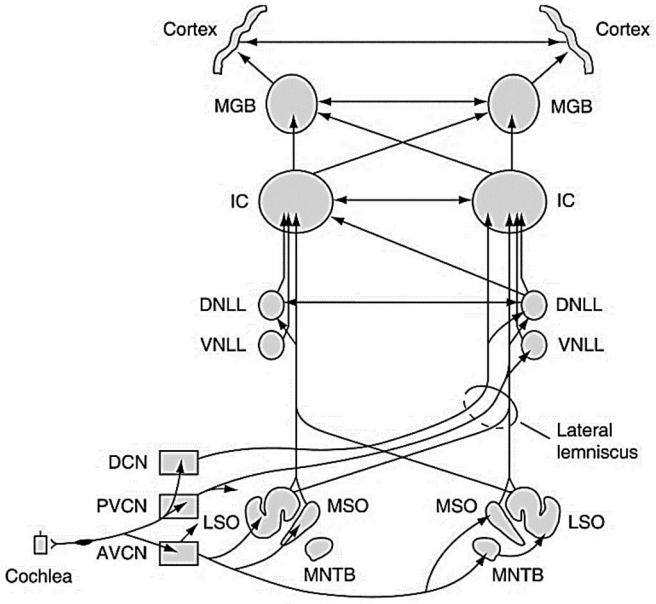

Figure 1. The main ascending pathways of the brainstem. DNLL: dorsal nucleus of the lateral lemniscus; IC: inferior colliculus; MGB: medial geniculate body; VNLL: ventral nucleus of the lateral lemniscus [2]. Reproduced by permission of Elsevier B.V.

the midline, travelling up in the contralateral (opposite) lateral lemniscus. At the same time, some fibres travel up in the ipsilateral (same side) lateral lemniscus. From the ventral CN, most of the neural fibres travel up to reach the contralateral superior olivary nuclei, whereas some neural fibres reach the ipsilateral superior olivary nuclei as well (Figure 1).

In summary, from both dorsal and ventral CN, some fibres cross the mid-line while others stay on the ipsilateral side – and for that reason, acoustic information from both ears travels bilaterally in each lateral lemniscus, and any supranuclear lesions will not lead to severe hearing impairment. Therefore, hearing problems can only be conductive or sensorineural but are rarely central. Fibres ascending through the lateral lemniscus from both cochlear nuclei and superior olivary nuclei, carrying the auditory information, converge at the inferior colliculus. From there, the fibres project ipsilaterally to the medial geniculate body (MGB) where the auditory information is refined and sent to the auditory cortex, which gives meaningful sound sensation to hearing human subject [1–3].

In normal-hearing human subjects with binaural hearing (hearing with two ears), the brain receives and processes auditory input from both ears to separate individual voices and speech from environmental noises. The critical function of the brain at this point is to combine and compare raw acoustic information that comes from two cochleae, and takes place in different cochlear nuclei, particularly in the olivary complex exploiting the sound intensity, timing difference and frequency aspects of what the cochleae have encoded in the auditory nerve action potential. From the output that comes from the olivary complex, the auditory cortex creates a three-dimensional landscape of the acoustic signal. This is an ordinary phenomenon in binaural, normal-hearing human subjects who can localise and understand the speech with no additional effort – the two advantages claimed to be the most important in binaural hearing [4].

Unilateral hearing loss (UHL) or single-sided deafness (SSD) are the terms that correspond to severe to profound sensorineural hearing loss (SNHL) in one ear, and normal hearing in the ipsilateral ear. These two terms are used invariably, whereas asymmetric hearing loss (AHL) is defined as the interaural threshold gap of 15 dB or higher hearing loss (HL) between the right and left ears at four contiguous frequencies as seen in the pure tone average (PTA) audiogram [5]. If the SSD occurs due to malformation of the external ear canal or middle ear ossicular chain ossification, then it is called conductive SSD, and it is different from SSD, which is a consequence of SNHL. In case of AHL/SSD, some aspects of action potentials that arise from the deafened/poorer hearing ear are degraded or completely missing relative to the better ear, that comparison between the two ears may become impossible for the brain.

New-born screening identifies one in one thousand being born with SSD, out of which the number increases to three in one hundred children by the time they reach school age [6–8]. The causes of SSD in children vary from bacterial meningitis, congenital cytomegalovirus (CMV), enlarged vestibular aqueduct syndrome (EVA) and premature birth. Cochlear nerve deficiency (CND) is often associated with congenital SSD in children for which CI is contraindicated [9]. In some cases, the cause of SSD is idiopathic. So far, CI is the only treatment option for restoring binaural hearing in SSD when the anatomical conditions permit.

This article will describe the basics, including the general benefits of binaural hearing, and the challenges which the human SSD subjects face. It will also cover the treatment options before the CI came into existence, the story of how MED-EL started its CI journey in SSD, various research efforts by clinicians across the continents – either sponsored, supported or site initiated by MED-EL – to evaluate the binaural hearing benefits of MED-EL CIs in SSD patients. Also, this article will highlight the research studies which supported MED-EL in its CI device approvals by the notified bodies and by the healthcare systems in granting reimbursement for CI as a treatment option for SSD recipients.

4.2. Benefits of binaural hearing

Loudness is an essential aspect of the sound signal. In normal-hearing human subjects, the two ears largely contribute to action potentials that reach the brainstem which is referred to as binaural loudness summation – also known as binaural redundancy. The feeling of a sound loudness relates to the number of action potentials triggered by the sound and integrated into the auditory pathway. In patients with SSD, the same increase in loudness would require the sound level to be increased by about 10 dB [10]. Not just the loudness benefits are observed with binaural hearing, but the treatment of acoustic information in the auditory pathway is more sensitive to small differences, which is highly beneficial in sound recognition in noise – but challenging with monaural hearing/single-sided deafness [11].

The sound signal that comes from a person's right side reaches the right ear earlier than it does the left ear. The time difference of the sound signal reaching both ears is called

interaural time difference (ITD), and the difference in the level of sound (loudness) reaching the two ears is called interaural level difference (ILD). With binaural hearing, the ITD and ILD are precisely encoded in the volleys of auditory nerve-action potentials in response to sound signal [11]. The brain detects and correlates the patterns of action potentials from both ears to sound like a single acoustic object, and the asymmetries between the two correlated inputs help in the *localisation of sound* in three-dimensional space. For sound sources positioned away from the head's midplane, the ITD is a consequence of the sound waveform arriving slightly earlier to the ear nearer to the sound source than to the ear further away. The ITD varies systematically as a function of the angular direction of the sound source. At frequencies below 1 kHz, the auditory neurons partially phase lock to the fine structure of the sound or its envelope, and by this way the ITD is preserved in action potentials that reach the medial nucleus of the superior olivary complex, enabling sound localisation. For frequencies higher than 1 kHz, the interaural level difference (ILD) or loudness differences between ears becomes the predominant localisation cue, with ILDs varying systematically as a function of frequency and source direction [12]. The ILD processing occurs in the superior lateral olive with excitation coming from ipsilateral ear and inhibition coming from the contralateral ear, thereby localising the sound of frequencies above 1 kHz. With monaural hearing, both ITD and ILD processing in the auditory pathway becomes impossible due to missing signals coming from one of the ears, making the sound localisation highly challenging. However, monaural cues allow localisation of sounds in the medial plane.

The simple presence of head in a natural sound field creates a diffraction pattern of sound waves, leading not only to ILDs but to different signal-to-noise ratio (SNR) in the two ears, whenever the signal and the noise from different directions compete with each other. The ear that is further to the source of noise will have an increase in SNR due to head attenuation of noise, and the ratio decreases at the ear that is closer to the noise source. This is known as the *head-shadow effect,* and it is a phenomenon of binaural hearing, helping the subject to focus on the ear that is turned towards the source of the main sound, leaving the other ear turned towards the source of noise [13]. The head shadow effect is frequency dependent. High-frequency information (>1,500Hz) is affected more than the low-frequency information because the wavelengths for high-frequency sounds are shorter. Therefore, high-frequency sounds will be attenuated much more than low-frequency information. High frequencies can be attenuated by up to 20 dB or more, and low frequencies can be attenuated by approximately 3–6dB [14]. Consequently, patients with SSD are at a disadvantage every time the critical sound comes from the impaired side, even in quiet environments, and the disadvantage increases in the presence of background noise.

4.3. Negative effects of SSD

Children born with SSD cannot get the full benefits of binaural hearing, and as a result, they experience a speech-language delay, general communication difficulties, psycholinguistic dysfunction, social-emotional issues, quality of life effects, academic and behavioural difficulties. Research shows that 22% to 35% of children with SSD fail at least one school grade, and up to 20% are identified as having behavioural difficulties [15]. In congenital SSD cases, the natural development of neural synapses in the auditory cortex is inhibited due to the absence of neuronal activity as no auditory input is fed through the deaf ear. The complaints from SSD patients are reduced speech understanding in loud surroundings, loss of acoustic orientation, reduced sound/noise localisation and early fatigue in conversation and frequent tinnitus disturbance.

4.4. Treatment options for SSD until the year 2003

In the late 1970s, contralateral routing of signal (CROS) hearing aids (HA) were introduced as the first treatment option for SSD condition but never had widespread patient acceptance [16]. In the early 2000s, bone-anchored hearing aids (BAHAs) in SSD patients came into practice, offering some degree of success, as first reported by Vaneecloo et al. in 2000 [17]. A significant portion of SSD patients (54% to 84%) have debilitating tinnitus in the deaf ear, which is often reported to affect their quality of life negatively [18]. Tinnitus may result in emotional distress, clinical depression and communication problems, and may even play a role in auditory perception irrespective of hearing loss. BAHA or CROS have not shown to suppress tinnitus. In the early times, CI was not regarded as an option for SSD, as it was assumed that the electric input from a CI in the deaf side would interfere with the acoustic input of the other side with normal hearing.

4.5. The emergence of CI as a treatment option for SSD

In 2003, Prof. Van de Heyning from Antwerp University Hospital in Belgium was the first to implant a MED-EL CI device in an SSD patient with the primary aim of

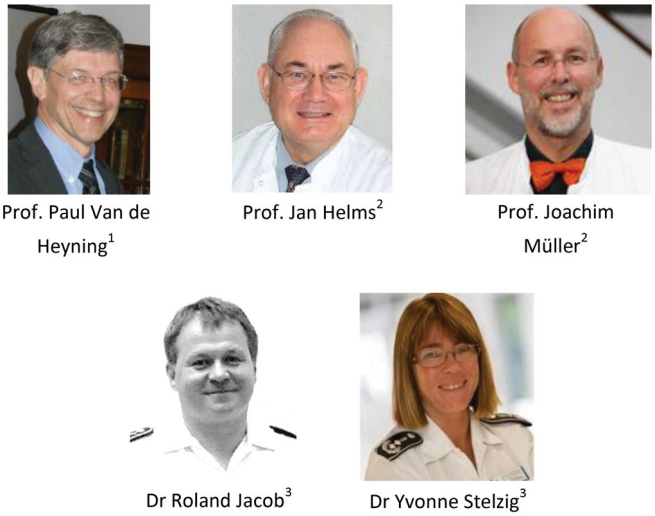

Figure 2. Pioneering CI surgeons who implanted MED-EL CI is SSD patients: [1]Antwerp University Hospital, Belgium, [2]Julius-Maximilian University of Würzburg, Germany, [3]Koblenz Military Hospital, Germany.

suppressing otherwise intractable tinnitus (Figure 2). This marked the beginning of MED-EL's scientific journey in treating SSD patients with its CI technology. Right after the first surgery, Prof. Van de Heyning initiated a prospective study to understand the effect of intracochlear electric stimulation *via* a CI in suppressing otherwise intractable tinnitus in the ipsilateral ear in SSD patients. The study was fully supported and sponsored by MED-EL but taking no role in the study design nor with data collection or analysis as the study progressed. While the research was taking place in Belgium, treating SSD patients with CI expanded to other EU countries.

In October 2005, the first patient in Germany received a CI for SSD – the implant with which aim was to restore the patient's binaural hearing was a MED-EL CI device. Prof. Helms consulted the patient, and the surgery was performed by Prof. Müller, Dr Jacob and Dr Stelzig in Koblenz Military Hospital in Germany. Dr Jacob continued his efforts to help SSD patients – who were mainly the military personnel – to regain binaural hearing with CI after the surgery. It was a personal communication from Dr Jacob that the soldiers affected with SSD had a much higher chance of dying in combat than normal-hearing soldiers. This was of great importance for Dr Jacob in treating the SSD patients with CI.

In 2008, the first prospective study focusing on tinnitus suppression with CI in SSD patients was published by Prof. Van de Heyning and his colleagues from the Antwerp University Hospital [19]. The study began in the year 2003 by recruiting twenty-two patients suffering from intractable tinnitus in their ipsilateral deaf ear. The patients were surgically implanted with MED-EL's COMBI + CI with the MEDIUM electrode (array length = 24mm) or a PULSARci^{100} with a FLEXSOFT^{TM} electrode (array length = 31mm). The study aimed to report on tinnitus loudness before and after CI treatment, with the follow-up time to up to twenty-four months. The study also reported on the tinnitus loudness with CI deactivated from each of the follow-up time points. The tinnitus loudness was measured on a linear scale of 0–10, with ten being the loudest and zero being the most silent. On average, the tinnitus loudness of twenty-two patients before CI treatment was 8.5 ± 1.3 which dropped to 3.5 ± 2.5 at one month postoperatively with CI activated, and the loudness increased to 7.0 ± 2.8 with CI deactivated. At the end of the study period of twenty-four months, the tinnitus loudness was at 2.5 ± 1.9 with CI activated and 6.1 ± 2.9 with CI deactivated (Figure 3). Data from this study showed no tinnitus reoccurring during the two years of follow-up; however, no reports on binaural hearing benefits, like speech understanding in noise and sound localisation abilities, were given. Still, this was a milestone research finding that paved the way to provide the SSD patients with a cochlear implant.

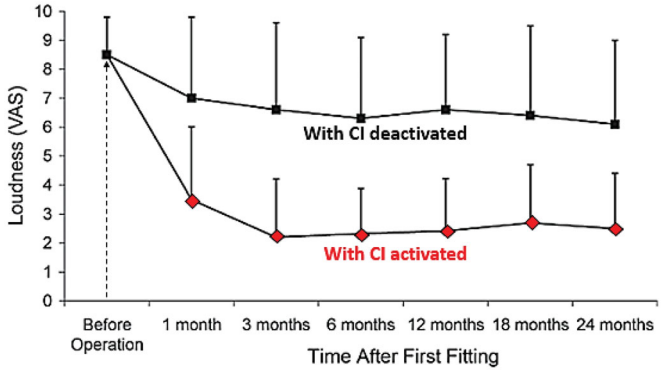

Figure 3. Tinnitus loudness as measured in the visual analogue scale (VAS) in SSD patients before (black square) and after (red diamond) CI treatment. Statistical analysis: Paired Student's *t*-test ($p < .05$). Graph created from data given in van de Heyning et al. [19].

In 2009, Dr Vermeire and Prof. Van de Heyning reported on binaural benefits of treating SSD patients with CI from the same group of SSD patients tested for tinnitus suppression with MED-EL CI at an earlier stage [20]. Enabling these SSD patients to use their CI in their ipsilateral (deaf) ear for a period of at least twelve months, they were assessed in their ability to understand speech in the presence of multiple speech streams or in competing noise, to localise sounds, identify the distance and movement associated with sound, quality and naturalness of sound, and to grade their listening effort required for quality of life (QoL) using The Speech, Spatial and Qualities of Hearing Scale (SSQ) questionnaire.

The grading system is applied on a linear scale from 0–10, with zero and ten representing minimal and complete sensitivity to the sound signal, respectively. Half of the patients in the group were using HA on the contralateral ear, whereas the other half had normal hearing (NH). The overall positive effect of the listening condition under binaural hearing is highly significant in the two groups. The improvement between preimplantation (HA group: mean = 2.5, SD = 1.1; NH group: mean = 4.2, SD = 1.3) and twelve months postimplantation in the binaural condition (HA group: mean = 4.2, SD = 1.4; NH group: mean = 6.0, SD = 1.4) was significant in both groups (Figure 4). It was further reported in the study that in daily living, the CI adds significantly to the acoustic hearing in both groups when it comes to speech understanding and quality of sound. Additionally, in the NH group, a significant beneficial effect on spatial hearing was found, whereas, in the HA group, the CI did not significantly add to spatial hearing. The results of the study suggested that CI can improve hearing in SSD combined with tinnitus patients.

In 2011, Dr Jacob and his colleagues published their long-term experience in restoring binaural hearing in SSD patients with CI from the German population [21]. Following the first SSD patient implanted with CI in 2005, additional twenty-four patients with SSD aged between 5–76 years were implanted with FLEXSOFT^{TM} electrode array at the Koblenz Military Hospital in Germany. Some of the SSD patients who received CI from this centre were aircraft engineers and military commanders with their job demanding sharp sound localisation ability. All twenty-five patients appreciated the high level of sound localisation and speech understanding in noise with their CI, in comparison to their prior use of CROS HA and BAHA.

Dr Katrien Vermeire
from Antwerp University
Hospital, Belgium

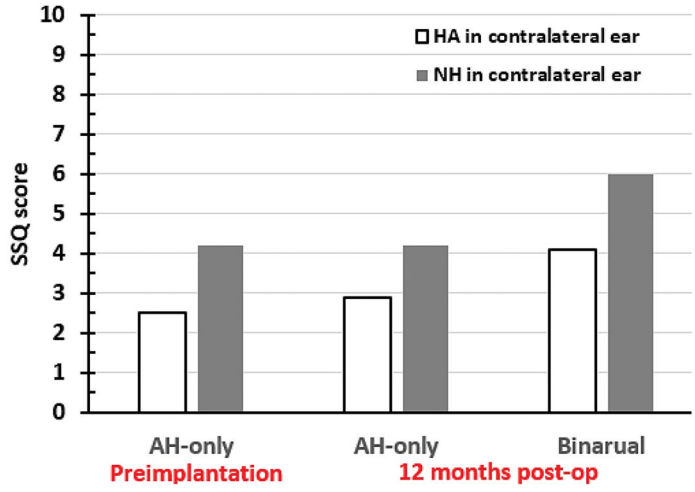

Figure 4. Total score of the SSQ for two groups; AH: acoustic hearing only; HA: hearing aid only; NH: normal hearing; Statistical analysis: Student *t*-test ($p < .05$). Histogram created from data given in Vermeire et al. [20].

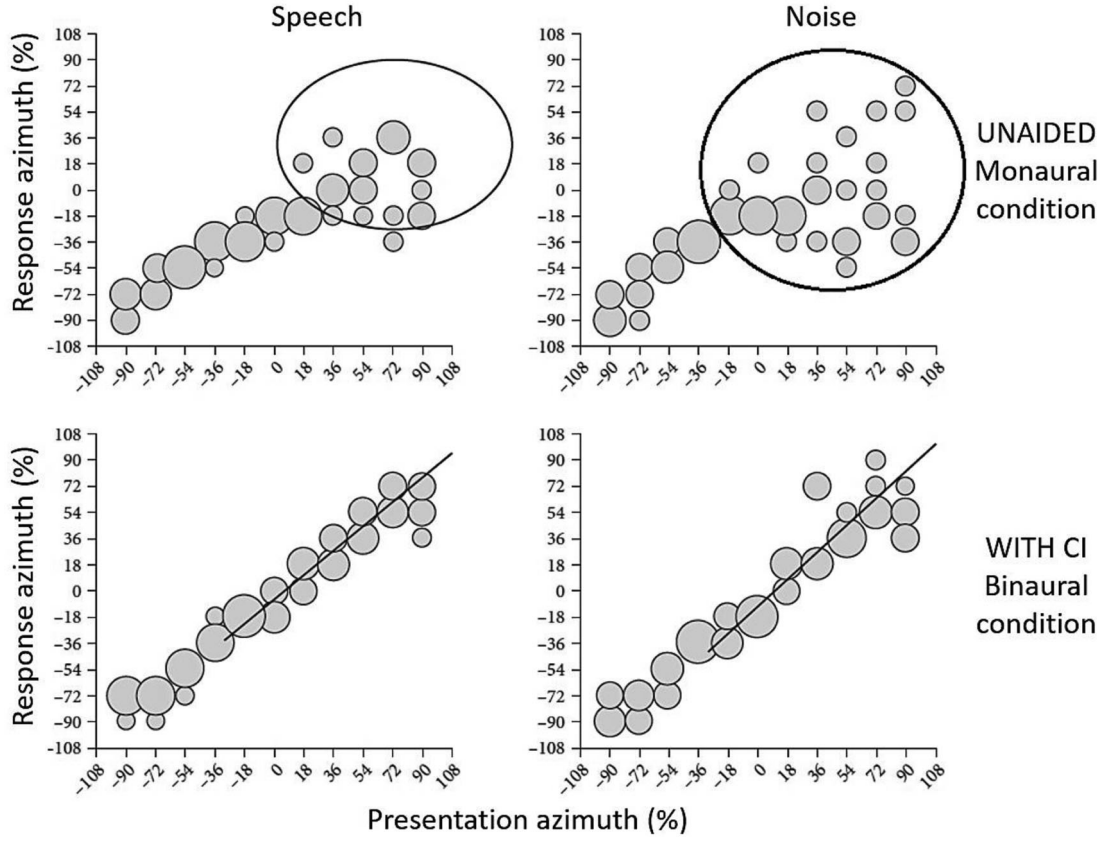

Figure 5. Data from one SSD patient implanted with CI, showing improvement in sound localisation. Presentation angle is plotted versus the response angle [21]. Reproduced by permission of Karger AG, Basel.

Figure 5 demonstrates the binaural benefit of sound localisation in one patient. In unaided condition, the patient struggled to localise the direction of both, speech and noise, whereas, with CI, the patient had no issue with localisation. In general, hearing fatigue while following long conversation is often a complaint with SSD patients and in this study, it was reported that three of the SSD patients were able to convert from part-time to full-time employment after CI treatment, suggesting little or no hearing fatigue experience with long conversations after CI treatment.

Dr Peter Nopp

Dr Peter Schleich

Figure 6. Director of Signal Processing, Research and Development, and Research engineer, respectively, from MED-EL headquarters in Innsbruck, Austria.

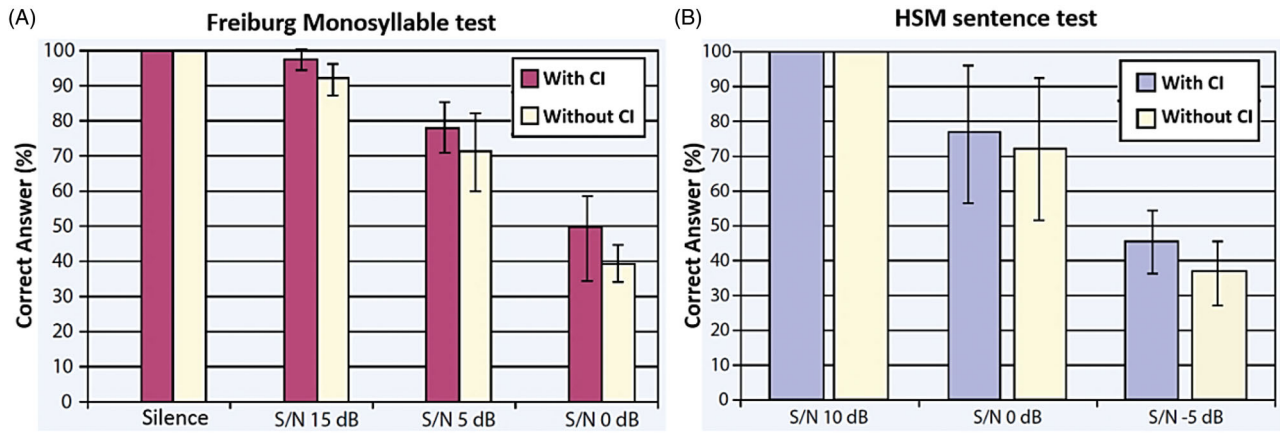

Figure 7. Freiburg monosyllable test and HSM sentence test in thirteen patients with 60 dB input loudness in silence and white noise (S/N: 5- and 15-dB) with and without CI activated [22]. Reproduced by permission of Springer Nature.

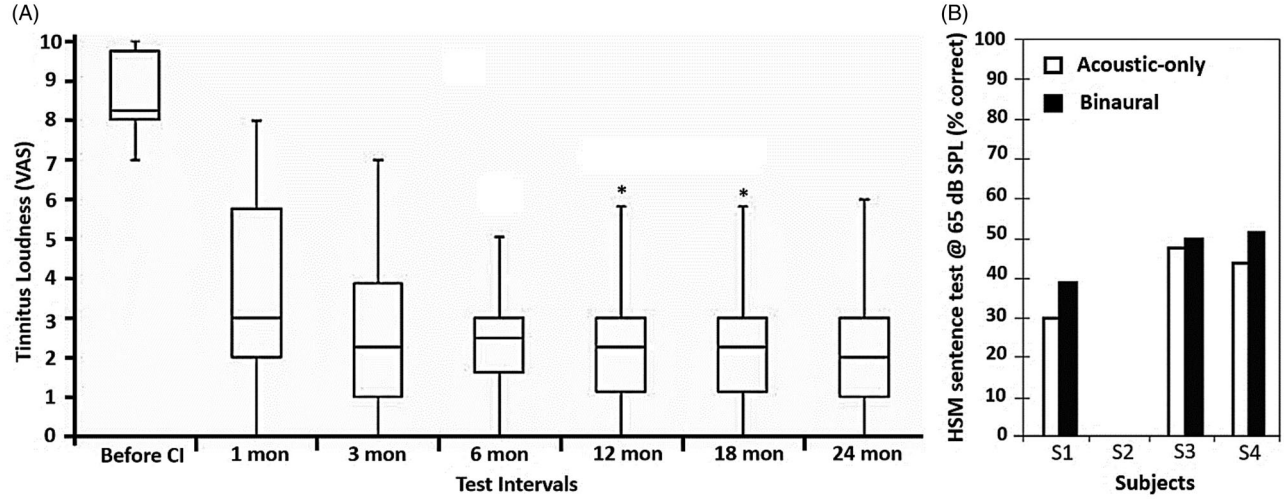

Figure 8. Tinnitus loudness on VAS, showing a decrease in tinnitus loudness with CI over time (A) [23]. CI in SSD patients ($n = 4$) with binaural hearing, showing better HSM sentence score compared to the acoustic only ear at −5 dB SNR (noise presented at 5 dB louder than the sentence) [24]. Statistical analysis: Student *t*-test ($p < .05$). Reproduced by permission of Springer Nature.

4.6. MED-EL's involvement in assessing CI implanted SSD patients

MED-EL, as a patient-oriented medical device company, took responsibility to engage directly with SSD patients implanted with CI on their deaf side to gain more insights into how CI influences their speech understanding. Dr Nopp and Dr Schleich, both employed at MED-EL, took the opportunity to perform audiological tests to evaluate the benefits of CI in SSD patients ($n = 13$) implanted at the Koblenz Military Hospital since 2005 [22] (Figure 6).

Thirteen patients implanted with a MED-EL CI device were available for the audiological tests that comprised of Freiburg monosyllable word test (Figure 7(A)) and HSM (Hochmair-Schulz-Moser) sentence test in noise (Figure 7(B)). The patients were exposed to the acoustic signal of 60 dB loudness in both, absolute silence and combination with white noise at different SNRs of 15-, 5- and 0-dB. On average, under all test conditions with CI activated, patients scored more per cent correct answers in comparison to the test condition without CI activated. Mimicking the real-world listening environment, where the background noise equalled the meaningful sound signal (signal-to-noise ratio (S/N) at 0 dB) in several situations, the SSD patients scored 45% correct with CI activated, which is 10% higher than without CI activated mode. This was yet another evidence that demonstrated the benefit of CI in SSD patients.

In 2011, a couple of other studies – from the Antwerp Medical University and Koblenz Military Hospital – reported on CI (MED-EL device) as an effective treatment option in minimising tinnitus in SSD patients as measured based on VAS scale [23] and as well better hearing in noise as tested with HSM sentence test in noise [24]. Figure 8(A) shows the tinnitus loudness based on VAS with a decrease in tinnitus loudness results with CI over time; Figure 8(B) shows the binaural hearing with better HSM scores compared to the acoustic-only ear. These are encouraging early results, demonstrating the benefits of CI in SSD subjects.

Table 1. List of studies that reported on the hearing benefits of MED-EL CI in SSD patient.

No.	Study title	No. of patients	Year	Country
1	Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation [19].	22	2008	Belgium
2	Neural tonotopy in cochlear implants: an evaluation in unilateral cochlear implant patients with unilateral deafness and tinnitus [25].	14	2008	Belgium
3	Curing tinnitus with a cochlear implant in a patient with unilateral sudden deafness: a case report [26].	1	2009	Germany
4	Binaural hearing after cochlear implantation in subjects with unilateral sensorineural deafness and tinnitus [20].	20	2009	Belgium
5	*Audiologische Ergebnisse mit Cochlea Implantat bei einseitiger Taubheit* [22] (Eng. Audiological results with a cochlear implant in unilateral deafness).	13	2011	Germany
6	Cochlear implantation as a durable tinnitus treatment in single-sided deafness [23].	26	2011	Belgium
7	Preliminary speech recognition results after cochlear implantation in patients with unilateral hearing loss: a case series [24].	4	2011	Germany

4.7. CE marking of MED-EL CI for SSD in the European Union

Until 2013, the CI was not officially indicated for SSD, although it was in off-label use by the clinicians on their responsibility and in the interest of restoring binaural hearing, especially in children. MED-EL took the first initiatives in bringing all scientific evidence together to demonstrate the binaural benefits of CI in SSD patients to the notified bodies. Table 1 lists the peer-reviewed publications that reported on the binaural hearing benefits of MED-EL CI in SSD patients, and that was submitted to the TÜV (notified body) for CE marking.

In 2013, MED-EL was the first CI manufacturer to CE-mark its CI device to be implanted in both adults and children affected by SSD. This was a colossal milestone in MED-EL's journey of expanding CI as a treatment option to more indications which were not considered for CI earlier but are certainly benefitting from CI. This allowed the clinicians in the European Union (EU) and countries recognising CE mark to officially implant CI in both adult and children suffering from SSD.

4.8. Importance of long electrode arrays in SSD patients

Tinnitus suppression by electric stimulation inside the cochlea *via* CI, mainly using long electrode array, has been reported by different studies from Belgium [19,20,23,25] and Germany [26]. However, electric stimulation in which portion of the cochlea results in the suppression of tinnitus was not reported earlier.

In 2012, Prof. Van de Heyning and his colleagues investigated seven SSD patients who were suffering from incapacitating tinnitus and were treated with MED-EL CI (FLEXSOFT^{TM} electrode array) [27]. Preimplantation, the average tinnitus loudness was 22.9 dB SPL. When activating the first four basal electrode channels, no significant changes in tinnitus sensation level were observed. Postimplantation, when all electrodes were activated, a significant decrease of the average tinnitus loudness was measured with reaching 13.6 dB SPL. After six months, the average tinnitus loudness decreased further down to 9.6 dB SPL (Figure 9).

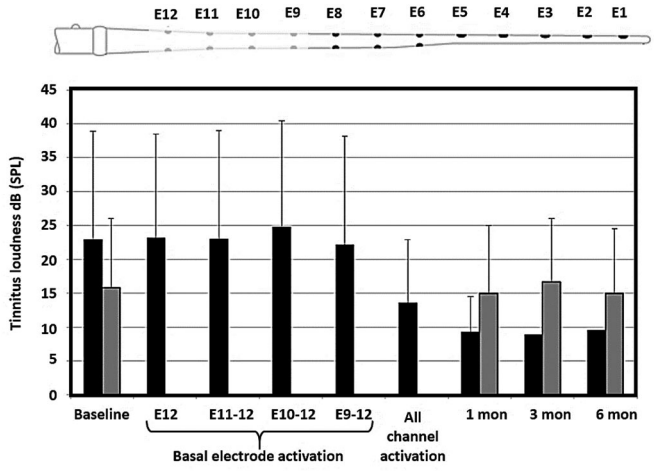

Figure 9. Psychoacoustic tinnitus loudness in dB at baseline and after CI with basal channels and complete CI stimulation for the CI group (black bars) and the control group (grey bars) [27]. Statistical analysis: Wilcoxon signed-rank test ($p < .05$). Reproduced by permission of Elsevier B.V.

The study concluded that electric stimulation of the basal eight millimetres of the cochlea does not seem to reduce tinnitus in SSD patients effectively. However, electric stimulation of the complete cochlea seems to be more effective, and that explains the importance of long length electrode covering a major portion of the cochlea.

One of the challenges of multichannel CI in SSD patients is offering a *matching CI hearing assisted by CI in the ipsilateral deaf ear to the acoustic hearing in the contralateral, normal functioning ear*. It is a known fact that the cochlea is tonotopically organised to process high to low frequency sound signals from the base of the cochlea to its apex, respectively (Figure 10). Even in normal hearing, the tonotopic representation of an acoustic signal, i.e. the cochlear place where temporal information is presented, is crucial to complex pitch perception, suggesting that for periodic sounds, the temporal information must be presented at the right tonotopic place in order to elicit a salient pitch percept [28]. Within the cochlea, electric impulses represent a particular frequency, and acoustic signal delivered through CI electrode should land in a location inside the cochlea where the neural fibres are responsible for processing specific frequencies – in simple terms, this phenomenon is called *place-pitch*. The electrode array length carrying the stimulating channels plays a significant role in closely matching electric stimulation to neural elements – both representing a specific acoustic frequency.

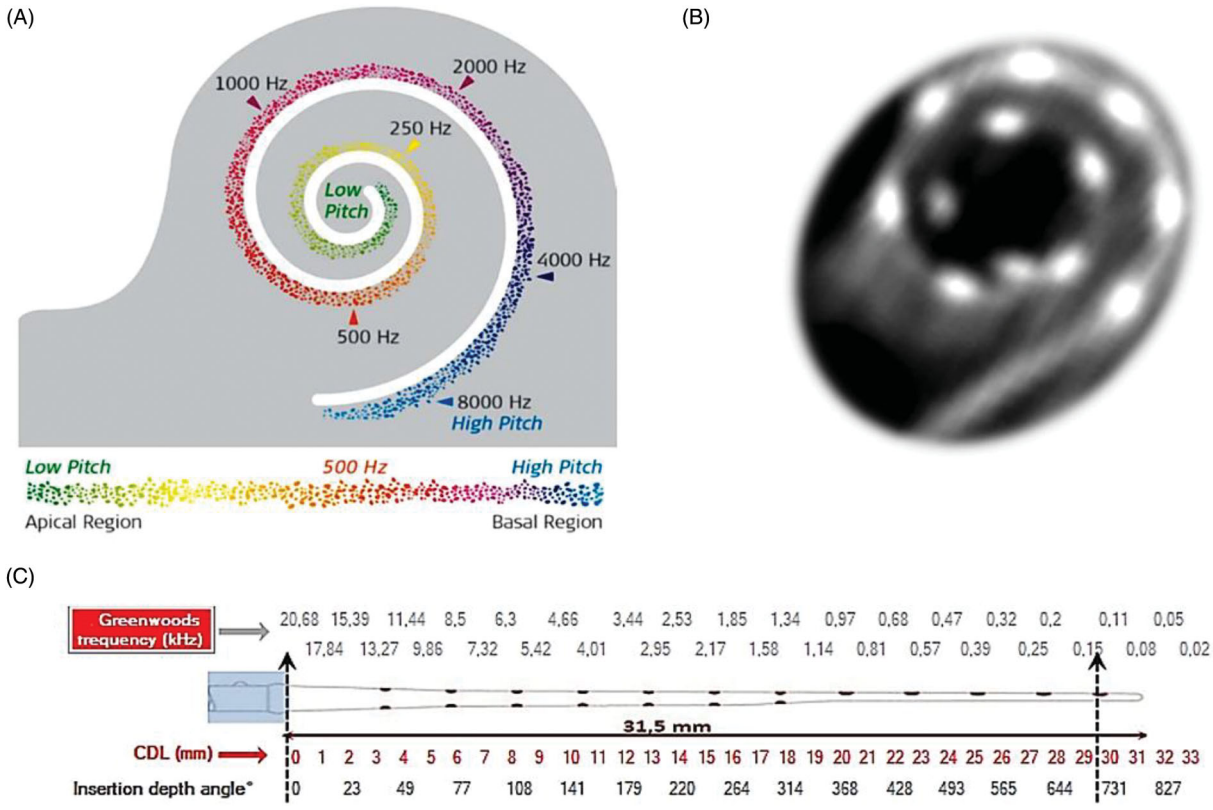

Figure 10. Tonotopic representation of human cochlea based on Greenwood frequency function (A). Postoperative radiographic image of a fully inserted FLEXSOFT^{TM} electrode array (B). Place-pitch of FLEXSOFT^{TM} over the Greenwood's frequency map of an average-sized cochlea (C). (image courtesy of MED-EL).

Figure 11. A team of sound coding engineers from MED-EL and [1]University of Innsbruck, Austria, [2]Antwerp University Hospital, Belgium (audiologist and CI surgeon), investigated the electric-acoustic pitch comparisons in SSD CI users.

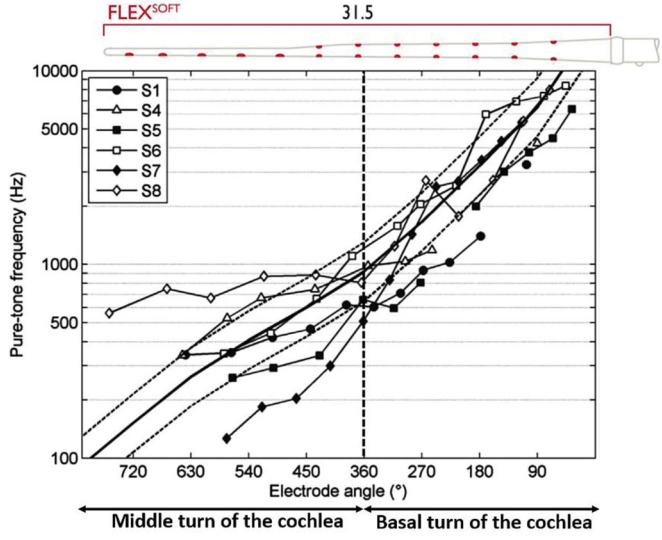

Figure 12. Individual frequency-place functions for electric stimulation in six subjects with reliable matches. The solid line represents the place frequency as predicted by Greenwood; the dotted lines indicate the Greenwood function shifted up and down by half an octave, respectively. The dotted vertical line separates the basal turn and middle turn of the cochlea at 360° insertion depth angle [29]. Statistical test: One sample *t*-test. Reproduced by permission of Elsevier B.V. Electrode array is added on top of the image to show how deep this electrode array would cover the cochlea.

In 2014, Dr Schatzer – presently appointed as the Team leader for Sound Coding at MED-EL, and at the time a post-doctoral researcher at the University of Innsbruck in Austria – together with other researchers investigated SSD patients ($n = 8$) implanted with MED-EL CI device in their deaf ear [29] (Figure 11).

That study aimed to investigate electrode place-pitch perception by stimulating individual channels along the CI electrode array in the deaf ear and ask the participants to match it with their acoustic hearing in the contralateral, normal-hearing ear.

In other words, the aim was to investigate the match between hearing assisted with CI in the deaf ear and the acoustic hearing in the contralateral, normal-hearing ear. The electrode array length was 24 mm (MEDIUM) or 31 mm (FLEXSOFT^{TM}), each carrying twelve independent stimulating channels and reaching to a maximum angular insertion depth of up to 758° – enough to electrically cover the basal and the middle turn of the cochlea. In terms of frequency coverage, it ranged from 8,500Hz at the base to almost 125 Hz at the apical end. The acoustic stimuli were pure tones with durations of 500 ms, and the level of electric and acoustic stimuli was loudness balanced before pitch matching. On average, the place-pitch mismatch generally increases with decreasing electrode insertion angle as measured from the round window – Figure 12 shows the electrode place-pitch according to Greenwood's frequency function. The mean place-pitch downward shifts of approximately one-third of the octave from Greenwood's prediction in the basal and middle regions were observed, which is highly appreciable, considering the crude form of electric signal matching the acoustic signal given through the CI electrode. In the absence of any temporal cues, place-pitch in the apical region becomes increasingly variable. This is consistent with electric stimulation models [30], and with observations for apical stimulation, temporal cues are more reliable pitch cues than place cues [31]. As shown in the second experiment in this and a later study by Rader et al. [32], the addition of appropriate temporal cues on apical electrode channels restores a close-to-natural tonotopic pitch perception in CI recipients with long electrode arrays. The outcome of this and subsequent studies scientifically demonstrated the importance of matching place (electrode) and rate (intracochlear neural elements responsible for desired frequency) of stimulation in a CI for tonotopic pitch perception, especially at low frequencies, and this is only possible if there is a physical match between the CI electrode array length and the cochlear duct length.

In 2016, the findings by Schatzer et al. [29] were further confirmed by Prof. Baumann and his colleagues from the Johann Wolfgang Goethe University Hospital Frankfurt in Germany. They evaluated seven SSD patients implanted with FLEXSOFT^{TM} (array length of 31.5 mm) and FLEX28^{TM} (array length of 28 mm) [32]. Such electrode array lengths reach almost to the end of cochlear middle turn where the neural elements process low-frequency acoustic stimuli. In their study, apical channels of these electrodes were stimulated at place-dependent rates (pulses/second), representing the tonotopic place frequencies at the respective electrode contacts as derived from postoperative computed tomography (CT) scans. SSD patients subjectively matched these stimuli to pure tones presented to their normal-hearing ear on the contralateral side. Figure 13 shows the collapsed data of matched acoustic frequencies as a function of precalculated electric stimulation rate where each data point represents the median of six trails of the pitch matching procedure for a given electrode. Median matched frequencies were in the range between 79.7 Hz and 1,683Hz, with electric stimulation rates between 106 Hz and 1,784Hz. The adjusted median pitch generally increased with increasing stimulation rate. The average slope calculated by linear regression analysis amounted to 0.958, which again reflected a linear one to one relation between predetermined electric stimulation and matched average pitch. In other words, the study demonstrated that place-dependent stimulation rates allow for an unparalleled restoration of tonotopic pitch perception in CI users. These two studies [29,32] along with Landsberger et al. [31] demonstrate the importance of covering the entire frequency range inside the cochlea with a longer CI electrode array for place matching, and rate coding at place-dependent

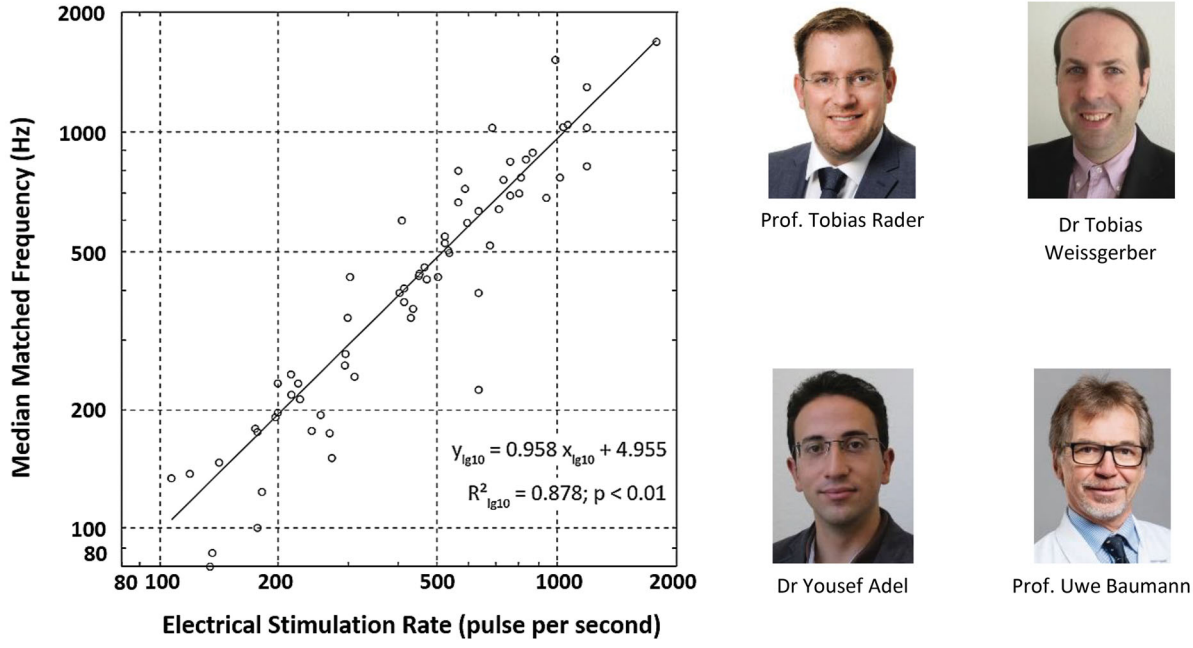

Figure 13. Matched pitch frequencies (medians) as a function of the electrode place-dependent electric stimulation rate [32]. Reproduced by permission of Elsevier B.V. Clinicians from Goethe University Hospital Frankfurt in Germany, evaluated the SSD patients implanted with MED-EL CI for place-pitch match.

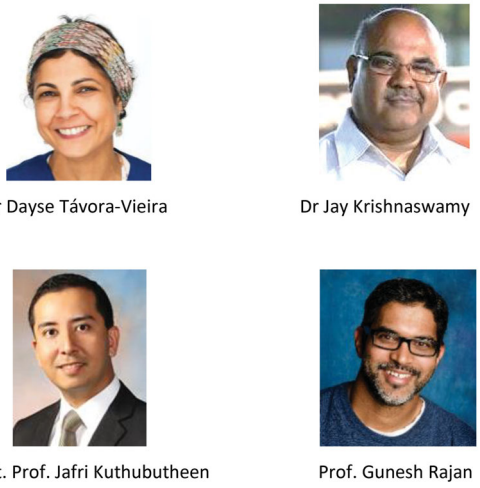

Figure 14. Audiologists and CI surgeons from the University of Western Australia, who were involved in the evaluation of SSD patients implanted with MED-EL CI device.

stimulation rates to help the CI recipient to experience close to natural hearing.

4.9. Long-term follow-up in CI implanted SSD patients

Whilst many studies reported on the short-term benefits of CI in SSD patients – which were enough to check the technology's proof of principle – the long-term benefits are what is essential for clinicians to get convinced with the technology.

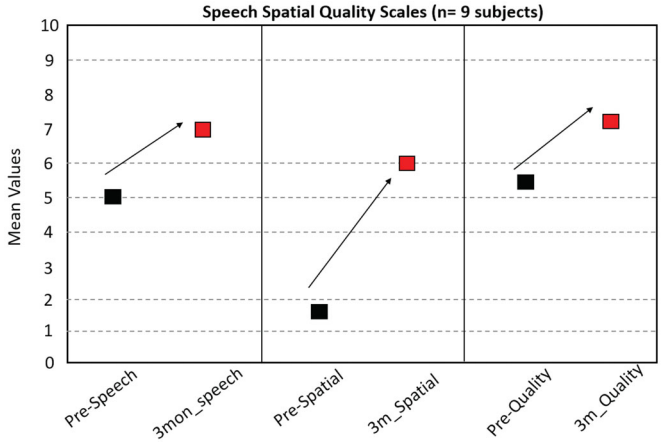

Figure 15. Results of SSQ subscales. Comparison of preoperative to three-months post-op scores. The data is displayed with mean values. Increase in mean values are seen from pre to post CI. Statistical analysis: Wilcoxon signed rank-test ($p < .05$). Plot created from data given in Távora-Vieira et al. [33].

In 2013, MED-EL took the initiative in moving the CI as a treatment option for SSD patients to Australia. Since CI was not approved to treat SSD patients in Australia at the time, MED-EL sponsored a study. Prof. Rajan and his colleagues from the University of Western Australia implanted MED-EL CI with FLEXSOFT^{TM} electrode array in nine unilaterally deaf patients, with and without tinnitus ipsilaterally [33] (Figure 14).

The SSQ was used to evaluate the subjective perception of hearing outcomes. All nine patients reported that the CI improved their hearing in the most challenging situations. This subjective improvement of the hearing was demonstrated in the SSQ scores at three months postoperatively, compared to presurgical scores (Figure 15).

In 2013, Prof. Rajan and his colleagues from the University of Western Australia and Sydney Cochlear Implant Centre conducted a prospective study to learn the long-term hearing benefits up to twelve months postoperatively of CI treatment in SSD patients ($n = 5$) [34]. Duration of unilateral HL was thirty-five years on average (ranging from twenty-seven to forty years of age), and the mean age at CI implantation was fifty-five years (ranging from forty-eight to sixty-eight years of age). All patients were implanted with the MED-EL CI device with FLEXSOFT^{TM} electrode array and with full intracochlear insertion. The SSQ results revealed that all SSD patients had significant improvement over time after surgery (Figure 16). Also, the results showed that CI recipients with more than twenty-five years of unilateral deafness could achieve a significant hearing improvement, as it was reflected from the SSQ questionnaire. Thus, patients with long-term unilateral hearing loss (UHL) should not be denied a CI and based solely on this criterion.

In 2015, the same group of specialists from the University of Western Australia reported on hearing benefits and tinnitus suppression in long-term follow-up. The follow-up lasted up to twenty-four months postoperatively after CI treatment in SSD patients ($n = 8$) [35]. All patients were implanted with the MED-EL CI device with FLEXSOFT^{TM} or FLEX28^{TM} electrode array on the ipsilateral deaf ear. Before CI surgery, the patients were asked to try a conventional CROS, and the BAHA mounted on the soft band for two weeks each to give the patients the option to experience a non-invasive or less invasive rehabilitation option for treating UHL. The subjective testing with SSQ questionnaire (scale of 0–10) showed a significant improvement in speech, spatiality and quality of hearing overtime until the twenty-fourth month of the test intervals. Mean scores for the subscale *speech* ranged from 4.69 ± 1.83 preoperatively to 7.65 ± 1.10 at twenty-fourth month postoperatively. Mean scores for the subscale *spatial* ranged from 2.61 ± 1.60 preoperatively to 7.37 ± 1.20 at the twenty-fourth month postoperatively. Mean scores for the subscale *quality of hearing* ranged from 6.16 ± 1.87 preoperatively to 8.15 ± 0.95 at the twenty-fourth month postoperatively (Figure 17(A)). The results of the *tinnitus reaction questionnaire* (TRQ) are shown in Figure 17(B) with the mean scores ranging from 48.8 ± 27.15 at preoperative testing and 1.75 ± 4.2 at twenty-fourth month, postoperatively. The results of this study indicated that in patients with UHL, the CI use improves the subjective perception of hearing and decreases the disturbance of tinnitus, which may, in turn, contribute to an overall positive subjective impression of benefit.

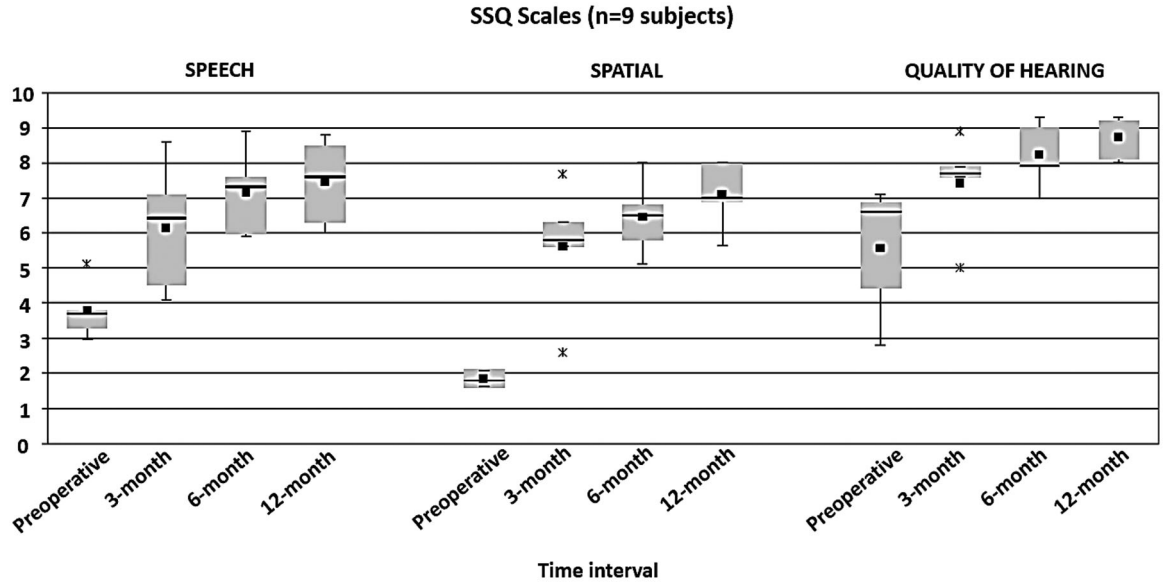

Figure 16. Results of the three SSQ scales measured preoperatively, and three, six and twelve months postoperatively. Mean values are depicted as black squares, median values as horizontal lines, and asterisks show extreme values, that is outliers [34]. Statistical analysis: ANOVA test ($p < .05$). Reproduced by permission of Wolters Kluwer Health/Lippincott Williams.

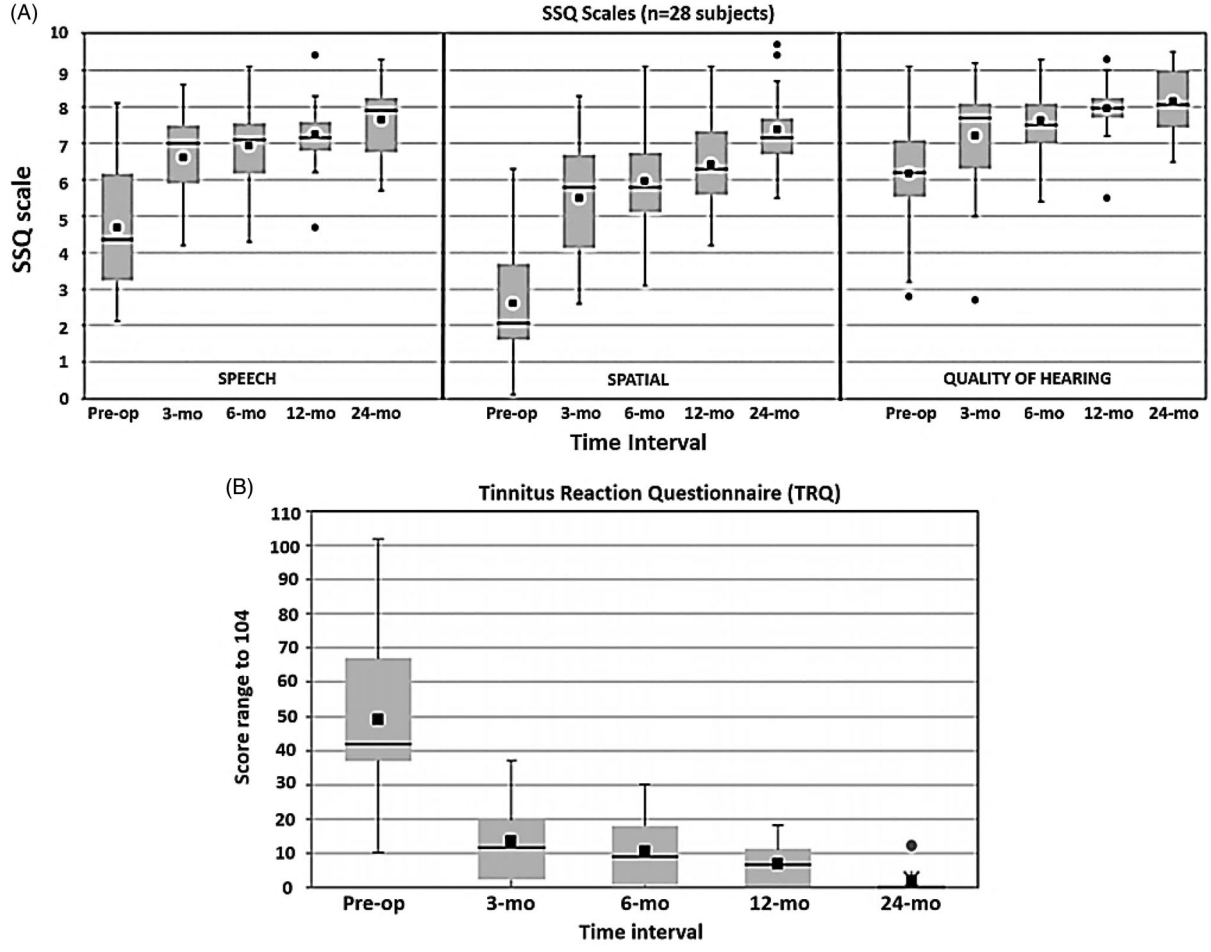

Figure 17. SSQ hearing subscale results over time. Median values are displayed as a horizontal line, mean values as black squares. Asterisks denote outliers (A). Tinnitus reaction questionnaire results over time. Median values are displayed as a horizontal line, mean values as black squares (B) [35]. Statistical analysis: ANOVA test ($p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

In 2016, Prof. Mertens and her colleagues from the Antwerp Medical University in Belgium performed qualitative/subjective assessment of their SSD patients ($n = 23$) who were implanted with MED-EL CI device, to conduct a long-term analysis of the tinnitus reduction [36]. The VAS scale was used to assess subjective tinnitus loudness

preoperatively, and at one, three, six, twelve and thirty-six months postoperatively, as well as at the long-term (LT) test interval. A simple *analogue* line with 10 cm in length was used for the test, anchored by *quiet* and *very loud*. The patients marked the points that represented their perception

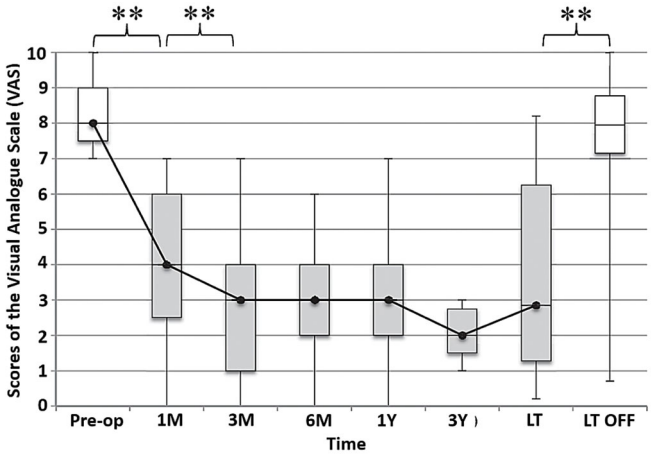

Figure 18. VAS scale for assessing tinnitus loudness preoperatively, and 1, 3, 6, 12 and 36 months postoperatively, and at the long-term test interval. White bars represent the CI_{OFF} condition and grey bars the CI_{ON} condition [36]. Statistical analysis: Wilcoxon signed-rank test ($p < .05$). Reproduced by permission of Elsevier B.V.

from the left end of the line to the marked point in millimetres. A significant reduction and thus, improvement were found between the VAS scores preoperatively (8) and the VAS score one month after the first fitting (4). A further significant decrease (3) was found three months after the first fitting. At the subsequent test intervals at six, twelve and thirty-six months after the first fitting and at the long-term of ten years, the $VAS\text{-}_{loudness}$ scores remained significantly stable. Upon switching *off* the CI, the tinnitus reverted to the preoperative level (Figure 18). One of the best parts observed in this long-term follow-up was that all of the twenty-three patients used their CI seven days a week, from waking up in the morning until going to sleep. The study demonstrated that the burden of discomfort was high with tinnitus and that patients were willing to use the CI all day long in order to help to suppress it.

In 2019, a joint report from the University of Western Australia and Antwerp Medical University evaluated the long-term benefits and hearing outcomes from a large cohort of CI users with SSD [37]. A total of thirty-three patients (twelve from Antwerp and twenty-one from Perth) received MED-EL CI device with FLEXSOFT^{TM} or FLEX28^{TM} electrode array. On average, the patients had five years of CI experience at their testing date (range: 4–10 years). The subjective hearing performance results from the SSQ measured preoperatively and after long-term CI use are shown in Figure 19(A). The total mean score measured preoperatively was 4.09 ± 1.58, and this increased significantly to 5.68 ± 2.44 after the long-term CI use. The results from the sound localisation measurements are presented in Figure 19(B) in terms of root mean square error (RMSE) values calculated in bimodal and acoustic hearing (AH) only conditions. The RMSE calculations ($n = 29$) in bimodal condition resulted in a mean value of 24.6 ± 13.8 degrees (range: 11.0–73.7 degrees), and the mean value increased to 60.0 ± 24.6 degrees in the AH condition (range: 13.5–107.0 degrees), showing the sound localisation benefits with binaural hearing.

Overall, all these reports demonstrate the long-term benefits of CI use in patients with SSD in improving their hearing abilities in background noise, as well as in suppressing tinnitus.

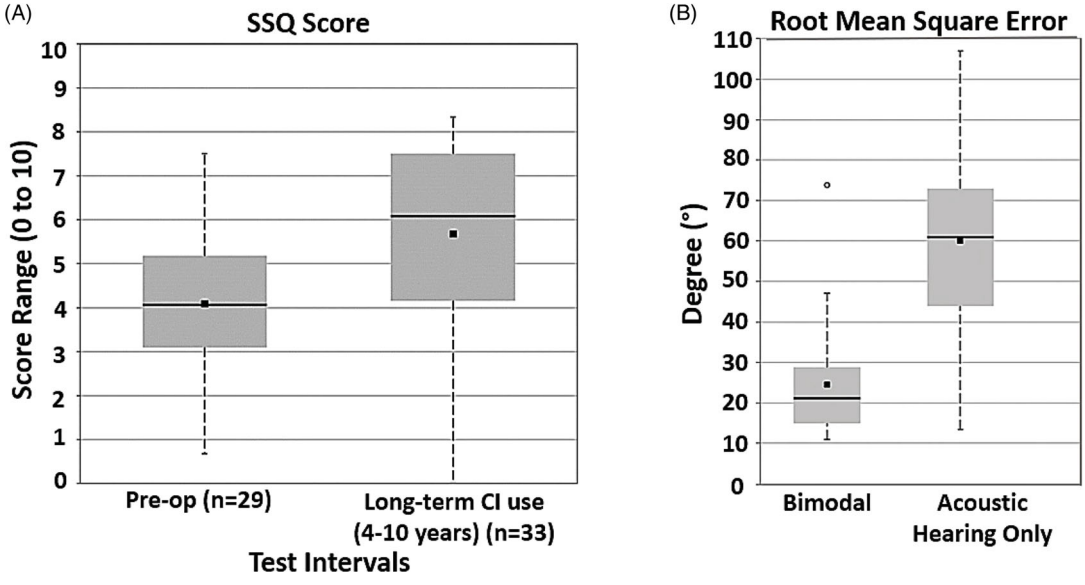

Figure 19. Results of the SSQ as measured preoperatively and after the long-term CI use. Higher scores indicate better subjective hearing performance (A). Results of localisation parameters, such as the RMSE for patients with SSD in bimodal and acoustic hearing conditions (B). Smaller RMSE values represent better localisation accuracy abilities. Mean values are depicted as black quadrants and median values as horizontal lines; the black circle represents an outlier [37]. Statistical analysis: Wilcoxon signed-rank test ($p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

4.10. Degree of acceptance of CI by SSD children

With normal-hearing on one ear and CI on deaf ear could be quite disturbing for the SSD patients if the CI hearing is not matching with the normal-hearing ear. Therefore, the acceptance of CI device by the SSD patients, especially paediatric, is a key factor.

Figure 20. Clinicians from Ruhr University Bochum, Germany, who evaluated the audiological and clinical results of CI in children with congenital SSD.

In 2017, Dr Thomas and his colleagues from Ruhr University Bochum in Germany reported their experience on the acceptance level of CI amongst twenty-one congenital SSD children aged <12 years [38] (Figure 20). Eleven out of twenty-one patients were implanted with MED-EL CI device: FLEX28™ electrode array (28 mm) in four patients and STANDARD (31.5 mm) in seven patients. Nine out of twenty-one patients were implanted with Cochlear™ (COH) device with Contour Advance® electrode array (18 mm) in four patients and Slim Straight electrode array (20 mm) in five patients. The remaining one patient was implanted with Advanced Bionics' HiFocus™ electrode array (18.5 mm).

Parents of these twenty-one patients were asked to define the following:

1. average daily wearing time of the speech processor (h/day)
2. level of acceptance of the speech processor by the child (0 = no acceptance, 10 = maximal demand for CI)
3. behaviour changes of the child which attracted the attention of the parents postoperatively (0 = no change, 10 = maximal change)
4. degree of stigmatisation by the cochlear implant (0 = no stigmatisation, 10 = maximal stigmatisation)
5. parental level of satisfaction (0 = no satisfaction, 10 = maximal satisfaction)
6. the decision in favour of repeating the cochlear implantation (0 = would not choose cochlear implantation again, 10 = would choose cochlear implantation again)

Table 2 summarises the demographics of all twenty-one patients, along with their parents' responses to the above questions. Just focusing on the MED-EL device implanted patients, all patients used the speech processor for 10–12 h/day, and in terms of child's acceptance of the speech processor, all patients graded close to the full acceptance. None of the MED-EL CI users showed any stigmatisation of the CI device, and parental satisfaction of their children's CI use was very high, with a minimum value of at least seven. When asked whether CI was the right choice, all MED-EL CI users graded with the maximum score, conveying the binaural benefits of CI in SSD, as well that the hearing offered by the CI on the deaf ear matches very well with the acoustic hearing of their normal-hearing ear.

Table 2. Patient age, implanted CI brand and parents' answers to the questionnaire [38].

No.	Age at implantation (years; months)	CI brand	Average daily use of audio processor (h)	Child's acceptance of audio processor	Postoperative behaviour change	Stigmatisation	Parental satisfaction with CI	Was CI the right choice?
1	7; 2	Cochlear™ CI24 RE	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
2	9; 0	Cochlear™ CI24 RE	0	0	None	7	5	5
3	8; 8	Cochlear™ CI24 RE	6	5	Positive & negative	8	7	8
4	4; 8	Cochlear™ CI24 RE	3	5	None	0	7	6
5	7; 2	Cochlear™ CI422	12	10	Positive	8	10	10
6	10; 6	MED-EL STANDARD	12	8	Positive	n/a	7	10
7	8; 0	AB HiFocus™	12	9	Positive	1	7	8
8	7; 1	Cochlear™ CI422	10	9	Positive	0	5	4
9	3; 6	Cochlear™ CI422	5	7	None	0	9	9
10	0; 9	MED-EL FLEX28™	10	9	Positive & negative	0	9	9
11	11; 3	MED-EL STANDARD	12	10	Positive	0	7	10
12	4; 6	MED-EL STANDARD	12	10	None	0	9	10
13	4; 1	MED-EL FLEX28	12	10	Positive	0	10	10
14	1; 2	Cochlear™ CI422	10	9	None	0	10	9
15	4; 8	MED-EL FLEX28™	12	7	None	0	6	9
16	6; 1	Cochlear™ CI422	12	6	Positive	0	10	10
17	1; 9	MED-EL FLEX28™	10	10	None	0	10	10
18	4; 8	MED-EL STANDARD	12	9	Positive	1	n/a	10
19	7; 1	MED-EL STANDARD	12	9	n/a	0	7	10
20	2; 6	MED-EL STANDARD	12	8	n/a	n/a	9	8
21	0; 10	MED-EL FLEX28™	10	n/a	n/a	n/a	n/a	n/a

Numbered scores, except for daily use, are visual analogue scale wherein 0 = none/minimum and 10 = maximum (n/a = not answered). CI indicates a cochlear implant. Cochlear™ CI24 RE array length = 18mm; Cochlear™ CI422 array length = 20mm; MEDEL FLEX28™ array length = 28mm; MEDEL STANDARD array length = 31mm, Advanced Bionics HiFocus™ array length = 18.5 mm.

The electrode array length of either 28 mm or 31 mm with MED-EL devices is of importance, as it offers close to complete electric coverage over the entire frequency range. This was not the case with other groups of patients implanted with shorter electrode array lengths from other CI brands, which, consequently, graded lower scores to both the parental satisfaction with CI and if the CI was the right choice. In terms of stigmatisation of CI, none of the MED-EL CI users was stigmatised, whereas patients implanted with other CI brands registered some degree of stigmatisation towards their CI.

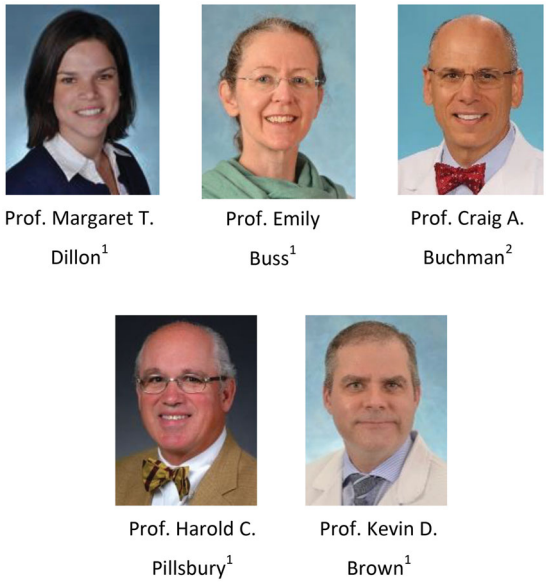

Figure 21. Clinicians from [1]University of North Carolina, USA, and [2]Washington University, USA, who were involved in the evaluation of tinnitus reduction and improvement of spatial hearing among SSD patients implanted with CI.

4.11. Evidence from the USA supporting CI as a treatment modality for SSD

From 2016–17, Prof. Dillon and her colleagues from the University of North Carolina at Chapel Hill in the USA implanted MED-EL CI devices with STANDARD electrode array in twenty adults who were suffering from moderate to profound SNHL in one ear, along with tinnitus [39] (Figure 21). The average patient age at the time of implantation was fifty years (range: 22–63 years), and the primary aim of CI was to restore binaural hearing. Tinnitus relief and hearing benefits with CI were subjectively evaluated by asking the patients to rank their tinnitus and hearing level before and up to twelve months after surgery.

Figure 22(A) plots perceived tinnitus severity as measured with the Tinnitus Handicap Inventory (THI) (twenty-five item questionnaire) where a lower value indicates less severe tinnitus. Patients reported a significant reduction in tinnitus severity over the study period, and this was noted as early as at the first-month interval, upholding until the study's end-point. Perceived hearing abilities, as measured with SSQ, are plotted as a function of the test interval in Figure 22(B).

A higher value indicates greater perceived ability. The total score demonstrates an improvement in perceived abilities between the preoperative and one-month postoperative intervals, with further improvement by the twelfth month. Overall, the study demonstrates benefits with CI in SSD patients in suppressing tinnitus and in improvising the localisation/hearing abilities.

4.12. FDA approval of MED-EL's CI for SSD patients

In 2017, MED-EL decided to strive for FDA (Food and Drug Administration) approval for its CI device to be officially recognised as a treatment option for SSD patients in the USA. Internally at MED-EL, Dr Ilona Anderson and Dr Allison Racey insisted and did the paperwork for the FDA submission. An FDA clinical trial was carried out by the clinicians from the University of North Carolina to evaluate the potential benefit of CI use for adults with UHL [40]. The cohort included twenty adults with moderate-to-profound SNHL in one ear, and near-normal hearing in the contralateral ear, as mentioned in the previous section [39]. The MED-EL STANDARD electrode was implanted in the impaired ear. Outcome measures included (A) masked sentence recognition with the target at 0° and the masker at −90°, 0°, or 90°, (B) sound localisation on the horizontal plane (11 positions, −90° to 90°), and (C) word recognition in quiet with the CI alone. The distribution of data for

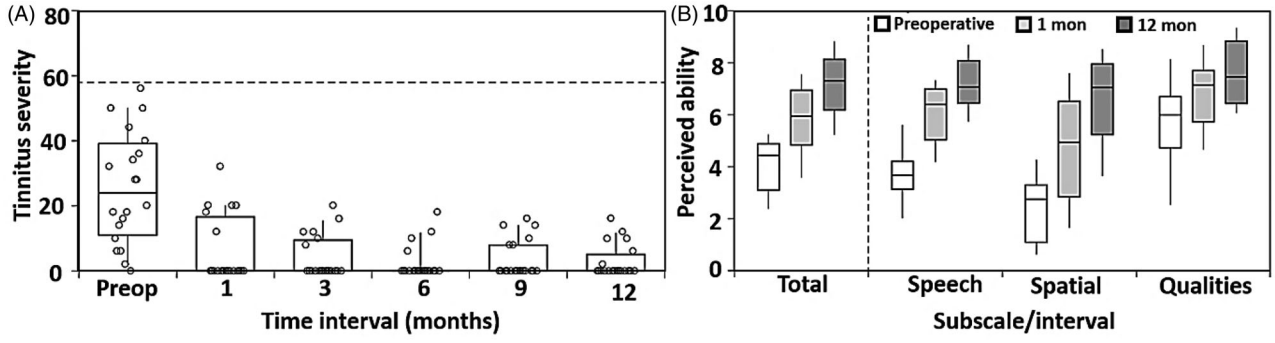

Figure 22. Subjective responses of tinnitus severity using THI (A) and SSQ (B) over the study period. The horizontal dashed line (in (A)) represents the candidacy criterion, where potential patients who ranked their tinnitus severity above the line were excluded. Boxes indicate the distribution of values with the horizontal lines indicating the median. Circle represents individual performance at each interval [39]. Statistical analysis: Post hoc and ANOVA test ($p < .05$). Reproduced by permission of Karger AG, Basel.

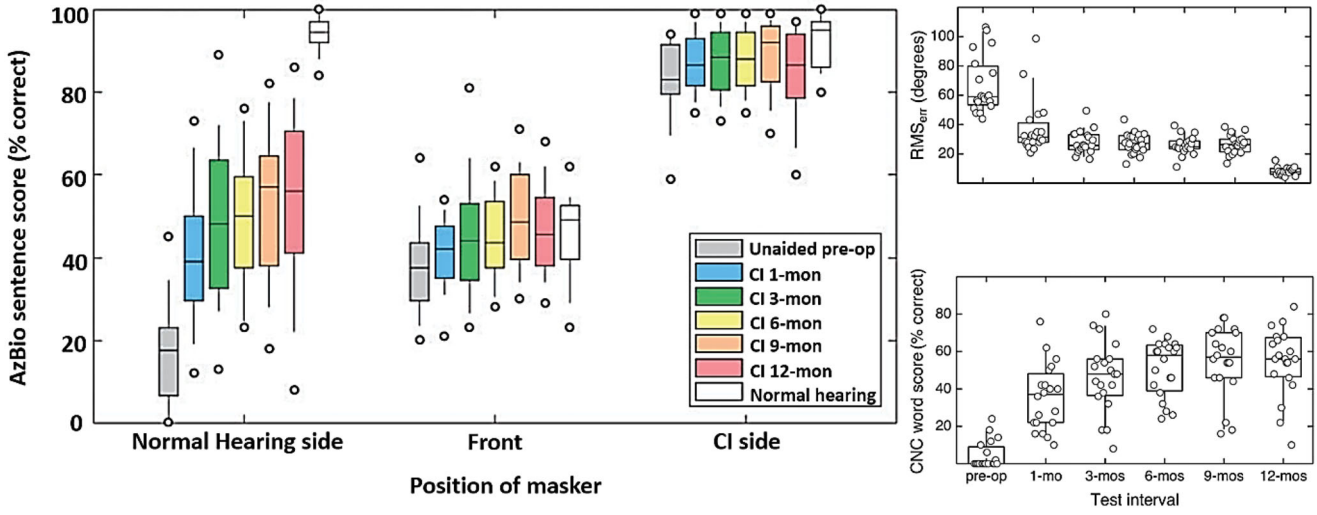

Figure 23. Plots of AzBio sentence recognition scores as a function of masker position (% correct). The x-axis indicates the position of the masker. Data obtained for masker at −90° and 90° for the control group and the CI group. Horizontal lines indicate median, boxes span the 25th to 75th percentiles, vertical lines span the 10th to 90th percentiles, and the circles indicate the minimum and maximum values. Box shading reflects the follow-up intervals of the CI recipient group. Within each condition, boxes are ordered by the time point of data collection (pre-operative on the left, twelfth month on the right), with normal hearing control data on the far right of each cluster. For CI recipients, preoperative data were collected unaided, and postoperative data were collected with CI (A). Overall RMSE with points representing values for individuals over test intervals (B). CNC word scores across test intervals for CI recipients. Preoperative testing was performed with a hearing aid, and subsequent assessments were performed with CI alone. The normal hearing ear was masked at all intervals. The results are plotted in % correct (C) [40]. Statistical significance: Linear mixed model ($p < .05$).

masked sentence recognition is plotted in Figure 23(A) as a function of the masker position relative to the ear with UHL for CI recipients. The most considerable benefit of introducing a CI occurred when the masker was presented on the side of the patient's normal hearing (contralateral to UHL), reflecting the head shadow effect. Comparing the performance of the unaided preoperative condition with the twelfth month of CI listening condition, the latter showed improvement in performance by an average of 36%. Despite these substantial gains, performance with CI at the twelfth-month test interval remained poorer than observed in the normal-hearing group, with an average difference of 42%. Figure 23(B) shows RMSE plotted as a function of test interval for CI recipients. Localisation error dropped with the introduction of a CI for all twenty listeners. There was also clear evidence of improvement within the postoperative period. For the CI recipients, scores on CNC (consonant-nucleus-consonant) words in quiet in the impaired ear rose from an average of 4% (range from 0% to 24%) with a hearing aid at the preoperative test interval to a mean of 55% correct (range from 10% to 84%) with the CI alone at the twelfth-month test interval (Figure 23(C)). There was also evidence of performance improvement in the postoperative period. Results of this study showed that adults with acquired moderate-to-profound UHL benefit from receiving a CI, demonstrating improved benefits for masked sentence recognition in a subset of conditions and improved ability to localise sound on the horizontal plane.

In 2019, the same group published additional evidence showing the importance of longer electrode array length in the low-frequency pitch perception with CI in SSD adults [41]. In simple words, when the CI electrode is physically placed in the location inside the cochlea where the neural elements are naturally responsible for processing specific

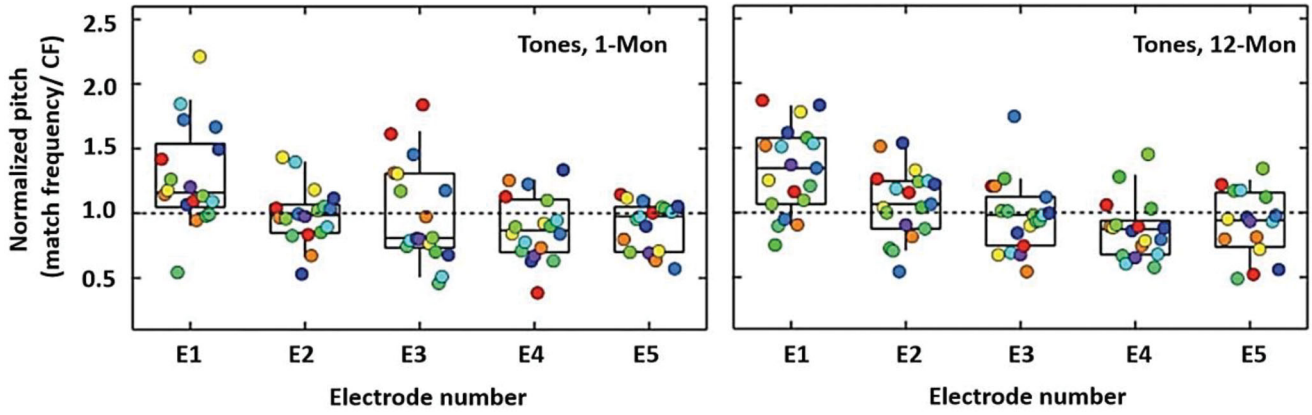

Figure 24. Normalised pitch matches for pure tone targets at one and twelfth-month intervals from the electric-acoustic phase. Coloured circles overlaid on the boxplot indicate the individual participant results. The horizontal line at 1–0 indicates a perfect match between the perceived pitch and the electrode's centre frequency [41]—statistical analysis: linear mixed model ($p < .05$). Reproduced with permission of ASHA.

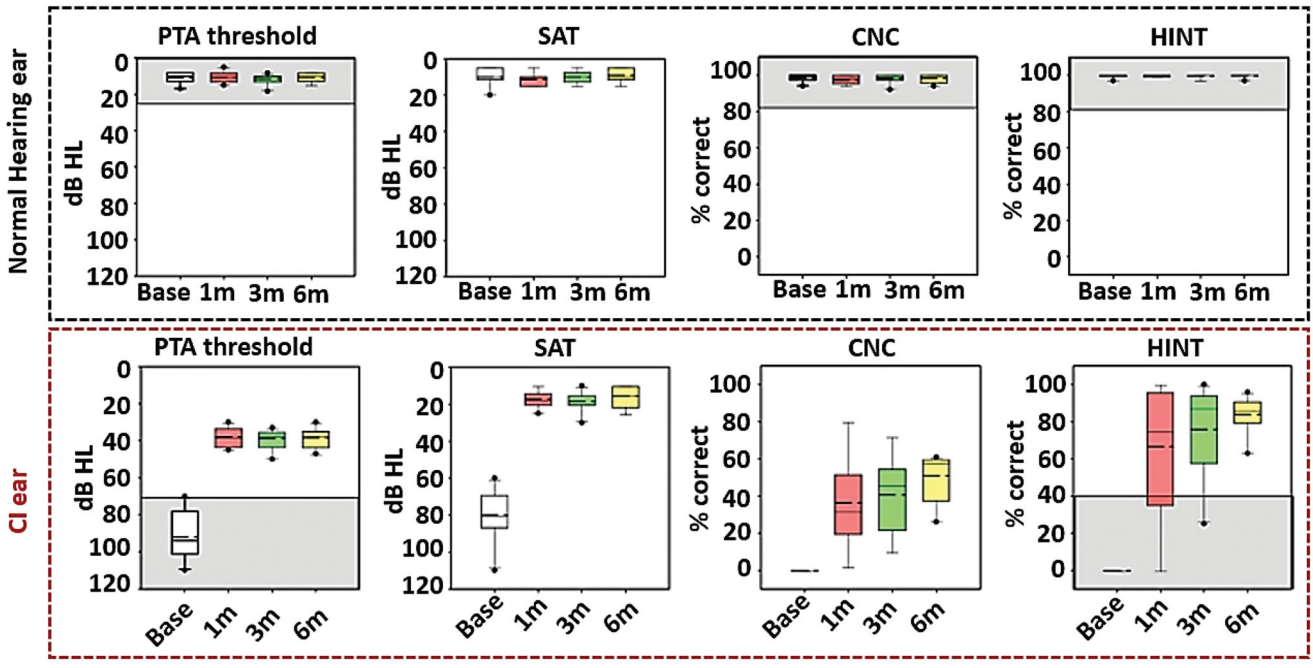

Figure 25. Boxplots of audiology measures as a function of the test intervals. The top panels (within black rectangle) show data with the normal hearing (NH) ear only and the bottom panels (within the red rectangle) show data with the CI ear only. From left to right, data are shown for PTA thresholds (across 0.5-, 1.0-, and 2.0-kHz), SATs, CNC word recognition in quiet, and HINT sentence recognition in quiet. The shaded areas in the top row indicate inclusion criteria for the NH ear; the shared areas in the bottom row indicate inclusion criteria for the CI ear. The boxes show the 25th and 75th percentiles, the error bars show the 5th and 95th percentiles, the circles show outliers, the solid lines show the median, and the dashed lines show the average [42]. Statistical analysis: Repeated measures ANOVA test ($p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

acoustic frequency, and if that electrode is stimulated at the desired rate, then the CI stimulated ear should perceive sound similar to the normal hearing ear. This is possible with MED-EL CI system that has the long length electrode arrays to cover the entire frequency range inside the cochlea for place coding/matching and Fine-Structure-Processing (FSP4) strategy for rate coding/matching in the four apical channels. In this study, the STANDARD electrode array was implanted in the deaf ear in twenty SSD patients that reached an average insertion depth of 707°. When rate coding was applied, the pitch perception between the normal hearing ear and the CI hearing ear matched very closely, both at one month and twelve months postoperatively, as shown in Figure 24 – with the dashed line at the normalised pitch value of 1.0 indicating a perfect match between the electrode centre frequency and the acoustic match frequency (pitch-match).

In 2019, another scientific report was published demonstrating the benefits of CI in SSD patients from the House Ear Institute in Los Angeles in the USA [42]. This was a MED-EL sponsored study with an objective to examine if comparing the benefits of CI in SSD patients with baseline performance before implantation or with normal hearing ear after implantation is clinically relevant. SSD patients ($n = 10$), whose average age was 57.6 ± 10.3 years with a mean duration of deafness of 3.2 ± 2.1 years, were implanted with MED-EL CI device. Figure 25 shows the audiological measures that include pure-tone average (PTA) thresholds for each ear, speech audibility thresholds (SATs), consonant-nucleus-consonant (CNC) words test and recognition of hearing in noise test (HINT) as a function of the test interval. Baseline preoperative PTAs and HINT scores for the CI ear were all within the inclusion criteria. The mean improvement for CNC word recognition relative to baseline was 66.8%, 76.0%, and 84.0% at one-, three- and six-months post-activation, respectively. The mean improvement in HINT sentence recognition in quiet relative to baseline was 36.4%, 40.7%, and 51.1% at one-, three- and six-months post-activation, respectively. For all outcome measures at all intervals, the normal hearing performance was significantly better than CI performance. For all outcome measures, CI performance at one-, three- and six-months post-activation was significantly better than baseline, with no significant difference among post-activation test intervals. The authors concluded that to fully understand the benefits of CI in SSD patients, both reference points (performance before implantation and normal hearing ear after implantation) should be considered.

Until 2019, no CI device was FDA approved in the USA to be officially used for the treatment of SSD. MED-EL was the first CI manufacturer who took the initiative of bringing the scientific pieces of evidence together, especially with long length electrode array that demonstrated the best binaural hearing benefits in SSD patients. Table 3 lists the key peer-reviewed publications reporting on binaural hearing benefits with MED-EL CI in SSD patients, and that were submitted to the FDA for its approval.

In 2019, MED-EL was the first CI manufacturer to receive FDA approval for its CI device to be implanted in patients with AHL/SSD. The age range includes adults and children as young as five years of age. As of March 2021, MED-EL is still the only CI manufacturer to have FDA

Table 3. List of key studies that reported on the binaural hearing benefits with MED-EL CI in SSD patients that was submitted to the FDA.

No.	Study title	No. of subjects	Year	Country
1	Successful outcomes of cochlear implantation in long-term unilateral deafness: brain plasticity [34].	5	2013	Australia
2	Cochlear implantation in children with congenital and non-congenital unilateral deafness: a case series [43].	4	2015	Australia
3	Cochlear implantation improves localisation ability in patients with unilateral deafness [44].	16	2015	Australia
4	Impact of cochlear implantation on speech understanding, subjective hearing performance, and tinnitus perception in patients with unilateral severe to profound hearing loss [36].	28	2015	Australia
5	Binaural auditory outcomes in patients with post-lingual profound unilateral hearing loss: 3 years after cochlear implantation [45].	22	2015	Belgium
6	Cochlear implantation as a long-term treatment for ipsilateral incapacitating tinnitus in subjects with unilateral hearing loss up to 10 years [36].	23	2016	Belgium
7	Prospective case-controlled sound localisation study after cochlear implantation in adults with single-sided deafness and ipsilateral tinnitus [46].	10	2016	Belgium
8	Cochlear implantation in children with congenital unilateral deafness: Mid-term follow-up outcomes [47].	3	2016	Australia
9	Evaluation of long-term cochlear implant use in subjects with acquired unilateral profound hearing loss: Focus on binaural auditory outcomes [48].	23	2017	Belgium
10	Cochlear implantation in cases of unilateral hearing loss: Initial localisation abilities [49].	20	2017	USA
11	Effects of cochlear implantation on quality of life in adults with unilateral hearing loss [39].	20	2017	USA
12	Effects of cochlear implantation on binaural hearing in adults with unilateral hearing loss [40].	20	2018	USA
13	Low-frequency pitch perception in cochlear implant recipients with normal hearing in the contralateral ear [41].	20	2019	USA
14	Evaluating the long-term hearing outcomes of cochlear implant users with single-sided deaf [37].	34	2019	Australia, Belgium
15	Benefits of cochlear implantation for single-sided deafness: Data from the House Clinic-University of Southern California-University of California, Los Angeles Clinical Trial [42].	10	2019	USA
16	Subjective benefits of bimodal listening in cochlear implant recipients with asymmetric hearing loss [50].	20	2020	USA

approval for its CI device to be implanted in AHL/SSD patients. This was another milestone in MED-EL's journey of expanding its CI to further indications of hearing loss. More and more reports on the benefits of CI in SSD patients, including children, are being published from various global centres which witness the wide acceptance of CI treatment in the SSD patient population.

4.13. Importance of early CI implantation in SSD children

Prof. Andrej Kral

Dr Jochen Tillein

Figure 26. Prof. Andrej Kral from Hannover Medical School, Germany, and Dr Jochen Tillein from MED-EL Germany, who studied the unilateral aural preference in non-human SSD subjects.

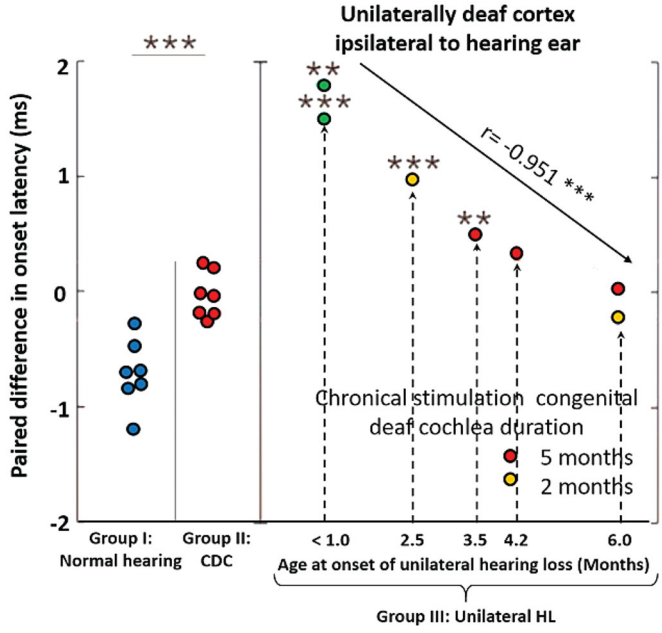

Figure 27. Medians of the paired differences in onset latencies for all groups. *Left*: the control group with normal hearing subjects shows a significant difference in the onset latency with shorter latency for the contralateral stimulation. None of the deaf subjects (CDCs) had a statistically significant difference between contralateral and ipsilateral latency; therefore, the pooled medians showed a significant difference between hearing and deaf subjects. *Right*: The single-sided deaf subjects reorganised the aural preference to the ipsilateral (trained) ear. Green points correspond to unilateral congenital deafened subjects with no hearing training. The red and orange data points correspond to subjects with later onset of unilateral deafness at various time points and with chronic electric stimulation [52]—statistical analysis: Two-tailed Wilcoxon-Mann-Whitney test ($p < .05$). Reproduced by permission of Prof. Andrej Kral.

Various studies have demonstrated the advantages of binaural over the monaural hearing in CI recipients, as well as that binaural implant users have some additional access to spatial cues. Children affected by congenital SSD could be at risk concerning the neurodevelopmental predilection towards the better hearing ear and may end up with social and educational deficits [51]. This opens questions such as how early they should be treated to help them avoid the neural plasticity development towards the better hearing ear and is the CI treatment beneficial for SSD children with longer duration of deafness.

In 2013, Prof. Kral, Dr Tillein and their colleagues investigated the effects of hearing training to the auditory cortex

on the onset latency of the cortical response to the electric stimulation in unilaterally deaf ears [52] (Figure 26). They studied three groups of non-human subjects with group-I having normal hearing, group-II having congenital/bilateral deafness (CDCs), and group-III was unilaterally deafened at various time points in life (<1 month, 2.5 months, 3.5 months, 4.2 months and six months).

Later onset of unilateral hearing loss is compensated by the prior well-trained auditory cortex. In normal hearing subjects, electric stimulation at the contralateral side would activate the auditory cortex of the ipsilateral side (recording side), resulting in a shorter onset latency for contralateral stimulation compared to the ipsilateral side stimulation.

In the CDCs group, there was no significant difference in the latency onset between ipsilateral and contralateral stimulation because subjects had hearing training on neither of the sides of the auditory cortex. In unilaterally deafened subjects with deafness onset in the ipsilateral ear much earlier in life and with no auditory training to the contralateral auditory cortex, the chronic electric stimulation showed shorter latency onset on the ipsilateral side of the cortex which is an opposite effect when compared to the normal hearing subjects. The paired differences between the latency onset on the contralateral and ipsilateral ears for these three groups revealed that in the normal hearing subjects, the paired difference was the lowest compared to all other groups, showing the shorter latency onset for the contralateral stimulation. For the CDCs, there was no difference between the two ears, and therefore the paired difference was close to zero. For the unilaterally deafened groups, subjects with the highest period of auditory training had the lowest paired difference in latency onset compared to those with least auditory training (Figure 27). This demonstrates the importance of early hearing restoration in a non-human subject model that had unilateral hearing loss, enabling it to have an as balanced hearing as possible.

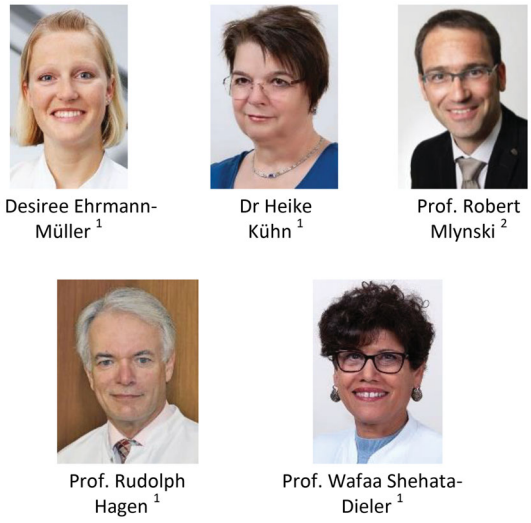

Figure 28. Clinicians from [1]University of Würzburg, Germany, and [2]University of Rostock, Germany, who were involved in evaluating the benefits of CI treatment in SSD patients with longer duration of deafness.

In 2017, Prof. Papsin and his colleagues from the Hospital for Sick Children in Toronto in Canada demonstrated that in young SSD children (≤3.6 years of age) – in combination with using electroencephalography of the cortically evoked activity – through chronic electric stimulation using CI on the deaf ear would restore bilateral auditory input to the cortex needed to improve binaural hearing [53]. This was an encouraging report to go for CI even if the children are deaf for a duration of around three years. However, the report did not included children implanted with MED-EL CI devices.

In 2020, Prof. Shehata-Dieler from the University of Würzburg in Germany and Prof. Mlynski from the University of Rostock in Germany and their colleagues investigated the benefits of CI treatment in seven SSD children with an average deafness duration of 7.8 years (range: 3.9–16 years) who were implanted with MED-EL CI device [54] (Figure 28).

Speech recognition using HSM sentence test in noise showed that listening with CI, compared to the unaided condition, significantly improved in all children in different

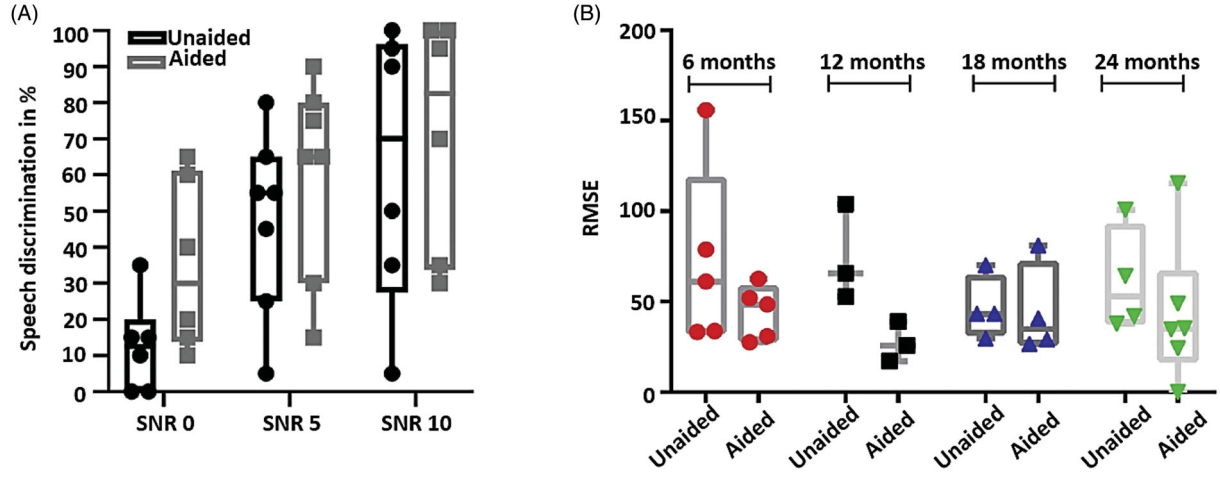

Figure 29. Speech perception in noise with the Würzburger two syllables test in different signal to noise conditions, unaided vs aided and best over time (A). RMSE over time. Localisation results are shown as the RMSE over time (6, 12, 18 and 24 months after first fitting) (B). The number of children is marked in points [54]—statistical analysis: paired *t*-test ($p < .05$). Reproduced by permission of Elsevier B.V.

settings, as shown in Figure 29(A). Improvement of the localisation ability with CI, as measured by the RMSE, is shown in Figure 29(B). All of the SSD children benefited with CI, and the study did not confirm an association between age at implantation and hearing performance. Although, the authors highlighted that younger implanted children tend to have better speech discrimination outcomes in noise.

In 2020, Dr Távora-Vieira and her colleagues from the University of Western Australia studied the cortical auditory evoked potentials (CAEPs), recorded from both, normal hearing on the contralateral ear and CI implanted ipsilateral ear in SSD patients ($n = 29$) with longer duration of deafness (average: 8.9 years; range: 0.2–41 years) [55]. The study aimed to explore if there is a difference between the normal hearing ear and the electric stimulation for speech detection at the cortical level. CAEPs are a series of negative and positive deflections referred to as the *N1-P2 complex* with latencies roughly around 100–200ms after stimulus onset. P2 latency is associated with speech perception with poor CI performers demonstrating a delayed P2 latency compared with normal hearing controls, and this may correlate with the effects of auditory training and experience. CAEPs were recorded when four speech tokens (/m/, /g/, /t/ and /s/) were presented at 55 dB SPL in free field with participants seated one meter and zero degrees azimuth to the loudspeaker. CAEPs showed no significant difference between the normal hearing and CI ear, indicating that the detection of sound in the auditory cortex occurred simultaneously, providing the cortex with auditory information for binaural hearing (Figure 30). The hypothesis set at the beginning of the study was that individuals with a long duration of deafness before implantation would explain the individual variability in latency. However, no trend was found to indicate that a longer duration of deafness in adult SSD subjects has adverse effects on their binaural hearing.

With all these pieces of evidence reported from the human population, it can be concluded that as early as possible CI treatment in SSD children would be preferable but SSD children with longer duration of deafness can also be CI treated, and that would bring significant improvement in their speech discrimination in noise and localisation ability.

4.14. The superiority of CI treatment over conventional treatment method in SSD

In countries where health insurance does not cover the costs of a CI, the CI treatment is not affordable, or in case of aetiologies that prevent an individual from receiving a CI (e.g. nerve aplasia), alternative treatment options are CROS hearing aids, BAHA or bone conduction hearing devices (BCD). However, outcomes with these conventional treatment options are limited, and their long-term usage rates are often limited.

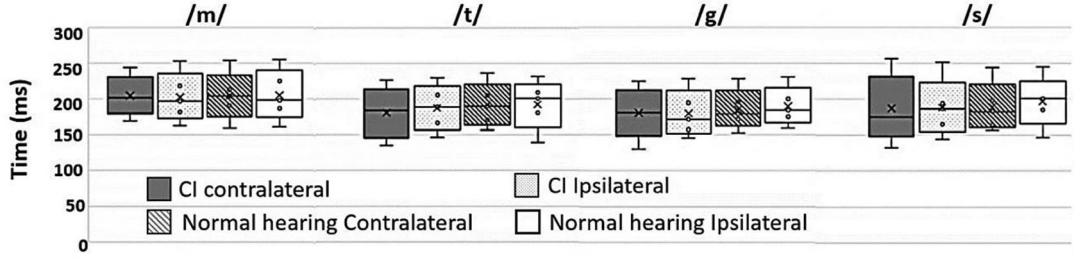

Figure 30. Latencies (ms) recorded for P2 from four different electrode montages for each speech token. Median values are displayed with the horizontal line, mean value as the black crosses [55]. Statistical analysis: Wilcoxon signed rank-test ($p < .05$). Adapted from Wedekind et al. published in PLOS ONE.

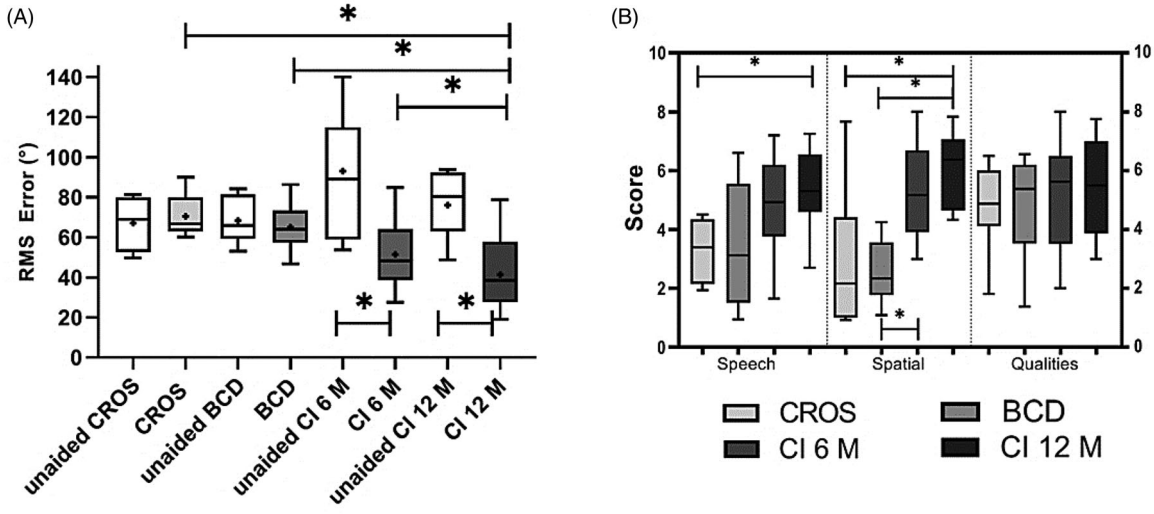

Figure 31. RMS error of sound localisation for groups treated with CROS/BCD and CI (A). SSQ assessment scale (B). Whisker box plots denote mean (minimum, maximum), the asterisks denote the statistically significant differences ($p < .05$) [56]—statistical analysis: Wilcoxon signed-rank test. Reproduced by permission of Wolters Kluwer Health, Inc.

In 2020, Prof. Hagen and his colleagues from the University of Würzburg, through a retrospective study, analysed the effectiveness of various treatment options for SSD [56]. Eighteen patients were implanted with CI, and sixteen had either CROS or BCD. Sound localisation abilities through RMSE and hearing outcomes, subjectively analysed using the SSQ questionnaire, were used as the marker for evaluating the effectiveness of various treatment options at six months and twelve months of usage. Figure 31(A) illustrates the RMSE for all tested conditions in both groups. Average RMSE was 66.72° for CROS, 63° for the BCD, 48.12° for CI after six months of use, and 38.79° for CI after twelve months of use. Smaller RMSE value indicates a lesser error in the sound localisation. Localisation performance was significantly better after twelve months of CI use in comparison to the CROS, BCD and six months of CI use. Figure 31(B) illustrates the SSQ questionnaire where it shows *speech* subcategory significantly improving with the CI condition (average of 5.33 at twelve months) over CROS (average of 3.23). In the *spatial* subcategory, again the CI condition (average of 6.11) was significantly better than CROS (average of 2.94) and BCD (average of 2.5). However, the *quality* subcategory showed no significant trends with the following mean scores obtained from each device: CROS (4.7), BCD (4.8), CI after twelve months (5.5). Overall, the study demonstrated better binaural hearing benefits with CI than with conventional treatment methods like CROS/BCD in SSD patients.

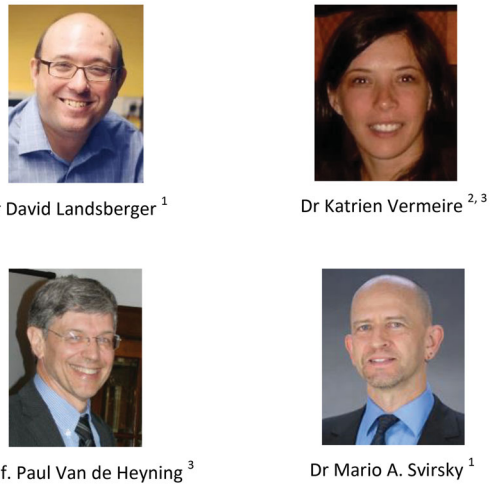

Figure 32. Clinicians from [1]New York University School of Medicine, USA, [2]Long Island University Brooklyn, USA, and [3]University of Antwerp, Belgium, who were involved in the assessment of music enjoyment in SSD patients implanted with CI.

4.15. Music enjoyment with two ears

While CI restores speech perception in quiet, it could also eliminate or distort many acoustic cues that are important for music enjoyment. In the year 2020, Dr Landsberger and his colleagues from New York University School of Medicine in the USA and the University of Antwerp in Belgium assessed music enjoyment in CI users, using a readily interpretable reference based on acoustic hearing [57] (Figure 32).

The comparison was made by testing the SSD participants with normal hearing (NH) in one ear and a CI in the contralateral ear. In twelve of them – out of which eight were implanted with MED-EL CI device in their deaf ear – thirteen stimuli for both, *Ring of fire* and *Rhapsody in Blue* songs, were used to assess their music enjoyment. The SSD–CI users were asked to rate music enjoyment on a scale using two fixed points obtained by presenting song segments separately to the normal acoustic hearing ear, CI ear and combination of both, acoustic and CI ear. Multiple stimuli with *Hidden Reference* and *Anchor* test (MUSHRA) score of two hundred allowed avoiding ceiling effects in listening conditions that might be more enjoyable than the single NH ear reference. An additional benefit of this

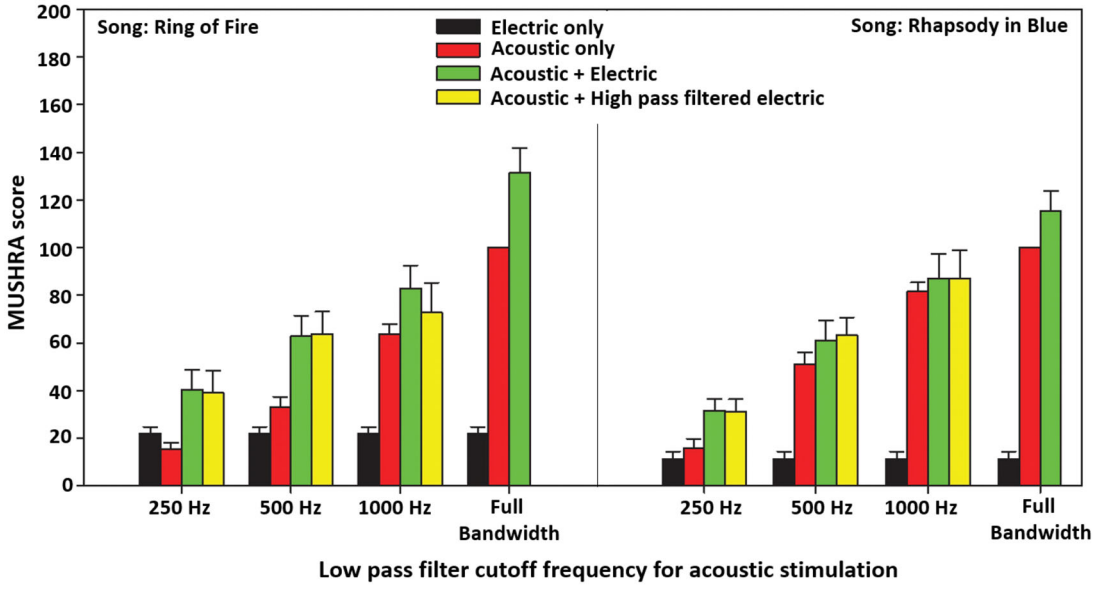

Figure 33. The left panel indicates results for *Ring of Fire,* and the right panel indicates results for *Rhapsody in Blue* songs. The set of bars are organised based on the low-pass filter (250-, 500-, 1000-Hz, or no low-pass filter) provided to the acoustic-hearing ear. Black bars indicate ratings to the electric ear alone, red bars indicate ratings to the acoustic-hearing ear alone, green bars indicate ratings when acoustic and a full bandwidth electric stimulation is provided. Yellow bars indicate ratings when cut off frequencies for the low-pass acoustic, and high-pass electric stimuli are the same. Error bars indicate ±1 standard error of the mean [57]. Statistical analysis: ANOVA test ($p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

approach was that enjoyment of music with a CI could be directly compared with the enjoyment of the same piece using normal acoustic hearing, although with a single ear.

Figure 33 summarises the results and the data is organised along the horizontal axis by the degree of low-pass frequency cut-offs, used for the stimuli presented to the acoustic-hearing ear. Red bars indicate ratings of the music presented only to the acoustic-hearing ear; black bars indicate ratings for the music presented only to the electric ear; green bars indicate ratings for music presented to both, the acoustic and electric ear; yellow bars indicate ratings for music presented to both ears such that the frequency ranges of the acoustic and electric stimuli do not overlap.

Ratings for the full bandwidth combination (green bars) were higher than ratings for the acoustic reference alone, showing two-ear enhancement in music enjoyment when adding the CI to the acoustic hearing ear for both songs. Enjoyment ratings of electric-only stimulation (black bars) were very low in the order of 22.0 for *Ring of fire* and 11.24 for *Rhapsody in Blue*. The enjoyment rating decreased with reduced low-pass filter frequencies. Ratings for combined acoustic and electric stimulation (green bars) were higher compared to the acoustic-only stimulation (red bars), regardless of the song segment or low-pass filter frequency. In summary, the results of the study demonstrated that SSD–CI users find music unenjoyable when listening only through the CI. However, when the music signal is presented to both ears simultaneously, the combination is significantly more enjoyable than using the acoustic-hearing ear alone. This points out to the two-ear enhancement in music enjoyment observed in SSD–CI users.

Figure 34. Researchers from various centres across the world who were interested to understand the distribution of SGCBs inside the human cochlea. [1]Uppsala University, Sweden, [2]Western University-Ontario, Canada, [3]Antwerp Medical University, Belgium, [4]Luzerner Kantonsspital, Switzerland, and [5]MED-EL headquarters, Austria.

4.16. Evidence of spiral ganglion cell bodies distribution

A CI electrode array electrically stimulates peripheral nerve fibres and the cell bodies inside the cochlea. Here comes the vital question on how deep inside the cochlea the spiral ganglion cell bodies (SGCBs) are present and how long the CI electrode array shall be. There are published peer-reviewed pieces of evidence that favour atraumatic deep insertion with longer CI electrode array lengths which result in a better hearing in comparison to the shorter arrays [58–60]. In the context of SSD patients and in order to match the CI hearing of the impaired ear with the natural hearing on the contralateral ear, it is of utmost importance to understand how many SGCBs are present beyond the basal turn of the human cochlea quantitatively, and how many channels of the CI electrode array are needed to cover them electrically.

In 2019, Prof. Rask-Andersen and Asst. Prof. Agrawal, along with the support of MED-EL and using synchrotron radiation phase-contrast imaging of cadaveric human cochleae, qualitatively showed the clear presence of SGCBs up to 700° of angular insertion depth along the inner wall of the cochlea [61] (Figure 34). The yellow structure in Figure 35(A) corresponds to the peripheral nerve fibres and SGCBs that extend close to the end of the second turn of the cochlea.

In 2020, Prof. Van de Heyning, Prof. Rajan and Dr Dhanasingh performed (Figure 34) a systematic literature review to quantify the number of SGCBs present in every segment of the human cochlea [62]. They reported that the basal turn of the cochlea with up to 270° angular insertion depth, starting from the round window entrance (segment I and segment II shown in Figure 35(B)), would carry approximately 50% of the total number of SGCBs. Segment III, which extends from 270° to 450°, would cover approximately 25% of the total number of SGCBs. Interestingly, segment IV, which extends from 450° to almost 700° of angular insertion depth, carries 25% of the total number of the SGCBs. For a CI electrode array to reach such depth and provide electric stimulation, the CI electrode array must be at least 28 mm long.

Putting the puzzle pieces together, it is much clearer now that:

i. the SGCBs distribution spirals up to 700° of angular insertion depth, and 25% of the total number of SGCBs are present well beyond the basal turn of the cochlea
ii. the 31mm long electrode array electrically covers the entire population of the neuronal elements

4.17. Reimbursement for CI in AHL/SSD

In countries with challenged healthcare systems, patients may have to cover the cost of the overall CI treatment by themselves. In countries with more advanced health care systems, strong scientific pieces of evidence, demonstrating the CI benefits have to convince, for the reimbursement to be justified. AHL/SSD is a sub-group within the hearing loss

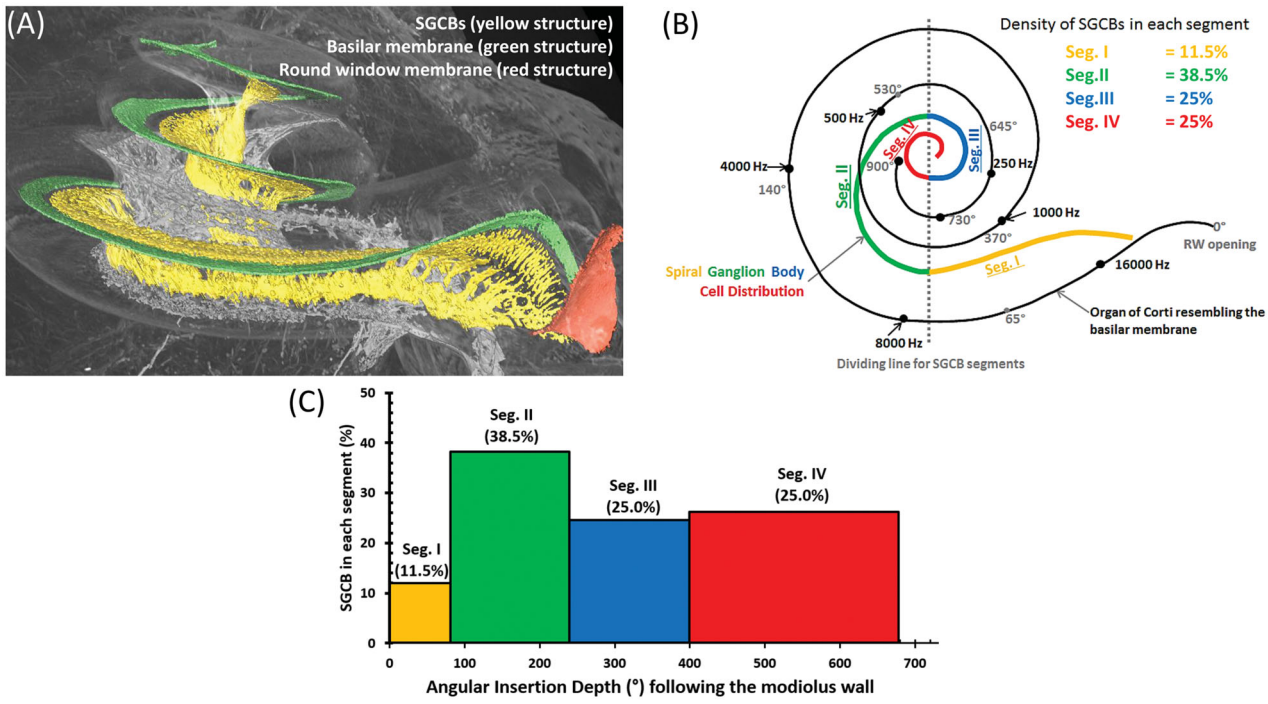

Figure 35. Synchrotron radiation phase-contrast imaging of cadaveric human cochlea showing the distribution of SGCBs close to the end of the second turn of the cochlea (A) [61] Reproduced by permission of Wolters Kluwer Health, Inc. Systematic literature review of articles published between 1931 and 2019, showing the presence of SGCB up to 680° of angular insertion depth. Segment IV (red spline) of the cochlea, which is beyond the basal turn of the cochlea, carries ~26% of the total number of SGCBs (B). Density of SGCBs in each segment as a percentage of the entire number of SGCBs (Y-axis) vs. angular depth (X-axis) (C) [62].

population where patients have a near-normal hearing on one side that helps them to live a normal/social life. Therefore, reimbursement for the CI treatment in AHL/SSD patients is challenging in many countries, including Belgium, from where the initial research of CI for tinnitus in SSD patients originated.

Prof. Fraysse and his colleagues from the University of Toulouse in France proposed a method of evaluating the cost-utility associated with every treatment method, including CROS–HA, BAHA and CI, available for SSD patients to find the rationale to recommend public funding. This is an ongoing study with the patient recruitment phase completed so far [63]. So far in France, CI in SSD is not reimbursed by the national health system.

In Canada, based on the guidance from the Ontario Health Technology Advisory Committee, the Quality business unit at Ontario Health recommended public funding of CI for adults and children with SSD [64]. They have found overall effectiveness, safety and need for the treatment in SSD, and calculated incremental cost-effectiveness ratio of between $17,783 and $18,148 per quality-adjusted life-year (QALY). At a willingness to compensate $100,000 per QALY, 70% of the simulations were considered cost-effective. For the same population, bone-conduction implants were not likely to be cost-effective.

In the USA, clinicians from the University of North Carolina published a white paper in support of insurance coverage for CI in cases of paediatric UHL. While many health insurance companies, and even Medicaid in some states, are providing coverage for CI, they urge other carriers to recognise this critical change in the FDA guideline and to follow suit, helping children to take advantage of the critical period of neural plasticity and promote binaural hearing as early as possible [65]. In several EU countries, including Austria, Germany, Hungary, Poland, Portugal, Slovakia and Spain, are known to reimburse the CI treatment in SSD patients [66].

4.18. Conclusion

Cochlear implantation in AHL/SSD is the *state-of-the-art* treatment option for both, children and adults with the normal presence of cochlear nerve. A good number of published pieces of evidence shows the binaural benefits of CI in SSD with moderate speech understanding in noise, sound localisation and suppressing tinnitus. Strong acceptance of MED-EL CI device in the SSD patients is mainly due to its advanced design features that include long electrode array lengths and nature-inspired sound coding strategy that accommodates place/rate coding along with frequency-specific group/time delays, helping to bring in close to natural hearing. MED-EL is the first CI manufacturer to obtain both CE marking and FDA approval for its CI device to be used in adults and children older than five years of age. Reimbursement is still a challenge in several market segments, but there is a demonstrated incremental cost-effectiveness ratio between with and without CI treatment. With the early research of CI in SSD, which began with the research collaboration with clinicians, the positive trend continues. It is one of MED-EL's core goals to continue with its CI technological advancements and to reach every patient within this segment of hearing loss.

Acknowledgments

The authors would gratefully like to acknowledge the key contributors to the development of the subject matter. Their contributions are outlined in this article. The authors further acknowledge Reinhold Schatzer from MED-EL for his valuable input and comments during several rounds of review meetings that contributed to the final version of this article.

Disclosure statement

This article is sponsored by MED-EL and has not undergone the regular peer-review process of Acta Oto-Laryngologica. Both the authors are affiliated with MED-EL.

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ACTA OTO-LARYNGOLOGICA
2021, VOL. 141, NO. S1, S106–S134
https://doi.org/10.1080/00016489.2021.1888504

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REVIEW ARTICLE

Signal processing & audio processors

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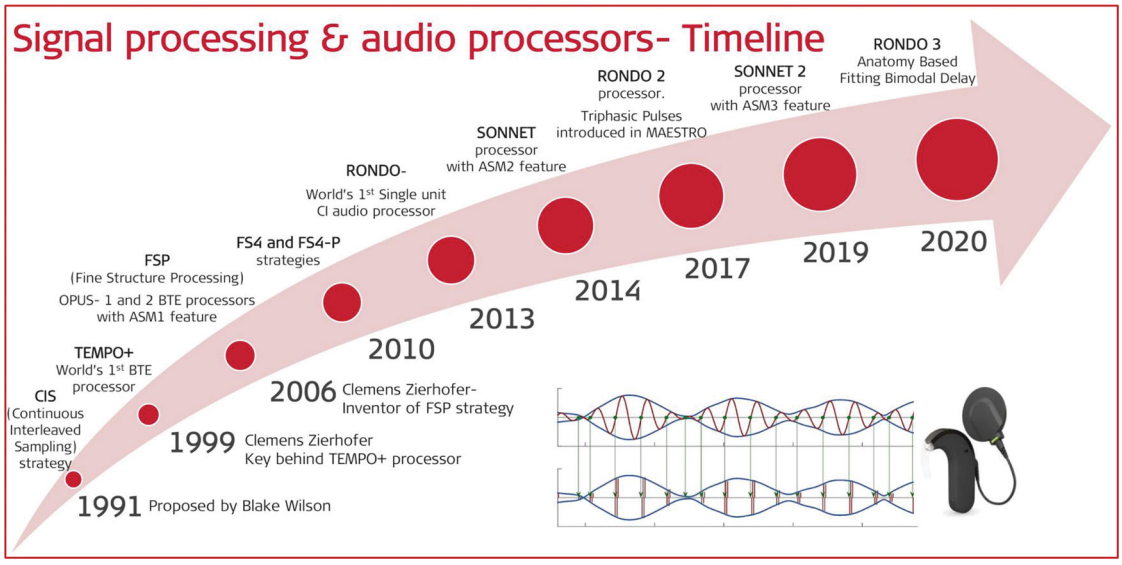
ABSTRACT

Signal processing algorithms are the hidden components in the audio processor that converts the received acoustic signal into electrical impulses while maintaining as much relevant information as possible. Signal processing algorithms should be smart enough to mimic the functionality of external, middle and the inner-ear to provide the cochlear implant (CI) user with a hearing experience as natural as possible. Modern sound processing strategies are based on the continuous interleaved sampling (CIS) strategy proposed by B. Wilson in 1991, which provided envelope information over several intracochlear electrodes. The CIS strategy brought significant gains in speech perception. Translational research activities of MED-EL resulted in further improvements in speech understanding in noisy environments as well as enjoyment of music by not only coding CIS-based envelope information, but by also representing temporal fine structure information in the stimulation patterns of the apical channels. Further developments include "complete cochlear coverage" made possible by deep insertion of the intracochlear electrode, elaborate front end processing, anatomy based fitting (ABF), triphasic pulse stimulation instrumental in the suppression of facial nerve stimulation, and bimodal delay compensation allowing unilateral CI users to experience hearing with hearing aids on the contralateral ear. The large number of hardware developments might be exemplified by the RONDO, the world's first single unit audio processor in 2013. This article covers the milestones of translational research around the signal processing and audio processor topic that took place in association with MED-EL.

ARTICLE HISTORY
Received 13 December 2020
Accepted 6 January 2021

KEYWORDS
Continuous interleaved sampling; fine structure processing; single unit processor; anatomy-based fitting; triphasic pulse stimulation; bimodal delay compensation



5.1. Introduction

In the cochlear implant (CI) systems, the sound signal is captured by the microphone in the externally worn audio processor. The audio processor converts the sound signal into detailed digital signals using signal-processing algorithms and transmits those to the implantable electronics *via* an inductive link. The implant electronics then convert these digital signals to electric impulses and transfer them to

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This article is a part of the compendium entitled 'Thirty years of Translational Research behind MED-EL' authored by Anandhan Dhanasingh (Director) (Anandhan.dhanasingh@medel.com) and Ingeborg Hochmair (CEO, CTO) (Ingeborg.hochmair@medel.com).
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the inner ear through the intracochlear electrode array. The auditory nerve then transfers the electric impulses received from the electrode array to the brain to interpret the sound signals. While the proper placement of the electrode array inside the cochlea – which covers the entire frequency range – without causing any structural damage is essential, it is equally crucial for the audio processors to process the sound signals without losing any of its key elements.

Before detailing how the audio processor in a CI system processes sounds, it is of importance to canvass through the same process in a normal hearing ear first. In a healthy hearing ear, the sound signal is processed at three levels – in the outer, middle and inner ear, as shown in Figure 1. *Pinna* and the external ear canal constitute the outer ear, and it is mainly the pinna that gives some form of *directionality* to the listener [1]. The pinna allows the normal-hearing listener to hear better with the acoustic signal coming from the front than from the rear side of the head. The outer and the middle ear filter the sound signals and provide some *pre-emphasis*, especially to frequencies around 1,000Hz, which carries speech information necessary for typical conversation [2]. The inner ear processes the sound signal in a frequency-specific manner, called *tonotopicity*, i.e. high frequencies (HF) are processed along the basilar membrane (BM) in the basal turn of the cochlea which is closer to the outer and middle ear, and the low frequencies (LF) are processed in the apical end of the cochlea which is further away from the outer and middle ear. Tonotopicity is the first important element in the frequency coding of a normal hearing ear. The other aspect of inner ear sound processing is the *travelling wave latency/LF delay*, i.e. HF sound signals are processed with the neural responses reaching the auditory cortex relatively faster than the LF sound signals. The LF delay comes from the delayed mechanical vibrational response of the BM that takes longer for LF than for HFs [3]. In other words, LF signals have longer latencies than HF signals, i.e. latency increases with decreasing frequencies and vice versa. Both tonotopicity and travelling wave latency are specific to certain locations along the BM. The BM in a normal acoustic ear acts as a gain-controlled amplifier, i.e. it amplifies low-level sound and compresses (*compression*) high-level sound – allowing the listener to hear even very soft sounds [4]. Around the apex of the cochlea where the LF signals are processed, the neural responses are produced in synchrony with sound frequency. In other words, the neural response rate (neural responses/second) is equivalent to the sound frequency in the apical location of the BM that is responsible for processing LFs, and this is called *phase-locking* – a phenomenon predominantly happening in the LF region [5].

The neural responses are phase-locked to the acoustic stimulus in the LF and are clearly clustered, whereas, in the HFs, those are not clustered but rather smeared. Phase locking is the second important element in the frequency coding of a normal hearing cochlea (Figure 2).

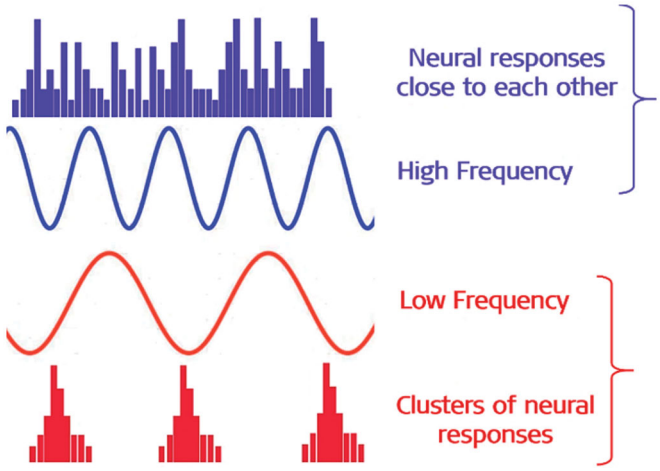


Figure 2. Low-frequency sound signals in the cochlear apex produce clusters of neural responses which the brain can identify separately, whereas the high-frequency sound signals in the cochlear base produce neural responses that are close to each other so that the brain cannot identify them separately. Image courtesy of MED-EL.

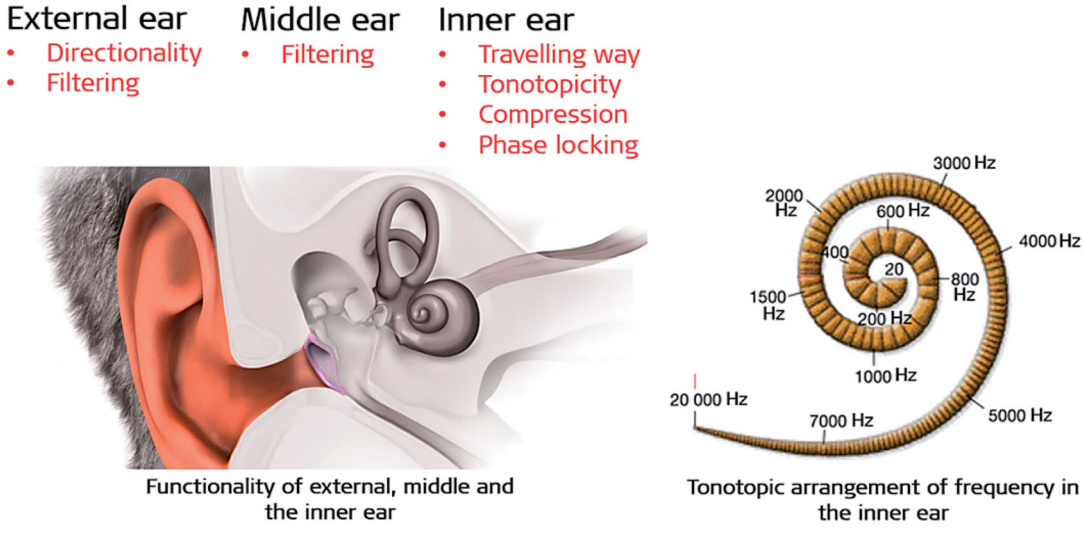


Figure 1. left-hand side picture depicts the functionality of the external, middle and the inner ear in a normal acoustic ear. The right-hand side picture shows the tonotopic arrangement of frequency in the inner ear. Image courtesy of MED-EL.

Figure 3. MED-EL's body-worn audio processor before 1991 and the world's first BTE audio processor in 1991 (image courtesy of MED-EL).

To sum-up the sound processing in a normal acoustic ear, the pinna offers directionality to the listener, the middle ear emphasises the frequencies around 1,000Hz, enhancing the speech perception. The tonotopic inner ear works as a frequency analyser and adds latency to the sound signal over the entire frequency range, whereas the phase-locking is specific to the LFs. The signal processing in the audio processor of the CI shall model or mimic all the functionalities of the normal acoustic ear, providing near-natural hearing experience to the hard of hearing patients. The signal processing chain can be divided into two major blocks, namely the front-end processing and sound coding. The front-end processing block tries to model the functionality of external and middle ear while the sound coding block aims at modelling the functionality of the inner ear.

This article starts with the brief introduction to the continuous interleaved sampling (CIS) strategy which is the basis of multi-channel sound coding strategies in modern CI systems among brands, with some modifications matching their inbuilt electronics. The article aims to cover the developments in the signal processing and audio processors over time within the MED-EL CI system. Following the developments in chronological order, sound coding will be discussed first along with the scientific evidence that demonstrated its benefits in CI users, followed by the front-end processing. Individualisation within sound coding will be briefly covered in the last section as well, highlighting MED-EL's latest unique advancements in sound coding strategies.

5.2. Sound coding

One of the blocks of signal processing is the sound coding strategy that aims to model the inner ear functionality, including tonotopicity, temporal processing *via* phase-locking and the travelling wave delays. This section covers all the sound coding strategies that were implemented in MED-EL's audio processors from 1990 until 2021, along with the scientific pieces of evidence that evaluated these strategies in MED-EL CI users.

5.2.1. Continuous interleaved sampling strategy

In 1990, when MED-EL hired its first team members, the audio processor of its CI system was body-worn, as shown in Figure 3, and was further developed to a *behind-the-ear* (BTE) audio processor in 1991, making it the world's first of its kind. The Continuous Interleaved Sampling (CIS) strategy was not a part of these audio processors at the time.

Before the invention of the CIS strategy, various stimulation strategies, ranging from low rate pulsatile stimulation using some kind of feature extraction, to multichannel analogue stimulation, were investigated. Simultaneous multichannel analogue stimulation raised concerns because significant interactions among channels reduced extractable information [6]. Bipolar stimulation to reduce these interactions resulted in considerable power consumption. Nevertheless, MED-EL's frequency adjusted, elaborate dynamic range compressed analogue stimulation signals, presented *via* just a single stimulation site (selected out of four possible sites), provided fortunate users with a monosyllabic word understanding of up to 40% and allowed them enjoyable music perception [7]. Its low power consumption made the world's first BTE audio processor possible [8].

In 1991, Prof. Wilson and his colleagues from the Research Triangle Institute in the USA proposed the CIS strategy to be set as a base in the CI – which result is of existential importance in the nowadays CI filed (Figure 4).

Figure 4. Prof. Blake Wilson proposed the CIS strategy, currently affiliated to Duke University, USA.

The CIS strategy that was newly developed at the time addressed the problem of simultaneous channel interaction using interleaved non-simultaneous stimuli which heavily reduced the power consumption.

In the classic CIS sound coding strategy, the microphone signal is first processed through a pre-emphasis filter that attenuates strong components in the speech above 1.2 kHz and emphasises signals that are below 1.2 kHz, as the speech information that is needed for normal conversation is around that frequency (stage 1). The output of the pre-emphasis is

further passed through multiple channels of processing that includes bandpass filters (BPF) (stage 2) for splitting the broadband signal into different frequency bands, rectification, as well as lowpass filtering for envelope extraction (stage 3). The envelope signals are compressed into the narrow dynamic range of electrically evoked hearing (stage 4). Trains of charge-balanced biphasic pulses are sequentially interleaved in time across electrodes to eliminate any overlap across channels, as shown in Figure 5 by the red dotted vertical lines. The pulse amplitudes derive from the envelopes of

Prof. Helms from the University of Würzburg in Germany was the primary investigator in the study that aimed at evaluating the hearing performance with the COMBI 40 CI system [10]. Dr Ingeborg Hochmair had drafted the study protocol and it had been refined and agreed upon in first of the COMBI 40 workshops in Alpbach, in Tyrol Austria in fall of 1993. These workshops have taken place regularly since then and are a welcome platform now for the presentations and exchange of new research outcomes and discussions. They also offer further educational credits.

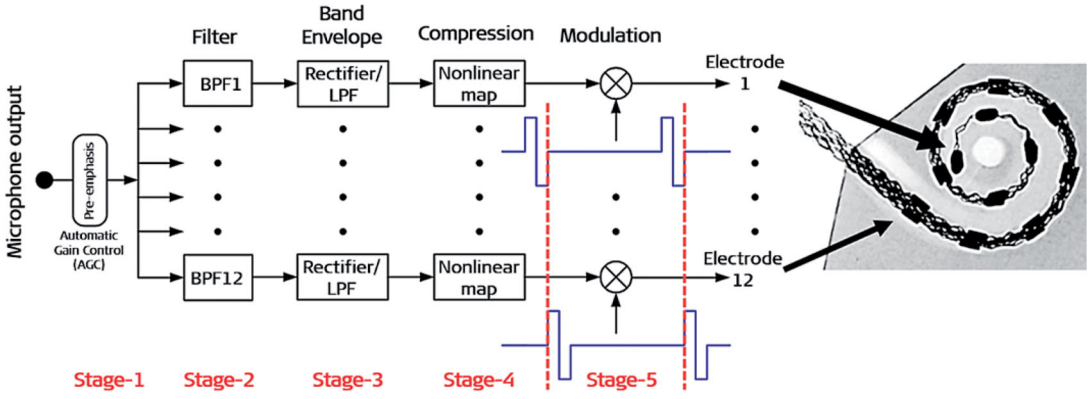


Figure 5. Block diagram of the CIS strategy. The pre-emphasis filter (Pre-emp)/automatic gain control attenuates strong components in the speech above 1.2 kHz. This filter is followed by multiple channels of processing, with each channel including stages of bandpass filtering (BPF), envelope detection, compression and modulation. The envelope detectors generally use a full-wave or half-wave rectifier (Rect.), followed by a lowpass filter (LPF). Carrier waveforms for two of the modulators are shown immediately below the two corresponding multiplier blocks (circle with an *x* mark). The outputs of the multipliers are directed to intracochlear electrodes (EL-1 to EL-12). The inset shows an x-ray image of the implanted electrode (in a cochlear model) to which the outputs of the speech processor are directed. Scheme created from Wilson et al. [9].

the bandpass filter outputs and are directed to intracochlear electrodes (EL-1 to EL-12) (stage 5).

All commercially available MED-EL CI systems feature the CIS strategy in their sound coding portfolio, with some modifications matching to their inbuilt electronics, resulting in further developed variants of the CIS strategy (CIS+, HDCIS). Prof. Wilson was awarded the Lasker-DeBakey Clinical Medical Research Award in the year **2013** for his contributions to the CI field, along with Dr Ingeborg Hochmair from MED-EL in Austria and Prof. Clarke from the University of Melbourne in Australia. Since the early '90s, MED-EL and Prof. Wilson had a close scientific collaboration that helped MED-EL to implement the CIS strategy in its CI system.

In January 1994, MED-EL introduced the COMBI 40 implant system, which was the world's first multichannel high-rate CI. It was an eight-channel system, designed to implement Prof. Wilson's CIS sound coding strategy faithfully. The system featured a maximum overall stimulation rate of 12,120 non-overlapping biphasic pulses/second (pps), allowing the implementation of a high-rate CIS strategy on eight channels (1,515pps/channel for eight active electrode channels). It featured a 31.5 mm long flexible electrode array for coverage of the entire cochlear length. The COMBI 40 implant electronics included individual safety capacitors, serially added to all its eight stimulating channels to prevent any direct current (DC) component from being delivered inside the cochlea.

The first sixty adult patients who received a COMBI-40 device at 19 prominent ENT-clinics in 7 different countries in Europe, took part in a multicentric clinical study. The mean age of the participants was 47.5 years with a mean duration of deafness of 5.3 years. The patients were evaluated with different speech tests, involving two-digit number test, sixteen consonant tests, the eight-vowel test, sentence test and monosyllabic word test without lip reading. Figure 6 shows the sentence and monosyllabic word score results that were collected at different time points, starting from the preoperative testing interval until twelfth-month post-fitting.

The score was zero prior to the CI surgery, which increased to 34% during the first month's test. This further increased to 48% at the sixth month, and to 54% at the first-year's test. The maximum value achieved after six months was 90%. The results were published in the year 1997.

Overall, improvements in speech understanding with the fast CIS strategy occurred soon after switch-on, and a very rapid learning curve with the implant was observed in most patients without lip reading. At the time, the CIS strategy was seen as a real tipping point, and the CI system COMBI 40 that implemented the CIS strategy was reported to be safe and effective in adults. Users who achieved 50% and more in monosyllable word understanding could typically use the telephone.

In 1996, MED-EL further upgraded the body-worn processor with CIS PRO + that helped to reduce the number of batteries from 4xAA to 2xAA, and this was the time when

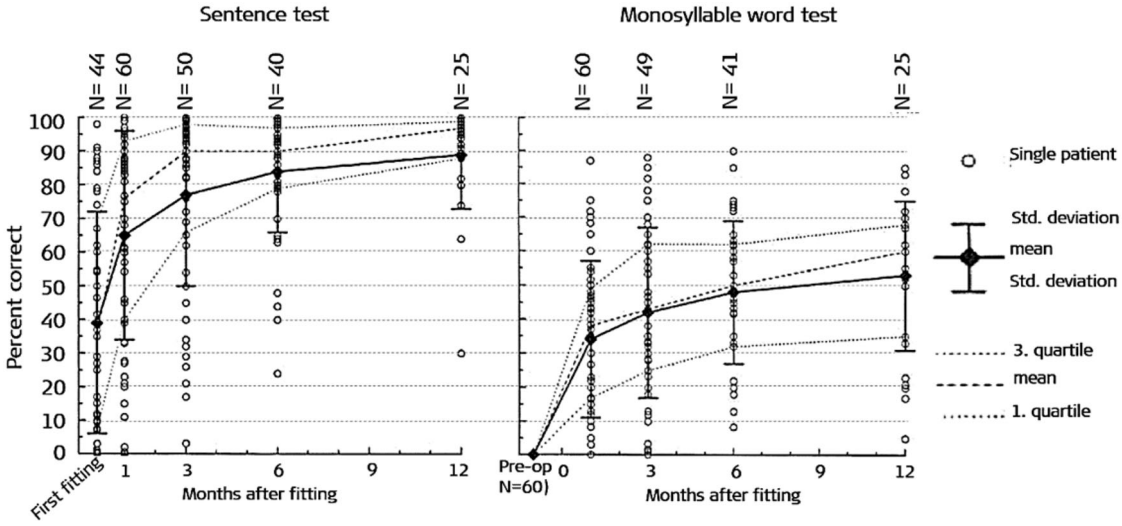


Figure 6. The sentence and monosyllabic word test conducted in patients implanted with MED-EL's COMBI 40 CI system at different time points, starting from pre-operative to twelfth-month post fitting [10]. Reproduced by permission of Karger AG, Basel.

MED-EL also upgraded its implant system from COMBI 40 to COMBI 40+ that featured twelve stimulating channels. The COMBI 40+ system had a maximum overall stimulation rate of 18,181.8pps across the twelve channels, which was the fastest system at the time.

In 1999, MED-EL launched the world's first BTE high-rate audio processor, TEMPO + BTE (Figure 7), based on a patent by Prof. Zierhofer from the University of Innsbruck in Austria (US patent number: 5983139). Prof. Zierhofer and Mr Stöbich, who is currently employed at MED-EL and who was a PhD student of Prof. Hochmair at the University

Prof. Clemens Zierhofer

Dr Bernhard Stöbich (MED-EL)

Figure 7. Prof. Clemens Zierhofer from the University of Innsbruck and Dr Bernhard Stöbich (from MED-EL and a PhD student at the University of Innsbruck at the time) were instrumental in the development of TEMPO + BTE audio processor. Image courtesy of MED-EL.

of Innsbruck at the time, were highly instrumental in the development of TEMPO + BTE audio processor.

The TEMPO + processor is capable of using high-rate stimulation (up to more than 18,000pps) and uses Hilbert transform instead of rectification and low-pass filtering for envelope detection. The Hilbert transform allows a more accurate determination of the signal envelope containing loudness-over-time and pitch information. The analysed frequency range was extended to 200–10,000Hz in the TEMPO + processor, compared to only 300–5,500Hz in the CIS PRO + body-worn processor. The TEMPO + obsoleted the body-worn processor in the year 1999.

In 2001, a multicentric study led by Prof. Helms from the University of Würzburg in Germany reported on the comparison of the TEMPO + BTE, and CIS PRO + body-worn processor in adult MED-EL CI experienced users [11]. The study comprised of forty-six post-lingually deaf adults who were native German-speaking and experienced users of MED-EL COMBI 40/40+ CI system. All participants partook in two test sessions, the first one immediately after receiving and fitting of the TEMPO + processor, and the second one approximately four weeks later. In both sessions, speech understanding with both processors with the same *signal-to-noise ratio* (SNR) was assessed in a free-field test using monosyllabic words which were widely used in German-speaking areas. Group scores for the monosyllabic word test are displayed in Figure 8. The grey column on the left shows the mean CIS PRO + score for the first test session, while the grey column on the right represents the respective mean score for the second session. TEMPO + results are shown in red in the same

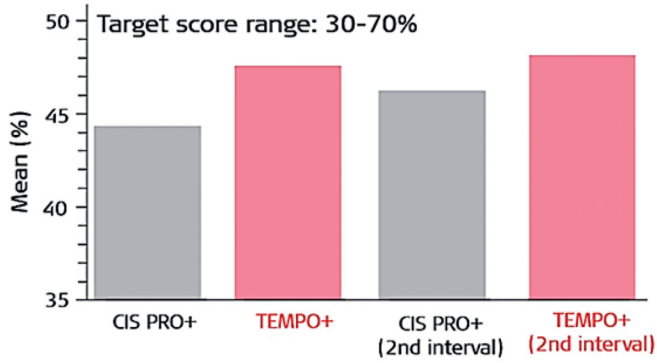


Figure 8. Mean correct scores for monosyllabic words ($n = 46$). Grey columns: mean group results for the CIS PRO + in the first (left) and the second (right) test session; red columns: mean group results for the TEMPO + in the first (left) and the second (right) test session. Histogram created from the data given in Helms et al. [11].

configuration as CIS PRO + results. Group mean scores are well within the target score range (30% to 70%). In addition, the group mean values for the CIS PRO + in the first test session are close to 50%.

In general, TEMPO + scores were higher than the CIS PRO + scores. Relating to the increase in mean scores of the first session from 44.6% to 46.7%, through the second session from 46.1% to 48.1%, towards the target score range, gives a relative increase of approximately 5%. The results obtained in the study indicated the superiority of the TEMPO + over the CIS PRO+. With the miniaturisation of the device, speech understanding has not been compromised. On the contrary, the TEMPO + provided higher levels of speech understanding than the CIS PRO+.

5.2.2. Limitations of CIS strategy

The CIS strategy has undoubtedly overcome the limitations of CA strategy by eliminating the significant interactions among channels by interleaved non-simultaneous stimuli. The CIS strategy presents the channel-specific envelope information of the sound signal derived from the bandpass filter outputs *via* rectification and low-pass filtering (stage 2 of CIS strategy, as shown in Figure 5) or *via* Hilbert Transform (stage 3 of CIS strategy, as shown in Figure 5). However, the envelope extraction largely discards the temporal fine structure (TFS) information present in the bandpass outputs [12].

In a normal acoustic ear, the envelope information is represented most prominently in neurons tuned to high frequencies, and temporal fine structure (TFS) is represented *via* phase-locking most prominently in neurons tuned to low frequencies. It is reasonably well-established that human sensitivity to such phase-locking to the TFS of stimuli is limited to frequencies below 1,500 Hz [13]. All CI systems that use CIS type strategies convey mainly the envelope information in different frequency bands, whereas TFS is largely missing, at least apart from the envelope modulations that mainly code the fundamental frequency of the sound only. Figure 9 shows the envelope and fine structure components of a sound wave.

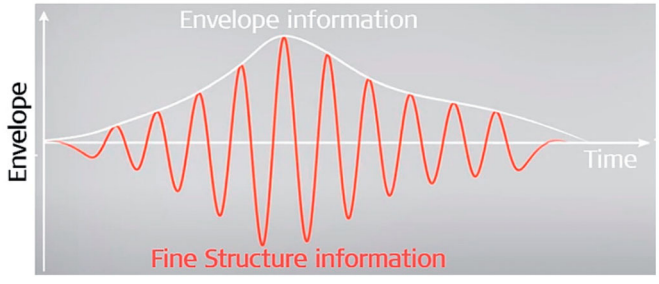


Figure 9. Simple illustration of the envelope and fine structure components of a sound signal (image courtesy of MED-EL).

5.2.3. Fine structure processing (FSP) strategy

In the normal acoustic ear, phase locking is an important phenomenon, predominantly occurring in the LF region, i.e. around the apex where the LF signals are processed and where the neural responses are generated in synchrony with the sound frequency. Every aspect of MED-EL's CI system is inspired by nature, and this concept is also applied to sound coding strategies. **In 1997**, Prof. von Ilberg from the Goethe University Frankfurt in Germany came up with the concept of electric-acoustic stimulation (EAS) to treat partially deaf patients with electric stimulation in the HF region and acoustic amplification in the LF region. The EAS concept gives users access to fine structure information through acoustic amplification of the LF region (Figure 10). Research has shown that EAS users hear better in comparison to the regular CI users, and especially so with regards to speech perception in noise and music appreciation. As a consequence of the results with EAS, MED-EL has developed the FineHearing™ technology to better model the natural acoustic hearing by providing sound-rate stimulation to apical electrode channels while retaining the constant-rate stimulation to the basal electrode channels, as depicted in Figure 10.

In 1999, the FineHearing™ technology (FSP) was initiated based on a patent by Prof. Zierhofer (US patent number: 6594525) from the University of Innsbruck in Austria (academic-industrial partnership program with MED-EL until 2005). In this patent, Prof. Zierhofer proposed the concept of channel-specific sampling sequences (CSSS) which

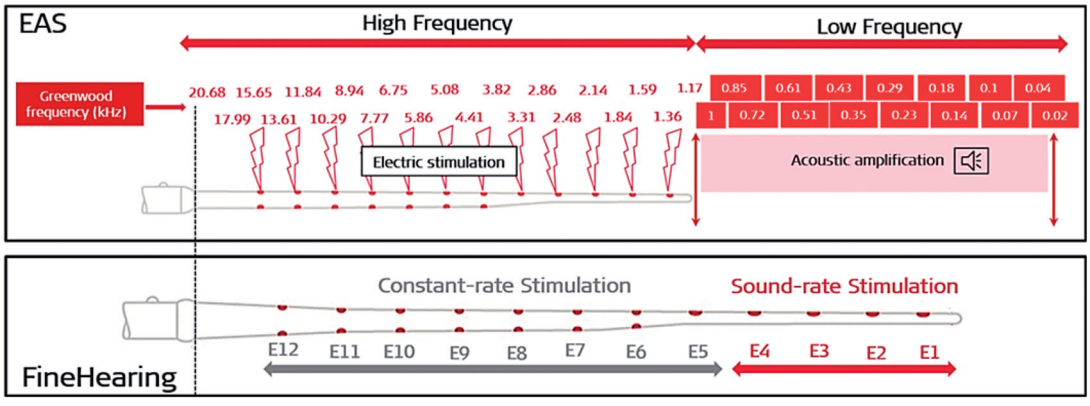


Figure 10. Illustration of EAS and FineHearing™ concept. EAS provides acoustic amplification of the functional LF region using hearing aids, and electric stimulation of the HF deaf region using a CI electrode array. FineHearing™ concept provides sound-rate stimulation (electric stimulation in synchrony with the sound rate) to the apical electrode channels that are physically placed well beyond the basal turn of the cochlea to have a place match and constant-rate stimulation to the basal electrode channels (image courtesy of MED-EL).

allow the representation of the temporal fine structure of a sound signal through a CI in addition to the envelope, and this was implemented in the OPUS BTE audio processor.

In 2006, the development of the FineHearing™, the fine structure processing (FSP) coding strategy by Dr Nopp und Dr Schleich from MED-EL was finished. FSP was the first coding strategy approved for clinical use to overcome the limitations of envelope based coding strategies, which do not use the timing of stimulation pulses as a carrier of information. The fine-structure coding strategy uses CSSS that monitors the bandpass filter output (stage 2 in the CIS strategy, as shown in Figure 5) for zero-crossings in band-pass signals, as shown in Figure 11. At times of positive zero-crossings, stimulation pulses are triggered in synchrony with the instantaneous frequency of the bandpass signal. The fine structure is derived up to frequencies of approximately 350 Hz and results in different electric stimulation patterns for apical and basal electrodes. Fine structure stimulation in the apical region of the cochlea results in neural responses in synchrony with the instantaneous sound frequency – in other words, the apical electrode channels will apply electric pulses at the same rate and in synchrony with the sound frequency. This brings the phase-locking functionality of the normal acoustic hearing to MED-EL's CI system. In contrast to the FSP strategy, the CIS strategy stimulates at a fixed rate. In addition, the lower cutoff frequency is decreased to 70 Hz for FSP, compared to 250 Hz for the CIS strategy. For FineHearing™ to work optimally, the apical electrode channels should reside in the LF region, i.e. covering the entire cochlea with an electrode array, which is called *Complete Cochlear Coverage* (CCC). All in all, the MED-EL CI system uses a flexible, atraumatic electrode array that is long enough to achieve CCC, and fine structure stimulation aims to closely mimic the functions of the normal hearing ear in deaf and hard of hearing recipients.

FSP was implemented in OPUS 2 BTE processors (US patent numbers: 8639359 and 9566434). The OPUS 2 processor was the first processor to feature a remote control – called FineTuner™. The latter enabled the user-friendly processor setting changes without a need for removing it from behind the ears. Dr Stöbich (Project Leader) and his colleagues from MED-EL developed the OPUS 2 processor.

In 2007, Prof. Arnoldner and his colleagues from the Medical University of Vienna in Austria evaluated speech perception, music perception and the general acceptance of the new FSP strategy implemented in the OPUS processor, compared to the CIS strategy implemented in the TEMPO + processor [14] (Figure 12). Fourteen postlingually deaf patients implanted with MED-EL CI devices participated in the study. The speech perception tests consisted of the two-digit number test, Freiburger monosyllabic word test and the HSM sentence test. Tests were presented in a soundproof room at 60- and 80-dB HL in quiet and in noise. Tests were performed at the baseline visit with TEMPO+ (CIS) speech processor, immediately after fitting of the new OPUS (FSP) processor, and consecutively at fourth, eighth and twelfth week after the first fitting.

Figure 13 shows the results of the speech recognition tests in quiet and in noise. Mean results improved for all patients from baseline visit (CIS) to visit 4 (FSP).

For the number test, scores rose from 78.9% (TEMPO+) to 85% (OPUS, visit 4), for the monosyllable test from 45.12% to 48.49%, and for the HSM test from 57.97% to 69.25%. In the noise condition, scores improved even more evidently for the HSM test – from 45.89% to 57.48% at 15 dB SNR, from 22.51% to 45.00% at 10 dB SNR, and from 8.83% to 21.63% at 5 dB SNR. These improvements were statistically significant for the numbers and the HSM tests in all conditions, with and without noise. The data presented in this study were the very first results of the new FSP coding strategy. The excellent outcomes with significant improvements in the speech tests encouraged MED-EL to implement and further fine-tune the coding strategy in its sound processors.

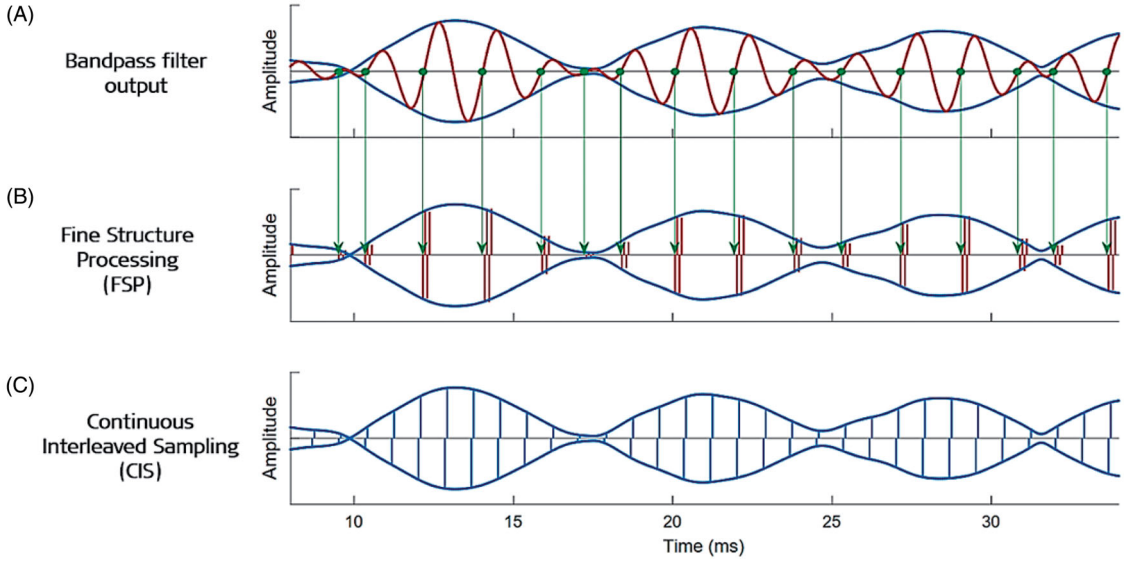


Figure 11. Differences between CIS and fine structure stimulation. Band-pass filter represents the original filtered signal, and the blue line represents the envelope function (A). Fine structure stimulation applies pulses at zero crossings of the band-pass output with an amplitude according to the envelope function (B). CIS stimulates at a fixed stimulation rate according to the envelope function (C). Image courtesy of MED-EL.

Figure 12. Clinicians from the Medical University of Vienna, Austria, compared the hearing performance with TEMPO+ (CIS) and OPUS (FSP) processors in adult CI users, implanted with MED-EL CI system (image courtesy of MED-EL).

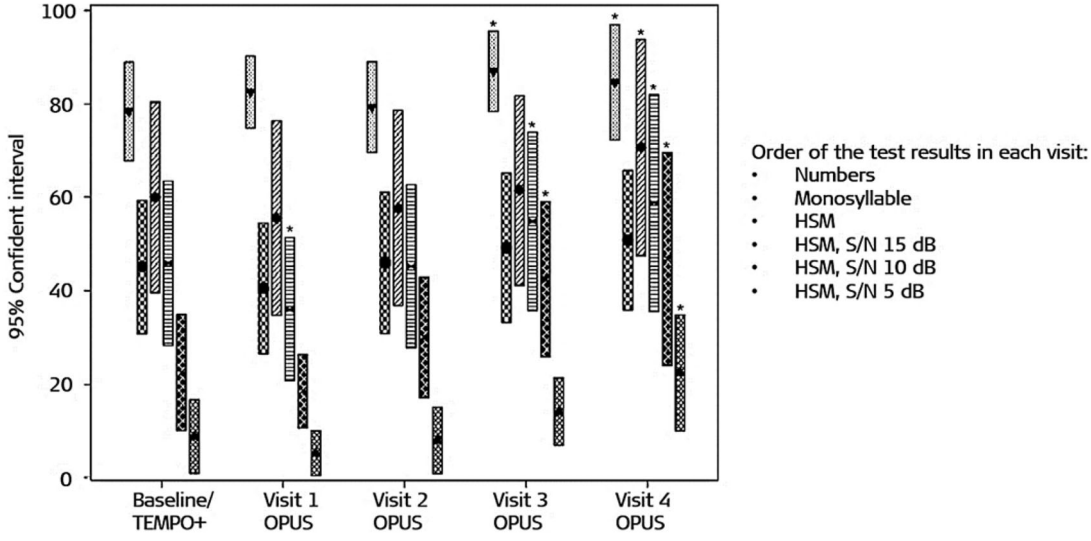


Figure 13. Speech test results for all patients at the baseline visit with TEMPO+ (CIS) immediately after fitting with OPUS (FSP) processors (visit 1) and four, eight and twelve weeks after that (visits 2–4). Bars indicate 95% confidence interval and the continuous improvement of mean values overtime for all tests is seen. Asterisks indicate statistical significance compared with the baseline visit [14]. Statistical analysis: Paired samples two-sided *t*-test ($p \leq .05$). Reproduced by permission of Taylor and Francis Group.

In 2010, Prof. Van de Heyning and his colleagues from Antwerp Medical University in Belgium investigated the effects of the new FSP strategy on speech perception in noise and quality of life through a prospective study, followed up to twelve months [15] (Figure 14).

Thirty-two patients were implanted with 31.5 mm long electrode array, as shown in Figure 10 (FineHearing™ segment) and were fitted with the TEMPO+ (CIS + strategy) processor. After an average of seventeen months of experience with the TEMPO + processor, participants switched

Figure 14. Clinicians from Antwerp Medical University, Belgium, studied the long-term effects of the FSP strategy in experienced CI users, implanted with MED-EL CI system.

over to the OPUS 2 processor. Twenty-two participants switched to the FSP sound coding strategy, and in remaining ten, the processor upgrade resulted in high definition continuous interleaved sampling (HDCIS) maps with no fine-structure channels assigned because of longer pulse durations in their maps. Thus, the latter participants were not able to benefit from improved fine-structure coding but were only able to benefit from the extended sound frequency range in FSP. The MAESTRO fitting software automatically did this conversion to HDCIS. Speech perception tests, including speech recognition in noise, were tested using the Leuven Intelligibility Sentence Test (LIST) that consists of thirty-five lists of ten sentences that are representative of daily communication. Participants were tested with the TEMPO + processor just before the switchover, and then with the OPUS processor at switchover, and after one, three, six and twelve months of OPUS use. At the twelfth-month interval, they were also tested in an acute manner with the TEMPO + processor that was fitted with the map they had been using just before switchover. Speech reception threshold (SRT) in noise for the FSP and HDCIS groups are shown in Figure 15.

Before switchover, i.e. with the TEMPO+ (CIS+) processor, the mean SRT was 16.2 dB, and it deteriorated to 19.5 dB at the acute switchover to OPUS processor using the unfamiliar FSP strategy, with no significant difference. During the first twelve months of FSP use, the SRT gradually improved to 9.7 dB, reaching statistical significance at the twelfth-month interval. When the participants switched back to the TEMPO + processor at the twelfth-month interval, acute testing showed a mean SRT of 10.6 dB, which was not significantly different to the result at twelve-months of OPUS processor use (Figure 15(A)). For the group of participants using HDCIS, mean values for speech perception in noise at different time intervals are shown in Figure 15(B). In this group, the mean SRT changed from 17.5 dB before the switchover to 17.7 dB at the acute switchover stage and 12.5 dB after twelve months of use. After twelve months of HDCIS use, when the participants switched back to TEMPO+ (CIS+) processor and were acutely tested with the CIS strategy, results did not show any significant difference in SRT compared to twelve months of use with HDCIS.

In 2011, a follow-up study of the abovementioned study was published by the clinicians from Antwerp Medical University, evaluating the long-term effects in the range of twenty-four months with a focus on the improvement in speech perception with FSP coding strategy [16]. Figure 16 shows the mean SRTs in noise for the FSP and HDCIS group at each test interval that extends to twenty-four months. After twenty-four months of FSP experience, the SRT decreased significantly from 9.7 dB SNR at twelve months to 3.0 dB SNR, as shown in Figure 16 within the FSP group with an asterisk. Whereas with the HDCIS group, the SRT in noise resulted in 10.9 dB SNR, which was not significantly different from the twelfth month's value of 12.5 dB SNR.

The results presented in these two studies show that by focusing on fine structure coding in the LFs, speech perception in noise can be enhanced. An important learning effect can be seen, indicating that it can take patients some time to be able to benefit from the FSP strategy.

In 2010, Prof. Skarzynski and his colleagues from the Institute of Physiology and Pathology of Hearing in Poland published about the benefit of CIS+, HDCIS and FSP strategies, both qualitatively and quantitatively, in sixty children implanted with a MED-EL CI system comprising with a long electrode array length of 31 mm [17] (Figure 17).

CI surgery had been performed in all children at an average age of 3.8 years, the average time of device use was

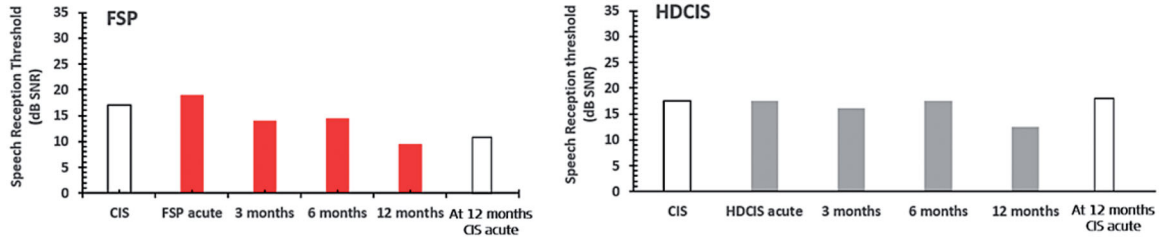


Figure 15. Results of speech reception threshold (SRT) in noise for the FSP group (A) and HDCIS group (B)—lower the SRT value, better the result is. Statistical analysis: Parametric student's test with significance calculated for $p < .01$. (Histograms created from the data given in Vermeire et al. [15]).

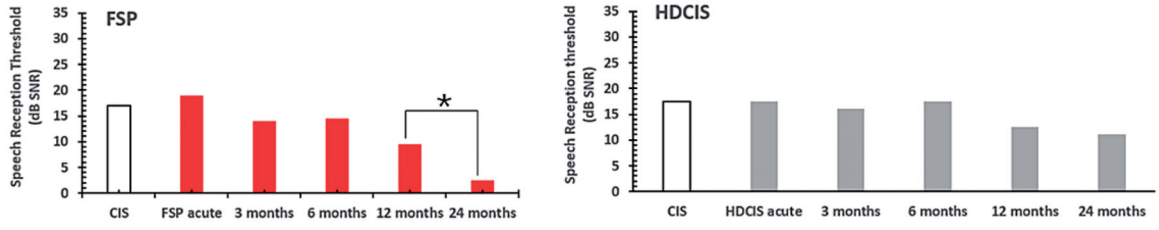


Figure 16. Mean SRT in noise for the FSP and HDCIS group up to twenty-four months after upgrade to the OPUS 2 audio processor. The white bar indicates CIS, red bars indicate FSP, and grey bars indicate HDCIS. Statistical analysis: Post hoc pairwise signed-rank tests to assess SRTs in noise change over time ($p < .05$). Histograms created from the data given in Kleine Punte et al. [16].

Figure 17. Clinicians from the Institute of Physiology and Pathology of Hearing, Poland, compared the benefits of CIS, HDCIS and FSP sound coding strategies, both quantitatively and qualitatively in children implanted with MED-EL CI system.

6.3 years, and the average age at upgrade was ten years. Adaptive Auditory Speech Test (AAST) is a closed-set procedure with the presented stimuli as trisyllabic words where the child chooses an answer from the six pictures shown. In the adaptive procedure, the speech level varies to obtain the SNR for a 50% correct score (speech reception threshold). The AAST was conducted for the HDCIS strategy at the interval I, and for all three strategies at intervals II and III. Visual Analogue Scales (VAS) were completed by the children to reflect subjective judgement with each coding strategy for music stimuli, as well as to make comparisons between coding strategies. The VAS scale for satisfaction required the child to mark whether the strategy was *bad*, *average* or *good* with smiley faces on a 20 cm scale to assist children in decision making.

Figure 18(A) shows the AAST test in noise with no significant interaction effect between strategy and interval and no overall significant effect for the interval. However, an overall significant effect was reached for strategies with FSP better than CIS + by 0.7 dB, and HDCIS better than CIS + by 0.8 dB HL. No statistically significant difference was found for HDCIS and FSP. Figure 18(B) shows the VAS satisfaction rating for music stimuli. VAS results for music stimuli at interval II revealed an overall positive effect for the strategy with FSP better than CIS + by 27.1% and HDCIS better than CIS + by 31.5%. However, no significant difference was seen in music stimuli between FSP and HDCIS. Results for music stimuli at interval III were also significant for strategy showing FSP better than CIS + by 32.4% and HDCIS better than CIS + by 22.3%. No differences were found for FSP versus HDCIS.

Overall, the FSP strategy offered better SRTs in noise and music acceptance compared to HDCIS and CIS+, and the importance of the study increased with the fact that the tested patients were children who did not need to undergo reimplantation in order to benefit from the new developments in the CI technology. This applies to other patients as well, as they do not require reimplantation to acquire the newest technological upgrades and hearing benefits.

In 2012, a clinical trial evaluating the effectiveness of the FSP strategy in experienced MED-EL CI users was reported by clinicians from various CI centres in Germany and was led by Prof. Müller [18] (Figure 19).

Figure 19. Clinicians from different German clinics and engineers from MED-EL, involved in the clinical trial results evaluating FSP strategy in experienced MED-EL CI implant users. [1]University of Würzburg, [2]Technical University of München, [3]Goethe University Frankfurt, [4]Carl Gustav Carus University Hospital Dresden, [5]University of Innsbruck, Austria, and [6]MED-EL, Innsbruck, Austria.

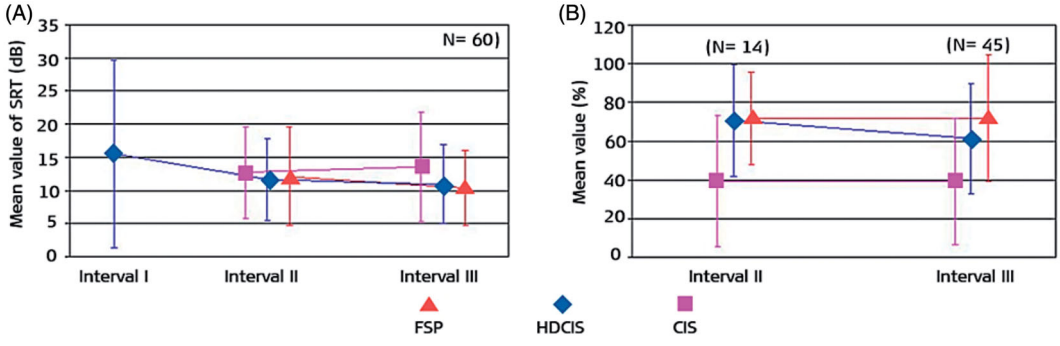


Figure 18. Results for the AAST test in noise as a function of interval (A) and VAS satisfaction scaling using the music stimuli (B) [17]. Statistical analysis: Two-way repeated measures ANOVA test. Reproduced by permission of Elsevier Ireland Ltd.

Forty-six postlingually deaf adults with a minimum of six months MED-EL CI experience participated in this study. Their mean age at implantation was fifty-four years, and the mean age at testing was fifty-six years. They all had at least two years of experience with a TEMPO + processor (CIS + strategy) prior to switchover to an OPUS processor (HDCIS/FSP). The study aimed to compare CIS+, HDCIS and FSP strategies, mainly in terms of speech perception test results in noise using a vowel test, the Freiburger monosyllable word test and the German OLSA sentence test in noise at three months post-switchover. For the OLSA test, the speech level was constant at 70 dB SPL, and the noise level varied in order to determine the SNR that resulted in a 50% correct for each individual. Data of speech perception tests are shown in Figure 20.

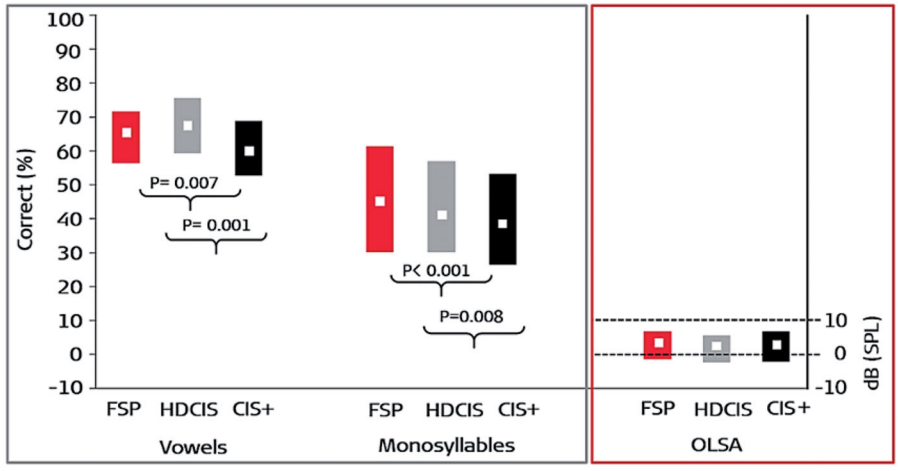


Figure 20. Speech perception scores at third-month post-switchover to OPUS processor (HDCIS/FSP) from TEMPO + processor (CIS). Participants were tested with vowels, Freiburg monosyllable and OLSA using the FSP, HDCIS and CIS coding strategies. Statistical analysis: Paired sample *t*-tests ($p < .05$). Box plot created from data given in Müller et al. [18].

At the test intervals, vowel scores were similar for FSP (64.4 ± 10.9%) and HDCIS (65.4 ± 12.5%). Those for FSP were significantly higher than those for CIS+ (59.6 ± 11.2%). HDCIS vowel scores were significantly higher than CIS + scores. Monosyllable scores showed the same behaviour for FSP (44.8 ± 19.03%) and HDCIS (42.3 ± 18.8%) however, FSP and HDCIS showed significantly higher scores in comparison to CIS+ (38.9 ± 17.8%). With the OLSA test, SRTs were slightly lower for FSP (3.0 ± 6.7 dB) and HDCIS (2.9 ± 7.0 dB) than for CIS+ (3.4 ± 7.7 dB), with no significant differences among them. Pitch scaling was another important test that was carried out in this study and which showed LFs sounding low-pitched with FSP strategy compared to CIS+, which reflects the benefits of the more natural low-frequency coding *via* sound-rate stimulation with FSP. The results from this clinical study demonstrated that users of FSP or HDCIS, as implemented in the OPUS processor, performed equal or better when tested with CIS+, as implemented in the TEMPO+.

In 2013, the interest in FSP coding strategy moved to China to evaluate the benefits of FSP strategy in Mandarin-speaking CI users. Mandarin is a tonal language in which, the pitch is used to distinguish different words. The study was conducted by Prof Han and his colleagues from Beijing Tongren Hospital, involving ten MED-EL CI users (with OPUS 2 processor), aged eighteen years or older [19] (Figure 21). The mean age at implantation was 31.1 years, and the speech performance was assessed before and after cochlear implantation using monosyllables in quiet and sentences in quiet test, called Mandarin Speech Test Materials (MSTM), Mandarin Hearing in Noise Test (MHINT) and Mandarin tone perception test. The Mandarin tone perception test was designed by Dr Krenmayr, an engineer from MED-EL [20].

Figure 22 shows the monosyllables in quiet, sentences in quiet, MHINT, and tone perception results in percentage correct. All the audiological tests showed no statistical significance at first fitting compared to preoperative scores. However, at three months, there was a significant improvement compared with preoperative scores with all speech tests. Monosyllables in quiet and sentences in quite improved significantly at six months, compared to preoperative scores. There was a significant improvement in speech perception in all speech tests at three months compared with the first fitting, and at six months compared with the first fitting. Tone perception did not improve significantly at first fitting compared to preoperative results, nor at three

Figure 21. Prof. Demin Han and Dr Xueqing Chen from the Beijing Tongren Hospital, China, conducted the study along with her colleagues. Dr Andreas Krenmayr is an employee at MED-EL who designed the Mandarin Perception Test.

months – but there was a significant improvement at six months. This was the first study that evaluated the FSP strategy in the Mandarin language, and overall, it showed significant improvement in Mandarin speech and tone perception of adult CI users who had no prior CI experience.

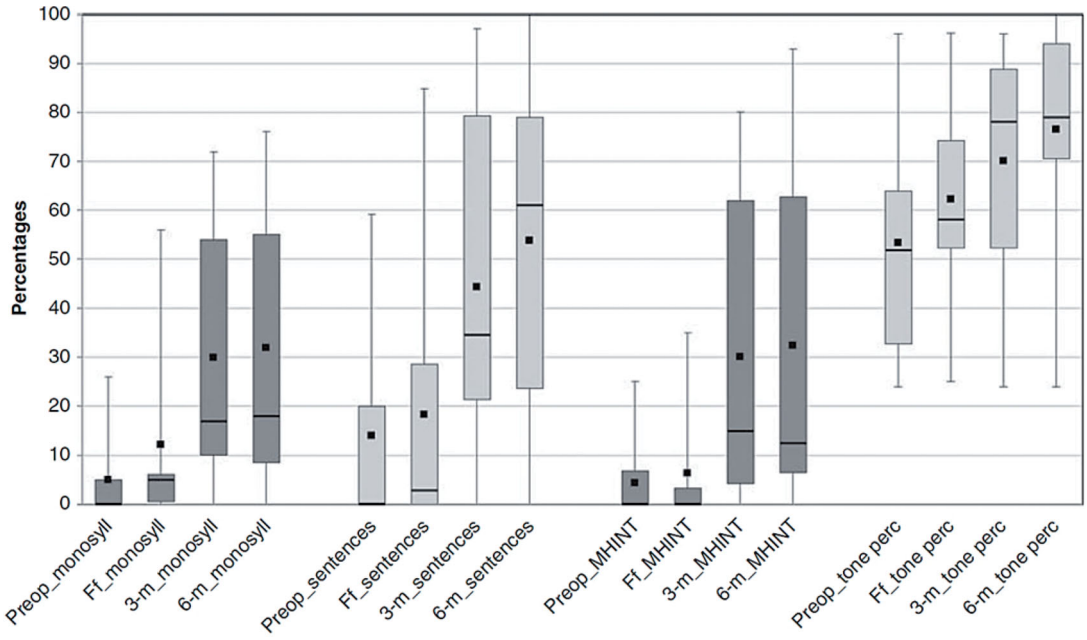


Figure 22. Results are shown in percentages correct for monosyllables in quiet (monosyll), sentences in quiet (Sentences), MHINT, and the tone perception test (Tone perc) over time. Horizontal lines on the box plot represent median values; black squares represent mean values. Ff: first fitting; 3-m: 3 months; 6-m: 6 months [19]. Statistical analysis: Repeated measurements ANOVA test ($p < .05$). Reproduced by permission of Taylor and Francis Group.

The six studies presented in this section reported on the benefits of FSP strategy implemented in OPUS audio processor over the CIS + strategy implemented in TEMPO + audio processor. By keeping the fine structure information in the sound signal by applying phase-locking low-frequency pulses to the LF apical channels in the FSP strategy, along with electric stimulation covering the entire frequency range, helps MED-EL CI users, including Mandarin speakers, to experience near-normal hearing and music acceptance, compared to CIS strategy.

5.2.4. Advancements in FSP strategy

With scientific evidence showing better hearing experience for patients with the FSP strategy, it shall be noted that the benefits of FSP over CIS came by adding fine structure information in the LFs between 70–350Hz. In general, FSP provided fine structure information on up to two apical channels, depending on the individual map parameters – in other words, with the FSP strategy, up to two apical channels are stimulated in synchrony with the sound frequency. FSP monitors for zero-crossings of the bandpass filter output and triggers stimulation pulse packages (CSSS) in synchrony with the sound frequency, as previously described in Figure 11.

In 2010, MED-EL got further improved its FSP strategy by providing fine structure information to four apical channels instead to only two, and hence the name FS4 strategy (Figure 23(B)). Within the FS4 strategy, if two channels are identified with the zero-crossing at the same time, as shown in Figure 23(A), then the system picks the channel that has higher amplitude for providing the fine structure

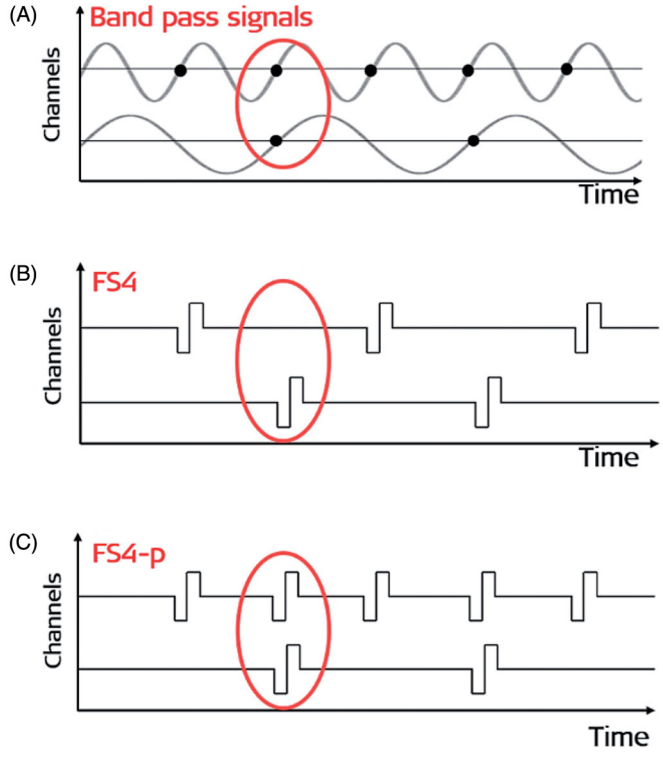


Figure 23. Zero-crossing of the bandpass output (A). FS4 strategy with single-pulse CSSS. In the event of zero-crossings coinciding on two or more FS channels, FS4 picks the channel with the highest instantaneous pulse amplitude for stimulation (B). The FS4-p strategy provides simultaneous stimulation pulses on two channels with coinciding zero crossings (C). Image courtesy of MED-EL.

information (Figure 23(B)). An additional variant was added to the FS4 strategy, called FS4-p. The FS4-p strategy presents fine structure information for more than one channel if zero-crossings appear at the same time, or *in parallel* (Figure 23(C)). However, two channels receiving zero-crossing at the same time is unlikely, but still possible.

This was mainly proposed by Dr Nopp, Dr Schleich, Dr Meister and Dr Schatzer (at the time with the University of Innsbruck) within the Sound Coding research group of MED-EL. The FS4-p strategy provides the possibility to have parallel stimulation in more than one apical channel at a time and needs an additional algorithm to compensate for the effects of simultaneous stimulation (Figure 24).

Figure 24. Signal Processing engineers from MED-EL who proposed the initial concept of FS4 and FS4-p. They were also instrumental in writing algorithms to handle the stimulation frame, sequence of channels, channel groups to be stimulated and in testing parameter variations.

This algorithm is referred to as the channel interaction compensation (CIC) algorithm, patented by Prof. Zierhofer. CIC compensates for the effects of simultaneous channel interaction by computing reduced amplitudes such that after direct electric field summation with simultaneous stimulation, the field distribution resulting from sequential stimulation is approximated. It should also be noted that FS4-p strategies can only be applied to implant systems that allow parallel stimulation and are not applicable to implant systems like COMBI 40 and COMBI 40+.

In 2014, Prof. Rajan and Dr Távora-Vieira from the University of Western Australia published data on subjective preferences and speech perception of unilaterally deaf CI users with FS4 and FS4-p [21] (Figure 25). Thirteen users who had received a CI from MED-EL with the FLEXSOFT^{TM} electrode array were fitted with OPUS 2 processor, and all patients had at least three months experience of using FSP strategy.

The patients were provided with two maps – FS4 and FS4-p – in a blinded manner for assessing their subjective preference towards these different coding strategies. They were asked to rate the two maps on five qualitative attributes daily, as indicated in Figure 26. While speech

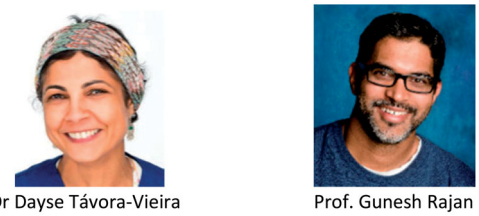


Figure 25. Clinicians from the University of Western Australia subjectively assessed the FS4 and FS4-p strategies in unilaterally deaf CI users implanted with MED-EL CI device.

perception scores were not significantly different among FS4 and FS4-p, all patients showed a subjective preference towards the FS4-p strategy. Providing the fine structure information to the four apical channels and in addition, providing such information simultaneously in more than one channel offered subjectively a more natural hearing experience to the MED-EL CI users.

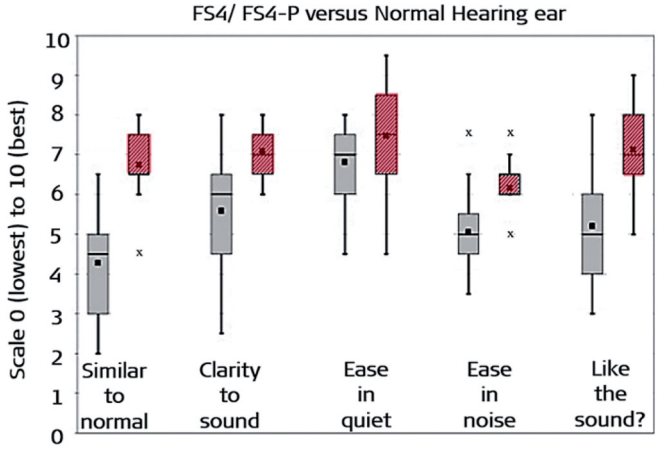


Figure 26. The group results for each of the five questions. FS4 is shown in grey boxes, and FS4-p is shown in red boxes. Mean values are depicted as black squares, medians as horizontal lines and asterisks are the outliers—statistical analysis: Wilcoxon signed-rank tests ($p < .05$). Box plot adapted from Távora-Vieira et al. [21].

In the same year, Dr Riss and his colleagues from the Medical University of Vienna in Austria compared FS4 and FS4-p with FSP strategy in thirty-three postlingually deaf adults. FSP was used as the default strategy [22], but each participant was fitted with these three different strategies for four months in a randomized and blinded order. After each run, an adaptive sentence test in noise (Oldenburger Sentence Test (OLSA)) and a monosyllable test in quiet were performed. Scores of the OLSA did not reveal any significant differences among the three strategies, but the monosyllable word test showed a statistically significant effect ($p = .03$) with slightly worse scores for FS4 (49.7%) compared with FSP (54.3%). Performance of FS4-p (51.8%) was comparable with other strategies. The results of this crossover study showed great variability between CI users, and overall, the average results were similar among all three tested sound coding strategies with regards to speech perception in noise. Nevertheless, the majority of the participants subjectively preferred one of the strategies of FS4 or

FS4-p over FSP. The study showed that each user might have an individual preference for FS coding strategy.

Today, MED-EL has all these sound coding strategies (HDCIS, FSP, FS4 and FS4-p) in its product portfolio giving the choices to the audiologists to try the ones that would provide the best hearing experience to the individual MED-EL CI users.

5.3. Front-end processing

Front-end processing aims to model the functionality of external and middle ear covering the *directionality* and *filtering* processes, respectively. This section will cover the innovations in front-end processing that were implemented in MED-EL's audio processors and the scientific studies that assessed the benefits of those in MED-EL CI users.

5.3.1. Automatic sound management 1.0

Automatic Sound Management (ASM) is a term created to bring together a set of front-end features that were implemented in the audio processors at various time points at MED-EL. *Automatic Gain Control* (AGC) is one of the features within ASM that attenuates high-level signal and enhances low-level signal, enabling the CI user to hear even a very soft sound signal. AGC recreates or models the sound level compression function of the basilar membrane and compresses the range of sound levels by mapping a dynamic input range of 75 dB to a narrower output dynamic range. This feature is available in all MED-EL audio processors, including in off-the-ear processors, existent since 2013. AGC is the first-ever and the only front-end feature that was implemented in MED-EL's COMBI 40 body-worn audio processor and is still available along with other advanced features in the latest SONNET2 BTE audio processor. The modern AGC in CI audio processor carries a dual time constant compression system (slow and fast detector). The slow detector is generally in control of the system gain and mainly determines the dynamic properties of the AGC. The exceptions are sudden intense transient sounds (like door slamming) when the AGC gain is determined by the fast detector, which immediately reduces the system gain.

In 1999, Dr Stöbich (at the time a PhD student), Prof. Zierhofer and Prof. Hochmair from the University of Innsbruck published on the evaluation of the AGC with dual time constant compression system under six different settings in MED-EL CI users fitted with COMBI 40+ audio processor [23] (Figure 27).

In *linear mode,* the AGC operates as a linear amplifier with a fixed gain of +20dB. The setting *standard* is the standard AGC (compression limiter) of the MED-EL COMBI 40 body-worn processor that has only one peak detector. The remaining four configurations, i.e. 3:1 *rapid*, 6:1 *rapid*, 3:1 *slow*, 6:1 *slow,* are slow-acting dual time constant structures. The Göttingen German language sentence test was used to test the CI users hearing performance under the abovementioned six different AGC settings, and the results are given in Figure 28. The results showed that CI users performed significantly better with all four dual front-end configurations than with the standard AGC in situations where intense transient sounds were present.

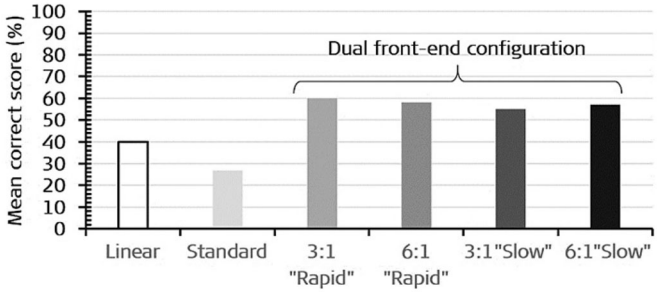


Figure 28. Mean correct score of six users fitted with MED-EL's COMBI 40 body-worn audio processor, tested with six different AGC settings. Histogram created from the data given in Stöbich et al. [23].

Overall, the results indicated that slow-acting front-end AGC could be used effectively in speech processors for CIs to expand the range of input levels that can be heard by the CI users compared with a linear amplifier without any need to adjust a processor control. This was an encouraging result that made MED-EL implement it in its audio processor. AGC was the only front-end feature that was a part of ASM 1.0 in all the audio processors, including the COMBI 40+ (CIS PRO+) BTEs including OPUS and OPUS2, and off-the-ear single unit, including RONDO and RONDO 2 which are described below.

In 2010, an important report was published by Dr Haumann, Prof. Lenarz and Prof. Büchner from Hannover Medical School in Germany in which they evaluated CI patients fitted with audio processors of various CI brands in more realistic listening situations [24] (Figure 29).


Dr Bernhard Stöbich


Prof. Clemens Zierhofer


Prof. Erwin Hochmair

Figure 27. Group of scientists from the University of Innsbruck evaluated the AGC with dual time constant compression system under six different settings in MED-EL CI users fitted with COMBI 40+ audio processors.


Dr Sabine Haumann


Prof. Thomas Lenarz


Prof. Andreas Büchner

Figure 29. Clinicians from Hannover Medical School, Germany, who evaluated audio processors of various brands under more realistic listening situations.

Groups of eleven participants each matched for performance in quiet with five different CI systems, with a total of fifty-five participants (similar age group), were tested with an adaptive test regime where the presentation level of the speech signal roved by ±10 or ±15 dB. The HSM sentences were presented at a roving level, and the noise was adapted to obtain the SNR for a 50% correct score, commonly referred to as the Speech Reception Threshold (SRT). Within each test sentence list, the presentation level of each sentence was randomly roved by either 0, +10 or −10dB in the ±10dB roving condition, and by either 0, +15 or −15dB in the ±15dB roving condition. The base (0 dB roving) presentation level was 65 dB SPL for both tests, hence ranges of 55–75 dB (±10dB roving) and 50–80 dB SPL (±15dB roving) were explored. Speech-shaped noise (CCITT noise) was used as the competing signal and it started 0.5 s before the sentence and finished 0.5 s after the sentence.

Although not significant, a clear trend ($p = .083$) was found for SRT values being higher (i.e. worse) for the ±15dB roving condition than for the ±10dB roving condition. Figure 30 shows the comparison between results for the individual CI brands. Results are widely scattered for all devices, although the scatter seems to be more pronounced in users of the Espirit 3 G processor. The users of OPUS 2 processor from MED-EL showed significantly lower SRT values ($p = .045$) for the ±15dB roving condition than for the ±10dB roving condition. For all other groups, these differences were not significant. Within ±10dB roving condition, post-hoc testing found significantly smaller SRT values for the OPUS 2 and Harmony group, than for the Freedom group. Within ±15dB roving condition, post-hoc testing revealed that all other groups apart from the Freedom group showed significantly smaller SRT values than the Espirit 3 G group. Similarly, the Harmony group and the OPUS 2 group showed significantly smaller SRT values than the Freedom group. Finally, the OPUS 2 group showed significantly smaller SRT values than the Auria group.

The investigators of this study thought that the technical parameters most challenged by a roving-level test are the input dynamic range (IDR) and automatic gain control (AGC) of the speech processors. The Auria and Harmony speech processors by Advanced Bionics are reported to have an IDR of 80 dB and for the OPUS 2 speech processor by MED-EL, an IDR of 75 dB is given. In contrast, for the Espirit 3G and Freedom speech processors by Cochlear Corporation, an IDR of only 30–45 dB is recommended. Furthermore, the speech processors by MED-EL and Advanced Bionics are reported to feature dual-loop AGCs, whereas for those by Cochlear™, a single loop AGC is reported. They concluded that their results show that speech

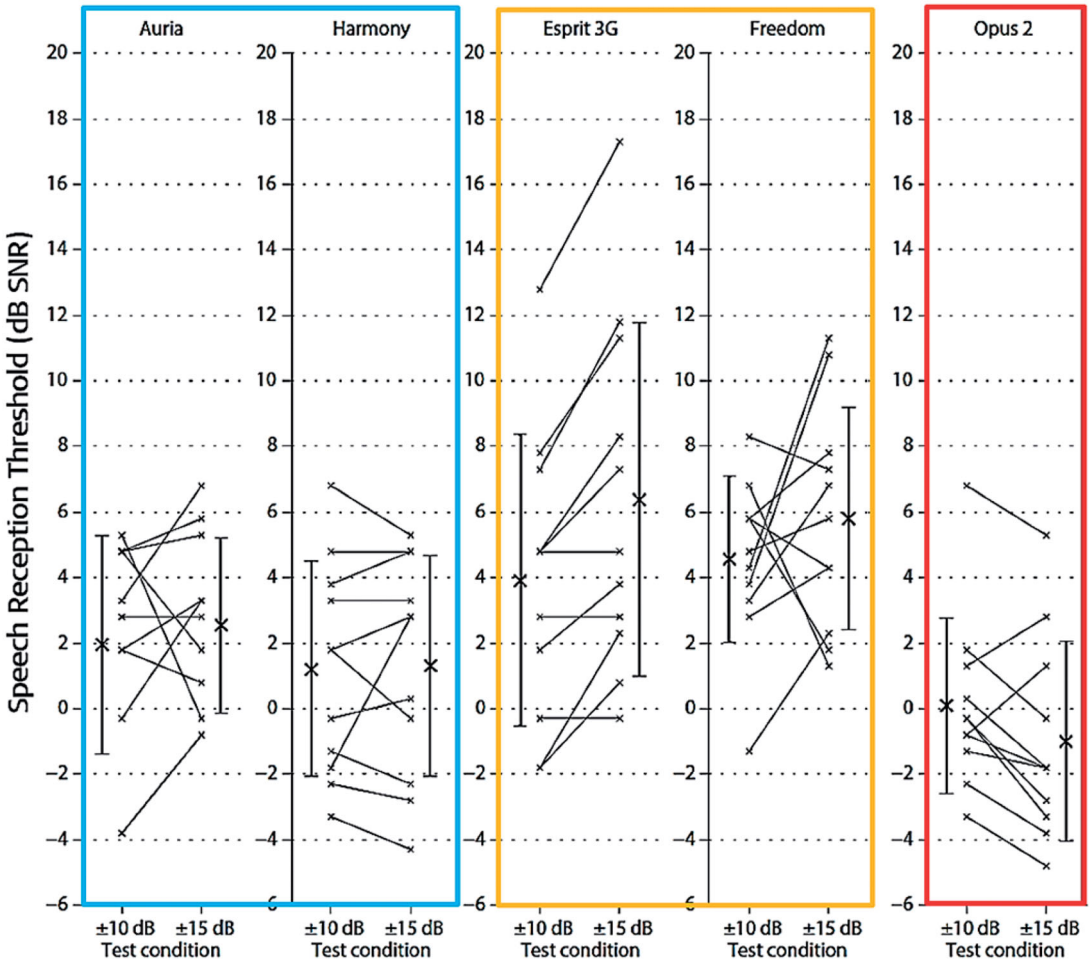


Figure 30. Individual results (small crosses) as well as mean values (crosses on the left and right) and standard deviation values (error bars) as a function of speech processor and test condition [24]. (±15dB is more difficult listening condition than ±10dB). Reproduced by the permission of Karger, Basel.

processors featuring a wider IDR and a dual-loop AGC are advantageous when tested under more realistic test conditions like the roving-level test used in their study.

In 2013, MED-EL, as the first CI manufacturer, developed a single unit audio processor that combined the processing unit, battery pack and the head-piece all in one unit, named RONDO. Figure 31 compares RONDO with OPUS 2 processor.

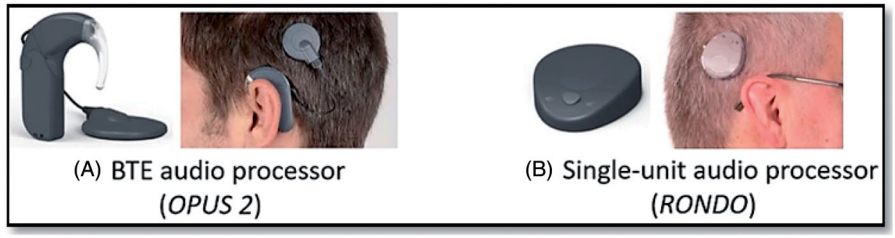


Figure 31. Comparison of BTE (OPUS 2) and single unit (RONDO) processor (image courtesy of MED-EL).

This was a significant change in the audio processor design, led by Dr Stöbich and his colleagues from MED-EL. It featured advantages over the BTE processor in terms of cosmetic look, as it could be hidden under hair and give comfort to people wearing glasses. One of the questions that arose was how the position of the single-unit audio processor, which is positioned away from the pinna, would affect the hearing performance of the CI users.

In 2014, Prof. Mertens and her colleagues from Antwerp University Hospital published on the assessment of the SSD patients who had received a MED-EL CI with a BTE audio processor and were offered the single unit RONDO audio processor, to study if there was any difference in hearing performances with the two different sound processor designs [25] (Figure 32).

Figure 32. Clinicians from Antwerp Medical University, Belgium, compared the effectiveness of a BTE processor with the single-unit audio processor by evaluating the hearing thresholds between them.

Ten SSD patients with severe tinnitus with an average age of fifty-six years were included in the study. All of them had an average of eight years of CI experience. The hearing performance assessment was first made with their BTE processor, followed by the application of the RONDO processor for twenty-eight successive days. Outcome measures included unaided and aided hearing thresholds, speech perception in noise and sound localisation. Subjective assessments included sound quality assessment, hearing (dis)ability using Speech, Spatial and Qualities (SSQ), spatial hearing abilities, tinnitus loudness and user feedback questionnaire, and microphone position. None of these tests showed any significant difference in hearing performance between these two audio processors.

The positive aspects of the single-unit processor (RONDO) were no skin pressure, no skin irritation and the comfort to wear glasses as observed from the feedback questionnaire. The study concluded that long-term BTE audio processor of SSD users could be upgraded to a single-unit audio processor without compromising their speech performance, aided hearing thresholds, sound localisation, objective speech quality, hearing abilities and tinnitus reduction.

In 2016, group of Clinicians from Germany led by Prof. Mlynski published their findings on the effect of RONDO audio processor on speech perception of experienced CI users compared to OPUS2 processor [26] (Figure 33).

Fifty subjects were enrolled in the study with a mean age of 56.1 years and mean duration of hearing loss of 20.2 years. The subjects had at least 3.2 years of OPUS 2 experience before upgrade to RONDO processor. Freiburg Monosyllable word test showed little changes between OPUS 2 (range 62.4–63.4% correct) and RONDO (range 60.3–61.9% correct). The German OLSA in noise showed again little changes between OPUS 2 (range 2.2–4.1 dB SNR) and RONDO (range 1.9–4.6 dB SNR) audio processors. The study concluded that RONDO provides comparable speech perception to the OPUS 2 and it is a suitable and safe alternative to traditional BTE audio processors.

In 2017, MED-EL launched the RONDO 2 single-unit processor, which is an advanced design of RONDO. RONDO2 came up with wireless charging, making it easy to

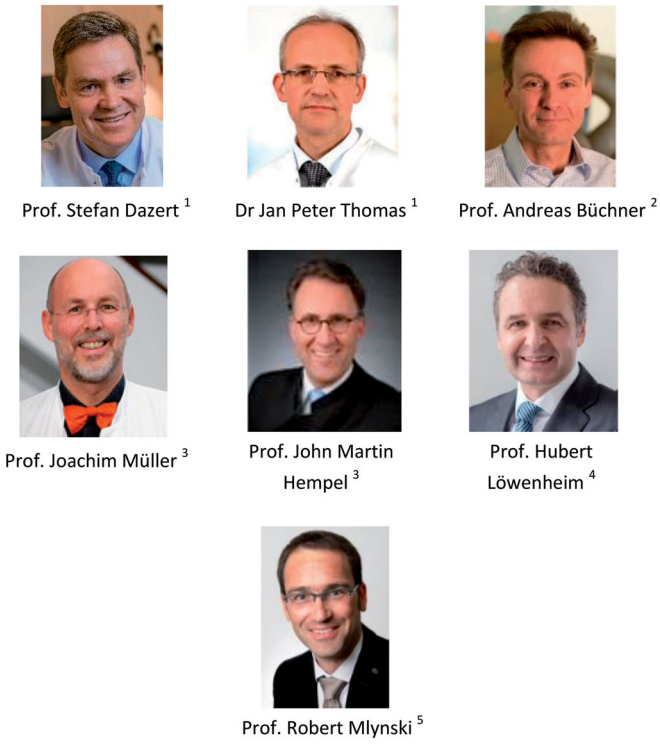


Figure 33. Clinicians from different clinics in Germany who were involved in the assessment of RONDO audio processor. [1]Ruhr-University Bochum, [2]Deutsches HörZentrum Hannover, [3]Ludwig-Maximilians University, Munich, [4]Tübingen University Hospital and [5]Rostock Medical University Center.

power up the device without the need of removing the battery from the processor. Because of its smaller size, it gets easily hidden under hair and gives comfort to people wearing glasses. It comes with WaterWear, which is a reusable waterproof cover that is easily attached and may be used in any type of water (Figure 34). Within MED-EL, it was Dr Duftner who had the project leadership role in product development.

5.3.2. Automatic sound management 2.0

Directionality is an important function of the external ear. With the help of the pinna, the ear can better collect sound signals from the front than from the rear side of the head. Using dual-microphone technology, the directionality feature in MED-EL's front-end processing offers three possibilities to its users – omnidirectionality, natural/fixed directionality, and the adaptive directionality. *Omnidirectional* functionality (the front microphone is enabled while the rear is disabled) treats any sound signal coming from all directions equally, whereas the natural/*fixed directionality* mimics the pinna that is focused to the sound signal coming from the front rather than the rear end. Similar to the human ear pinna, natural directionality is omnidirectional in the low frequencies and increasingly directional towards the front with increasing frequency. The *adaptive directionality* adapts the directionality patterns in a frequency-depending manner, depending on the acoustic scenario in the back hemisphere of the user. Finally, auto-adaptive directionality switches between omnidirectional for lower signal levels and adaptive for medium and high signals. *Wind noise reduction* (WNR) is another function that was added to the front-end processing of the SONNET processor. The signals from the microphones are used to monitor any wind noise, and in case of any detection of such, it applies the wind noise suppression network. Wind noise is mainly in the LFs, and the mild mode of WNR acts without reducing the target sound signal. The strong mode provides heavier wind noise reduction but also affects the target sound signal to some extent.

Figure 34. RONDO-2 single-unit processor. Dr Alexander Duftner from MED-EL assumed the project leader role for this product development.

Figure 35. Dr Ernst Aschbacher (Team Leader- Front-end processing) and his colleagues from Signal Processing research group at MED-EL was responsible for implementing dual-microphone in SONNET audio processor. SONNET audio processor showing dual microphone that gives the directionality function and WNR to the audio processor. AudioLink is a universal connectivity device that connects the audio processor with media players and mobile phones using Bluetooth connectivity. Image courtesy of MED-EL.

Directionality and WNR functions were made available in the SONNET and SONNET EAS audio processors. SONNET and SONNET EAS are available since **2014** with these two additional front-end processing features under the term Automatic Sound Management 2.0 (ASM 2.0). The SONNET processors are complemented by the AudioLink universal connectivity device that allows to stream from mobile phones, tablets, TVs and much more, directly to the SONNET audio processor. At MED-EL, it was Dr Aschbacher and his colleagues from the Signal Processing research group who were responsible for implementing dual microphones (Figure 35).

In 2018, Prof. Baumann and his colleagues from Goethe University Frankfurt in Germany compared the speech perception in quiet and in noise between two EAS audio processors (DUET and SONNET EAS) to assess the impact of front-end processing, including microphone directionality (MD) and WNR [27] (Figure 36).

Dr Tobias Weissgerber | Prof. Timo Stöver | Prof. Uwe Baumann

Figure 36. Clinicians from Goethe University Frankfurt, Germany, compared the speech perception in quiet and noise between two audio processors to assess the impact of front-end processing, including microphone directionality and wind noise reduction function.

DUET has fixed omnidirectional microphone directionality, whereas SONNET EAS processor offers three modes of microphone directionality (MD), as mentioned above. Ten EAS patients, implanted with MED-EL EAS system and with at least one year of DUET processor use prior to the switchover to SONNET EAS processor, were enrolled in this study. Speech perception in quiet was assessed with Freiburg Monosyllables test for both processors, and mainly this test served as reference and additional verification of proper fitting of the SONNET EAS processor. Speech perception in noise was assessed with Oldenburg sentence test with the noise level fixed at 65 dB SPL and speech level was set adaptively according to the number of words perceived correctly to measure the SRT.

The results of speech perception in quiet are shown in Figure 37(A), and the scores ranged between 75.8 ± 10.7% (SONNET with mild WNR) and 80 ± 12.8% (DUET EAS) with no statistical significance. SRT with DUET EAS was −1.7 ± 2 dB SNR, and with the SONNET EAS using the omnidirectional microphone and WNR off was −2.3 ± 1.9 dB SNR, with no statistically significant difference. Compared with DUET EAS, the SRT with fixed MD natural (SONNET EAS default setting) was 2.2 dB better, and with adaptive MD 3.5 dB better (Figure 37(B)). The results obtained from these experiments showed that the SONNET EAS processor with the front-end features like directionality and WNR provide experienced EAS users with significantly better speech perception, particularly in noisy conditions.

In 2018, Dr Dorman and his colleagues from Arizona State University in the US published data on the effectiveness of dual-microphone technology in the SONNET audio processor in bilateral CI adult users ($n = 10$) [28]. Sentence understanding scores in terms of percentage of words correct were tested under one CI and in two CIs in quiet and in noise, simulating real-life test environment. In a restaurant simulating type test environment, the listeners were seated in the centre of eight loudspeakers arrayed in a 360° arc. Sentences from AzBio sentence lists were presented from the loudspeaker at 0° azimuth, and directionally appropriate restaurant noise was presented from all eight loudspeakers, including the speaker from which the target sentences were delivered. For the single CI omni-in-quiet conditions, the mean scores were as follows: omni-in-quiet was 83% correct, omni-in-noise was 28% correct, natural-in-noise was 44% correct, adaptive-in-noise was 51% correct. In bilateral CI test conditions, the mean scores were as follows: omni-in-noise was 40% correct, natural-in-noise was

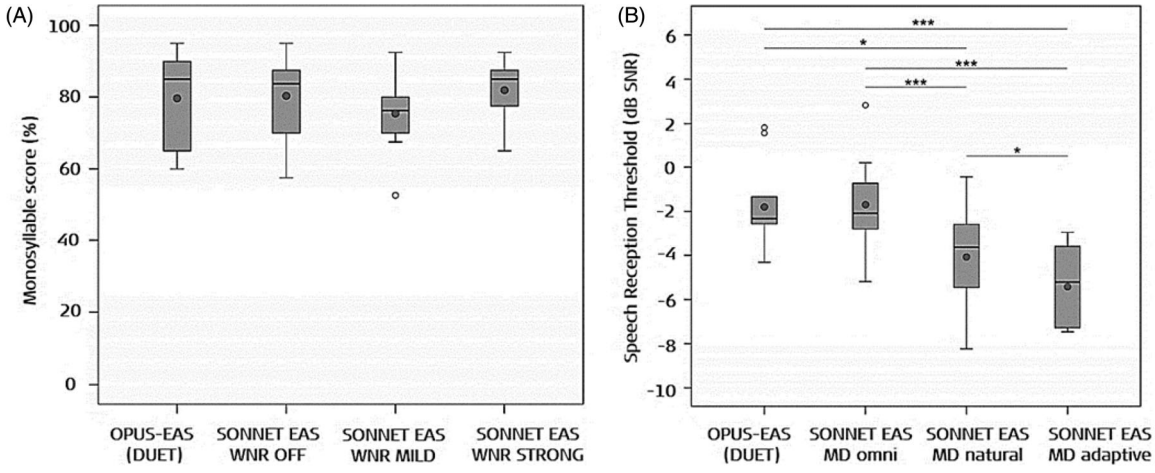


Figure 37. Boxplots of monosyllable scores obtained with the DUET EAS and SONNET EAS processors in three different WNR settings. (A). Boxplots of SRTs with audio processors DUET EAS and SONNET EAS with MD omnidirectional, natural and adaptive directional microphones (B). Grey circles indicate the mean value; open circles indicate outliers [27]. Statistical analysis: RM-ANOVA and Bonferroni-Holm correction method ($p < .05$).

59% correct, adaptive-in-noise was 71% correct. The results (Figure 38) show that in both single and bilateral CI conditions, the natural and adaptive settings allowed significantly higher scores than the omni- setting. Comparing the single and bilateral CI test conditions, the bilateral CI condition scores were significantly better than the corresponding scores in the single CI test conditions. The data show that both, the natural and adaptive microphone settings significantly improved speech understanding in the noisy environment under both, single and bilateral CI condition, and that they do not impair sound source localisation, with retaining low-frequency sensitivity to signals from the rear. However, the bilateral CI scores were higher than the single CI scores.

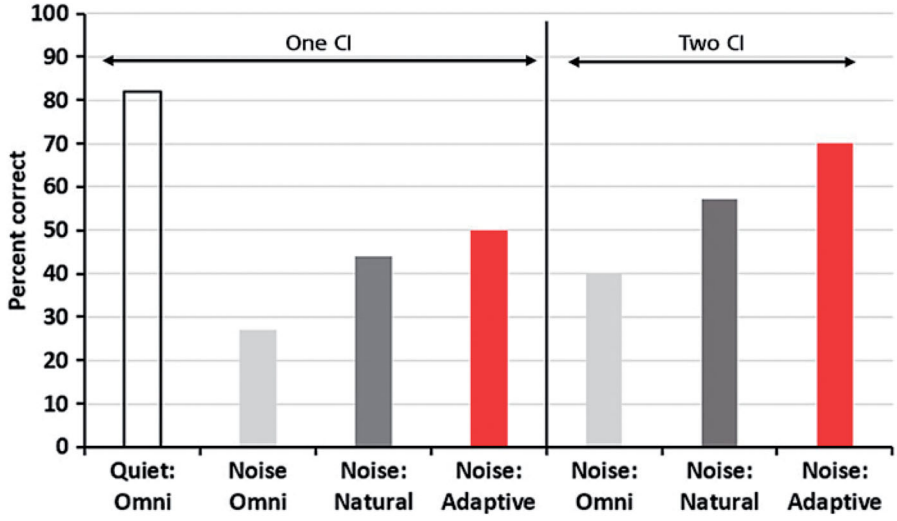


Figure 38. Percentage correct word recognition in quiet and in restaurant noise with one CI and with bilateral CIs as a function of microphone setting (Histogram created from the data given in Dorman et al. [28]).

In 2020, Prof. Caversaccio and his colleagues from the Bern University Hospital in Switzerland published their work comparing the sound-source localisation of bilateral CI users with omnidirectional (OMNI) and pinna-imitating (PI) – which is the dual microphone in the SONNET audio processor [29] (Figure 39).


Dr Wilhelm Wimmer [1]


Prof. Martin Kompis [2]


Prof. Georgios Mantokoudis [2]


Prof. Marco Caversaccio [2]

Figure 39. Researcher and clinicians from the University of Bern, Switzerland. [1]Hearing Research Laboratory and [2]Bern University Hospital.

Twelve experienced bilateral CI users who wore the SONNET audio processor for at least four weeks were included in the study, and they scored 70% or better with monosyllabic words at 60 dB SPL. The default audio processor modes consisted of FS4 strategy with activated PI directionality mode and WNR disabled. Participants were seated in the centre of a horizontal circular loudspeaker setup with a radius of 1.1 m in the acoustic chamber. Mainly, the static sound source localisation was evaluated in the study of participants with the OMNI and PI microphone directionality modes. Within the sound source localisation test, participants indicated the estimated position using a 1° angle resolution dial-on touchpad. For each test step, two pink noise stimuli with a duration of 200 ms at a sound pressure level of 65 dB were used, separated by a one-second intra-stimulus interval. The perceived stimulus shift was indicated by the participants using a touchpad.

Figure 40 shows the absolute localisation accuracy for each stimulus direction for the OMNI and PI modes. The localisation performance in OMNI mode was the worst in the dorsal azimuth at 150°, 180° and 210° angle with RMSE values of 42 ± 18° angle, 41 ± 27° and 44 ± 27° angle, respectively. The best localisation performance was observed at a 120° angle, 240° angle with 17 ± 9° angle, and 15 ± 9° angle, respectively. In PI model, the localisation errors at the dorsal azimuths (150°, 180° and 210° angles) were reduced, leading to a similar performance compared to the frontal azimuths (330°, 0° and 30° angles). In simple words, for the static sound localisation, the greatest benefit was a reduction in the number of front-back confusions (FBCs). The FBC score was reduced from 27% with OMNI mode to 18% with PI mode. Also, the ability to discriminate sound sources at the sides was only possible with the PI mode.

In 2020, Prof. Hagen and his colleagues from the University Hospital of Würzburg in Germany and engineers from MED-EL published a comparison of the speech understanding in noise and hearing in the real-life situation of MED-EL CI users when fitted with OPUS 2 and SONNET

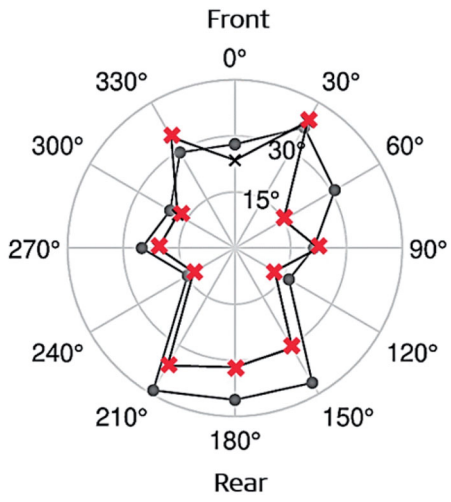


Figure 40. Averaged RMSE for the omnidirectional (OMNI-circles) and pinna-imitating (PI; red crosses) microphone modes in the static sound source localisation test [29]. Statistical analysis: Two-sided Wilcoxon signed-rank tests ($p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

audio processors [30]. Thirty-one participants were assessed for speech understanding in two types of acoustic noise and wind noise. A four-speaker setup was used, and speech was presented from 0° and noise from 90°, 180°, and 270°. Wind noise was simulated with a fan. Oldenburg Sentence Test (OLSA) was used to assess the 50% speech recognition threshold (SRT in dB) in a noisy setting (SRT is a measure of the level difference at which 50% of speech can be correctly identified in the presence of simultaneous masking noise). Figure 41(A) shows speech perception results tested under speech shaped noise (S0N0). Under the test condition, Nat + Mild and OMNI + Off, SONNET was not significantly (statistical and clinical) better than OPUS 2. The same trend was seen with SONNET in Adp + Strong compared to OPUS 2 processor. Within the SONNET processor, none of the modes showed any significance both statistically and clinically. Figure 41(B) shows speech perception results tested under babble noise (S_0N_{III}), and the SONNET in both Nat + Mild and Adp + Mild were significantly (statistical and clinical) better than with the OPUS 2, but not SONNET in OMNI + Off or OMNI + Mild with OPUS 2. Within SONNET, Nat + Mild was significantly (statistical and clinical) better than with OMNI + Mild. Figure 41(C) shows speech perception results tested under speech shaped noise (S_0B_{III}) and the SONNET in Nat + Mild and Adp + Mild was significantly (statistical and clinical) better than with the OPUS 2, but not SONNET in OMNI + Off or OMNI + Mild with OPUS 2. Within SONNET, Nat + Mild and Adp + Mild better (statistical and clinical) than with OMNI + Mild. Figure 41(D) shows the speech perception results tested under wind noise (S_0W_{45}), where OPUS2 was significantly (statistical and clinical) better than with the SONNET in all the MD modes. Within SONNET, participants in SRT were better when WNR was activated.

The study concluded that SONNET provides the same or significantly improved speech understanding when compared to OPUS 2 in noise. While OPUS 2 was superior in the wind condition when compared to the SONNET in

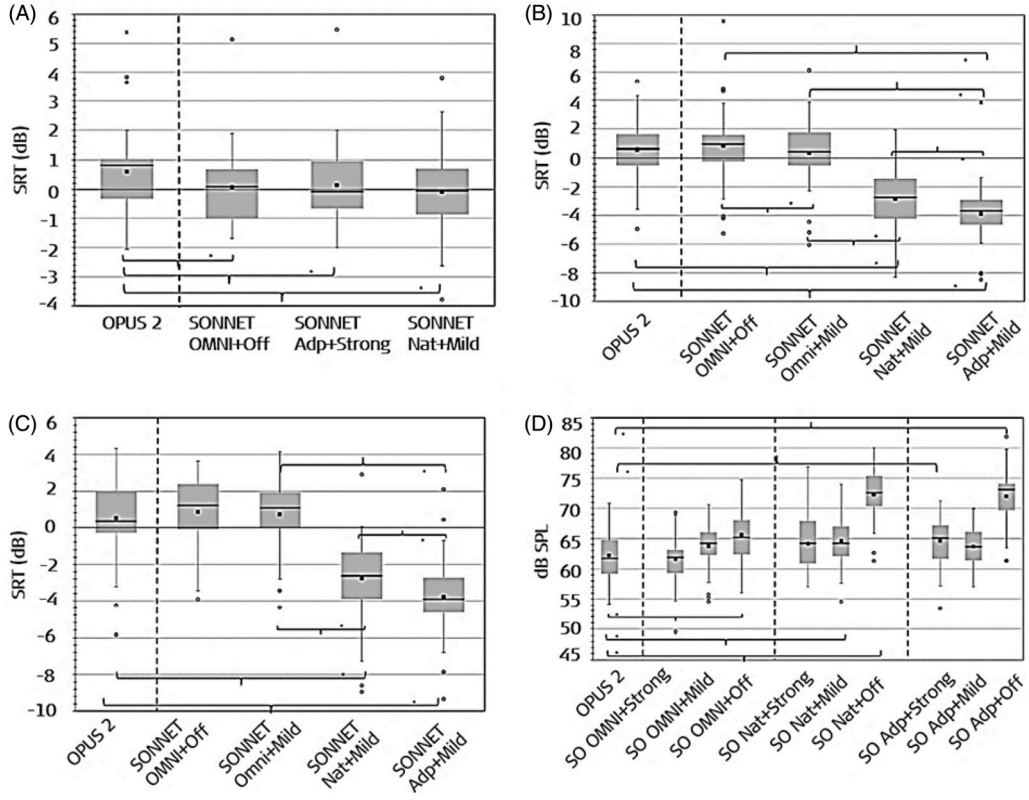


Figure 41. Scores of OLSA test in (A) speech shaped noise (S_0N_0 setup), (B) babble noise (S_0N_{111} setup), (C) speech shaped noise (S_0B_{111} setup), and (D) in the wind without additional noise (S_0W_{45} setup). Black squares represent mean values; horizontal lines are the median. The black circles depict outliers. The black crosses depict extreme outliers [30]. Statistical analysis: the asterisks depict significance differences ($p \leq .05$). Reproduced by permission of Taylor and Francis Group.

some settings, SONNET was superior in real-life listening situations (SONNET with WNR acts better than OPUS2).

Overall, the studies listed in this section demonstrate the benefit of having dual-microphone in the audio processor, which helps the users to regain natural directionality mimicking the pinna function.

5.3.3. Automatic sound management 3.0

In 2019, MED-EL further advanced the front-end processing features by including Ambient Noise Reduction (ANR), Transient Noise Reduction (TNR) and the Adaptive Intelligence (AI) into the ASM portfolio. These three features, in addition to all other above-listed features, were altogether brought under the term ASM 3.0 and were made available in SONNET 2 audio processor, which is the most advanced BTE audio processor in 2021. ANR monitors for ambient/stationary noise level and reduces the stimulation level on each channel based on the signal-to-noise ratio. TNR reduces transient noises by controlling stimulation levels on the high-frequency channels only. AI classifies the sound signal into one of the five classes – Quiet, Speech, Speech in Noise, Noise, and Music – and controls the ASM 3.0 features (directionality, ANR, TNR, WNR) accordingly to maximise the benefits for the CI user. It was Dr Aschbacher and his colleagues from MED-EL who added these front-end features to SONNET 2 audio processor. Apart from the technical advancements, this processor has the AudioLink universal connectivity device to connect to any media devices, and WaterWear may be used for water resistance.

In August 2020, MED-EL received FDA approval for its RONDO 3 single-unit processor. The ASM 3.0, wireless charging, wireless connectivity and smaller size made it the most advanced single-unit audio processor. Within MED-EL, it was Mr Philipp Schmidt, MSc, who had assumed the project leadership role in developing the RONDO 3 processor as a product.

5.4. Individualisation in sound coding strategy

Literature reveals that the size, shape, anatomy and the frequency map of human cochleae vary individually [31]. This is the valid reason for MED-EL to offer electrode arrays in different lengths to achieve an electrode-place match inside the cochlea. A perfect electrode-place match inside the cochlea would enhance FSP coding strategy to work at its best in helping CI users to hear naturally. MED-EL came up with a unique concept called Anatomy-Based Fitting (ABF) that would assign centre frequencies to individual electrode channels based on patient-specific Greenwood's frequency map. The other situation where the individualisation in sound coding is needed is when the patient is wearing HAs on one side and CI on the other side. It is known from the literature that HAs have higher latencies compared to the CI. To address this issue, MED-EL implemented artificial time delays to its CI system and named it Bimodal Delay Compensation. Undesirable facial nerve stimulation is experienced by some CI patients due to their special inner-ear anatomical condition. To address this patient group, MED-EL modified the shape of the biphasic stimulation pulses to triphasic stimulation pulses with the aim of minimising the undesirable stimulation of the facial nerve. This section details all these three different individualisation concepts in MED-EL's sound coding strategies.

5.4.1. Anatomy based fitting

In 2015, Dr Landsberger from New York University School of Medicine in the US, Prof. Van de Heyning from Antwerp University Hospital in Belgium, and their colleagues jointly reported that reliable low-frequency pitch perception in CI requires apical electrodes and a rate-place match [32]. They re-analysed pitch-matching data in SSD MED-EL CI recipients presented earlier by Schatzer et al. [33] with concluding that for a perceptually accurate encoding of sound frequency *via* temporal rate of stimulation, as in MED-EL's fine-structure coding strategies, fine-structure rate stimulation has to be presented on cochlear locations not shallower than 430°. The ratio of the change in acoustic frequency (in dB) and the corresponding change in rate required for pitch-match (also in dB) has to be 1.0 as shown in Figure 42 (horizontal black dotted line). For cochlear locations deeper than 430°, the ratio is not significantly different from *1* (red symbols in Figure 42), whereas it is significantly different from *1* at shallower cochlear locations (yellow symbols in Figure 42). In addition, Landsberger et al. [32] showed that low-rate stimuli are only perceived as *clean*, *not noisy*, and *not annoying* when presented on electrode channels in the second cochlear turn. When presented more basally, most of the tested MED-EL CI recipients perceived them as *not clean*, *noisy*, and *annoying*.

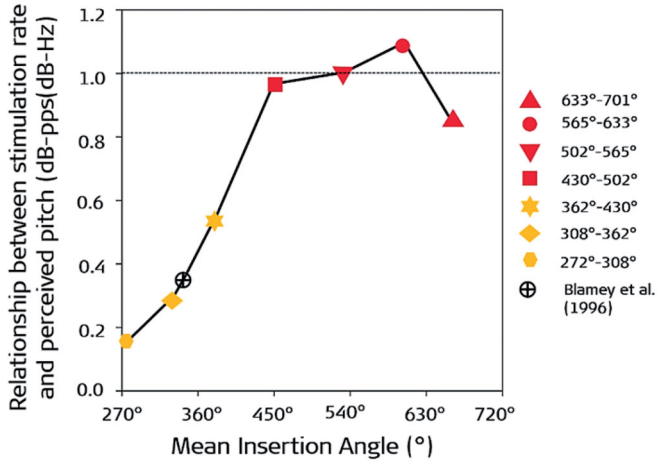


Figure 42. Data plot from table 3 from Schatzer et al. (2014) [33]. The ratio of the change in perceived acoustic frequency (in dB) to the change in stimulation rate (in dB) is plotted as a function of the mean insertion angle for each of the cochlear regions. For a rate of stimulation of properly encoded pitch, the relationship between the rate of stimulation and the frequency corresponding to the perceived pitch must equal one, as shown by the black dotted line. The data from a similar study by Blamey et al. [34]. (1996) in Cochlear™ CI22 users are consistent with the data in Schatzer et al. (crossed symbol). Reproduced by permission of Wolters Kluwer Health, Inc.

In 2016, Prof. Baumann and his colleagues from the Johann Goethe University Frankfurt in Germany demonstrated that in SSD patients ($n = 7$) implanted with FLEXSOFT^{TM} (array length = 31.5 mm) and FLEX28^{TM} (array length = 28mm), the FSP strategy enabled CI users to have matched low pitch perception in the implanted ear (ipsilateral), compared to the normal acoustic hearing ear (contralateral) [35]. FLEXSOFT^{TM} and FLEX28^{TM} electrode arrays reach an angular insertion depth of close to 700° and 600°, respectively, which is closer in place to LFs <300Hz, as shown in Figure 43.

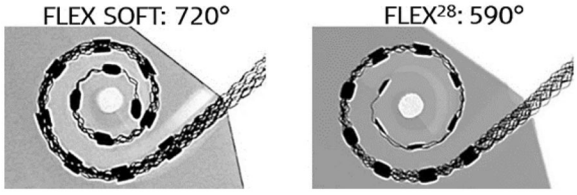


Figure 43. Angular insertion depth of FLEXSOFT^{TM} and FLEX28^{TM} electrode arrays in an average-sized cochlear model (image courtesy of MED-EL).

When apical channels of these electrodes are electrically stimulated at a defined rate (pulses/second) representing the corresponding acoustic frequency, then these SSD patients can subjectively match with their normal hearing on the contralateral ear and say whether the electric hearing matches with their natural acoustic hearing, as given in Figure 44.

Per Greenwood's frequency function, at an intracochlear insertion depth of 630°, the neural fibres are responsible for processing frequencies closer to 150 Hz. To match the 150 Hz perception with CI, the electrode array shall be physically placed at that insertion depth, and the electric stimulation should be provided at a rate of 150pps. If the apical channels were placed at an insertion depth of 630° and provided with fixed stimulation rates (1,500pps), it sounded more like above 300 Hz (Figure 44(A)). Whereas, if the apical channels were provided with place-dependent stimulation rates, the SSD users felt like it sounded more natural as they were able to match the CI pitch percept with their normal-hearing ear (Figure 44(B)). Similar pitch matching results in SSD patients with MED-EL CI were reported earlier by Vermeire et al. in **2010** [15] and Schatzer et al. in **2014** [33].

Like with any other features in the MED-EL CI system that are inspired by nature, it is the wish of MED-EL to follow this principle by allocating centre frequencies to the patient-specific electrode contact positions based on Greenwood's frequency-place map. In order to achieve a reliable LF pitch perception with a CI, it requires a good match between electrode place and stimulation rate. The fact that the cochlear size varies a lot among the human population [30], selecting a proper electrode array length which matches the cochlear size, plays a key role in achieving a good match between electrode place and stimulation rate. Measuring the basal turn diameter of the cochlea, commonly called as *A-value,* could be used in the estimation of cochlear duct length (CDL) by applying dedicated mathematical equations [36–38]. Based on the predicted CDL, applying Greenwood's frequency map would provide the patient-specific frequency map. By combining the CDL, frequency map and the audiogram of the patient, choosing an appropriate electrode array length would be the concept proposed towards *patient-specific* CI electrode array

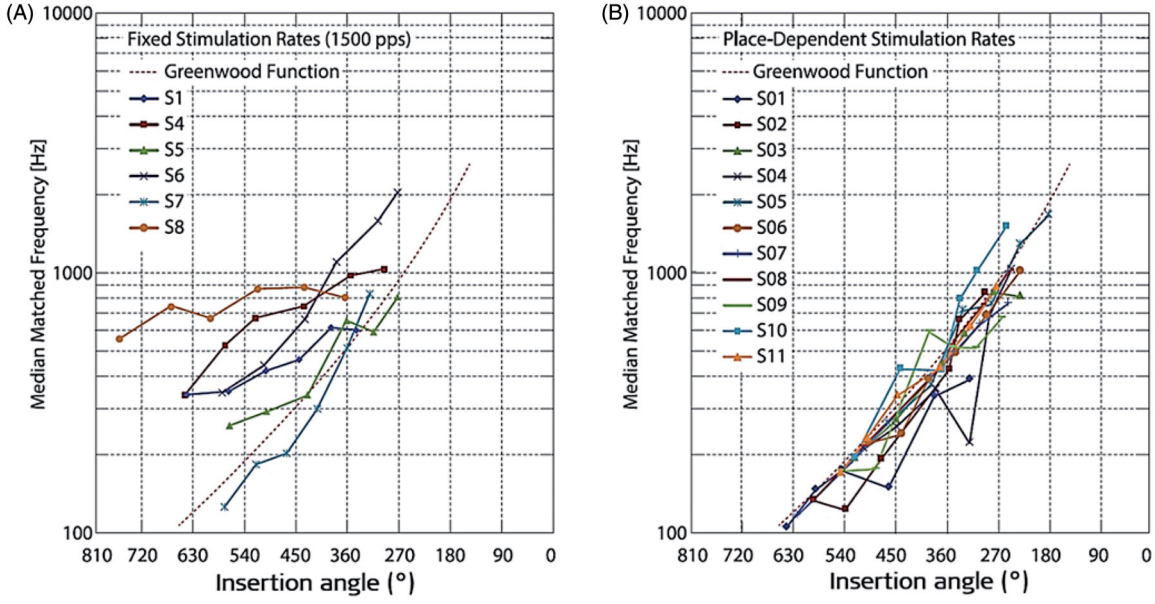
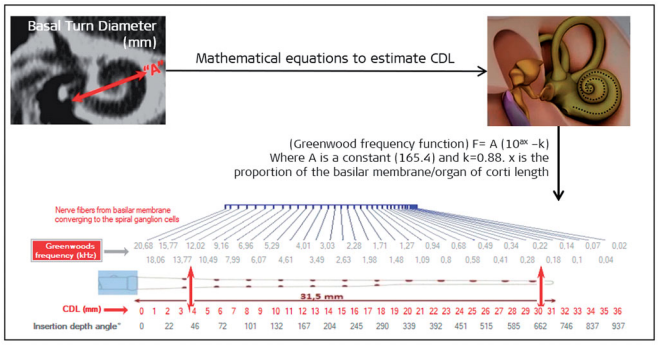


Figure 44. Individual frequency-place functions for electric stimulation obtained with place independent electric stimulation rate. When the apical channels are supplied with fixed-rate stimulation providing only place cues, then their LF pitch perception was highly variable across participants and generally not matching with the Greenwood's frequency function in the LFs (A). When the apical channels are supplied with place-dependent stimulation rates, then the LF pitch perception was closely matching with the Greenwood's frequency function in the LFs (B) [35]. Reproduced by permission of Elsevier B.V.

selection (Figure 45). This was a concept MED-EL proposed in the year 2011 and developed the research-based CDL software in 2014 (link to download), which was even clinically used, as reported by Dr Stefanescu et al. in 2018 [39].

With technological advancements over time, the CDL research software was further finetuned, and today it is available for clinical use under the name OTOPLAN® which includes other features, including three-dimensional segmentation of the key temporal bone anatomical structures, identify the individual electrode channel insertion depths from the post-operative image. OTOPLAN® is a tablet-based otological planning software tool that was developed in collaboration with CAScination AG, a Swiss company, and Dr Assadi from MED-EL was taking care of the project logistically.




Dr Anandhan Dhanasingh


Dr Claude Jolly


Dr Masoud Zoka Assadi

Figure 45. Illustration of a single measurement of the cochlea (A-value) from the preoperative images, applying dedicated mathematical equations, the patient-specific CDL is estimated. With the estimated CDL, applying Greenwood's frequency function would provide the patient-specific frequency map. Image courtesy of MED-EL. Preoperative audiogram of the patient shows if there is any functional LF residual hearing. By applying these parameters, an optimal electrode array length may be chosen. The patient-specific electrode array length selection concept was proposed by Dr Dhanasingh and Dr Jolly (US patent number: 9037253) from MED-EL. Dr Assadi is acknowledged for translating CDL research software to OTOPLAN®.

One of the key features in the OTOPLAN® software is that by loading the postoperative image of the electrode inside the cochlea, the software offers the possibility to identify the individual electrode array channels and its corresponding angular insertion depths, as shown in Figure 46. By combining this information with the patient-specific Greenwood's frequency map, it is possible to assign the channel frequency bands to the individual electrode contacts, based on the tonotopic frequency of that electrode contact.

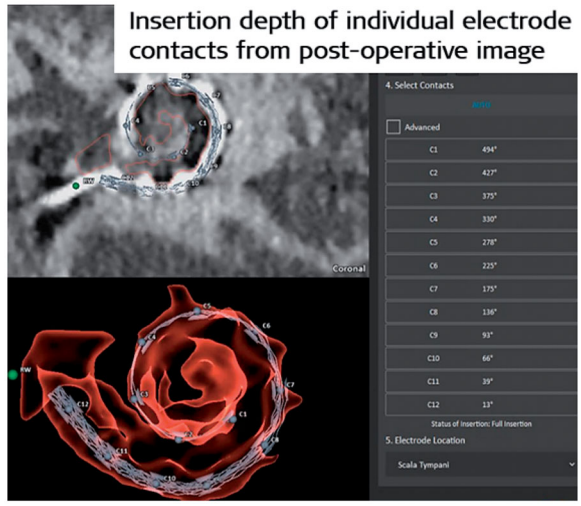


Figure 46. A screenshot from OTOPLAN® software that shows the identification of individual electrode channels, its corresponding angular insertion depth along with the centre frequency based on Greenwood's function. Image courtesy of MED-EL.

In 2020, Dr Nopp, Dr Kals, and Dr Penninger from MED-EL took the overall concept and added additional algorithms to the information received from the OTOPLAN® tool to bring it inside the MED-EL's CI clinical system software MAESTRO 9.0 (Figure 47).


Dr Peter Nopp


Dr Mathias Kals


Dr Richard Penninger

Figure 47. Engineers from the Signal Processing research team who combined the patient-specific electrode array length selection tool, OTOPLAN®, and added additional algorithms to come up with the concept of anatomy-based fitting (ABF).

From the MAESTRO system software, it is then possible to assign the patient/anatomy-specific centre frequencies to each of the electrode array channels. The algorithms developed within the anatomy-based fitting concept mainly offer electrode place-rate match to the mid-frequencies (800–3,000 Hz) where the speech information is mainly coded. This is done on an individual basis taking the cochlear size variation and the electrode insertion depth seen from the post-operative imaging into consideration.

In 2019–20, clinicians from the University of North Carolina at Chapel Hill in the US applied OTOPLAN® to their clinical practice to identify the angular insertion depths (AID) associated with MED-EL's various FLEX electrode array variants [40] (Figure 48).

The study aimed at investigating a patient population implanted with MED-EL electrode arrays of various lengths to establish if the variations in angular insertion depths in different cochlear sizes result in frequency-to-place mismatch [40]. Forty-seven patients were implanted with

Figure 48. Clinicians from the University of North Carolina at Chapel Hill who applied OTOPLAN® in the clinical practice in investigating the AID of MED-EL's FLEX electrode array variants and analysed the frequency-to-electrode place mismatch for the CI-alone and EAS™ users.

FLEXSOFT™/STANDARD array, forty-eight with FLEX28™, and eleven with FLEX24™. From the postoperative CT scans ($n = 106$), OTOPLAN® estimated that the CDL ranged between 29.4 mm and 39.5 mm. The CDL was found to be negatively correlated with the electrode angular insertion depths (Figure 49(A)). Every cochlea is unique in its size and shape and has its own frequency map and if the chosen electrode array is short (e.g. FLEX24™), then there will be a higher mismatch between the frequency allocation and the electrode place (Figure 49(B)) for maps with frequency allocations covering at least the speech frequency range.

emerging concept and a key component of individualized CI fitting that aims to make the fitting process simple and efficient, saving time for audiologists.

5.4.2. Bimodal delay compensation

Travelling wave latency is a function of the inner ear which the MED-EL CI system models in the filtering process of the sound coding strategy (stage 2, as shown in Figure 5). With natural acoustic stimulation, there is a certain time needed for the acoustic wave to travel from the external ear canal to reach the auditory cortex. All the steps in between result in certain latency/time delay, which can be measured from the wave V of electrically evoked auditory brainstem response (eABR). In contrast, with electric stimulation, all delays in the transmission of a sound wave in the external ear canal are missing. A further complication is that interaural stimulation timing in bilateral CI, SSD, or bimodal stimulation varies with the frequency/pitch of the sound signal. If this interaural stimulation timing is not adjusted during the sound processing stage, then this could create an imbalance or mismatch in the interaural stimulation timing in the SSD patients with CI on their deaf ear in bimodal setting, thus resulting in a much-degraded hearing on the deaf ear and compromising spatial hearing [41].

MED-EL's CI system implements group delays through its sound coding strategies across all frequencies resulting in stimulation pulses with some delays, thus mimicking natural hearing. Latencies measured through eABR for various frequencies in MED-EL CI users (Figure 50, red curve) fitted with OPUS audio processor, represent closer match to the

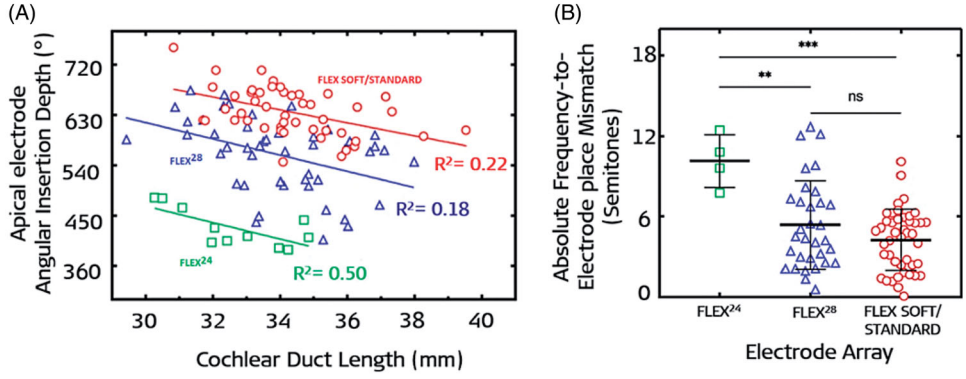


Figure 49. Correlation between CDL and angular insertion depth of the apical electrode contacts for complete insertions of FLEX24™, FLEX28™ and FLEXSOFT™/STANDARD electrode arrays (A). Relationship between absolute frequency-to-electrode place mismatch at 1,500Hz and electrode array type for CI-alone users with complete insertion (B) [40]. Statistical analysis: Pearson correlation used in evaluating the relationship between AID and CDL and multiple linear regression was used in assessing the relationship between the degree of frequency mismatch and angular separation between electrode contacts. Reproduced by permission of Wolters Kluwer Health, Inc.

It makes more sense to choose an electrode array length which matches the cochlear size, and therefore the optimal AID, and minimised frequency-to-electrode place mismatch can be achieved. These two preliminary studies are encouraging results for the clinical application of OTOPLAN®, which can be confidently used in the ABF. ABF is an

latencies measured in a normal acoustic ear (Figure 50, green curve), as reported by Zirn et al. from the Freiburg Medical University in Germany in the year 2016 [42].

In general, the latencies increase with decreasing frequencies which is reflected in the MED-EL CI system, although it is lower by 1 ms above 1 kHz in the MED-EL CI system

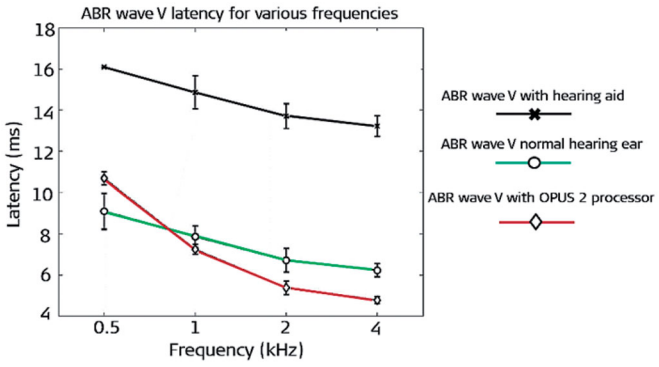


Figure 50. ABR waves V latencies across four different frequencies in normal hearing participants wearing a hearing aid (black curve), in normal hearing ears of SSD CI recipients without a hearing aid (green curve: nature), and the implanted ears [42] of those CI recipients (red curve: MED-EL implantees). Reproduced by permission of Elsevier B.V.

compared to normal hearing latencies. The black curve in Figure 50 represents the latencies caused by the hearing aid, which take longer to process the sound signal before it is amplified and released to the ear canal.

In 2019, group of clinicians from Medical University of Innsbruck in Austria, led by Prof. Stephan investigated the effects of adding additional delays (0.5-, 1.0-, 2.0- and 4.0-ms) to frequencies above 1 kHz [43]. The test was conducted in twelve SSD adults fitted with MED-EL's OPUS 2 processor. The effects of adding additional delays were evaluated in terms of sound source localisation score and SRT. The overall performance in sound source localisation and SRT measured as SNR (SNR for 50% speech intelligibility was used) is given in Figure 51(A,B), respectively. The study participants achieved their best performance, i.e. the maximum percentage of correct answers and smallest angular errors, at a tested signal delay of 1 ms. For the larger signal delays of 2- and 4-ms, performance in sound localisation progressively decreased. In terms of speech performance, the SRTs observed in this group of SSD CI users were between −4 and −5dB SNR for all tested signal delays, which is close to the performance of a normal-hearing person with SRT usually between −7dB and −8dB SNR.

The results show that the signal delay in the pre-processing of a CI audio processor affects the binaural hearing performance of CI users with SSD to a certain degree. In particular, in sound localisation, an improvement was seen at 1 ms signal delay. The effects of signal delay on speech intelligibility in noise was that performance deteriorated with larger signal delays with no improvement at any particular signal delays.

RONDO 3, which is available since 2020, is compatible with any HA if a HA is used on the contralateral ear. HAs result in relatively longer time delays across the frequencies compared to a CI, as shown in Figure 50 (black curve), since the sound processing delay of the HA is in the order of 3–10ms, added on top of the travelling wave and neural delays in the acoustically stimulated ear. If the CI is used on one side and HA is used on the other side, then there will be a mismatch in the interaural time difference (ITD), experienced by a bimodal listener. To avoid this mismatch, the bimodal delay compensation feature in the RONDO 3 and SONNET 2 processors can adjust for the higher time delays in the HA.

5.4.3. Triphasic pulse stimulation

Facial nerve stimulation (FNS) is characterised by facial muscle movement or facial tickling sensation, which can be a side effect of intracochlear electric stimulation with the CI in some cases, regardless of a CI brand. In severe cases, it may lead to patient intolerance to the extent of preferring not to use the CI. The undesired FNS after CI surgery is reported with cochlear conditions like osteoporosis, otosclerosis, bony dehiscence between the facial nerve (FN) and basal turn of the cochlea, and inner ear malformations. The reason for the FNS in such cochlear conditions is mainly due to unusual current leakage from the cochlea, and as a result, the threshold and maximum comfort levels (MCL) of the auditory nerve need to be increased to get the desired

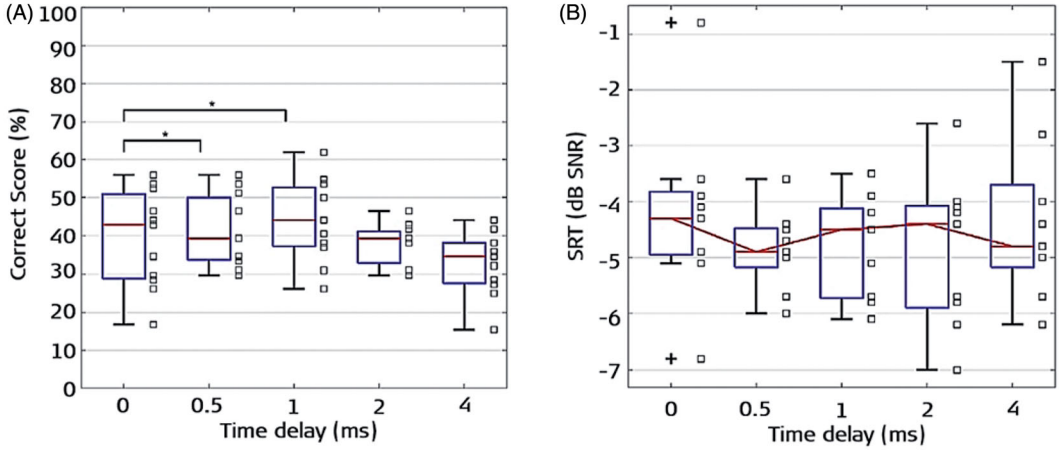


Figure 51. Scores for correct sound localisation in per cent (A) and SRT expressed in SNR for signal delays of 0 ms (standard use), 0.5 ms, 1 ms, 2 ms and 4 ms (B) [43]. Statistical analysis: Repeated measures ANOVA ($p < .05$). Reproduced by permission of Elsevier B.V.

hearing/loudness sensation. Due to the increased stimulation levels, the FN which runs close to the basal turn of the cochlea can also get stimulated. It is known from the literature that FNs have a higher sensitivity to electric pulse shapes than the hearing nerve. To control the FN costimulation and to reduce the stimulation levels, certain CI fitting procedures are established, such as raising the pulse width or increasing the interphase gaps. If reprogramming is not enough, then deactivation of single electrode contacts may be necessary, but this comes at the price of compromising speech comprehension [44]. Although the pre-curved modiolar hugging electrodes are generally believed to reduce the FNS due to its closer proximity to the central modiolar trunk and sufficient distance from the FN, clinical data has shown that electrode designs and modiolar proximity do not influence the prevalence of FNS [45].

The generally applied biphasic pulses (Figure 52(A)) in CI are charge-balanced and consist of two opposing polarities of similar phase durations (T) in which the negative charge cancels the positive charge and keeps the neuronal elements in a state of equilibrium. In contrast to biphasic pulses, triphasic pulses (Figure 52(B)) consist of two negative phases of the same duration (T/2) and one positive phase of double of that duration ($2 \times T/2$), all with the same amplitude, thus resulting in an overall charge-balanced pulse. Because of two-phase reversals in triphasic pulses ($2 \times T/2$), or in other words, splitting the negative phase (cathodic phase), it becomes less effective for extracochlear activation of the facial nerve. These two properties of the triphasic pulse stimulation are favourable for keeping the inadvertent FNS under control or at a minimum level which patients do not detect. Nevertheless, with a reduction in stimulation effect, the loudness sensation and neural responses evoked by triphasic pulses would be lower than the loudness sensation evoked by biphasic pulses with the same current level. To keep the loudness sensation to the desired level in patients fitted with triphasic pulses, the MCL may be raised without eliciting FNS, as shown in Figure 52(C).

of triphasic pulse stimulation in suppressing undesired FNS in a group of patients ($n = 15$) who underwent CI surgery between 2014 and 2017 [46] (Figure 53).

Figure 53. Clinicians from Tübingen University Hospital, Germany, and engineers from MED-EL applied triphasic pulse stimulation in CI patients to eliminate/minimise inadvertent FNS. Mr Werner Sürth and Dr Reinhold Schatzer came up with the triphasic pulse stimulation concept (US patent number: 9265944).

The aetiology of HL in these patients were hypoplastic cochlear nerve, temporal bone fracture, EVA, otosclerosis, sudden HL and unknown reasons. Before evaluating the reduction of FNS and hearing ability, the patients experienced a triphasic map for a mean period of at least twenty-five months. Out of fifteen patients, ten had a complete suppression of undesired FNS, and three had partial suppression with triphasic settings. Two patients, however, did not show any suppression of FNS with triphasic settings and had EVA as well as unknown reasons as the HL aetiology. The MCL was evaluated for biphasic versus triphasic pulse setting in these fifteen patients. The median MCL level in

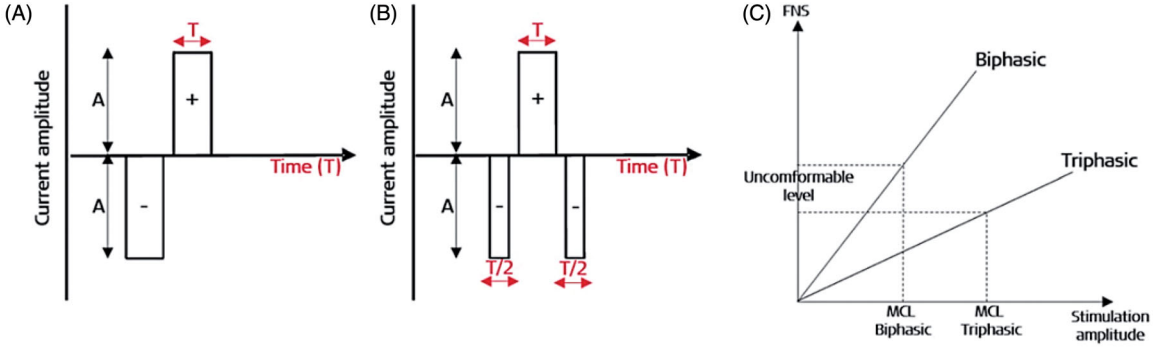


Figure 52. Balanced biphasic pulse stimulation (A) and triphasic pulse stimulation (B) showing two negative phases of duration (T/2) and one positive phase duration (T) (image courtesy of MED-EL). Model of expected benefit with triphasic pulse stimulation on FNS (C) (image recreated from Bahmer et al. [44]).

In 2017, MED-EL received CE marking for the triphasic pulse stimulation fitting option which was made available for clinical use through its fitting software MAESTRO 7.0.

In 2017, Prof. Löwenheim and his team along with engineers from MED-EL in Austria evaluated the effectiveness

the triphasic setting (51.12qu) was found substantially higher than in biphasic setting (36.37qu), and the mean MCL levels could be raised by 150% in triphasic, compared with the biphasic setting, without triggering the FNS (Figure 54(A)). The hearing results, as measured with Freiburger

monosyllable test at 65 dB and 80 dB SPL, showed patients achieving median speech scores of 28% and 45%, respectively, with the biphasic setting. The results increased to the median speech scores of 40% at 65 dB SPL and 63% at 80 dB SPL with the triphasic setting (Figure 54(B)). The difference in speech scores between these two fittings showed a significant improvement for the triphasic setting, especially at 65 dB and not at 80 dB SPL, which patients appreciated in everyday usage.

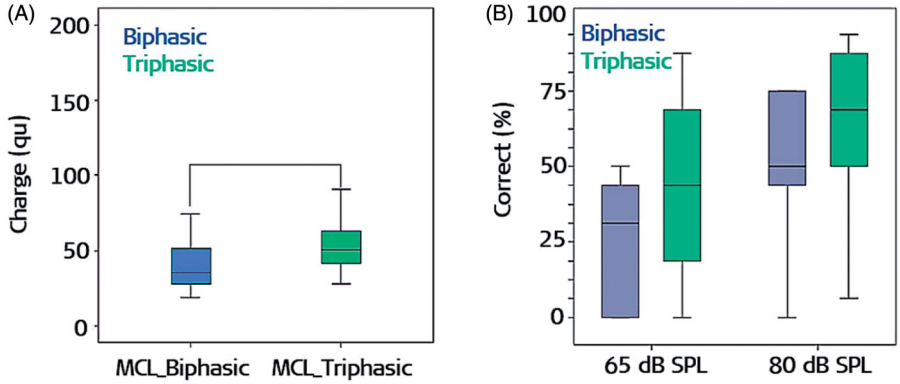


Figure 54. Average MCL values in the biphasic and triphasic pulse stimulation modes (A). Freiburger monosyllables at 65- and 80-dB SPL (B) [46]. Statistical test: bivariate analyses were performed using independent sample *t*-tests and Mann-Whitney U tests. Reproduced by permission of Wolters Kluwer Health, Inc.

In 2020, the triphasic pulse stimulation mode reached the Middle East and was successfully applied by Prof. Alzharani and his colleagues in eleven CI recipients (sixteen ears) who had unintended FNS with the activation of the audio processor [47,48] (Figure 55).

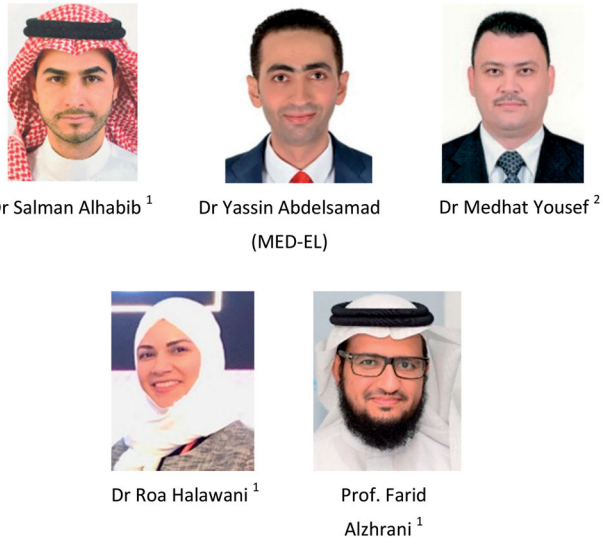


Figure 55. Clinicians from [1] King Abdullah Ear Specialist Centre, Saudi Arabia, [2] Menoufia University Hospital, Egypt, and engineer from MED-EL applied triphasic pulse stimulation in CI patients to eliminate/minimise inadvertent FNS.

The average number of electrode channels responsible for FNS were six for biphasic stimulation – with the average audio processor usage of 23.6 months – with no success of controlling the FNS. The fitting program was changed to triphasic stimulation which showed successful resolution of the FNS in thirteen ears, and the remaining three ears were resolved by deactivating one channel. The patients used their audio processor with the triphasic stimulation fitting map for an average of 17.5 months. The speech discrimination score level at 65 dB HL was better with triphasic stimulation (average of 75.25% ± 26.13) compared to biphasic stimulation (average 58.25% ± 26.13) and the improvement in the speech discrimination score was seen with triphasic stimulation (Figure 56).

With positive results of triphasic stimulation pulses in resolving FNS, as well as in improved speech discrimination scores and MCL, as shown by these two scientific pieces of evidence, the triphasic mode may be recommended to all patients with FNS following CI surgery with MED-EL CI devices.

5.5. Conclusion

Signal processing is a highly technical topic that is often perceived as complex for people untrained in the field to grasp it in depth. In this article, MED-EL's signal processing was approached in an easy language and compared it with the functionalities of the normal acoustic ear. The overall aim of signal processing in a CI system is to capture essential information hidden in any meaningful sound signal and provide it to the inner ear in the form of electric pulses. Dual microphone, AGC compression function, compensation of artificial time delays and phase-locking the rate of LF stimulation pulses with the sound frequency are some of the features that support MED-EL's signal processing that aims in modelling the normal acoustic hearing. The audio processor design at MED-EL, starting from the body-worn CIS PRO type in the early 90 s until the latest RONDO 3 version of the single-unit processor in **2020**, is an achievement by itself as every version of the audio processor included improved features adding more benefits and comfort to the users.

The signal processing algorithms implemented in MED-EL audio processors, starting from the CIS PRO and TEMPO + to the RONDO 3, were evaluated in close collaboration with clinicians around the world to demonstrate the safety and efficacy of the audio processors. It involved

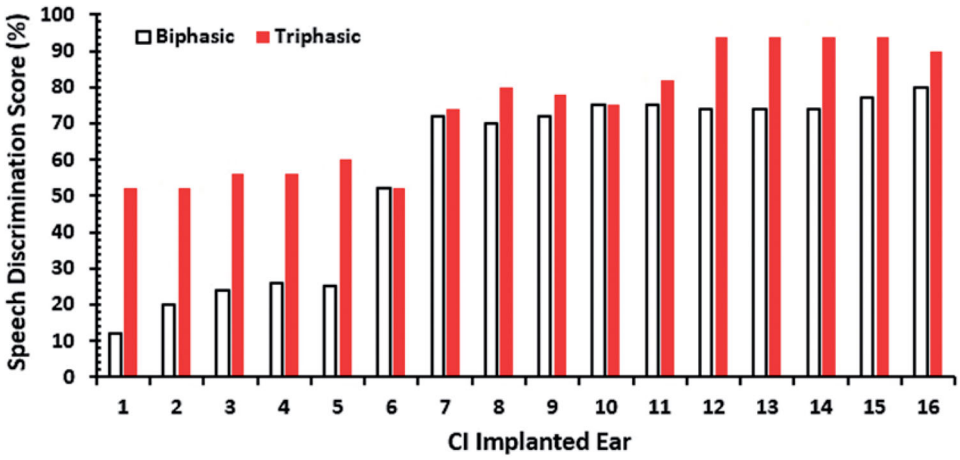


Figure 56. Comparison of the measured speech discrimination scores at 65 dB for the biphasic and triphasic pulse pattern groups. Statistical test: Parametric paired *t*-test to test the significance between the group data. Histogram created from the raw data provided by Alhabib et al. [47].

numerous hours of efforts from the signal processing research team and as well from clinicians. As a result, all the strategies mentioned above were successfully implemented in the audio processors and are being used by MED-EL CI patients successfully. Signal processing and the audio processor is yet another topic within MED-EL that followed the translational science path in successfully bringing the concept from the laboratory setting to patients.

Acknowledgments

The authors would gratefully like to acknowledge the key contributors to the development of the subject matter. Their contributions are outlined in this article. The authors further acknowledge Peter Nopp and Reinhold Schatzer from MED-EL for their valuable input and comments during several rounds of review meetings that contributed to the final version of this article.

Disclosure statement

This article is sponsored by MED-EL and has not undergone the regular peer-review process of Acta Oto-Laryngologica. Both the authors are affiliated with MED-EL.

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ACTA OTO-LARYNGOLOGICA
2021, VOL. 141, NO. S1, S135–S156
https://doi.org/10.1080/00016489.2021.1888505

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REVIEW ARTICLE

Drug delivery in cochlear implantation

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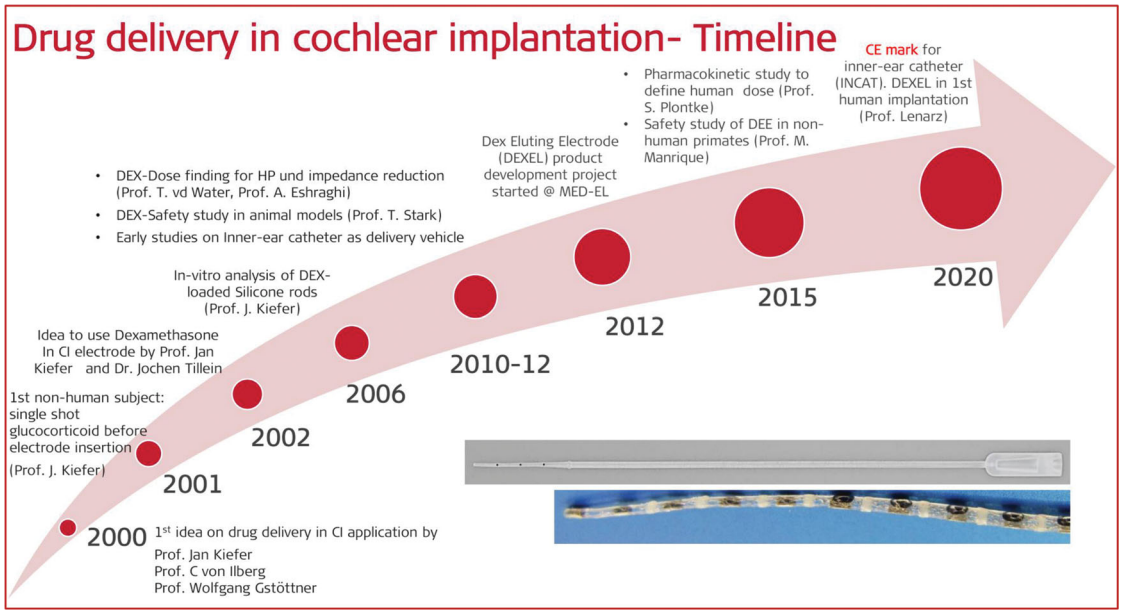
ABSTRACT

Intra-cochlear fibrous tissue formation around the electrode following cochlear implantation affects the electrode impedance as well as electrode explantation during reimplantation surgeries. Applying corticosteroids in cochlear implantation is one way of minimizing the intra-cochlear fibrous tissue formation around the electrode. It were J. Kiefer, C. von Ilberg, and W. Gstöttner who proposed the first idea on drug delivery application in cochlear implantation to MED-EL in the year 2000. During the twenty years of translational research efforts at MED-EL in collaboration with several clinics and research institutions from across the world, preclinical safety and efficacy of corticosteroids were performed leading to the final formulation of the electrode design. In parallel to the drug eluting CI electrode development, MED-EL also invested research efforts into developing tools enabling delivery of pharmaceutical agents of surgeon's choice inside the cochlea. The inner ear catheter designed to administer drug substances into the cochlea was CE marked in 2020. A feasibility study in human subjects with MED-EL CI featuring dexamethasone-eluting electrode array started in June 2020. This article covers the milestones of translational research towards the drug delivery in CI application that took place in association with MED-EL.

ARTICLE HISTORY
Received 13 December 2020
Accepted 6 January 2021

KEYWORDS
Fibrous tissue; electrode impedance; drug eluting electrode; pharmacokinetic; cochlear catheter



6.1. Introduction

Cochlear implants (CI) used to be considered only for individuals with profound sensorineural hearing loss (SNHL) until 1997 when Prof. von Ilberg from Johann Wolfgang Goethe University Frankfurt in Germany proposed the concept of combining acoustic amplification of the low-frequency residual hearing with a hearing aid (HA), and electric stimulation of high-frequency hearing loss (HL) with a CI [1]. Nowadays, individuals, including children, who have near-normal hearing in the low-frequency regions and their HA cannot achieve the full hearing potential, may greatly benefit from the Electric Acoustic Stimulation (EAS™) hearing system to restore the high-frequency hearing through electric stimulation, and low-frequency hearing by acoustic amplification [2]. Thanks to the soft and flexible MED-EL CI electrode array design, the reports show that

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This article is a part of the compendium entitled 'Thirty years of Translational Research behind MED-EL' authored by Anandhan Dhanasingh (Director) (Anandhan.dhanasingh@medel.com) and Ingeborg Hochmair (CEO, CTO) (Ingeborg.hochmair@medel.com).

their insertion causes minimal or no trauma to the intracochlear structures, resulting in complete residual hearing preservation in the majority of partially deaf patients [3]. The scala tympani (ST), inside which the CI electrode array is intended to be placed, is a biologically active environment (Figure 1). The perilymph which fills it is rich in proteins and can readily adsorb on to the surface of a CI electrode array that leads to a process of fibrous sheath formation and new bone formation over the electrode array [4,5]. Although the CI electrodes are fabricated/coated with biocompatible medical-grade silicone, such fibrous tissue formation around the electrode array is still a natural body reaction. The fibrous sheath around the electrode array would act as a barrier around the stimulating electrode surface, impeding the electric impulses which are released into the perilymph. This may result in increased neuronal stimulation thresholds over time [6]. The fibrous sheath from the primary CI implantation could pose a risk of obliterating ST in some cases, making the electrode array insertion a challenging task in potential reimplantation surgeries [7]. The other source of intracochlear fibrous tissue formation could be the electrode array-related trauma to the blood vessels that are visible on the floor of the ST (Figure 1) [8].

For the success of revision surgeries or for replacing the CI treatment with any future biological therapies which envision regeneration of impaired hair cells or other structures, the explantation of the CI electrode array should result in zero trauma to the intracochlear structures. One of the factors on which the success of EAS^{TM} depends is the degree to which the low-frequency residual hearing can be preserved [9]. Any fibrous tissue formation inside the ST could damage the residual hearing either overtime or soon after the introduction of the electrode array. Thus, preventing the fibrous sheath formation around the electrode array, thereby reducing the electrode impedance, would be highly beneficial. It is known from the cardiac pacemaker field that delivering corticosteroids, such as dexamethasone (DEX), near the implanted electrode contact lowers the stimulation thresholds by minimising the fibrous sheath formation [10]. Corticosteroids such as DEX, methylprednisolone or triamcinolone, have been used for a long time in the treatment of certain inner ear conditions, such as sudden sensorineural

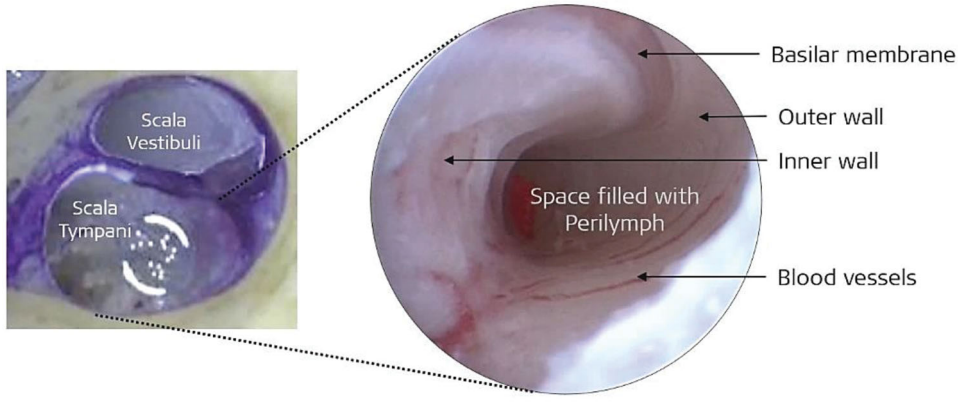

Figure 1. Cross-section of the cochlea showing ST and scala vestibuli (SV) (image courtesy of Prof. Thomas Lenarz from Hannover Medical School, Germany). The enlarged image of ST shows the basilar membrane on the top, outer wall on the right side, inner wall on the left side, and blood vessels on the floor of ST [4]. Enlarged image reproduced by permission of Wolters Kluwer Health, Inc.

Figure 2. Scientists involved in the BIOEAR project, studied the neurotrophic effects of drugs in preserving and regrowing neurons in the inner ear.

HL or Meniere's disease [11]. Over the years, MED-EL joined hands with several research groups around the world to evaluate the application of corticosteroids for minimising the fibrous tissue formation in the inner ear.

This article will canvass through the beginnings of MED-EL's journey of CI in combination with drug deliveries, including international scientific key collaborations in evaluating the safety and efficacy of corticosteroids in the inner ear, and the efforts in translating the research findings into the development of a novel intracochlear drug-eluting CI electrode array and a tool for drug delivery.

6.2. Beginning of drug delivery related research at MED-EL

In 2000, Prof. Pyykko from the University of Tampere in Finland, Prof. Bredberg from Karolinska Institute in Sweden, Prof. Ulfendahl from Karolinska Institute in Sweden, Prof. Miller from the University of Michigan in the USA, Prof. Schrott-Fischer from the Medical University of Innsbruck in Austria, Prof. Rask-Andersen from Uppsala University in Sweden, Professor Martini from the University of Ferrara in Italy, Prof. Lenarz and Prof. Stöver from the Hannover Medical School in Germany and Dr Garnham from MED-EL in Austria cooperated within the framework of a European Union (EU) funded project, BIOEAR (grant agreement ID: QLG3-CT-2002-01563) [12] (Figure 2). The project aimed to treat the auditory nerve pharmacologically after CI surgery, to protect it from implantation trauma and to regrow its peripheral processes.

Neurotrophins and similar drugs require delivery over an extended period to achieve a worthwhile effect. MED EL's role in the project was to develop the delivery system required to deliver Glial cell Derived Neurotrophic Factor (GDNF) through the implant and into the perilymph. At about the same time, MED-EL supported a few other collaborations on the topics of surfacing for neurite growth onto the electrode surface (University of Bochum, Germany), plasma treatment of silicone (University of Sheffield, UK), elapsed time photography of human neurite growth (Uppsala University, Sweden), and a cochlear trauma model (Utrecht University, Netherlands). For MED-EL, the safe and effective extended delivery of large, fragile proteins throughout the cochlea was a challenging entry-level project. However, the knowledge, skills and partnerships gained by the company from aptly pursuing this challenging goal have been influential in the field and led to recent product developments with the potential to improve the sound quality of CIs further. Scientific collaborations with the Universities of Uppsala, Innsbruck, Hannover Medical School and Johann Wolfgang Goethe University Hospital Frankfurt on inner ear anatomy and pharmacology to further improve CI outcomes, continue to this day. The work with neurotrophic factors to enhance the neural substrate in the implanted cochlea continued through several other EU funded projects, including NANOEAR (an exploration of the use of nanoparticles in the ear, coordinated by Prof. Pyykko from the University of Tampere in Finland, grant agreement ID: 26556 [13]) and NANOCI (an exploration of neurite re-growth onto the electrode array, coordinated by Prof. Senn from University of Bern in Switzerland, grant agreement ID: 281056 [14]). Around this time, MED-EL identified a gap in the need for possibilities to asses cochlear status and to support/fund research towards future therapies.

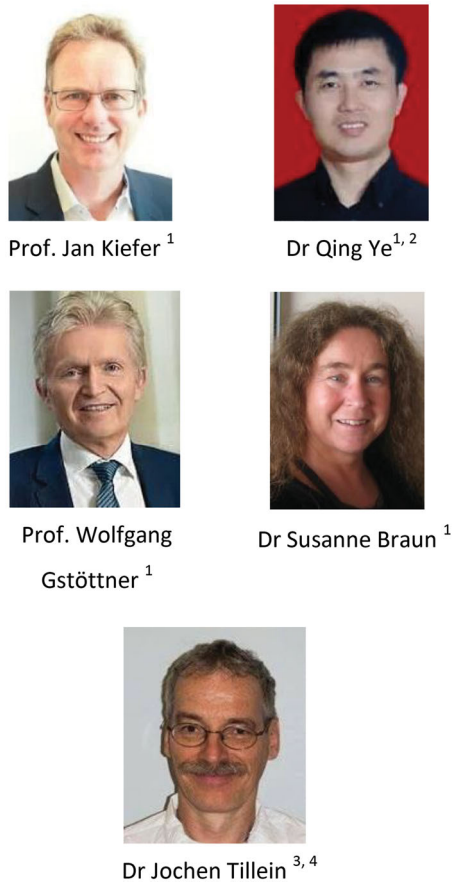

Figure 3. Team of clinicians and scientists from [1]ENT department- Johann Wolfgang Goethe University Hospital Frankfurt, Germany, [2]Fujian Provincial Hospital, China, and [3]Institute of Physiology- Johann Wolfgang Goethe University Hospital Frankfurt, Germany, [4]MED-EL, who took part and supported this first study in evaluating the effectiveness of corticosteroids. In 2007, Dr Braun became a part of MED-EL.

6.3. Beginning of drug delivery in the CI application concept at MED-EL

Around the time when EAS endeavours started in the late 1990s/early 2000s, the interest in intracochlear drug delivery also started and drug delivery became a translational research topic within MED-EL. MED-EL began with its EAS endeavours in the late 1990s/early 2000s. Prof. Kiefer in Frankfurt at that time was already applying a steroid locally at the time of implantation to reduce inflammation caused by opening the cochlea and insertion of a foreign body. The significance and usefulness of this approach were therefore evaluated by Dr Tillein in the Institute of Physiology, that was headed by Prof. Rainer Klinke (Figure 3).

In 2001, a study from Johann Wolfgang Goethe University Hospital Frankfurt and MED-EL started to evaluate the effectiveness of corticosteroids in hearing preservation after CI surgery [15]. The following three questions

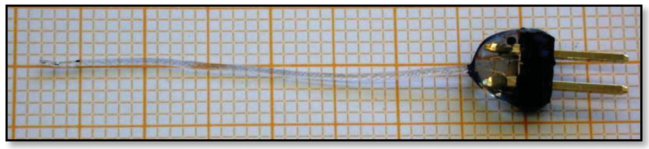

Figure 4. Electrode array carrying two stimulating platinum contacts along with a two pin-connector for compound action potential (CAP) measurements (image courtesy of MED-EL).

formed an objective of the study:

i. Does a locally applied glucocorticoid lead to hearing preservation or threshold recovery after CI surgery during a time of three months?
ii. What is the pharmacological effect of locally applied glucocorticoids in nonimplanted cochleae?
iii. Does a locally applied glucocorticoid influence postsurgical tissue growth in ST?

The experimental group of non-human subjects was unilaterally implanted with MED-EL's custom-made research electrode with a diameter of 0.5 mm, which consisted of an array with two platinum contacts and wires embedded in a medical-grade silicone electrode carrier. The intended intracochlear insertion depth of the array was 3 mm. The electrode had a percutaneous connector for providing electric stimulation, as shown in Figure 4.

The contralateral cochlea was opened *via* cochleostomy, but no electrode was inserted. The experiment was separated into three cohorts with a single-dose bilateral application of (a) 40 mg/ml triamcinolone (Tria), (b) 24 µg dexamethasone (DEX), and (c) artificial perilymph (AP) that was infused utilising a 10 µl Hamilton syringe into the cochleae *via* cochleostomy.

To obtain hearing thresholds, compound action potentials (CAP) for three different frequency ranges were measured before and after drug/AP application and implantation, on days 1, 3, 7, 14, 21, 28, 60, and 90. At the end of the three-month experimental period, histological analysis was performed to quantify the amount of tissue growth in the basal turn of the ST. This was then correlated with the shift in the hearing threshold. For the implanted group (Figure 5(A)), the AP treated ears showed the highest hearing threshold, while the DEX treated ears revealed the lowest across the whole experimental period. The Tria treated ears indicated a gradual recovery through the observation time. Within the cochleostomy group (Figure 5(B)), the AP treated ears exposed a complete recovery in all frequency regions measured, whereas the two glucocorticoid-treated groups did not show such recovery in any of the frequency regions tested. However, a small glimpse towards hearing threshold

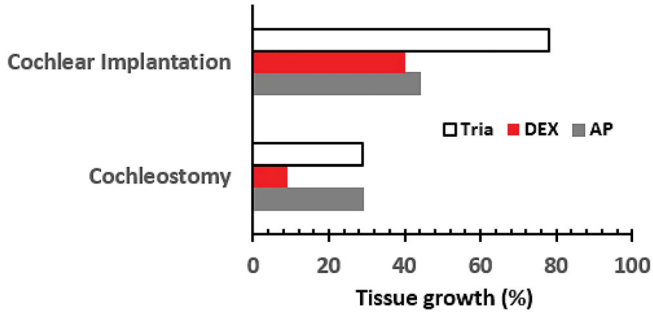

Figure 6. Tissue growth three months after surgery for all three groups. Statistical test: Spearman correlation analysis (2-tailed, $\alpha = 0.05$). Histogram created from data given in Braun et al. [15].

recovery was seen in the DEX group, which lasted until the twenty-eighth day, as well as in the Tria group with lasting until the twenty-first day. To address the question if there was any benefit of glucocorticoids seen on the hearing or not, the threshold shifts of the cochleostomy group was subtracted from the implanted group for every glucocorticoid-treated ear and the AP-treated ear (Figure 5(C)).

The benefit of local glucocorticoid treatment was primarily seen in the basal region, which was most affected by the implanted array (3 mm from the RW). This corresponded to the high frequencies (data not shown in Figure 5), but the

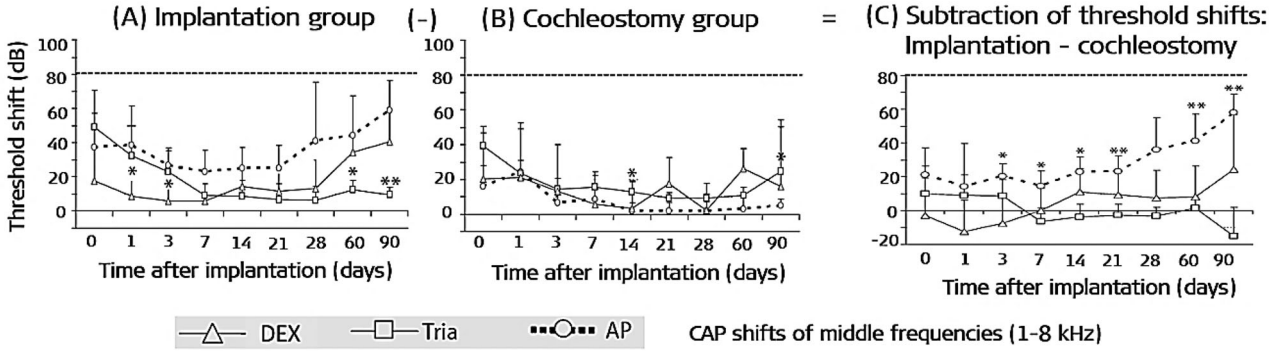

Figure 5. CAP threshold shift of middle frequencies (1–8 kHz). There is a difference in the time course of efficacy between the two glucocorticoids, on days 1 and 3. Significantly smaller threshold shifts were present in DEX ears, whereas in the Tria ears, this was the case on days 60 and 90 (A). No difference was seen between DEX and AP ears while hearing threshold shifts in the Tria ears were significantly bigger on days 14 and 90 (B). Efficacy of the pharmacological treatment in implanted ears was determined by subtracting the threshold shifts of the cochleostomy ears from the implanted ears (C). From the third day onwards, threshold shifts were significantly larger in untreated (AP) implanted ears, while the shifts in implanted ears treated with glucocorticoids did not differ from the equally treated nonimplanted ears [15]. Statistical test: Wilcoxon-Mann-Whitney U test at $\alpha = 0.05$. * $p \leq 0.05$, ** $p \leq 0.01$. Reproduced by permission of Karger AG, Basel.

middle frequency region adjacent to the high-frequency region also showed some benefit due to glucocorticoid treatment. In contrast, the hearing in implanted ears treated only with the AP further deteriorated towards the end of the experimental observation time. Tissue growth, as observed by histological analysis, showed various degrees in both, implanted and cochleostomy cochleae, with a tendency for more pronounced growth in the implanted ears (Figure 6).

Overall, it was concluded that a single dose treatment with glucocorticoids is adequate for a longer-term effect of twenty-eight days with DEX and ninety days with Tria and that there was no significant correlation between the amount of tissue within the cochlea and the HL. Although the experiments of this study took place in 2002, the study was published in 2011.

Figure 7. Clinicians/researchers from the University of Ferrara, involved in the evaluation of electrode arrays of different stiffnesses for its aptitude to cause various degrees of HL.

In 2002, it was Prof. Kiefer and Dr Tillein, who proposed the use of DEX in CI application to minimise inflammation reactions inside the cochlea, thereby preserving the low-frequency residual hearing, and MED-EL began a journey in understanding its otoprotective efficacy against trauma associated with the CI surgery.

6.4. Electrode insertion trauma model

Investigations into the use of drugs to protect hearing from electrode insertion trauma (EIT) required a model in which various factors, determining HL, could be evaluated. Prof. Martini and his colleagues from the University of Ferrara in Italy, along with MED-EL's support, wanted to understand the implications of electrode array stiffness on EIT-associated HL [16] (Figure 7).

MED-EL fabricated electrode arrays of two different stiffnesses, one without any electrode wires inside (soft electrode) and the other with an electrode wire inside (stiff electrode), as shown in Figure 8(A). These two electrode arrays were implanted in a non-human subject model, applying a soft surgical implantation protocol. Group-A corresponded to the soft electrode implanted, group-B corresponded to the stiff electrode implanted, and group-C corresponded to cochleostomy with no electrode implanted. The CAP threshold was measured for all three groups by applying tone-pips of frequencies 4-, 8-, 16-, and 32-kHz. CAP thresholds for high frequencies (16 + 32 kHz, Figure 8(B)) and low frequencies (4 + 8 kHz, Figure 8(C)) were measured for the time points including before conducting any surgical procedure (baseline value) and on days 0 (immediate post-op), 3, 7, 14 and 30. The CAP thresholds for high frequencies followed an oscillatory behaviour (Figure 8(B)) with the recovery at day three (group A), and at day seven, there was an extensive deterioration of hearing thresholds (groups A and B). At day fourteen, there was an overall threshold recovery, and at day thirty, the hearing thresholds in groups B and C had improved, while they had deteriorated in group A. CAP thresholds for low frequencies showed a different pattern, compared to high frequencies, across all three groups (Figure 8(C)). The threshold shifts were smaller by a margin of approximately 20 dB (groups A and B). Group C showed a linear recovery pattern, without the oscillations observed in the high frequencies. Groups A and B showed a threshold recovery until day fourteen and after that, a delayed threshold deterioration.

The insertion of the rigid electrode (group B) produced a greater increase in threshold than the soft electrode (group A),

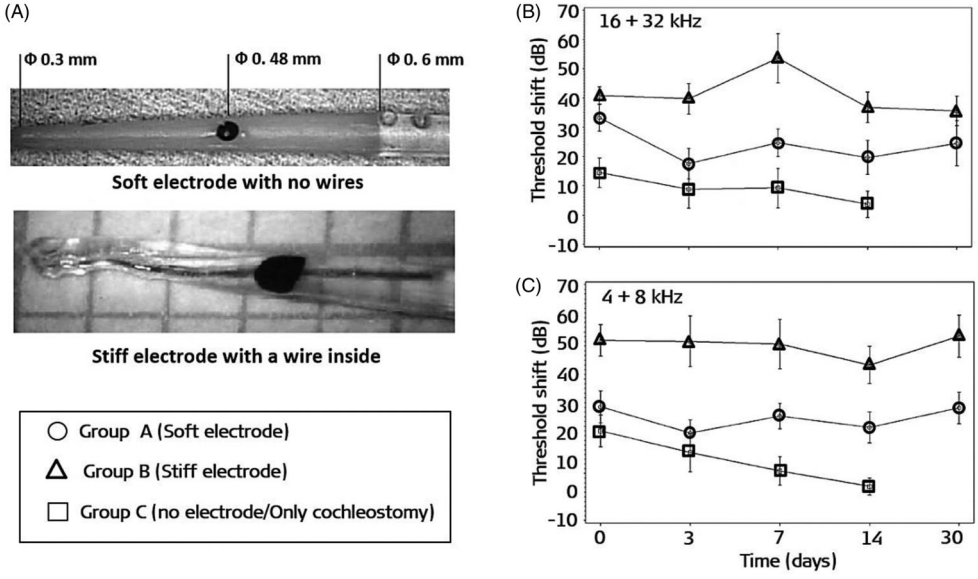

Figure 8. Soft and stiff electrodes fabricated by MED-EL for this study (A). Average threshold shifts in dB SPL at the high-frequency band (16 + 32 kHz) (B) and at low-frequency bands (4 + 8 kHz), (C) measured immediately after the surgery ($t = 0$ days) and at $t = 3$, 7, 14 and 30 days postoperatively [16]. Statistical analysis: unpaired t-test ($p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

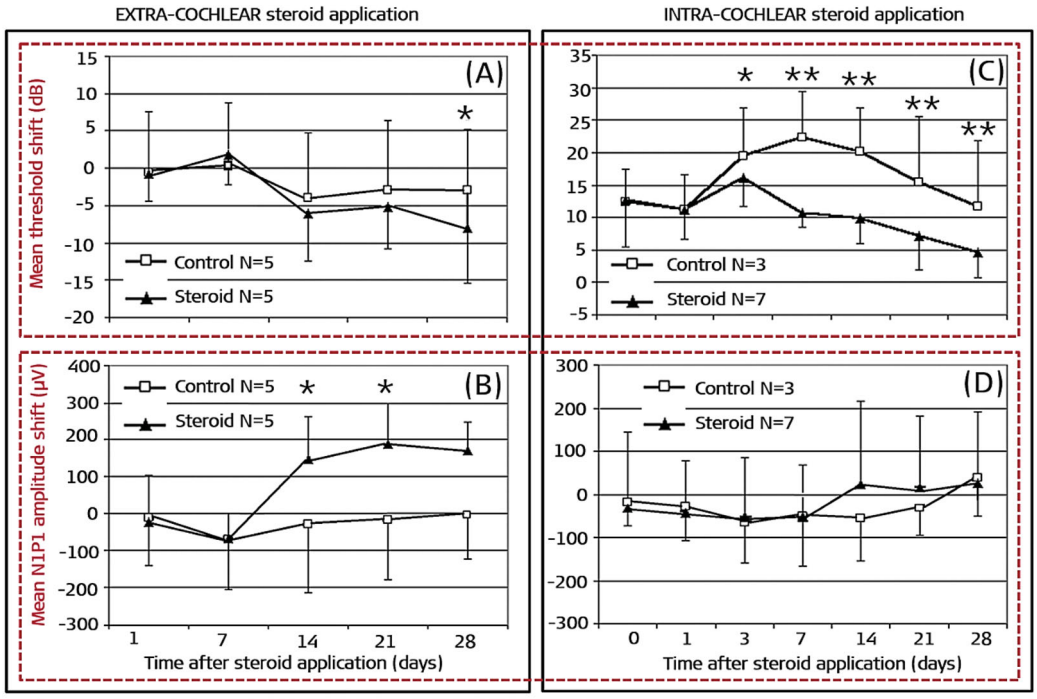

Figure 9. Mean CAP threshold shifts after extracochlear application of triamcinolone, showing higher values for steroid group compared to the control ear, starting two weeks postoperation until the end of the study, at week 4 (A). Mean maximal amplitudes of CAP in response to click stimuli increased significantly on days 14, 21 and 28 for the steroid groups with the extracochlear application, compared to control ears (B). For the intracochlear steroid application, the steroid group showed significantly lower mean threshold shifts compared to the control ears (C), and the mean maximum amplitudes started to recover from day 14 in the steroid group, which was about 1 week earlier than in control group (D) [17]. Statistical test: paired *t*-test was used to analyse pre-op and post-op results within groups; Mann-Whitney U-test was used for comparison of group results ($p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

and this was observed in both low- and high-frequency bands, although the differences of the threshold shifts were not found statistically significant. From this observation, it can be understood that the presence of a rigid electrode is associated with a major mechanical trauma of the cochlear structures and the presence of a rigid electrode alters the cochlear hydrodynamics more in comparison to the effects of a soft electrode. The study concluded that a soft surgery approach and a soft electrode could reduce the mechanically induced threshold shifts.

6.5. Safety and efficacy of triamcinolone

In 2006, the journey extended to address the ototoxicity and the positive effects of steroids in inner ear applications during CI surgery. The reason for selecting triamcinolone over DEX in this study was that one of the involved researchers, Prof. Kiefer, was already routinely using triamcinolone in his clinical EAS surgical practice by dipping the CI electrode in Volon A® solution before implanting it. Therefore, the research group, with MED-EL's support, took the opportunity to evaluate the safety and efficacy of triamcinolone by applying it to a non-human subject model in two different ways [17]. The first method saw an extracochlear application through a depot with 1mm^3 foam, soaked in 0.2 mg triamcinolone gel (5 ml of Volon A 40 crystalline triamcinolone acetonide suspension (40 mg/ml)), placed at the RW, inducing no surgical trauma in the experimental group ($n = 5$). The second method introduced 0.12 mg of the triamcinolone suspension (3 mL of Volon A 40) by injecting it intracochlearly *via* 1 mm cochleostomy approach to evaluate the possible safety and protective effects in the experimental group ($n = 6$).

The contralateral ears of both groups were used as control and were treated with Ringer's solution, applied by its respective methodology. To test the hearing thresholds, a hook electrode was anchored at the bony ridge above the RW and connected to a percutaneous connector at the vertex to serve as a recording electrode for the acoustic evoked compound action potentials (CAPs). The CAPs were tested regularly – on days 1, 3, 7, 14, 21 and 28 post-surgery – to check if there was any hearing recovery occurring over time, with and without steroid application.

Extracochlear application of triamcinolone showed no statistically significant differences in the mean CAP threshold shift relative to the preoperative values, compared to the control group, during the four weeks of the experiment. However, the steroid group showed a trend of decreasing threshold shift from day seven until day twenty-eight (Figure 9(A)). As for the CAP amplitudes, which are a measure of hair cells health, those showed significantly higher values in the steroid group, starting from the second week onwards, compared to the control group (Figure 9(B)). The intracochlear application of triamcinolone

Figure 10. Prof. Christoph Arnoldner from the Medical University of Vienna.

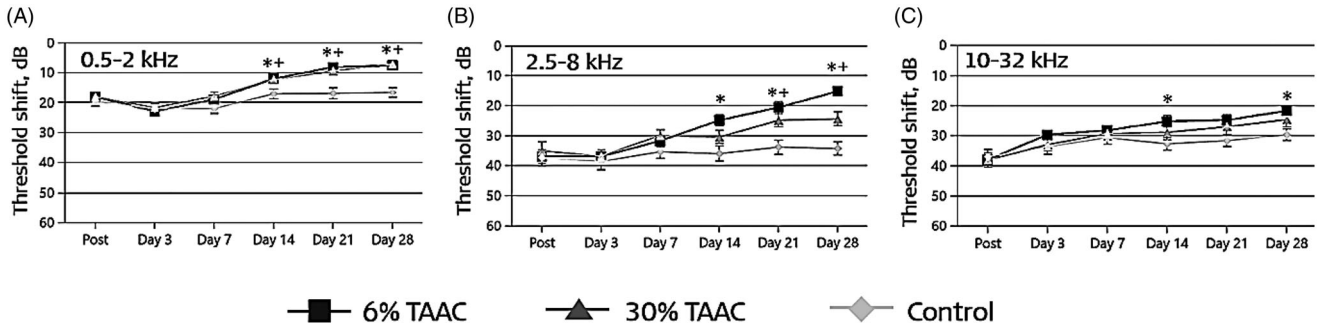

Figure 11. CAP threshold shifts at different frequency ranges. (A) Low, (B) middle, (C) high frequencies. Symbol indicate $p < .05$. *6% TAAC versus control; +30% TAAC versus control. Error bars indicate standard deviation. CAP threshold shifts recovered significantly better in the TAAC-treated groups [18]. Reproduced by permission of Karger AG, Basel.

and saline that involved surgical intervention on the cochlea resulted in HL in both groups. However, the CAP thresholds in the steroid group started to recover from the seventh day and returned close to the pre-application level on day twenty-eight (Figure 9(C)). In contrast, recovery of CAP thresholds in control groups was unsatisfactory throughout the experiment and did not reach the pre-application level on day twenty-eight. The CAP amplitudes of both groups returned to preoperative values, although the recovery was seen earlier in the steroid group around the second and third week when compared to the control group (Figure 9(D)). In summary, the study portrayed that the topical application of steroids did not have any negative influence on the hearing thresholds, but had positive effects on amplitude of CAPs, which was a positive indicator of steroids in recovering some hearing caused by the surgical intervention.

In 2019, Prof. Arnoldner and his colleagues from the Medical University of Vienna published their findings supported by MED-EL on sustained-release of triamcinolone acetonide (TAAC) hydrogel in reducing hearing threshold shifts in a model for CI with hearing preservation [18] (Figure 10).

Two groups of experimental subjects were injected with 50 µL of the TAAC in two different concentrations (6% w/w and 30% w/w of TAAC to the hydrogel material) through perforation in the RW membrane, a day before the surgery. These experimental subjects were implanted with a custom-made electrode with one platinum contact from MED-EL (diameter of 0.3 mm at the tip and 0.5 mm at a distance of 4 mm) for an insertion depth of 5 mm through a 0.8 mm diameter cochleostomy. The control group received the hydrogel injection without TAAC. CAP threshold shifts were measured at different frequency ranges and was found to be that TAAC hydrogels resulted in significantly reduced hearing threshold shifts in low, middle and high frequencies as shown in Figure 11.

These two are example studies that were supported by MED-EL, that demonstrates the safety and efficacy of triamcinolone, which is another steroid widely used in the ontological treatment.

6.6. Antioxidants in hearing preservation following CI implantation

The search for new drugs with the aim of preserving residual hearing following a CI surgery is currently carried out by several research groups across the world. One of the recent focuses is on the dietary supplementation of antioxidants in preserving residual hearing, following CI surgery. During insertion of the CI electrode array into the cochlea, depending on the mechanical properties of the electrode array, a certain degree of intracochlear trauma could occur, which could potentially lead to cascading molecular effects such as inflammation and oxidative stress. The loss of residual hearing after CI surgery is thought of as closely related to the oxidative stress, which is based on the formation of reactive oxygen species. There is literature evidence indicating that the dietary antioxidant supplementation has become a therapeutic strategy to prevent, delay, or both, the risks of SNHL [19]. Prof. Eshraghi and his colleagues from the University of Miami Ear Institute in the US reported on the preservation of a greater number of hair cells from the organ of Corti (OC) explants of the cohort treated with a combination of dexamethasone, mannitol and antioxidants, like L-N-acetylcysteine (LNAC), in comparison to the control group [20]. Prof. Miller from the University of Michigan in the US initially proposed that dietary antioxidant supplementation could be used to preserve residual hearing following CI surgery.

Figure 12. Clinicians from the Hannover Medical School, Germany, who evaluated the effectiveness of ACEMg in preserving residual hearing.

In 2020, Prof. Lenarz and his colleagues from Hannover Medical School published the results from the concept of

treating CI patients with a measurable preoperative residual hearing with dietary antioxidant supplementation, a study sponsored by MED-EL [21] (Figure 12).

The supplement (ACEMg) is a combination of (vitamin A) β-Carotene (3.0 mg), (vitamin C) ascorbic acid (83.33 mg), (vitamin E) DL-α-tocopherol acetate (44.5 mg) and magnesium (52.5 mg), all in one tablet. The patients were prescribed six tablets a day for a study period of one hundred and three days, following CI surgery. To evaluate the effectiveness of ACEMg in preserving residual hearing, twenty-five patients were analysed as part of the ACEMg group, and twenty-four patients as the placebo group (substance with no therapeutic value). Both groups were

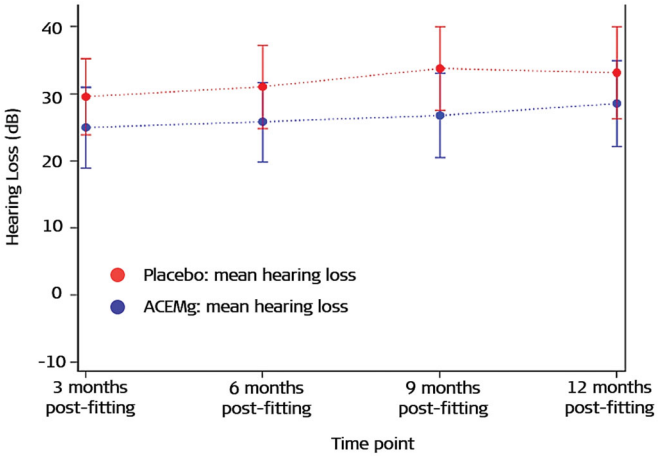

Figure 13. Mean HL over time in ACEMg and placebo group. At all observed time points, the HL in the placebo group was higher compared to the HL detected in the ACEMg group. In both groups, the HL increased over time. Adapted from Scheper et al. published in Trials [21].

implanted with MED-EL CI devices, carrying any of the following FLEX electrode array variants: 20 mm long FLEX20^{TM}, 24 mm long FLEX24^{TM}, 28 mm long FLEX28^{TM} and a custom-made electrode array, measuring 16 mm. The primary objective of the study was to compare the change in hearing thresholds at 500 Hz from the baseline to three months after the first fitting between ACEMg and placebo groups. The measured HL in the placebo group was 30.21 (±15.84) dB, and in ACEMg group, it resulted in 26.00 (± 17.56) dB (Figure 13). There was no statistically significant difference, but a 4.15 dB smaller mean HL was observed in the ACEMg-treated patients, compared to the placebo group. This tendency of residual hearing preservation three months after the first fitting was still detectable one year after the implantation with an average of 36.25 dB HL in the placebo group, and an average of 29.80 dB HL in ACEMg-treated group. It was concluded that dietary intake of ACEMg in patients aged fifty-five years and younger might lead to better hearing preservation three months after the first fitting and last for at least thirteen months after surgery.

This study was part of the first clinical trial investigating a drug effect of dietary supplements on residual hearing in CI patients. This first-in-human trial suggests that a perioperative oral administration of ACEMg is safe and may provide protection of residual hearing in CI patients.

6.7. Dexamethasone (DEX) as an otoprotective drug in CI application

Around 2000, MED-EL was invited to support a new laboratory at the University of Miami Ear Institute in the USA by Prof. Balkany and Prof. Van De Water to investigate the use of drugs together with CI. The request was put

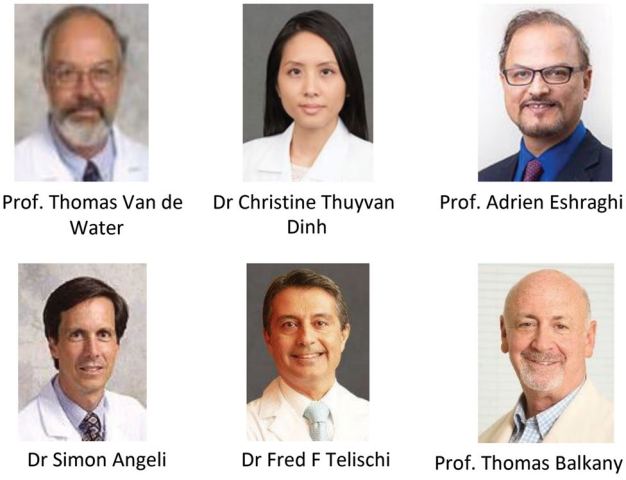

Figure 14. Clinicians from the University of Miami Ear Institute, USA, who were involved in the early studies designing the models for implantation trauma, and in evaluating the efficacy of steroids and antioxidants.

to Prof. Van De Water to find the best drug candidate to reduce the risk of HL during and after CI surgery. The first candidate selected was an apoptosis inhibitor D-JNKI-1, later renamed as AM-111 by the company Auris Medical (https://aurismedical.com/) which took it on for product development. Together with Prof. Eshraghi, Dr Angeli, Dr Telischi, and Dr Dinh, the Miami team developed models of implantation trauma and compared the efficacy of D-JNKI-1, various antioxidants, the steroid DEX against HL caused by implantation trauma, dose-response curve et cetera. The work in this laboratory continues to this day under the supervision of Prof. Eshraghi (Figure 14).

In 2000, the University of Miami Ear Institute in the USA, involving key clinicians as mentioned above, performed laboratory experiments in evaluating the otoprotective property of DEX following electrode EIT-induced HL [22].

The experimental ears were divided into four groups, namely (1) control group consisting of the contralateral unoperated ear serving as internal control, (2) untreated group with electrode insertion trauma (EIT), (3) EIT with intracochlear delivery of artificial perilymph (AP), and (4) EIT with dexamethasone base (DEX) in AP. In control and EIT-induced group, the HL was achieved by inserting an electrode analogue with a ball diameter of 0.14 mm through a cochleostomy located at the basal turn of the cochlea, approximately 1 mm from the round window (RW) membrane niche. The electrode was carefully withdrawn afterwards. In third and fourth groups, the micro catheters were inserted into the ST *via* the cochleostomy and used to locally deliver *via* a mini osmotic pump containing AP or DEX/AP solution (70 mg/ml) for eight days – and starting immediately after the surgery – into the perilymph of ST. Auditory function thresholds were measured before the

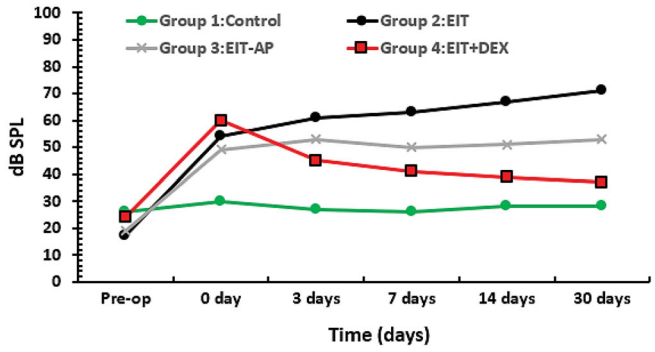

Figure 15. DEX treatment conserved auditory function thresholds at 16 kHz after electrode insertion trauma. Group-1: control ears ($n = 44$) (A), group-2: electrode insertion trauma (EIT, $n = 15$) (B), group-3: EIT + AP ($n = 15$) (C), and group-4: EIT + DEX ($n = 14$) (D). Statistical test: Analysis of variance with post hoc tests (Tukey-Kramer honestly significant difference) ($p < .05$). Graph created from data given in Vivero et al. [22].

surgery and on post-EIT days 0, 3, 7, 14 and 30 for both, control and experimental ears of the non-human subjects through auditory brainstem responses (ABRs) in response to pure tone stimuli (0.5-, 1-, 4- and 16-kHz). The ABR thresholds remained stable, with no drastic changes throughout the experimental time (Figure 15, green curve).

Before surgery, the group-2 subjects showed significantly lower mean thresholds (better hearing) than control (group-1). Immediately after surgery, the experimental ears (operated ears of group-2, -3 and -4) had higher (worse hearing) mean thresholds than control ears in response to 16 kHz. In general, the mean value changes in ABR thresholds of group-2 (EIT (Figure 15, black curve)) and group-3 (EIT + AP (Figure 15, grey curve)) compared to group-1 subjects were between 20–40dB sound pressure level (SPL) immediately after surgery (post-EIT, day 0), followed by a gradual worsening over time. In contrast, in group-4 (EIT + DEX (Figure 15, red curve)), the mean changes in ABR thresholds compared to group-1 (control) were 30–40dB SPL at 16 kHz immediately after surgery, followed by a gradual improvement over time, with a total recovery of the initial HL at three days postoperatively, staying stable until the end of the experiment at day thirty. In summary, the study showed otoprotective capability for the conservation of hearing, at least for the experimental period of thirty days. This study further encouraged MED-EL to develop a long-term drug-eluting CI electrode array that would benefit patients with preservation of residual hearing and the decrease of intracochlear inflammation, allowing an improved outcome in combined electric-acoustic stimulation.

In 2019, Prof. Arnoldner and his colleagues from the Medical University of Vienna, published their findings on the long-term effects of DEX-loaded hydrogels combined with DEX-eluting cochlear electrodes in a low-insertion trauma Guinea pig model [23]. They found out that DEX did not further reduce hearing loss and tissue formation although a slight tendency in this direction was visible. Regarding the sensorineural elements investigated in their study, auditory nerve fibers were significantly protected by the DEX-eluting electrode, an effect that tended to be even higher when the DEX-eluting electrode was combined with the DEX-loaded hydrogel.

6.8. The long-term effect of DEX on cochlear morphology and hearing preservation

In the previous study by Prof. Eshraghi and his colleagues, they reported on the short-term otoprotective DEX efficacy, where it was described how ABR thresholds remained significantly lower in their DEX experimental group within thirty days [22]. This finding opened the door to new questions – what would be the long-term otoprotective effect and what effect would it have on the intracochlear cellular levels.

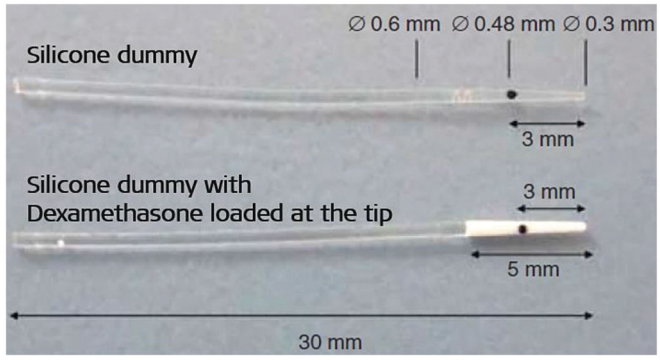

Figure 16. Silicone-made CI electrode dummies for non-human subject implantation with and without DEX load. The black dot indicates the insertion depth of 3 mm (Image courtesy of MED-EL).

In 2006/2007, MED-EL teamed up with the German group of the abovementioned clinicians (Figure 3) to evaluate the long-term impact of a DEX-releasing silicone electrode on hearing preservation and on the cochlear morphology in the range of six months [24]. An earlier similar long-term experiment had been limited to either four/five weeks, or three months [15]. Experimental cohorts ($n = 35$) were divided into two groups: DEX group ($n = 18$) and control group ($n = 17$). Both cohorts were unilaterally implanted with either a silicone dummy rod with noDEX or silicone rods containing 2% weight for weight (w/w) DEX, fabricated by MED-EL, as shown in Figure 16.

To check the hearing threshold levels, tone-burst evoked ABRs were performed at various time points starting preoperatively, followed by immediate postoperative measurements, and continued weekly until the twenty-fourth week. Histological analysis was performed to check for any presence of tumour necrosis factor (TNF)-α positive macrophages which would indicate an inflammation. ABR thresholds of both groups were measured with tone-bursts with carrier frequencies (f_c) of 1 kHz and 16 kHz (Figure 17(A,B)). Neither of the groups exhibited significant differences in the ABR thresholds preoperatively but did so immediately after surgery. The maximum HL occurred a day postoperatively, increasing until the end of the first week in both groups. Afterwards, the recovery of ABR thresholds was seen in both groups, but the DEX group exhibited higher recovery than the control. The differences between the two cohorts became more apparent and significant from the third week onwards and lasted until the end of the study, at the twenty-fourth week. The inflammation was the result of surgical trauma caused by drilling the bulla and the cochlea, followed by

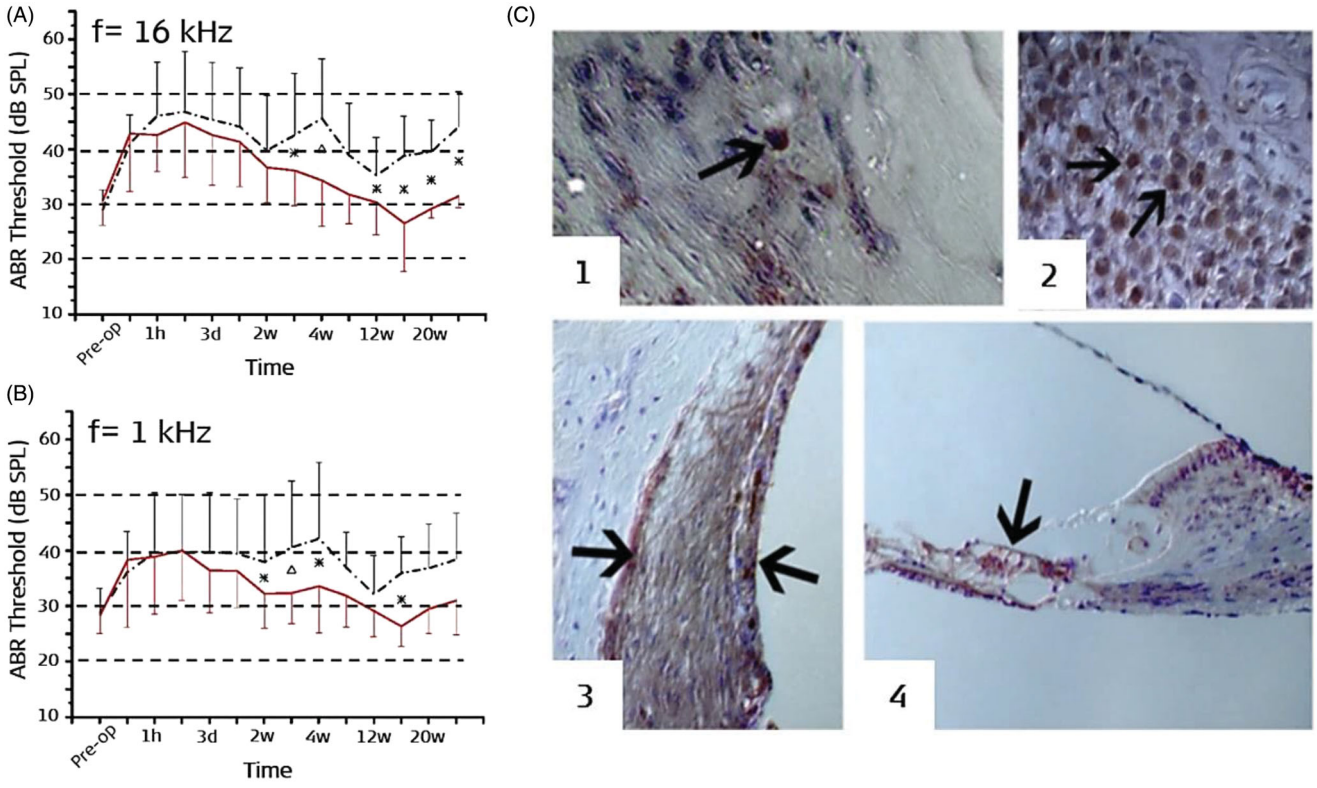

Figure 17. ABR thresholds (solid red line: DEX group, black dashed line: control group) with tone-bursts with carrier frequencies of 1 kHz (A) and 16 kHz (B). H&E staining showed TNF-α positive cells in new fibrous tissue (C_1), spiral ganglion cells (C_2), spiral ligament (C_3), and in the organ of Corti (C_4) [24]. Statistical test: Differences between groups were compared using the nonparametric Mann-Whitney U test for two independent samples ($p < .05$). Reproduced by permission of Elsevier B.V.

intra-cochlear electrode placement. Such inflammation would produce TNF-α cytokines inside the macrophages, which are highly visible with standard hematoxylin and eosin (H&E) staining. Compared to the DEX group, the control group had higher levels of TNF-α positive stained cells present in the new fibrous tissue (Figure 17(C_1)), spiral ganglion cells (Figure 17(C_2)), spiral ligament (Figure 17(C_3)), and in the organ of Corti (Figure 17(C_4)).

The difference between the groups may be explained as a positive DEX-related indication, and overall, the study evidenced positive effects on long-term hearing preservation, as well as on the inflammation suppression. The study showed significant recovery of auditory function from one to twelve weeks postoperatively, supporting the hypothesis that CI incorporating DEX can release drug chronically and reduce postoperative insertion trauma.

6.9. Risk of DEX in postoperative infections

DEX, with its known otoprotective properties, also has the theoretical potential to increase the risk of postoperative infections due to its antiproliferative and immunosuppressive properties. Any reduction in tissue growth around the electrode array at its entry point into the cochlea could extend the time taken to establish a seal of the cochlea. This could potentially be detrimental for the CI treatment, and these were the key questions that needed an investigation at the time.

In 2011–12, a team of clinicians from the Technical University of Munich and the Institute of Infectious Diseases and Zoonoses-Faculty of Veterinary Medicine-Munich, Germany, along with MED-EL's support, joined to evaluate the risk of pneumococcal meningitis after implantation of DEX-eluting CI electrodes in a non-human subject model [25,26] (Figure 18). Thirty otologically healthy experimental non-human subject ears were used in this study. Experimental ears were randomly assigned into two groups: DEX group and noDEX group. The DEX group ($n = 15$) was implanted unilaterally with a drug-releasing electrode dummy containing 10% w/w dexamethasone, and in the noDEX group ($n = 15$), the same type of dummy electrode, without any drug, was implanted unilaterally.

Dr Thomas Stark [1]

Prof. Reinhard Straubinger [2]

Figure 18. ENT surgeons from clinics in Germany: [1]Technical University of Munich, [2]Institute of Infectious Diseases and Zoonoses-Faculty of Veterinary Medicine- Munich, and their colleagues who were involved in evaluating if DEX could enhance postoperative infections following CI treatment.

Dummy electrodes (silicone rods without platinum contacts) with and without DEX were fabricated with an overall length of 30 mm, but the length of the array that was intended to be placed inside the cochlea was only 5 mm long, as shown in Figure 16. The electrode was introduced

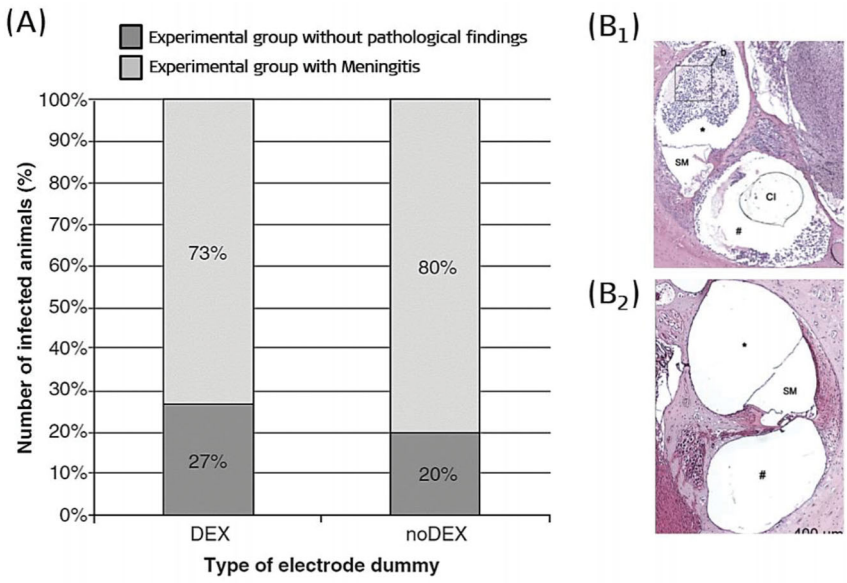

Figure 19. Experimental group implanted with DEX eluting electrode developed meningitis in 4/15 (27%) subjects, and the experimental group implanted with non-eluting electrode dummies developed meningitis in 3/15 (20%) subjects (A) [25]. Reproduced by permission of Taylor and Francis Group. Mid-modiolar section of the cochleae showed the presence of inflammatory cells in the subjects that got meningitis (B_1), and no presence of inflammatory cells in the subjects that did not get the meningitis infection (B_2) [26]. Statistical tests: Mann-Whitney U test and Fisher's exact test ($p < .05$). Reproduced by permission of Elsevier B.V.

into the left cochlea, which was accessed through a cochleostomy of 0.7 mm diameter, and the right ear was kept as a control. A broad-spectrum of antibiotics was given for three days following the surgery to keep the implanted ears protected from infections. Five weeks after the cochlear implantation, the implanted ears from both groups were exposed to Streptococcus Pneumoniae by inoculation of 10 µl of bacterial solution into the middle ear. Under general anaesthesia, the bacterial inoculate was administered through an opening of the bulla wall and placed with gel foam at the RW to avoid any leakage through the eustachian tube. For specimen collection and as the final step in the experiment, a CSF- and a 1 ml sample of blood for the bacterial count were collected under general anaesthesia. The inoculation had manifested in the form of meningitis in 23% of the total implanted ears: 4/15 (27%) in DEX and 3/15 (20%) in noDEX (Figure 19(A)). The experimental subjects were closely monitored and euthanised as soon as symptoms of infection were displayed and there was no significant difference on the meningitis rate between the two groups, although DEX group showed a higher percentage of subjects without pathological findings. The group with meningitis attack was seen with inflammatory cells inside the cochlea (Figure 19(B_1)) which was not the case with the group of subjects that did not show any signs of meningitis attack (Figure 19(B_2)).

This was critical scientific evidence which showed that at the typical concentrations intended for human use, DEX does not enhance postoperative infections, making it a promising drug candidate to be coated over CI electrode array for a long-term release in the range of >6 weeks.

6.10. Attempt towards developing a DEX loaded human CI electrode array

As per the above-listed research studies performed before 2010, showing the positive effect of DEX in inner ear treatment in non-human subject models, MED-EL took the next steps in exploring the fabrication of DEX loaded CI electrode array for human application.

In 2010, MED-EL created a scientific collaboration with the Iran Polymer and Petrochemical Institute (IPPI) in Tehran in Iran [27] (Figure 20).

The primary aim of the collaboration was to study the feasibility of mixing DEX with the medical-grade silicone which is used in the fabrication of CI electrode array, as well as to understand its release profile from the cured silicone elastomer, in saline solution for an extended period of six hundred and thirty days. HPLC (high precision liquid chromatography) technique was used to determine the amount of DEX released from the electrode samples loaded with 0.25%, 0.5%, 1%, and 2% w/w of DEX in silicone. The cumulative amount of DEX (in µg) released from the devices loaded in different percentages of DEX is compared in Figure 21(A), which clearly shows a direct proportion between drug loading and the released amount, that is, 2%, >1%, >0.5%, and >0.25% w/w.


Dr Farhid Farahmand

Dr Claude Jolly

Figure 20. Researchers from Iran Polymer and Petrochemical Institute (IPPI) and MED-EL who studied the feasibility of fabricating hybrid electrode array by mixing DEX to the medical-grade silicone.

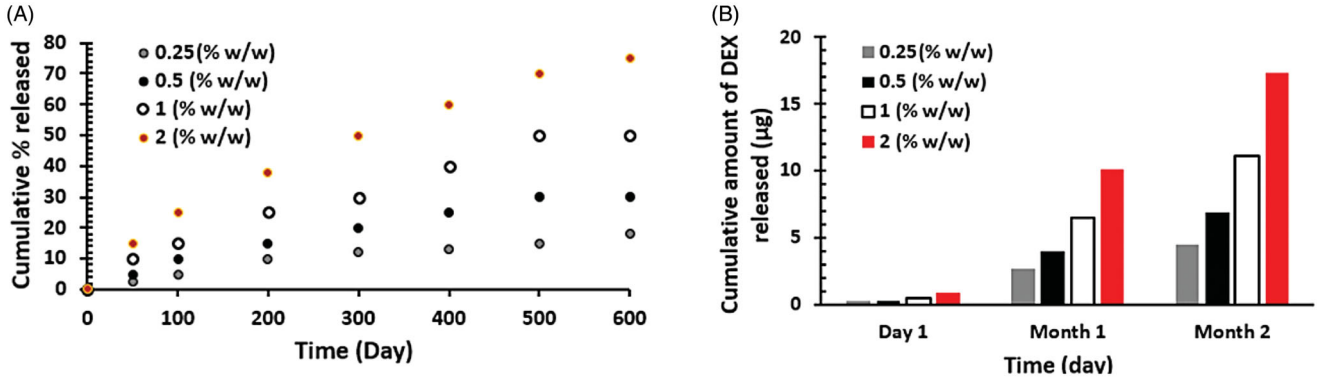

Figure 21. Total cumulative amount of DEX (µg) released from devices loaded in different percentages of DEX (0.25%–2% w/w) for 600 days release time (A). The daily dosage of DEX released (µg/day) from devices (B). Plot and histogram created from data given in Ghavi et al. [27].

The DEX dosage delivered daily (in µg) was calculated using the data obtained from samples of different loadings, and a burst release was seen in the first few days for all samples, which increased with increased loading and lasted for the first fifty days of DEX release period, as shown in Figure 21(B). The study demonstrated the excellent mixing profile and batch-to-batch reproducibility for all samples. The results indicated that 0.2–1µg and 1–5µg of DEX was released in the first 24 h and the first week of in-vitro experiments, respectively, from samples of various loading of 0.25%, 0.35%, 0.5%, 1% and 2% w/w based on the final cured CI device.

In 2013, the same team reported on the reduction in inflammatory reactions caused by the EIT following DEX-eluting CI electrode array in a non-human model [28]. The control groups implanted with noDEX electrode and with no electrode but only cochleostomy showed fibrocyte higher in number compared to the group implanted with DEX eluting electrode arrays.

6.11. DEX-eluting CI electrode array

As described in the previous sections, from **2002 to 2012**, dedicated joint efforts from various international research groups and MED-EL developed preclinical evidence on the safety and efficacy of corticosteroids in CI applications. MED-EL envisioned a drug-eluting electrode array which would be preloaded with a defined amount of corticosteroid. The expected advantage of the drug-eluting electrode array was that the release of DEX over a more extended period would provide a sustainable effect on minimising inflammation after implantation, reducing fibrosis and electrode impedance, and potentially also reducing the risk of residual HL. Furthermore, it would reduce any additional efforts of the operating surgeon in applying corticosteroid to the ST separately.

In 2012, MED-EL started a development project around the DEX-eluting electrode array, called DEXEL (Figure 22). The reasons for DEX as the chosen corticosteroid were its potency, its universal use in otological applications, and that it was a well-understood drug in the field. The idea was to mix medical grade silicone with a predefined amount of

Figure 22. Top: picture of MED-EL's DEX-eluting electrode array with the DEX-containing silicone rings, loaded between the stimulating electrode channels (image courtesy of MED-EL). Bottom: Chemist and Pharmacologist from MED-EL who were heavily involved in the development of DEXEL.

DEX and apply it radially between the stimulating contacts in the form of rings, making them an integral part of the electrode array.

DEX would then gradually diffuse from the silicone into the perilymph upon placement into the ST. The process between the idea and the final design went through an extensive course of establishing the manufacturing procedure to, i.e. obtain a reproducible drug content and drug release profile in relation to predefined shelf life. Furthermore, the effects of DEXEL electrode on the mechanical properties of the electrode array (compared to previous electrode arrays), its trauma potential to the cochlea,

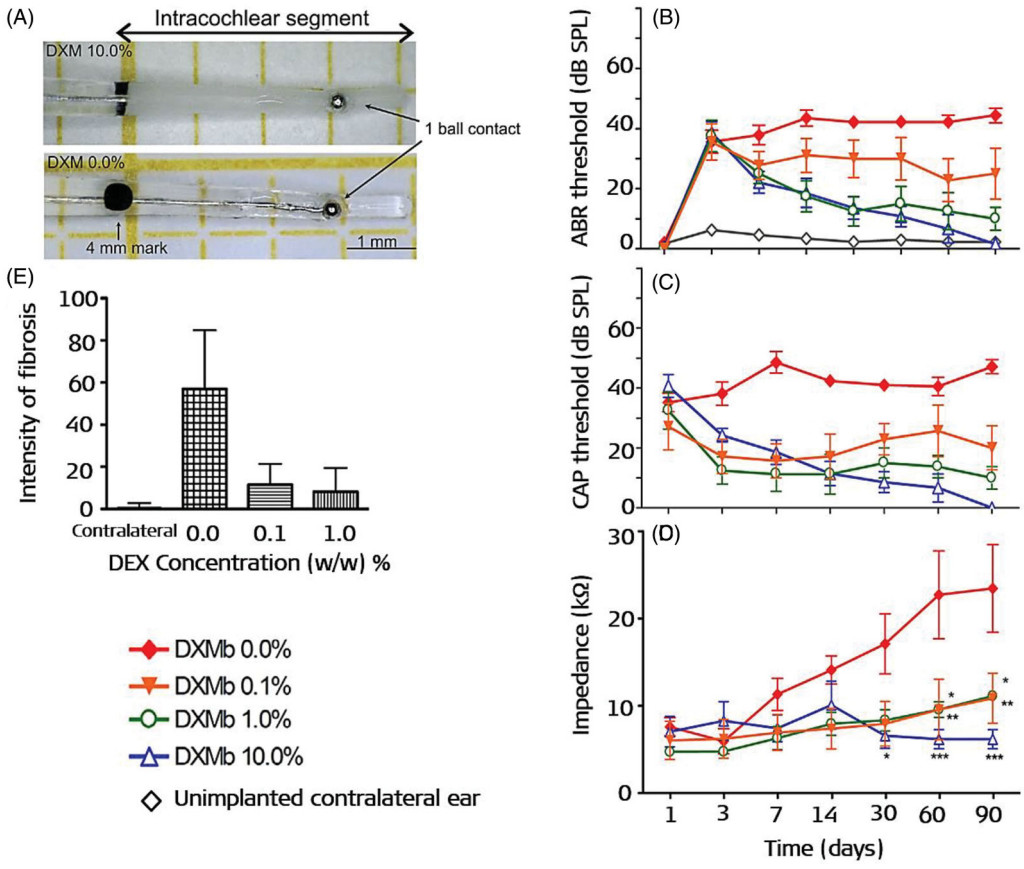

Figure 23. DEX-eluting electrode arrays with DEX concentration of 10% and 0% (A) (image courtesy of MED-EL). ABR thresholds (B), CAP thresholds (C) and electrode impedance (D) of all the experimental groups implanted with electrode arrays loaded with DEX of concentrations 0.0%, 0.1%, 1.0% and 10.0% (w/w). Semi-quantitative analysis of fibrous tissue in cochlea samples implanted with electrode array loaded with different concentrations of DEX (E) [29]. Statistical test: Two-way ANOVA with Bonferroni posthoc testing was applied for ABR and CAP threshold comparisons and impedance comparisons between groups. One-way ANOVA with Tukey's post-test was applied for scala tympani fibrosis histology studies ($p < .05$). Reproduced by permission of Elsevier B.V.

and its usability during surgery were evaluated amongst other parameters. However, to obtain a complete picture in order to decide over the final electrode design, further pre-clinical studies were necessary. In addition to the important safety findings obtained by Stark et al. [25,26], five studies were sponsored by MED-EL. They have investigated (i) the effective concentration of DEX loaded onto the electrode array that conserves hearing after EIT [29], (ii) effect of DEX on reducing the fibrous tissue formation and thereby keeping the electrode impedance on a lower level [30,31], and (iii) release profile of DEX from silicone in-vivo [32,33], that are presented below in this section, turned out to be the key to progress towards a clinical phase in the DEXEL development.

6.11.1. Safety and efficacy of DEX-eluting electrode in rodents

In 2012, Prof. Van de Water and his colleagues from the University of Miami Ear Institute in the US studied the effective concentration that minimises the hearing threshold and fibrous tissue formation following EIT [29]. Silicone-made electrodes loaded with different concentrations (w/w) of DEX (0.0%, 0.1%, 1.0% and 10%) were fabricated by MED-EL. Figure 23(A) shows the electrode sample loaded with 10.0% and 0.0% (w/w) of DEX and with a ball contact at the tip to create EIT. The electrodes were implanted in the experimental group *via* cochleostomy approach, retracted back and inserted again, intending to cause elevations in ABR thresholds of 30 dB SPL or greater across all frequencies. The electrophysiological hearing assessment using ABR, CAP and electrode impedance was performed before surgery, and post-EIT on days 1, 3, 7, 14, 30, 60 and 90. On the ninetieth day post-EIT, the ears from the experimental and the contralateral unimplanted control group were collected for histology analysis, and staining of the hair cells bundles was performed to quantify the fibrosis tissue formation.

The insertion of the CI electrode array that did not contain DEX (0.0%) initiated a significant increase in ABR and CAP threshold values when compared to the values obtained from unimplanted contralateral cochleae (Figure 23(B)). Significant elevations in ABR and CAP thresholds were demonstrated immediately after implantation of 1% and 10% DEX electrode array, and these shifts progressively declined until ninetieth-day post-EIT (Figure 23(B,C)).

Besides, there were significant differences in ABR and CAP thresholds between 0% DEX and both, 1% and 10% DEX electrode arrays, at ninety days post-EIT. ABR and CAP

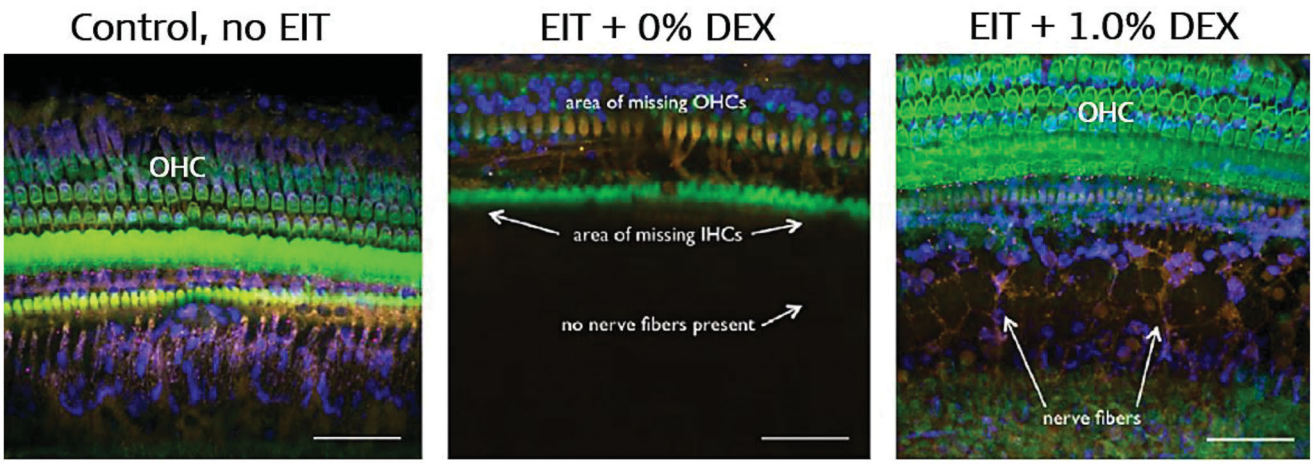

Figure 24. Immunostained organ of Corti ninety days post-EIT showing the normal presence of OHC, IHC and nerve fibres in the control specimen with no EIT. Absence of nerve fibres and missing IHC and OHC in specimens that had EIT but no DEX. Presence of OHC and nerve fibres in specimens that had EIT and 1.0% of DEX [29]. Reproduced by permission of Elsevier B.V.

thresholds from 10% DEX electrode implanted ears approached pre-trauma levels by ninetieth-day post-EIT. The impedance measurements for the 0.0% DEX electrodes started to increase after one week and then progressively increased over time, reaching a maximum level at ninety days post-EIT. The mean impedance at day one post-surgery remained below 10kOhms for all electrodes. At thirty, sixty and ninety days postimplantation, the impedance of 10% DEX containing electrodes was significantly lower compared to the EIT 0% DEX mean values. The impedances for the electrodes containing 1% and 0.1% DEX remained stable during the experimental period, achieving statistical significance when compared with the 0% DEX electrode array impedance values at two and three months postimplantation (Figure 23(D)). The semi-quantitative analysis of the cochlea samples through histological staining showed that the fibrous tissue formation was smaller in cochleae implanted with 0.1% or

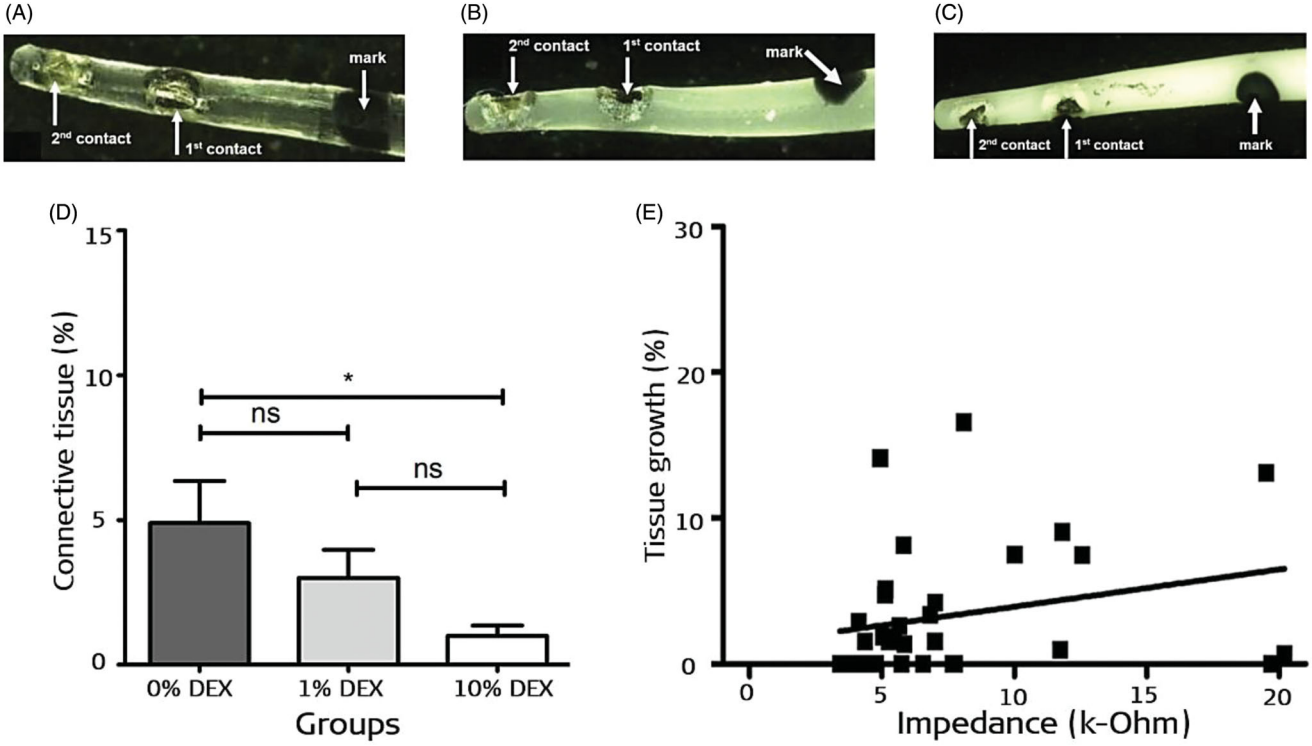

Figure 25. Electrode arrays have two active contacts (the first contact is more basal and the second more apical), and a black marker dot at 3 mm length from the apical end indicates insertion depth (images courtesy of MED-EL). Control electrode array without DEX (0%) (A), electrode arrays containing 1% DEX (16 ng/day delivery rate) (B), and electrode array containing 10% DEX (49 ng/day delivery rate) (C). Connective tissue formation in the ST of implanted ears treated with 1%, 10% or 0% DEX. Tissue growth is plotted as the percentage area filled in the ST. Mean tissue growth for the whole cochlear length analysed (basal turn) showing a significant difference between the 10% DEX treated cochleae and 0% DEX (D). Correlation between tissue growth and impedance; tissue growth around the electrode array significantly correlated with the measured impedance on the more apical electrode (E) [30]. Statistical analysis: Shapiro-Wilk normality test and Spearman-Rho nonparametric correlation tests were used ($p < .05$). Adapted from Wilk et al published in PLOSONE [30].

1.0% concentration of DEX loaded electrode arrays compared to cochleae implanted with 0.0% DEX (Figure 23(E)).

Figure 24 shows the immunostaining of the organ of Corti specimens with a clear presence of outer hair cells (OHC) in the control group that had no EIT and in the experimental group that underwent EIT but treated with 1.0% DEX. Whereas, the experimental group that underwent EIT but with no DEX showed areas of missing OHC, inner hair cells (IHC) and nerve fibres.

Overall, the study demonstrated that silicone electrode arrays loaded with 10% and 1.0% DEX protected the sensory cells. Regarding the EIT-induced HL, a permanent increase in ABR and CAP thresholds, impedance and fibrosis was observed over ninety days post-surgery.

In 2016, Prof. Lenarz and his colleagues from the Hannover Medical School in Germany investigated the changes in electrode impedance and fibrous tissue growth around the electrode following CI surgery, using DEX-eluting electrode in a non-human subject model [30]. CI electrode arrays loaded with 1% and 10% DEX (weight/weight) concentrations and control electrode arrays with noDEX (0% w/w) were fabricated by MED-EL, as shown in Figure 25(A–C). Each of these three different electrode arrays was implanted unilaterally in nine ears each and the ears received electric stimulation for sixty minutes weekly, using MED-EL's CI system. The ears implanted with control electrode arrays did not receive any electric stimulation apart from during the electrode impedance measurements. At the end of the experimental period, the ears were histologically evaluated for the presence of fibrous tissue growth around the electrode array inside the ST. Cochleae treated with 10% DEX had significantly reduced areas of connective tissue compared to 0% DEX treated cochleae, as shown in Figure 25(D). Figure 25(E) shows a positive correlation between impedance increase over time and fibrous tissue growth around the electrode array. The study concluded that fibrosis was reduced with DEX treatments and that the amount of reduction in fibrosis was directly related to the increasing concentration of DEX in the electrode array. Also, the reduction in fibrosis kept the electrode impedance at a lower level, showing the pharmacological effects of DEX in the inner ear treatment.

Dr Cristina Zulueta Santos Dr Raquel Manrique Huarte Prof. Manuel Manrique

Figure 26. ENT surgeons from the University of Navarra in Pamplona, Spain, performed the CI surgeries in ten non-human primates *Macaca fascicularis* to evaluate the safety and efficacy of DEX-eluting electrode array.

Overall, from all these four studies, it was well understood that the trapped DEX from the silicone carrier diffuses into the surrounding fluid environment, minimising the fibrous tissue formation around the electrode array and keeps the electrode impedance at a low level.

6.11.2. Safety and efficacy of DEX-eluting electrode in non-human primates

With several studies reporting on the safety and efficacy of DEX in combination with CI in non-human subject models [15,17,18,22–26], and to bring the concept of DEX-eluting electrode array closer to clinical study in humans, there was a need to test it in a higher animal model which would resemble human species more closely.

In 2015, MED-EL sponsored a study which focused on the performance and safety of DEX-eluting electrode, implanted to non-human primates, *Macaca fascicularis* [31]. The study aimed to look at the impedance, eCAP and eCAP recovery function, which can reflect the anti-inflammatory and otoprotective properties of DEX. The study took place at the University of Navarra in Pamplona in Spain, led by Prof. Manuel Manrique (Figure 26).

Ten healthy normal hearing *Macaca fascicularis* were used in the study and were divided into two groups. The experimental group underwent unilateral implantation with a modified MED-EL CONCERTO CI with FLEX28^{TM} as a base, for drug percolation by assembling the DEX-eluting silicone rings between the stimulating channels as shown in Figure 18 (n = 5). The control group ($n = 5$) underwent unilateral implantation of an unmodified MED-EL's CONCERTO CI with FLEX28^{TM}. In both cohorts, the electrode array was intentionally implanted with only five to six channels intracochlearly to accommodate the fact of non-human primate's smaller cochlear size of 25 mm on average [34]. The first cohort's electrode array carried a total of 15.75 µg of DEX, distributed along the whole array, and the four rings located between the contacts, placed intracochlearly, carried ~7µg (Figure 27(A)).

The impedances of the implanted five to six electrode channels were measured by using MED-EL's CI fitting software MAESTRO 7.0 at various time points for both cohorts, and the average impedance values of all measured channels are shown in Figure 27(B). At two months postoperatively, the DEX group showed significantly lower impedances in comparison to the control group, and this trend was seen throughout the study period of six months. This could be rationalised with the anti-inflammatory properties of DEX which would have reduced the tissue growth around the electrode array, causing the electric current flow with less resistance, compared to the control group that had no DEX coating on the electrode array. The eCAP response to the electric stimulation at eight hundred current units (cu) from the five to six implanted electrode channels showed significantly higher amplitudes in the DEX group, compared to control (Figure 27(C)). This trend was seen from the time of implantation until the end of the sixth months' study period. eCAP is a direct measure of neural responses generated by the auditory nerve fibres, and in this context, higher eCAP amplitudes within DEX cohort may be explained by the otoprotective properties of DEX on the sensory cells,

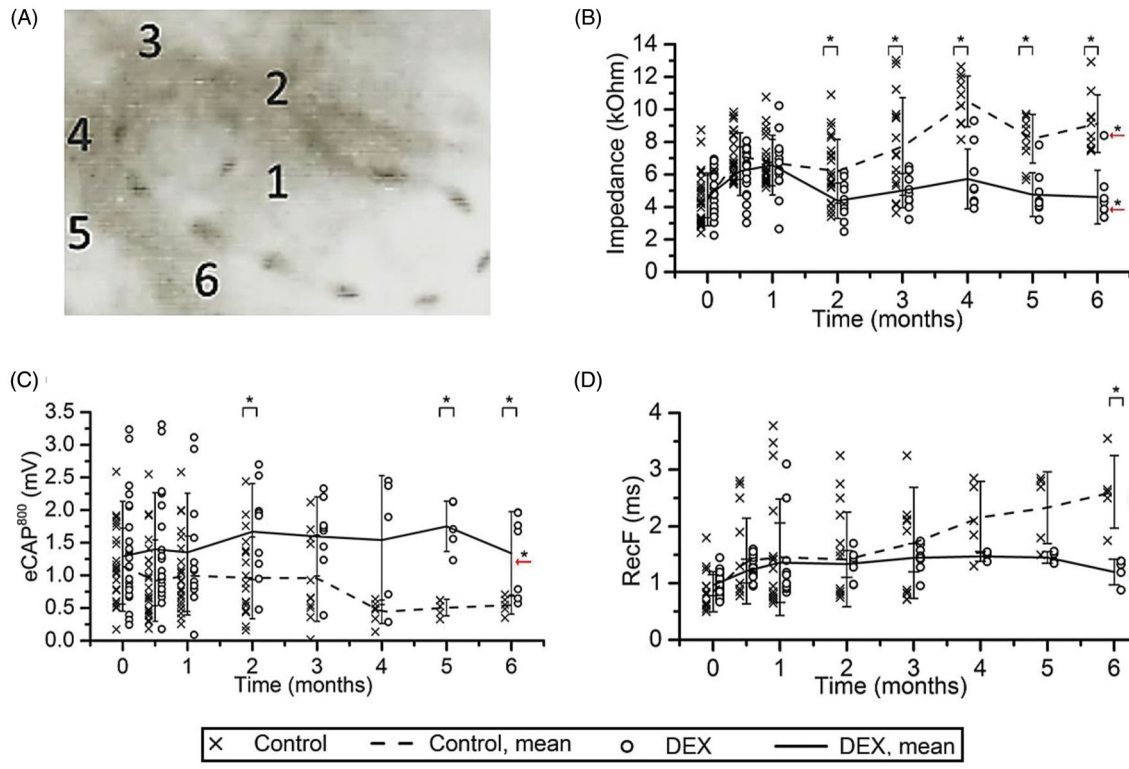

Figure 27. The postsurgical image showing six stimulating channels inside the non-human primate's cochlea (A) (image courtesy of Prof. Manrique). Mean impedance values from all six stimulating channels showing lower impedance values for the DEX-eluting electrode group, compared to the control group (B). eCAP responses to 800cu stimulation showed that the DEX-eluting electrode group had higher eCAP amplitudes on average, compared to the control group (C). eCAP recovery function showed shorter recovery times for the DEX-eluting electrode group, starting two months post-surgery, lasting until the end of the study (D) [31]. Statistical analysis: Student's t-test with Wilcoxon Man-Whitney U test ($p < .05$). Reproduced by permission of Wolters Kluwer Health, Inc.

implicated by the surgical trauma. An additional explanation for the higher eCAP amplitudes within DEX cohort is that the eCAP amplitude depends on the impedance of the recording electrode, which is reduced by the DEX effect, making it accessible to more neurons.

Compared to the control group, the eCAP recovery function showed shorter recovery time in the DEX cohort, starting two months postoperatively and lasting until the end of the study (Figure 27(D)). Again, this can be explained with the otoprotective properties of DEX which could have offered protection to neural fibres against surgical trauma, enabling them to have a more efficient response to individual pulses within a pulse sequence.

Overall, the study presented positive prospects with adding DEX-loaded silicone rings between the stimulating channels, out of which the DEX diffuse almost 100% within six months. DEX can suppress fibrous encapsulation, thereby it keeps the impedance values low, as well as it protects the neural fibre efficient functionalities. This was another milestone achieved in the development project of the dexamethasone-eluting electrode (DEXEL). Still, to obtain a fully comprehensive picture, the pharmacokinetic behaviour of DEX in the cochlea was missing.

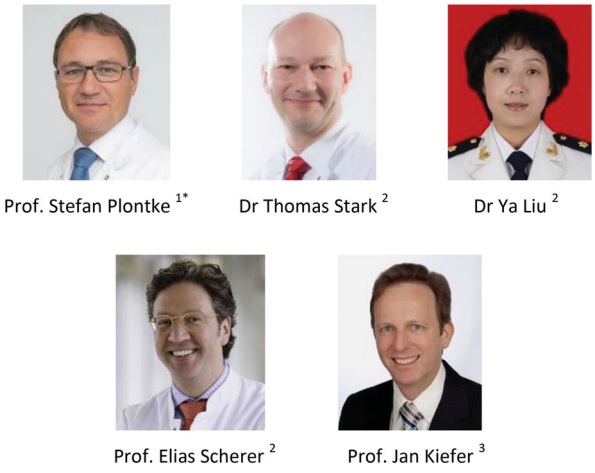

Figure 28. Team of clinicians from [1]Martin Luther University Halle-Wittenberg, Germany, [2]Technical University of Munich, Germany, [3]HNO-Zentrum, Regensburg, Germany, and their colleagues, were involved in the pharmacokinetic study of dexamethasone-releasing silicone CI electrode array. Dr Ya Liu was a PhD student at the time at the Technical University of Munich, but originally from Beijing Naval General Hospital, China. *Image courtesy of Prof. Stefan Plontke: Fotostelle Universitätsmedizin Halle.

6.11.3. Pharmacokinetics of dexamethasone (DEX)

Once the DEXEL electrode is placed inside the ST, DEX begins its release from the silicone into the perilymph-filled environment. For the creation of a safe and effective DEX-releasing CI electrode array, it is crucial to determine the therapeutic window of DEX in the inner ear, which leads to the amount that is actually needed in the array. An important preclinical dataset to define the dose for the human

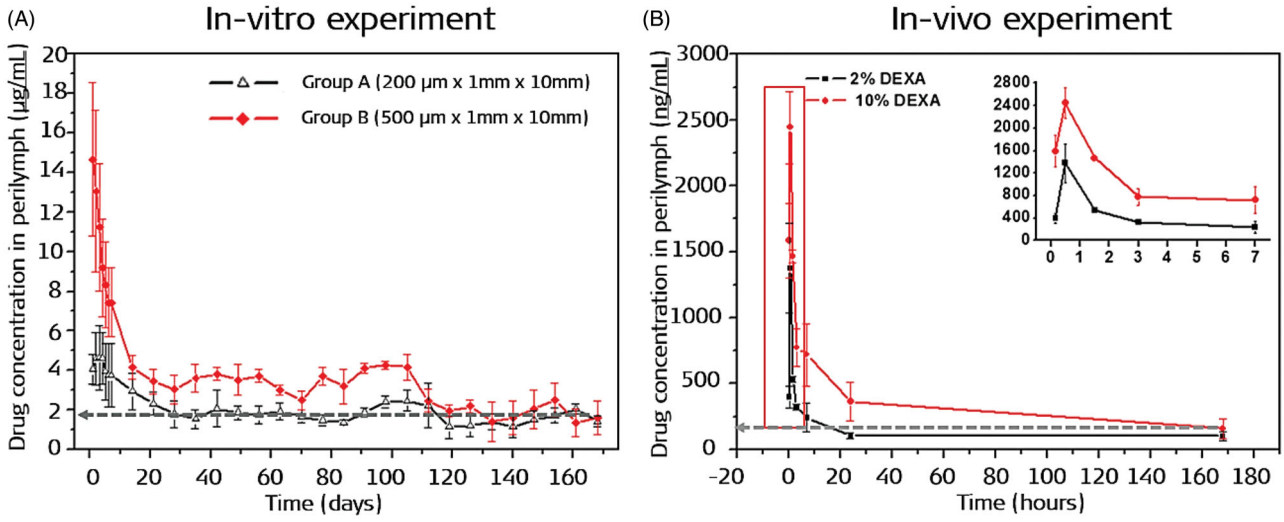

Figure 29. Real-time concentrations in groups A and B from the in-vitro experiment. The concentration in group B was consistently higher than in group A for fifteen weeks, although the difference between the two groups became smaller over time. After the sixteenth week, there was no difference in concentration between the two groups (A). DEX concentration-time curves in subjects' perilymph (B). The image on the top right represents a detailed display of the curves within 7 h after implantation. The peak concentration occurred 30 min after surgery in both groups and then decreased rapidly until 3 h after surgery. From 3 h to one day, the perilymph concentration in the 10% DEX group was significantly higher than in the 2% DEX group, after which the difference became non-significant [32]. Statistical test: differences between the groups were compared using the nonparametric Mann-Whitney U test for two independent samples ($p < .05$). Reproduced by permission of Springer Nature.

application could be derived from the pharmacokinetic studies.

In 2016, Prof. Plontke, Prof. Kiefer and their colleagues reported on the release profiles of DEX from the silicone-made CI electrode array from both in-vitro and in-vivo experiments [32] (Figure 28).

The in-vitro experiment was designed to characterise the release profiles of DEX from two sizes of silicone films (200 µm × 1 mm × 10 mm (group A) and 500 µm × 1 mm × 10 mm (group B)), incorporated with 2% DEX in a simulated human inner ear fluid environment (Figure 29(A)). The in-vivo experiment was designed to measure the drug concentration in the perilymph of ST (Figure 29(B)). Experimental ears were implanted with two varieties of silicone rods as an electrode array, loaded with 2% and 10% DEX, in twenty-one ears each. In the in-vitro experiment, the silicone films of two different sizes loaded with 2% DEX were placed in a capillary with a volume of 160 µl (artificial perilymph), which was close to the volume of human perilymph. The flowrate of human perilymph was taken as 24 µl/day, and therefore 24 µl of artificial perilymph was sampled every day from the in-vitro experimental setup to measure the drug concentration. Figure 29(A) shows the drug concentration in artificial perilymph, with group B showing consistently higher concentration than group A until the fifteenth week, and there was no difference in concentration between the groups after that.

In the in-vivo experiment, 8 µl of perilymph was extracted from the apex of the experimental cochlea at various time points, which was diluted with 17 µl of artificial perilymph for the measurement of DEX concentration, using HPLC. Figure 29(B) shows the drug concentration in the perilymph of experimental ear with a burst release in both, 2% and 10% DEX groups. The peak concentration occurred thirty minutes post-surgery in both groups and then decreased rapidly until three hours post-surgery. From three hours to one-day post-surgery, the concentration in 10% DEX group was significantly higher than in 2% DEX group, and after that, the difference became non-significant.

One-week post-surgery, the concentration was 101.21 ± 34.04 ng/ml in the 2% DEX group, and 159 ± 74.64 ng/ml in the 10% DEX group. In the in-vitro experiment, drug metabolism and drug distribution routes through tissues were not considered, and therefore the drug was released slower than in the in-vivo experiment. On the other hand, the drug kinetics of both experiments were somewhat similar: (1) regardless of the drug content in silicone, the concentration in the release medium became similar after a period of burst release, (2) balanced drug distribution was seen in-vitro for twenty weeks and in-vivo

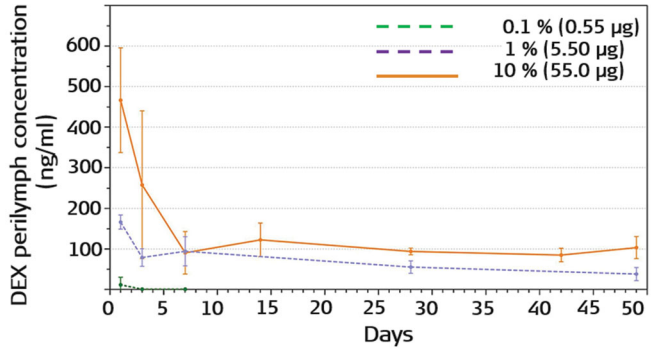

Figure 30. Dependence of perilymph DEX concentration in the ST of implanted cochleae with 0.1%, 1% and 10% loaded DEX silicone rods after implantation. A burst release phase lasting 1–7 days—depending on silicone drug loading—was followed by a steady-state phase characterised by constant drug concentrations. Adapted from Liebau et al published in Frontiers in Neurology [33].

for at least one week, (3) silicone with higher drug content predictably maintained a longer period of drug release. In summary, both 2% and 10% initially achieved measurable levels of DEX in the cochlea; however, a more sensitive assay was needed for long term comparisons.

From 2014 on, parallel to the above study, another study was taking place at the Martin Luther University Halle-Wittenberg in Germany, conducted by Dr Liebau and his colleagues, to examine how DEX concentrations in the electrode carrier influence drug levels in the perilymph at different time points [33]. The electrode carrier was loaded homogeneously with 0.1%, 1% and 10% concentrations of DEX and the electrode carriers were implanted into the ST of experimental cochleae ($n = 45$) *via* cochleostomy. After implantation, DEX concentrations in perilymph and cochlear tissue were measured at several time points over a period of up to seven weeks. Perilymph samples were taken from ST using the method of apical sampling, and DEX concentration was measured using liquid chromatography-mass spectroscopy. The DEX levels in the perilymph for 1% and 10% loaded rods showed an initial burst followed by stable concentrations during the observed period. A higher variance of DEX concentrations was observed during the burst release than in the steady-state phase (Figure 30).

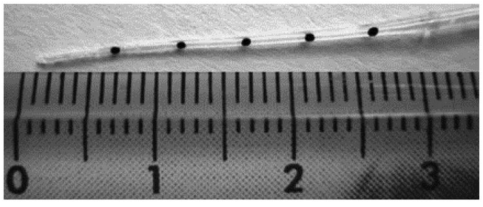

Figure 31. Silicone dummy of a STANDARD electrode array from MED-EL, with an open channel that runs through the length of the array (image courtesy of MED-EL).

This study shows that the drug concentrations in the inner ear fluid can be controlled by the DEX load of the electrode carrier. Based on the results, MED-EL designed DEXEL electrodes for the non-human subject model, with which further pharmacokinetic data were obtained by Prof. Plontke and his colleagues. The results of that yet unpublished part led to the design of the human DEXEL electrode.

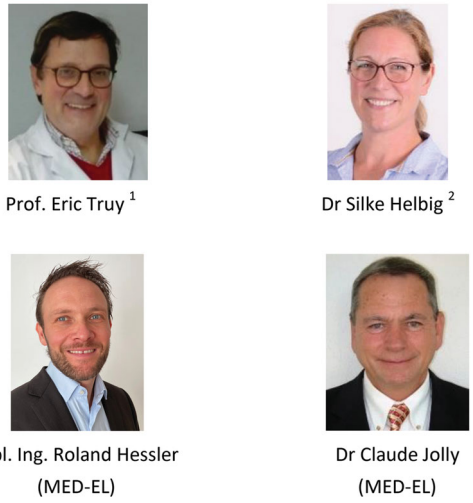

Figure 32. A team of ENT surgeons from [1]University of Lyon, France, and [2]Johann Wolfgang Goethe University Hospital Frankfurt, Germany, along with engineers from MED-EL, who were involved in the evaluation of safety and functionality of IEC in cadaveric cochleae.

6.12. Single-use drug delivery vehicle concept by MED-EL

While various safety and efficacy studies of corticosteroid in CI surgery research were taking place in different centres globally, either in combination with the CI electrode array or as standalone drug treatment, MED-EL took initiatives to develop an inner ear drug delivery vehicle as a standalone device to enable the delivery of any drug of surgeon's choice. The first version of the inner ear catheter (IEC) which MED-EL designed, resembled its STANDARD CI electrode array (31.5 mm), but with no metal wire bundle inside with an open channel that runs through the length of the array was part of the design, as shown in Figure 31.

To evaluate the safety and functionality of the IEC, a team of ENT surgeons and radiologists from France and Germany performed laboratory tests with the surgical placement of the catheter in cadaveric cochleae, followed by imaging and histological evaluation [35]. MED-EL engineers supported the study in terms of fabricating the inner ear catheters (Figure 32).

A 10–15mm insertion depth was recommended, and the IEC had a Luer lock connection at its back end to connect standard type syringes and one fluid outlet at the front end. The fluid outlet was located directly at the tip and pointed towards the apical end. The conical IEC had the same shape as the STANDARD electrode array (0.5 mm diameter at the apical tip and 0.8 mm diameter at the basal end), but it was softer due to the absence of metal wire bundle. A Hamilton syringe connected to the Luer lock was used for flushing the drug solution through the apical end to fill the ST space (Figure 33(A)). A total of thirteen fresh human cadaveric temporal bones were used in this study, and a standard mastoidectomy and posterior tympanotomy were performed to reach the RW. The IEC was inserted into the ST to an insertion depth of 15 mm, followed by slow injection of 10–15µl of iodine solution. The reason for the iodine solution was that it could be detected radiographically. To understand the trauma to the intracochlear structures caused by the catheter insertion, and especially any deviation from ST to SV, the cadaveric temporal bones were CT-scanned to see the distribution of iodine. As expected, the IEC did not deviate to SV, and this was captured in the CT scans (Figure 33(B)), with iodine staying in the lower compartment in both, basal and second turn of the cochlea (red arrow marks). At a later stage, the histological evaluation of the cadaveric temporal bone with catheter inside confirmed the ST placement (Figure 33(C)). After removing the catheter from the ST, a 24 mm long MED-EL CI electrode array was inserted (Figure 33(D)), followed by a histological evaluation to see if subsequent electrode array insertion caused any degree of trauma and to inspect the

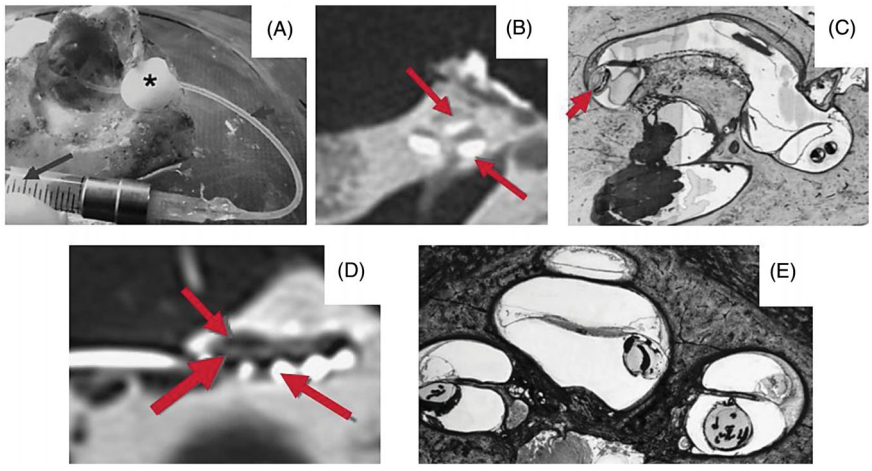

Figure 33. The back end of the catheter merged with a Luer lock system for the glass Hamilton syringe to be connected (A). The iodine solution was injected using the catheter, which stayed in the ST even in the second turn of the cochlea, as seen in CT imaging (B). Histological analysis of the cochlea with the catheter inside showed the presence of catheter wholly positioned in the ST with no deviation to SV (C). CI electrode array insertion, following the catheter removal, stayed completely inside the ST, as seen in the CT imaging (D) and the corresponding histological analysis visually confirmed the ST position (E) [35]. Reproduced by permission of Wolters Kluwer Health, Inc.

Figure 34. Chemist and engineer from MED-EL who were part of the team reconfiguring the catheter design.

successful ST placement visually – Figure 33(E) confirms the latter.

The design of the IEC with a Luer lock system to connect it to the Hamilton glass syringe for flushing the liquid out was found to be good enough for the bench test. Nevertheless, to translate it to human application, MED-EL fine-tuned the design (Figure 34). Overall, this was a comprehensive study which confirmed the functionality without any adverse effects of the IEC, which was designed for delivering any drug of surgeon's choice.

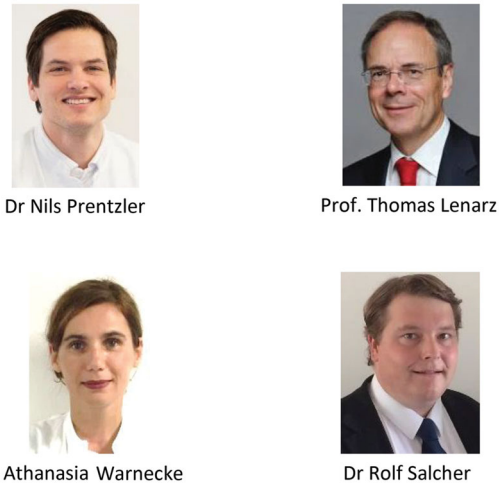

Figure 36. Clinicians from Hannover Medical University, Germany, took part in evaluating the ease of use of IEC in regular CI surgeries.

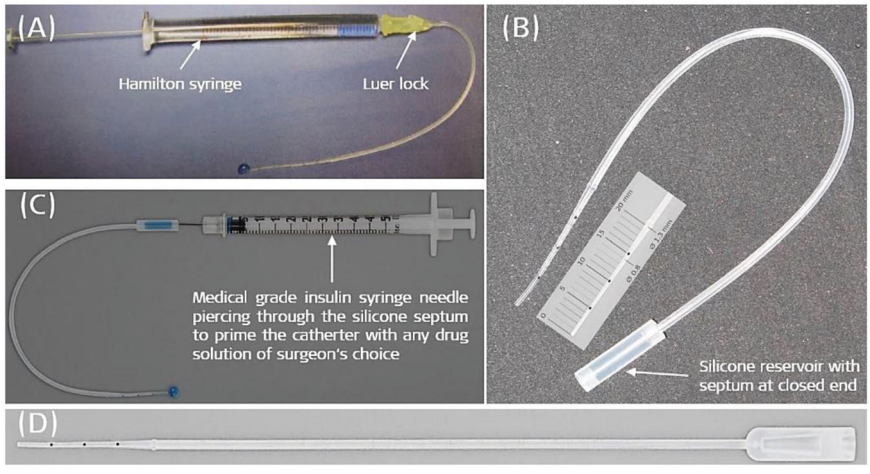

Figure 35. Version 1 of the IEC with Luer lock mechanism, connecting the Hamilton glass syringe to the backend of the catheter (A). Reconfigured catheter design with silicone reservoir with a septum at the back end of the catheter, and the reduction of intracochlear part of catheter length to 20 mm (B). Insulin syringe needle piercing and filling the reservoir with a drug solution (C). The current version of the commercially available IEC (D). Image courtesy of MED-EL.

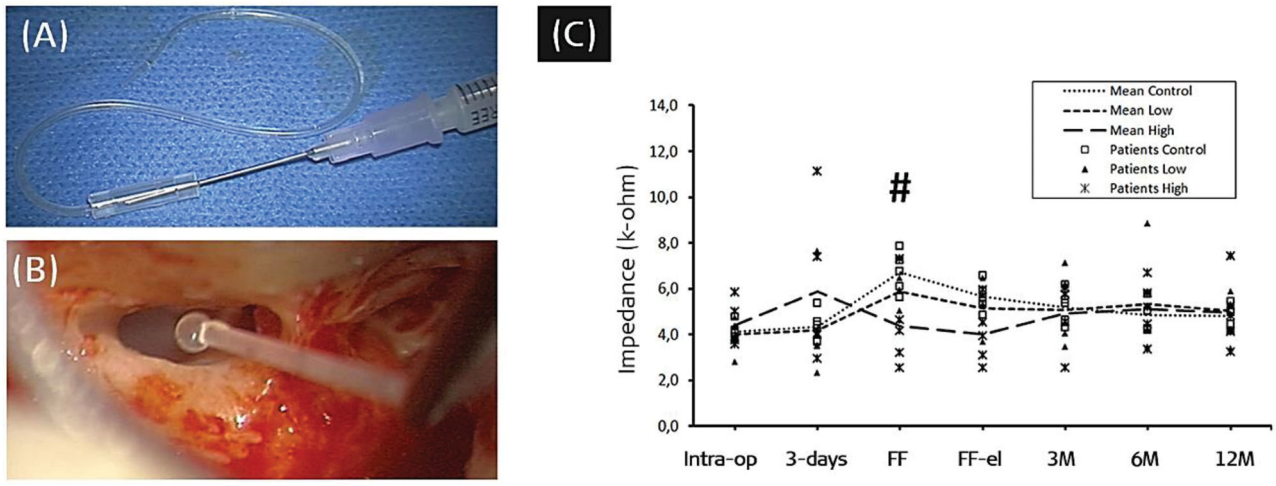

Figure 37. Insulin syringe needle pierced into the silicone reservoir (A) (Image courtesy of MED-EL). The IEC immediately after removing it from the cochlea (B) (Image courtesy of Prof. Thomas Lenarz, Hannover, Germany). Average impedance values of twelve stimulating electrode channels for the two different dosed triamcinolone compared to the control group (C). Adapted from Prenzler et al published in Frontiers in Neurology [36].

In parallel to the DEXEL project, MED-EL was striving to bring the IEC to clinical use. The main driving force behind this was the promising assessment of alternative approaches in combating the HL with new drug combinations, already extensively sought within the CI field, as well as of delivering vehicles of those.

In order to bring the IEC concept to clinical use, refinement of the IEC design was needed. Engineers from MED-EL reconfigured the IEC with silicone-made reservoir, sealed with silicone septum at the back end of the catheter (Figure 35(B)). The Hamilton syringe (Figure 35(A)) was replaced with a medical-grade insulin syringe. The insulin syringe may be loaded with any drug solution, and the IEC reservoir throughout the full length may be flushed/primed with a drug solution as shown in Figure 35(C). Figure 35(D) shows the fine-tuned version of IEC.

6.13. Application of IEC in the human inner ear before CI surgery

The reconfigured design made the IEC suitable for clinical human use. **In 2015**, the IEC was used for the first time in human CI surgery. The catheter served as a drug delivery vehicle in applying triamcinolone to the cochlea before implanting a FLEX28^{TM} electrode array [36].

The delivery was performed at Hannover Medical University by a group of clinicians, led by Prof. Lenarz and Prof. Warnecke in a regular CI surgery (Figure 36). Upon getting the Hannover Medical School's ethics committee approval, a total of ten adult CI candidates with no significant residual hearing and who chose MED-EL's SYNCHRONY implant system with FLEX28^{TM} were enrolled in the study. Five out of ten patients received an intracochlear steroid injection of 20 mg/ml (high dose) with IEC, whereas the remaining five patients acted as a control group and received no steroid injection. Figure 37(A) shows the preparation of IEC by connecting it to the insulin syringe, preloaded with triamcinolone. With RW membrane opened, the patients from the experimental group received a very slow intracochlear flushing of crystalloid suspension, which contained triamcinolone diluted with ringer solution (9:1) *via* a fully inserted IEC. The flushing was stopped when the milky suspension discharge was observed, expelling towards the RW (Figure 37(B)). At that point, the IEC was slowly taken out, and implantation of the FLEX28^{TM} electrode array followed.

Electrode impedance field telemetry (IFT) was obtained at different time points after implantation, using MED-EL's standard telemetry system to perform measurements on all twelve electrode channels in both groups. Outcomes of a previous study that included five patients treated with triamcinolone of concentration 4 mg/ml (low dose) were compared to the outcomes of this study. It was reported that no perioperative adverse events were seen in any of the patients with the surgeries performed by three experienced CI surgeons. Handling of the IEC was described as easy, with the overall procedure of IEC application not extending the surgery times significantly. The course of the impedances over time is depicted in Figure 37(C). Similar impedance values were seen in all three groups on the day of surgery. The average impedance increased on day three until the first fitting (FF). After initial activation, impedance values decreased immediately (FF-el). At the third month post-surgery, impedances had further decreased slightly and afterwards, up to the twelfth month, impedances stayed relatively stable in the control group. Patients of the low-dose triamcinolone group showed slightly lower impedances at initial activation before and after electric stimulation, compared to controls. This effect was completely missing during the third month's appointment. From thereon, the course of mean impedance values stayed very similar to the control group.

Overall, the IEC was found to be a safe and feasible device for deep intracochlear drug delivery, used just before cochlear implantation, and this way of drug administration seemed to be far more superior to methods such as

extracochlear drug delivery at the RW, as the latter may result in poor intracochlear distribution. However, the single-dose steroids' positive effect on low IFT seemed not to be long-lasting – a fact directing towards the need for a long-term elution, such as the previously described DEX-eluting electrode array.

In 2020, MED-EL CE-marked the IEC under the name INCAT (Inner Ear Catheter) to be used in patients for the intracochlear administration of substances including steroids.

In 2020 June 30th, the first-in-human intracochlear implantation of DEXEL as a part of feasibility study was performed by Prof. Lenarz and his colleagues from Hannover Medical School in Germany. These were remarkable milestones in MED-EL's journey of drug delivery in CI application.

6.14. Conclusion

The aim of modern CI treatment is to restore natural hearing, including in cases with multiple surgical interventions. However, any disturbances caused by the intracochlear introduction of a CI electrode array, even a minimal, may potentially result in some degree of inflammation. Any subsequent resulting fibrosis around the electrode array could jeopardise the benefit of CI technology in patients. While advancements in surgical techniques and implant technologies aim to minimise the related surgical array insertion trauma, other factors, such as foreign body reaction and the subsequent fibrosis formation, are beyond the control of operating surgeons and device manufacturers. Here comes the importance of corticosteroids, such as of dexamethasone with its role of minimising the electrode array-related intracochlear inflammation. From the research point of view, it is fascinating to study the best modes of delivering the corticosteroids deep inside the cochlea and their role in combination with the electric stimulation from the CI electrode array. While corticosteroids are known for their anti-inflammatory and anti-suppressive properties, they could enhance infection following surgery. Therefore, a profound understanding of CI-combined corticosteroid safety and efficacy in the long-term release was found essential. To establish how efficiently the corticosteroid could be combined with the electrode array and to establish the best methods to do so, as well as how efficiently could they diffuse into the perilymph, was a complicated process. Thanks to the collaborating clinicians and researchers from various clinics around the world, these questions were successfully answered. Their highly valued expertise and enthusiasm in performing top-notch experiments to evaluate the safety and efficacy of dexamethasone-eluting electrode arrays contributed to realising the novel ideas.

The hearing loss treatment field is moving towards the direction of reversing HL through pharmaceutical treatments and during the research phase, a universal delivery vehicle might be of researcher's interest to test various combinations of pharmaceutical agents. In such cases, MED-EL's INCAT might be a convenient tool for intracochlear administration of any drug of surgeon's choice. This chapter aimed to capture the key scientific studies which helped MED-EL to understand the safety, efficacy and pharmacokinetics of corticosteroids in combination with CIs that would minimise the intracochlear inflammation, resulted by electrode array insertion related trauma. While this journey is only halfway through, MED-EL is fully committed to complete it on a high note with further expanding its scientific collaboration with clinicians around the world, whose research interests match with MED-EL's – to restore hearing among all patients, globally. The dexamethasone-eluting CI electrode is yet another of MED-EL's projects that followed the translational science path from the laboratory setup in answering fundamental questions till reaching the first-in-human use.

Acknowledgments

The authors would gratefully like to acknowledge the key contributors to the development of the subject matter. Their contributions are outlined in this article. The authors further acknowledge Carolyn Garnham and Soeren Schilp from MED-EL for their valuable input and comments during several rounds of review meetings that contributed to the final version of this article.

Disclosure statement

This article is sponsored by MED-EL and has not undergone the regular peer-review process of Acta Oto-Laryngologica. Both the authors are affiliated with MED-EL.

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ACTA OTO-LARYNGOLOGICA
2021, VOL. 141, NO. S1, S157–S177
https://doi.org/10.1080/00016489.2021.1888506

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REVIEW ARTICLE

Special electrodes for demanding cochlear conditions

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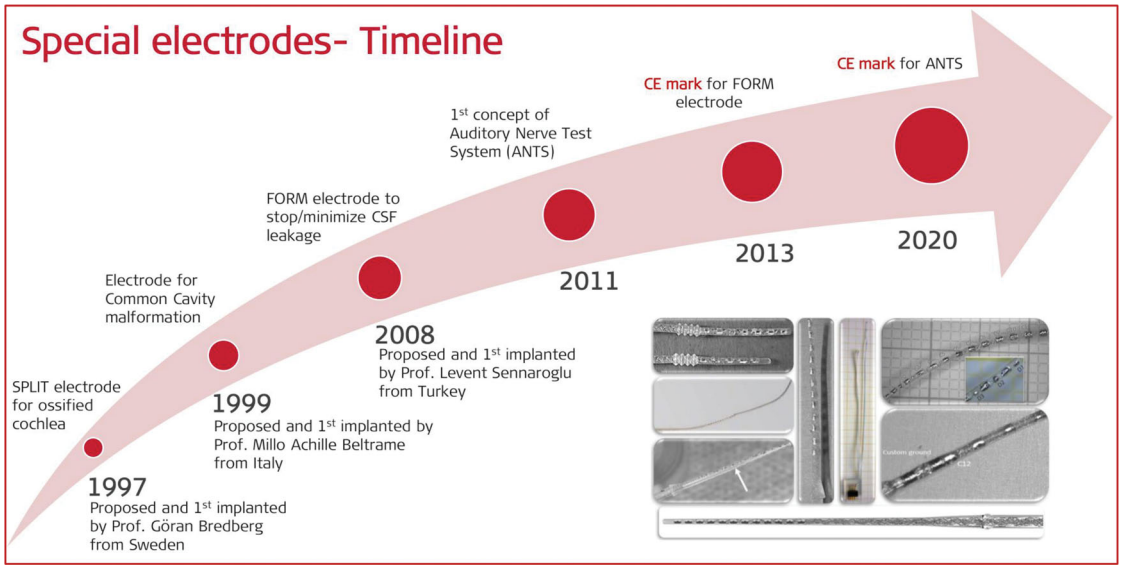
ABSTRACT

Optimal matching of an electrode array to the cochlear anatomy plays a key role in bringing the best benefit of CI technology to the users. Even within the category of normal anatomy cochlea, the size variation is huge justifying MED-EL's FLEX electrode array to be available in five different lengths. Within the malformed inner-ear category the anatomical variation is huge, convincing MED-EL to custom-design the electrode array as per the request from the operating surgeons. Thanks to G. Bredberg, M. Beltrame, L. Sennaroglu, J. Gavilan, S. Plontke, T. Lenarz, J. Müller, and few others for their valuable suggestions on unique electrode designs satisfying various needs. Translational research efforts at MED-EL in cooperation with CI surgeons from across the world led to the implantation of a variety of electrode array designs in patients with special cochlear needs.

ARTICLE HISTORY
Received 13 December 2020
Accepted 6 January 2021

KEYWORDS
Cochlear size variation; inner ear malformation; ossified cochlea; common cavity; incomplete partition; cochlear nerve deficiency; intra-labyrinthine schwannoma



7.1. Introduction

One of the success-determining factors of the cochlear implant (CI) treatment lays in electrode array design which mimics the cochlear anatomy. More precisely, this has to do with the fact that the electrode array bridges neural elements with the stimulating part of the implant that gets input from the audio processor. The neural elements then carry the electric signal to the auditory cortex, helping patients to perceive sound.

The cochlea is so unique in its size, shape, anatomy and pathology that one electrode array design or its length may hardly match with every variation. Some cochleae, for example, lack a proper neural connection between cochlea and the next level in the auditory pathway which might be hard to evaluate from the clinical radiographs, and meningitis-infected cochleae develop intracochlear fibrous tissue or even a new bone formation, posing a challenge for the electrode array insertion.

Like other medical fields, the CI field is also evolving towards personalised treatment, and since 1990, MED-EL has developed the broadest cochlear electrode portfolio on the market, tailored for every cochlear variation. Such personalised approach would not be possible without strong and valuable scientific collaboration with expert surgeons across the world, and the combination of innovative CI

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This article is a part of the compendium entitled 'Thirty years of Translational Research behind MED-EL' authored by Anandhan Dhanasingh (Director) (Anandhan.dhanasingh@medel.com) and Ingeborg Hochmair (CEO, CTO) (Ingeborg.hochmair@medel.com).

electrode designs with atraumatic surgical techniques ensures high performance with hearing restoration.

This article brings forward the science behind MED-EL's special electrode array designs and the corresponding patient benefits.

7.2. FLEX electrode array series

The very first multichannel microelectronics CI developed by Erwin and Ingeborg Hochmair (Figure 1) was implanted by Prof. Kurt Burian in Vienna on 16 December 1977 already encompassed a quite soft long electrode.

Figure 1. Dr. Ingeborg Hochmair, who developed the electrode concept with two rows of contacts on opposite sides of the silicone electrode carrier.

This electrode had two rows of contacts on opposite sides of the silicone electrode carrier. The contacts were arranged in this manner such that independent of possible rotations during electrode insertion, 1 of the 2 contacts in opposite rows would end up underneath the fibers in the osseous spiral lamina and/or the ganglion if the ones in the lamina should not be there anymore [1]. After MED-EL hired its 1st team member in 1990, the C40 implant system was developed. It had eight stimulating channels with a double line of electrode channels and was implanted from January 1994 on. The number of channels and therefore contacts were increased to twelve double-lined channels in 1996. The electrode array was named STANDARD, and it measured 31.5 mm in length, upholding its clinical existence up to this day. The STANDARD electrode array was evidenced as a significant choice for structure preservation, as recently reported by Sierra et al. [2]. As hearing and structure preservation became the objective in every CI surgery, the STANDARD electrode array was further fine-tuned by reducing its diameter at the apical end and by changing the five apical double-lined channels to single-line channel distribution, but retaining its original array length of 31.5 mm. The improved electrode version was named FLEXSOFT™ in 2004. Dr. Jolly, Dr. Jäger, Mr. Nielsen and Mr. Mayr from MED-EL were highly involved in the development of the FLEX electrode array series (Figure 2).

Until 2004, mainly patients with profound sensorineural hearing loss (SNHL) were considered as CI candidates, and therefore the 31.5 mm long electrode array was necessary to cover the entire frequency range. Since the introduction of the combined electric and acoustic stimulation (EAS™) concept for patients with partial deafness and functional low-frequency residual hearing that can be amplified with the hearing aid (HA), there was a need for a medium length, yet flexible, electrode array. To satisfy this need, MED-EL came up with the FLEX24™ electrode array, which measures 24 mm in length, and which was successfully

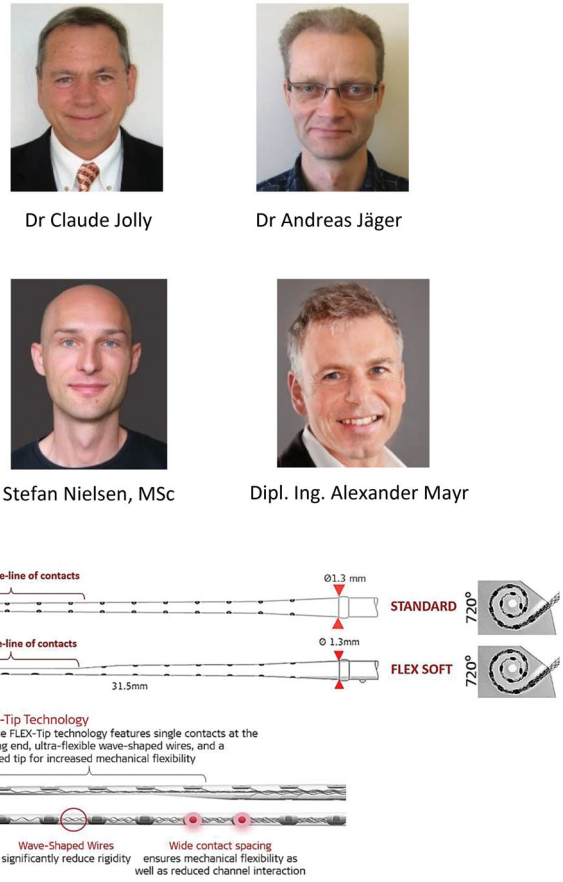


Figure 2. Engineers from MED-EL who conceived and realised the FLEXSOFT™ electrode array (top panel). STANDARD and FLEXSOFT™ electrode arrays comparison showing double line and the single line of channels, respectively, at the apical end. Wavy wires and wide contact spacing are unique features on MED-EL's electrode arrays. Image courtesy of MED-EL.

implanted in a paediatric patient with low-frequency hearing preservation in 2004. Over the years, several research studies have pointed out that the human cochlea is highly variable in its size and shape [3,4] and that prompted MED-EL to introduce other variants to FLEX series with array lengths of 20-, 26- and 28-mm (Figure 3(A)) to match even more variations of cochlear geometry. Choosing an electrode array based on cochlear size, as measured from the preoperative radiographs, and hearing level determined by auditory thresholds (Figure 3(B)), could lead to the personalised CI electrode treatment to which MED-EL is highly committed.

As shown in Figure 2, the atraumatic features of FLEX electrode arrays include wavy wires, rounded tip, wide contact spacing, and smaller cross-sectional dimensions that result in very minimal electrode array-related complications inside the cochlea, compared to electrodes from other CI brands [5,6].

7.3. Special electrodes for abnormal inner ear anatomies and complications

Normal anatomy inner ear as seen from the clinical radiographs in axial and coronal views would show the clear presence of three different cochlear turns, three semi-

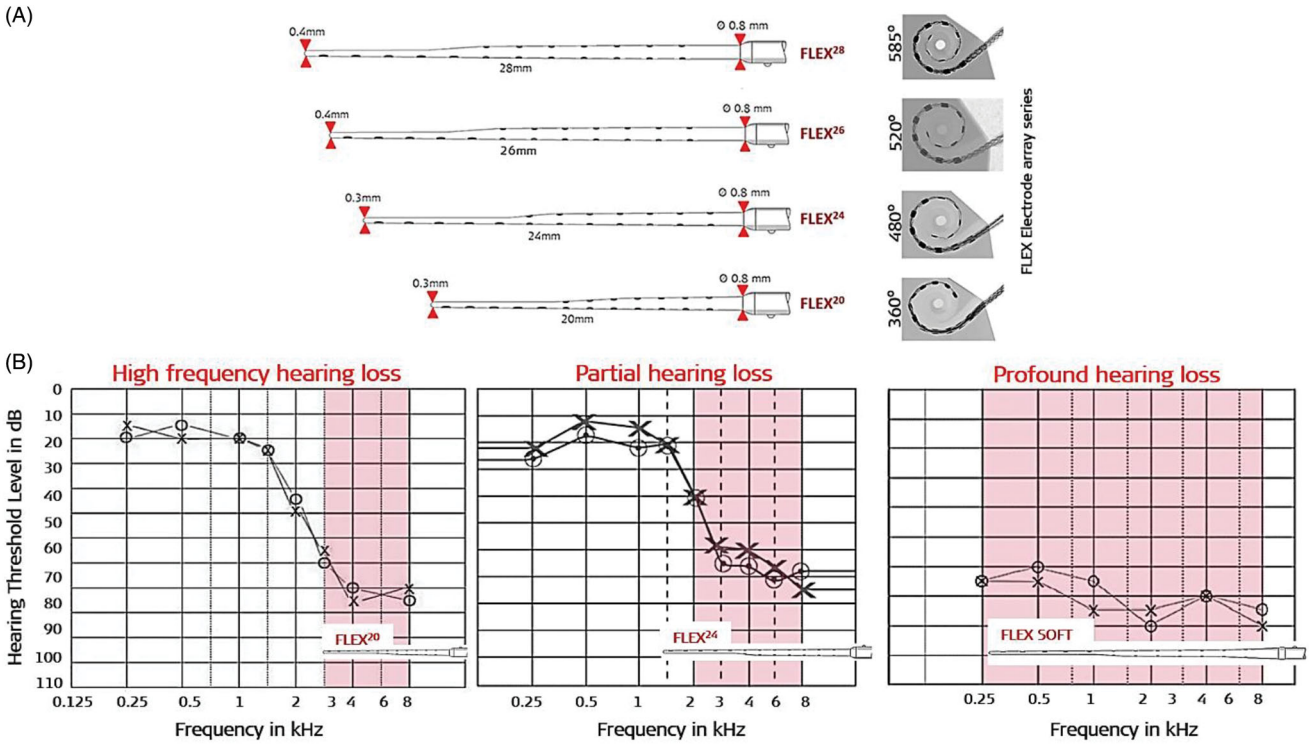


Figure 3. FLEX electrode array series with different array lengths (in addition to the previously mentioned FLEXSOFT™), offering various angular insertion depths (A). Audiograms of various hearing loss conditions and proposed electrode array lengths (B). Image courtesy of MED-EL.

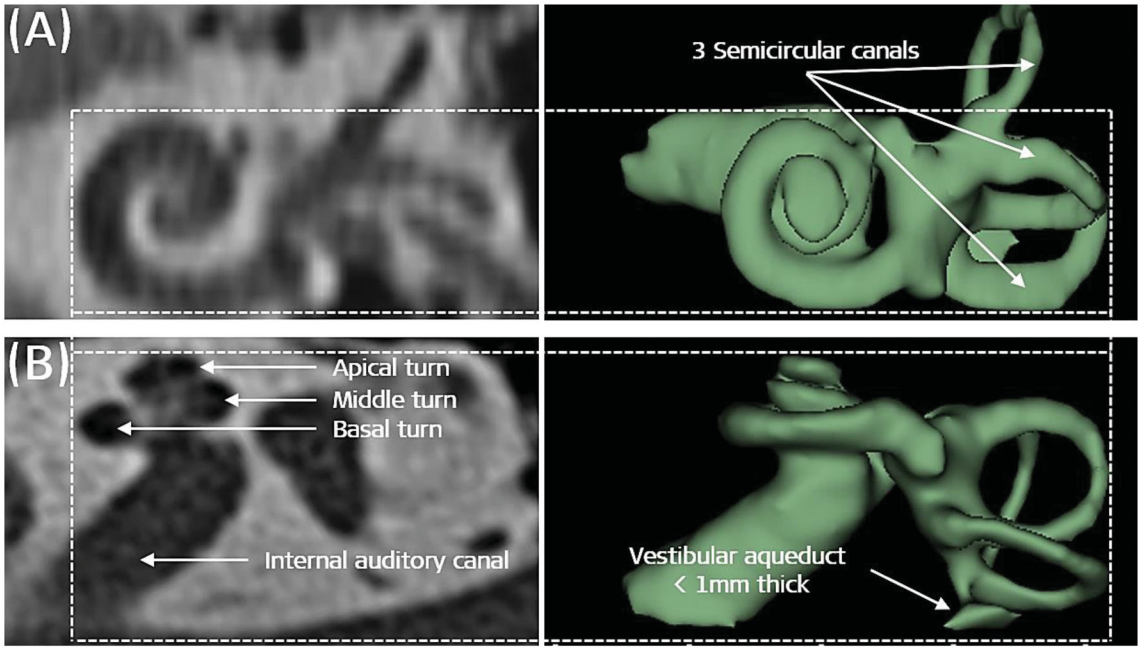


Figure 4. Normal anatomy cochlea as seen in oblique coronal view (A) and in axial view (B). Image courtesy of MED-EL.

circular canals, an internal auditory canal having a structural connection with the cochlea, and a <1 mm thick vestibular aqueduct (Figure 4(A,B)).

Deviation from the typical presence of any of the above-mentioned inner ear structures may be brought under *abnormal anatomy* medical term. Literature has evidenced the presence of abnormal inner-ear anatomies with an incidence rate varying from 15% to 30% among the SNHL population [7,8]. Well reported inner ear malformation types include incomplete partition (IP) type I, type II (Mondini's deformation), type III (also called x-linked malformation), cochlear hypoplasia (CH) and common cavity (CC), as shown in Figure 5.

Of all the malformation types, CC is considered as the most severe as the cochlear portion cannot be distinguished from the rest of the inner-ear structures, making it difficult

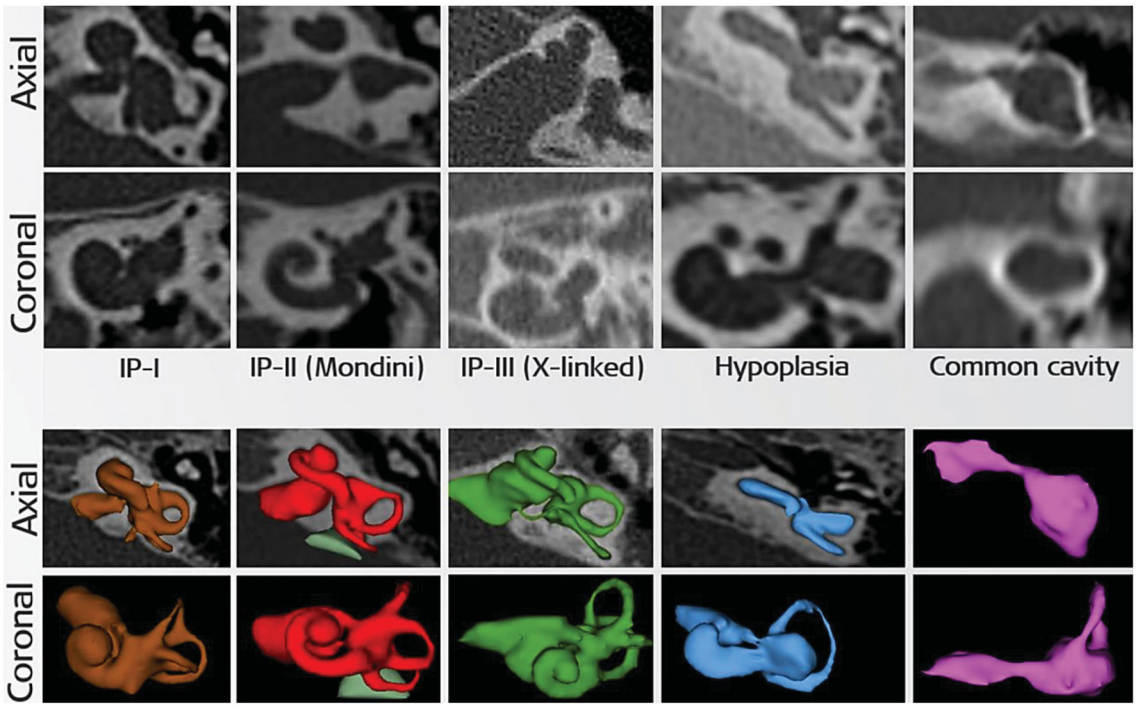


Figure 5. Inner-ear malformation types seen in 2-dimensional (2D) and 3-dimensional (3D) views. Image courtesy of MED-EL.

to insert a standard electrode safely without risk of deviating to the wide internal auditory canal (IAC) opening. CH (also known as underdeveloped cochlea) is evidenced in various sizes, shapes and degrees of severity and again, a generic electrode array design may not be a good match for each of these variations.

IP type III is characterised by the clear absence of modiolus trunk and the presence of a wide IAC opening at the cochlea itself, hindering it from a smooth electrode array insertion. Because of the wide IAC opening, a cerebrospinal fluid (CSF) gusher is expected in the majority of IP type III cases, and if untreated, then the CSF leakage could lead to the potentially fatal meningitis infection. IP type I and IP type II malformations have very minimal, from up to 50% and up to 75% of the basal turn developed, respectively, and the remaining part of the cochlea is in a cystic form. In such cases, an electrode array choice which to achieve an angular intracochlear insertion of 360° is preferable, and these two types of malformations are mostly characterised by enlarged vestibular aqueduct (EVA). EVA is associated with mild to severe endolymphatic oozing when the cochlea is opened for electrode array insertion.

An ossified cochlea is mainly a result of meningitis infection or a consequence of a temporal bone fracture – which the sooner it is detected, the easier the CI electrode array may be implanted before the outset of cochlear ossification. In extreme conditions, such as in a complete cochlear ossification, a regular electrode array insertion may not be possible. Apart from these well-reported inner ear malformation cases, there are other less frequent complications, including inadvertent facial nerve stimulation (FNS), thin cochlear nerve with ambivalent capabilities of carrying electric stimulation, intralabyrinthine cholesteatoma which requires partial dissection of the cochlear promontory to be removed, and other conditions. MED-EL has always made sure that every cochlear condition is addressed with utmost importance. In association with clinicians, MED-EL did everything possible to come up with unique/special electrode array solutions to match with every variation of the cochlear anatomy and to avoid or minimise the above-listed complications.

7.3.1. Cochlear ossification and special electrode

Ossification inside the cochlea could be a result of bacterial infection entering the cochlea through the cochlear aqueduct (CA) (Figure 6(A)) which is connected to the cochlea close to the round window (RW) membrane.

Ossification is also seen in cases that encountered trauma leading to temporal bone fracture, as shown in Figure 6(B). Whatever be the cause of ossification, the sooner it is detected, the fewer challenges it poses with inserting an electrode array. In extreme conditions, such as in a complete cochlear ossification, inserting a generically designed electrode array with a standard surgical approach may not be possible. The degree of ossification can vary from very mild at the RW membrane part only, to severe or complete cochlear ossification [9], as seen in Figure 6(C). Inserting an electrode array to each of these ossified cochlear variations requires careful planning. Ossification at the RW or at the basal turn may be

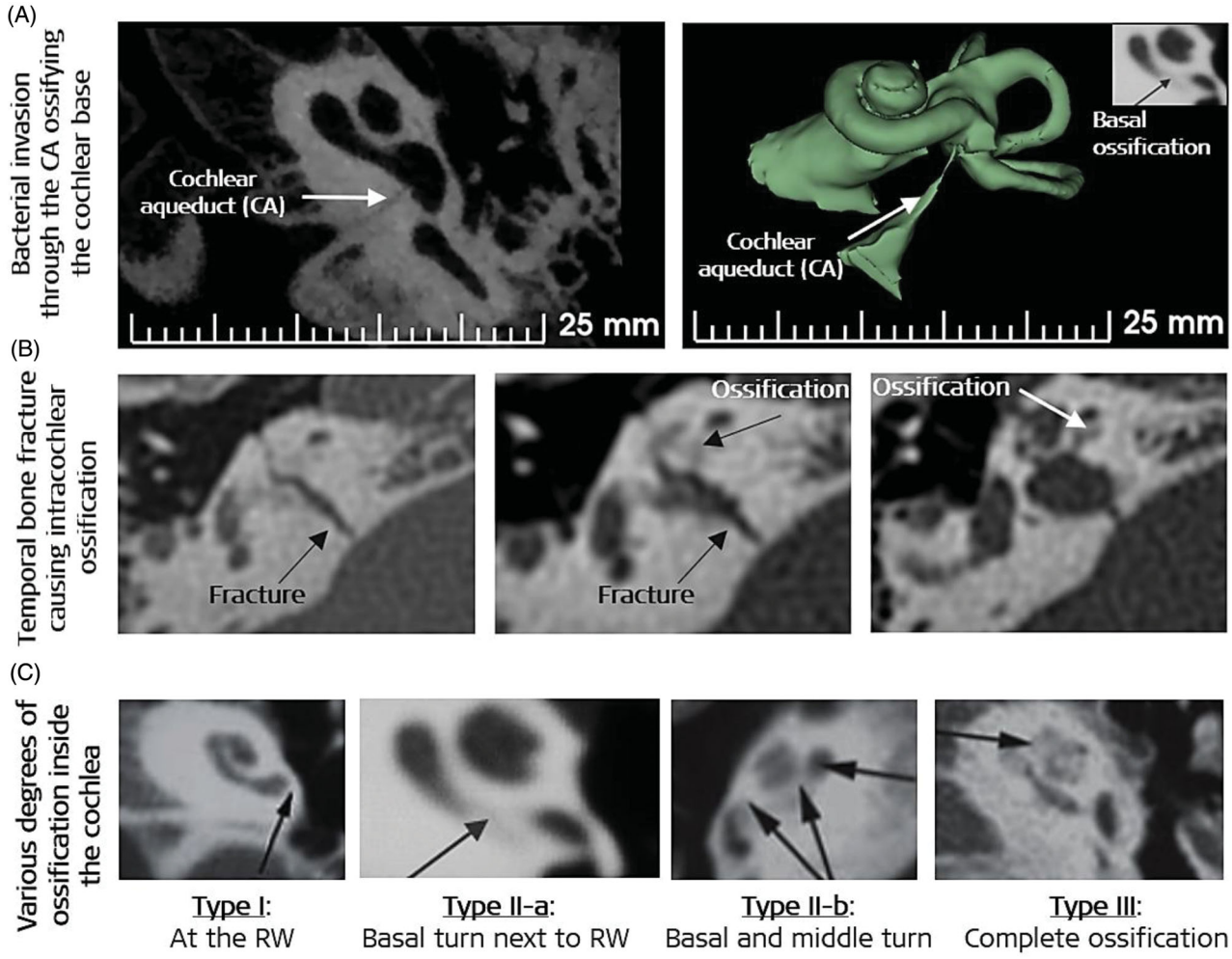
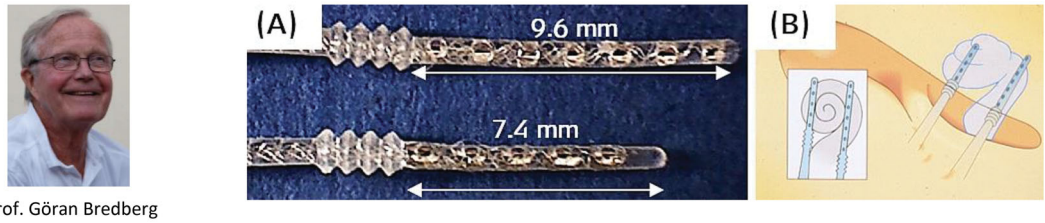


Figure 6. Cochlear aqueduct (CA) canal connecting to the basal turn of the cochlea near the RW entrance, as seen in 2D and 3D views (A). Temporal bone fracture and resulting ossification inside the cochlea (B). Different degrees of ossification (C) [9]. Image (A and B) courtesy of MED-EL., and (C) reproduced by permission of Taylor and Francis Group.



Prof. Göran Bredberg

Figure 7. Prof. Göran Bredberg, who proposed the concept of a double branch split electrode. Two-branch split electrode with more extended branch carrying seven contacts, and shorter branch having five contacts (A). Image showing two drilled accesses in upper and lower part of the basal turn, to place the two-branch split electrode arrays (B). Image courtesy of MED-EL.

removed by drilling through it, and the electrode array with the most suitable length may be implanted with minimal or no effort. However, if the ossification has reached the middle turn or the entire cochlea, then the standard surgical insertion of a regular electrode array may not be possible.

In 1997, Prof. Bredberg from Karolinska Institute in Stockholm in Sweden came up with a special electrode array concept that featured a double array with short lengths (Figure 7(A)). MED-EL has developed it and named it as SPLIT GB, where GB stands for Göran Bredberg. This electrode was designed to be used in combination with a special surgical technique whereby two openings into the ossified cochlea, corresponding to the upper and lower basal turns, are made to accommodate the two branches of the electrode, as shown in Figure 7(B).

The surgical technique is performed as follows: an inferior cochleostomy that corresponds to the scala tympani in the lower basal turn, and a superior cochleostomy just in front of the oval window (OW), corresponding to the upper basal turn. Such placement results in the coverage near the spiral ganglion and the modiolus, and the two electrode


Prof. Peter Roland


Dr Clough Shelton

Figure 8. Surgeons from two different centres in the USA who implanted the SPLIT GB electrode array in patients with fully ossified cochlea and reported the postoperative hearing results.

array branches are programmed for stimulation from base to apex. Two patients were implanted with this special electrode array in the same year, and they both reported good sound perception and pitch discrimination [10]. Over time both, the split electrode array and the surgical approach were widely accepted by clinicians across the world and were implanted in approximately two hundred patients worldwide.

In 2004 and 2005, reports on the sound and speech perception with split electrode implantation came from the University of Texas Southwestern and Utah Health Sciences Centre, USA [11,12] (Figure 8).

The Texas group evaluated eight paediatric patients, and the Utah group four patients (two adults and two paediatric) with meningitis infection-related inner-ear ossification who were implanted with SPLIT GB electrode array. After implantation, the eight patients from Texas' study showed a decrease in aided speech detection thresholds (SDT) at six months postoperatively, compared to the preoperative scores, and the Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS) scores increased from 8.0 to 23.8 on average. As for patients from the Utah study, the first patient (adult) showed an improvement with the aided Pure Tone Average (PTA) by 19 dB, and the HINT scores increased from 0% to 72%. The second patient (adult) had a 44 dB gain in aided PTA by the twelfth postoperative month. However, the latter patient showed no significant improvement in speech perception but continued to use the implant as it was helpful with engaging in oral communication. Third and fourth patients (both paediatric) had undetectable SDT before implantation, but by the twelfth month after surgery, the SDT improved to reach 15 dB and 45 dB, respectively. IT-MAIS scores increased from the preoperative value of 4 for both patients to 35 and 31, respectively. The authors of the two studies concluded that split electrode array implantation was a safe and effective treatment option in the case of complete cochlear ossification.

Recently, **in 2018**, Prof. Schmutzhard and his colleagues from the University of Innsbruck in Austria reported on the successful implantation of the SPLIT GB electrode array (Figure 9) assisted by an electromagnetic navigation system (EMNS) in a patient with a very advanced form of otosclerosis [13]. The mean aided threshold determined at seven months after surgery was 32 dB, and the patient reported improved understanding of speech at first switch-on. At the follow-up fitting session, speech intelligibility of monosyllables had improved from 0% to 50%, and from 0% to 60% at presentation levels of 65 dB and 75 dB, respectively. These pieces of evidence encourage that in extreme ossified cochlear conditions in which placing the standard electrode is not possible, the SPLIT GB electrode may be implanted confidently.

The specially designed SPLIT GB electrode array was made and remains available as a custom-made device (CMD) under the council directive 93/42/European Economic Community (EEC) [14]. CMD relates to any device specifically made per a duly qualified medical practitioner's written prescription which gives, under his or her responsibility, specific design characteristics and is intended for the sole use of a specific patient. Under CMD, even if the device is not approved by a notified body, such as by FDA or TÜV, it is still possible to implant the device in patients, provided that the device is qualified by the appropriate laboratory tests by the device manufacturers.

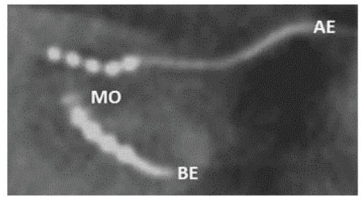
7.3.2. Common cavity-type malformation and special electrode

The CC malformation was first described by Edward Cock [15] in 1838 as a disruption in the differentiation of inner ear structures during the fourth and fifth week of gestation [16]. Figure 10(A,B) show samples of normal cochlear anatomy, and of the classic CC, respectively. The CC is seen without complex intracochlear neural structures, and instead, it is only filled with cochlear fluid. Neural elements are likely laying in the walls of the cavity, and therefore an ideal electrode array placement would be along the cavity


Prof. Joachim Schmutzhard


Prof. Herbert Riechelmann


Prof. Kurt Stephan



Postoperative x-ray image of the SPLIT electrode array in a completely ossified cochlea

Figure 9. Clinicians from Innsbruck clinic, Austria, implanted the SPLIT GB electrode array in their patient with advanced otosclerosis, and a postoperative image is showing the proper placement of the electrode. Postoperative x-ray image showing the placement of the double branch electrode [13]. AE: apical electrode, MO: modiolus, BE: basal electrode. Reproduced by permission of Wolters Kluwer Health, Inc.

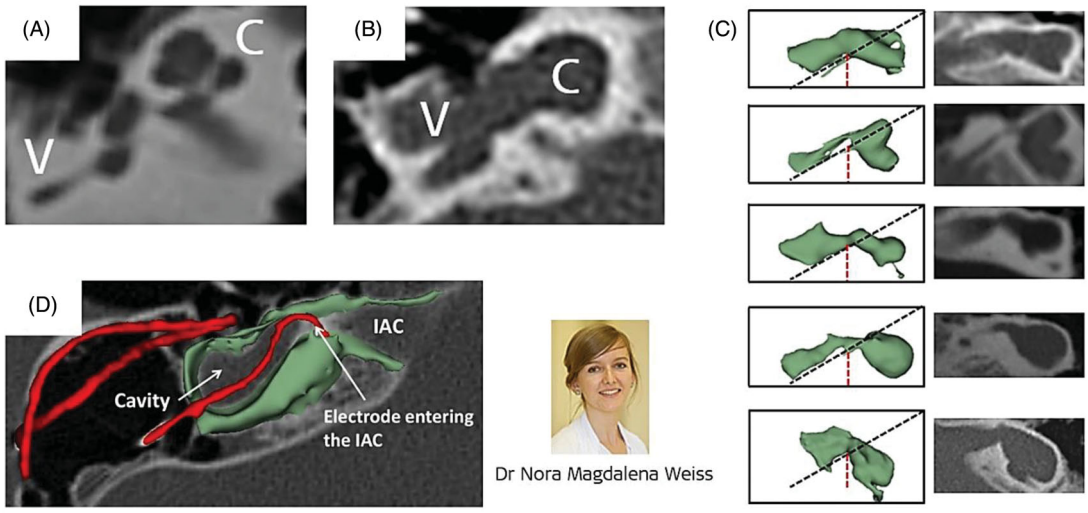


Figure 10. Cochlea with normal anatomy as seen in axial view (A); classic CC malformation showing both, cochlea and vestibule fused to form a single cavity (B); absence of cochlear part and presence of vestibular cavity (C); incorrect insertion of an electrode array which reached the IAC (D). Image courtesy of MED-EL. Image of Dr. Nora Magdalena Weiss from University of Rostock, Germany, who studied the difference between classic CC and cavity that represents vestibular portion with the clear absence of cochlear portion.

wall. Cochlear aplasia (absence of cochlea) with a dilated vestibular cavity is the result of developmental arrest in the third week of gestation [15]. This type of vestibular cavity with an evident absence of the cochlear portion is often mistakenly considered as CC, as shown in Figure 10(C) [17]. Placing a straight electrode array inside a classic CC or in a dilated vestibular cavity with cochlear aplasia carries the risk of electrode entering the wide IAC, as shown in Figure 10(D).

In 1999, Prof. Beltrame from Rovereto in Italy came up with a special electrode design that would ensure no part of the electrode would enter the IAC, and it was Dr. Jäger from MED-EL who realised the concept into a functional device. Figure 11(A) captures the special electrode array, which includes a silicone dummy extension at the tip to ensure the stimulating channels lining along the cavity wall where the neural elements are present (Figure 11(B)). Bench experiments showed the proper placement of the electrode array inside the plastic CC model (Figure 11(C)). This special electrode was first implanted in the year 1999 in a two-year-old girl who was suffering from congenital profound SNHL in her right ear [18]. Instead of using a regular posterior tympanotomy approach to reach the inner ear, Prof. Beltrame reached the cavity through a trans-mastoid double

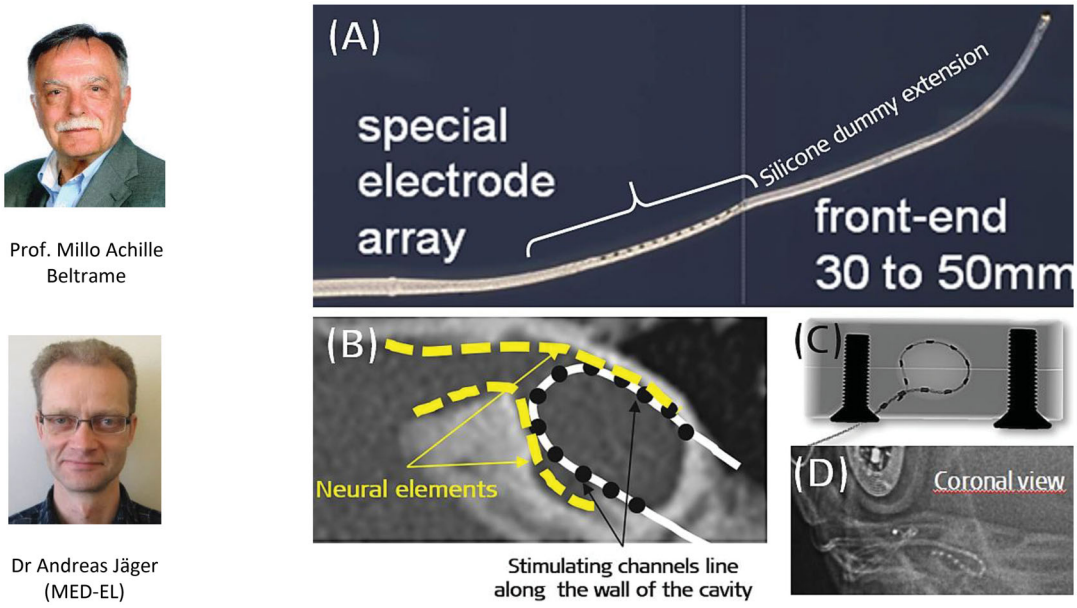


Figure 11. Special electrode array with silicone dummy extension conceptualised by Prof. Beltrame and realised by Dr. Andreas Jäger (A). Neural elements are believed to be present along the cavity wall, as shown by the yellow dotted line (B). X-ray image of the special electrode in a plastic cavity model (C); postoperative image showing special electrode inside the CC type cochlea (D). Image (D) courtesy of Dr. Mary Shanks, Kilmarnock.

posterior labyrinthotomy approach. At this point, the silicone dummy part was introduced into the superior opening until it was seen through the inferior opening. With the help of a hook, the silicone dummy end was pulled out of the inferior opening and followed by gentle pushing of the active part of the electrode array through the superior opening until the electrode array aligned against the cavity wall, as shown in Figure 11(D). Small pieces of connective tissue were then packed around the electrode array to close the two labyrinthotomy sites. Two months after the device activation, the child was responding to environmental sounds and showed good results in the detection and identification of sound. Over time, this special electrode design and the surgical approach were well accepted by clinicians across the world.

In 2013, a multicentric study from Italy, Australia, Spain, UK, Syria and the USA reported on long term speech perception and audiological performance of children with CC type cochleae implanted with MED-EL's special electrode array [19] (Figure 12).

Figure 12. Clinicians from [1]Sydney Medical School, Australia, [2]Hospital Nino Jesus, Spain, [3]Medical College Damascus University, Syria, [4]Beth Israel Medical Center, USA, [5]University of Southampton, UK, [6]Southmead Hospital, UK, [7]Hospital San Cecilio, Spain, [8]Crosshouse Hospital, UK, [9]Krankenhaus Martha-Maria München, Germany, [10]Hospital Son Espases, Spain, implanted the CC special electrode to their patients and reported on patients' speech and audiological performance.

Altogether nineteen patients with CC malformation type, accompanied by CSF gusher, were included in the

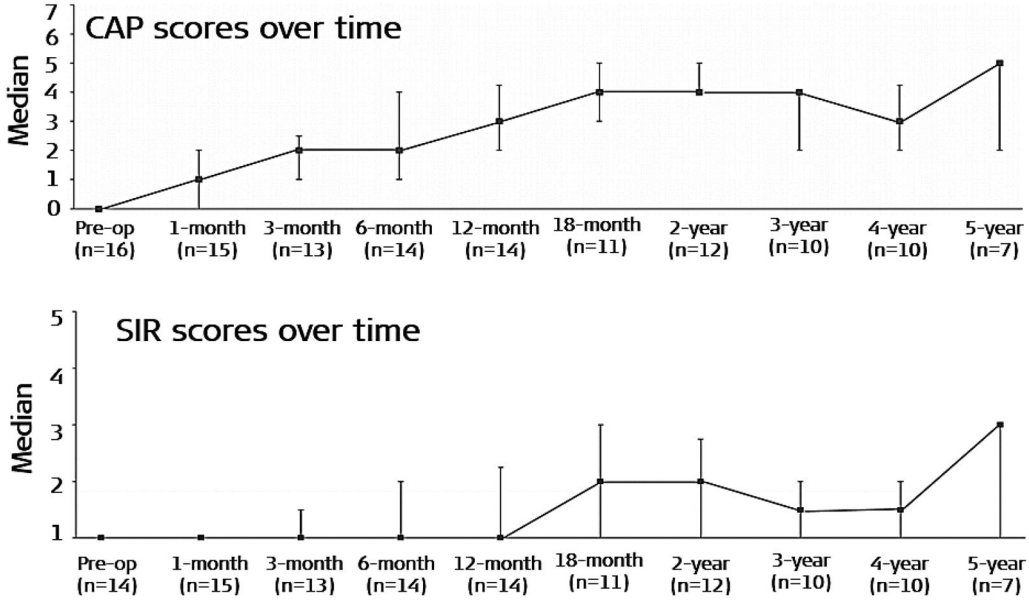


Figure 13. Long term audiological and speech performance as evaluated through categories of auditory performance (CAP) and speech intelligibility rating (SIR) scores of patients implanted with CC special electrode from various clinics across the continents [19]. Statistical test: Friedman test to check for a significant difference over the test period. Reproduced with permission of Elsevier Ireland Ltd.

multicentric study in eleven different centres across the world. All patients were implanted with MED-EL's special electrode. Categories of Auditory Performance (CAP) and Speech Intelligibility Rating (SIR) were performed to evaluate the listening skills rated from 0 (worst) to 7 (best) and speech intelligibility rated from 1 (worst) to 5 (best) at various time intervals, starting at one month before the surgery, at the first fitting, at 1, 3, 6, 12 and 18 months, and at 2, 3, 4 and 5 years after the first fitting. The auditory perception results showed a chronological improvement over time, and CAP was found to be strongly associated with the SIR only after six months following the device activation (Figure 13). Two years after the implantation, median scores of CAP with 4/7 and of SIR with 2/5 were observed. The authors concluded that such special CI is a safe and effective treatment option in children with CC, and the majority of subjects showed significant benefits with audiological development after implantation.

Under the CMD council directive [14], MED-EL delivered the CC special electrodes that were implanted so far about two hundred children until today (2021). The main risk associated with the cochlear implantation in general in CC malformation condition is the chance of the electrode entering the IAC, and this special electrode design aims to avoid that risk while ensuring the electrode array placement as close as possible to the cavity wall where the neural elements are present [20].

7.3.3. Cochlear hypoplasia and short electrode array

Cochlear hypoplasia (CH) is defined as an underdeveloped cochlea, in which the cochlea and vestibule can be differentiated from each other but where cochlear size is smaller than the average. CH has the developmental arrest occurrence in the sixth week of gestation [15]. The size of the cochlear portion varies a lot from as tiny as a small bud (Figure 14(A)) to as big as two turns of the cochlea (Figure 14(F)).

The best-suited electrode array for such underdeveloped cochleae must be chosen based on the available cochlear lumen length. For samples shown in Figure 14(A,B), a CI might not be the choice of treatment as the cochlear size is too small for a CI electrode array placement and in such cases, an ABI may be a more suitable treatment option. MED-EL has developed a short electrode array with an active array length of 12.1 mm and named it COMPRESSED, as twelve stimulating channels were compressed within such a short length (Figure 15).

A compressed electrode with an array length of 15 mm may be chosen for the samples shown in Figure 14(C,D), whereas an array length of 20–24 mm may be chosen for samples shown in Figure 14(E,F). Figure 16 shows a 20 mm long electrode array covering 360° of angular insertion depth in a hypoplastic cochlea. Cochlear hypoplasia could be associated with the absence of vestibular portion and sometimes with hypoplastic IAC, which requires detailed

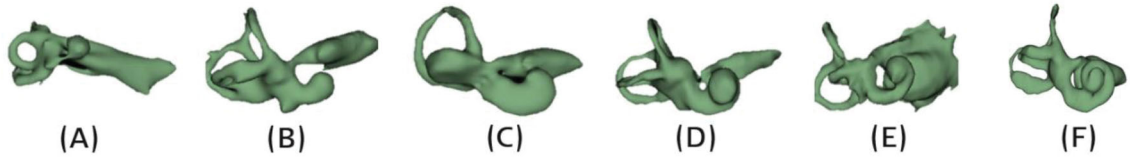


Figure 14. CH with different degrees of severity, starting from tiny bud-like appearance (A) to little development of the cochlea (B), to half of the basal turn (C, D), and one full turn of the cochlea (E, F). Image courtesy of MED-EL.

Figure 15. COMPRESSED electrode with active stimulation length of 12.1 mm, which includes all twelve channels. Image courtesy of MED-EL.

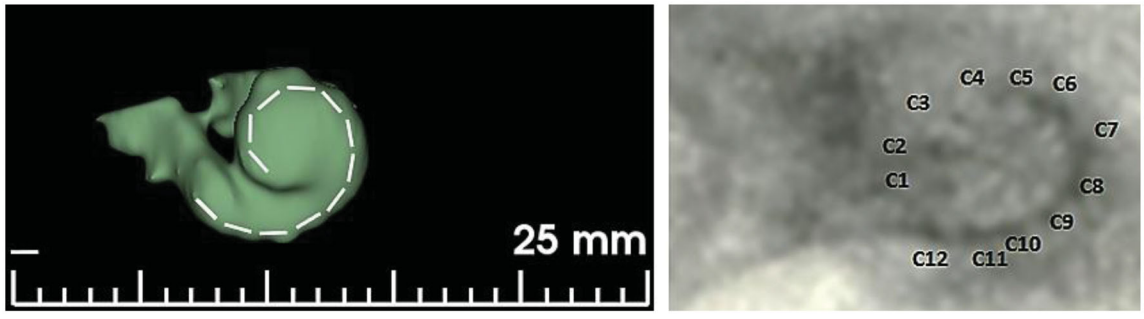


Figure 16. Hypoplastic cochlea with one full turn developed and 20 mm long electrode array covering 360° of angular insertion depth (right-hand side image: courtesy of Dr. Classen, Bloemfontein, South Africa).

analysis, based on the intraoperative images. As far as the CI electrode array length is concerned, choosing a length based on the cochlear size would ensure its optimal placement.

7.3.4. Incomplete partition type malformations and special electrode array

Incomplete partition (IP) type malformation has three subtypes, namely type I, type II and type III. IP type I is also known as cystic cochleovestibular malformation, where the cochlea has no bony modiolus, resulting in an empty cystic cochlea and is accompanied by a dilated cystic vestibule with the developmental arrest at the fifth week of gestation [16]. IP type II has the developmental arrest at the seventh week of gestation [16], and as a result, the cochlea and the vestibular portion are entirely separated. In such cases, the cochlea consists of 1.5 turns, although the apical and the middle turns are undifferentiated in the form of a cyst. The vestibular aqueduct is mostly seen enlarged (Figure 17) in both, IP type I and type II, which could lead to endolymphatic oozing when the cochlea is opened for electrode insertion. CSF gusher is often accompanied by IP type III malformation as it has a wide IAC that opens directly to the cochlear basal turn. Leakage of cochlear fluid following the CI surgery could lead to infections, and the surgical technique of tightly packing the cochlear opening with connective tissue is one possible way to address this issue.

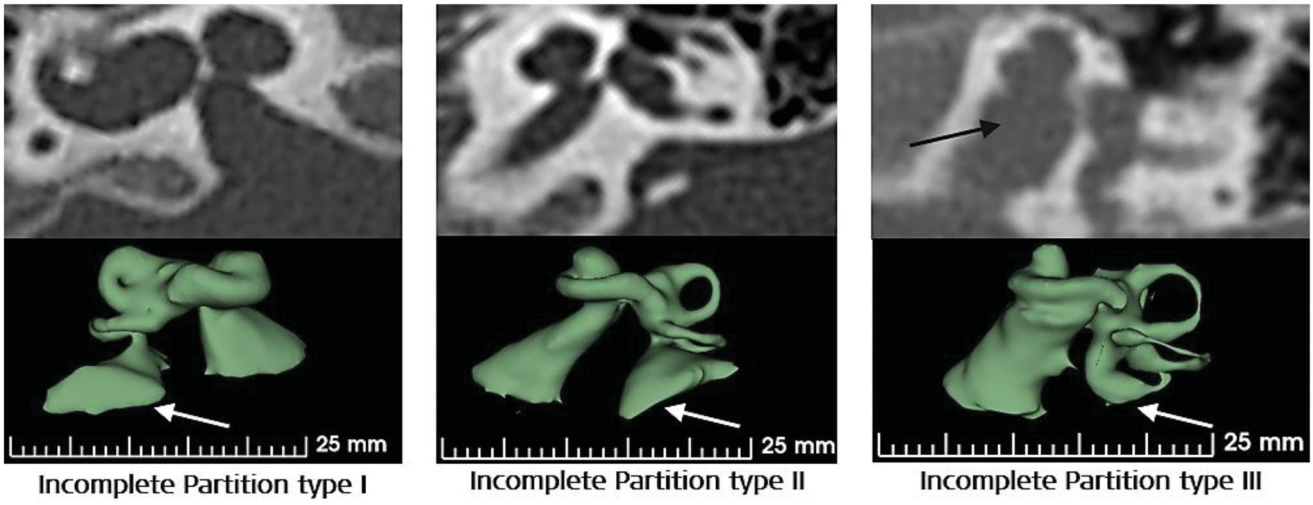


Figure 17. Three different types of incomplete partition type malformation showing the presence of enlarged vestibular aqueduct, as pointed by the white arrow mark. Image courtesy of MED-EL.

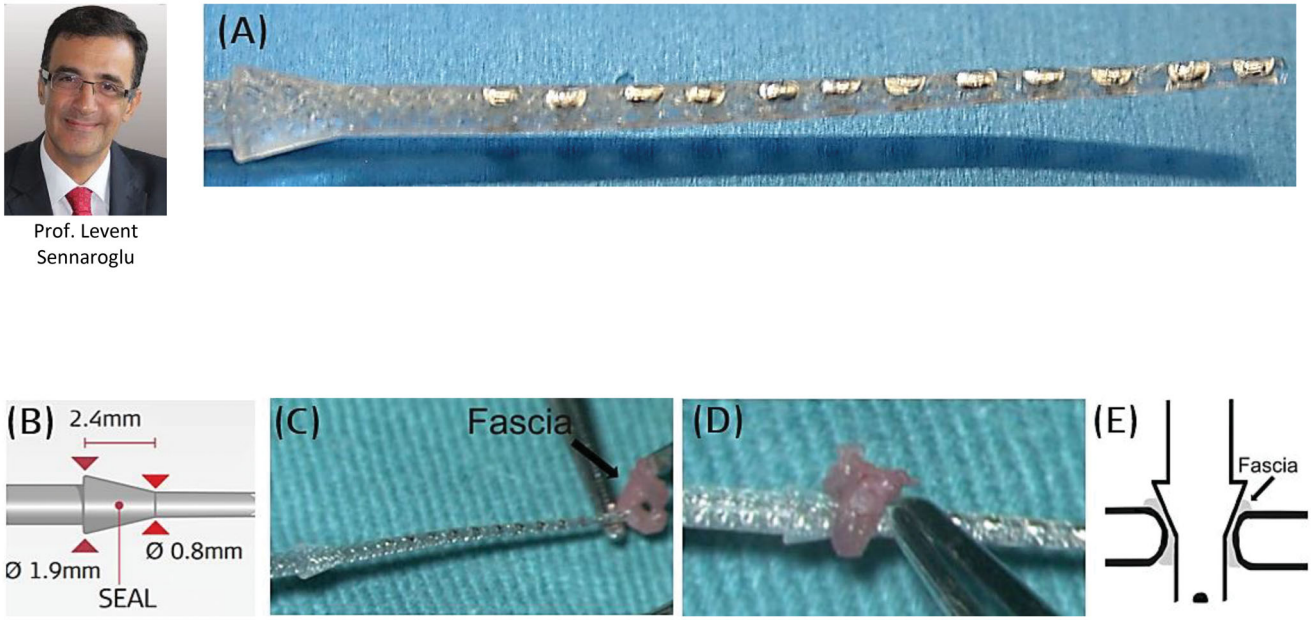


Figure 18. FORM electrode array with cork type insertion stopper (A). CORK stopper dimensions (B) (Image courtesy of MED-EL). Ring of fascia loaded on to the electrode array (C, D). Image showing the CORK type stopper sealing the cochlear opening (E) [21]. Reproduced by permission of Elsevier Ireland Ltd.

In 2008, Prof. Sennaroglu from the Hacettepe University in Ankara in Turkey came up with the concept of a cork-like insertion stopper type electrode that would provide the additional cochlear sealing capability to the electrode array (Figure 18(A)).

The CORK stopper has a diameter of 1.9 mm at the thickest seal part and 0.8 mm at the thinnest part with a length of 2.4 mm (Figure 18(B)). For these CORK dimensions to seal the cochlear opening effectively, a ring of muscle tissue around the electrode array (Figure 18(C,D)) is recommended and the size of the cochleostomy should not be larger than 1.5 mm in diameter (Figure 18(E)). MED-EL took the concept, developed the prototype and named the electrode array as CORK. Prof. Sennaroglu and his colleagues implanted the CORK electrode in fifty patients with various inner-ear malformations including IP type I, IP type II, IP type III, EVA, CH and cochlear base defect, between the years 2008–13 [21]. If CSF gusher is observed during the surgery and if the CORK stopper has sealed the cochlea effectively, then no postoperative rhinorrhea is expected. Rhinorrhea is a condition in which the CSF leakage from the inner ear passes through the eustachian tube and escapes through the nasal passages. In the named study, the authors reported CSF gusher in all three IP type malformations during the surgery, and the cochlea was sealed effectively with the CORK type stopper in combination with fascia ring around the electrode array, and only one case experienced rhinorrhea (Table 1).

Table 1. Patient distribution based on inner ear malformation types, gusher and postoperative rhinorrhea [21].

	CORK electrode		
Malformation types	Gusher (+)	Gusher (−)	Rhinorrhea
IP-I	5	6	1
IP-II	12	10	
IP-III	3		
EVA	1		
CH	1	6	
CBD	2		

IP-I: incomplete partition type I; IP-II: incomplete partition type II; IP-III: incomplete partition type III; EVA: enlarged vestibular aqueduct; CH: cochlear hypoplasia; CBD: cochlear base defect.

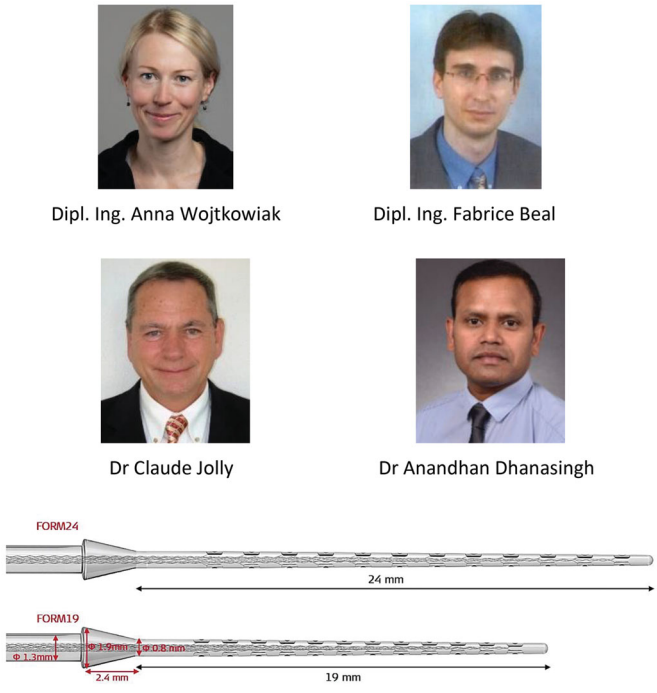


Figure 19. Engineers from MED-EL who were involved in the development of FORM electrode series; FORM electrodes seen in two different array lengths (FORM24, FORM19). Image courtesy of MED-EL.

In 2013, MED-EL received CE mark for its CORK electrode, making it accessible for clinical use within the EU and countries that accept the CE mark. The CORK electrode was officially named FORM electrode and was made available in 19 mm (as FORM19™) and 24 mm (as FORM24™) array length variations. Within MED-EL, several engineers, as shown in Figure 19, were involved in the FORM series development project, in which intensive laboratory tests were performed to understand the sealing properties of the cork-shaped stopper with preventing fluid leakage in phantom cochlear models. The FORM electrode arrays in combination with an effective surgical approach minimise postoperative complications associated with intraoperative CSF gusher or endolymphatic oozing.

7.4 Intracochlear test electrode to monitor the auditory nerve functionality

The auditory nerve (AN) must be intact for hearing perception with a CI. In some instances, such as in cases of tumour removal from the IAC or in cases with severely malformed cochleae (e.g. hypoplastic cochlear type or hypoplastic IAC, as shown in Figure 20), it may be necessary to assess the viability of the AN to predict the outcome of cochlear implantation. Intracochlear electric stimulation with a CI electrode and recording electrically evoked auditory brainstem responses (eABR) via surface electrodes is a

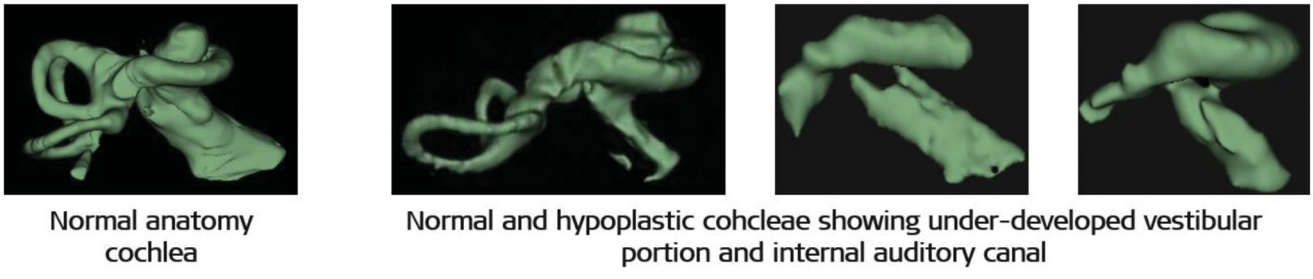


Figure 20. 3D images of normal-anatomy and hypoplastic cochleae, showing narrow internal auditory canal. Image courtesy of MED-EL.

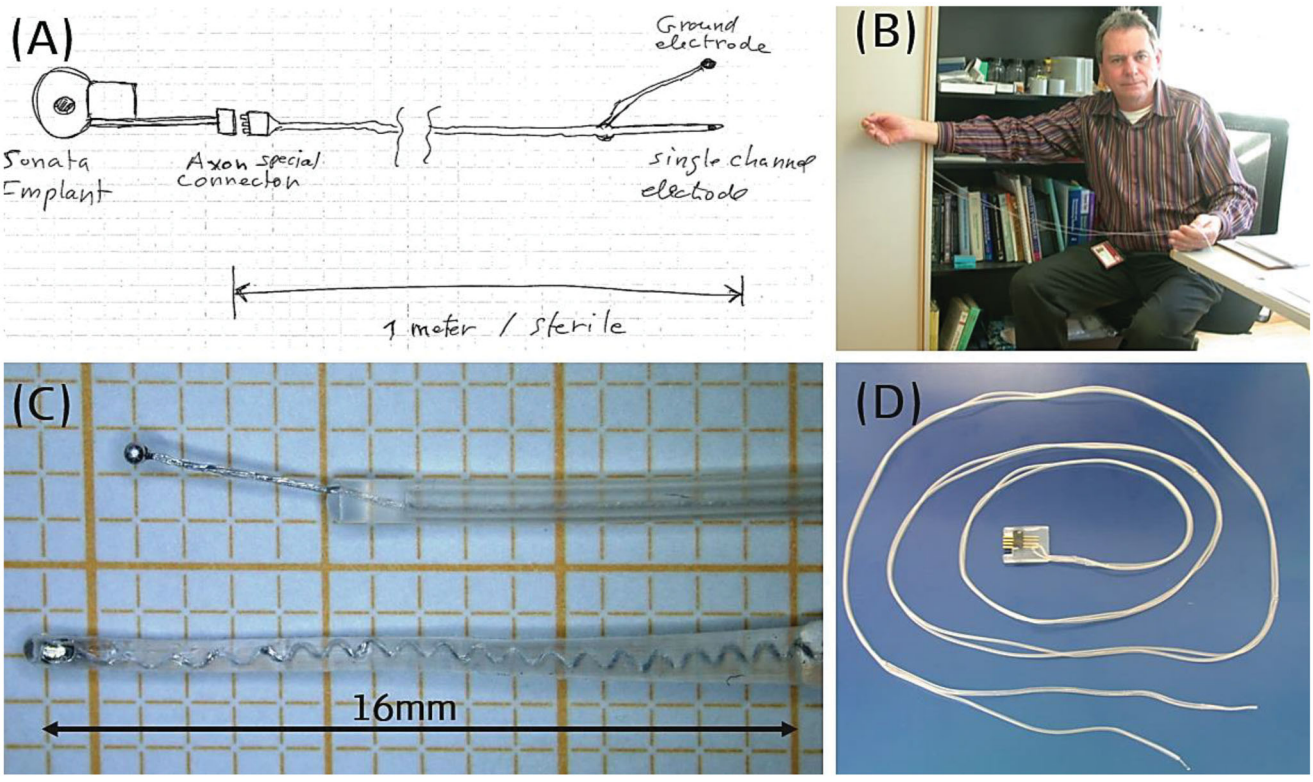


Figure 21. The concept of intracochlear test electrode from paper (A) to prototype (C, D), Dr. Jolly (MED-EL) holding the prototype (B). Image courtesy of MED-EL.

well-established method for determining the integrity of the auditory pathways [22]. While the electric stimulation of the RW membrane during surgery gives a reliable estimation of the AN status, in many cases the responses may not be detected – either due to artefacts or due to higher charge levels necessary to elicit a response, but which are not possible to apply as they would exceed the safety limit [23].

For CI surgeons, a successful eABR recording straight after the electrode insertion translates to the hearing sense of the operated patient. To establish the AN integrity/functionality, an actual CI would need to be used in such challenging cases. In accommodating this with bearing the implant costs in mind, Dr. Polak and Dr. Rodrigo Dacosta from MED-EL came up with an intraoperative single-use intracochlear test electrode which may be delicately placed inside the cochlea for electric stimulation to check the integrity/functionality of AN by recording the eABR responses.

In 2011, MED-EL had its first concept (Figure 21(A)) and a working prototype of the intracochlear test electrode array which measured 16 mm in length and carried one stimulating contact channel at its tip (Figures 21(B,C)).

Since the electric stimulation must come from an external stimulation device to the test electrode and bringing it close to the patient with their mastoid surgically opened was thought to be unsafe at the time – therefore the excess electrode lead was made to a length of one metre long with a connector at the end (Figure 21(D)). With numerous feedbacks from the clinicians and design iterations, the final configuration featured an excess electrode lead length shortening to 10 cm, and the number of stimulating channels tripling along 18 mm array length (Figure 22).

In 2017, there were two studies, one from Spain led by Prof. Lassaletta along with Prof. Gavilán [24] and the other from Turkey led by Prof. Sennaroglu [25], that aimed to evaluate the possibilities of electrically stimulating the cochlea through the test electrode and recording eABR responses to check the AN functionality (Figure 23). The study conducted in Turkey included eleven patients in total (normal anatomy: 4; incomplete partition: 4; cochlear hypoplasia: 2; common cavity: 1), and the study conducted in Spain included ten patients with normal anatomy who were all candidates for CI due to profound HL >100 dB.

Figure 22. Final version of human intracochlear test electrode. Image courtesy of MED-EL.

The cochlea was exposed through a regular CI surgical approach, and the test electrode was inserted with a soft surgical technique. The test electrode connector was coupled with MED-EL's MAX Programming Interface (MAX BOX) to generate a biphasic pulse, controlled through MED-EL's CI system fitting software MAESTRO. The eABR recording needle electrodes were placed in the appropriate anatomical location, and the lead was connected to Nicolet™ EDX Synergy Recording System (Natus; Middleton, Wisconsin, USA), triggered by the MAX BOX (Figure 24).

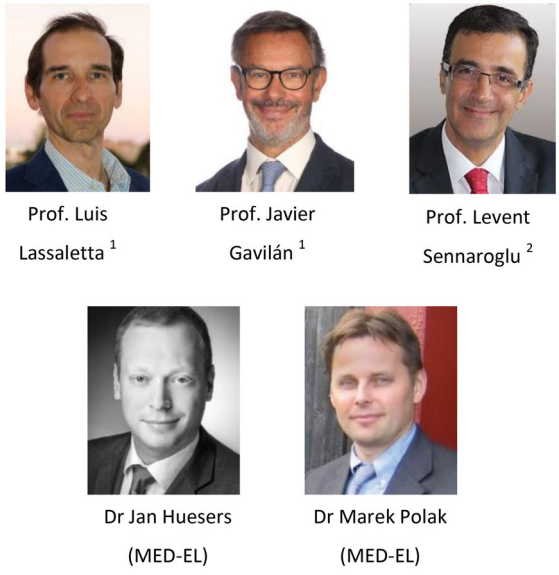


Figure 23. Clinicians from [1]La Paz University Hospital, Spain, [2]Hacettepe University, Turkey, and engineers from MED-EL, used the test electrode in patients with a questionable cochlear nerve functionality for electric stimulation, followed by eABR recordings.

With the above test setup, eABR measurements were performed by stimulating the apical and middle channels against the external reference electrode. After the test electrode evaluation, all patients with successful eABR responses – interpreted as an indication of functional AN – received a CI, and patients without successful eABR responses – interpreted as an indication of dysfunctional AN – received an ABI. Wave V appearance in eABR response upon electric stimulation in the cochlea is seen as an indicator of healthy and normally functioning AN. In patients with normal cochlear anatomy, electric stimulation from the test electrode at various current stimulation levels showed the presence of wave V in eABR responses in both studies (Figures 25(A,C)). In patients with such responses, a regular CI was implanted, and electric stimulation from the CI was applied at different current levels which confirmed the wave V presence – the indicator of AN functionality (Figures 25(B,D)). The study performed in Turkey involved one patient with AN aplasia in whom the test electrode results showed no elicitation of wave V in the eABR responses when stimulated by the test electrode with any current levels (Figure 25(E)), and therefore the patient was implanted with ABI. With ABI stimulation, wave V started to appear in the eABR response with around 3.5 ms latency (Figure 25(F)). These two studies demonstrated the safety and benefits of employing the intracochlear test electrode in ambiguous cases with deciding between CI and ABI.

In January 2020, the intracochlear test electrode was CE marked under the product name ANTS (Auditory Nerve Test System) for use in the European Union (EU) and countries that accept CE marking. At MED-EL, it was Dr. Miri who assumed the project leader role for developing the ANTS from the CMD status to an official product until its CE marking, and the project was supported by Dipl. Ing.

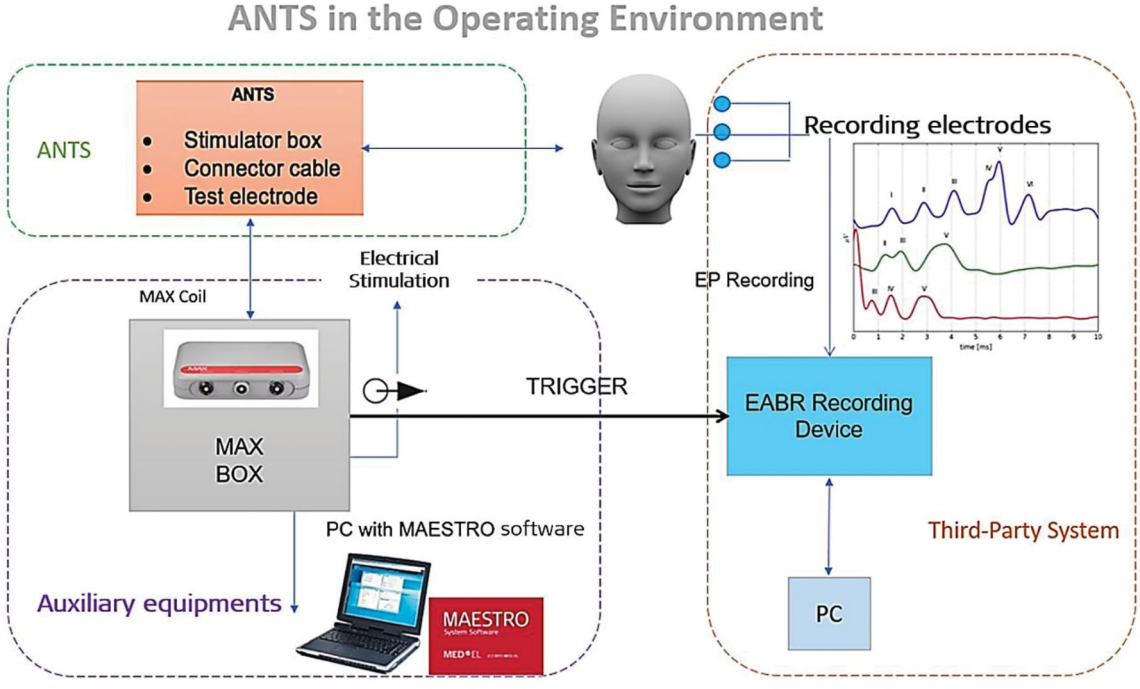


Figure 24. Test set-up in applying the test electrode and in recording the eABR responses. Image courtesy of MED-EL.

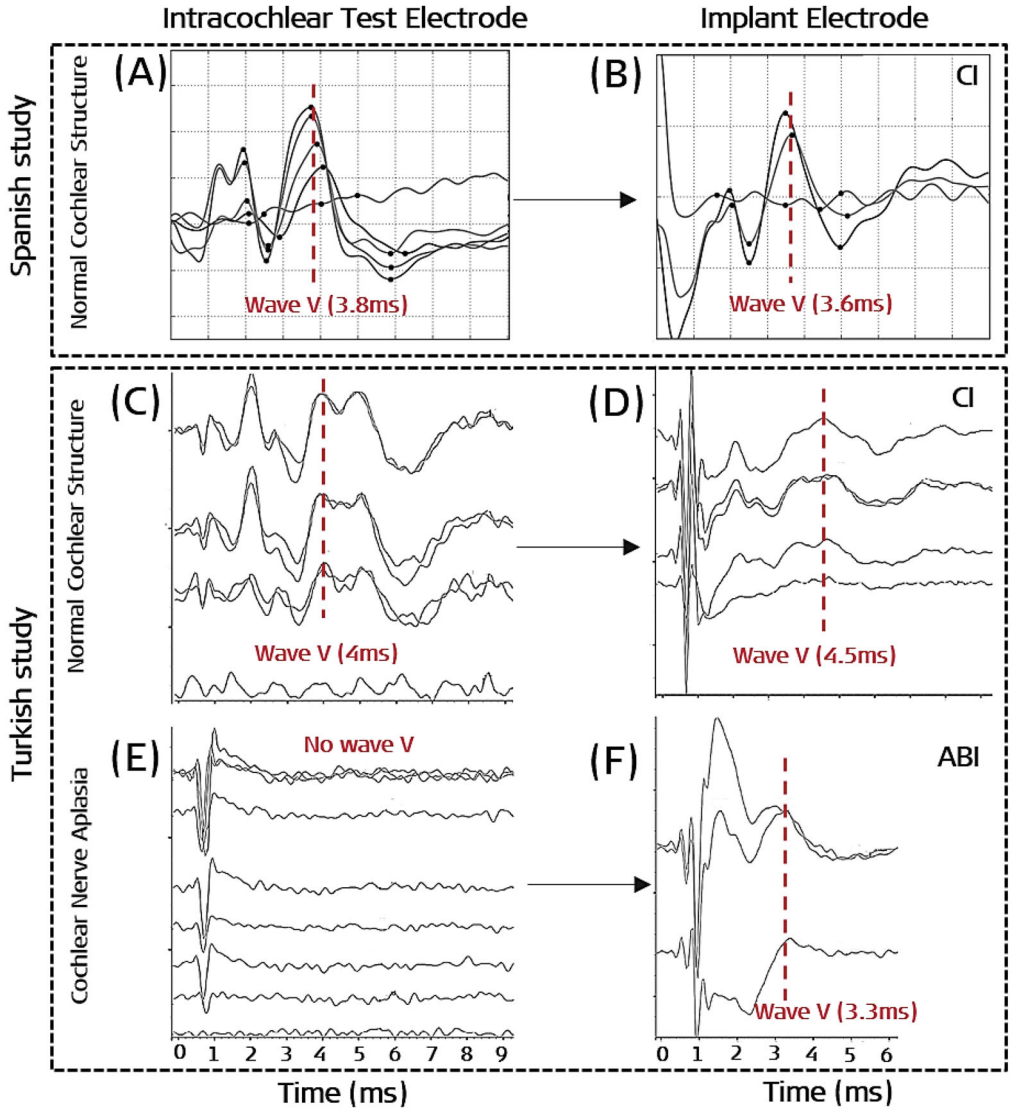


Figure 25. eABR responses recorded from normal anatomy cochlea by applying electric stimulation from the test electrode (A, C) and from CI (B, D). eABR responses not seen from cochlea with cochlear nerve aplasia when electric stimulation was applied from the test electrode (E), and responses are seen with electric stimulation from ABI (F). A and B: both from the studies from Spain [24]; C–F: results from the study from Turkey [25]. A and B: Reproduced by permission of Wolters Kluwer Health, Inc. C–F: Reproduced by permission of Prof. Levent Sennaroglu, Hacettepe Medical University, Turkey.

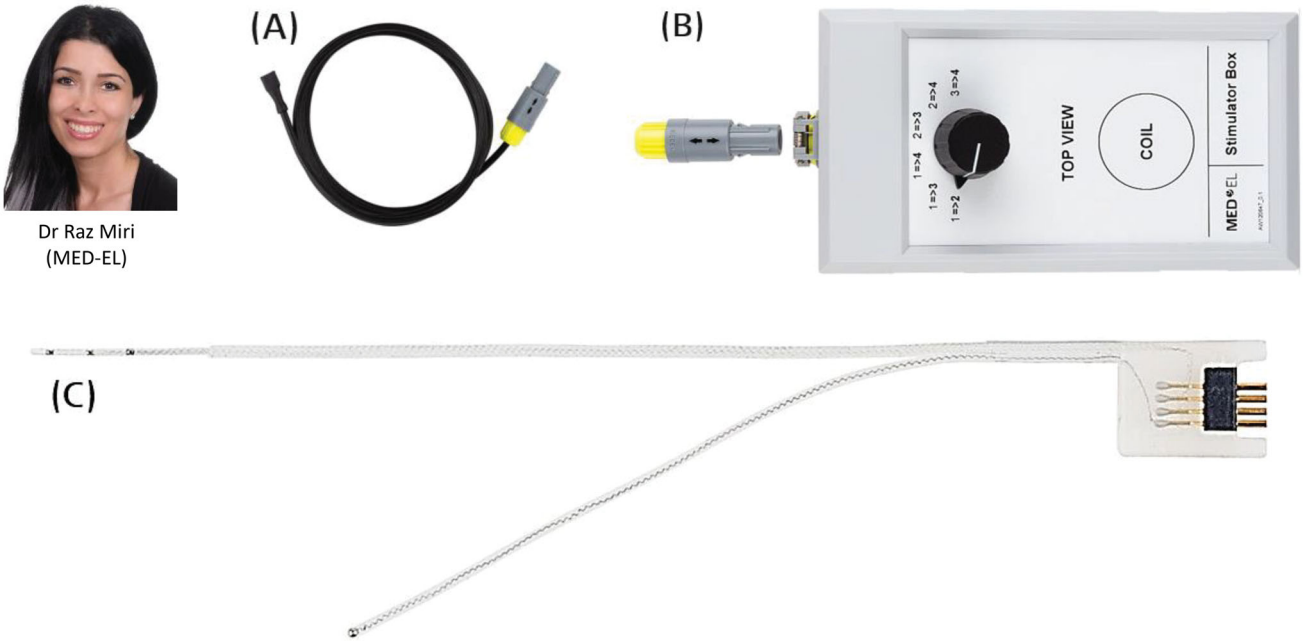
Beal and his colleagues. Figure 26 shows three parts of the ANTS.

In August 2020, there was an announcement from the Washington University School of Medicine in St. Louis that they have successfully used MED-EL's ANTS in monitoring the functionality of the AN while removing vestibular schwannomas [26]. The surgical removal of schwannoma, followed by hearing restoration with CI, was performed by Dr. Wick and Prof. Buchman (Figure 27), as part of the clinical trial for ANTS' FDA approval.

In October 2020, Prof. Arnoldner and his colleagues (Figure 28) from the Medical University of Vienna and Paracelsus Medical University in Salzburg, Austria, demonstrated the effectiveness of ANTS in monitoring the functionality of AN while removing vestibular schwannomas [27]. Five patients were included in this study, out of which three showed positive intraoperative eABR responses during the vestibular schwannoma removal and are currently full-time CI users. The two patients who showed negative intraoperative eABR responses during the vestibular schwannoma removal had no auditory perception with CI. They concluded that the preservation of eABR seems to predict good subsequent hearing outcomes.

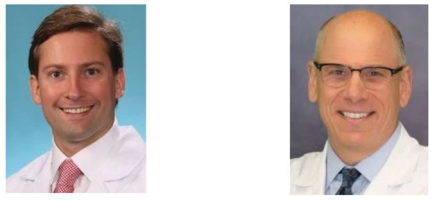
7.5. Promontory stimulation to monitor the auditory nerve functionality

While the application of ANTS is one way of evaluating the AN functionality in patients selected as candidates for CI or ABI, the Promontory Stimulation (PromStim) System is another way of checking the viability of AN in patients with narrow IAC accessing the RW through the external ear canal. PromStim works in the same way as ANTS, with a difference of electric stimulation being performed at the RW niche, leaving the other test set-up identical to the ANTS. PromStim was conceptualised by a group of MED-EL engineers and clinicians from Spain and developed as a product by MED-EL at a later point (Figure 29).



Dr Raz Miri
(MED-EL)

Figure 26. Dr. Raz Miri, the project leader of the ANTS. The ANTS part. Connector cable (A) that connects the stimulator box (B) to the intracochlear test electrode (C). Image courtesy of MED-EL.



Dr Cameron Wick

Prof. Craig Buchman

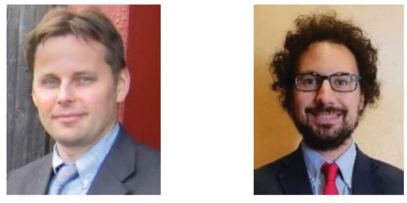
Figure 27. Surgeons from the Washington University School of Medicine in St. Louis, USA who used ANTS for monitoring the AN functionality while surgically removing vestibular schwannoma, followed by cochlear implantation.

Figure 28. Prof. Christoph Arnoldner from the Medical University of Vienna.

Dr Manuel Sainz Quevedo [1]

Dr Julio Rodrigo Dacosta [2]

Prof. Constantino Morera [3]



Dr Marek Polak [2]

M.Sc. Giacomo Mandruzzato [2]

Figure 29. Clinicians and Engineers who conceptualised and developed the PromStim electrode as a product. [1]Hospital San Cecilio, Granada, Spain, [2]MED-EL Innsbruck, Austria, [3]University of Valencia, Spain.

In 2018, the PromStim system was evaluated by Prof. Hempel and Prof. Müller from the Großhadern Clinic in Munich in Germany (Figure 30).

The study comprised eleven patients in whom the CI candidacy could not be determined by regular audiological tests [28]. Under local anaesthesia, a transtympanic rounded-bent tip electrode (Figure 31(A)) was temporarily placed at the RW niche (Figure 31(B)), and the surface ground electrodes were placed on the zygomatic bone at the angle of the mandible.

Prof. John-Martin Hempel

Prof. Joachim Müller

Figure 30. Clinicians from Munich who were involved in the evaluation of AN functionality by the application of electric stimulation at the RW niche using PromStim.

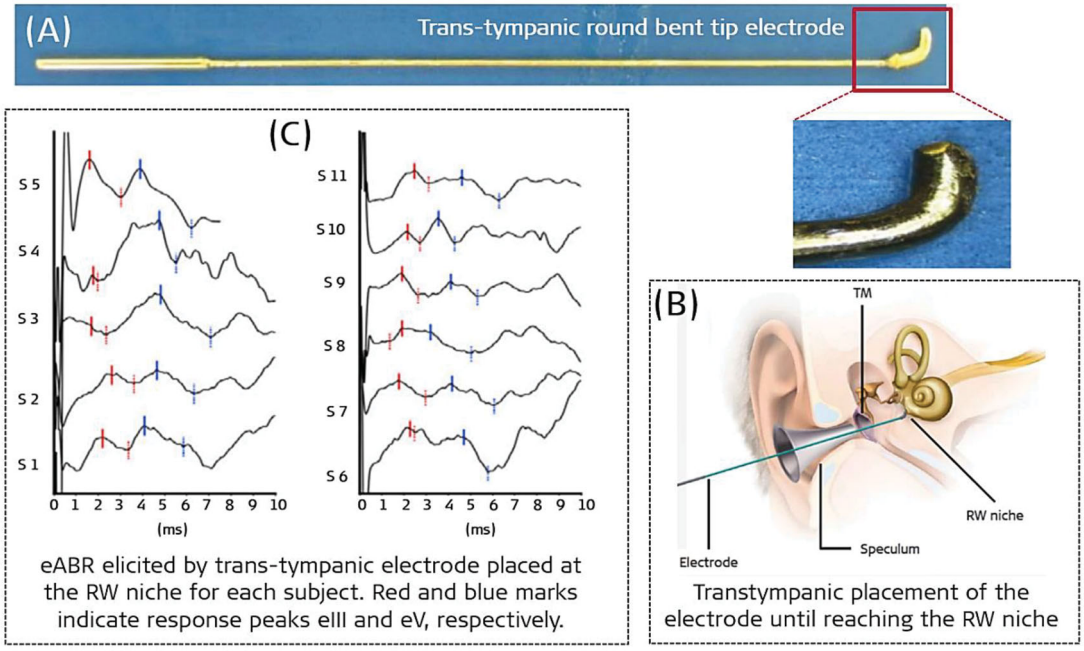


Figure 31. Transtympanic rounded-bent tip electrode that facilitates easy placement at the RW niche (A). Illustrative representation of the transtympanic electrode placement at the RW niche (B). PromStim eABR responses for all eleven patients (C) [27]. Image courtesy of MED-EL.

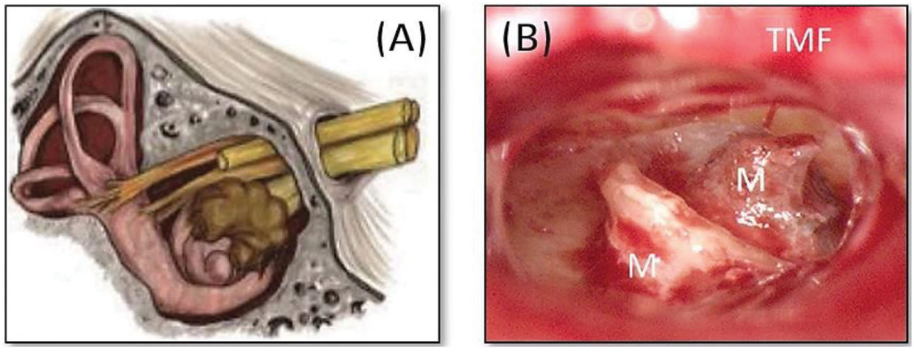


Figure 32. Intracochlear schwannoma (www.intechopen.com) (A) and partially dissected cochlea with a complete schwannoma removal (B) [28]. Image B is a courtesy of Prof. Stefan Plontke, Halle, Germany.

Biphasic alternating pulses with a phase duration of 100 μs and a stimulation rate of 34 Hz were used. The amplitude of electric pulses was increased with 100 cu/step until a response was detected. Positive PromStim eABR results were confirmed in all patients with the presence of reproducible auditory responses after electric stimulation (Figure 31(C)). These data show the validity of the PromStim system in evaluating the viability of AN in patients where regular audiological tests do not provide decisive results.

7.6. Inner ear schwannoma removal and special electrode array

Intralabyrinthine/intracochlear schwannomas are benign tumours, as shown in Figure 32(A), which mimic various common cochleovestibular diseases, and magnetic resonance imaging (MRI) scanning is widely used for observation of tumour growth's pace. Surgical removal of the tumour is the final solution when the tumour reaches a size that is big enough to pressurise the surrounding structures, causing symptoms like vertigo, HL, or both. Following the tumour removal, hearing restoration with CI has become the standard treatment. Surgical removal of schwannoma that is trapped deep inside the cochlea often requires dissection of a considerable portion of the cochlear capsule, as shown in Figure 32(B), posing a challenge for the optimal placement of electrode array.

Prof. Plontke from Martin Luther University Halle-Wittenberg in Germany is well known for his expertise in surgical removal of intralabyrinthine schwannomas, and with a joint effort between him and MED-EL, a specially shaped electrode array to fit in a dissected cochlea was successfully developed [29]. As the postsurgical observation period requires periodic MRI scans to watch for new tumour developments, the implanted CI device must feature a high MRI compatibility to avoid surgical removal of the implant magnet for scanning. MED-EL's SYNCHRONY CI System accommodates the frequent MRI exposure as it features free rotation in the presence of an external magnetic field, and thus avoiding additional surgical interventions.

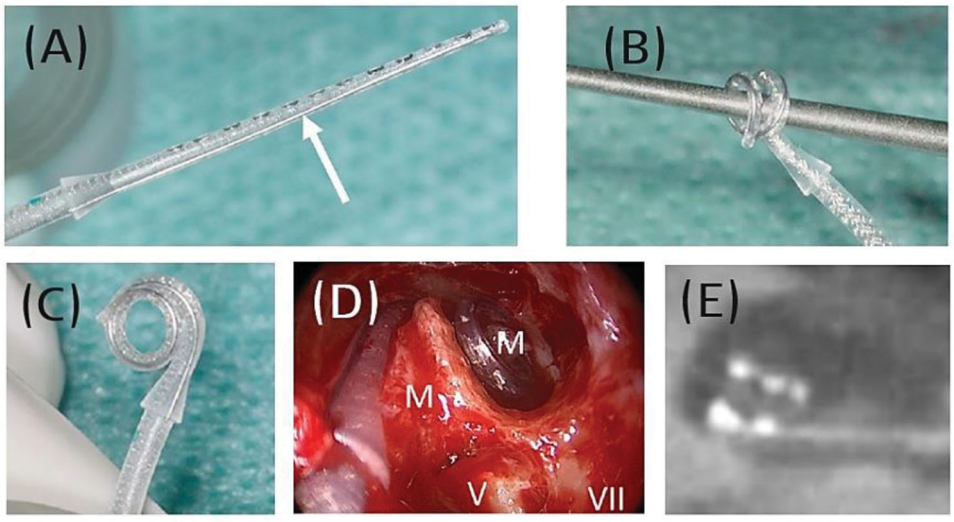


Figure 33. Special electrode with a malleable memory shaped element (A). The electrode array is shaped by rolling the electrode array over a surgical tool (B, C). Shaped electrode takes the optimal position inside the dissected cochlea (D). Postoperative image showing the shaped electrode covering two turns of the cochlea (E) [28]. Image courtesy of Prof. Stefan Plontke, Halle, Germany.

Figure 34. Clinicians from [1]Martin Luther University Halle-Wittenberg, Germany; [2]University of Medicine and Pharmacy Grigore T. Popa, Romania; [3]Klinikum Stuttgart, Germany; [4]Engineer from MED-EL, Austria. *Image courtesy of Prof. Stefan Plontke: Fotostelle Universitätsmedizin Halle.

The special electrode array that was designed by Dr. Dhanasingh from MED-EL for this particular cochlear condition that carried a malleable memory shaped array backbone, as shown in Figure 33(A).

This malleable element enables the electrode array shaping to surgeon's preference (Figures 33(B,C)), placement into the dissected cochlea and coverage of the entire modiolus trunk (Figure 33(D)). MED-EL has delivered CI devices with the special electrode array under CMD regulations which were implanted between 2018 and 2019 in four patients with intracochlear ($n = 1$), intra-vestibulocochlear ($n = 1$) and trans-modiolar ($n = 2$) schwannomas. All four surgeries resulted in successful schwannoma removal and optimal electrode array placement with covering well beyond the basal turn, as seen from the postoperative radiographs (Figures 33(E)). The study involved joint efforts from clinicians from Halle and Stuttgart in Germany, Romania and in association with MED-EL (Figure 34).

The intraoperative eABR responses showed the presence of wave V in three patients, as shown in Figure 35(A), and all four patients showed significant improvement in hearing as seen from the monosyllable word test in quiet listening condition at six months after surgery (Figure 35(B)).

While the special electrode array design offers the support needed for its optimal surgical placement, the overall surgical procedure of removing a schwannoma is complex and performed only by the most adept neuro-otologists.

7.7. List of unpublished special electrodes from MED-EL

While the special electrode array designs presented in this article are those which were publicly reported, several other, publicly undisclosed designs that were designed by Dr. Jolly and Dr. Dhanasingh from MED-EL were successfully implanted in patients under CMD regulations. They are listed below:

7.7.1. Insertion probe device to dilate cochlear fibrous tissue

Various reasons, such as meningitis infection or temporal bone fracture, result in intracochlear fibrous tissue formation, which is a natural process, but which obstructs the CI electrode array insertion.

To overcome this issue, MED-EL came up with a concept of insertion probe device with two ends, as shown in Figure 36, which was later developed into a commercially available product by Dipl. Ing. Wojtkowiak from MED-EL. The stiff end is useful in dilating the fibrous tissue obstruction within an intracochlear depth of 20 mm while the flexible end is checking how deep the cochlear lumen is for the electrode array placement.

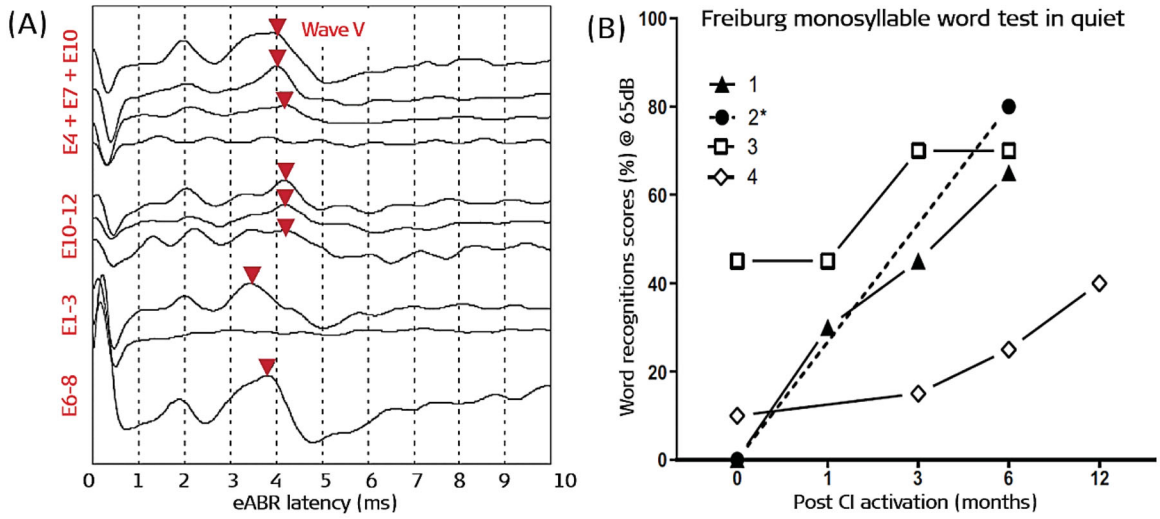


Figure 35. eABR responses from the dissected cochlea with electric stimulation from the special electrode array (A). Freiburg monosyllable word test scores of patients implanted with special electrode array showing improvement in hearing performance (B) [29]. Image courtesy of Prof. Stefan Plontke, Halle, Germany.

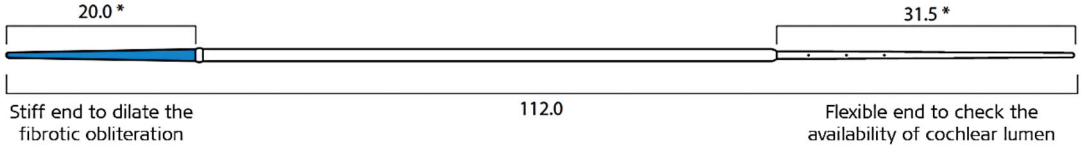


Figure 36. Insertion probe device with two different ends. The short blue coloured end is made stiff for a length of 20 mm to dilate the fibrous obstruction, whereas the long end is made as flexible as MED-EL's FLEX electrode arrays to check the depth of the cochlear lumen. * Dimensions in millimetre. Image courtesy of MED-EL.

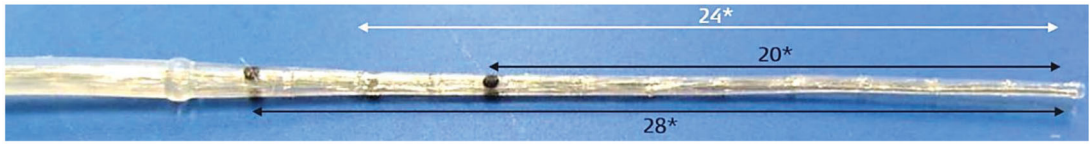


Figure 37. Stiff probe device with three insertion depth markers. Image courtesy of MED-EL.

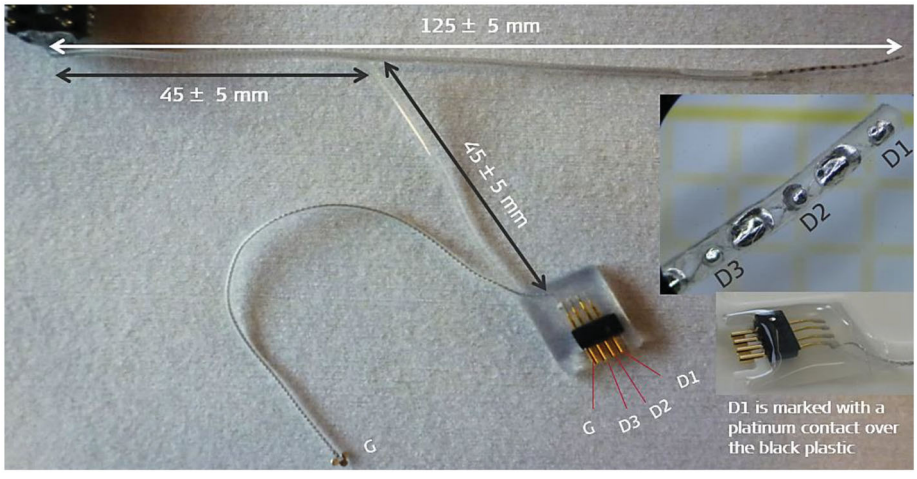


Figure 38. Electrode array that carries three additional diagnostic channels at the apical end of the electrode array. The diagnostic contacts are wired separately and have its connector for connecting it to external devices to record the cochlear microphonics. Image courtesy of MED-EL.

Some pathological conditions carry fibrotic obstruction beyond the basal turn of the cochlea and to address such need, another insertion device with the stiff property, as shown below, was designed with carrying three insertion depth markers (Figure 37). This device was successfully used in >10 patients in obliterating fibrotic tissue inside the cochlea and was followed by regular electrode array insertion.

7.7.2. Electrode array with diagnostic contacts

CI electrode array placement inside the cochlea with good functional low-frequency residual hearing is a delicate process. In 2014/15, it was attempted to record cochlear microphonics during the electrode insertion process. To do so, there was a need to add additional contacts within the electrode array, as proposed by Prof. Lenarz from Hannover Medical School in Germany, and MED-EL has fabricated such array with three additional diagnostic contacts, as shown in Figure 38 (channels D1, D2 and D3).

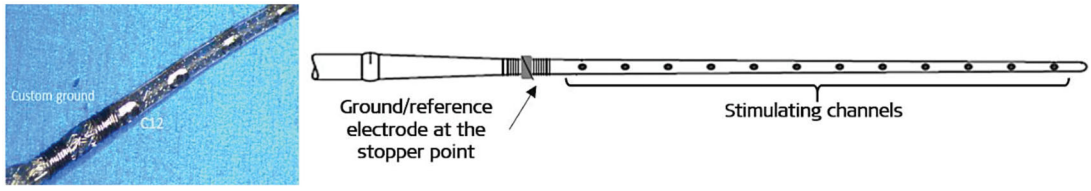


Figure 39. Electrode array that carries a reference electrode at the stopper point. Image courtesy of MED-EL.

7.7.3. Electrode array design to minimise facial nerve stimulation

FNS, a consequence of CI electrode stimulation, represents an issue, especially with otosclerosis. FNS occurs mainly because of the widespread of the current from the promontory which reaches the FN. To minimise it, MED-EL (Dr. Jolly) came up with the concept of bringing the reference electrode close to the electrode array's stopper, and thereby the current spread is to be kept between stimulating channels and the reference electrode at the stopper location (Figure 39). Such an electrode was implanted in few patients with some success in minimising the FNS.

7.7.4. Short electrode array for high-frequency deafness

To address the need for an electrode array for patients with near-normal hearing in the low-to-middle-frequency region and with HL only in the high-frequency region, under Prof. Lenarz's proposal, MED-EL developed a 16 mm long electrode array that would cover 270° of angular insertion depth. The electrode was implanted in a few patients (Figure 40).

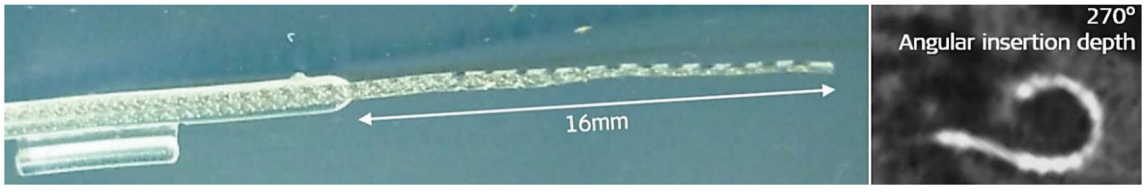


Figure 40. Short electrode array with 16 mm length to cover up to 270° of angular insertion depth. Image courtesy of MED-EL.

7.7.5. Extra-long electrode array for extra-large cochlea

Cochlear size measurement is becoming a standard during the preoperative patient assessment, and reports are showing extra-large cochlear size with cochlear basal turn diameter in the range of 10–11 mm. To address the needs of such particular cochlear cases, Prof. Müller from Großhadern Clinic in Germany proposed to MED-EL to develop a 34 mm long electrode array (Figure 41) which was implanted in some patients – successful full insertion was achieved in all of them.

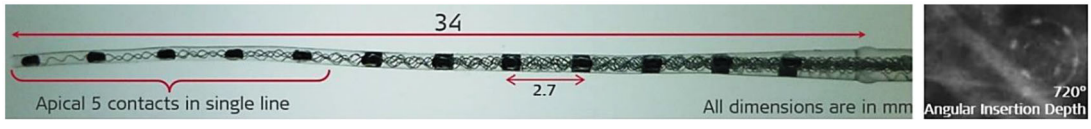


Figure 41. Extra-long electrode array length of 34 mm to match extra-large cochlear size. Image courtesy of MED-EL.

Figure 42. Short electrode array in the range of 13 mm array length along with a CORK type insertion stopper. Image courtesy of MED-EL.

7.7.6. Compressed electrode with CORK stopper

A smaller cochlear portion is usually associated with the cochlear hypoplasia type malformation. If the surgeon predicts a CSF gusher due to the wide IAC opening, then it is better to have a short array length that matches the smaller cochlear size and to have the insertion stopper in the form of a CORK to seal the cochlear opening effectively, as shown in Figure 42. MED-EL fabricated a very short, 13 mm long electrode array that carried a CORK type stopper as per the request from the surgeons, Dr. Carol Xie from Saint Thomas Hospital in London, UK and Prof. Shakeel Saeed from the Royal National ENT Hospital, London, UK. The array was implanted in four patients so far in the UK.

7.8. Reimbursement

Reimbursement is a vital factor in keeping many businesses alive, including MED-EL. Under CMD regulations and based on the operating surgeon's prescription, the CI device, coupled with special electrodes, may be reimbursed by the healthcare systems in most cases. Successful reimbursement was one of the encouraging aspects for MED-EL to invest time, money and efforts in developing special electrodes as per the request from the operating surgeons.

7.9. Conclusion

Although cochlear anomalies are rare, patients with such conditions shall nevertheless receive optimal treatment, even if it requires additional efforts from both, clinicians and medical device manufacturers. The effectiveness of the overall CI treatment lies in the optimal electrode-neural interface, which is the core reason for MED-EL to go to great lengths in designing special electrodes to match every cochlear condition. Close collaboration with clinicians is the key to innovation in the medical device field, and every special electrode presented in this article is the apparent result of a strong collaboration between clinicians and MED-EL.

The presented special electrode array designs in this article illustrate MED-EL faculty's diligent and passionate stand towards continuous technological advancements, especially of its CI electrode arrays. It is within the core of the company's philosophy to address the needs of every patient, be it even of one single, with challenging cochlear conditions. MED-EL makes every effort within its scope to design and produce a special/modified CI device, even if it means exceeding the break-even cost.

MED-EL continues its mission in supporting every single HL patient with special CI devices and expanding its scientific network by creating close collaborations with clinicians. This article is yet another example of the translational science path that MED-EL takes in developing its products; its design concepts are based on unique patient needs first, translated to prototypes, followed by bench testing, and the translational science circle is concluded only with the successful patient outcome.

Acknowledgments

The authors would gratefully like to acknowledge the key contributors to the development of the subject matter. Their contributions are outlined in this article. The authors further acknowledge Claude Jolly from MED-EL for his valuable input and comments during several rounds of review meetings that contributed to the final version of this article.

Disclosure statement

This article is sponsored by MED-EL and has not undergone the regular peer-review process of Acta Oto-Laryngologica. Both the authors are affiliated with MED-EL.

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ACTA OTO-LARYNGOLOGICA
2021, VOL. 141, NO. S1, S178–S184
https://doi.org/10.1080/00016489.2021.1888516

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REVIEW ARTICLE

Translational research around five categories of CI

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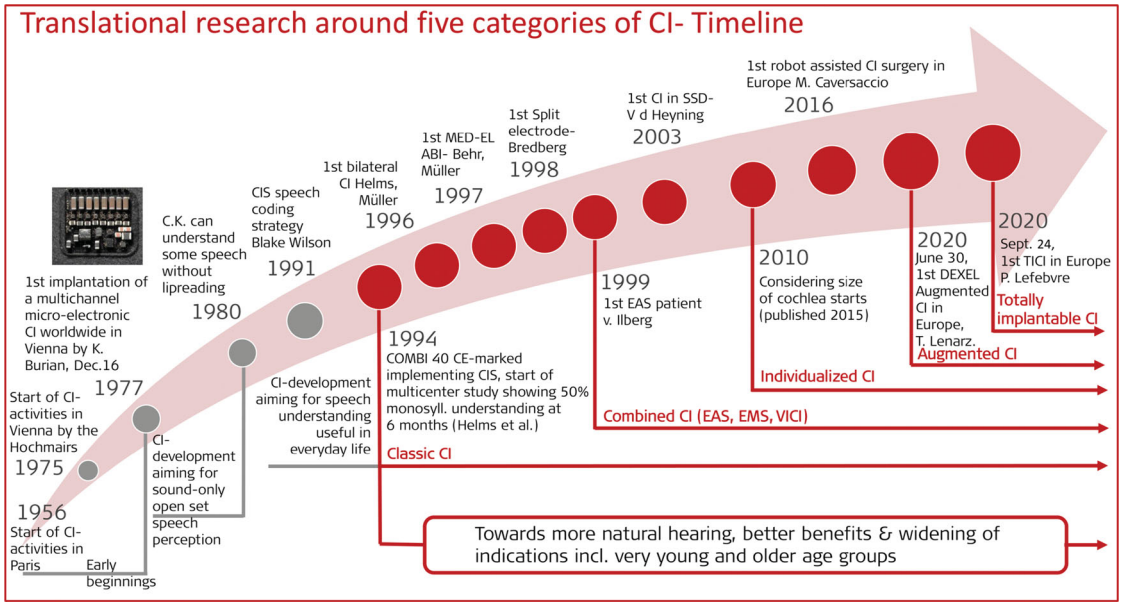
ABSTRACT

Five categories of cochlear implants are introduced: The 'classic CI', the 'combined CI' – which can be combining a CI based on electric stimulation with acoustic stimulation (EAS) or with mechanical stimulation (EMS) or with electrical stimulation of the vestibular system (VICI) –, the 'individualised CI', the 'augmented CI' and the 'totally implantable CI'. The translational research activities leading to and within these categories have been, are and will be numerous and are the subject of the compendium for which this paper is the concluding chapter. Early translational research has resulted in the 'classic CI' in 1994. From then on translational research enabled the developments respectively the new indications and reimbursement of CI-systems for bilateral CIs, CI in single sided deafness, the auditory brainstem implant, speech coding and signal processing advances, electrophysiologic measurements for evaluation of cochlear health, all within the classic CI category. Starting points for the four newer categories of CI are either ideas of professionals treating hearing loss or of CI developers. The translational research performed also triggered research that led and leads to improved understanding of the fundamental mechanisms of hearing.

ARTICLE HISTORY
Received 13 December 2020
Accepted 6 January 2021

KEYWORDS
Cochlear implants; categorisation; translational research; classic cochlear implant; eas; individualised cochlear implant; augmented cochlear implant; totally implantable cochlear implant



8.1. Introduction

This paper is a reflection on the overall goals, learnings and successes of translational research in hearing loss treatment solutions at MED-EL, discusses the question of how much one can strategically concentrate on the direct route to approval in translational research versus how much research around a certain key topic is necessary and optimal to conduct or initiate. It suggests five categories of CIs, all being further developed at this time. It also tries to provide a glimpse into the future of CIs and deliver some insights from a personal perspective.

Comprehensive literature exists on translational research and on how to categorise it. This compendium reports about translational research around the CI within all categories from the very first research question or idea from

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This article is a part of the compendium entitled 'Thirty years of Translational Research behind MED-EL' authored by Anandhan Dhanasingh (Director) (Anandhan.dhanasingh@medel.com) and Ingeborg Hochmair (CEO, CTO) (Ingeborg.hochmair@medel.com).

outside or inside the company to reimbursement in those countries, were reimbursement is possible.

Hearing is a multifaceted ability, and people with 'normal hearing' exhibit large variations in hearing abilities in terms of hearing in quiet, speech perception in noise, in otherwise difficult listening situations, localising a sound source and in enjoying sound, especially music. Remarkable hearing abilities can be found in some blind people, with amateur and professional musicians, singers or artists playing a musical instrument, and composers.

Respect for nature's delicate structures inside the cochlea has always been one of the guiding principles for our approach. Some clinicians were convinced in the late seventies and early eighties that electrodes should only be placed in extracochlear locations in order not to compromise any intracochlear structures. On the other hand, pioneer Prof. Helms' approach was very successful early on already: He, Profs. Gstöttner and Baumgartner, as well as all the investigators in the COMBI-40 multicentre study that started in 1994, tried to reach as deep into the cochlea as possible with a long electrode to make use of the tonotopic arrangement of the excitable structures along the cochlea and, thus, provide access to the entire pitch-range for the recipients. Candidates who received a CI in the nineties were typically profoundly deaf. Results were excellent already then, typically reached soon – mostly within three to six months [1] – and superior to systems with shorter electrodes [2–4].

The outcomes of hearing loss treatment with MED-EL CIs, including classic indications, bilateral CIs, CIs in single sided deafness SSD, electric – acoustic stimulation EAS and malformed cochleae for recipients from very young to very old age, are extremely impressive, especially when considering that the natural organ of hearing is enormously complex, delicate and not completely understood. The CI outcomes seem like miracles to many. In fact they are the result of much, hard, diligent and collaborative work by expert teams over many years. Now it is up for society, politicians, health systems, as well as educational systems to help providing access to CIs to everyone who will benefit from them and whose QoL (quality of life) will be improved, but who will also have a better chance in education, and by the ability to communicate with everyone, to live a full life, not generate costs for untreated hearing loss, and rather have a better chance to take part and contribute to society.

Reflecting on the timelines explained in this compendium of new developments and respective hearing solutions for various new candidate groups, what impresses first is how long these timelines are. It indeed needs a lot of patience and perseverance to last from the first idea or basic research inquiry to approval and reimbursement of something new in this field of CIs, part of the implantable active medical devices field. The question of what is the most direct, most efficient, fastest path to approval and reimbursement based on research and collection of evidence is omnipresent in a team of researchers, specialists for design & development, clinical research, regulatory affairs, reimbursement, innovation managers and executives. Some amount of less focused basic research around the focused research goal is required, at least in order to be sure that there will be some understanding of why and how the positive therapeutic effect happens, to understand the 'mode of action'.

Classic CIs in general, and the MED-EL CIs in particular, have reached a mature stage of development. They are based on electric stimulation. There can be a combination with acoustic stimulation in case there is still enough natural hearing present before and after implant surgery. Many of the recipients of our CIs can forget about their hearing loss while they use the CI during their daily life.

8.2. Where to go from here?

The main goal now and for the near future is to explain variations in outcomes and to reduce those. This means individualising or personalising the treatment with CI for an individual candidate with a specific stable or progressing hearing loss and, thus, maximising the outcome for everyone in the meaning of precision medicine. Choice of best suited electrode and choice of an implant that is future-ready by being signal-transparent is essential. If achieved, then new results from research can be implemented into an upgrade audio processor or downloaded into the implant electronics of a TICI (Totally Implantable Cochlear Implant) at any time post-implant surgery and for decades after. Such research and development will result in further improved hearing in quiet and in noise, more enjoyment for music, improved sound localisation possibilities and in a shorter learning curve for recipients.

Furthermore, time and personnel resources for all professionals engaged during all stages of the patient journey, including rehabilitation and training, need to be minimised by making everything easier and better for everyone involved. Preventative and curative effects of the CIs on cognitive decline need to be maximised.

Most of the above can be achieved with the classic CI, which is the CI based on electric stimulation only. Slow, constant speed electrode insertion at the most suitable insertion angle of a straight, soft and flexible electrode helps with hearing and structure preservation. Objective physiological measurements evaluating cochlear health during the insertion help with hearing preservation and provide input for appropriate fitting. Surgical techniques, e.g. preventing blood from ingress into the cochlea, avoiding suction close to the entrance point into the cochlea, etc. help with hearing preservation. Oral application of vitamins A, C, E and magnesium have also been demonstrated to help with hearing preservation [5].

Individualisation of electrode selection [6] and anatomy-based fitting can maximise outcomes for the individual person, and very impressive benefits in terms of music appreciation and even active music performance have been reached [7–9].

8.3. Milestones and the five categories of cochlear implants now and in the future

Figure 1 shows CI development phases of the past and the five categories introduced in this paper that co-exist at this time, and will extend into the years to come.

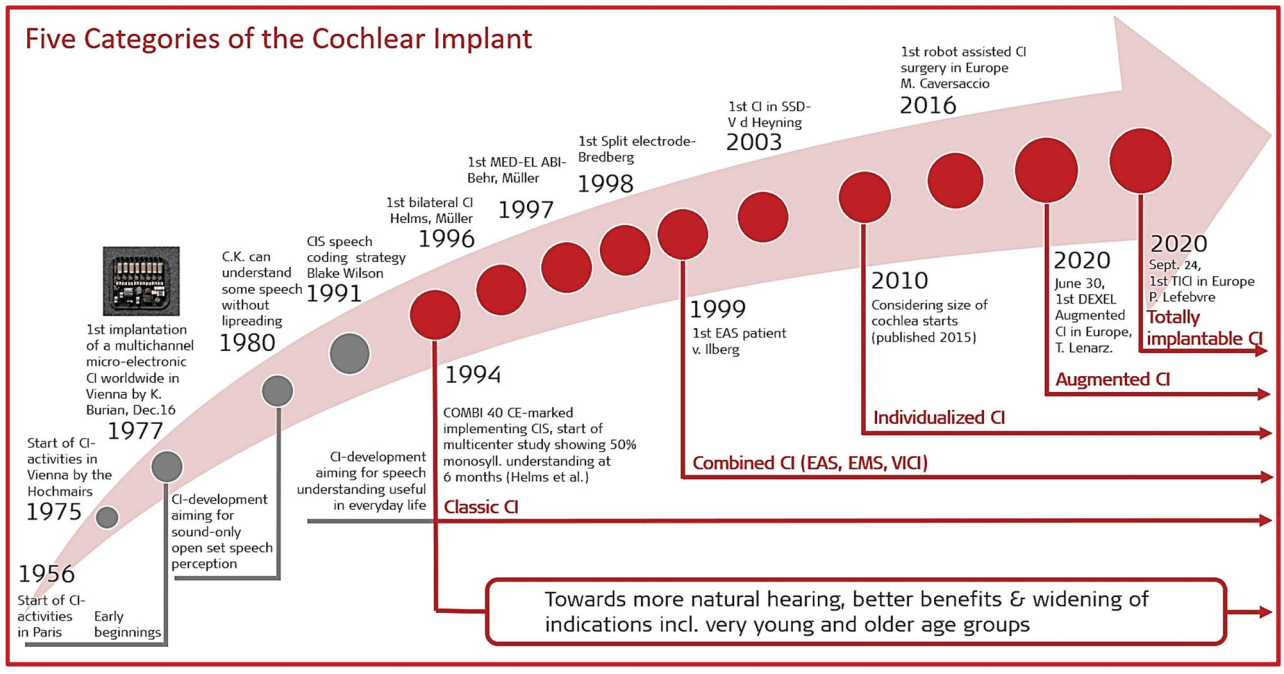

Figure 1. Milestones with Cochlear Implants reached through translational research and the beginnings of the five categories of CIs co-existing currently and extending into the future.

8.3.1. Early beginnings of the CI

The early CIs were an aid to lip-reading. Developments towards multichannel CIs started at several universities and were achieved by well-known early pioneers. The first modern multichannel microelectronic CI (predecessor of MED-EL devices) was implanted in Vienna on December 16, 1977 [10].

8.3.2. CI-Development aiming for some speech understanding without lip-reading

This phase reached its goal in March 1980 [11] when pioneer patient C.K. could understand words and sentences without lipreading in quiet through a small body worn sound processor.

8.3.3. CI-Development aiming for speech understanding useful in daily life

During this phase early speech coding was further developed including a combination of stimulation with biphasic pulses and analogue stimulation until the speech coding strategy CIS (continuous interleaved sampling) by Blake Wilson was published [12]. Ultimately this phase resulted in a fast stimulation multichannel transcutaneous device with long, flexible scala tympani electrode implementing the CIS-speech coding strategy, the COMBI 40 [13], which was CE-marked in late 1993. The phase ended when the device was first implanted in January of 1994. A multicentre study revealed for the first-time speech perception sufficient to converse over the telephone with unknown speakers (50% median and mean monosyllabic word understanding six months after first fitting) [1]. A reflection on earlier work can be found in Hochmair et al. [14].

From then on, the strive in research has been and is towards more natural hearing, better benefits and widening of indications, expanding into very young and old age groups.

Towards natural hearing, better benefits and widening of indications

8.3.4. Category classic CI

Efforts started in 1994 and continue into the present (2021) and future to make 'electric hearing' through a CI sound more and more natural, improve outcomes and widen indications, also including younger and older age groups, as well as hearing preservation through technological, surgical and neurophysiological efforts supported by training, connected care, remote care and connectivity developments, bilateral CIs, CIs for single-sided deafness and asymmetric hearing loss, and bimodal stimulation (CI in one ear with a hearing aid in the other ear).

8.3.5. Category combined CI

EAS: In case useful natural low frequency hearing can be preserved, the combination of electric stimulation with acoustic amplification EAS can be used [15]. For EAS a shorter electrode sparing the cochlear region with still present functional hair cells can be used in cases with a non-progressive stable hearing loss. The only additional component in the CI-system is an acoustic component included in the external audio processor.

EMS: For Electromechanical stimulation a combination of a CI and a vibratory actuator as part of the implant for mechanical stimulation is under development. Further encouragement for the development came from a single patient case implanted in Hannover [16].

VICI: The combination of a CI and electric stimulation of the vestibular organ in case of a co-existing loss of vestibular function is under development. The stand-alone vestibular implant [17] also under development is not included in Figure 1 because it is not a combination with a CI. The first VICI combination device was implanted as a custom-made device (CMD) by Jean-Philippe Guyot and Isabel Kos in 2007 in Geneva [18,19].

8.3.6. Category individualised CI

Individualisation is currently routinely used for the MED-EL device in most clinics with big CI programmes. A surgical planning software supports the selection of the best-suited electrode length and supports anatomy-based fitting after surgery. Neurophysiologic measurements are performed during electrode insertion to support hearing and structure preservation. Manual insertion or, since recently, robot-assisted surgery [20] and/or slow insertion speed equipment may be used. Many parameters are involved in individualisation. The optimal electrode length needs to be determined. Cochlear geometry [6], residual hearing and its likely preservation and stability, likelihood to use the acoustic component in case of an EAS-system, cochlear health, other factors as well as the candidate's expectations and motivations should be considered.

8.3.7. Category augmented CI

This is a combination of a CI and a substance that is released into the cochlea either before, during or for a short time after the implant surgery, or is chronically eluted from the electrode over a defined period of time. MED-EL's first augmented CI with dexamethasone eluting from the intracochlear electrode has been successfully implanted on 30 June 2020 in Hannover within a feasibility study. Other substances are being researched currently. There are many genetic origins of hearing loss. Genetic testing of candidates for a CI helps to predict the progressiveness of the hearing loss and choose a certain electrode length accordingly. It also helps to identify candidates with a perspective of poorer outcome. For subgroups of these candidates, certain types of augmented CIs are under development. The combination of a CI and gene therapy for a certain genetic disorder is the subject of translational research for genetically based hearing losses. The first use of an intracochlear catheter inserted into the cochlea to deliver substances there before insertion of the CI-electrode happened in 2015 applying Prednisolone, a report on 11 cases applying Triamcinolone followed in 2018 [21].

8.3.8. Category totally implantable CI

The TICI is a CI system that can be used without a component external to the skin. Rechargeable battery, microphone and the audio processor circuitry are all implanted. MED-EL's first totally implantable CI, the first TICI in Europe has been successfully implanted on 24 September 2020 in Liége within a feasibility study taking place at Liége and LMU Munich.

8.4. Remaining tasks for the CI field are

1. To optimise the best possible outcomes.
2. To improve average realistic outcomes, given that not every chain in the patient journey is working out optimally in everyday reality.
3. To improve the outcomes of poor performers.
4. To find or improve special solutions for various candidate groups: for those with very short, very long cochleae, with malformed cochleae, poorly or non-functional auditory nerves, without a cochlea, those with neuropathy, with central auditory processing deficiencies, those with cognitive decline, starting dementia, the very young, the very old, people with various degrees and quality of natural hearing still present in the low-frequency range or/and other frequencies, those with SSD (single-sided deafness) or AHL (asymmetric hearing loss) and those who want to continue using a hearing aid on the opposite ear in combination with their CI.

Precision medicine in the field of CIs means that precise preoperative image analysis, audiology and counselling leads to the selection of the optimal personalised electrode choice for the individual candidate. Precision – maybe robot-assisted – surgery with low-speed electrode insertion support will be predictable and reliable and save the still naturally present hearing. Cochlear health status as well as parameters for fitting are measured intra- and post-operatively. Fitting and re-fitting will be performed autonomously and automatically. Check of system function and user performance works remotely. Everyone involved can be trained easily and quickly. Sustaining device function and outcomes will be based on close to zero repair costs and external component upgrades in regular intervals of several years.

Currently, the CI is perceived as the first replacement of a human sense that it truly was. After the many years of research and development, the MED-EL CI is now on its way to be perceived as hearing ability on top of the natural hearing that a certain individual still has. If we could promise to a candidate with a hearing loss: 'Your natural hearing will be the same after the implant surgery as before the surgery, and you will gain an additional, worthwhile improvement in hearing abilities,' it would sound convincing to many candidates who still have considerable amounts of natural hearing. The indication for our CI will shift more and more into the current domain of hearing aids. An advantage of a CI based on electric stimulation over acoustic stimulation is that the electric hearing has been shown to be stable over decades.

CIs have been around for more than three decades by now (albeit for a much shorter time than hearing aids), but different models are still very different, and to determine the optimal solution for an individual candidate with an individual hearing loss together with this candidate requires very skilled, experienced professionals.

The hope is that these decisions could, in the future, be made with the help of and based on outcome predictions independent of all other possible influences. Understanding in noise as well as music enjoyment will then be more homogenous and at a higher level.

On a personal note, I have encountered many compromises in health systems around the world, that would be extremely beneficial to overcome. Questions to wonder about:

1. Although there is continuous progress and close to 100% of children born deaf in highly developed countries receive at least one, mostly two CIs, more than half of the children who were born deaf around the globe five years ago have not received a CI and are now too old to receive one since valuable time has been lost and the plasticity of their auditory pathway has decreased without appropriate input. It is difficult to accept that this still happens on a global level despite more than twenty-five years of CI availability for young children, and when many thousands of young people who had been born deaf and did receive CIs at a very young age in the nineties cannot be distinguished easily from their hearing peers, and have enjoyed mainstream education, can communicate with everyone and have a wide variety of jobs, including very demanding ones, are quite respected in society, and also perform in jobs where they need to rely on oral communication a lot.
2. Hearing loss still stays untreated in many cases in many countries, even though untreated HL costs in excess of $750bn annually [22], and despite hearing loss is the single biggest factor influencing cognitive decline and developing dementia [23]. Of course, individuals have to be free to make their own decisions, including not to opt for a CI, but we all have to get considerably better at informing individuals with a hearing loss about possibilities for treatment and about providing access to these possibilities.

There will always be a further ongoing development. For a CI candidate, it is not a good idea to wait with his/her decision to go for a CI until the next generation comes out. As with smartphones or laptops, one would wait forever, since there is always a next generation under development, but the hearing loss should be treated without delay to avoid its sequelae.

8.5. Conclusion

The CI, including the classic CI, combined CI, the individualised CI, the augmented CI and the totally implantable CI currently represents one of the most complex groups of devices for treatment of a chronic condition – sensorineural hearing loss. Its recipients will require support for at least several decades consisting of external device availability, serviceability and repairability, further development of audio processors, fitting possibilities, connectivity solutions and rehabilitation/training support.

Already in the very beginning of our translational research and again in the early nineties there was the foresight to make all our implants transparent for further speech coding and signal processing insights and research outcomes, such that users of legacy devices can always participate in further research and innovation achievements. The foresight then also included that the implants should withstand therapeutic and diagnostic procedures like MRI in order to avoid underdiagnosis. Work on this topic started in Innsbruck in 1996 under Prof. Erwin Hochmair's [24] later also Martin Zimmerling's guidance and is covered by several patents [25]. This was realised to the degree that thirty years later there is an MRI guarantee brought in place for all prior and current MED-EL CIs – from 1994 until today (2021) – to not get damaged by an MRI of 1.5 Tesla, and in the more modern models, 3.0 Tesla.

The promise to recipients of CI technology is to take care of them in terms of their hearing for as long as they want to use the technology. The time span of this support is probably longer than with most other active implants as more than fifty percent of recipients of CIs are young children.

The encompassing field of the CI is the most fascinating and rewarding research and development area that I could ever imagine. I feel humble and thankful to the team of dedicated colleagues at MED-EL since 1990, when the first of them joined, and the researchers and clinicians who informed us about their new ideas and with whom we could then partner to develop their ideas and research work into products, treatments and new indications. I also feel forever thankful for the opportunity to become an actor in this field and together with the numerous fantastic pioneers have been able to move this field forward to the benefit of a growing group of several hundred thousand people who have received our technology. They are three months young to over one hundred years old, have a hearing loss, or since recently another challenge (on its own or in combination with a hearing loss), impacting their quality of life. We will make sure to the best of our abilities that this effort continues to broaden its innovative basis for many decades to come.

There are compromises to be made between lots of research to improve benefit to the individual recipient and to grow understanding of the basic mechanisms involved versus spending resources in building infrastructure for diagnosis, surgical treatment and aftercare for the CI in emerging and developing countries. Sometimes I think that because I was trained as an engineer and natural scientist, we focus too much on research, other days I think only more research will lead to the ultimate reduction in efforts for everyone involved that will enable global society to provide access to this wonderfully effective treatment to absolutely everyone who can benefit from it.

This is a dilemma, but it is an exciting and fascinating dilemma that requires decisions into one of the two directions practically every day. Surely, basic research made possible by the CI as an access possibility to hearing-impaired ears, and often enabled and sponsored by CI companies, has been essential for a much better understanding of the fundamental mechanisms of natural human hearing. The

research work of Helge Rask-Anderson in Uppsala, Sweden and his network of researchers in Innsbruck, Austria and London, Canada into micro-anatomy and various basic mechanisms of the inner ear is an excellent example here [26–28].

I would like to express huge compliments and thanks to all those who are proving every day that the field of CI is a truly unique and remarkable area with a wealth of research activities resulting in improving benefits for the recipients on an almost daily basis. A huge compliment also to those pioneers who started and/or drive the development of the CI programmes in new countries and regions of this world. It is never a repetition of an effort, as countries, population characteristics, infrastructure and other specifics are so incredibly variable around the world. People working diligently towards establishing ever more effective and efficient CI programmes around the world are connected internationally, often with our support, such that they can learn from each other and exchange their experience, thereby achieving faster progress.

This global network with a common goal, to make this world hear better, may succeed to provide access to CIs to the majority of children born deaf around the globe from this year, 2021 on, or deafened at a very young age, before they are five years old. May it also succeed to deliver access to any of the categories of CI, other hearing implants or hearing loss treatments for the majority of people of all ages with acquired hearing loss by the year 2040. There are many innovations in the pipeline; some will be able to progress through their long timeline, a characteristic for our field, and will have reached reimbursement by then.

Comprehensive experience and learnings from translational research during the last 30 years in co-operation with numerous clinics and research organisations will be essential in maintaining the process and the pace of innovation in the future within the five categories of Cochlear implants as well as with other active implants under development.

Ingeborg Hochmair Doz. DI Dr.techn. Dr.med.h.c. mult, KommRat, Co-founder, CEO and CTO of MED-EL.

Acknowledgment

Co-operative research activities have received valuable funding from the EU and national research funding agencies. In Austria the biggest contributions came from the Austrian Science Fund FWF, the FFG and the C. Doppler Society.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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https://doi.org/10.1080/00016489.2021.1915014

Acknowledgements

Authors would like to acknowledge the following MED-EL colleagues for all their efforts and expertise that helped to bring the whole document together.

Erwin Hochmair

Prof. Hochmair is greatly acknowledged for his overall technical review of the whole document and for his valuable suggestions.

Dijana Mitrovic

Ms. Mitrovic is highly acknowledged for all her efforts in editing the entire document, from linguistic to technical expertise.

The following colleagues are acknowledged for their overall support.

Manfred Pieber

Claude Jolly

Marek Polak

Reinhold Schatzer

Peter Nopp

Carolyn Garnham

Sören Schilp

Jochen Tillein

Susanne Braun

Radesh Najran

Johanna Boyer

Prem Ranjan

Anita Gruber

Jone Gerdvilaite

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Ingeborg Hochmair holds a doctoral degree and venia legendi (Univ-Doz.) in electrical engineering from the Technical University of Vienna, Austria. She started her career in 1976 as a research assistant and, together with Prof. Erwin Hochmair, developed the first microelectronic multichannel cochlear implant implanted in Dec 1977 in Vienna. After a research stay at the Institute for Electronics in Medicine at Stanford University in the US and numerous publications and patents, she worked as a consultant for the 3M Company in St. Paul in the US on neuroprostheses. She worked as a postdoctoral research scientist at the Institute of Applied Physics at the University of Innsbruck, Austria, between 1982 and 1989. Since 1990 she has, as CEO and CTO, built up the company MED-EL, which she had co-founded with her husband, Prof. Erwin Hochmair. She has been honoured as a pioneer of the modern CI by receiving the Lasker-DeBakey Clinical Medical Research Award in 2013, together with Prof. Graeme Clark and Prof. Blake Wilson. For her scientific achievements, she has received a number of prizes, such as the Leonardo da Vinci Award (1980) and Sandoz Award (1984). In 1995 she won the Businesswoman of the Year Award (Prix Veuve Clicquot) and the following year the Wilhelm Exner Medal and the Russ Prize of the US National Academy of Engineering (2015). She has received honorary doctorates from the Faculty of Medicine at the Munich University of Technology (2004), Innsbruck University of Medicine (2010), University of Bern (2018) and Uppsala University (2020). She has authored more than 100 research articles and was the inventor or co-inventor of over 40 patents.