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Experiences from Cochlear Implantation and Auditory Brainstem Implantation in Adults and Children

Electrophysiological Measurements, Hearing Outcomes and Patient Satisfaction

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Abstract
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Cochlear implants (CIs) and auditory brainstem implants (ABIs) are prostheses for hearing used in patients with profound hearing impairment. A CI requires an operational cochlear nerve to function in contrast to an ABI. ABIs were initially designed for adult patients with neurofibromatosis type 2 (NF2), suffering from bilateral vestibular schwannomas. Now ABIs are also used for patients, both adults and children, with congenital cochlear malformations, cochlear nerve hypoplasia/aplasia, and cochlear ossification. The aims of this thesis are to evaluate hearing outcome in patients implanted with a CI after long-term deafness. An extended period of deafness has earlier been considered as a contraindication for CI surgery. Further, we analyzed if electrically evoked auditory brainstem responses (eABRs) can predict CI outcome and pinpoint the optimal selection of treatment such as CI or ABI. We also disclose our experiences from ABI surgery in Uppsala, such as implant use, hearing outcome, complications, and satisfaction among the patients. Finally, we evaluated the results and benefits of ABIs in non-NF2 pediatric patients.

Results show that patients with an extended deafness period and durations over 20 years can achieve speech understanding and benefit from CIs. Patients with long-term deafness and limited years of hearing before deafness did not perform as well as those with shorter deafness duration and longer hearing experience did. eABR seems to have a definite role in the diagnostic armamentarium, to better consider alternative surgical strategies such as ABI. No eABR waveform predicted a poor CI outcome. There was no correlation between speech perception and eABR waveform latencies or eABR waveform quality. A majority of the ABI patients used their ABIs and benefited from them for at least some period. ABI assisted voice control in a majority of the full-time users and they reported improved understanding of speech with the implant switched on. No severe complications from ABI surgery or ABI stimulation were noted. The patients were generally satisfied, even if their hearing remained very limited. All pediatric patients but one used the implant continuously and benefited from it.

Keywords: cochlear implant, auditory brainstem implant, electrically evoked auditory brainstem responses, long deafness duration, neurofibromatosis type 2

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Not everything that counts can be counted,
and not everything that can be counted counts.
Albert Einstein

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Lundin, K., Stillesjö, F., Rask-Andersen, H. (2014). Experiences and Results from Cochlear Implantation in Patients with Long Duration of Deafness. *Audiol Neurotol Extra*, 4(2):46–55.

II Lundin, K., Stillesjö, F., Rask-Andersen, H. (2015). Prognostic Value of Electrically Evoked Auditory Brainstem Responses in Cochlear Implantation. *Cochlear Implants Int,* 16(5):254-261.

III Siegbahn, M.*, Lundin, K.*, Olsson, G-B., Stillesjö, F., Kinnefors, A., Rask-Andersen, H., Nyberg, G. (2014). Auditory Brainstem Implants (ABIs) – 20 Years of Clinical Experience in Uppsala, Sweden. *Acta Otolaryngol*, 134(10):1052-1061.
**These authors contributed equally to this paper.*

IV Lundin, K., Stillesjö, F., Nyberg, G., Rask-Andersen, H. (2016). Self-Reported Benefit, Sound Perception and Quality-of-Life in Patients with Auditory Brainstem Implants (ABIs). *Acta Otolaryngol*, 136(1):62-67.

V Lundin, K., Stillesjö, F., Nyberg, G., Rask-Andersen, H. (2016). Experiences from Auditory Brainstem Implantation (ABI) in four Paediatric Patients. *Cochlear Implants Int,* Epub ahead of print.

Contents

Abbreviations

ABI	Auditory brainstem implant
ABR	Auditory brainstem response
ACE	Advanced combination encoder
AMI	Auditory midbrain implant
ANSD	Auditory neuropathy spectrum disorder
ART	Auditory response telemetry
ASSR	Auditory steady state response
BP	Bipolar
C-level	Most comfortable level
CAP	Categories of auditory performance
CI	Cochlear implant
CIS	Continues interleaved sampling
CL	Current level *(CL is used by Cochlear and represents the amplitude of the pulse in microamperes on a log scale, ranging from 0-255)*
CMV	Cytomegalic virus
CN	Cochlear nucleus
CNS	Central nervous system
CT	Computed tomography
cu	Current unit *(cu is used by MED-EL, and 1cu is approximately 1μA)*
dB	Decibel
DCN	Dorsal cochlear nucleus
eABR	Electrically evoked auditory brainstem response
EP	Evoked potential
eSRT	Electrically evoked stapedius response threshold
HA	Hearing aid
HIV	Human immunodeficiency virus
HL	Hearing level
Hz	Hertz
IC	Inferior colliculus
IHC	Inner hair cell
MP	Monopolar
MRI	Magnetic resonance imaging

MS	Monosyllabic
MSPS	Melbourne speech perception score
NF2	Neurofibromatosis type 2
NRT	Neural response telemetry
OHC	Outer hair cell
P300	Event-related potential
Pa	Pascal
PABI	Penetrating auditory brainstem implant
PTA	Pure tone average
QoL	Quality of life
qu	Charge unit *(qu is used by MED-EL, and 1qu is approximately 1nC)*
RF	Radio frequency
SD	Standard deviation
SPEAK	Spectral peak
SPL	Sound pressure level
T-level	Threshold level
ToM	Theory of mind
VCN	Ventral cochlear nucleus
VS	Vestibular schwannoma

Preface

Communication among humans is crucial and comprises many elements such as hearing, behavior, facial expression, gestures, and tone of voice. While hearing is not the sole element of communication, it plays a central role. Hearing is likely to be the sense that first makes us aware of the world around us, at an age as early as gestational week 20, and it is potentially the last sense that abandons us when we pass away (Konradsson, 2011). Hearing impairment cannot be considered an isolated deficit since it is associated with a number of psychosocial limitations (Lenarz et al., 2002). Lack of communication often leads to social isolation.

If the majority of hair cells in the cochlea are damaged, or if the cochlea or auditory nerve is malformed or absent, hearing loss is profound and permanent. A cochlear implant (CI) or an auditory brainstem implant (ABI) are prostheses for the hearing sense and can recompose the ability to hear in profoundly deaf patients. Artificial hearing via the CI or ABI can range from the ability to hear environmental sounds and lip reading enhancements, to gaining open-set speech perception and being able to manage telephone conversations.

CI is today a routine treatment for patients with profound hearing loss, whilst ABI is still rare, complicated and in the beginning of its era. There are more than 300 000 CI users globally, and the number of ABI users is approximately 1200. The less common ABI patient group instantly caught my interest when I first met some of these patients in 2005. The complexity of their situation and hearing impairment is a challenge to manage. There are no ‘usual’ cases among this patient group. They are all individually unique and each case represents a hearing rehabilitation challenge.

Although CI is a routine treatment, new groups of patients are becoming eligible. Today, patients that have experienced a considerable duration of deafness are eligible for a CI and can benefit from it, in addition to patients with partial deafness. These novel patient groups further challenge the rehabilitation process and have pushed boundaries with unexpected results. Meeting patients with CIs and ABIs provides significant meaning to my professional life and career. It is a privilege to be a part of a hearing implant team that helps

introduce these patients to a world with more sounds and improved communication. With this thesis, I hope to contribute knowledge to this field so that current and future CI and ABI patients may benefit.

Background

Sound

Sound comprises pressure waves, generated from a sound source, that propagate through a medium with the speed of sound. The speed of sound is dependent on the surrounding medium. The amplitude of the pressure wave is measured in pascal (Pa) and can be expressed on a relative logarithmic scale in decibel (dB). The decibel scale is related to the human hearing range and the human ear can perceive sounds from a sound pressure level (SPL) of 0 dB (20 μPa) to approximately 130 dB (~60 Pa). The number of pressure variations per unit of time is known as the frequency and is measured in hertz (Hz, number of periods per second). The human ear can perceive frequencies from 20–20 kHz and is most sensitive to frequencies corresponding to human speech, i.e., approximately 2–5 kHz. The SPL of normal speech 1 meter in front of a speaker is approximately 60–65 dB (Arlinger, 2007).

Hearing

The human auditory organ receives air-led vibrations (pressure waves) and, via the outer and middle ear, these are transformed into mechanical vibrations, and further transmitted to the inner ear. The inner ear converts the vibrations into electrical nerve impulses that are relayed to the brain. The nerve signals are processed and interpreted in the auditory cortex.

The inner ear comprises the cochlea and the vestibular organ. Both of these are embedded in the temporal bone. The cochlea contains three fluid-filled channels that spiral around the modiolus. The outer channels, the scala vestibuli and scala tympani, are filled with perilymph while the middle channel, the scala media, is filled with endolymph. The scala vestibuli and scala tympani are connected at cochlea apex via the helicotrema. The scala media is separated from the scala vestibuli by the Reissner's membrane, and from the scala tympani by the basilar membrane (Figure 1).

The organ of Corti (the hearing organ) containing the hair cells is located on the basilar membrane. It comprises a single row of inner hair cells (IHC) and three to five rows of outer hair cells (OHC). There are approximately 3500

IHCs and 12,000 OHCs in total (Gelfand, 2010). At the cochlear base, the basilar membrane is narrower, thicker, and stiffer than at the apex. At the base, the hair cells and their sterocilia are also shorter than at the apex. The underlying mechanism for the frequency analysis of incoming sound relates to the physical properties of the basilar membrane and hair cell characteristics. Auditory sensitivity and frequency resolution also depend on an outer hair cell-based amplification in the cochlea.

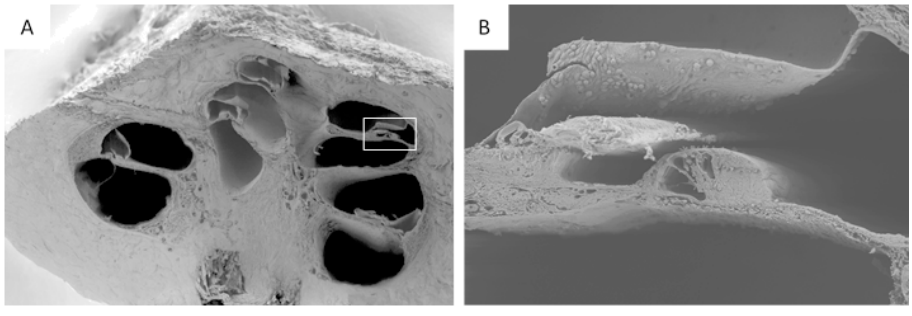

Figure 1. A) The modiolus in the center is surrounded by the scala tympani, scala vestibuli, and scala media. The modiolus houses the neural bodies of the auditory nerve. The framed area is magnified in B. B) The organ of Corti and the hair cells are situated on the basilar membrane, the tectorial membrane is above, and the Reissner's membrane comprises the uppermost layer. Helge Rask-Andersen©

When sound waves reach the eardrum, the vibrations are transmitted via the middle ear ossicles to the oval window. The pressure in the scala vestibuli increases when the oval window moves inwards and a pressure wave propagates through the cochlea. This produces a travelling wave in the basilar membrane (described by George von Békesy who received the Nobel Prize in Physiology or Medicine in 1961) and the organ of Corti becomes set to move. When the organ of Corti moves, the hair cells bend due to contact with the tectorial membrane. This generates receptor potentials in the hair cells due to inherent ion channels that, via the release of the transmitter substance glutamate, further activate the associated afferent nerves to generate an action potential in the cochlear nerve. The round window in the cochlea forms a release valve to generate perilymph pressure variations and undergoes reverse movements compared with the stapes. The traveling wave propagates along the cochlea and forms frequency-dependent amplitude maxima at various distances. High frequencies generate maximum displacement of the basilar membrane at the cochlear base and low frequency sounds at the cochlear apex. Frequencies below 20 Hz pass through the helicotrema without causing any movement of the organ of Corti and are therefore inaudible.

The mechanical frequency analysis, where the frequency of the incoming sound determines what part of the organ of Corti will be activated, is described

by the place theory. For incoming high frequency sounds, a small part of the basilar membrane is displaced, compared with low frequency sounds, activating a relatively larger proportion of the basilar membrane. To overcome this difference in frequency resolution phase locking occurs for frequencies below 4–5 kHz. Phase locking means that the electrical activity in the auditory nerve is directly related to the frequency of the incoming sound so that the nerve impulses arise at a given phase (Arlinger, 2007; Gelfand, 2010). Greenwood (1990) developed a frequency-position function that allowed for estimation of the location of a specific frequency on the organ of Corti.

The two types of hair cells have different functions. The OHCs are predominately connected to efferent nerve fibers and enable the central nerve system (CNS) to influence hearing organ sensitivity and function. The IHCs are mainly connected to afferent nerve fibers that lead from the organ of Corti to the brainstem. The electrical impulses from the hair cells are transmitted to the spiral ganglion cells that are located in the cochlear modiolus. There are approximately 35,000 spiral ganglion cells (Spoendlin & Schrott, 1989; House, 2011; Gelfand, 2010) and these are mainly connected to the inner hair cells. The spiral ganglion cells have myelinated axons; however, the neural cell bodies are unmyelinated in humans. The auditory nerve terminates in the ventral (VCN) and dorsal cochlear nucleus (DCN). The cochlear nucleus (CN) contains different types of nerve cells, each responsible for different parts of information from the auditory nerve. From the CN, the information from the different cell types are sent in separate pathways up the brainstem. Some neurons cross at the midline several times, and most of the information from the right ear reaches the opposite side of the brain, and vice versa. On route to the auditory cortex in the brain, the signal, or parts of the signal, passes the olivary complex, the lateral lemniscus, and the inferior colliculus (IC). From the IC, information reaches the corpus geniculatum mediale in the thalamus, and from there, via the radiatio acustica, it reaches the auditory cortex in the temporal lobe. Information in the left and right side of the auditory cortex is coordinated in the corpus callosum (Figure 2). In the majority of individuals, most of the speech processing in the auditory cortex is performed by the left side of the brain.

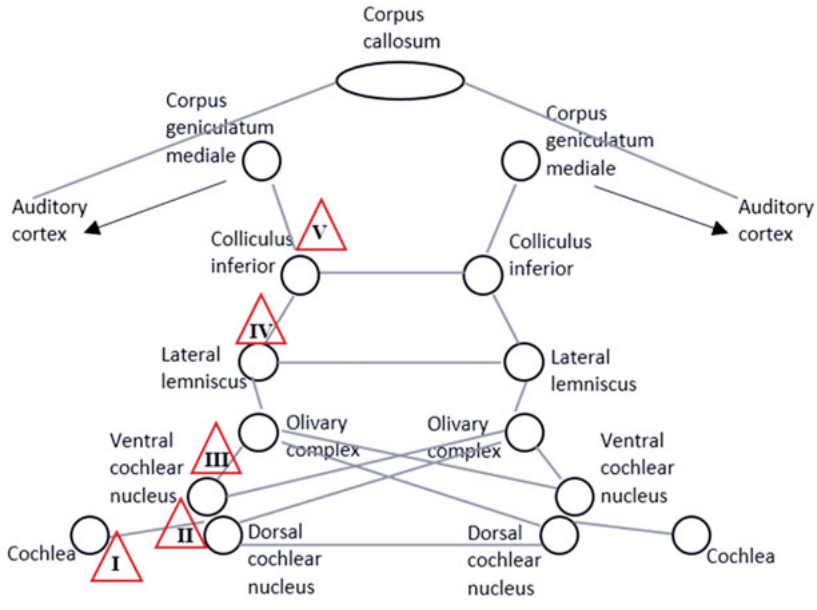

Figure 2. Schematic illustration of auditory pathways and generators of the components I–V in the auditory brainstem response (ABR).

Tonotopical organization from the cochlea is maintained through the entire hearing system in a complex manner. Basal axons enter via the dorsal part of the DCN, while apical axons enter via the VCN and also parts of the DCN (Gelfand, 2010). Sando (1965) described a twisting of the nerve fibers in the CN that result in a three-dimensional tonotopical organization. Komune et al. (2015) stated that each subunit of the CN has its own tonotopy. The tonotopical organization of the CN does not run along the surface, instead it runs orthogonal to the surface, with low frequencies near the surface and high frequencies deeper in the CN (Shannon, 2015).

Hearing loss

In profoundly deaf patients, the hair cells in the inner ear are commonly damaged and have lost the ability to transmit electrical impulses through the cochlear nerve. Infrequently, the reason for deafness can be a severely ossified, malformed, or absent cochlea or auditory nerve.

Congenital hearing loss is commonly caused by genetic aberrations (approximately two thirds of patients) (Deklerck et al., 2015). Genetic hearing loss can be either non-syndromic (hearing loss is the sole disability) or syndromic.

Syndromes occur in almost half of the children with hearing impairment. Several syndromes are associated with hearing loss or deafness, such as Wardenburgs, Goldenhars[1], Treacher-Collins, Turners, Ushers, or CHARGE[2]. The most common cause of non-genetic hearing loss is the cytomegalic virus (CMV) (Arlinger, 2007; Karltorp, 2013). It has been reported that 40% of children with hearing impairment may have other developmental problems (Fortnum & Davis, 1997).

Among adults, the common causes of hearing loss are inherited hearing loss, presbyacusis (age-related hearing loss), noise exposure, chemicals/medicines toxic to the hearing system, Meniere's disease, and vestibular schwannomas (acoustic neuromas).

Neurofibromatosis type 2

Neurofibromatosis type 2 (NF2) is a genetic autosomal dominant disease that occurs in approximately one in 25,000–50,000 births (Asthagiri et al., 2009; Ferner et al., 2011; Evans et al., 1992; Evans, 1998). The disease was first described by the Scottish surgeon Wishart in 1822 (Evans et al., 2000). The number of NF2 cases in Sweden is unknown; however, the Swedish Medical Agency (Socialstyrelsen) estimates that approximately four children born per year will go on to develop NF2 (Socialstyrelsen, 2009). The risk of inheriting the disease is approximately 50%. In NF2, approximately 50% of cases have an affected parent and 50% are the result of a new mutation (Evans et al., 1992; Evans, 1998). The average age at disease onset is 18–24 years (Evans, 1998). The penetrance is almost 100% at the age of 60 (Asthagiri et al., 2009).

NF2 is characterized by the development of bilateral vestibular schwannomas (VS), in addition to intracranial meningiomas, spinal tumors, peripheral nerve tumors, and presenile lens opacities. There are two types of the disease. The Wishart type is more aggressive with earlier onset and multiple tumors. The Gardner type manifests in later stages of life with fewer tumors and occasionally only bilateral VS (Evans et al., 1992). While the tumors are unmalignant, their location and multiplicity results in significant morbidity and early mortality (Evans et al., 1992; Evans, 1998). The development of bilateral VS leads to progressive sensorineural hearing loss, tinnitus, and loss of balance in many cases. One third of NF2 patients have affected vision in one or both eyes due

[1]Goldenhar syndrome is characterized by asymmetries of the face, malformations of the vertebra, eye issues, and occasionally malformed ears. Approximately 1–2 children with Goldenhar syndrome are born in Sweden per year (Socialstyrelsen, 2015).
[2]CHARGE syndrome is characterized by eye, heart, nose, genitals, and ears defects, and retardation of growth and/or development. Approximately 10 children with CHARGE syndrome are born in Sweden per year (Socialstyrelsen, 2012).

to the disease (Evans, 1998). Other symptoms of the disease are facial paresis, seizure, pain, muscle weakness, paresthesia, nausea, vomiting, and headache (Ferner et al., 2011).

The growth of VS tends to be faster in patients diagnosed at an earlier age. The risk of mortality increases with decreasing age at diagnosis and in patients with intracranial meningiomas (Baser et al., 2002). NF2 has a tendency to worsen over time as the tumors increase in size, with most patients requiring surgical intervention (Stivaros et al., 2015). The main focus of VS surgery is to limit the neurological symptoms with the additional aim of preserving facial and hearing function if possible. The facial nerve can pass through the tumor area and may be difficult to recognize. Radiosurgery, typically utilizing gamma knife, may offer an alternative to surgery in pertinent cases.

NF2 frequently causes deafness, either as a direct result of the tumors, or due to the life-saving surgery performed to remove the tumors (Ferner et al., 2011). VS causes hearing loss through the compression and stretching of the auditory nerve. However, the mechanism behind tumor-induced hearing loss is not clearly understood because hearing loss can have an unpredictable onset and its progression can be gradual, stepwise, relapsing and remitting, sudden, or complete (Asthagiri et al., 2012). In a study of 56 NF2 patients, Asthagiri et al. (2012) concluded that hearing loss may be the result of elevation in intralabyrinthine protein.

Cochlear and auditory brainstem implants

A CI or an ABI are prostheses for hearing that can be implanted in patients with severe hearing impairment to bypass the non-functioning inner ear (CI), or the non-functioning or absent auditory nerve (ABI). In contrast with the ABI, the CI requires a functioning cochlear nerve to operate. The implant system comprises one external part (the sound processor) and one internal part (the implant) (Figures 3, 5, & 6).

The sound processor contains one or more microphones that collect sound signals. The signals are then processed by the sound processor microcomputer that analyzes incoming sound, and makes adjustments to increase audibility of the incoming speech signal by reducing background noise and enhancing the speech signal [front end]. Following this, the signal is divided into different frequency bands according to the number of active electrodes on the implant [filters]. A digital code is produced for the stimulus parameters to represent the incoming sound signal [strategy and amplitude mapping]. The coded signal, together with power, is transmitted by radio signals through the skin to the implant [RF encoder] containing information on which electrode is to be

stimulated, and at what level. The implant receiver is placed behind the mastoid bone, and decodes the signal into power and signal [decoder/encoder], organizes the stimulation pattern [controller], and facilitates the electrical currents that are sent to the electrode array [back end] in the scala tympani (for a CI) or the electrode plate placed on the CN (for an ABI). Modern implants have the ability to send information from the implant back to the speech processor via telemetry. Sound processor and implant principles are shown in Figure 3.

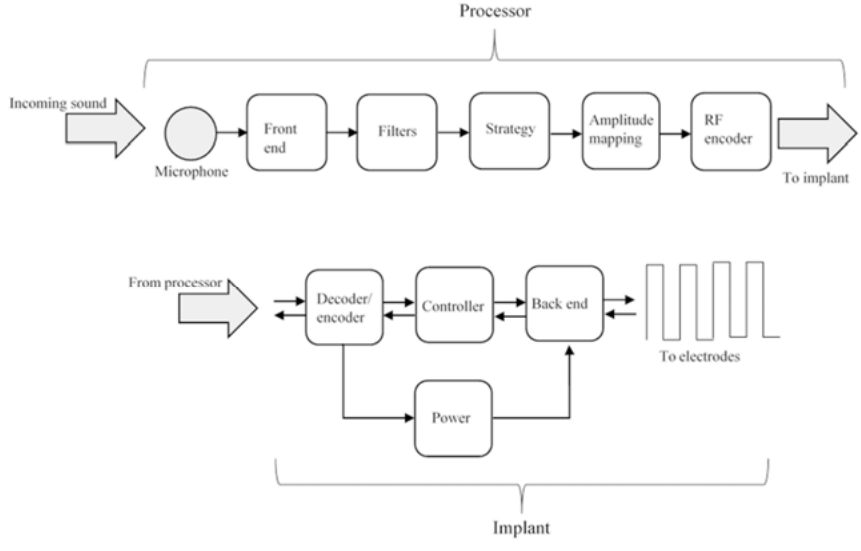

Figure 3. The principles of a sound processor and an implant. Modified illustration from Clark (2003).

Stimulation strategies

The stimulation strategy describes the algorithm used to transform the important features of incoming sound into an electrical code. There are a number of strategies that are commonly utilized by modern CIs; however, while they are relatively dissimilar, their performance between patients is essentially the same (Wolfe & Schafer, 2015). The Spectral Peak (SPEAK) and Advanced Combination Encoder (ACE) strategies are frequency-based strategies that focus on the spectral properties of the incoming sound, while Continuous Interleaved Sampling (CIS) is time-based, focusing on the temporal cues. The strategies SPEAK, CIS, and ACE, utilized in modern implants from MED-EL (Innsbruck, Austria) and Cochlear (Lane Cove, NSW, Australia), are described below.

SPEAK

In the SPEAK strategy, incoming sound is divided into frequency bands and the bands with the highest amplitude are selected for stimulation. The number of bands selected depends on the number of maxima used (typically 8–12). Biphasic pulses, at a fixed rate (typically 250 pps) are sent to the electrodes. The SPEAK strategy can be used with implants from Cochlear (Wolfe & Schafer, 2015; Clark, 2003).

CIS

The CIS strategy can be utilized with implants from both MED-EL and Cochlear and is considered a pioneer for current strategies. The incoming signals are divided into discrete frequency bands and the waveform envelopes from the band-pass filters modulates a high-rate pulse train. The stimulation frequency is fixed (typically 800–1600 pps) and the amplitude of stimulation corresponds to the energy present in that frequency band. All electrodes are sequentially stimulated. MED-EL additionally has variants of CIS called CIS+, HDCIS, FSP, FS4, and FS4-p. In CIS+, the frequency is expanded and in HDCIS sequential stimulation on adjacent electrodes is used to create virtual channels at a higher stimulation rate. In FSP, bell-shaped overlapping band pass filters are used to create in-between pitches, a method of current steering. FSP also modulates the timing of the stimulation for low frequencies i.e., the stimulation frequency changes adaptively to correspond with the frequency of the incoming signal. All other channels are stimulated with HDCIS in FSP. In FS4 and FS4-p, the fine structure processing is utilized on up to four of the most apical channels and it offers higher temporal accuracy compared with FSP. FS4-p is also capable of stimulating two of the most apical channels in parallel (Wolfe & Schafer, 2015; Clark, 2003).

ACE

The ACE strategy is similar to SPEAK, but has a higher rate of stimulation. This strategy is utilized by Cochlear. The stimulation rate per channel (typically 900–1800 pps) is dependent on the number of selected maxima (typically 8–12). ACE(RE), a variant of ACE has an even higher stimulation rate, and in the variant MP3000, unimportant information is rejected so that the signal is conveyed in a more efficient manner (Wolfe & Schafer, 2015; Clark, 2003).

Stimulation modes

The stimulation mode describes how the electrodes on the implant are ‘connected’ to form an electrical circuit. The electrical circuit comprises the current source/signal generator, the active electrode on the electrode array/plate, and the reference/ground electrode. The electrode contact, cochlear fluids, and other tissues adjacent to the active electrode contact serve as the reactive ele-

ments in this electrical circuit (Wolfe & Schafer, 2015). The two modes described below are the most commonly utilized stimulation modes in clinical practice today.

Monopolar mode

In the monopolar (MP) mode, the active electrode is an electrode on the electrode array/plate, and the reference electrode is located on an electrode lead separated from the active electrodes and/or on the implant housing. Typically, only the active electrode, not the reference electrode, is located in the cochlea or at the CN. Today, the MP mode is the default setting for CIs and produces the lowest threshold- (T) and most comfortable- (C) levels. The MP mode is necessary for the faster stimulation strategies such as CIS and ACE. For Cochlear devices, that have two reference electrodes, MP1+2 refer to the utilization of both reference electrodes: '1' refers to the external reference electrode and '2' refers to the reference on the implant housing (Figure 4 A, B).

Bipolar mode

In the bipolar (BP) mode, an electrode adjacent to the active electrode serves as the reference electrode. For implants from Cochlear, BP+1 on a CI indicates that the active and reference electrodes are separated by one electrode. For the Cochlear ABI, BP+5 means that the active and reference electrodes are separated by one electrode. While the BP mode provides more focused stimulation than the MP mode, the MP mode has proven superiority mainly because the BP mode requires higher stimulation levels that slow down the stimulation rate. As the BP configuration widens, the number of channels to stimulate decreases. On the ABI, for example, BP + 5 provide 15 possible channels. The BP mode can be utilized with the SPEAK strategy (Figure 4 C, D).

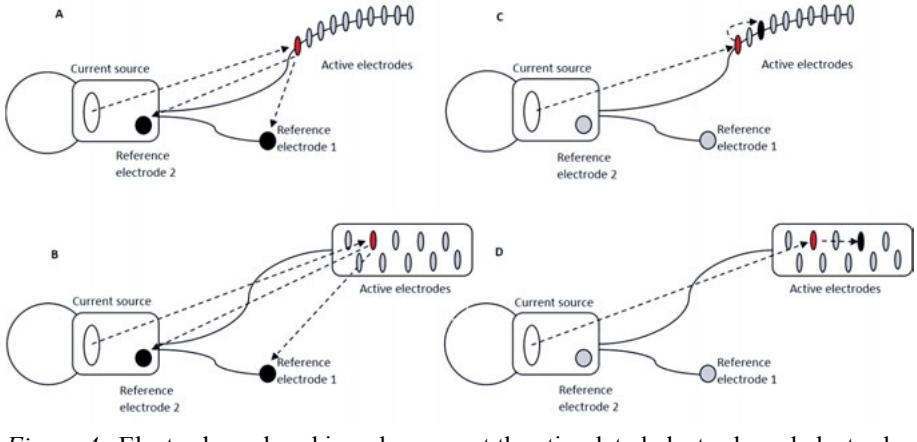

Figure 4. Electrodes colored in red represent the stimulated electrode and electrodes colored in black the ground/reference electrode. (A) monopolar mode on a CI (B) monopolar mode on an ABI (C) bipolar mode on a CI, BP+1 (D) bipolar mode on an ABI, BP+5.

Cochlear implants

On a CI, the electrode array lies close to (but not attached to) the spiral ganglion cells in the cochlea (Clark, 2003) (Figure 5). Duration of deafness, age at implantation, etiology, and hearing in the contralateral ear are some of the factors that are thought to influence CI outcome (Boisvert et al., 2011, 2012a, b; Friedland at al., 2003; Távora-Vieira et al.,2013; Holden et al., 2013; Moon et al., 2014). Today, more than 300 000 patients globally have CIs (Yawn et al., 2015).

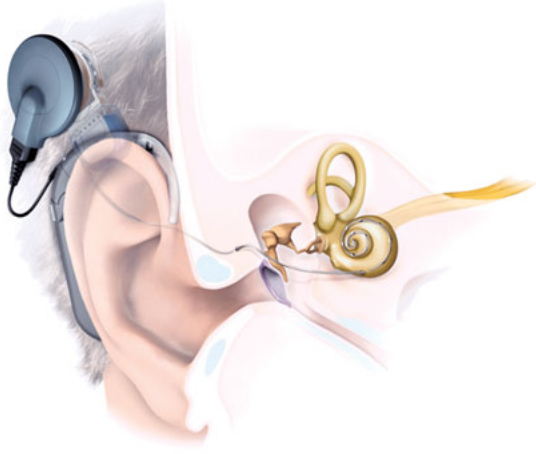

Figure 5. The principles of a cochlear implant. MED-EL (Innsbruck, Austria)©

Auditory brainstem implants

The principles of an ABI are the same as those of a CI, with the exception that the electrode array is replaced by an electrode plate (Otto et al., 2002) (Figure 6). The ABI is designed for patients with bilateral auditory nerve lesions that occur mainly in bilateral VS, a main characteristic of NF2 (Kalamardies et al., 2001; Sanna et al., 2012; Shannon et al., 1993). Implantation is usually performed at the time of tumor removal, when hearing preservation is not feasible due to the size of the tumor or when the patient is completely deaf (Kalamardies et al., 2001; Vincent, 2012). The ABI can also be implanted during the first tumor removal, when hearing still remains on the contralateral ear. In these cases, the implant may not be activated until later, when hearing loss has also progressed on the opposite side, and the implant might be a so called ‘sleeper’ (Grayeli et al., 2008). The general agreement among surgeons performing ABI implantations is that the insertion of the implant does not increase the rate of complications related to surgery in NF2 patients (Colletti et al., 2010); this has also been demonstrated in a study by Nevison et al. (2002).

In contrast to a CI, the contacts on the electrode plate do not usually lie in correct tonotopical order. Pitch perception for a single channel varies with strength of stimulation and seldom provides a clear perception of pitch. This is probably due to the three-dimensional tonotopical organization of the CN (Sando, 1965; Otto et al., 2002). In addition, the current penetrates the CN at different levels depending on the amount of current sent to the implant, and current spread changes with stimulation strength (Nevison et al., 2002; Colletti et al., 2009; McCreery, 2008).

For most patients, an ABI helps them hear environmental sounds, enhances lip reading, provides sound awareness, and assists in voice control (Vincent, 2012; Behr et al., 2014; Lenarz et al., 2001; Grayeli et al., 2008; Otto et al., 2002; McCreery, 2008). Though rare, some patients have demonstrated open-set speech perception with an ABI (Lenarz et al., 2001; Colletti et al., 2005; Shannon, 2015; Matthies et al., 2014). Factors that influence outcomes commonly discussed in the literature comprise tumor size, duration of deafness, pre-implant radiosurgery, electrode placement, anatomy, degree of damage to the brainstem due to tumor removal, and the number of activated channels on the implant (Kalamarides et al., 2001; Grayeli et al., 2008; Colletti et al., 2005; Gharabaghi et al., 2008; Azadpour & McKay, 2014; McCreery, 2008). Today, more than 1200 patients globally have an ABI and the inclusion criteria have widened to include non-NF2 patients, both adults and children (Shannon, 2015).

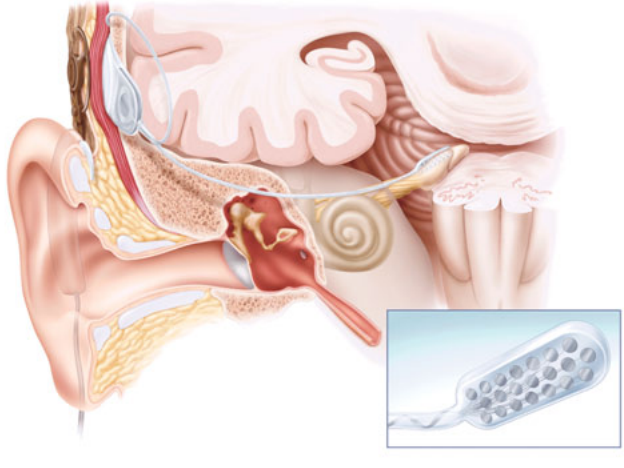

Figure 6. The principles of an auditory brainstem implant. Cochlear (Lane Cove, NSW, Australia)©.

Auditory brainstem responses

The auditory brainstem response (ABR) measurement is an objective way to test the hearing system and is used for two main purposes; to estimate hearing thresholds and to determine retro-cochlear pathologies (Arlinger, 2007). This technique can also be utilized as a tool to examine if the stimulation from a CI or an ABI reaches brainstem structures. In the first 10 ms after a click stimuli is presented to the ear, a number of small waves can be recorded from the scalp. The principle behind recording ABR is that stimuli are presented to one or both ears and scalp electrodes detect changes in voltage from the skin. An amplifier is required because the amplitude of the recorded signal is extremely small. A computer is used for analog to digital signal conversions, filtering to remove unwanted frequencies, and for averaging data so that the ABR-signal can be extracted from noise (Atcherson & Stoody, 2012). The first five waves of the ABR are numbered I–V (Moore, 1983) (Figure 7).

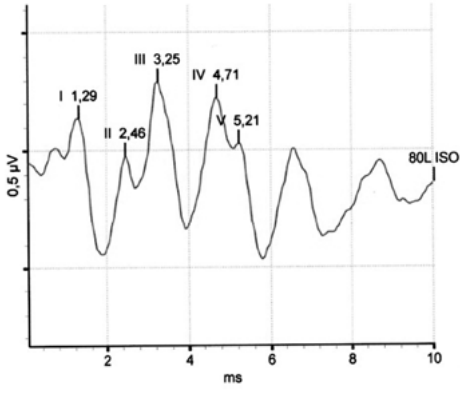

Figure 7. The first five waves (I–V) in the acoustic ABR response.

Jewett et al. (1970) was among the first to describe the ABR as used today. Waves I to V represent the spread of the auditory signal from the cochlea through the brainstem. In general, the waveform amplitude increase and the latency decrease with increasing stimulus level. Wave V is the most robust and consistent waveform, and is less affected by changing stimulus parameters compared with earlier waves (Moore, 1983). The origin of wave I is the cochlea, or the very beginning of the cochlear nerve. Wave II is likely to be generated in the cochlear nerve, close to the entrance of the brainstem. Wave III is believed to be generated mainly in the superior olivary complex, wave IV in the lateral lemniscus and/or inferior colliculus, and wave V in the inferior colliculus (Figure 2). With the exception of waves I and II, all waves are believed to have multiple generators (Gelfand, 2010; Arlinger, 2007; Elderling & Osterhammel, 1980; Jewett & Williston, 1971; Moore, 1983, 1987; Parkkonen et al., 2009). Characteristics of the recorded waveforms are dependent on a

number of parameters such as stimulus intensity, type of stimuli, stimulation rate, filter settings, electrode placement, muscle activity, age, sex, and temperature (Atcherson & Stoody, 2012).

Electrical evoked auditory brainstem responses

As an alternative to stimulating the ear with an acoustic stimulus, stimulation can be performed via the CI or ABI; electrical evoked auditory brainstem responses (eABR). The recorded waveforms are essentially the same as those of acoustic ABR when stimulating via a CI; however, the first wave are absent and the latencies are shorter. When stimulating via a CI, wave I is missing because the implant stimulation occurs in the cochlea where wave I is generated and this wave is commonly shaded by the stimulation artifact (Abbas & Brown, 1988; Cinar et al., 2011; Gordon et al., 2007; Firszt et al., 2002a) (Figure 8). When stimulating via an ABI, waves I and II are missing because stimulation occurs at the CN (Frohne et al., 2000; Herrmann et al., 2015; Nevison et al., 2002) (Figure 9). Waveform shapes are also considerably different when stimulating via the ABI. One explanation may be that the stimulation occurs at one of the possible generators of wave III, and because waves III, IV, and V are thought to have multiple generators; however, this presently remains unclear.

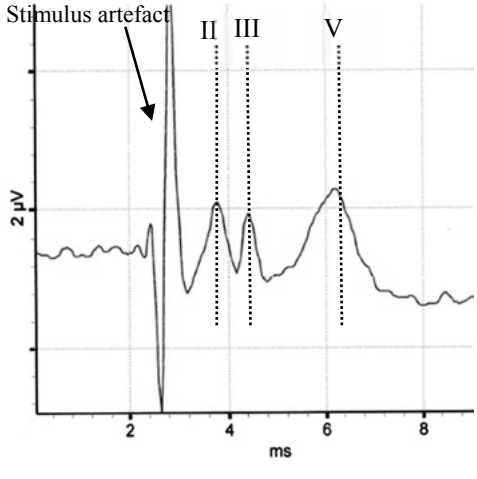

Figure 8. Waves II, III, and V in the eABR when stimulating via a CI.

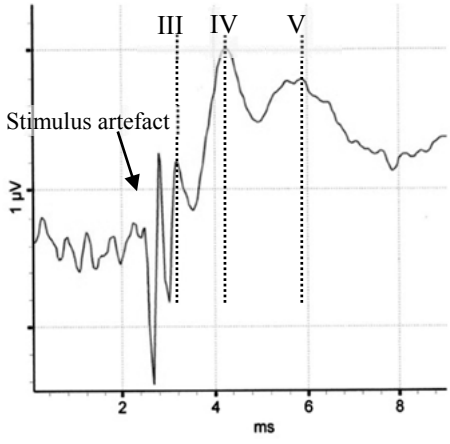

Figure 9. Waves III, IV, and V in the eABR when stimulating via an ABI.

History of cochlear and auditory brainstem implants

Cochlear implants

In the late 1790s, Alessandro Volta, an Italian professor of physics, performed one of the first experiments of auditory nerve electrical stimulation. He performed the experiment on himself and perceived a jerky cracking or bubbling noise, but did not repeat the experiment because it was an unpleasant experience. Murdy (2013) described an experiment performed on a deaf woman by the English portraitist and electricity researcher Benjamin Wilson even earlier, in 1748. Over the following 50 years, a few more studies in this area were published (described by Clark, 2003). In 1868, Brenner published his results from a systematic investigation of auditory system electrical stimulation. In 1925, several radio engineers described the perception of tones by electrical stimulation near the ear. This was the beginning of the modern era of electrical hearing (Simmons, 1966). In 1950, the Swedish neurosurgeon Lundberg stimulated a patient's auditory nerve with a sinusoidal electrical current and found that it was perceived as noise by the patient (Gisselson, 1950).

In 1957, Djourno and Eyriés reported a case involving the placement of an electrode on the auditory nerve in a patient that had both cochleae removed. This comprised the first attempt of direct electrical stimulation of the auditory nerve in humans. The patient could hear rhythm that enhanced lip reading (Djourno & Eyriés, 1957). Dr William House, in Los Angeles, was inspired by the work of Djourno and Eyriés and developed, together with the engineer Jim Doyle, an extra cochlear single channel implant that was implanted in the first two patients in 1961 (Ramsden, 2013). Both patients reacted to speech and environmental sounds; however, after 2 weeks the implants were removed

due to redness and swelling around the receivers (House, 1987, 2011; Mudry, 2013). House, together with the engineer Jack Urban, later developed the first commercial CI that could be used outside the laboratory (House & Urban, 1973; Eshraghi et al., 2012). William House is widely regarded as the 'father of CI' (Eshraghi et al., 2012). Blair Simmons at the University of Stanford implanted a six channel implant in 1961 (Simmons, 1966). The term CI was first coined by Simmons during a microsurgery workshop in 1967 (Mudry, 2013). In 1973, the first international conference on electrical stimulation of the acoustic nerve as a treatment for profound sensorineural deafness in humans was held in San Francisco. By then, the term CI was well established in the medical literature.

The first independent evaluation of CI was published in 1977 by R. Bilger and F. Black. They evaluated 13 patients and concluded that the next step was to further explore multichannel CIs. They believed that multichannel CIs were likely to be required in order to acquire speech understanding with CIs (Bilger & Black, 1977; Murdy, 2013; Eshraghi et al., 2012). The report, known as the 'Bilger Report' is considered a landmark in the development of CIs (Eshraghi et al., 2012). In the 1970s and 80s, the development of multichannel implants continued at several universities in the USA, Austria, Belgium, Germany, Australia, and France. Michael Merzenich at the University of California, San Francisco, conducted a number of studies on multichannel CIs in cats during the 1970s. Graeme Clark at the University of Melbourne, Australia, implanted his first multichannel CI in 1978 (Clark et al., 1981; Pfaltz, 1987). It became the first commercial multichannel CI, manufactured by Cochlear/Nucleus Ltd. (Murdy, 2013). Ingeborg and Erwin Hochmair, Austria were also among the pioneers in the era of multichannel CIs in the late 1970s (Yawn et al., 2015).

Finally, collaborations between university researchers and the industry formed the CI companies. House and Urban collaborated with 3M and created the House/3M single channel CI. Gream Clark's work on multichannel implants in Australia formed the Nucleus (Cochlear) company. The team, led by Robin Michelson and Michael Merzenich, at the University of San Francisco initiated collaboration with Advanced Bionics, originally evolved from two medical device companies that specialized in pacemakers and micro-infusions. At the Technical University of Vienna, Kurt Burian, the head of the Ear Nose and Throat clinic collaborated with electrical engineers Ingeborg and Erwin Hochmair and eventually founded MED-EL. In France, the research by Henri Chouard, a student of Eyriés, and Mac Leod formed Neurelec (Eshraghi et al., 2012). Later, a company called Nurotron was formed by electrical engineer Fan-Gang Zeng. This company aims to provide CIs in China (Chaikof, 2013).

An important aspect of the development and success of CIs was the coding strategies used to stimulate the auditory nerve. Blake Wilson, at the Research Triangle at Duke University in North Carolina, was one of the inventors of the

CIS-strategy that is still utilized today and is considered a pioneer of current strategies. The CIS strategy utilizes interleaved high rate pulsatile non-simultaneous stimulation (Wilson et al., 1991).

Auditory brainstem implants

House and Hitselberger described the first case of a NF2-patient that received a single channel ball electrode on the VCN at the time of tumor removal in 1979 (Hitselberger et al., 1984; Edgerton et al., 1982). Unfortunately, the implant failed after 2 months; however, it improved lip reading during its working period. After 2 years of deafness, the patient was re-implanted with a two-channel electrode, enhancing lip reading again, enabling the patient to hear environmental sounds, and improving voice control. The first ABI comprised a modified CI with percutaneous connectors and ball electrodes placed on the CN (Shannon, 2015). The first implanted ABIs comprised single channel implants (Sennaroglu & Ziyal, 2012); however, shortly after this, multichannel devices were developed. In 1989, the House Ear Clinic in collaboration with Cochlear developed the first commercial ABI with eight electrodes (Shannon, 2015). The ABIs on today's market are also produced by other companies; MED-EL, Advanced Bionics, and Neurelec (Sennaroglu & Ziyal, 2012).

Trials have been performed to investigate alternative designs of the ABI electrode plate due to the complex tonotopical organization of the CN. The ABI placed on the surface of the CN only accesses part of the CN neurons and may not efficiently transmit information through the auditory pathway (Azadpour & McKay, 2014). A trial with a penetrating ABI (PABI) was performed in 2003 (Shannon, 2015; Otto et al. 2008). Ten patients were implanted in the CN. The stimulating thresholds were much lower compared with the ABI, with no channel interference, and the patients perceived high pitched sounds with a clear quality. Unfortunately, none of the ten patients gained significant open-set speech perception with the PABI device and no significant improvement in PABI outcomes compared with the ABI were recorded. Since the PABI was more difficult to manufacture and to implant, no further trials of the device were performed. Lim et al. (2008) reported on clinical trials investigating an auditory midbrain implant (AMI) designed to be placed in the IC. The AMI is a penetrating electrode and has been placed in the IC of five patients. The exact placement of the electrode array within the midbrain appears to have a large impact on its performance (Lim et al., 2008). Lenarz et al. (2006) stated that the well-defined tonotopical structure of the IC should be favorable for implantation. McCreery (2008) speculated that the best solution may potentially be an implant that combines surface electrodes with penetrating electrodes. The implant may be best placed on another structure, such as the IC, rather than the CN since it is frequently damaged in NF2 patients due to tumor removal. McCreery (2008) commented on the problems related to how to encode sound to the implant, in order to compensate for the various types of

nerve cells in the CN responsible for different parts of information from the auditory nerve.

Cochlear and auditory brainstem implants in Sweden

Professor Göran Bredberg was the first to implant an extra-cochlear CI in Stockholm in 1984. In 1990, Professor Sten Harris in Lund first implanted a CI in a child. In Uppsala the first CI patient was implanted in 2001 by Professor Helge Rask-Andersen. Today, teams in Lund, Göteborg, Linköping, Örebro, Stockholm, Uppsala, and Umeå routinely implant patients with CIs, and there are approximately 3100 CI recipients in Sweden (December 2015).

Uppsala University hospital are currently the only hospital in Scandinavia implanting ABIs, and Professor Helge Rask-Andersen from Uppsala, first came in to contact with the ABI-technique in 1988–89 when visiting the House Clinic in Los Angeles. Shortly after in 1993 in Uppsala, he met a young, almost completely deaf man with NF2 who instantly required life-saving surgery. Professor Rask-Andersen contacted the House Clinic, and Dr Brackmann and Dr Hitselberger operate on the patient in Sweden. The patient was implanted with an eight channel ABI from Cochlear. The first child was implanted with an ABI in 2009 under the supervision of Professor Vittorio Colletti. Today 28 ABIs have been implanted in Uppsala in patients from Sweden, Norway, Denmark, and Iceland (January 2016). Most of these implantations were performed by the neurosurgeon Gunnar Nyberg.

Rehabilitation of hearing in implant patients requires teamwork. The team in Uppsala comprises an audiologist, an audiological physician, a surgeon, an engineer, a hearing therapist, a medical social worker, a speech and language therapist, and a coordinator. Other teams in Sweden are similarly composed. For ABI patients with NF2, the situation is far more complex since, in addition to their hearing loss, they require additional medical support. A variety of professionals from different hospitals are involved in the management of the progressing disease.

New indications for cochlear and auditory brainstem implants

The classic indication for CI in Sweden are as follows: a score below 50% on phonetically balanced monosyllabic (MS)-words in the best ear (with an optimal fitted hearing aid (HA) in the free-field or via earphones), an audiometric threshold of 50 dB SPL or higher at 4 kHz with an optimal fitted HA in the

best ear, or a PTA > 70 dB HL (0.5, 1, 2, and 4 kHz) in the best ear (Socialstyrelsen, 2011a). The patient should be well rehabilitated and have had reasonable long deafness duration before implantation. For ABIs, until recently, the only indication comprised patients above the age of 12 with NF2.

However, it has become accepted that CIs can also be utilized in other patient groups. Patients with high frequency deafness, with almost normal auditory thresholds at low frequencies, are now being implanted to gain high frequency hearing (Skarzynski et al., 2007; Lorens et al., 2008; Erixon et al., 2012; Erixon & Rask-Andersen, 2015). The first hearing preservation surgery in Uppsala was performed in 2008 with a 24 mm electrode array through the round window. Individual cochlear length and electrode insertion depth are critical issues to consider for this patient group. A number of studies regarding cochlear length, hearing preservation, and hybrid hearing were conducted in Uppsala by Erixon et al. (2009, 2012) and Erixon & Rask-Andersen (2013, 2015). Even single-sided deaf patients can now receive implants, and CIs are occasionally utilized as a tinnitus treatment, although this is not yet common in Sweden (Arndt el al., 2015; Ramos Macías et al., 2015; Vermeire & Van de Heyning, 2007; Van de Heyning et al., 2008).

Today, patients with a considerable duration of deafness can be successfully implanted (Boisvert et al., 2011, 2012a, b; Friedland at al., 2003; Távora-Vieira et al., 2013; Moon et al. 2014). However, an extended period of deafness prior to CI was previously considered a contraindication. The Swedish Medical Agency (Socialstyrelsen) discusses a deafness duration limit of 15 years in their publication 'Indications for Unilateral Cochlear Implants in Adults' (Socialstyrelsen, 2011a). The cell-biological research performed in Uppsala has had a direct clinical impact regarding implantation of patients with long term deafness. Studies have shown that human auditory nerves behave differently from nerves in animals (mainly rodents). The deterioration of the auditory nerve in humans following hair cell loss is slow, and neurons persist as 'amputated' or monopolar cells with connections to the brain stem remaining. Human spiral ganglions can persist electrically excitable with a CI, even after a long duration of deafness. The unmyelinated cell bodies may help to preserve the auditory nerve despite long periods of inactivation, potentially due to connexin 43-mediated gap junction signaling in the surrounding satellite glia cells (Liu et al., 2014).

ABIs, that were initially designed and used for NF2 patients with bilateral VS, are presently also used for adults and children with congenital cochlear malformations, cochlear nerve hypoplasia/aplasia, or cochlear ossification after meningitis (Colletti et al., 2005; Kaplan et al., 2015; Noij et al., 2015; Shannon, 2015). Professor Vittorio Colletti in Italy was the first to implant pediatric patients lacking an auditory nerve (Colletti et al., 2002a). The outcomes for

non-tumor patients are expected to be better than those of NF2 patients due to the unaffected brainstem. Colletti et al. (2009) found large differences in the performance between NF2 patients and non-tumor patients. The first pediatric non-NF2 patient in Uppsala was implanted by Gunnar Nyberg in 2009.

These new groups of CI and ABI patients increase demand on the medical teams responsible for implantation and rehabilitation. The decision to implant a NF2-patient, a child with an ABI, or a patient with a long deafness duration with a CI may be considered a philosophical question. What level of hearing from the implant is 'enough' for a successful implantation? Is it when the patient is able to perceive a specific score on a speech perception test, or when the patient reports benefit from the implant, irrespective of speech perception outcomes? Should it be a question of health economics and how much is hearing worth? Useful hearing does not include speech perception alone. However, it is important that we improve our knowledge and tools to predict the outcome of implantation, in order to help patients decide on implantation and advise them on rehabilitation process expectations.

Thesis aims

The aims of this thesis were to:

- Evaluate hearing outcomes in patients implanted with a CI after a long duration of deafness (deafness duration > 20 years), and investigate if there is a deafness duration limit for these patients.
- Determine if intra-operatively measured eABR can predict CI hearing outcome.
- Investigate if eABR can be utilized as a tool for selecting between CI or ABI implantation in pertinent cases.
- Describe the clinical experiences from ABI surgeries in Uppsala with regard to surgery, complications, and technical aspects.
- Explore ABI use, hearing outcomes, and patient satisfaction (is it worth the effort according to patient evaluation?) for ABI patients implanted in Uppsala.
- Evaluate the potential benefits of ABIs in non-NF2 pediatric patients.

Materials and Methods

Paper I

This retrospective study was based on patient archives and medical records. The following data were collected: pre and postoperative speech perception, cause of deafness, deafness duration in the CI-ear, whether the patient was an implant user or not, hearing situation/deafness duration in the contralateral ear, age at implantation, intraoperative electrophysiological measurements; electrical Stapedius Reflex Thresholds (eSRT), Neural Response Telemetry (NRT), Auditory Response Telemetry (ART), and eABR.

Patients

All patients operated in Uppsala, with a minimum deafness duration of 20 years in the implanted ear (mean 40 years, range 20–72 years), were evaluated. Twelve adult patients, eight women and four men (13 implanted ears), were included. Mean age at implantation was 58 years (range 39–80 years). Patients underwent surgery between 2002 and 2013. Preoperative pure tone average (PTA; 0.5, 1, 2, and 4 kHz) was ≥ 110 dB HL (via earphones) and the MS-word scores were 0% in the ear to be implanted for all patients (with HA). Deafness duration was defined as the time in years since the sudden loss of hearing or, in progressive cases, the time in years since the patient was unable to benefit from HAs. Patient no. 10 (Table 1) had a MS-word score of 76% (with HA) in the contralateral ear prior to CI; this did not fulfill the CI criteria since hearing ability was considered to be too high. However, the patient could not use HAs due to iterated ear infections. She had bilateral chronic otitis media, ossicular chain disruption, and subtotal perforation of the tympanic membrane in the contralateral ear.

Patients were divided in three groups for analyses. Group 1 comprised patients who were also deaf in the contralateral ear (n = 5). Group 2 used a HA in the contralateral ear (n = 6). Group 3 included patients with severe peri or prelingual hearing loss (n = 2). The patient demographics are shown in Table 1.

Table 1. *Age at implantation, deafness duration, hearing in contralateral ear and age at onset of deafness.*

Patient no.	Age at implantation (years)	Deafness duration in the CI-ear (years)	Non-implanted ear	Age at onset of deafness in the CI-ear (years)
Group 1: deaf in the contralateral ear				
2	80	72	Deaf for 72 years	8
3	45	20	Deaf for 36 years	25
6, ear 1	39	22	Deaf for 35 years	17
6, ear 2	41	37	Deaf for 22 years, CI for 2 years	4
9	64	56	Deaf for 56 years	8
Group 2: HA in the contralateral ear				
1	72	39	HA-user for 30 years PTA: 86.3 dB HL MS 4% at 80 dB SPL (bilateral MS 0%)	33
4	65	47	HA-user for 15 years PTA: 91.3 dB HL MS 28% at 80 dB SPL (bilateral MS 18%)	18
5	64	50	HA-user for 44 years PTA: 0.5 kHz (80 dB HL) and 1 kHz (110 dB HL) MS 18% at 80 dB SPL (bilateral MS 10%)	14
10	54	30	HA-user for 30 years PTA: 93.5 dB HL MS 76% at 80 dB SPL (bilateral MS 74%)*	24
11	69	31	HA-user for 10 years PTA: 91.3 dB HL MS 12% at 75 dB SPL (bilateral not measured)	38
12	64	31	HA-user for 27 years PTA: 85 dB HL Bilateral MS 50% at 70 dB SPL	33
Group 3: bilateral peri or prelingual hearing loss				
7	47	Perilingual severe hearing loss for 35 years PTA: > 110 dB HL	HA-user for 35 years PTA: 0.5 kHz (95 dB HL), 1 kHz (115 dB HL), and 2 kHz (110 dB HL)	
8	49	Prelingual severe hearing loss PTA: > 110 dB HL	HA-user for 49 years PTA: 0.5 kHz (95 dB HL), 1 kHz (105 dB HL), and 2 kHz (105 dB HL)	

CI = Cochlear implant, HA = Hearing aid, MS = monosyballic words, PTA = pure tone average *Cannot use hearing aids due to iterated ear infections.

Device description and fitting

An implant from Cochlear (CI24RE(CA), CI422 or CI512) was used in eight patients (nine ears) and an implant from MED-EL (C40+, Concerto FLEX 28, or Concerto STD) was used in four patients. The patients were fitted 3–4 weeks postoperatively using a processor from Cochlear (Freedom or Nucleus 5) or MED-EL (Tempo+ or Opus2). The patients attended four appointments with the CI-team at the clinic during the first 2 weeks, and at 1, 3, 6, and 12 months post implantation.

Audiometry

Patients were evaluated preoperatively with a conventional pure tone audiogram. A list of 50 MS phonetically balanced words was used to test speech perception (Svensk Talaudiometri, C-A Tegnér AB, Stockholm, Sweden, 1998). The tests were performed in a sound-treated booth according to standard procedure. Speech perception tests (with HA or CI) were measured in free field with the loud speaker at 0° at a fix height. Preoperative best-aided MS-word scores (at a sound level chosen by the patient) and postoperative MS-word scores with CI only (at 65 dB SPL) were analyzed. Postoperative speech perception data were collected 6 months or 1 year after surgery. All audiometry tests were performed in the same sound-treated booth.

Statistical analysis

Linear regression analysis was used to analyze the association between postoperative performance, and deafness duration and hearing experience. In addition, the association between hearing experience divided by age at implantation (percentage of hearing years in life) and postoperative performance was evaluated. Furthermore, the relationship between preoperative bilateral hearing and postoperative CI speech perception was analyzed. The number of patients included in this study was small and no post-hoc analyses were performed to account for repeated measurements; this requires consideration when interpreting the results. We decided not to evaluate data using a multiple regression analysis because the number of patients was too small.

Ethics

The study was approved by the Uppsala Ethical Review Board (16/4-2014, Dnr: 2014/069).

Paper II

Since 2011, eABR measurements have been routinely performed during CI surgery in Uppsala. In this paper, we analyzed the eABR waveform quality, latencies, and inter-peak intervals separately for electrodes covering the basal, middle, and apical parts of the CI in adult patients. These responses were explored to assess their potential in the prediction of CI outcomes with regard to speech perception, as measured by MS-word recognition. In addition, four children with expected cochlear nerve absence were included in the study. Our aim was to investigate whether eABR can be utilized to predict CI outcomes and aid ABI decision-making in pertinent cases.

Patients

All adult patients operated on in Uppsala between 2011 and 2013, in whom eABR measurements were intraoperatively measured, were included in this study (n = 74). Mean age at implantation was 65 years (median 69 years, range 18–87). Four children were investigated in this study, including two with CHARGE syndrome (aged 2 and 3 years), one with VACTERL[3] association (aged 2 years), and one with Goldenhar syndrome (aged 2 years). All children were investigated with high resolution magnetic resonance imaging (MRI) prior to implantation, and eABRs were recorded as an additional measure to exclude a partially working hearing nerve.

Device description

Implants from Cochlear (CI24RE(CA), CI422 or Hybrid L24) were used in 37 implantations, and implants from MED-EL (Sonata FLEX 24 or 31, or Concerto FLEX 20, 24, 28, or 31) were used in 37 implantations in the adult group. Of the four children included, two were implanted with an implant from Cochlear (CI24RE(CA) and CI422) and two were measured using a test electrode from MED-EL, comprising an 18 mm long simplified CI with three contacts in the cochlea.

eABR measurements

All recordings were made during surgery directly after implant insertion. Two separate systems were used, one for recording and one for stimulation. The stimulation system comprised the Cochlear or MED-EL programming system, utilizing the CI as a stimulator. The recording system comprised an evoked

[3]VACTERL association is characterized by a combination of abnormalities of the vertebra, anus, heart, trakea, esophagus, kidney, and limbs. Approximately 15 children are born with VACTERL association in Sweden per year (Socialstyrelsen, 2011b).

potentials (EP) system that was triggered to record from the stimulation system. Two different recording systems were utilized in the clinic, the Otometrics Chartr 200 (GN Otometrics, Taastrup, Denmark) and the GSI Audera (GSI, Minneapolis, USA). Recording needle electrodes were positioned at the Vertex (Act), C7 (Ref), and at the hairline on the neck (ground). Three different electrodes were stimulated for each patient, one each in the low-, mid-, and high-frequency regions on the implant. The stimulation pulse width was 25 μs and the current level was 235 CL (CL is a cochlear term and represents the amplitude of the pulse in microamperes on a log scale, ranging between 0–255) for Cochlear devices. The stimulation pulse width was 30 μs and the current level was 1000 cu (cu is a MED-EL term; one cu is approximately one μA) for MED-EL devices. These conditions produced approximately the same stimulus charge from both systems and exceeded most patients' C-levels in their sound processor maps. The recording system averaged 1000 sweeps, and was filtered by a low pass filter at 3 kHz and a high pass filter at 10 Hz (GSI Audera), or by a low pass filter at 5 kHz and a high pass filter at 5 Hz (Otometrics Chartr 200). Latencies were measured using the result from an alternating stimulation, or as an average of the latencies from the positive and negative stimulations in cases where alternating polarity was not used. In most cases, eABR responses were verified by inverting the polarity of the stimulation, resulting in an inversion of the artifact without inverting the eABR waveform. Figure 10 shows a typical result from the different modes of stimulation. The most identifiable peaks (II, III, and V) were marked according to standard clinical procedure.

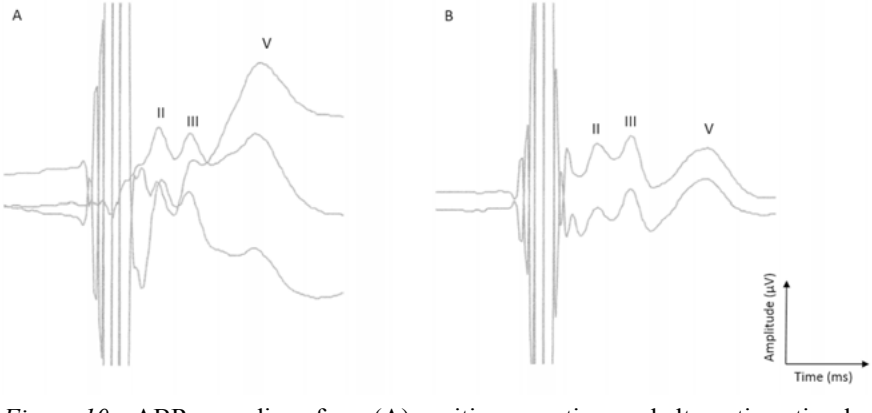

Figure 10. eABR recordings from (A) positive, negative, and alternating stimulations, and (B) positive and negative stimulations.

Waveform assessment

A modified classification table as described by Gibson et al. (2009) and Walton et al. (2008) was used to classify the quality of the eABR waveforms (Table 2). We decided to simplify the table by including only the presence of waves, omitting amplitude measures, because we only stimulated at a single level and amplitudes change according to the level of stimulation. Abbas and Brown (1988) and Kim et al. (2008) claimed that amplitudes undergo most changes when the stimulation level is modified, while latency changes are relatively small. A score of 3 represents a superior eABR quality, with all the waves II, III and V present, and 0 an absent eABR response. A total waveform score was constructed by adding the scores from the three measured electrodes (0–9).

Table 2. *Implant evoked electrical auditory brainstem response waveform score; table modified from Gibson et al. (2009) and Walton et al. (2008).*

Score	***Presence of waves***		
	***II** (Y/N)*	***III** (Y/N)*	***V** (Y/N)*
3	Y	Y	Y
2	N	Y	Y
1	N	N	Y
0	N	N	N

Y = Yes, N = No

Hearing evaluation

A list of 50 MS phonetically balanced words (Svensk Talaudiometri, C-A Tegnér AB, Stockholm, Sweden, 1998) was used to test speech perception in a sound-treated booth in free field at 65 dB SPL with the loud speaker at 0º azimuth. Only MS-word scores with CI were analyzed. In patients lacking speech recognition (0% in MS-word test), bi-syllabic word testing and the three-digit test (Svensk Talaudiometri, C-A Tegnér AB, Stockholm, Sweden, 1998) were also performed. The tests were performed in a sound-treated booth according to standard procedure. Speech perception data were collected at 6 months or 1 year after surgery.

Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) v. 22.0 (IBM, New York, NY, USA). Paired t-tests were used

to compare latencies between wave V at the three different locations (base, middle, and apex), and Bonferroni adjustments were made for the three repeated measures. The Wilcoxon signed rank test was used to compare waveform scores for the three different locations (base, middle, and apex) with Bonferroni adjustments for three repeated measures. Linear regression analysis was used to explore linear relationships between waveform scores, waveform V latencies, wave III–V intervals, and MS-words. For waveform V latencies and wave III–V intervals, Pearson's correlation coefficient (r) was calculated and for waveform scores the Spearman's rank correlation coefficient (r_s) was calculated.

Ethics

The study was approved by Uppsala Ethical Review Board (19/11-2014, Dnr: 2014/437).

Paper III, IV and V

Papers III and V were retrospective studies, based on patient archives and medical records. In paper III, patient archives were searched for information on the following variables: pre-surgical size of the vestibular schwannoma (patients with NF2), occurrence of gamma knife treatment before ABI surgery, surgical approach, and if there was any side effects from surgery. We also searched for side effects from implant use, electrode activation pattern, implant use, patient's hearing sensations, and categories of auditory performance (CAP) score (Archbold et al., 1998). Paper V described the diagnostic considerations, intraoperative electrophysiological measures, fitting, and postoperative auditory performance in pediatric ABI patients. Paper IV was based on the answers from a questionnaire-based survey.

Patients

Between 1993 and 2013, ABI implantation surgery was performed on 24 patients at Akademiska University Hospital, Uppsala, Sweden. Of these patients, 20 had NF2. Median age at surgery for the NF2 patients was 25.5 years (range, 15–75 years). A few patients (n = 4) were non-NF2 pediatric patients. These pediatric patients had congenital inner ear and cochlear nerve malformations due to Goldenhar syndrome (n = 2, age 2 and 9 years), or CHARGE syndrome (n = 1, age 2.5 years). One had acquired bilateral deafness at the age of 2 years due to post meningitis cochlear ossification and was implanted at the age of 4 years. All 24 implanted patients were included in paper III.

In paper IV, deceased patients (n = 4) and patients with no hearing sensations from the implant (n = 1), or those with an implant not yet activated (n = 1) were excluded. Eleven adult patients (11/14, 79%) and two pediatric patients (2/4, 50%) agreed to participate in the study and completed the questionnaire. The age range of the adult group was 23–73 years (mean age 43 years) and they all had NF2. The two pediatric patients were aged 6 and 8 years, and were deaf due to cochlear ossification after meningitis and Goldenhar syndrome.

In paper V, the pediatric patients described above, who were programmed and followed-up in Uppsala, were included together with one additional child with cochlear aplasia that was implanted at the age of 3 years in 2015. A boy with Goldenhar syndrome was implanted at the age of 2 years (patient no. 1), a boy with CHARGE syndrome was implanted at the age of 2.5 years (patient no. 2), a boy with post-ossification meningitis was implanted at the age of 4 years (patient no. 3), and a girl with cochlear aplasia was implanted at the age of 3 years (patient no. 4). Patient demographics for paper V are summarized in Table 3.

Device description

Patients in papers III and IV received an ABI manufactured by Cochlear. In paper III, the implants CI8+1M (n = 1), ABI22M (n = 3), ABI24M (n = 19), and ABI541 (n = 1) were used. The patients in paper IV used ABI22M (n = 1) or ABI24M (n = 12). In paper V one of the patients was implanted with an implant from MED-EL (Synchrony ABI) while the remaining patients received implants from Cochlear (ABI24M (n = 2) and ABI541 (n = 1)). The processors used were Spectra, Sprint, Esprit 3G, Freedom, Nucleus 5, and Nucleus 6 for the implants from Cochlear, and the Sonnet for the MED-EL implant.

The decision to implant pediatric non-NF2 patients (paper V)

Patients no. 1 and 4 underwent high resolution MRI investigations in combination with psychoacoustic testing, auditory steady state response (ASSR) testing, and ABR testing prior to implantation. No responses were obtained. In patient no. 1, the MRI result was inconclusive and there was a slight possibility of a partly existing auditory nerve. Therefore, the patient was first implanted with a CI, and eABR and NRT measurements were performed revealing negative outcomes. Following this, the surgery proceeded with the insertion of the ABI. Patient no. 4 had bilateral cochlear aplasia. Following MRI and hearing tests, patients no. 2 and 3 were implanted with bilateral CIs at another clinic, with negative outcomes.

Table 3. *Patient demographics for paper V (gender, etiology, age when hearing loss was identified, use of HA and CI prior to ABI, age at ABI implantation, implanted ear and ABI device).*

Patient no.	Gender	Etiology	Age when hearing loss was identified	HA prior to ABI	CI prior to ABI	Age at ABI implantation	Ear implanted	ABI device
1	M	Goldenhar syndrome	6 months	Yes, HA at the age of 1 year	Yes* unilaterally implanted at the age of 2 years	2 years	Right	Cochlear Nucleus ABI24M
2	M	CHARGE syndrome	2 months	Yes, HA at the age of 3 months	Yes, implanted at the age of 1.5 and 2 years (bilateral)	2.5 years	Right	Cochlear Nucleus ABI541
3	M	Post-ossification meningitis	2 years (meningitis at the age of 2 years)	No	Yes, bilaterally implanted at the age of 3 years	4 years	Right	Cochlear Nucleus ABI24M
4	F	Cochlear aplasia	8 months	No	No	3 years	Left	MED-EL Synchrony ABI

ABI = Auditory brainstem implant, CI = Cochlear implant, F = Female, HA = Hearing aid, M = Male *Child was implanted with a CI, but this was explanted during the same surgery and replaced with an ABI.

Surgery description

Surgery was performed on all patients except one using the translabyrinthine approach. A mastoidectomy and labyrinthectomy with closures of the eustachian tube and external ear canal were performed. A bed for the receiver stimulator was drilled into the occipital/temporal bone. The tumor was then removed (NF2 patients) with the additional aim of preserving the facial nerve. All patients underwent facial nerve registration. After the removal of the tumor, the lateral recess of the fourth ventricle area (foramen Luschkae) was visualized with the remaining cranial nerve VIII, cranial nerve VII, and the

choroid plexus. Cranial nerves IX and X were also visualized. The rest of the cranial nerve VIII was followed to find the CN complex, where the electrode plate was placed. In all patients, with the exception of the three first surgical procedures, and the surgery performed in 2015, the ABI was inserted by the same surgeon. Electrical stimulation through the electrodes was performed and the electrode plate was adjusted, if possible, according to stimulation response, and subsequently fixed with fibrin glue and abdominal fat or temporal fascia. The reference electrode was placed under the temporal muscle. The pediatric patient implanted with a MED-EL Synchrony ABI in 2015 was implanted using the retro-sigmoid approach.

Intraoperative measurements

To ensure correct placement of the ABI array, eABRs were measured during surgery. Two separate systems were used, one for recording and one for stimulation. The stimulation system was either the Cochlear or the MED-EL programming system, utilizing either the implant or the MED-EL ABI placing system as a stimulator. The recording system comprised EP equipment that was triggered by the stimulation system to initiative recording. The EP equipment used was the GSI Audera, the Otometrics Chartr 200, or the Nicolet Spirit (Natus, Pleasanton, USA). The recording needle electrodes were placed at the vertex (active), C7 (inverting), and the neck at the hairline (ground). The stimulation pulse width was 150 μs for the Cochlear implants and 60 μs for the MED-EL implant. The stimulation rate was 35 Hz (Cochlear) or 34 Hz (MED-EL). The stimulation level was initiated at 150 CL (Cochlear; CL is a Cochlear term that represents the amplitude of the pulse in microamperes on log scale, ranging between 0–255) or 100 cu (MED-EL; cu is a MED-EL term; one cu is approximately one μA) and then increased until a response was observed.

The recording system averaged 1000–2000 sweeps (i.e., the number of sweeps required to obtain a clear response). If the eABR response was unclear, the response was verified by inverting the polarity of the stimulation. If no response or responses from only part of the ABI was recorded, the ABI was repositioned, if possible, and the measurements were repeated. Two tracings from intra-operative eABR measures are shown in Figure 11. The electrode placement on the ABI plate from the two different manufacturers and the MED-EL ABI placing system are shown in Figure 12A, B, and D. In all patients with an implant from Cochlear, eABRs were recorded directly via the ABI in bipolar mode. The MED-EL ABI placing system was used for patients with the MED-EL ABI. This was placed on the CN, and eABR measurements were obtained in BP mode to ensure the correct placement of the implant. After the implant was placed, eABRs were also measured via the ABI in both the BP and MP mode.

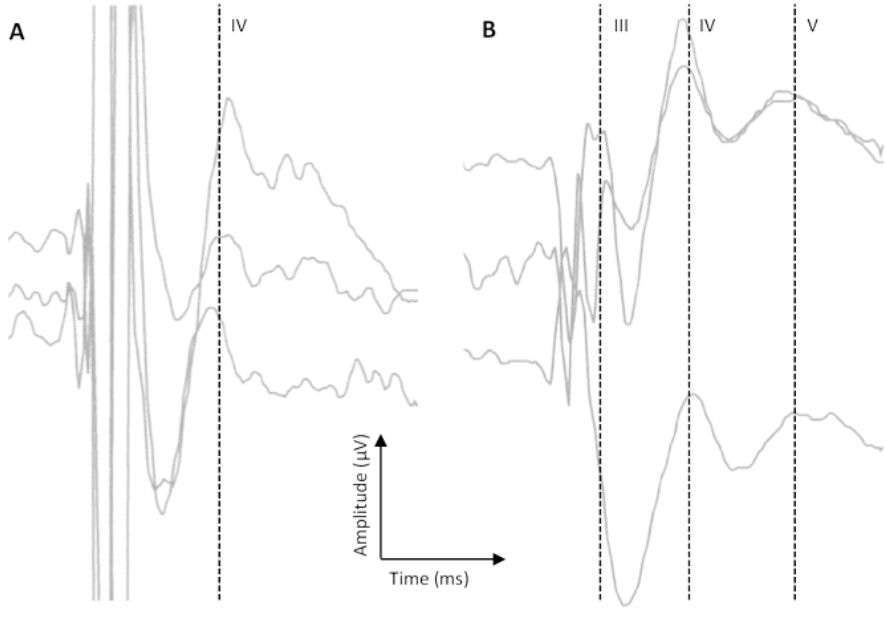

Figure 11. Intraoperative eABR measures from an ABI. Waveforms III, IV, and V are marked in the figure. (A) Cochlear Nucleus ABI24M (Lane Cove, NSW, Australia). (B) MED-EL Synchrony ABI (Innsbruck, Austria).

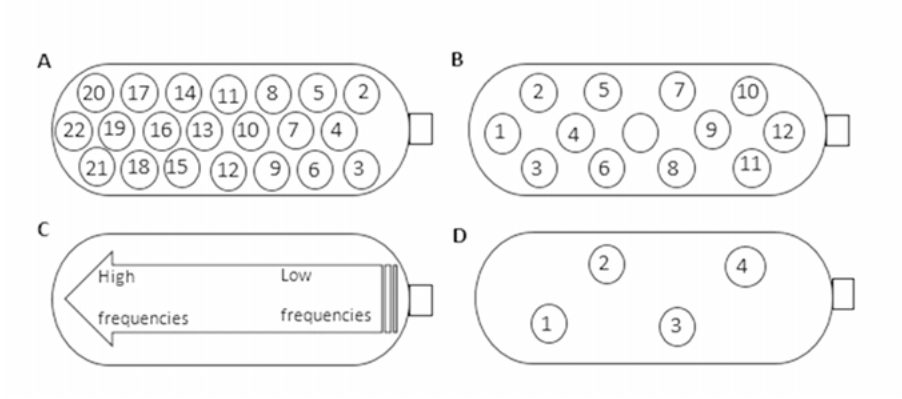

Figure 12. (A) Electrode from Cochlear (Lane Cove, NSW, Australia), dimension: 3 x 8.5 mm. (B) Electrode from MED-EL (Innsbruck, Austria), dimension: 3 x 5 mm. (C) Theoretical frequency order on the implant. (D) ABI placing system from MED-EL dimension: 3 x 5 mm.

Processor fitting in adult patients

The first programming session was performed in the operating theatre with cardiological monitoring and experienced anesthetists, due to the potential risk of stimulating other structures. The timing of activation typically varied between 6 and 8 weeks after surgery. All adult patients used implants from Cochlear. All electrodes were first checked in the MP1+2 mode to determine those suitable for utilization in the map. Channels that produced no or unpleasant stimulation were either removed or the pulse width was increased in an attempt to eliminate the side effect. We attempted to determine both the T- and C-levels for all of the channels. If the majority of the channels induced side effects in the MP1+2 mode, alternative modes such as MP1, MP2, or BP+5 were evaluated (BP+5 is the stimulation between every second electrode on the ABI array). There was no strict rule regarding when to switch to another stimulation mode. The stimulation strategy used for most patients was SPEAK, and for a few patients the stimulation strategy comprised ACE. Figure 13 shows the number of useful electrodes found after the initial testing for all patient except the patient implanted with a MED-EL implant in 2015. Figure 14 demonstrates the frequency of activation of all 21 channels on the ABI for the whole NF2 group, with the exception of the patient with an eight-channel implant and the "sleeper" patient. In Figure 14, '1'corresponded to the channel activated in all patients and '0' to the channel being activated in none of the patients. The frequency of activation for the different channels on the ABI array is also shade-coded in the insert of Figure 14.

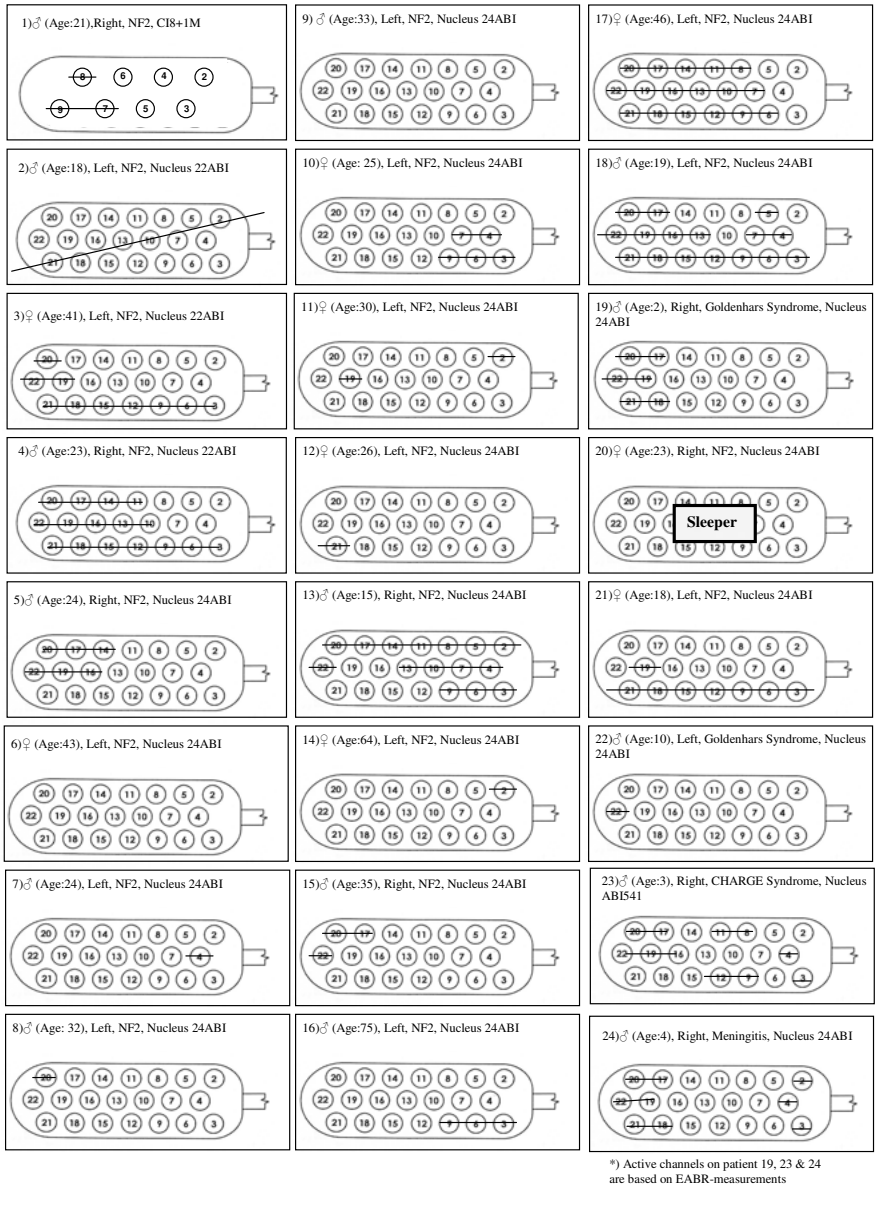

Figure 13. Active channels at switch on, in adults and children.

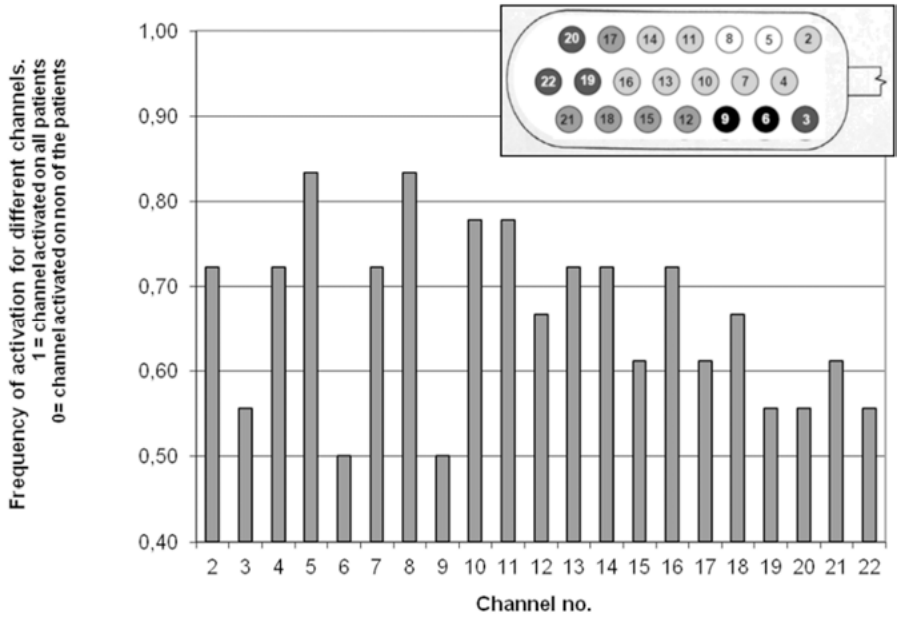

Figure 14. Chart demonstrating the activation of various channels of the ABI. Inset shows the topographic location of these channels. Darker colors indicate electrodes less frequently activated.

After the initial test, patients visited the clinic several times for programming. They typically stayed at the clinic for 2–3 days for the first processor programming, and then rechecked after approximately 1, 6, and 12 months. Pitch ranking was performed in most of the adult patients after the T- and C- levels were set. The channels were presented at the C-level, as previously described by Vincent (2012) and Colletti et al. (2002b). The activated channels were first classified by the patient as high, medium, or low-pitched sound, and divided into three groups. Subsequently, each group was organized internally according to pitch. The channels were compared two by two and placed in tonotopic order and, finally, a sweep through all activated channels confirmed the accurate tonotopic order. If the correct order was not achieved by the programming, the order was altered and the task was repeated.

Pitch ranking can be a time-consuming and a difficult task to perform. If the patient showed inconsistencies when asked to classify and compare sounds, or if they did not hear any pitch differences when different electrodes were stimulated, the task was postponed to a later programming session. The patient was then provided a standard map with electrodes arranged in order from low to high pitch (Figure 12C), as described by Otto et al. (2002). Figure 15 summarizes the tonotopical arrangements on the ABI for the 11 adult patients'

where pitch ranking was able to be performed. It is necessary for the patients to be seen regularly for programming and potential re-programming to ensure that they have the best possible map. The aim was to follow-up the patients once a year for programming. The frequency and duration of the follow-up programming sessions was highly dependent on patient motivation, medical condition, and ability to travel to the ABI clinic. In some cases, the follow-up visits were performed at a hospital closer to the patient's home.

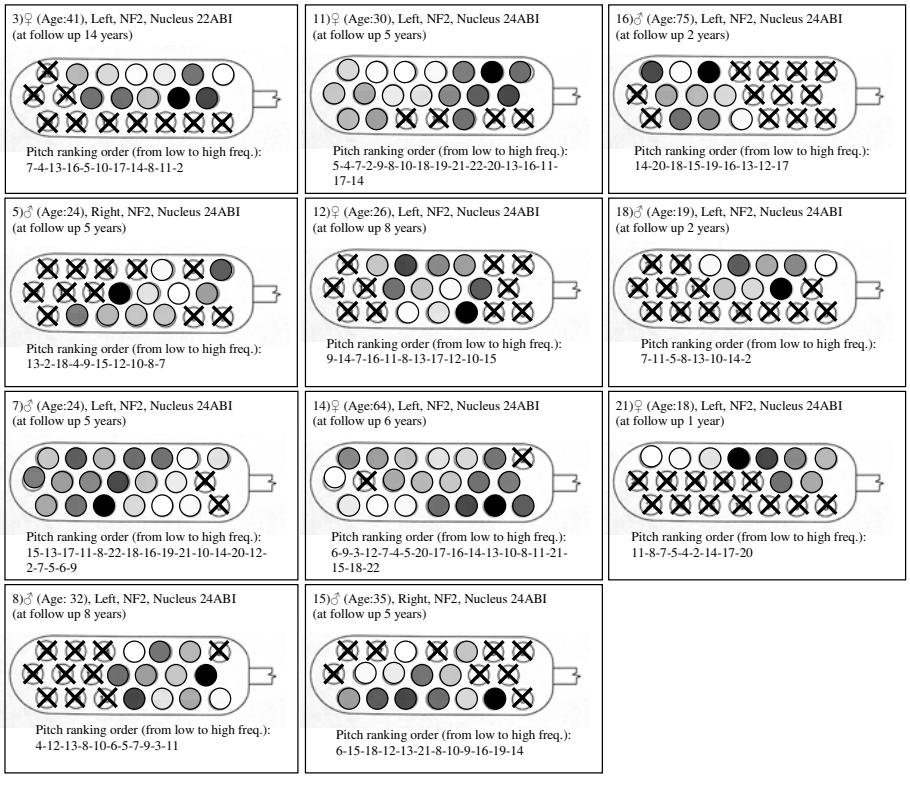

Figure 15. Pitch ranking: black represents the lowest pitch and white the highest. X = electrode not activated.

Processor fitting in pediatric patients

In pediatric cases, the children were re-assessed with eABR under general anesthesia the day before the initial fitting session, 6–8 weeks after surgery. For patients no. 1, 2, and 3, bipolar stimulations were utilized (BP+5), and for patient no. 4, MP stimulation was used. This difference reflected the various recommendations from the implant manufacturers on how to program and map in children. As many channels as possible were stimulated and the eABR thresholds were assessed. The EP setting and electrode placement were the same as those used for the intraoperative measurements. The stimulation levels were augmented on all channels to ensure that no other neural centers were

stimulated at higher levels. If a side effect occurred, depending on its severity and the level at which it occurred, the channel was either turned off or carefully monitored in future programming sessions with the awake child. This testing was performed to ensure a safe stimulation span during the fitting sessions. An initial map was also created and run in the operating theatre at a high level to ensure that no aberrant stimulation would occur with the map running.

During the first one or two fitting sessions, the child was monitored using a pulse oximeter. Together with the engineer responsible for the fitting, a pediatric audiologist was present. Intraoperative thresholds and the maximal tested levels from the eABR measurements were used to obtain a response from the child and create the initial map with the sound processor. The maximal tested levels from the eABR measurements were not exceeded. The order of the electrodes went from low to high pitch, as theoretically described (Otto et al., 2002) because the children were unable to perform pitch ranking (Figure 12C). During first week of fitting, the child visited the clinic for 2–3 days, followed by individually planned visits depending on how programming progressed. Typically, patients visited after 2 weeks, 4 weeks, and every third month. One year after the initial fitting, appointments were made every 6 months. At these visits, the child and family also had appointments with a speech and language therapist, a medical social worker, and an audiological physician. Free field audiometry testing was performed with the ABI to test the response levels to sound, and the results were used as a guide for fitting. Additionally, the results from the appointments with the speech and language therapist, as well as information from the parents and/or the child's school or preschool, were used to adjust the fitting map. Hearing performance was assessed by CAP (Archbold et al., 1998).

Patient questionnaires (paper IV)

Questionnaires were sent to the patients, or to the parents in pediatric cases, by post. The following two questionnaires were used:

1. A questionnaire regarding ABI use, the perception of environmental sounds, and the benefits of ABI (see Appendix 1 for the questionnaire). This questionnaire was used to access the actual ABI usage and perceived benefit, as estimated by the patients or the parents.
2. A disease-specific quality-of-life (QoL) questionnaire for neurofibromatosis type 2 NFTI-QoL (Swedish) (Hornigold et al., 2012) (see Appendix 2 for the questionnaire). This questionnaire was only used for the NF2 group; it rated the QoL parameters for the NF2 patients via eight questions.

Questionnaire 1 was developed over several years at the clinic and was based on frequently discussed topics with the ABI patients at their annual visits. Questionnaire 2 was translated from English to Swedish for use in this study.

Statistical analysis (paper IV)

The data from all questions (Q1–8) from the NFTI-QoL questionnaire were separately compared with the data from the study by Hornigold et al. (2012). The Mann Whitney test was used for the non-parametric data. Statistical analyses were performed using the SPSS 22.0 software. A p value < 0.05 was considered statistically significant.

Ethics

These studies were approved by the Uppsala Ethical Review Board (7/11-2013, Dnr: 2012/388 and 13/10-2014, Dnr: 2012/388/1). All patients, or their parents in pediatric cases, were asked to provide written informed consent in paper IV.

Results

Paper I

Six patients had open-set speech perception (MS-words) in the CI-ear 6–12 months after surgery. For bi-syllabic words, seven patients had open-set speech understanding. One patient was not evaluated at 6 months. The deafness duration in the CI-ear for the six patients with MS-word speech perception varied between 20–47 years.

Three patients used the implant mainly to perceive environmental sounds and improve lip reading (no. 5, 8, and 9). Patient no. 5 experienced 50 years of deafness in the implanted ear and perceived only non-auditory sensations from the implant. The patient had used a HA in the contralateral ear for 44 years. Hearing loss initiated early in the CI-operated ear (age 14). This patient was the only one that showed no electrophysiological response intraoperatively and the MS-word score was 10% bilaterally before surgery. Patient no. 8 had severe prelingual hearing loss with impaired speech production, and patient no. 9 had bilateral hearing loss for 56 years prior to CI surgery. Patient no. 9 experienced tinnitus during implant use, but used it part time to improve lip reading.

One patient with 72 years of bilateral deafness (no. 2) experienced severe tinnitus from implant use and became a non-user. Another patient with 37 years of deafness in the implanted ear, who was aged 4 years at the time of deafness onset in the implanted ear (no. 6, ear 2) had a previous successful implantation in the contralateral ear, and did not use the second implant. The two patients in group 3 with peri or prelingual hearing loss (no. 7 and 8) benefited from the CI and used it full-time.

Postoperative speech perception, electrophysiology, deafness duration, subjective experiences of the patients, etiology, and CI usage are summarized in Table 4. A statistically significant correlation was found between postoperative speech perception and deafness duration in the implanted ear in groups 1 and 2 ($r = 0.84$, $p^{**} < 0.01$, Figure 16A). There was also a statistically significant positive correlation between the age at onset of deafness in the implanted ear and postoperative speech perception for group 1 ($r = 0.99$, $p^{*} < 0.05$, Figure 16B). There was a statistically significant correlation between postoperative speech perception in the implanted ear and the hearing experience divided by

age at implantation (percentage of hearing years in life) for groups 1 and 2 ($r = 0.80$, $p^{**} < 0.01$, Figure 16C). Additionally, there was a tendency for group 2 patients, who had better bilateral preoperative word discrimination, to have better word discrimination with the CI ($r = 0.81$, $p = 0.099$, Figure 16D). However, no post-hoc corrections were performed for the above data. In Figure 16, patient no. 6-ear 2 and patient no. 11 were not included. This was because patient no. 6-ear 2 did not initiate implant use and no postoperative speech perception data were collected, whereas patient no. 11 was recently fitted and had not yet been tested at the time of this study.

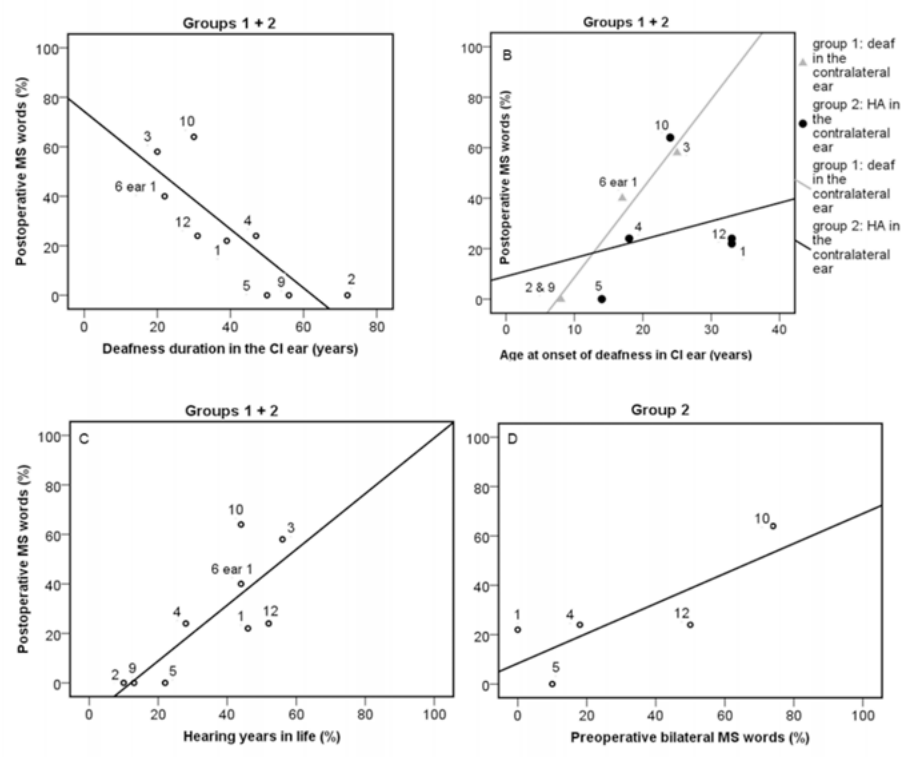

Figure 16. Diagram showing the relationship between postoperative speech perception (MS-words) in the CI-ear and (A) deafness duration ($r = 0.84$, $p < 0.01$, groups 1 + 2), (B) age at onset of deafness ($r = 0.99$, $p < 0.05$, group 1), (C) age at onset of deafness in the CI-ear divided by age at implantation ($r = 0.80$, $p < 0.01$, groups 1 + 2), (D) preoperative bilateral speech perception ($r = 0.81$, $p = 0.099$, group 2).

Table 4. *Postoperative speech perception, electrophysiology, deafness duration, patient comments, cause of deafness, and CI use.*

Patient no.	Post op MS-words (%) in CI-ear	eABR/eSRT/ART-NRT	Deafness duration in the CI-ear (years)	Patient comments (cause of deafness in brackets)	User
Group 1: deaf in the contralateral ear					
2	0	Y/Y/Y	72	Receives hearing sensations from implant, but not speech perception. Experiences severe tinnitus from implant use resulting in the patient becoming a non-user. (Meningitis)	N
3	58	Y/Y/Y	20	Feels much more confident and less tense after CI. Can manage basic telephone calls. (Meningitis and scarlatina)	Y
6-ear1	40	NM/Y/Y	22	Satisfied with the CI. Listens to music with the CI. Can use the telephone with "known" speakers. (Not known)	Y
6-ear2	-	Y/Y/Y	37	Struggles to become motivated at starting the use of the second implant but decides 1 year postoperatively to not proceed. Experiences headache from implant use and describes the sound as vibrations. (Not known)	N
9	0	?	56	Uses implant as a complement to lip-reading. Experiences tinnitus from implant use and therefore becomes a part-time user. (Meningitis)	Part time
Group 2: HA in the contralateral ear					
1	22	NM/NM/Y	39	Patient is very happy and reports a great improvement in quality of life. Does not turn down invitations to social events as she did prior to CI. Obtains 56% on bi-syllabic word test in the CI-ear. (Deafness after cholesteatoma surgery)	Y
4	24	NM/Y/Y	47	Satisfied user that reports the sound from the CI to be "clear" and of good quality. (Recurring otitis media)	Y
5	0	N/N/N	50	Reports mostly a feeling, not sound, from implant use. Continues to use the CI and reports some benefit. Can hear, or feel, high frequency sounds better. Slightly disappointed. (Recurring otitis media)	Y
10	64	NM/NM/Y	30	Feels that she can trust the CI hearing. Can use the telephone and listens to music. (Not known)	Y
11	NM*	Y/Y/Y	31	(Sudden deafness)	
12	24	Y/Y/Y	31	Uses CI full-time, feels that it is a good compliment to HA. Problems with facial nerve stimulation due to high stimulation levels. Experiences vertigo after CI that still affects her after 1 year. (Deaf after otosclerosis surgery)	Y

Group 3: Bilateral peri or prelingual hearing loss				
7	NM	Y/Y/Y	New sounds continuously detected. Satisfied with the CI. Has some troubles getting used to high frequency sounds. Reports that is easier to talk to colleagues now. Works full-time. Obtained 12% bi-syllabic word test in CI-ear.	Y
8	NM	Y/Y/Y	Is very happy with the implant even though this was not measured on speech tests. Hears surrounding sounds and reports a love of the letter 's'. Continuous hearing improvement.	Y

ART = Auditory response telemetry, CI = Cochlear implant, eABR = Electrically evoked auditory brainstem response, eSRT = Electrically evoked stapedius response threshold, HA = Hearing aid, NM = Not measured, N = No, NRT = Neural response telemetry, Y = Yes. *Patient recently fitted

Paper II

eABR latencies and waveform quality assessment

Latencies for waves II, III, and V are displayed in Table 5. Latencies increased towards the base of the cochlea. Significant differences in latency were found between wave V in the low-frequency region and the high-frequency region on the implant ($p^{**} < 0.01$, 95% confidence interval of the mean difference 0.09–0.46 ms), and between wave V in the mid- and the high-frequency region on the implant ($p^{**} < 0.01$, 95% confidence interval of the mean difference 0.06–0.33 ms). Wave V values for the mid- and low-frequency regions on the implant were the most robust waveforms. We identified wave V in 66 of 74 (89%) recordings in the implant low-frequency region. In eight patients, wave V could not be observed. In five of these cases, the measurement failed due to technical reasons, in two cases the measurement was not performed on those electrodes, and in one case wave V was undetectable. Therefore, in all but one of the 67 successful recordings (99%), wave V was detected in the implant low-frequency region. In the implant mid-frequency region, we identified wave V in 64 of 74 (86%) recordings. In ten cases, wave V was not observed. In five of these cases, the measurement failed due to technical reasons, and in the other five cases wave V was undetected. Therefore, in all but five of the 69 successful recordings (93%), wave V was detected in the middle region on the implant.

Waveform quality, as assessed by scores 0–3, was the highest in the low- and mid-frequency regions on the implant (mean scores 2.3 and 2.1, respectively) compared with 1.0 in the implant high-frequency region. There was a statistically significant difference between waveform scores in the low and mid-frequency regions on the implant compared with the implant high-frequency region ($p^{***} < 0.001$). Wave III–V interval increased towards the implant high-

frequency region (Table 6). It was not possible to fully evaluate how the difference in electrode lengths contributed to the waveform score since the number of patients in each implant length group varied extensionally. However, mean waveform score was highest for the longest electrode (31 mm).

Table 5. *Means, standard deviations (SD), number (n), and medians for eABR waves II, III, and V. Latencies are expressed in ms with 95% confidence interval for means in brackets.*

Wave II latency				**Wave III latency**				**Wave V latency**			
Mean	SD	n	Median	Mean	SD	n	Median	Mean	SD	n	Median
Low-frequency region on implant											
1.42 (1.36–1.48)	0.17	32	1.42	2.17 (2.11–2.22)	0.21	57	2.12	3.99 (3.90–4.07)	0.36	66	3.98
Mid-frequency region on implant											
1.45 (1.35–1.54)	0.25	28	1.42	2.23 (2.17–2.29)	0.22	56	2.20	4.15 (4.06–4.24)	0.35	64	4.14
High-frequency region on implant											
1.46 (1.31–1.60)	0.23	12	1.43	2.28 (2.17–2.39)	0.25	22	2.29	4.32 (4.17–4.48)	0.41	29	4.42

Table 6. *Means, standard deviations (SD), number (n), and medians for scores and wave III–V intervals. Intervals are expressed in ms. 95% confidence intervals for means in brackets.*

Score (0–3)				**Wave III–V interval (ms)**			
Mean	SD	n	Median	Mean	SD	n	Median
Low-frequency region on implant							
2.3 (2.14–2.51)	*0.8*	67	2	1.78 (1.70–1.86)	0.28	57	1.79
Mid-frequency region on implant							
2.1 (1.92–2.34)	0.9	69	2	1.89 (1.82–1.96)	0.25	56	1.86
High-frequency region on implant							
1.0 (0.66–1.25)	*1.2*	62	0	1.94 (1.82–2.06)	0.26	20	2.00

Hearing evaluation

There were no correlations between MS-word scores and wave V latency in the three different regions (low r = –0.1 p = 0.4, mid r = –0.2 p = 0.07, and high r = –0.1 p = 0.6), or wave III–V intervals in the three different regions (low r = –0.05 p = 1.0, mid r = –0.2 p = 0.2, and high r = 0.04 p = 0.9) using linear regression analysis (Figure 17). We also failed to find any correlation between MS-word scores and total score ($r_s = 0.2$, p = 0.3), or the scores in the three different regions (low $r_s = –0.07$ p = 1.0, mid $r_s = 0.06$ p = 0.7, and high $r_s = 0.2$ p = 0.3) using linear regression analysis. No adjustments for repeated measures were performed due to the lack of correlations.

Table 7 shows the cases in which wave V was undetected for reasons others than technical failures in the implant mid- and/or low-frequency regions, and the cases in which patients exhibited no open-set speech discrimination on any of the performed speech tests. A negative outcome was defined as a patient with no recordable speech discrimination with CI (scoring 0% on MS-words, less than 10% on bi-syllabic words, or less than 25% on the three-digit test). Results show that if the patient had no detectable wave V in the low-frequency region on the implant, the outcome would most certainly be unsuccessful. Patients with no speech perception with CI had eABR wave V in the low-frequency region in 75% of the cases. One patient in particular, with a total waveform score of 9 and deafness duration before CI surgery of 72 years, received hearing sensations from the implant (no speech perception), but could not use it because the implant induced severe tinnitus.

Children with cochlear abnormalities

Among the four children, no eABR waveforms were detected in any of the stimulations (total score 0). In these cases, stimulation levels were increased to determine that no waveforms occurred at higher levels. One child tested via a Nucleus CI24RE(CA) implant received an ABI during the same surgery. In one child, the surgery proceeded with the intention to implant an ABI, but had to be terminated for surgical reasons. One child did not receive an implant, decided by the parents and medical staff before surgery due to negative eABR measurements. One child was implanted and monitored by a Nucleus CI422 implant, and programmed 4 weeks after surgery. The child used the implant for 6 months, but did not show any reaction to sound even though levels in the CI were set at the maximum.

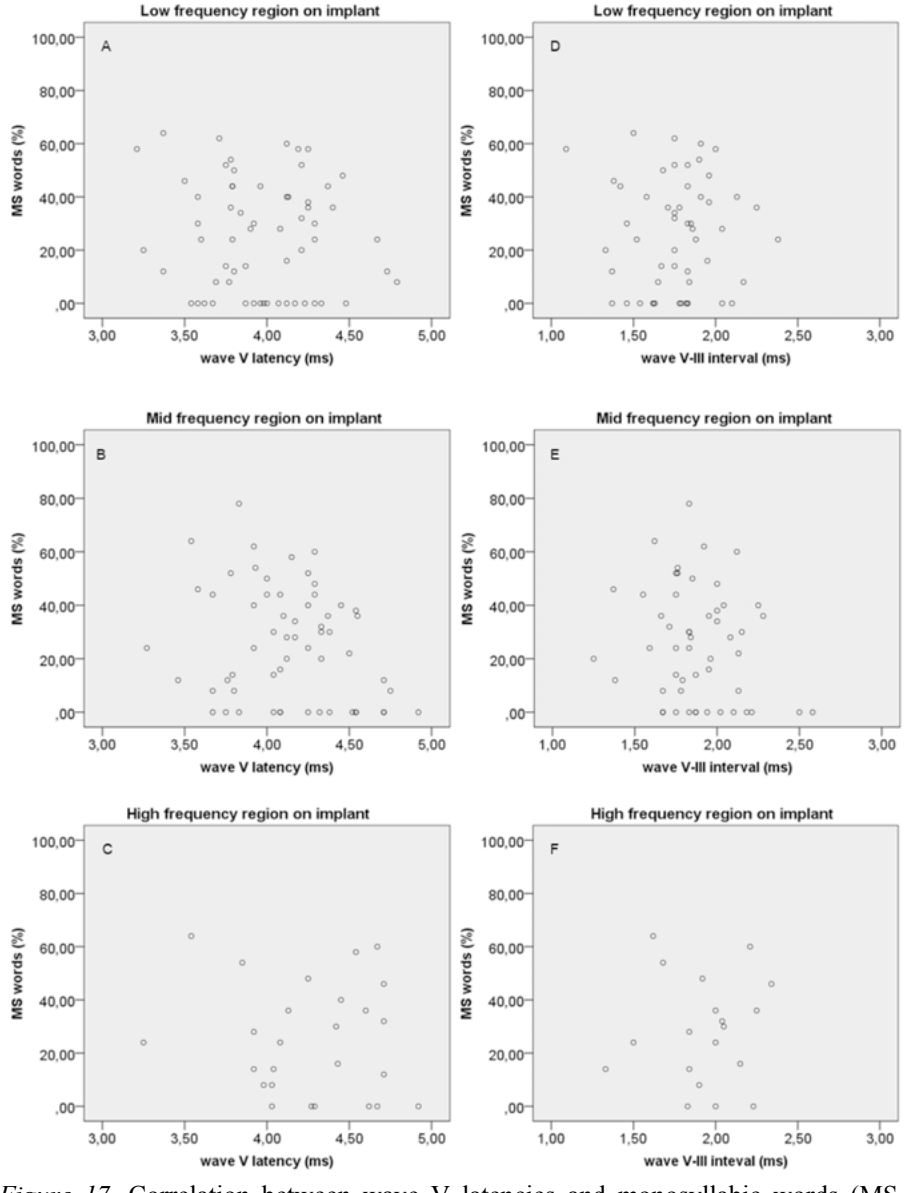

Figure 17. Correlation between wave V latencies and monosyllabic words (MS-words) with CI; (A) low frequencies (r = –0.1, p = 0.4) (B) mid frequencies (r = –0.2, p = 0.07), and (C) high frequencies (r = –0.1, p = 0.6). Correlation between wave III–V interval and MS-words with CI; (D) low frequencies (r = –0.05, p = 1.0) (E) mid frequencies (r = –0.2, p = 0.2), and (F) high frequencies (r = 0.04, p = 0.9).

Table 7. *Patients with absent wave V in the mid- and/or low-frequency regions on the implant, and patients with no speech discrimination (0% on MS-words test, < 10% on bi-syllabic words and < 25% on the three-digit test).*

Patient no.	Wave V (low-freq.)	Wave V (mid-freq.)	Total wave form score (0–9)	Comment (electrode length in brackets)
Patients with an absence of wave V in the mid- and/or low-frequency regions on the implant				
12	No	No	0	Patient had very high levels in the map postoperatively. Detected only sound, with no speech discrimination. Acoustic neuroma in the CI-ear. Used CI full-time for environmental sounds. *Implant: Concerto28 (28 mm)*
22	Yes	No	2	Patient with otosclerosis. Sudden loss of hearing. Contralateral ear deafness for 30 years. Patient was in a coma for 5 weeks due to Legionella 1 year before CI-surgery. Scored 25% on the auditory only three-digit-test. *Implant: CI422 (25 mm)*
31	Yes	No	1	Patient with otosclerosis and high levels in the map postoperatively. Scored 24% on the MS-word test. *Implant: CI422 (25 mm)*
41	Yes	No	2	Young patient (18-years-old at time of surgery) with high-frequency deafness. Scored 58% on the MS-word test. *Implant: Concerto24 (24 mm)*
55	Not measured	No	-	Patient reported mainly a feeling from implant stimulation postoperatively. Deaf for 50 years prior to CI. No speech discrimination. Used CI but considered stopping *Implant: Concerto31 (31 mm)*
Patients with no speech discrimination				
9	Yes	Yes	9	Deaf for 72 years prior to CI. CI use resulted in severe tinnitus. Non user. *Implant: Concerto31 (31 mm)*
12	No	No	0	Patient had very high levels in the map postoperatively. Detected only sound, no speech discrimination. Acoustic neuroma in the CI-ear. Used CI full-time for environmental sounds. *Implant: Concerto28 (28 mm)*
48	Yes	Yes	5	Reported sound and a feeling from implant use. Deaf for 37 years in the CI-ear prior to CI. Non user. *Implant: CI422 (25 mm)*
49	Yes	Yes	6	Severe prelingual hearing loss. 50-years-old at implantation. Used CI full-time for environmental sounds. *Implant: CI422 (25 mm)*
55	Not measured	No	-	Patient reported mainly a feeling from implant stimulation postoperatively. Deaf for 50 years prior to CI. No speech discrimination. Used CI but considered stopping. *Implant: Concerto31 (31 mm)*
74	Yes	Yes	4	Not measured. Did not show up to appointments. Unknown if patient used CI. *Implant: Hybrid L (17 mm)*

Paper III

Patient benefits, implant use, hearing sensations, and implant characteristics

The results reported below are the patients' reported benefits and auditory perceptions, and the observed auditory perceptions at follow-up (at the last follow-up visit for the patient, i.e., when the patient was an implant user), presented as CAP. The CAP scores were collected at the follow-up visits by the medical social worker in collaboration with the speech and language therapist, and in some cases under guidance from the patients' records. There was no formal testing for the adult patients. Follow-up time varied from 0 ('sleeper', meaning implant not activated, patient no. 20) to 16 years (patient no. 3).

NF2 patient group

The NF2 patient group comprised 20 patients. The majority (n = 12) of the NF2 patients reported a benefit from their implant and used it (Table 8). Three patients died, 2 (no. 1), 8 (no. 6), and 11 (no. 7) years after ABI activation, from NF2 during the follow-up period, but all lived long enough to report a benefit from their implant. One patient (no. 20) was considered a so-called 'sleeper' and the implant was not activated because she had contralateral hearing. The only patient (no. 2) who did not use his implant did so because of an absence of auditory signals. Six patients (no. 4, 7, 13, 16, 18, and 21) were part-time users for a limited period of time for various reasons as follows: severity of NF2 disease with visual impairment in two patients, lack of motivation in one patient, and depression and anxiety in one patient. One patient stopped using his implant because the sound would disappear after a few minutes of use, the cause for this was unclear. Patient no. 21 had her implant activated despite remaining contralateral hearing and used the implant modestly, but was considered a part-time user. For the NF2 patients, hearing sensations varied as follows: no auditory input (CAP 0) (n = 1; no. 2), ability to detect or identify surrounding sounds such as door knocks, footsteps, and speech sounds (CAP 1–3) (n = 9: no. 4, 5, 7, 8, 9, 13, 16, 17, and 18), ability to discriminate speech sounds without lip-reading (CAP 4) (n = 6; no. 3, 6, 10, 12, 14, and 15), and open-set speech discrimination in one patient (CAP 7) (n = 1, no. 11) (Table 8).

The number of electrodes with auditory sensations at activation varied between zero (no. 2) and 21 (no. 6 and 9) (Figure 13). The patient without auditory sensations did not receive any benefit from the implant. Figure 14 demonstrates the activation of various channels of the ABI and shows that certain channels were less frequently activated (electrodes 3, 6, 9, 19, 20, and 22) in the NF2 patients in this study.

The number of active channels remained fairly consistent over time. The average number of active channels at switch-on was 13.3 and at the last follow-up was 11.6 (varied from a loss of nine channels to gaining four channels). We found no correlation between numbers of active electrodes or tumor size and CAP score. Nine of the 20 NF2 patients had undergone gamma knife treatment before ABI surgery. Seven of these patients reported benefit from their implant and were users, and two patients used their implant for a shorter period of time and were categorized as part-time users. No obvious adverse effects on implant function were observed in this specific patient group.

Table 8. *Age at surgery, tumor size, gamma knife treatment (GKT), CAP score, and user status for the NF2-group.*

Patient no.	Age at surgery (years)	Tumor size (mm)	GKT	CAP score	User status
1	21	40	N	?	Y
2	18	36	N	0	N
3	41	28	Y	4	Y
4	23	40	Y	3	Part-time
5	24	36	N	3	Y
6	43	35	Y	4	Y
7	24	45	N	3	Part-time
8	32	35	Y	3	Y
9	33	50	N	3	Y
10	25	49	Y	4	Y
11	30	30	N	7	Y
12	26	40	N	4	Y
13	15	30	N	3	Part-time
14	64	36	Y	4	Y
15	35	36	Y	4	Y
16	75	20	N	2	Part-time
17	46	50	Y	3	Y
18	19	35	Y	2	Part-time
20	23	IM	N	-	Sleeper
21	18	20	N	Contralateral hearing	Part-time

CAP = categories of auditory performance (Archbold et al., 1998), GKT = Presurgerical gamma knife treatment, IM = Intrameatal tumor, N = No, NF2 = neurofibromatosis type 2, Y = Yes

Pediatric non-NF2 patient group

For the pediatric non-NF2 patients, hearing sensations were as follows: two patients (no. 19 and 22) were able to speak a few words and discriminate surrounding sounds (CAP score 3 and 4), and one patient (no. 23) had absent psychoacoustic signals. The child who showed no psychoacoustic responses to signals was re-tested 1 year postoperatively using eABR. There was an absence of adequate responses and computed tomography (CT) indicated that the electrode had potentially modified its position. Patient no. 24 had bilateral

ossification of the cochlea due to meningitis at 2 years of age. Since the bilateral cochlear implantation performed on this patient was unsuccessful, he received an ABI at the age of 4 years. The follow-up period for this patient was short; however, his preliminary CAP score after 3 weeks of implant use was 1. Pediatric patient data are shown in Table 9.

Table 9. *Age at surgery, diagnosis, CAP score, and user status for the pediatric patient group.*

Patient no.	Age at surgery (years)	Diagnosis	CAP score	User status
19	2	Goldenhar syndrome	3 (at follow-up 4 years)	Y
22	10	Goldenhar syndrome	4 (at follow-up in Denmark 2.5 years)	Y
23	3	CHARGE syndrome	0 (at follow-up in Denmark 1.5 years)	Part-time
24	4	Meningitis	1 (at follow-up 3 weeks)	Y

CAP = categories of auditory performance (Archbold et al., 1998), N = No, Y = Yes

Side effects from implant use

Side effects from implant use were reported by 14 patients (adults and children who did not have a sleeper, 14/23, 61%). The reported side effects were tingling sensations in the face, tongue, and contralateral side of the body (arms/legs), in 11 patients (11/23, 48%). One patient reported twitching of the face muscles due to stimulation of the ABI. In most cases, these side effects could be eliminated by inactivating the electrode(s) or by changing the mode of stimulation. One patient reported headache and vertigo from implant stimulation (no. 1). None of the patients had severe side effects such as bradycardia or other autonomous phenomena as a result of implant stimulation. Another side effect was infection around the magnet (no. 2) after MRI and magnet reinsertion. Infection resolved after revision and antibiotic treatment. In the pediatric patient group (no. 19, 22, 23, and 24), there was no sign of non-auditory sensations. However, it was difficult to validate this for three of the four children due to their young age and, consequently their ability to report. No severe side effects were observed.

Side effects from surgery

In the NF2 patient group, 11 patients (11/20, 55%) experienced side effects from surgery. Facial nerve palsy was present in eight cases (no. 1, 7, 11, 12, 13, 14, 15, and 16), of which one fully recovered (no. 11). Subdural hematoma requiring surgical evacuation occurred in one case (no. 17), and was treated conservatively in another case (no. 15). Severe postoperative infection occurred in two cases (no. 4 and 17), one was meningitis (no. 4), while the other was septicemia due to prolonged intensive care and tracheotomy use. Both of

these patients were able to keep their implants, with five and four active electrodes, respectively, and both reported benefit from implant use after recovery. There was subcutaneous liquor leakage in three cases (no. 4, 7, and 21), one of these cases (no. 4) was subjected to wound revision due to infection (see above), lumbar drainage, and prolonged antibiotic treatment. The other two patients were treated with prolonged banding of the head. In the pediatric patient group, complications occurred in three cases (3/4, 75%). Subcutaneous liquor leakage occurred in two cases (no. 19 and 22) and was treated with prolonged banding of the head. One of these patients (no. 22) had mild wound infection at the same time that was treated with antibiotics. One patient had postoperative nausea that required extra attention and observation (no. 23).

Paper IV

Questionnaire regarding ABI use, perception of environmental sounds, and ABI benefit.

Adults

Eight (8/11, 73%) of the adult patients "always" used their implants, and three (3/11, 27%) were non-users. One of the full-time users had used the implant less frequently in the early period. Two of the non-users had used the implant more frequently from the beginning (Q1 and 2). Results from the questionnaire regarding environmental sounds for the full-time users (n = 8) are shown in Figure 18 (Q3–9). The mean score on ABI user satisfaction (full-time users n = 8) with regard to speech perception via the implant was 2.1 (median = 2; range 0–4; 0 = not at all satisfied, and 4 = very satisfied; Q10). The mean score on ABI user satisfaction (full-time users, n = 8) regarding environmental sound perception via the implant was 2.6 (median = 2.5; range 0–4; 0 = not at all satisfied, and 4 = very satisfied; Q11). Ten of the adult patients reported that they would make the same decision to receive an ABI if they were able to reconsider their decision, and that they would recommend an ABI to someone else in their situation (Q12 and 13). One patient answered both yes and no on the question regarding receiving an ABI (Q12). One patient did not answer Q12 and Q13.

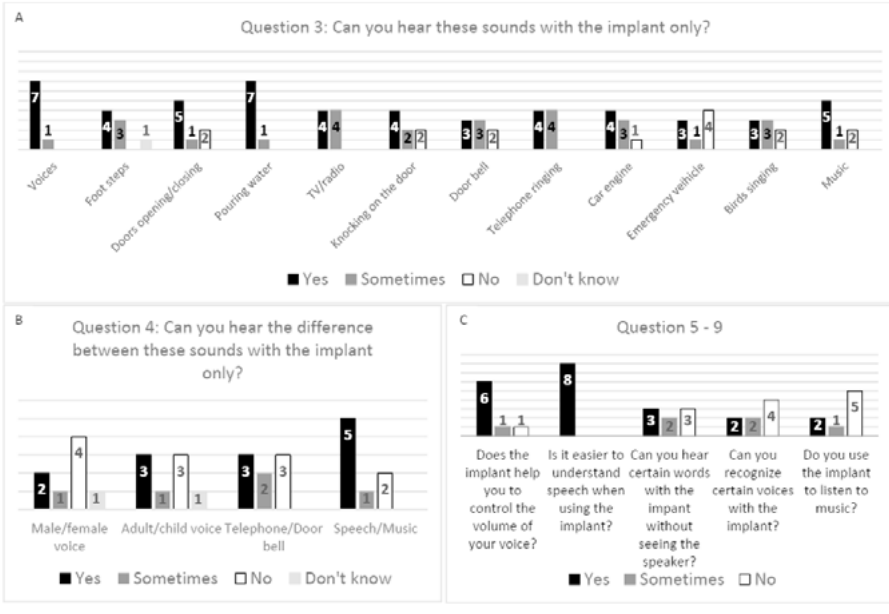

Figure 18. Results from the questionnaire regarding ABI use, perception of environmental sounds, and ABI benefit for the adult group. (A) Question 3. (B) Question 4. (C) Questions 5–9.

Children

The two children used their implants full-time. One child reported using the ABI more at the time of the questionnaire than in the past (Q1 and 2). The results from Q3 and Q4 are presented in Table 10. The implant helped the children to control the volume of the voice (always for one child and sometimes for one child, Q5). Only one child understood speech better with the implant switched on (Q6). Both children could hear certain words with the implant only (Q7). Only one child recognized certain voices using the implant (Q8), and only one child sometimes used the implant to listen to music (Q9). The parents scored 1 and 2 on how satisfied they were with their child's speech perception via the implant (0 not at all satisfied, 4 very satisfied; Q10) and 2 on how satisfied they were with their child's perception of environmental sounds via the implant (0 not at all satisfied, 4 very satisfied; Q11). The parents of both children stated that they would make the same decision again for their child to receive an implant, and that they would recommend an implant to another parent in their situation (Q12 and Q13).

Table 10. *Results from the questionnaire regarding ABI use, perception of environmental sounds, and the ABI benefit for the pediatric group (Q3 and Q4).*

Question 3: Can your child hear these sounds with the implant only?

Patient no.	*Voices*	*Foot steps*	*Doors opening/closing*	*Pouring water*	*TV/radio*	*Knocking on the door*	*Door bell*	*Telephone ringing*	*Car engine*	*Emergency vehicle*	*Birds singing*	*Music*
1	Y	D	Y	D	Y	Y	Y	Y	S	Y	D	S
2	S	S	S	S	S	D	D	D	S	D	N	S

Question 4: Can your child hear the difference between these sounds with the implant only?

Patient no.	*Male/female voice*	*Adult/child voice*	*Telephone/door bell*	*Speech/Music*
1	Y	Y	D	Y
2	S	D	D	D

D = Don't know, N = No, S = Sometimes, Y = Yes

NFTI-QoL

A statistically significant difference was observed in a comparison between our data from the NFTI-QoL and that from Hornigold et al. (2012) only for Q3 (facial weakness, $p < 0.05$). The patients in our study reported more problems on Q3. The results from the NFTI-QoL are presented in Tables 11 and 12, together with the results from Hornigold et al. (2012). Hearing problems had the largest negative effect on the QoL in this study (reported to some extent by 100% of the patients and as disruptive to usual activities by 91%). The patient's role and outlook on life had the second largest effect on QoL. Problems were reported to some extent by 91% of the patients, and as disruptive to usual activities by 73%. Balance and dizziness had the third largest effect on the QoL, and were reported to some extent by 91% of the patients, and as disruptive to usual activities by 73%. No correlation was found between the NFTI-QoL score and ABI use. The non-users and the users scored equally on the NFTI-QoL, and the total mean was 10.3–11.3 (range 7 to 15–18) for the non-users and 11.0 (range 4–15) for the users. The range was 10.3–11.3 for the non-users because one patient did not answer Q8. A score of 10.3 corresponded to the lowest score (total score 15), and 11.3 corresponded to the highest score (total score 18) on that question.

Table 11. *Results from the NFTI-QoL. The number of patients in brackets.*

	No. of answers		**0** Not present		**1** Present, but causes no difficulty with usual activities		**2** Causes some difficulty with usual activities		**3** Stops usual activities	
	Present study	Hornigold et al. (2012)	Present study	Hornigold et al. (2012)	Present study	Hornigold et al. (2012)	Present study	Hornigold et al. (2012)	Present study	Hornigold et al. (2012)
Q1	11	50	9% (1)	16% (8)	18% (2)	6% (3)	55% (6)	64% (32)	18% (2)	14% (7)
Q2	11	50	0% (0)	16% (8)	9% (1)	18% (9)	64% (7)	48% (24)	27% (3)	18% (9)
Q3	11	50	9% (1)	54% (27)	46% (5)	20% (10)	36% (4)	20% (10)	9% (1)	6% (3)
Q4	11	37	18% (2)	40% (15)	36% (4)	19% (7)	46% (5)	41% (15)	0% (0)	0% (0)
Q5	11	50	46% (4)	38% (19)	18% (2)	42% (21)	27% (3)	16% (8)	9% (1)	4% (2)
Q6	11	50	9% (1)	18% (9)	27% (3)	32% (16)	27% (3)	32% (16)	46% (5)	18% (9)
Q7	11	50	64% (7)	52% (26)	27% (3)	24% (12)	9% (1)	22% (11)	0% (0)	2% (1)
Q8	10	50	50% (5)	42% (21)	30% (3)	30% (15)	10% (1)	18% (9)	10% (1)	10% (5)

Table 12. *Results from the NFTI-QoL.*

	Mean score (standard deviation in brackets)		
	Present study (n = 11)	Hornigold et al. (2012) (n = 50)	Mann Whitney (p)
Q1. Dizziness and balance	1.82 (0.87)	1.78 (0.90)	0.95
Q2. Hearing	2.18 (0.60)	1.68 (0.96)	0.12
Q3. Facial palsy	1.45 (0.82)	0.78 (0.97)	0.02*
Q4. Sight[a]	1.27 (0.79)	1.00 (0.91)	0.39
Q5. Mobility and walking	1.00 (1.10)	0.86 (0.83)	0.80
Q6. Role and outlook of life	1.91 (1.04)	1.50 (0.99)	0.23
Q7. Pain	0.45 (0.69)	0.74 (0.88)	0.36
Q8. Anxiety and depression[b]	0.80 (1.03)	0.96 (1.01)	0.61
Total score [a,b]	10.40 (3.7)	9.41 (5.5)	-

[a]n = 37 for Q4 in Hornigold et al. (2012).

[b]n = 10 for Q8 in the present study.

* a p-value <0.05 is considered statistically significant

Paper V

Patient no. 1 (Cochlear Nucleus ABI24M)

Intra-operative eABRs were recorded using the electrode combinations 22-4, 2-8, 8-14, 14-20, 3-9, 9-15, 15-21, 4-2, 4-3, 10-12 and 10-11 (see Figure 12A for more information). eABR responses were obtained for all of the above combinations at a pulse width of 150 μs and a level of 150 CL. In the majority of the above electrode combinations (electrode 22-4, 4-2, and 4-3 excluded), a large negative potential was observed after the expected waveforms. The surgeon modified the implant position, but this had no effect on the eABR response.

The day before the initial fitting, the eABR responses were re-assessed in the BP+5 mode (2-8, 8-14, 14-20, 4-10, 10-16, 16-22, 3-9, 9-15, and 15-21) and also in the 4-22 combination. eABR responses were observed from all of the combinations, except for 15-21 and 16-22. A pulse width of 100 μs was utilized. A side effect, a large negative potential also observed at implantation, was observed at stimulation levels just above the eABR threshold with all of the combinations tested, with the exception of 2-8. A live-map was run (SPEAK, 250 Hz, BP+5, C-levels 165 CL, T-levels 100 CL, and pulse width 100 μs) and did not result in any abnormal patient reactions.

At the initial fitting session, no clear responses were observed from the child. The child went home with a map with C-levels set at 20 CL under the eABR threshold. At the subsequent fitting sessions, the levels were increased. Two weeks after the first fitting the child started to show responses to auditory stimuli. The reactions of the child to ABI stimulation were considerably inconsistent over a long period; however, the processor was worn full time when awake. After 1 year, the eABR measurements were reassessed and the stimulation levels were increased further. The child had 15 channels activated in the map (15 is the maximum number of active channels in a BP+5 ABI map), Figure 19A. Later, after the fitting sessions, a transitory balance problem occurred when the stimulation levels were increased.

Six years postoperatively, the child reacted consistently to ABI stimulation in general, but inconsistently to sounds above 3000 Hz, tested both via the programming system and by the sound processor in free field with warble tones. The speech and language therapist concluded that the child had difficulties hearing consonants in comparison with vocals. The child was later diagnosed with a cognitive disability. The CAP score at the latest clinic visit (6 years postoperatively) was 4 and the processor was used all day. A CAP score of 4 means that the child could discriminate consistently any combination of two of Ling's sounds without lip reading. The patient had a SPEAK BP+5 map with a pulse width of 100 μs, eight maxima, and C-levels between 210 and

255 CL. Hearing thresholds with the ABI measured with warble tones in free field are shown in Figure 20A. Unfortunately, there was a technical implant failure 6.5 years postoperatively and the child was scheduled for a re-implantation.

Patient no. 2 (Cochlear Nucleus ABI541)

Intra-operative eABR measurements utilized the electrode combinations 22-4, 22-16, 4-10, 21-15, 14-20, 3-9, and 2-8 (see Figure 12A for additional information). The eABRs responses were observed for all of the above combinations at a pulse width of 150 μs and at a level of 150 CL. In all combinations, except the combination of electrodes 14-20, a negative potential occurred in the waveform after the expected waveforms.

The day before the initial fitting, the eABRs were reassessed in BP+5 mode (2-8, 3-9, 4-10, 5-11, 6-12. 7-13, 8-14, 9-15, 10-16, 11-17, 12-18, 13-19, 14-20, 15-21, and 16-22). A clear response was observed only from stimulating electrode 5 (a pulse width of 200 μs and level 200 CL). No responses were observed from electrodes 3, 4, 8, 9, 11, and 12. On all of the other electrodes, there were small very unclear responses, even when the pulse widths were widened to 300 μs and the levels were raised to 175 CL. The large negative potential observed at implantation was not observed at this point. A live-map was run (SPEAK, 250 Hz, BP+5, C-levels 175 CL, T-levels 100 CL, and pulse width 300 μs) with no abnormal patient reactions.

No clear responses were observed from the child at the initial fitting session, or even after 1 year of fitting, even though the levels were increased. The eABRs were measured again 1 year after the first fitting and showed no response. Stimulation at a pulse width of 300 μs with levels up to 210 CL was performed. Furthermore, a complementary CT-scan showed that the electrode had slightly changed its location.

Patient no. 3 (Cochlear Nucleus ABI24M)

The initial intra-operative eABR measurements did not respond to stimulation. After repositioning the implant, responses were obtained from stimulation with the combinations 22-16, 16-10, 10-14, and 14-20 (see Figure 12A for additional information). An unclear response was noted when stimulating with the combination 3-9. The pulse width was 150 μs and the level was 220 CL.

The eABR measurements were re-performed in BP+5 mode the day before the first fitting on electrodes 2-8, 4-10, 8-14, 10-16, 14-20, 15-21, and 16-22. Thresholds between 150–170 CL were obtained from all of the tested electrodes. The pulse width was 150 μs. A tendency for the response to fatigue was observed after stimulation.

On the first day of fitting, the child reacted to stimulation of some of the tested channels with a slight nod of the head. During the first weeks of programming, when stimulating the three electrodes 2, 3, and 4 the child pointed at his mouth; this was interpreted as a side effect in which the stimulation produced some type of feeling in the tongue. These electrodes were switched off, even though it was not an obvious side effect. The child had 12 active electrodes in the map (Figure 19B). Three weeks after the first fitting, the parents informed us that the child reacted to some domestic sounds and that it was easier to communicate with the child with the implant switched on. Calmness and silence were necessary for the child to react to ABI stimulation. The child needed to be focused and had to concentrate to hear.

One year after the first fitting, the child reacted clearly to sound and ABI stimulation, and the parents reported that the child imitated sounds and more easily distinguished vowels than consonants. When tested by the speech and language therapist, the child reacted to all of the "Lings" speech sounds. The child wore the processor all day, but removed it sometimes if the surroundings were too noisy. The CAP score at the latest visit to the clinic (2.5 years postoperatively) was 4. The patient had a SPEAK BP+5 map with a pulse width of 150 μs, seven maxima, and C-levels between 182 and 203 CL. The hearing thresholds, with the ABI measured with warble tones in free field, are shown in Figure 20B.

Patient no. 4 (MED-EL Synchrony ABI)

The first eABRs were recorded via the MED-EL ABI placing electrode with four contacts (Figure 12D). The combinations 1-4, 2-3, 1-2, 3-4, and 1-3 at a pulse width of 60 μs and a level of 300 cu produced clear responses. The eABR measured on the ABI on electrodes 1, 5, 6, 8, and 12 gave clear responses at a pulse width of 60 μs and a level of 300 cu. Electrode 9 produced a clear response when stimulated at a level of 500 cu (see Figure 12B for further information).

The day before the initial fitting, the eABRs were repeated, and responses were found at all electrodes, with the exception of electrode 3 and 6; however, the levels were higher than the intraoperative levels.

At the initial fitting session, a clear reaction from the child was observed for three electrodes. No indications of side effects were observed, and the stimulation did not appear to be unpleasant at any of the electrodes. All 12 electrodes on the implant were active, as presented in Figure 19C. After 3 months the child used the ABI full-time and reacted to sounds such as her baby sister crying and her name being called. The parents stated that the child's own voice had changed. The CAP score at the last visit to the clinic (at 3 months) was 2.

A CAP score of 2 indicated that the child responded to speech sounds. The patient had a HDCIS MP map with a pulse width of 40.42 µs and C-levels between 17 and 26 qu (qu [charge unit] is a MED-EL term; 1 qu corresponds to approximately 1 nC).

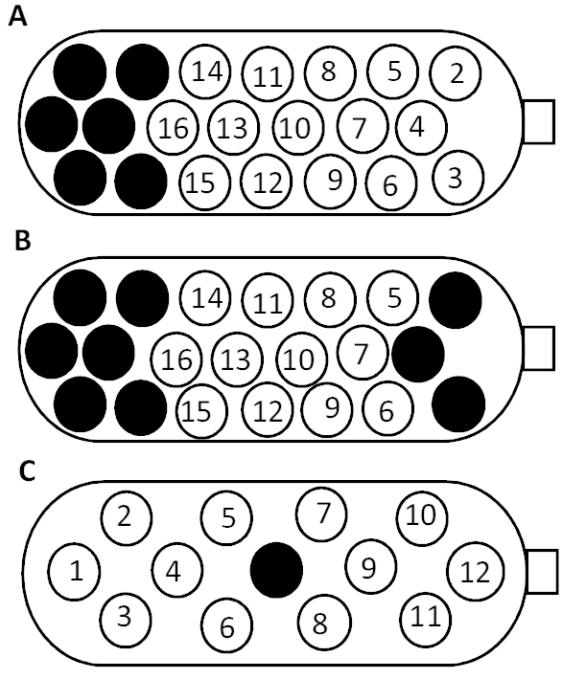

Figure 19. Active electrodes on the implant. Deactivated electrodes are colored in black. (A) Patient no. 1. (B) Patient no. 3. (C) Patient no. 4.

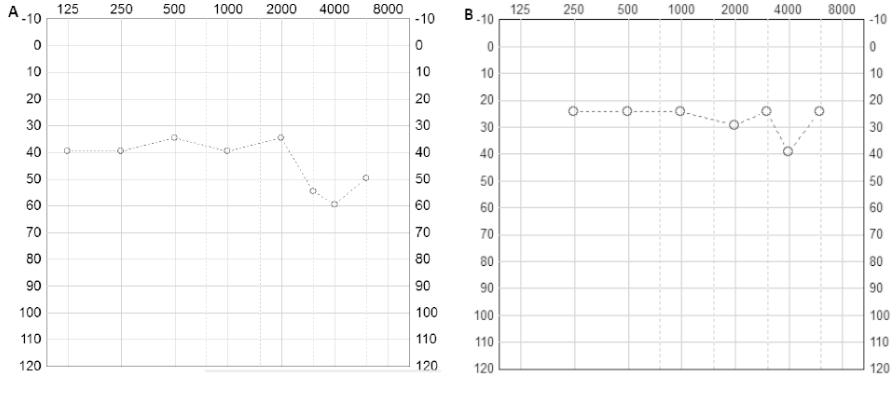

Figure 20. Hearing thresholds with the ABI measured in free field with warble tones. Horizontal axis showing tested frequency in Hz and vertical axis the sound level in dB SPL. (A) Patient no. 1, 6 years postoperatively. (B) Patient no. 3, 2.5 years postoperatively.

Discussion

CI is an ongoing story of success and the number of patients that can benefit from these devices is increasing. ABIs, that today are comparable to the early era of CIs, is also in an expanding phase with new patient groups. We have witnessed the introduction of new indications; however, based on our experience, it is difficult to establish absolute limits for when CIs and ABIs may be beneficial. It is essential to provide patients with a demanding hearing situation the appropriate treatment and expectation. New neurobiological findings indicate that animal models may be insufficient to fully understand how the human neuro sensorial elements are affected by hair cell loss (Liu et al., 2014). The ability of human hearing nerves to survive many years of total deafness is unexpected and of fundamental importance for making clinical decisions in numerous cases. Despite the success of CIs and ABIs, the results from this thesis demonstrate the need to continue research to further investigate the human inner ear and the central auditory pathways.

Paper I

The main conclusion from this study was that patients with an extended deafness duration (> 20 years) can achieve speech understanding and benefit from CIs. Important issues to consider are the overall hearing experience, deafness duration, and the age at onset of deafness. In this study, patients with a long deafness duration and limited years of hearing experience before deafness did not perform as well as those with shorter deafness durations and longer periods with hearing experience before deafness. Careful preoperative counseling is necessary because outcomes are difficult to predict.

The fact that patients with long-term bilateral deafness can achieve useful speech understanding with CIs indicates that auditory neurons are preserved and are electrically excitable, despite many years of inactivity (Liu et al., 2014). The slow retrograde degeneration of the human auditory nerve following loss of auditory mechanoreceptors suggests that there are important biological differences between humans and animals. The resistance to degeneration has also been confirmed by histological studies (Linthicum & Fayad, 2009; Liu et al., 2014; Nadol, 1997; Teufert et al., 2006).

Our data, combined with the findings made by Friedland et al. (2003), Moon et al. (2014), and Boisvert et al. (2012 a, b) imply that it is important to consider age at the onset of deafness in patients with bilateral hearing loss. The auditory cortex needs to obtain a specific amount of qualified auditory information for a certain number of years to create the necessary and stable associative couplings or 'hearing memories' to sense sounds and comprehend language. Moon et al. (2014) found that patients with a deafness duration exceeding 30 years, who became deaf before the age of 13 years, performed significantly worse. Our results support these data. In the present study, patients with long deafness durations (≥ 50 years) in the CI-ear and limited years of hearing experience before deafness (≤ 14 years) did not perform as well as those with shorter periods of deafness and longer periods of hearing experience before deafness. It was not possible to determine an absolute limit due to the small number of patients studied. However, the age at onset of deafness and the deafness duration are critical factors to consider.

Friedland et al. (2003) concluded that each year of additional deafness results in a loss of 1 percent point in postoperative word recognition score. Gomaa et al. (2003) found that each additional year in deafness yields a reduction of 0.7 percent points in postoperative word perception. In the present study, we observed similar results when analyzing groups 1 and 2, i.e., every year of deafness resulted in a loss of approximately 1 percent point in postoperative word recognition score. In contrast, Zeh & Baumann (2015) found in their study of 1355 CI-users that patients of all ages and deafness durations showed the same increase in benefit, measured by speech perception pre- and postoperatively.

Boisvert et al. (2012b) assessed the influence of ear choice, in patients who use HA in one ear and are deaf in the other ear, on CI outcome. The surgeon may consider implanting in the completely deaf ear or the contralateral ear with residual hearing (HA-ear). The authors found similar bilateral outcomes after CI implantation for both groups even though the patients implanted in the HA-ear performed significantly better when tested with the CI-ear only. They suggested that there are few disadvantages to implant in the lowest performing ear. We agree that the surgeon may choose to implant in the lowest performing ear, despite a long period of complete deafness when residual hearing is present in the other ear. A pertinent neural population may exist in most cases. In our experience, the outcome is predominately satisfactory, and the patient can use a combination of an HA and the CI after surgery.

Two patients experienced tinnitus from implant use. They both had long-term bilateral deafness (56 and 72 years) due to meningitis with an onset of deafness at a young age (8 years). Patients with meningitis are generally considered to have less favorable results and these two patients were not typical CI candidates.

The only patient not showing intraoperative electrophysiological responses described a 'feeling', instead of sound, from implant stimulation. There may have been a better solution for the patient if the surgery had been terminated without a CI. For instance, a decision based on the lack of electrophysiological responses. Further investigations are required to determine the reliability of intraoperative measurements via the CI and if such decisions can be based upon these factors. At the time of this publication, the patient has stopped using the implant due to lack of benefit.

This study was conducted over a long period of time resulting in a degree of uncertainty in the data. Although the audiometry, surgery, processor fitting, and documentation in archives and files were performed by professionals in a standardized manner, certain aspects may have changed over time. Surgical and fitting techniques, and implant and sound processor technology have improved. It is difficult to determine the variable 'deafness duration' exactly and its accuracy has potential to vary between patients. However, we believed that it was necessary to evaluate this patient group in order to make better decisions regarding implantation of patients with long deafness durations in the future, despite the data uncertainty.

Since the number of patients included in this study was small, the statistical results have to be interpreted with caution. In addition, patient age at implantation showed a correlation with postoperative speech perception ($r = 0.72$, $p^* < 0.05$). However, results are not only influenced by age at implantation and duration of deafness, but also by the age at which deafness occurs. The true dependent variables are difficult to investigate. The regression analyses performed in this study should be considered a tool for visualization and interpretation of these data.

Presumably, the CI outcome for some of these patients will continue to improve since the time factor 'learn to listen' with the implant appears to be longer for patients with a long deafness duration. Similarly, the MS-word perception scores were assessed only once as a part of the regular CI follow-up. More precise assessments would have been obtained if the measurements had been repeated. However, the main finding of this study is that patients with long deafness durations (> 20 years) can acquire speech perception with CIs already 6–12 months after implantation.

Paper II

In most patients, eABR via the CI is relatively straightforward during surgery. Wave V for the low-frequency regions on the implant was registered in all patients with a successful CI outcome. Patients with no eABR waveforms

showed poor CI outcome in terms of speech perception. eABR appears to be particularly useful for guiding the surgeon in the decision between CI and ABI implantation.

A critical issue relates to the potential for evaluating outcome and if the patient will benefit from a CI, despite lack of eABR responses. Jeon et al. (2013) found that patients with auditory neuropathy spectrum disorder (ANSD) did not constantly display eABR responses, despite a good CI outcome. Walton et al. (2008) compared eABR waveform quality for children with and without ANSD. The children with ANSD had significantly worse CI outcomes, in addition to a reduction in waveform quality compared with non-ANSD children. In contrast, Greisiger et al. (2011) did not report any significant differences in eABR amplitude or waveform between children with ANSD (n = 8) and non-ANSD children. In the cases in our study, where no eABR responses were obtained, the CI outcomes were unsuccessful and patients did not demonstrate speech discrimination. Recently, one additional implanted patient with human immunodeficiency virus (HIV) showed no eABR responses and the CI did not enable sound perception.

Our results, showing longer latencies and indistinct waveforms in the high-frequency region on the implant compared with the low-frequency region, are consistent with those of earlier investigations (Gordon et al., 2007; Firszt et al., 2002a; Miller et al., 1993). Zimmerman et al. (1995) and Gordon et al. (2007) showed that humans with hearing loss generally display smaller populations of spiral ganglion cells in the cochlear base (high-frequency region) compared with the apex (low-frequency region). Since the number of patients using a specific electrode length varied extensively in this study, statistical analysis regarding the influence of different electrode lengths on waveform scores was not performed. The length, size, and shape of the cochlea also varies greatly between individuals. In a study of 73 adult cochleae, Erixon et al. (2009) concluded, that the length of the first turn could vary between 20.3 and 24.3 mm. However, we observed that the mean total waveform score was highest for the longest electrodes (31 mm).

Similar to Firszt et al. (2002b), we found no correlation between speech perception outcome (MS-words) and waveform latencies or waveform quality. However, absent waveforms predicted a lack of or a poor CI outcome. Walton et al. (2008) and Gibson et al. (2009) found a positive correlation between waveform quality and the Melbourne Speech Perception Score (MSPS). The MSPS comprises a seven-point scale; a minimum of score 4 is needed to develop speech perception. The authors assessed eABR responses on 22 electrodes and the maximum total score that could be obtained was 66. Walton et al. (2008) found that patients with eABR scores > 56 were more likely to obtain a MSPS ≥ 4. The present study assessed eABR only on three electrodes,

and the MS-word test was used to assess speech perception outcomes. The reason for assessing eABR on only three electrodes was to avoid prolonging surgery because measurements are an integral part of the regular clinical intraoperative CI test protocol. One explanation for the different results could be the different speech perception measures used. Gallégo et al. (1998) found that the wave III–V interval is a strong predictor by assessing 17 patients using a phoneme-test. They analyzed eABR at eight different levels to correct for the different postoperative map-levels required by patients. Our study used a different speech perception score and would have potentially been more precise if we had been able to record the electrophysiology from all electrodes at different levels and match these with the patient´s map as waveform latency reductions and amplitude increases as stimulation levels are augmented. Lammers et al. (2015) compared prelingual and postlingual deaf adults, and found that after early deafness onset and an extended period of deafness, wave V latency was longer than for postlingual patients that experienced early auditory perception. They also found a positive correlation between wave V latency and post-surgery speech perception scores. The waveform amplitude tended to be low for prelingual patients with poor speech perception.

Battelino et al. (2009) performed eABR prior to CI using a golf club stimulation electrode close to the round window. They were able to record eABR in only 64% of their 104 cases. They evaluated CI outcome with pure tone audiometry after CI. In 46 patients, a positive eABR strongly correlated with a positive CI outcome. We obtained similar results because all patients who showed a positive eABR were able to detect sound through the implant, although speech perception varied among these patients. However, we observed that many of the patients who significantly benefited from the implant did not show eABR responses when stimulating the high-frequency region on the implant. We therefore believe that stimulation should be performed as deep as possible (i.e., at the tip of the CI) in the cochlea in order to exclude a patient from being implanted based on eABR measurements.

Kubo et al. (2002) showed that the eABR amplitude growth curve correlated well with consonant recognition scores in CI patients 1 month following surgery. However, there was no correlation 3, 6, and 12 months after implantation. We do not know if this is applicable to our data, since we only considered speech reception data from 6 or 12 months after implantation. Kubo et al. (2002) also concluded that the event-related potential (P300) latency was the best indicator of hearing ability after CI, indicating that the higher auditory system is of greater importance for speech perception. We decided to measure eABR because, unlike P300, these results do not depend on the degree of consciousness.

We do not believe it is cost beneficial to perform eABR using a CI in the decision making process between CI and ABI, as done for two of the four children in this study. The reason we did this was the uncertainty of the radiologist to establish the presence of a patent or hypoplastic auditory nerve. Therefore, it was necessary to make a cochlear implantation. In the other two pediatric cases, eABR were assessed using a test-electrode from MED-El. It consists of an 18 mm long basic CI array with three contacts inside the cochlea. Such a device may be more useful and cost effective in future decision making between CI and ABI. Possibly, an even longer device than the current version may be beneficial.

Measuring eABR appears to be a useful tool in difficult cases with inner ear malformations, in addition to long term deafness. eABR may be helpful for the surgeon and team in the assessment of whether a patent or hypoplastic auditory nerve may provide sufficient electric information to the auditory cortex. However, several factors such as anatomical condition, cognition, age at implantation, deafness duration, cause of deafness, and age at onset of deafness contribute to the final outcome; eABR responses cannot be considered as sole predictors. However, we believe that this method provides important additional information and appears to have a definitive role in the diagnostic armamentarium for the improvement of decision-making with regard to complementary surgical strategies such as ABI. We believe that eABR via the CI (measured by stimulation on the apical part of the electrode array at maximum stimulation levels) can be used to determine if the patient will benefit from the CI.

Papers III, IV, and V

The main conclusion from papers III, IV, and V is that a majority of the patients used their ABIs at least for a period of time. The patients were generally satisfied with their ABIs, even if their hearing remained limited. The patients reported that they would make the decision to receive an implant again if a similar situation arose. No severe side effects were observed from implant use and, while surgical side effects were present due to the removal of tumors, they did not appear to be augmented by the implantation in NF2 cases.

In a study of 11 adult NF2 patients, Lenarz et al. (2002) concluded that the ABI can greatly assist in communication especially since many NF2 patients also have visual disorders caused by the tumors. The ABI provides them with a sense of self-confidence for facing the outside world. Some of the quotes from the questionnaires in study IV supporting this included: *"The implant makes me feel safe*", *"It gives me more control of what happens around* me", "*It feels like I'm in a bubble without the implant*", "*If the implant would have*

worked as it did in the beginning I would make the same decision again (to get an implant)", "*The implant gives me self-confidence*", and "*It was tiring to go through the surgery and the fitting of the ABI, but I do not regret it for a second as it makes me feel safe and gives me self-confidence*". Adult patients described that hearing via an ABI is an attention-demanding task and they have to focus meticulously to hear and comprehend. ABI-hearing is not a passive process and sounds are bounded in noise, even in quiet surroundings. In the study by Lenarz et al. (2002), noisy surroundings were concluded to be the most disturbing situation for ABI patients. The following quotes from the patients in study IV confirm this: *"Can discriminate some sounds in the right environment. If it is a lot of background noise it is hard to sort the sounds*" and *"Has taken the implant off in noisy environments"*.

All but one patient (that did not answer the question in paper IV), reported that they would recommend an ABI to someone else in their situation, highlighting the value of the partial hearing that the ABI provided in this patient group. In total, 13 out of 18 (72%) patients who were asked to participate in study IV, choose to respond to the questionnaires (adults and children). It may be assumed that the non-responders (5/18, 28%) would have responded in a more negative manner. Four of the non-responders were non-users.

Fitting the ABI to adults (NF2 patients)

Our aim of administering follow-up examinations for each ABI patient at least once a year was not feasible in all cases due to NF2 disease. During the follow-up visits, we focused on determining the tumor burden and MRI results together with the ABI function. In some patients, the disease progressed, making ABI use and participation in structured auditory testing difficult.

In most cases, the side effects from ABI stimulation could be eliminated by inactivating electrodes or changing the mode of stimulation. Pitch ranking was a demanding task for the patients in most cases, but became easier with time when the patient was more used to the sounds from the implant. It is likely that patients with a good tonotopical organization will strongly benefit from it.

We analyzed the incidence of activation of various channels on the implant. Interestingly, it showed that some electrodes were less frequently activated (electrodes 3, 6, 9, 19, 20, and 22). These results indicate that the position of the electrodes on the implant may not be optimal and the results may be highly dependent on brainstem anatomy. Rosahl and Rosahl (2013) showed that the human CN in non-tumor patients displayed considerable variation in size and shape between individuals. Such variations can greatly influence the stimula-

tion pattern, be attributable to some of the variations in the functional outcomes, and may explain why some electrodes were less frequently activated in the present study. The average number of active channels at switch-on was 13.3, and at the last follow-up was 11.6. Nevison et al. (2002) reported an average usage of 12.4 channels at switch on and 8.6 channels at a later stage in the map.

Fitting the ABI to children (non-NF2 patients)

Intra-operative eABR responses were obtained in all of the children who received an ABI. However, at the reassessment prior to the first fitting, the results varied from clear to very vague eABR responses. Additionally, a large, late, negative potential was detected at some stimulations intraoperatively. It could be speculated that these responses are derived from the vestibular nuclei because one patient had transitory balance problems at higher stimulation levels during fitting. According to Lenarz et al. (2001), dizziness is the most common side effect from implant stimulation, and Frohne et al. (2000) concluded that potentials with latencies longer than 5 ms occurred from side effects. In contrast, we found in study III that the most common side effect was a tingling sensation in a localized area of the body. Lenarz et al. (2001) reported this to be the second most common side effect after dizziness. Herrmann et al. (2015) concluded that only electrodes with an auditory component (either only auditory or auditory in combination with a side effect) showed an eABR response. The eABR measurements the day before the first fitting may be used as a reference for stimulating specific electrodes.

We found that it was difficult to distinguish auditory sensations from side effects when fitting the ABI to a pediatric patient. A non-distressful side effect can produce a pleasurable reaction in the child and an auditory sensation can result in an unpleasant reaction (Colletti & Zoccante, 2008). No severe side effects have been observed to date.

ABI hearing outcomes in adults (NF2 patients)

In one patient there were no auditory sensations after ABI. The reason for this could not be determined with certainty because the radiological investigation showed no signs of electrode displacement. One patient stopped using the implant because the sound decreased after a few minutes of use and the reason for this fatigue effect could not be determined. The best performer had a CAP score of 7 (the patient could use the telephone with a known speaker). After evaluating various parameters, such as the duration of deafness and tumor size, that were not different from the other patients, we could not establish the reason for the exceptional success and performance. Similar cases have been

described by other ABI centers and they have shown the potential of the current technique. In this case, a distinct pitch ranking pattern was recorded with high pitch electrodes on the opposite side to the low pitch ones. Nevison et al. (2002) suggested that a reduced performance is almost certainly due to stimulation of an auditory structure that does not permit good access to the tonotopic arrangement of neurons. The patient also used a piano to practice sound awareness and pitch with the implant.

Most of the adult full-time users reported that their ABI assisted them in voice monitoring (always or sometimes), and their understanding of speech improved when the implant was switched on. In the study by McSorley et al. (2015) 90% of the patients found the ABI useful for speech understanding in conjunction with lip-reading. ABIs can improve lip reading; this has also been reported by other authors (Vincent, 2012; Lenarz et al. 2002). Five of the adult patients in our study could constantly or occasionally obtain word discrimination from the ABI only. Three adult patients even listened to music through their ABI. In study III, we found no correlations between postoperative CAP score and presurgery tumor size, gamma knife treatment, or number of activated channels on the implant. Almost all of the ABI users reported that the limited hearing from the ABI was of great importance for them. They described the following benefits of the ABI: "*self-confidence"*, "*makes them feel safe"*, "*makes them feel as they are participating in the world"*, and "*makes them aware of what happens around them".*

Hearing outcomes with the ABI in children (non-NF2 patients)

Electrode dislocation occurred in one patient, the reason for this was unclear; however, the patient with CHARGE syndrome had an unusually wide foramen Luschkae that may explain the migration of the electrode, even though it was thoroughly fixed against the brainstem. It is of note that in most patients the electrode did not show signs of migration, even in patients with recurrent tumors. Lenarz et al. (2001) described one case of postoperative electrode migration due to a very large lateral recess. The patient underwent revision surgery for optimal electrode placement. No revision surgery was performed on the patient in the present study, as decided by the ABI team and parents. Unfortunately, a technical implant failure developed in one patient. The child benefited greatly from the implant over 6.5 years. At the time of this publication, the child has been successfully re-implanted with a MED-EL Synchrony ABI on the right side in November 2015, and the fitting started in January 2016.

All but the one patient (with the dislocated electrode, described above) used the implant and benefitted from it. From our experience, it appears that it takes longer to 'learn to hear' with an ABI compared with a CI. The reactions from

the children were very vague in the first 6 to 12 months. Additionally, it appears that hearing performance continues to improve even after several years. Colletti et al. (2014) followed 64 children with an ABI and found a latency of at least 3 years before reaching the individual CAP 'top score'. They also found that the age at implantation and etiology influenced outcome. Children with early implantation (before the age of 2 years) and those with no other disorders but cochlea or cochlear nerve pathologies showed the best outcomes. The children with prior hearing (post-meningitis ossification and trauma cases) were the greatest performers and showed rapid increases in performance over the first 3 years of ABI use. The median CAP score for children with cochlear ossification or trauma was 6–7 after 3 years of ABI use. For children with other disabilities besides cochlea or cochlear nerve pathologies, the median CAP score increased considerably slower and only reached scores of 2–3 after 3 years (Colletti et al., 2014). Children with ABIs are generally implanted late in comparison with children with CIs who are implanted as early as 6–8 months. This may be one explanation for the finding of Colletti et al. (2014), that children with prior hearing are the best performers. This may potentially have not been the case if the ABI were implanted as early as CIs. Other authors have speculated that the auditory cortex never matures in CI users if they are implanted after the age of 3.5 years (Jiwani et al., 2013). This situation should also apply to ABI users.

Two of the children in study V experienced greater difficulties in hearing consonants compared with vowels. Nevison et al. (2002) also found that the results for consonant confusion tests were lower than vowel confusion tests in their study of 26 adult ABI users. While most children benefit from sounds generated from the ABI, sign language is crucial for these children. The implant alone cannot provide a level of hearing that can be relied upon for speech and language development. In addition, if implant failure occurs, the outcome of a re-implantation is uncertain; not many cases of ABI re-implantation have been performed globally or have been described in the literature. The ability to understand and react to thoughts, emotions, and feelings in others and oneself, referred to as Theory of Mind (ToM), is often delayed in deaf children of hearing parents (Sundqvist et al., 2014; Jones et al., 2015). This is presumably due to the lack of a fluent communication. This patient group, children with ABIs, probably require as much communication as possible to develop a sufficient communication and ToM, since their parents are not commonly fluent in sign language and they are implanted at older ages (2–3 years). The auditory development in a normal hearing child is thought to be as short as 3 years before it declines (Karltorp, 2013). A child with an ABI is most likely to benefit from both sign language input and sounds from the implant, although sign language must be considered their main language.

Variability in hearing outcome

The reason for the variable ABI results is unclear. Tumors in NF2 patients may affect the anatomy in the region of foramen Luschkae and the CN, and negatively influence the physiological response. Nevison et al. (2002) found that a larger tumor (> 4 cm) presents a worse prognosis for ABI-hearing; however, we could not confirm this, perhaps because our outcome measure (CAP) was too broad. Therefore, the general results from ABI in non-NF2 patients may be better. This has also been observed at other ABI centers. Colletti et al. (2005) suggested that the absence of distortion of the auditory brainstem in non-NF2 patients makes it possible to achieve an effective and fairly well-organized activation of the auditory pathways. The results of this study are consistent with earlier reports describing auditory performance and the large inter-individual variability in ABI outcome (Goffi-Gomez et al., 2012; Colletti et al., 2005; Sanna et al., 2012; Colletti et al., 2010).

There was a relatively large number of ABI non-users (7/18, 39% from study IV) and it can be speculated why this number is so high. Some used the implant from the beginning, but then stopped using it for different reasons. In some cases, the progress of the NF2 disease is the reason for not using the implant. For some patients, the sound from the ABI was likely to be a large disappointment. Before implantation, the main focus is not on the implant but on tumor removal. Some of the patients have hearing before the surgery and wake up deaf after tumor removal. It is difficult to achieve patient hearing satisfaction with an ABI compared with pre-surgery hearing levels and it is not easy to provide the correct preoperative information.

The sounds perceived from the implant varied greatly among patients. The reason for these variances may be related to the potential of the ABI to effectuate tonotopic stimulation of the neurons in the central auditory pathway, since tonotopy is a fundamental feature of the auditory system (Colletti et al., 2002a; Nevison et al., 2002). It may be that fewer active electrodes stimulating neurons in an improved tonotopic manner is superior to a larger number of interactive electrodes with large-field stimulation. The outcomes could potentially be improved if the implant could better access the tonotopy of the CN, perhaps through a different implant design. Trials have been performed with penetrating implants, but have been unsuccessful (Shannon, 2015; Otto et al. 2002). The signals presented by the ABI should potentially differ from the signals presented by a CI, improving results. Today, exactly the same stimulation is performed by a CI in the cochlea as that by an ABI on the CN.

The hearing prognosis with an ABI may have been better for the meningitis pediatric patient compared with the other children, because this patient had postlingual deafness (normal hearing for 2 years before deafness). To date, the

results from the questionnaire in study IV do not support this finding. However, the follow-up period varied greatly between the two patients, and another study (Otto et al., 2002) has shown that patients with more than 2 years of ABI usage perform better than those with less experience, and that the improvement in hearing performance increases, even up to 8 years after implantation. Colletti et al. (2002a) speculates that there could even be an advantage for congenitally deaf children because they may not have a pre-defined tonotopic arrangement in the CN. The neural plasticity of these children could induce tonotopical arrangement from ABI stimulation. Postlingually deaf children may possess neural pathways with an established tonotopical arrangement that would increase the difficulty of a tonotopical fit with an ABI (Colletti et al., 2002a). However, Colletti et al. (2014) concluded that children with preoperative hearing and no other disabilities other than hearing loss have the best ABI outcomes.

QoL

Similar to the studies by Hornigold et al. (2012) and Ferner et al. (2014), results from the NFTI-QoL in study IV showed that hearing problems and the patient's role and outlook of life, in conjunction with dizziness and balance problems, had the largest negative effect on QoL in the NF2 patient group. Hornigold et al. (2012) showed that the magnitude of the problems was ordered from dizziness and balance issues as the largest, followed by hearing problems, and role and outlook on life. In our study, hearing caused the greatest problems followed by role and outlook on life, and dizziness and balance problems. It is not clear in the study by Hornigold et al. (2012) whether the patients were using ABIs. The results differed significantly on Q3 (facial palsy) in the comparison between the current study and the study of Hornigold et al. (2012). An explanation for this finding could be due to translation issues because the questionnaire was translated from English to Swedish, even though the questionnaire has been translated back and forth, and was checked for consistency. Another explanation could be that our patients had more facial nerve problems than those in the study by Hornigold et al. (2012). Furthermore, all of the patients in our study had undergone surgery at least once due to NF2, we do not know if that was the case for the patients in the study by Hornigold et al. (2012). Nevison et al. (2002) concluded that affected facial nerve function is a common side effect of NF2 tumor removal. We observed these patients at regular appointments, and their responses to Q3 appeared to be reasonable.

The NFTI-QoL was validated by Hornigold et al. (2012) by correlating the NFTI-QoL with the SF-36 and EuroQOL, and by administering the NFTI-QoL to groups of patients with solitary vestibular schwannomas (non-NF2) and healthy controls. No further validation was performed in this study. We expected patients scoring the highest on the NFTI-QoL to be the non-users;

however, study IV did not confirm this since the users and the non-users provided similar answers on the NFTI-QoL.

Limitations

These studies have several limitations. First, the CAP score used for evaluations may not be specific enough for analyzing hearing outcomes with ABI correlated with other factors. Second, we did not succeed in our aim of administering follow-up examinations for ABI patients once a year, mainly due to disease progression, making ABI use and participation in structured auditory testing difficult. Third, data in study III were collected over a long time period (20 years). However, since ABI is very rare, we believe that this could not have been performed in any other way.

Furthermore, questionnaire 1, assessing ABI usage and environmental sound perception, was not validated and the answers should therefore be interpreted with caution. The reason for using this simple, non-validated questionnaire was that the existing questionnaires regarding hearing were unsuitable for our patient group. The level of ABI-hearing could not be compared with hearing via a conventional hearing aid or a CI. Nevison et al. (2002) and McSorley et al. (2015) used a questionnaire designed by Nevison et al. in their studies to collect information such as ABI use, when the processor was switched off, and usefulness in quiet and noisy surroundings. Since that questionnaire was not available for us, we decided to use our own questionnaire with questions regarding usage, perception of environmental sounds, and patient satisfaction, developed from the ABI-team's own experiences derived from the many annual ABI-patients visits at our clinic. Questionnaire 2 was translated from English to Swedish. The English version of the NFTI-QoL (Hornigold et al., 2012; Ferner et al., 2014) was validated for patients with NF2 aged 16 years or older. No validation was performed for the translated questionnaire. The questionnaire was, however, translated back and forth and checked for consistency by a professional translator. It may have been more appropriate to conduct interviews for these patients due to the complexity of their situation and hearing.

Conclusions

Patients with extended deafness duration (> 20 years) can achieve speech understanding and benefit from CIs. In this study, patients with a long deafness duration and a limited number of years of hearing experience before deafness did not perform as well as those with shorter deafness durations and longer periods with hearing experience. Careful preoperative counseling is necessary because outcomes may still be difficult to predict.

Absent eABR waveforms predicted no or poor CI outcome. We found no correlation between speech perception outcomes (MS-words) and eABR waveform latencies or eABR waveform quality.

When no eABR waveform responses were obtained, the CI outcomes were unsuccessful. We believe that this method has a definitive role in the diagnostic armamentarium for the improvement of the selection of complementary surgical strategies such as ABI.

The majority of the patients used their ABIs and benefitted from them for at least a period of time. No severe complications from ABI surgery or ABI stimulations were recorded. Side effects from ABI stimulation could, in most cases, be eliminated by re-programming the ABI.

Almost all of the ABI users reported that the limited hearing from the ABI was of great importance. The patients were generally satisfied, even if their hearing remained very limited. ABI assisted voice control in a majority of the full-time users, and all of these patients reported improved understanding of speech with the implant switched on.

All pediatric patients but one used their implant all the time and reported benefits from it. From our experience, it appears to take longer to ‘learn to hear’ with an ABI compared with a CI. Additionally, hearing performance can continue to improve over time, even after several years. It was difficult to distinguish auditory sensations from side effects when fitting the ABI to a pediatric patient.

Based on these findings:

- CI should be considered an option, even for patients with an extended period of deafness.

- Intraoperative eABR can be used to help make the decision to implant with either a CI or an ABI, and to predict if the CI is going to be beneficial for patients with a long duration of deafness.

- ABI should be considered an option for patients with NF2, cochlear malformation, cochlear nerve hypoplasia/aplasia, or cochlear ossification after meningitis.

Future perspectives

CI is a success story and since its development during the 1960s and 70s, there have been great technological advancements, broadened indications, and bilateral implantation. New indications increase demand on preoperative investigations, in addition to rehabilitation. Thorough evaluation of implanted patients' hearing outcomes is required to gain further experience in order to counsel new patients. Results in speech performance have been unexpectedly good and bilateral users have shown additional gains through improvements in speech perception in noise and sound localization. However, there is still a need for considerable advancements in technology, mode of nerve stimulation, hearing preservation, and electrode design. In the future, strategic treatment and localized drug therapy for the inner ear should be possible. CIs are continuously evolving and additional indications such as severe tinnitus, single sided deafness, and advanced high frequency sensorineural hearing loss in the elderly are likely to be introduced.

ABIs generally do not advance hearing as much as CIs. A more central stimulation of the auditory pathways appears to bypass essential properties in the relay of auditory signals, influencing speech perception and auditory performance. It is therefore necessary to acquire further information on the human central auditory pathways including the CN to improve electrode design, stimulation modes, and programming in patients with bilateral vestibular schwannomas and severe ear malformations. More knowledge about the tonotopic organization and variational anatomy of the CN are necessary to design better electrode arrays and improve functional outcome. An essential aspect is the formation of detachable electrode plates since re-implantation is difficult and poses special skills on the surgeon and is potentially dangerous due to damage to the vulnerable CN structures. The discussion of bilateral ABIs has already started and it will probably be more common in the future.

Sammanfattning på svenska

Hörsel är mycket viktig för mänsklig kommunikation även om kommunikation också innehåller många andra element såsom ansiktsuttryck, gester, röstläge och kroppsspråk. Troligtvis är hörseln det sinne som först gör oss medvetna om världen runt omkring oss, redan i fostervecka 20, och kanske det sista sinne som lämnar oss när vi dör. Brist på en fullgod kommunikation leder ofta till social isolering.

Om majoriteten av hårcellerna i hörselsnäckan är skadade eller om hörselsnäckan eller hörselnerven är missbildade eller saknas så är hörselnedsättningen grav och permanent. Ett cochleaimplantat (CI) eller ett hjärnstamsimplantat (ABI) är proteser för hörselsinnet som på artificiell väg kan ge hörsel. Den syntetiska hörseln från ett implantat kan variera från att ge omgivningsljud och vara ett stöd för läppavläsning till att ge öppen taldiskrimination så att man kan klara av telefonsamtal.

CI är idag ett rutiningrepp och över 300 000 patienter har implanterats i världen. Nya patientgrupper inkluderas ständigt för hörselrehabilitering med CI, såsom de med lång dövhetsduration, diskantdövhet och tinnitus. ABI är fortfarande ovanligt och endast ca 1200 patienter är implanterade i världen. Den största patientgruppen med ABI är vuxna med Neurofibromatos typ 2 (NF2), men på senare tid implanteras även patienter (både barn och vuxna) med missbildade eller förbenade snäckor eller avsaknad av hörselnerver. Dessa nya grupper av patienter med CI och ABI ökar kraven på både utredning innan implantation och rehabiliteringsprocessen efteråt.

Syftet med avhandlingen är att:

- Utvärdera hörselresultaten för patienter som implanterats med CI efter en lång tids dövhet (duration av dövhet > 20 år).

- Undersöka om intraoperativt mätt elektrisk hjärnstamsaudiometri (eABR) kan förutspå hörselresultaten med CI.

- Undersöka om eABR kan användas som ett verktyg för att välja om patienten ska implanteras med ett CI eller ett ABI.

- Beskriva de kliniska erfarenheterna av ABI i Uppsala såsom kirurgi, komplikationer och tekniska aspekter.

- Undersöka användning, hörselresultat, och hur nöjda patienterna är efter ABI implantation i Uppsala.

- Undersöka om och hur ABI är av nytta för barn som inte har NF2.

I arbete I utvärderades alla patienter opererade i Uppsala, mellan 2002 och 2013, som hade en dövhetsduration på minst 20 år. Vi fann att dessa patienter kunde få öppen taldiskrimination med CI. De patienter som hade varit döva längst och hade en begränsad tid med hörsel innan dess presterade dock inte lika bra som de med en kortare dövhetsduration och en längre tid med hörsel innan dövhetens inträffande. Det är nödvändigt med en noggrann utredning och diskussion med patienten preoperativt då resultatet av CI kan vara svårt att förutspå i denna grupp.

I arbete II mätte vi eABR intraoperativt via CI:t på alla vuxna patienter som implanterades i Uppsala mellan 2011 och 2013. Vi fann inga korrelationer mellan hörselresultat och vågformslatenser eller kvalitén på eABR-svaret. Uteblev eABR-svaret helt kunde vi dock se att de patienterna inte heller fick någon nytta av sitt CI. Vi drar slutsatsen att den här metoden är användbar för att kunna se om en patient kommer ha nytta av sitt CI och för att välja mellan CI och ABI i speciella fall.

I arbete III utvärderades alla 24 operationer med ABI som utförts i Uppsala 1993-2013. Majoriteten av patienterna använde sitt ABI, åtminstone en tid, och hade då nytta av det. Inga allvarliga komplikationer kunde ses varken från kirurgin vid implantationen eller från stimuleringen med implantatet. Sidoeffekter från ABI-stimuleringen kunde i de flesta fall undvikas genom omprogrammering.

I arbete IV undersöktes 18 ABI-patienters användning, nytta, nöjdhet och hörsel med hjälp av en enkätstudie. Avlidna patienter, samt patienter som inte fått sitt ABI inkopplat eller de som inte hade någon hörsel från sitt ABI ingick inte i den här studien. Tretton av de 18 tillfrågade patienterna valde att delta i enkätstudien. Nästan alla patienter som svarade rapporterade att hörseln från ABI hade stor betydelse för dem även om den var begränsad. Alla patienter som använde implantatet på heltid rapporterade att det var lättare att förstå tal när implantatet var på.

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hörselresultaten dröjer länge innan de är uppe på sin maximala nivå. Det är speciellt svårt att skilja mellan hörsel och sidoeffekter för denna patientgrupp.

Baserat på dessa arbeten föreslår vi att:

- CI bör vara ett alternativ även för patienter med en lång dövhetsduration.

- Intraoperativt mätt eABR kan användas för att välja mellan CI och ABI eller för att se om patienten kommer att få nytta av sitt CI.

- ABI bör vara ett alternativ för både patienter med NF2 och patienter med cochleära missbildningar, avsaknad av hörselnerv eller förbenade snäckor.

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Appendix

Appendix 1: Questionnaire regarding ABI use, the perception of environmental sounds and the benefit of ABI

Questionnaire regarding ABI use, the perception of environmental sounds and the benefit of ABI

Date:……..

Patient ID/Label: xxxx-xx

1. How often do you use your implant right now?

- ❑ Always
- ❑ Every day, approximately …… hours per day
- ❑ A few times a week
- ❑ Seldom, a few times a month
- ❑ Never

Comments……
……..

2. Did you earlier use your implant more or less than you do right now?

- ❒ Yes, I did use it more often before
- ❒ Yes, I do use it more often now
- ❒ No, I have always used it as I do right now

Comments (why has it changed?)……...
……
……..

3. Can you hear these sounds with the implant only? (*If you can't see the sound source, just hear it. You don't have to recognize the sound, just detect it.****)***

	Yes	**NO**	**Sometimes**	**Don't know**
Voices	☐	☐	☐	☐
Footsteps	☐	☐	☐	☐
Doors opening/closing	☐	☐	☐	☐
Pouring water	☐	☐	☐	☐
TV/radio	☐	☐	☐	☐
Knocking on the door	☐	☐	☐	☐
Doorbell	☐	☐	☐	☐
Telephone ringing	☐	☐	☐	☐
Car engine	☐	☐	☐	☐
Emergency vehicle	☐	☐	☐	☐
Birds singing	☐	☐	☐	☐
Music	☐	☐	☐	☐

Comments……
……
……
……

4. Can you hear the difference between these sounds with the implant only?

	Yes	**NO**	**Sometimes**	**Don't know**
Man voice – female voice	☐	☐	☐	☐
Adult voice – child voice	☐	☐	☐	☐
Telephone ringing – doorbell	☐	☐	☐	☐
Speech – music	☐	☐	☐	☐

5. Does the implant help you to control the volume of your voice?

- ❑ Yes
- ❑ No
- ❑ Sometimes

6. Is it easier to understand speech when using the implant?

- ❑ Yes
- ❑ No
- ❑ Sometimes

7. Can you hear certain words with the implant without seeing the speaker?

- ❑ Yes
- ❑ No
- ❑ Sometimes

8. Can you recognize certain voices with the implant *(do you know who is talking without seeing the speaker)?*

- ❑ Yes
- ❑ No
- ❑ Sometimes

9. Do you use the implant to listen to music?

- ❑ Yes
- ❑ No
- ❑ Sometimes

10. Estimate how satisfied you are with speech perception via the implant

Not at all satisfied *Very satisfied*

☐ ☐ ☐ ☐ ☐

11. Estimate how satisfied you are with environmental sound perception via the implant

Not at all satisfied *Very satisfied*

☐ ☐ ☐ ☐ ☐

12. If you were able to reconsider getting an implant, would you make the same decision?

- ❑ Yes, I would make the same decision.
- ❑ No, I would refuse an implant.

Why/Why not?

……

……

13. Would you recommend an individual in the same situation to get an implant?

- ❑ Yes
- ❑ No

Comments……

……

……

……

Thanks for participating!

Appendix 2: Neurofibromatosis 2 Impact on QoL (Hornigold et al., 2012)

Neurofibromatosis 2 Impact on QOL

Instructions for completing the NFTI-QOL

Please complete the following information: Age:_____ years

Gender: Male ❑ Female ❑ (please check)

Patient ID/Label: XXXX-XX

For each of the questions on the next page, please tick the one box that describes how you feel today

Usual activities include: work; housework; study; sport; social; family or leisure activities

Q1. Do balance or dizziness problems stop you performing your usual activities?

No balance problems or dizziness	❑0
Balance or dizziness problems but no difficulties	❑1
Balance or dizziness problems cause me some difficulties	❑2
Balance or dizziness problems stop my usual activities	❑3

Q2. Do hearing problems stop you performing your usual activities?

No hearing problems	❑0
Hearing problems but no difficulty	❑1
Hearing problems cause me some difficulty	❑2
Hearing problems stop my usual activities	❑3

Q3. Does facial weakness stop you performing your usual activities?

No facial weakness	❑0
Facial weakness, but no difficulty	❑1
Facial weakness causes some difficulty	❑2
Facial weakness stops my usual activities	❑3

Q4. Do problems with your sight stop you performing your usual activities?

No problems with sight	❑0
Sight problems, but no difficulty	❑1
Sight problems cause me some difficulty	❑2
Sight problems stop my usual activities	❑3

Q5. Do you have any problems in mobility and walking?

No problems in mobility and walking	❑0
Some difficulty but can manage on my one	❑1
Unable to walk around without some help	❑2
Unable to walk at all	❑3

Q6. Has your medical condition affected your role and outlook on life? (e.g. confidence, vulnerability, relationships, caring for family, career, having children)

No effect or positive effect	❑0
Small negative effect	❑1
Moderately negative effect	❑2
Large negative effect	❑3

Q7. Pain; throughout or lives, most of us have had pain from time to time such as mild headaches, sprains and toothaches. Have you had pain *other than this* in the last week?

None	❑0
Mild pain	❑1
Moderate pain	❑2
Severe pain	❑3

Q8. Do you currently suffer from anxiety or depression?

No	❑0
Mild anxiety and depression	❑1
Moderate anxiety and depression	❑2
Extreme anxiety and depression	❑3

If you have further comments regarding the effect of NF2 on your QOL, please write them here:

You have now completed the NFTI-QOL. Thank you for your input.

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