Objective Measurements and Cochlear Implants Imaging

Ph.D. Thesis

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Abstract

In Norway, about one out of 2000 babies born is deaf, which means up to 20–30 children are born deaf every year. Some become deaf later due to diseases like meningitis or because of disease during pregnancy. In recent years, in particular, the Cochlear Implant (CI) has become a well-established treatment for deaf children and adults. The Department of Otorhinolaryngology at Oslo University Hospital (OUS) is responsible nationally for all deaf children in Norway.

A CI offers the possibility to deaf people of partially restoring their hearing. A CI consists of two major parts - a sound processor (SP) and a stimulator/implant. The SP's microphone picks up sound and analyses it in terms of frequencies and volume. This information is sent via radio frequencies to the implant inside the head. The implant stimulator transfers a biphasic pulse to one of its electrodes along the electrode array inside the inner ear (cochlea). These pulses bypass damaged hair cells and directly stimulate the hearing nerve sections/fibres.

Objective Measurements in Cochlear Implants: During electrical stimulation and when sending information via radio frequencies to the implant, a huge electrical artefact is caused. The artefact is several 1000 times larger than the small electroencephalogram (EEG) response of a few µV that we want to measure. Use of filters, triggering, averaging of the signal, and subtraction methods make it possible to also measure these responses for CI recipients. None of these objective measurements are regularly implemented in the clinical routine or frequently used for SP programming. So far, no objective measurement method has been found to find out how much a patient is hearing, or how loudly. For CIs, two further objective measures were implemented which are only possible with a CI, because an implant is required to take these measurements. Electrically evoked stapedius reflex threshold (ESRT) is a measurement carried out during surgery. Certain electrodes get stimulated while the surgeon observes the reflexes of the stapes muscle. The threshold can be determined by lowering the current or charge delivered to the electrodes and therewith to the hearing nerve fibres. The other measurement is the Evoked Compound Action Potential (ECAP) which measures the response of the nerve fibres inside the cochlea after electrical stimuli from the implant.

Imaging in Cochlear Implants: Before surgery, all paediatric and adult patients with expected complications at OUS have to undergo a Magnet Resonance Imaging (MRI) and all patients a Computed Tomography (CT) scan, which gives the surgeons an anatomical overview. After surgery, an intra-operative X-ray picture is performed to verify the correct placement of the electrode array inside the cochlea. Conventional X-ray imaging gives a general overview

without an exact picture of electrode placement, such as for example displacement into scala vestibule.

Project Outline: This project shall investigate if the combination of various objective measures for CI programming can be of help or even improve the programming. Hereby the following investigations need to be done.

Starting with the surgery ESRT, ECAP and electrical evoked auditory brainstem responses (EABR) measurements can be carried out. The ESRT can give information if the whole auditory loop is functioning. ECAP measurements may indicate more sensitive regions, flip over and distance to the modiolus or nerve fibres. An intra-operative X-ray examination can give only an approximate indication about the electrode placement. A post-operative flat panel CT scan may give more detail about the electrode placement. The combination of ECAP measurements, such as sweep, spread of excitation and recovery function and flat panel CT scans may make it possible to detect problem areas or an electrode dislocation. This could provide valuable information, because problem electrodes may be excluded during SP programming or handled with special care. EABR measurements may indicate the coupling of the electrodes to the nerve fibres. In addition, this could be a valuable measurement for auditory neuropathy spectrum disorder (ANSD) patients, where a dis-synchrony of the nerve fibres is assumed.

Data Analysis: ECAP, EABR, and ESRT levels will be compared with subjective speech recognition tests, in quiet and noisy conditions. Flat panel CT scans and electrode placement will be compared to speech performance and objective measure levels.

Project Goal: This project aims to find new procedures/implementations for programming a CI SP. Better programming produces better hearing, which leads to better social integration. There is a need for research on whether objective measures can be a predictor of speech recognition performance. This could be used to suggest different therapy approaches.

Conclusion: The studies have shown that there is a significant relationship between observed intra-operative EABR measures and post-operative speech recognition. Both the FD-CT scan and per-operative fluoroscopy improved the CI electrode placement during CI surgery. These methods have helped us minimize poor clinical results by monitoring the exact position of the electrode array during surgery. ECAP and EABR measurements can also help identify in correct placement of the electrode array. Unfortunately intra-operative objective measures in our study, such as ECAP, ESRT, and electrode impedances did not provide statistically significant correlations that may help to predict the programming T- and C-levels for all patients.

Preface

This thesis has been submitted to the Faculty of Mathematics and Natural Sciences at University of Oslo in partial fulfilment of the requirements for the degree of Philosophiae Doctor (Ph.D.). The research has been conducted at University Hospital Oslo, Department of Ear Nose Throat, The Intervention Centre and the Robotics and Intelligent Systems Group (ROBIN) at the Department of Informatics during the period 2010-2016, under the supervision of Greg Eigner Jablonski, Ole Jakob Elle, Per Kristian Hol and Jon K. Shallop.

Acknowledgements

List of Publications

Papers Included in Thesis

I

Greisiger R, Tvete O, Shallop J, Elle OJ, Hol PK, Jablonski GE

Cochlear implant-evoked electrical auditory brainstem responses during surgery in patients with auditory neuropathy spectrum disorder

II

Greisiger R, Shallop JK, Hol PK, Elle OJ, Jablonski GE

Cochlear implantees: Analysis of behavioral and objective measures for a clinical population of various age groups

III

Greisiger R, Tvete O, Shallop JK, Hol PK, Elle OJ, Jablonski GE

Cochlear implant electrically evoked auditory brainstem responses and postoperative speech recognition in cochlear implant patients

IV

Greisiger R, Korslund H, Shallop JK, Hol PK, Elle OJ, Bunne M, Jablonski GE

The use of objective measurements, intraoperative fluoroscopy and flat detector CT to improve electrode array placement in difficult cochlear implant surgical cases

Contents

Chapter 1

1 Introduction

This chapter provides an overview of the thesis, presents the motivation and challenges for the research, formulates the research objective, and ends with an outline of the thesis.

1.1 Motivation

Since 1997, my work with Cochlear Implant (CI) patients at University Hospital Freiburg, Germany, University Hospital Basel, Switzerland, Speech and Language School St. Gallen, Switzerland and Oslo University Hospital (OUS), Norway, has led to the dream of improving outcomes with a CI. These outcomes are often related to good speech recognition, but there could be several other important aims when working with CIs such as, for example, reducing surgery trauma so as to preserve as much as possible of the residual hearing and delicate structures of the inner ear. Another goal could be to achieve optimal placement of the electrode array during surgery. Furthermore, the time to reach an optimal sound processor (SP) programming should be as short as possible, especially for small children who do not give reliable feedback during device programming. Many researchers reported large variations within patients. How is it possible to accommodate the best possible programming for these patients? Motivation for this project was to study these variations and to optimise the process of cochlear implantation, so that all patients can get the most out of their CI.

1.2 Challenges

During many years of work with patients I became aware of the complexity of the human system and variation of the individual needs of patients. Patients have very different hearing histories, anatomical situations, motivation, etc. We cannot expect to find a "one approach fits all" solution. To date, we have had more than 1500 patients with a CI at OUS, all 1500 of whom are individual patients who need individual treatment. A solution that worked fine for one patient does not necessarily work for another patient. The challenge will be: is it possible to find solutions that can be used for all these individual patients? Are there methods that will be applicable for all patients?

Introduction

1.3   Research Objectives

The main research objective for this thesis is to:

Find objective measures and attempt to understand them in the context of electrode placement.
This objective can be divided into several sub-goals:

> Find correlations between intra-operative measurements and programming levels.
> Find objective measures that can be used as predictors for speech recognition.
> Investigate if imaging and objective measures can be used as a tool for challenging cases.

The placement of the electrode array is a very critical moment during cochlear implantation and therefore imaging is required to visualise it. Secondly, the coupling of the electro-neural interface should be measured using objective measurements already in place during surgery which might indicate how well the auditory signals are transferred along the auditory pathways.

1.4   Thesis Outline

This thesis is a collection of papers. The 4 appended papers constitute the research contributions of this thesis in their original publication format. The rest of the thesis is organised as follows. Chapter 1 gives an introduction to the thesis. Chapter 2 presents background information relevant to the research. Chapter 3 summarises the research process and gives an overview of the papers constituting the research contribution. The reader is referred to the appended papers for more thorough reading of the methods developed. Chapter 4 presents conclusions and proposes future work.

Background

Chapter 2

2   Background

In the 1980s, the CI was introduced at Rikshospitalet (OUS). Since then, cochlear implantation has become a well-established treatment in Norway for deaf and profound hearing-impaired people with approximately 125 CI surgeries per year. All deaf children who receive a CI are treated at OUS. Adult patients may receive a CI at Haukeland Hospital in Bergen, St. Olav's Hospital in Trondheim or at OUS.

This chapter is organised using a timeline structure. First, sounds, acoustics and hearing are explained, followed by an introduction to the CI system and surgery. Then an introduction covers intra-operative objective measurements and CI imaging. The chapter finishes with the programming of the SP after CI surgery and finally speech recognition tests.

2.1   From Sound to Hearing

The ear analyses and interprets sound waves. Hearing is required to develop speech and is an important instrument for human communication (Lang and Lang, 2007). Normal human hearing sensitivity ranges from 20Hz to 16kHz and can detect sound pressure from 20µPa (or 20µN/m^2) (Klinke and Bauer, 2005). This chapter describes what sound is, how sound is picked up by the ear, transformed by the middle and inner ear and finally transmitted via the auditory brainstem to the auditory cortex.

2.1.1   Sound and Acoustic

Sound waves are changes in air pressure, where larger changes in air pressure are equivalent to a louder sound. The sound pressure is measured in Pascal (1 Pa = 1 N/m^2), also called the amplitude. The changes in speed of the sound pressure are called frequency and are measured in Hertz (Hz, oscillations per second). Sounds can be distinguished as tones, sounds and noise. A tone is a sinusoidal oscillation consisting of just one frequency. A voiced speech sound has a base tone and overtones. Noise is a sound of many frequency and levels at the same time.

In the medical/audiological context sound pressure is converted into a logarithmic scale called sound pressure level (SPL) and is measured in decibels (dB). The definition of SPL is:

Sound Pressure Level = 20 log P_x/P_0 [dB]

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Where $P_0 = 2\times10^{-5}$ Pa is the reference sound pressure and P_x the actual measured sound pressure. The dB scale is used in many other situations, so to avoid confusion the addition dB SPL is used for the level of sound pressure.

The physical description of sound is called acoustics. In contrast to physiological processes, biochemical and anatomical processes of hearing are referred to as auditory or auditive (Schmidt et al., 2010).

2.1.2 The Sound Transmission to and Conversion of the Inner Ear

Sound pressure waves reach the outer ear and will travel though the ear canal to the ear drum. The three small bones (ossicles) of the middle ear are the bridge for the acoustic waves from the outer ear to the inner ear. The bones function as an impedance converter as well as a protector for loud sounds. A muscle (stapes muscle) is attached to the stapes and contracts if loud sounds are detected from the auditory brainstem. The bone chain can no longer move as freely and protects the inner ear. This reflex is called the stapedius reflex and its importance for the research work will be described in chapter 2.4.3. The oval plate of the stapes bone is placed on the oval window of the cochlea. The cochlea is a snail shaped structure and referred to as the inner ear and has 2 ½ windings. The inner ear converts the physical movement of the ossicles, caused by sound pressure waves on the ear drum, into electrical signals (see Figure 1). The cochlea consists of liquid-filled canals, the scala vestibuli (upper), scala media (middle) and scala tympani (lower), which are approximately 35 mm long. These canals are separated by the basilar and Reissner membrane. The organ of Corti is placed along the basilar membrane and consists of inner and outer hair cells. The hair cells actually convert physical movement to electrical signals, where the 3500 inner hair cells mainly transfer the signal further and the 16,000 outer hair cells amplify the movement. Each inner hair cell is tuned to an individual frequency, where the high frequencies are placed on the base of the cochlea and the low frequencies towards the apex. When a sound wave hits the ear drum, the movements will be transferred along the ossicle to the foot plate of the stapes onto the oval window of the cochlea. Inside the cochlea, this movement propagates further as a travelling wave along the basilar membrane. The frequency of the sound pressure wave determines which part of the basilar membrane will move. The basilar membrane carries the sensory cells/hair cells. A movement of the basilar membrane causes the hair cells to move, and here the stereocilia on top of the hair cells move back and forth. Small openings of the stereocilia cause the liquid of the scala media (perilymph) to enter the hair cell and thus cause its re-polarisation, transmitting Glutamate (inner hair cells), which induces the afferent nerve fibres to elicit an action potential (Schmidt et al., 2010, Silbernagl et al., 2007, Klinke and Bauer, 2005, Kahle et al., 2003, Gelfand, 2004).

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Figure 1 (1) Sound waves enter the outer ear and travel through the ear canal to the ear drum, causing it to vibrate. (2) Vibration of the ear drum sets into motion the three small bones of the middle ear, which in turn, transfer the vibration from the ear drum to the inner ear. (3) The inner ear, also known as the cochlea, senses the vibration and converts it into electrical signals. (4) The hearing nerve transmits electrical signals from the cochlea to the brain, where they are interpreted as sound.

2.1.3 Auditory Pathways - from Ear to Cortex

The neuronal excitation elicited by the inner hair cell will be transmitted to the auditory cortex. On the way to the cortex the signal travels along the auditory nerve through the auditory brainstem where a cascaded series of neurons are passed and can be measured using evoked response audiometry (ERA). At the brainstem an interconnection exits between both ears. Time and level differences from both ears can be detected and used to localise the sound source. At brainstem level the stapedius muscle triggers in the case of high sound pressure (Martin and Clark, 2012, Møller, 2006). The signal passes several neurons on the way to the auditory cortex. Some stages are mentioned here which are of importance for this thesis. The transduced signal from the inner hair cells travels through the ganglion spirale before it leaves the cochlea through the 8th cranial auditory nerve, when it passes the nucleus cochlearis, superior olivaris complex, lemniscus lateralis and colliculus inferior. The last neurons of the auditory brainstem transit to the mid brain and continue to the thalamus. Finally the signal reaches the auditory cortex; here the activities of the auditory system get analysed (see Figure 2). Pattern recognition and speech understanding occur here. (Schmidt

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et al., 2010, Silbernagl et al., 2007, Hall, 2007, Klinke and Bauer, 2005, Kahle et al., 2003, Møller, 2003)
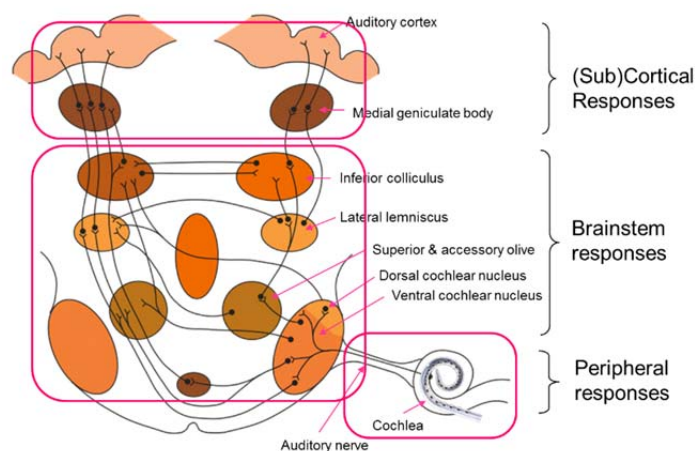
Figure 2 displays the auditory pathways with relevant neurons for audiological measurements and cross couplings (image by courtesy of Cochlear Ltd.)

2.1.4 Hearing Measurements and Hearing Tests

Many measurements and tests have been developed to measure the level of hearing. This section will only cover some of the most important ones and those with the most relevance for the work of this thesis. First, this section is divided into tests and measurements, for a test feedback from the patient/subject is required. A very typical test is an audiogram (see Figure 3), where the patient has to respond to tone at a certain loudness level so that the threshold can be finally determined.
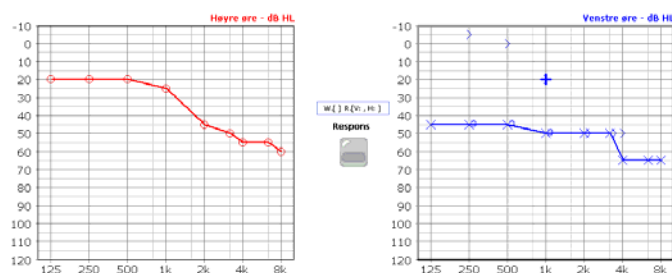
Figure 3 shows an audiogram indicating frequency depending on hearing loss (in dB).

Other examples are sound localisation tests, which consist of a set of loud speakers that patients have to detect as the sound source. Speech tests will be covered in a later chapter. In contrast to hearing tests (e.g. audiogram), hearing measurements (e.g. auditory brainstem response) do not require feedback and the transmission of the acoustic signal can be measured without asking the patient. Many measurements have been established over more than 50 years in hearing research. In the following, just a few of them performed as part of the pre-evaluation for candidacy of a CI will be mentioned and briefly explained. Firstly, an

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otologist examines the ear canal and the ear drum. An impedance measurement can show if the ear drum is moving freely and not blocked by, for example, liquid in the middle ear, which would be called a conductive hearing loss. The contraction of the middle ear stapedius muscle can be measured as well if stimulated by loud sound. This can be measured by a change in the movement of the ear drum. The function of the inner ear can be measured by the use of otoacoustic emissions (OAEs). Here, an acoustic signal may reach the inner ear and will move the basilar membrane, which eventually causes the outer hair cells to be stimulated and so produce a change in length. This change in length is coupled back to the ear canal where a probe in the ear canal can pick up the response. This type of measurement checks the outer hair cell function, but does not check the inner hair cell function, which is important for hearing and retro-cochlea (auditory pathways behind the cochlea) transmission. This is covered by auditory brainstem responses (ABR). For ABR measurements, surface-mounted electrodes are placed on the patient's head to measure the far field response of the auditory pathways. An acoustic signal is sent via a probe in the ear canal. The acoustic signal can have different characteristics such as frequency, amplitude and duration. It can be a chirp, tone burst or click stimuli. If the auditory pathway responds to the sound, an EEG signal will be picked up by the surface-mounted electrodes. Usually, 2000 measurements will be averaged and responses from the outer hair cells (cochlea microphonics [CM]), beginning of the 8th nerve (wave I) and end (wave II), colliculus neuclei (wave III), superior olivaris complex (wave IV), lemniscus lateralis (wave V) and inferior colliculus (slow negative ten) can be measured. The morphology of the wave forms, timing of the responses (latencies) and amplitudes, can give an indication of the hearing loss, depending on the input signal and amplitude (see Figure 4). ABR measurements are widely used as new-born hearing screening. The ABR measurements will be covered again in a later chapter; a different type of this measurement has been part of the research work in the thesis. A different approach for ABR measurements follow the Auditory Steady State Response (ASSR), where a frequency-specific response can be obtained and a kind of "audiogram" can be measured. The measurements described so far just measure the hearing, but not the recognition, which can be done with cortical measurements, where the activity of the auditory cortex to acoustic stimulation can be recorded (Stach, 2010, Kaga, 2009, Hall, 2007).

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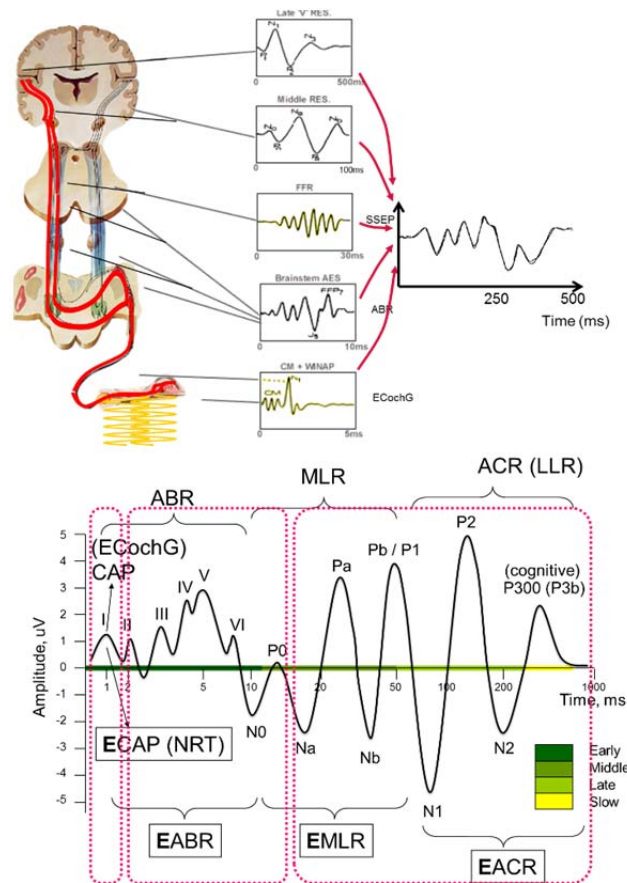
Figure 4 Auditory pathways for the left ear and their corresponding responses either due to acoustic stimulation or electrical stimulation via a cochlear implant (indicated by the "E"). Note that timing will be slightly different between acoustic and electric stimulation (image by courtesy of Cochlear Ltd.).

2.1.5 Hearing, Speech and Auditory Cortical Development

Without hearing it would not be possible to learn or to understand speech without lip reading. Hearing controls the production of speech. Human speech has undergone 300,000 years of evolution (Klinke and Bauer, 2005). Speech signals contain physical characteristics, which have been assigned a certain thematic relevance. Voice is generated by the larynx and emphasised by the resonance of the mouth and throat volumes (oropharynx). The resonance of the oropharynx emphasises frequency components, which result in formants, the basis of recognisable speech sounds (phonemes). Speech will be recognised and understood in the auditory cortex, where billions of connections are established to memorise sound patterns from previous stimulation/activation. The auditory cortex is able to compare an incoming auditory signal, for example a spoken word, with a prior experienced signal stored in memory, and may be recognised and understood (Schmidt et al., 2010). Cortical maturation begins in pregnancy and develops during childhood. During these early years speech

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understanding develops. Studies on deaf-born children who received a CI have shown that there is a critical phase, during which speech has to be learned. Until the age of 7 years, the auditory cortex is in the sensitive period where speech can be learned. Born-deaf children who received a CI before the age of 3.5 years had similar cortical responses as normal hearing children. Deaf-born children who received a CI after the age of 7 have poor speech recognition (Kral and Sharma, 2012, Sharma and Campbell, 2011, Stach, 2010, Kral and Eggermont, 2007, Sharma et al., 2005).

2.1.6 Hearing Impairment

The previous chapters have described the complexity of the auditory system. A malfunction of some or a combination of several parts could cause hearing impairment. In the following section a brief summary will explain the reasons of hearing impairment and deafness.

Conductive hearing losses (HL) are, for example, cerumen, liquid in the middle ear, otosclerosis, or otitis media inflammation of the middle ear. Sensorial hearing loss are, for example, cochlear otosclerosis, pathologies of the cochlea -> morphological changes in hair cells: age-related HL, noise-induced HL, HL caused by ototoxic agents (drugs). Ototoxic antibiotics may cause hearing loss by changing important biochemical processes, leading to metabolic exhaustion of hair cells which can eventually lead to cell death. Hearing impairment may also result from hereditary causes. The degree of HL is profound when mutations affect genes which cause hair cell loss, while it may be less severe or progressive in nature when mutations disrupt genes which affect hair cell function or that of the tectorial membrane (Naz and Institute for New Technologies (Maastricht Netherlands), 2012). Infectious diseases such as meningitis and certain viral infections can also cause destruction of cochlear hair cells, causing hearing impairment. Congenital hearing disorders most often affect cochlear hair cells and result in HL of a cochlear type. The HL is usually bilateral and high frequencies are affected more often than low frequencies, but the audiograms may have widely different shapes. In some cases, the largest HL is in the mid-frequency range ("cookie bite" audiograms). The cause of most congenital hearing impairments is unknown, but conditions during pregnancy such as rubella or cytomegalovirus (CMV) infections can increase the risk of congenital hearing impairment. It has been shown that the gap junction protein connexin 26 is involved in many cases of congenital deafness. Congenital hearing impairment may progress after birth and may reach various degrees of severity. Birth complications, infectious diseases and bacterial meningitis were the most common causes of childhood hearing impairment before immunisation came into common use. Changes in blood flow in the cochlea, thromboses or bleedings of the labyrinthine artery or surgical injury to the artery results in deafness in that ear. Injuries to the cochlea from trauma or sudden HL

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(sudden deafness) is characterised by sudden unexplained onset. The HL is often total, although fortunately almost always only in one ear. It can occur without any other symptoms and changes in function of the auditory nervous system. Lesions to the auditory nerve are the most common cause of disorders of the auditory nervous system. Neural hearing disorders can be any disease or disorder process that affects the peripheral and central nervous system which can, of course, result in auditory disorder, if the auditory nervous system is involved. Vestibular Schwannoma can also originate from the auditory nerve. (Adams and Rohring, 2004, Møller, 2006). Auditory Neuropathy Spectrum Disorder (ANSD) is a recently described hearing disorder characterised by abnormal auditory nerve function (absent ABRs) in the presence of normal cochlear receptor hair cell activity reflected by preserved OAEs and/or CMs. Individuals with ANSD have impaired speech comprehension and sound localisation (Kaga and Starr, 2009, Starr et al., 2003). ANSD has been shown to affect approximately 10–15% of all children with sensorineural hearing loss (Cardon and Sharma, 2013). ANSD in patients who received a CI has been investigated in this thesis (Greisiger et al., 2011).

2.2 Cochlear Implant Systems

A CI system is a complex technical device, which has undergone rapid improvement over the last three decades. In this section, a general overview is given, with a particular focus on certain features which were important for the scientific investigations. To date, three different brands are used at OUS, and although differences exist in manufacturers' hardware, there are several common components for all CI devices.

The CI is an electronic device that consists of two major parts – the SP and the implant (see Figure 5). The implant is placed under the skin with electrodes positioned in the cochlea to stimulate the auditory nerve. Electrical currents induce action potentials in the auditory nerve fibres and these are transmitted to the brain. It thus bypasses damaged or missing hair cells within the cochlea that would normally code sound. It consists of a receiver-stimulator, which receives power and decodes instructions for controlling the electrical stimulation, and an electrode array, which has electrodes placed near the auditory nerve (generally in the cochlea) to stimulate residual auditory nerve fibres (Cooper and Craddock, 2006). The processor picks up sound, analyses and converts the signals before transmitting it through the skin to the implant (Zhou and Greenbaum, 2009, Cooper and Craddock, 2006, Ernst et al., 2009, Miller, 2006, Waltzman and Roland, 2014, Clark, 2003).

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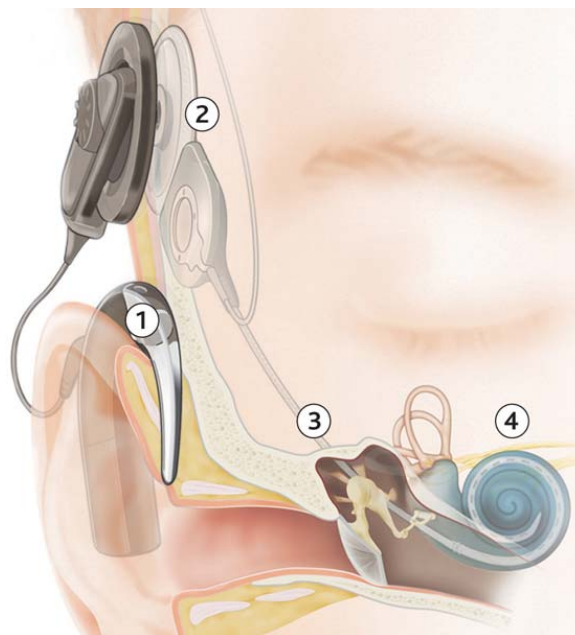
Figure 5 displays an overview of the cochlear implant system. (1) The microphone of the sound processor picks up sound, which will be transformed into digital signals by the sound processor. (2) This information is transferred though the coil to the implant under the skin. (3) The implant sends signals to the electrode array inside the cochlea. (4) The hearing fibres inside the cochlea pick up the electrical signals and send them along the auditory pathways to the cortex (image by courtesy of Cochlear Ltd.).

2.2.1 External part – Speech/Sound Processor and Transmitting Coil

The SP converts speech and sound signals into its frequency and amplitude components and transmits the signals through the skin to the implant. The SP consists of a front end similar to a hearing aid with different microphone characteristics and noise suppression modes which capture acoustic signals in the user's environment and transduces the input into an electrical signal. Next, the signal is analysed by a digital signal processor (DSP) in the external SP to classify the input according to intensity and frequency, and to convert the signal into an electrical code that will represent these features at the auditory nerve. The coded signal is then converted from a digital signal back into an electrical signal and sent to the radio frequency (RF) coil via a transmitting cable. At the RF coil, the electrical signal is converted to an electromagnetic signal and transmitted via electromagnetic induction to an internal receiving coil (antenna) that is directly wired to the internal stimulator. Magnets are located in the centre of both the external RF coil and internal receiving coil, which provides adhesion of the external RF coil to the head and alignment directly over the internal receiving coil. The RF signal, which is device specific, also serves as the power supply for the internal stimulator. When the magnetic lines of flux (RF) pass over the internal receiving coil, an

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electrical signal is induced in the internal coil and passed onto the internal stimulator. This is a challenge for the SP battery, which not only has to drive the external part but also has to power up the implant by the use of RF (see Figure 6).

The SP offers several program positions, volume and/or microphone options to give the user adjustment possibilities for the appropriate sound situation. Most SPs are controlled by remote controls these days and these can be used for function control as well, which is especially important for use in children. Modern SPs have connectivity possibilities for various receivers such as frequency modulated (FM) signal systems, Bluetooth or telecoil to connect to various audio sources (Cooper and Craddock, 2006, Cochlear, acced 2015).

Figure 6 From left to right the speech/sound processors from MED-EL®, Cochlear®, Advanced Bionics® (image by courtesy of MED-EL, Cochlear Ltd. and Advanced Bionics).

2.2.1.1 Frequency Mapping

In order to convey pitch information, the CI system mimics a place-pitch map within the cochlea, such that the more basal electrodes encode higher frequencies and more apical electrodes encode lower frequencies (see Figure 7 and 8). This frequency organisation produced by the implanted electrode array is commonly referred to as an electrode-place map. The electrode-place map in CI users is programmed according to the frequency-to-place map found in normal hearing (Waltzman and Roland, 2014). Depending on the insertion depth of the electrode array there is a frequency shift between acoustical and electrical stimulation (Landsberger et al., 2015, Svirsky et al., 2015a, Svirsky et al., 2015b). In the most current CI systems, the external SP uses digital bandpass filtering, Fast Fourier transformation (FFT), or Hilbert transformation to divide the complex input signal into individual frequency segments, referred to as channels.

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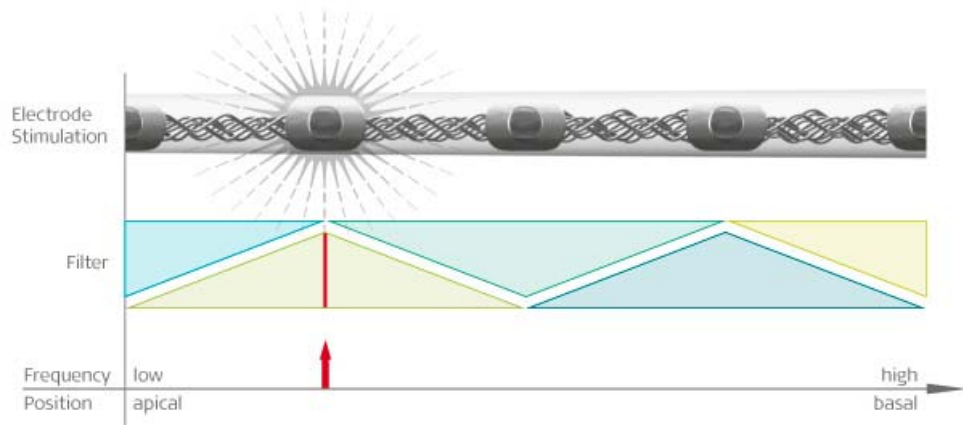
Figure 7 illustrates the frequencies band pass filter and the corresponding stimulated electrode (image by courtesy of MED-EL).
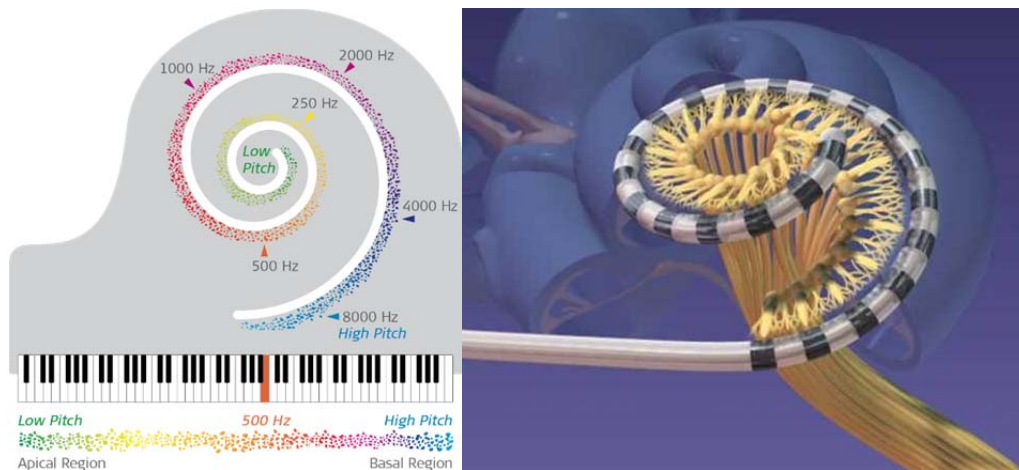
Figure 8 on the left shows the frequency mapping of the human cochlea. Highest frequencies placed at the base of the cochlea and lowest at the centre of the cochlea (helicotrema). The right image visualises the electro-neural interface where the stimulation of the individual electrode contacts bypass the damaged or non-functioning hair cells and stimulate the nerve fibres or ganglion spirale directly (image by courtesy of MED-EL (left) and Cochlear Ltd. (right)).

2.2.1.2 Stimulation Strategy - Signal Processing

The stimulation mode describes how the electrodes are used to form a stimulating pair of electrodes, called a channel, in contrast to the stimulation strategy which defines in which way these electrode pairs or channels will be stimulated. A signal coding strategy describes the algorithm used to transform the important features of the incoming acoustical signal (i.e., amplitude, frequency, and temporal cues) into an electrical code. This code attempts to represent these features in a meaningful manner to the auditory nerve. Although, relatively

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large differences exist in the default signal coding strategies used by recent CI systems, clinical trials demonstrate comparable performance across the systems of the three different CI manufacturers (Wolfe and Schafer, 2014). The following section briefly describes the main CI signal coding strategies used at our hospital.

The Continuous Interleaved Sampling (CIS) strategy is available in the CI systems for the three manufacturers used at OUS. The acoustic signal is sent through a bank of bandpass filters that separates the input signal into discrete frequency bands (in the case of the MED-EL system) or a fast Fourier Transform (FFT). The filter bank has an overall bandwidth from approximately 100 to 8,000 Hz, and the number of filters usually equals the number of stimulation channels (MED-EL: 12; Advanced Bionics: 16; Cochlear: 12 out of 22) at the electrode array-neuron interface (Wouters et al., 2015). A logarithmic or power-law transformation is used to map the relatively wide dynamic range of the derived envelope signals onto the narrow dynamic range of electrically evoked hearing (compressor) for each bandpass (Cooper and Craddock, 2006). The output from the compressor is then sent to a pulse generator. The amplitude of the pulse train from the generator is modulated on the basis of the input received from the compressor. Thus, the amplitude of the signal within each band is represented by the amplitude of the pulses within that same band. Finally, the modulated pulse trains in each channel are delivered to their respective electrode contacts (Wolfe and Schafer, 2014).

MED-EL uses the so-called FineHearing® Strategy (www.medel.com) in their system which is a CIS strategy using the time code of the signal to achieve Channel-Specific Sampling Sequences (CSSS) (Figure 9).
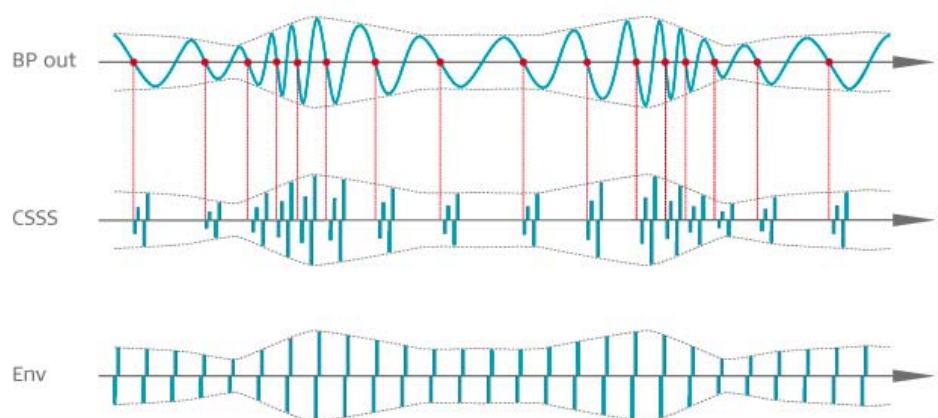
Figure 9 In FineHearing®, time coding is achieved using Channel-Specific Sampling Sequences (CSSS). CSSS are a series of stimulation pulses which are triggered by zero-crossings in a channel's bandpass filter output (image by courtesy of MED-EL).

Background

The Cochlear system offers several sound coding strategies but, except for a few patients, our hospital uses the default coding strategy, Advanced Combination Encoder (ACE). ACE is also an *n*-of-*m* strategy. For a given input sound, the acoustic energy present in each of the *m* channels is determined, and stimulation is administered to only the *n* channels with the highest amplitude inputs. The value "n" typically varies from 8 to 12. For a program with 22 channels, the maxima selected will stimulate the corresponding channels; the remaining channels are not going to be stimulated. The default settings of Cochlears CustomSound® programming interface suggests 900Hz stimulation rate and 8 maxima, which will result in a maximum overall stimulation rate of: 900Hz*8=7200Hz(Wolfe and Schafer, 2014).

Advanced Bionics sound coding strategy is a CIS-based strategy called HighResolution (HiRes®) known as HiRes Fidelity 120® (see Figure 10), which incorporates current steering. Current steering attempts to increase the number of perceptual channels in the frequency domain by simultaneously stimulating two neighbouring electrode contacts to create a locus of stimulation that falls somewhere between those two contacts. Through the use of current steering, HiRes Fidelity 120 creates up to 120 virtual channels. Additional channels may increase the number of frequency percepts and spectral resolution and, therefore, should improve speech recognition in noise, sound quality and music appreciation (Wolfe and Schafer, 2014).
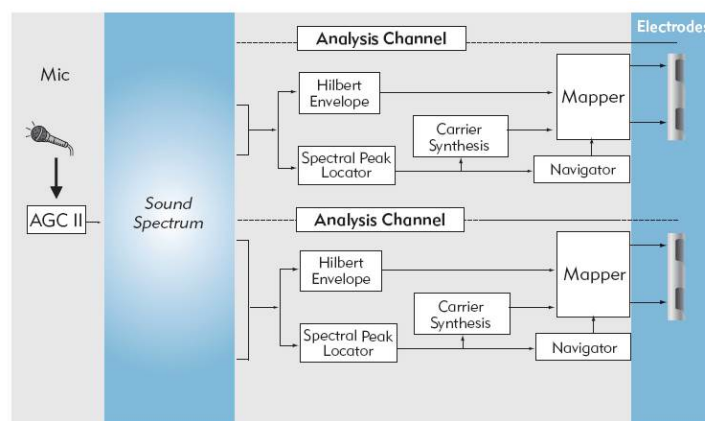
Fidelity 120 Signal Processing Path

Figure 10 shows a schematic of the signal path from the microphone, automatic gain control (AGC), signal analysis, filtering the signal and mapping to the specific electrode contact depending on the dedicated frequency band (image by courtesy of Advanced Bionics Corp.).

2.2.2 Internal Part – Implant

The implant consists of three major parts, the receiving and transmitting coil, the stimulator with the current source and electronic circuit board, and the electrode array. The coil

Background

receives the signal from the external SP via RFs. The coil can be used as a transmitting antenna/coil as well as to transfer, for example, impedance and nerve response measurements. The internal stimulator, which also contains a DSP, converts the electrical signal into a digital code. The electrical pulses are then sent along the electrode lead to the stimulating intra-cochlear electrode contacts, where the pulses stimulate auditory nerve fibres innervating the cochlea. All implants currently used at OUS have an intra-cochlear electrode array and extra cochlea reference electrode(s) which is either an electrode, in the case of the Cochlear system (see Figure 11) or a reference electrode attached to the housing of the stimulator, in the case of Advanced Bionics and MED-EL. Cochlear consists of both a housing reference electrode and a reference electrode placed in the muscle.

Figure 11 shows the different implant housings of the three systems used at OUS. From left to right are shown: Cochlear 512, MED-EL Concerto, Advanced Bionics HiRes 90k (images by courtesy of Cochlear, MED-EL and Advanced Bionics).

2.2.2.1 Electrode Arrays

The electrode array is placed inside the cochlea close to the stimulating nerve fibres. The electrode arrays vary depending on the manufacturer (see Figures 13–15). The manufacturers also have different electrode array configurations depending on patients' needs, such as ossified or malformation cochlea. In the case of a standard cochlea other considerations are taken into account, e.g. hearing preservation and/or structure preservation. Basically, there are three different types of electrode arrays: short, long and preformed electrodes. The electrode arrays are equipped with a different number of electrode contacts: 12 (MED-EL, see Figure 14), 16 (Advanced Bionics, see Figure 13) and 22 (Cochlear, see Figure 12).

Background

Figure 12 shows electrode arrays from Cochlear. These two versions are mostly used at OUS. On the left is a slim-straight electrode (422/522), which has a very thin diameter and can be inserted up to 25 mm in length. On the right is a Contour Advanced electrode, which is the most-used electrode type to date at OUS. This electrode array is preformed to achieve a "hugging" placement to the modiolus (images by courtesy of Cochlear Ltd.).

Figure 13 shows the different electrode configurations of the Advanced Bionics system. To the left is a pre-formed electrode array called Helix and to the right an electrode array which is called "mid-scala" (images by courtesy of Advanced Bionics).
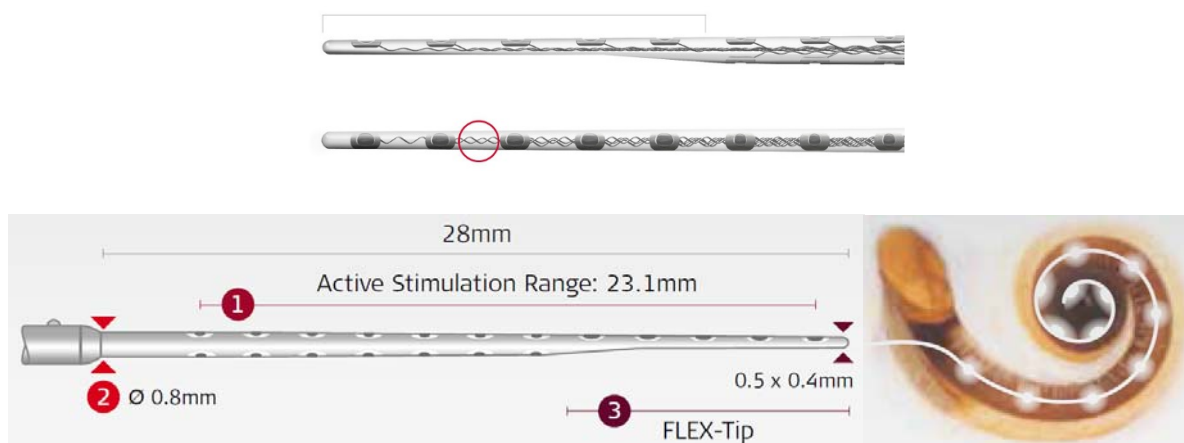
Figure 14 shows two versions of the MED-EL electrode array. At the top is the FLEX electrode array, which has just one electrode contact for the 5 most apical electrodes; all other electrodes have contacts on both sides. Below, a standard electrode array with electrode contacts on both sides. The wiring of cables is in a zigzag shape, which gives the electrode more flexibility while bending inside the cochlea. The lower image shows a MED-EL Flex28 electrode array with the so-called complete cochlea coverage. The FLEX28 electrode array is the standard choice if a MED-EL system is chosen at OUS. (1) 19 platinum electrode contacts, spacing over a 23.1 mm stimulation range; (2) Diameter at basal end: 0.8

Background

mm; (3) FLEX-Tip for minimal insertion trauma. Dimensions at apical end: 0.5 x 0.4 mm (images by courtesy of MED-EL).

2.2.2.2 Stimulation Mode

The electrode coupling strategy (or stimulation mode) indicates how channels are connected to form an electrical circuit through which current can be delivered to the auditory nerve. In a complete electrical circuit, current travels from the power source to a resistive component and then to a return location. CI stimulation must also be delivered through a complete circuit (Wolfe and Schafer, 2014). For the Common Ground (CG) stimulation, one electrode contact is active and all other electrode contacts serve as a ground electrode. Bi-polar (BP) combinations can vary between the stimulating electrode and a neighbouring reference or ground electrode; here the pairs can be widened so that they can "hop" over the directly neighbouring contact. The coupled contacts are referred to as BP+1, BP+2 and so on. Today, the most common stimulation mode is the mono-polar mode where current flows from one intra-cochlea electrode contact to an extra-cochlea reference electrode. This stimulation mode allows narrower pulse width and higher stimulation rates. The reference electrode can be an electrode on the housing of the stimulator/receiver and/or a reference electrode placed in muscle behind the ear (see Figure 15).
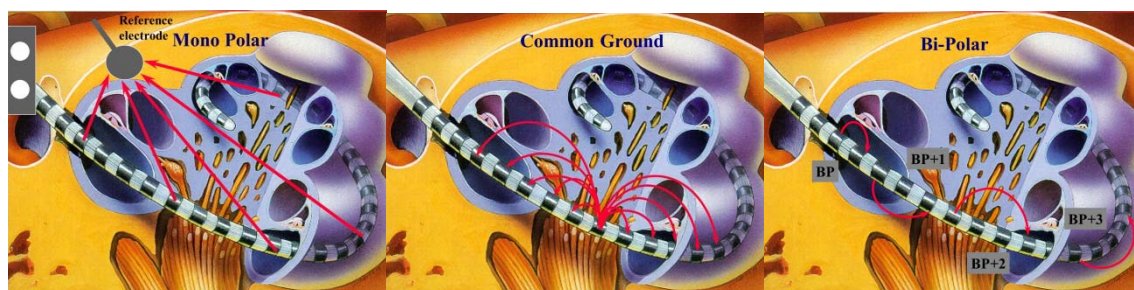
Figure 15 shows from left to right, the different stimulation modes: mono-polar, Common Ground (CG) and various bi-polar (BP) combinations.

2.2.2.3 Stimulation Rate - Stimulation Levels - Pulse Width

CIs deliver biphasic electrical pulses (see Figure 16) to electrode contacts across the electrode array. Increase of stimulus intensity can be obtained in two ways. First, the amplitude (or height of each phase of the pulse) of the current (in amperes) can be increased. Second, the stimulus intensity can be increased by lengthening the pulse width. The pulse width describes the duration of each phase of the biphasic programming stimulus and is typically measured in microseconds. Therefore, the total magnitude of a biphasic, electrical pulse is determined by the amplitude of the current and the width of each pulse.

Background

The total energy in the stimulus is specified in charge units (Current amplitude * Pulse width = Total charge in Ampere seconds (As)) (see Figure 16) (Wolfe and Schafer, 2014).

The stimulation rate typically refers to the number of biphasic pulses that are delivered to an individual electrode contact within 1 second and is specified in pulses per second (pps). Total stimulation rate is usually calculated by determining the product of the per channel stimulation rate and the number of active channels stimulated for an incoming stimulus (per channel stimulation rate * number of active channels stimulated = total stimulation rate). For example, if an incoming sound is delivered to 10 channels, and the per channel stimulation rate is 1,200pps, the total stimulation rate is 12,000pps (Wolfe and Schafer, 2014).
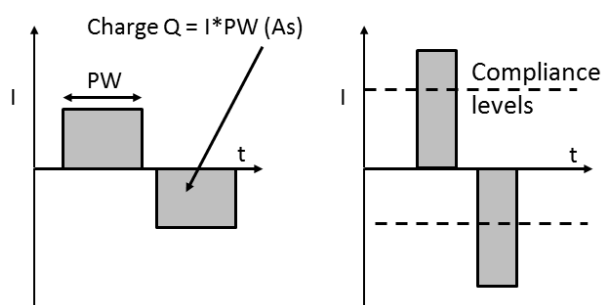
Figure 16 shows a schematic drawing of a biphasic pulse. The charge is determined by amplitude times pulse width. The electrode impedances determine the limit of the maximum current the implant can deliver. Once the compliance levels are reached, the pulse amplitude may be decreased and the pulse width increased to be below compliance limits.

2.3 Cochlear Implant Surgery

In general anesthesia a posterior-superior auricular incision (5–6cm long) is made. The skin flap is elevated followed by the incision of the temporalis muscle. A subperiosteal pocket is created for positioning the implant and the ground electrode. A mastoidectomy is performed. The horizontal semicircular canal and the short process of the incus are identified in the fossa incudis. The posterior tympanotomy is performed in order to visualise the round window niche, taking care to avoid injury to the chorda tympani and facial nerve. Entry into the scala tympani is accomplished either through a cochleostomy created by drilling over the basal turn of the cochlea anterior and inferior to the annulus of the round window membrane, or trough incision of the round window membrane (round window approach). Posteriorly to the mastoidectomy a bone bed well, tailored to the device to be implanted, is created and the implant is fixed in place with a periosteal flap (Figure 17). The electrode array is then carefully inserted either through the cochleostomy or round window into the scala tympani of

the cochlea. The reference electrode is placed under the cranial part of the sub-periosteal pocket. The wound is closed in two layers. After the placement of the electrode array objective measurements are performed. The whole surgical procedure, including objective measurements, takes about 2–3h.
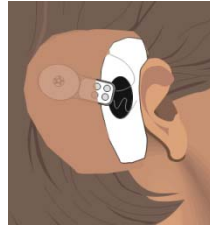
Figure 17 showing the placement of a cochlear implant stimulator behind the ear. The implant is moved into position behind the ear through an incision of 5–6cm.

2.4   Objective Measurements in Cochlear Implants

The success of CI implementation has meant that deaf children can receive a CI at an earlier age. This has become a challenge for management of the CI device. First, objective measurements can be used to detect failures, such as faulty electrode contacts or an implant failure. Secondly, they may be used for device programming. For programming, the SP and detection of malfunctioning parts, patient feedback was required if objective measurements were not available. With objective measurements, these could, ideally, be measured without feedback from the patient. Currently, the following areas in CI treatment take advantage of the use of objective measurements to …

> … verify the device function.
> … identify malfunctioning electrodes.
> … verify the integrity and function of the auditory pathways.
> … obtain a baseline of neural function for tracking potential changes over time.
> … assist in programming the CI SP.
> … measure discrimination of different stimuli.
> … measure the plasticity of the auditory system.
> … optimise electrode position.

A critical component for successful CI use and objective measurements is that there must be a functioning auditory nerve (Hughes, 2012).

Covering the whole field of objective measurements and their use would exceed the scope of this dissertation; therefore the following sections focus on explaining some of the objective measurements which were part of the scientific work of the thesis.

Background

2.4.1 Electrophysiological and Non-physiological Measurements

The measurement of spontaneous electrophysiological activity is described as electrophysiological measurements. For CIs, electrophysiological measurements are routine procedure both intra- and post-operative. Intra-operative measurements can indicate interaction of the "electro-neural-interface" (the electrode array) with the nerve fibres. Non-physiological measurements are, for example, device function test, current fields and impedances tests (Hughes, 2012). These tests do not measure a response from the auditory system or nerve fibres. In the following sections the most commonly used electrophysiological and non-physiological measurements deployed at OUS are described.

2.4.2 Evoked Compound Action Potentials (ECAP)

The ECAP is measured by delivering biphasic electrical pulses to an intra-cochlear electrode contact in order to stimulate the auditory nerve and then by using a nearby intra-cochlear electrode contact to record the neural response. The advantage of this measurement is that no additional equipment is required (i.e., the measurement may be performed with the recipient's implant, the manufacturer's programming software, and either the recipient's SP or a special cable and coil provided by the manufacturer). The ECAP response originates from and is measured within the bony cochlea and is essentially not susceptible to myogenic and other forms of electrical artefact that commonly complicate the measurement of evoked potentials (EPs) (see Figure 18). As a result, the ECAP may be measured while the recipient is awake and active. The ECAP measurement can be advantageous for several reasons including: (1) it indicates a stimulus level that definitely should be audible to the recipient, (2) it confirms the responsiveness of the auditory nerve to electrical stimulation, (3), it confirms device function, (4) it serves as an objective baseline of physiologic function to which subsequent measurements can be compared, and (5) although most researchers have suggested that the ECAP possesses a weak to moderate correlation to Threshold (T-levels) and upper-stimulation levels (C-levels), it may certainly be used as a tool to guide the clinician in determining stimulation levels for recipients who cannot provide reliable feedback about the loudness of the signals they receive from their implant.

ECAPs offer several advantages over more central auditory physiological responses. First, they are relatively immune to the effects of anaesthesia, so they can be used for intra-operative assessments. Second, contamination by myogenic activity (muscle artefact) is not an issue, because the responses are measured using intra-cochlear electrodes instead of surface/scalp electrodes. As a result, patients do not need to lie still, sleep, or be sedated during ECAP measurements. Third, because the ECAP is measured within the cochlea (i.e. closer to the neural generator site), the responses are much larger than those obtained

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further afield with surface/scalp electrodes (several repetitions of about 1000 sweeps). Consequently, the test time for ECAPs is substantially shorter than for brainstem or cortical measures. Finally, ECAPs are present within the first year of life, so they are much less influenced by maturational effects as compared to cortical potentials (Hughes, 2012).

For obtaining an ECAP response the artefact on the recorded signal needs to be reduced/removed. In the following the two most common artefact reduction methods are outlined:

Alternating polarity is a method that is commonly used with acoustic auditory brainstem and electrically evoked auditory brainstem response (EABR) measurements (see also next sections 2.1.3, 2.1.4 and 2.4.4). Alternating polarity is the only method currently used in Advanced Bionics' Neural Response Imaging (NRI), is the default method in MED-EL's Auditory Nerve Response Telemetry (ART) and is an alternative method in Cochlear's Neural Response Telemetry (NRT). When the polarity of the stimulus current pulse is reversed, the artefact reverses in polarity, but the physiological response does not. When the alternating responses are averaged the artefact primarily cancels out, leaving the neural response.

Forward-Masking Subtraction Method takes advantage of neural refractory properties (nerve fibres need to "recover" before they can give a response again) to separate the ECAP from the stimulus artefact (Abbas et al., 1999, Brown et al., 1998, Dillier et al., 2002). Figure 19 displays the principles of the forward-masking subtraction method. A single pulse called the probe elicits a neural response as well as a stimulus artefact (see frame A in Figure 19). Then, a pair of pulses, called the masker and the probe, is separated by a short time interval, and referred to as the masker-probe time interval (MPI). The masker elicits a neural response and stimulus artefact. When the MPI is sufficiently short, the second pulse, the probe, occurs during the absolute refractory period for the neurons that discharge in response to the masker. The probe pulse only generates artefact, with no embedded neural response. When the artefact response to the probe in the second frame (see Figure 19 B) is subtracted from the response of the first frame (Figure 19 A), the neural response to the probe alone in the first frame is resolved. The last two frames (see Figure 19 C and D) are used to remove the artefact and neural response from the masker in the second frame. The third frame (Figure 19 C) consists of the masker pulse alone, which elicits a neural response and stimulus artefact. The final frame (Figure 19 D) is a zero-amplitude current pulse, which represents the artefact associated with switching on the current source. When applying the formulae A-(B-(C-D)) only the neural response remains. A typical N1-P1 neural response is displayed in Figure 19 on the right (Hughes, 2012).

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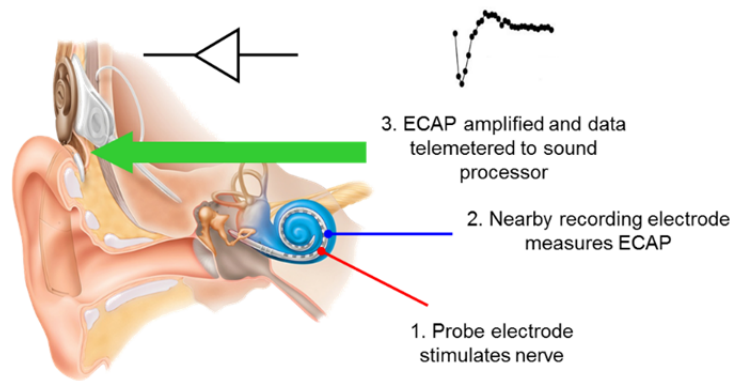
Figure 18 shows the principal of ECAPs. A probe electrode stimulates the nerve fibres (1) and a neighbouring electrode records the response of the stimulation (2). The measured ECAP is amplified and data will be sent to the sound processor and connected PC for analysing (3) (image by courtesy of Cochlear Ltd.).
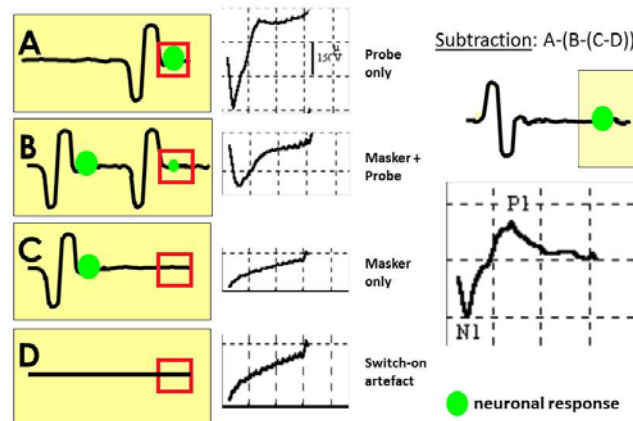
Figure 19 displays the principle of the subtraction method, also called the masker-probe subtraction method. (A) Probe-only stimulation causes a recording of a stimulus artefact with neural response. (B) A masker stimulation before the probe stimulation will result in a stimulus artefact from the masker and the probe where the masker will be followed by a neural response. The probe stimulation follows a small or no response depending on the timing between the masker and the probe; if the time is short the nerve fibres are in refractory state and will not respond to stimulation. (C) Is masker stimulation only and finally (D) is a "no stimulation" measurement to measure the "switch-on" artefact of the system. A–D measurements will be subtracted and just the neural response, without any artefact, will be shown.

The threshold of the ECAP (T-ECAP) and amplitude growth function (AGF) are two common expressions used for ECAP measurements and will be explained in the following section. Two primary measures are derived from the AGF, the slope and the threshold. The slope represents the ECAP response growth as a function of stimulus level, and the threshold

Background

represents the minimum amount of current needed to elicit a measurable neural response. ECAP thresholds have been used clinically to estimate behavioural levels used to program SPs (Hughes, 2012). Figure 20 displays a typical AGF. A regression line is calculated to determine the zero crossing, which is defined as the T-ECAP.
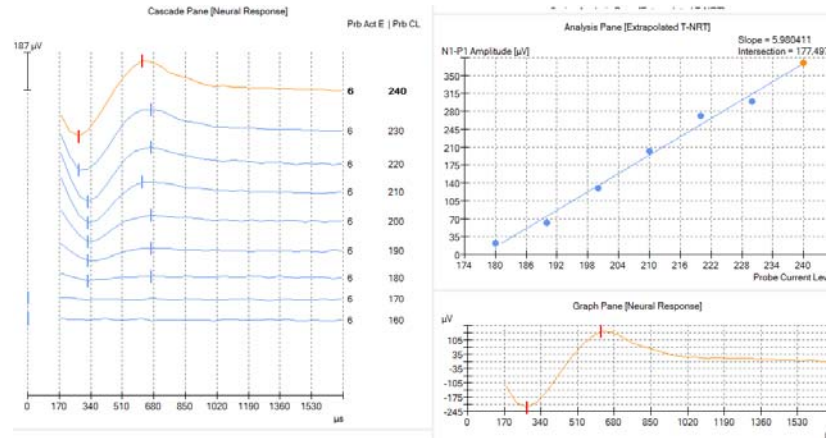
Figure 20 is an example of an AGF of a NRT (ECAP) response. The left pane shows a series of ECAP measurements at different stimulation levels (240Cl-160CL). The right upper pane shows the amplitude growth function (AGF) and a determined zero crossing at 177CL, which is defined at the threshold of the ECAP, or T-ECAP. The lower right pane shows a single response with N1 and P1 peak picker set for amplitude determination.

2.4.3 Electrically Evoked Stapedius Reflex Threshold (ESRT)

Electrically evoked stapedius reflexes (ESR) show the same reflex as their acoustic counterparts, except that the stimulation of the auditory system is made by electrical stimulation via the CI. The stapedius reflex is a muscular contraction within the middle ear in response to loud sounds and has been briefly described in chapter 2.1.2. The stimulus (loud acoustic sound or electrical current from a CI stimulator) elicits a response in the afferent auditory nerve fibres (eighth cranial nerve), which travels to the ipsilateral (same side as the stimulation source) cochlear nucleus, then to the motor nuclei of the facial nerve (seventh cranial nerve) on both the ipsilateral and contralateral (opposite side of the stimulation source) sides (Hall, 2007). The reflex arc is completed via the efferent path from the motor nuclei to the facial nerve, which innervates the stapedius muscles on both the ipsilateral and contralateral sides. The stapedius muscle, which attaches to the stapes, contracts bilaterally. This contraction stiffens the ossicular chain, resulting in decreased compliance of the middle ear system (Hughes, 2012). Clinically, ESRTs can be measured using the CI programming equipment. The stimulus that is usually used to elicit ESR is typically the same stimulation rate as used for programming the SP. The Cochlear system uses approximately 500ms

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pulse trains by default. For recording the stapedius reflex there are two major clinical possibilities. A probe (hermetically sealed) in the contralateral ear (pressurised) can be used that measures the contraction of the muscle, by measuring the increased impedance of the ear drum. Alternatively, visual observation of the contraction of the stapes muscle can be used to measure the ESR. This can be carried out intra-operatively during CI surgery; an audiologist electrically stimulates the intra-cochlear electrodes and increases the current until a reflex can be visually observed by the surgeon looking through the OR microscope. After a stapedius reflex is observed the ascending-descending technique is carried out, whereby higher current levels are initially used which are then decreased until the stapedius reflex disappears. This is defined as the threshold of the stapedius reflex or ESRT. At our hospital, only the visual observed ESRT technique is used and the results published in the articles refer to this technique. Many studies have investigated the clinical use of both methods. Kurt Stephan has been a pioneer in ESRT measurements and was already using this technique in the 1980s to find a tool that would help the audiologist in the programming of SPs (Stephan et al., 1988). Later, authors reported on the use of ESRT in SP programming and found good correlations between ESRTs and programming levels (Allum et al., 2002, Almqvist et al., 2000, Battmer et al., 1990, Bresnihan et al., 2001). ESRT measurements have been used at our clinic for many years and the reported results have encouraged us to include these measurements in our standard clinical protocol during CI surgery. The results will be reported in the article section.

2.4.4 Electrically Evoked Auditory Brainstem Response (EABR)

The EABR is a synchronous physiological response from the auditory nerve to structures in the brainstem. As with its acoustic counterparts, the EABR is characterised by waves I through V (see chapter 2.1.3), although wave I (and sometimes wave II) can be obscured by stimulus artefact. Each wave represents a different synapse point or structure within the auditory pathway. Waves I and II are presumed to arise from the distal and proximal portions of the auditory nerve, respectively; wave III from the cochlear nucleus; wave IV from the superior olivary complex; and wave V from the lateral lemniscus and inferior colliculus (Hughes, 2012, Hall, 2007).

ABRs are acoustic EPs whereby a probe is placed in the ear canal and soundwaves stimulate the organ of hearing. For implant evoked EABR the inner ear (cochlea) can be stimulated electrically. This can be done by placing a needle electrode at the round window niche (see Figure 21). Several researchers have investigated this approach, for example before CI surgery, to test if there are responses to electrical stimulation (Alfelasi et al., 2013, Kileny et al., 1992, Nikolopoulos et al., 2000, Pau et al., 2006). The other possibility for

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stimulating the inner ear electrically is by the use of the intra-cochlear electrode array of a CI. Here, the programming software of the companies is used to stimulate individual electrodes at desired stimulation levels. The stimulating unit triggers an EP measuring unit that can record the responses form the electrical stimulation along the auditory pathways (see Figure 22). During recording the RF of the CI system needs to be switched off otherwise no responses are measurable due to large frequency artefacts. EP systems usually average 2000 measurements to eliminate signal artefacts. This technique, of stimulating intra-cochlear electrodes for EABR measurements, was used for the research work in this dissertation. A typical EABR of a CI patient is shown in Figure 23. Many researchers have tried to find a correlation between EABR responses and programming levels (Brown et al., 1994, Brown, 2003, Firszt et al., 2002a, Firszt et al., 2002b, Kumakawa et al., 2004, Shallop et al., 1991). Others have tried to find a correlation between EABR and speech recognition performance (Jeon et al., 2013, Makhdoum et al., 1998, Lundin et al., 2015). Researchers have also investigated the differences in EABR for different aetiologies, such as ANSD, different electrode array placement, such as medial or lateral, or for cochlea malformations (Firszt et al., 2003, Kim et al., 2008, Greisiger et al., 2011, Runge-Samuelson et al., 2009).
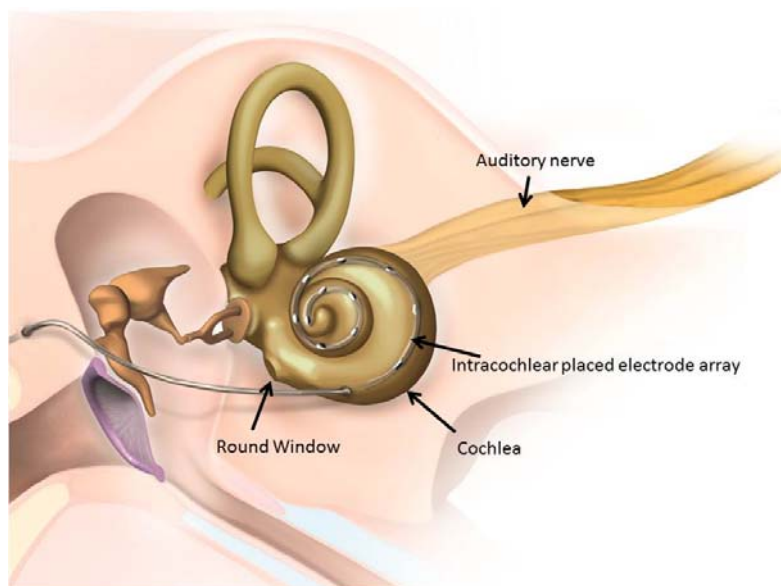
Figure 21 showing the middle and inner ear (cochlea) with electrode array placed inside the cochlea. For EABR measurements either a needle electrode placed at the round window or the intra-cochlear electrodes can be used to stimulate the nerve fibres, which may elicit a response along the auditory pathways that can be measured via surface-mounted electrodes (image by courtesy of MED-EL).

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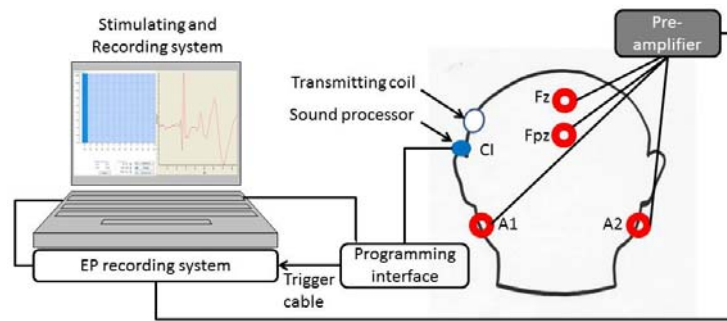
Figure 22 shows the setup for EABR measurements. A PC is used to control the evoked potentials (EP) recording system and the CI programming software which includes EP-stimulating software. The SP and transmitting coil are connected to the programming interface, which is connected to a PC with installed programming and stimulation software. The programming interface triggers the EP recording system. After stimulation, the SP's transmitting coil is switched off for 10ms to allow recording without RF from the stimulating system. Surface mounted electrodes on the patient's head (Fz, Fpz, A1, A2) can pick up the response from the brainstem, pre-amplify the signal and transfer it to the recording system (EP) for further analysis.
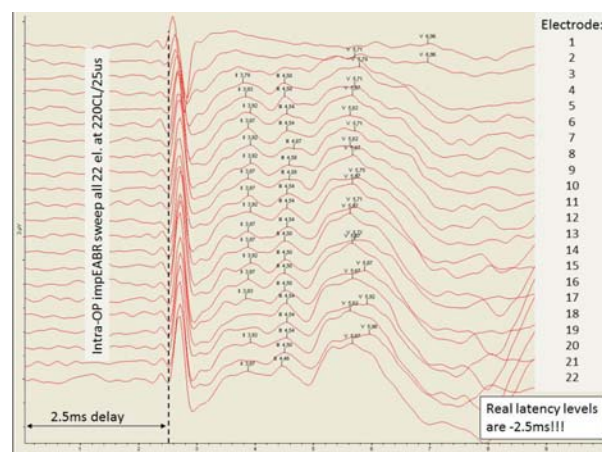
Figure 23 displays an intra-operative EABR measurement of a Cochlear Freedom device. Onset of the stimuli is at 2.5ms visible as a large stimulus artefact. At 3.8ms the response wave eII, at 4.5ms wave eIII and at approximately 5.8ms the wave eV. Shown are, from bottom to top, the electrodes from most apical (22) to most basal (1).

2.4.5 Electrode Impedances

Impedance measures are important to determine whether intra-cochlear and extra-cochlear electrodes are functioning appropriately. Impedance measures can also provide information about the properties of the tissue in contact with the electrode's surface (electrode-tissue interface) (Hughes, 2012). Many researchers have observed and investigated changes in

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electrode impedance over time. Once the implant is stimulating the electrodes, impedances typically decrease and stabilise within the first few months of device use (Busby et al., 2002, Henkin et al., 2006, Henkin et al., 2003, Hughes et al., 2001, Neuburger et al., 2009, Saunders et al., 2002, Vargas et al., 2012, Zadrozniak et al., 2011, Greisiger et al., 2015). Impedance change already occurs over a few minutes of stimulation intra-operatively. During surgery, this may cause incorrect intra-operative objective measurements, such as ECAP, so the device companies offer built-in conditioning features for preventing false measurements with "unconditioned" electrode impedances (see Figure 24 of intra-operative impedance measures). In case of customised measurements, such as EABR measurements, the electrodes must be conditioned before measuring (Greisiger et al., 2015). Impedance measurements are used for each device programming session at OUS. In case changes occur, electrode channels may need to be switched off. Usually electrodes will be switched off if there is an open circuit (see Figure 25), short circuit (see Figure 26) or if the patient experiences uncomfortable or even painful sensations due to electrical stimulation.
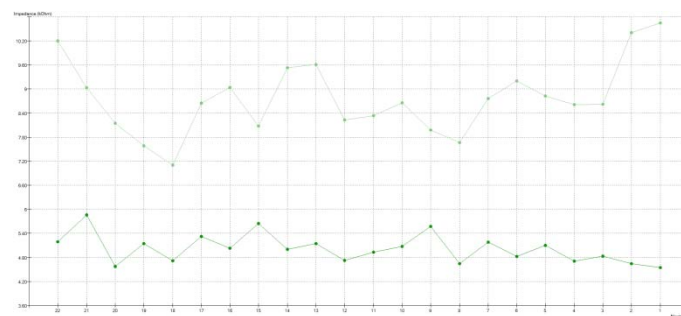
Figure 24 shows impedance values just after insertion (upper graph) and approximately 20 minutes (lower graph) after all intra-operative measurements were completed. This is a measurement of a Cochlear Freedom device.
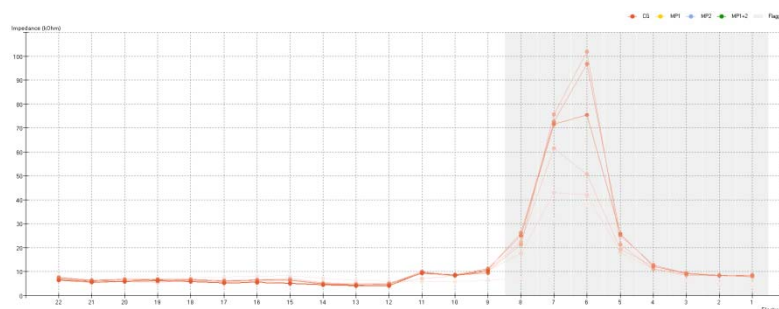
Figure 25 indicating high impedances (open circuit) around electrode 6 and 7 for a Cochlear Freedom device.

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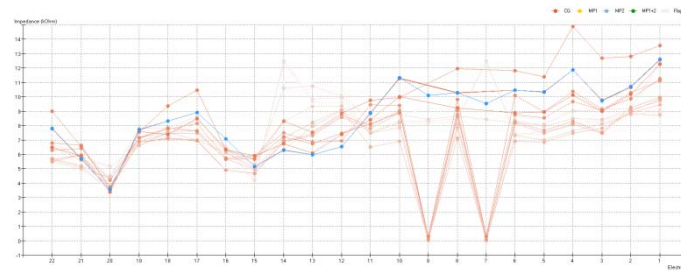
Figure 26 displays impedance measurements of a Cochlear Freedom implant, where electrodes 9 and 7 have a short circuit.

2.4.6 Voltage Compliance Levels

Most implant systems use current sources for stimulating the electrode channels, where a fixed amount of current is specified by the system and the amount of supply voltage (from the external battery) is varied depending on the impedance of the electrode and surrounding tissue. For electrodes with relatively high impedances, the device is limited to smaller current values before voltage compliance is reached (more voltage is needed to achieve the desired current level) (Hughes, 2012). In case compliance levels are reached, modifications for programming the SP are required. For the MED-EL system, which uses a charge-balanced method, the pulse width of the biphasic stimulus will be automatically increased to stay below compliance limits. For the Cochlear system, a change in pulse width needs to be carried out manually. This can be an easy task for patients who give reliable feedback, but for small children it can be difficult to achieve similar loudness levels. Better loudness levels may cause sound to become distorted at compliance levels, as some adult patients complain. While the pulse width increases the pulses get longer and therefore the stimulation rate may reduce. Figure 16 in section 2.2.2.3 displays the relation between pulse width amplitude and compliance levels schematically.

2.5 Cochlear Implant Imaging

As part of the pre-investigation, CT imaging of the cochlea, temporal bone and surroundings is done prior to every CI surgery, whereby the surgeon can obtain valuable information such as anatomic position, size, and if the cochlea is filled with liquids (peri- and endolymph). MRI is performed for all children and all difficult surgical situations. This chapter describes the use of imaging techniques either during or after surgery to investigate the placement of the electrode array inside the cochlea or general placement of the CI with stimulator and electrode arrays (intra-cochlear electrodes and extra-cochlear electrodes, such as reference electrodes).

Background

2.5.1 Importance of Cochlear Implant Imaging

In 1996, Cohen et al. stressed that information concerning the positions of the individual electrodes of a CI array is important for analysing speech recognition or psychophysical data and for optimising speech-processing strategies (Cohen et al., 1996). Post-operative imaging has been a standard procedure for many clinics to verify the electrode placement after CI surgery since the early 1990s (Marsh et al., 1993). Usually, a simple plain film X-ray image is done to confirm electrode array placement inside the cochlea. For CI surgery a mobile X-ray system can be used. Figure 27A shows an example of an X-ray image performed with a mobile system in 2006 at OUS. Unfortunately, the image quality was not good enough to provide detailed information. Another scan was required, this time a flat panel detector (FD-CT) scan, at the OUS Intervention Centre (IVS). Figure 27B shows the result of a FD-CT scan which gave much more detail and was the basis for re-surgery. In Figure 27C the final placement of the re-implanted electrode array is shown; a full length insertion could be achieved. At IVS in 2008, we launched a temporal bone study with inserted electrode array to investigate electrode placement inside the cochlea. The results were very promising, because the exact position of the electrode array could be determined. This has encouraged us to use the imaging possibilities at IVS for studies and difficult surgical cases.
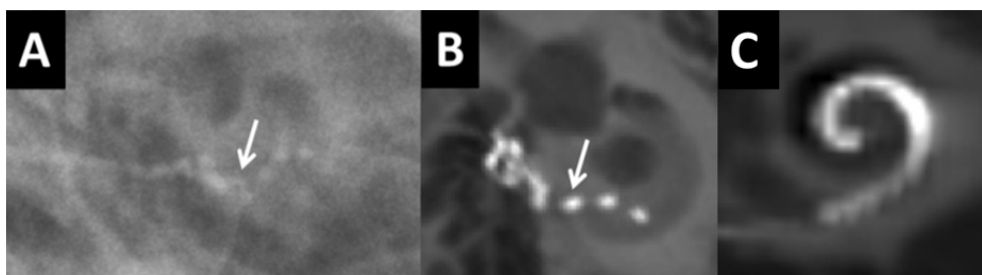
Figure 27 (A) Fluoroscopy image performed in 2006 with a mobile intra-operative C-arm system. It was assumed that 5 electrode contacts were inside the cochlea. (B) In 2009 a FD-CT scan provided better resolution and showed that just 3 electrode contacts were inside the cochlea. The revision surgery showed full insertion of the Cochlear Contour electrode array (C).

CI imaging has turned out to be of high value when combined with objective measurements. In the following is an example to demonstrate the value of CI imaging. In Figure 28 the measurement results of nerve response (ECAP) and EABR are shown. These are the responses for the same patient's left and right ears. This patient had a similar hearing history on both sides. For the ECAP and EABR measurements the responses indicated that the right side had approximately 2–3 times greater responses. This was an unusual finding which could not be explained just by examining the objective measures. A FD-CT scan was carried

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out on both sides and a difference in electrode array positioning inside the cochlea could be detected (see Figure 29). The right electrode array was placed in the lower canal (scala tympani) of the cochlea and the left implant was placed in the upper canal (scala vestibule) of the cochlea. This small displacement has caused a relatively large difference for the ECAP and EABR. Other researchers have demonstrated similar results, that a displacement of the electrode array in the upper scala instead of the lower scala can cause poorer speech recognition scores (Aschendorff et al., 2007, Finley et al., 2008)
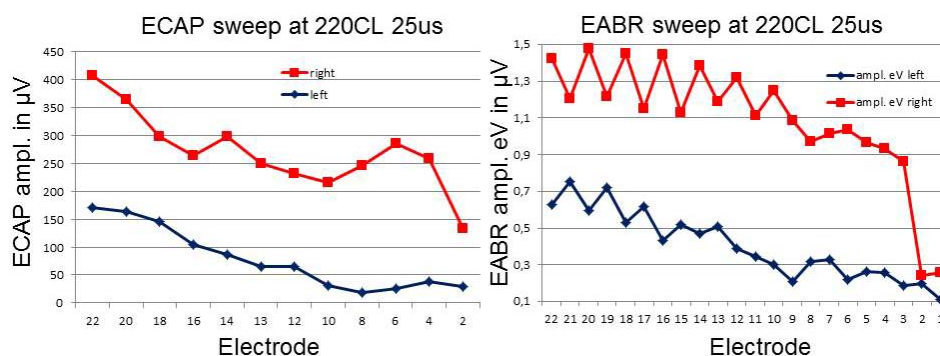
Figure 28 shows on the left side a diagram with results of ECAP measurements and on the right diagram results of EABR measurements. These measurements are from the same patient, who has had a very similar hearing history on both sides. As stimulus for left and right, as well as for ECAP and EABR measurements, 220CL at 25us were used. The results are very different. The responses on the right side are greater. Imaging was required (see next figure) to understand why this is the case.
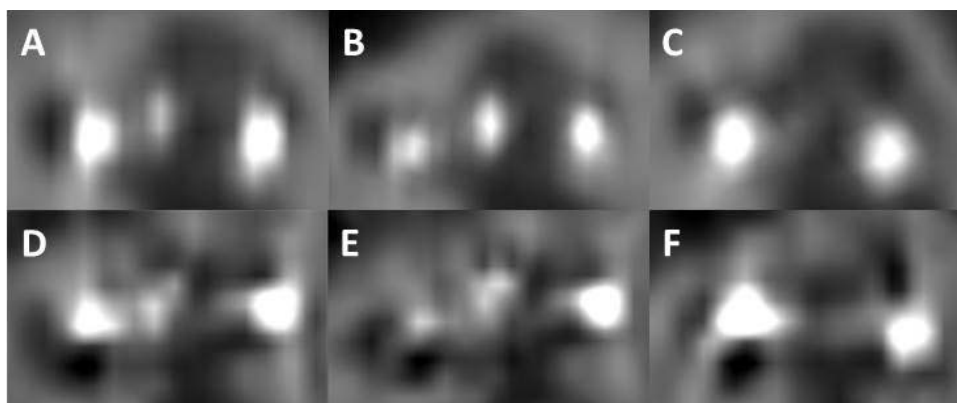
Figure 29 shows a FD-CT scan cross sections of a right (A–C) and left (D–F) cochlea of the same patient implanted with Cochlear Freedom implants. Images A–C show the electrode array (white) in the lower section of the cochlea, which is an indication that the electrode array was placed in the desired scala tympani. Figures D–E show a dark area below the white electrode array, which is the scala tympani, the electrode being placed in the scala vestibule.

Background

2.5.2 Imaging Technologies – X-ray, Fluoroscopy, FD-CB-CT Scan

The imaging technologies used in this dissertation will be explained in this section.

X-ray imaging measures the transmission of X-ray photons through tissue. An external X-tube transmits photons through a section of the body – some pass straight through the body, some are scattered and emerge at unpredictable angles, and some are completely absorbed. The X-ray photons are measured by a detector on the opposite side of the body. (Bourne, 2010).

Fluoroscopy The purpose of fluoroscopy is to display images semi-continuously in real time in order to perform functional studies, and to guide surgery and interventional procedures. Modern digital fluoroscopy does not use a continuous X-ray beam. Instead, a series of short exposures – pulses – are made at a time interval. (Bourne, 2010).

Flat Detector Computed Tomography (FD-CT). Images are formed by rotational movement of the C-arm of an angiographic system. A 3D volume is reconstructed from a partial rotation of the C-arm.

2.5.3 Intervention Centre - Technology and Concept of Reconstruction

The angiographic equipment with FD-CT scan possibilities which was used for the studies at IVS (Siemens® Artis® Zeego®), has pre-programmed acquisition 3D programs for different organs and different investigations. For CIs we choose a 3D program for native reconstructions. The acquisition time differs between 5 and 20 seconds. It is crucial that the patient does not move during the exposure.

The C-arm of the Artis Zeego can be moved in all horizontal and vertical directions, with the temporal bones in the isometric centre. The parameters, such as the number of frames per second, the angel of each rotation and the speed of the rotation, are all pre-programmed. All images, the raw data, are stored as a volume. When a 3D acquisition has been finished on the Artis, the images are automatically transferred to the Syngo® Workplace for reconstruction.

The Syngo Workplace is a computer in the exam room next to the hybrid suite. A secondary reconstruction has to be performed manually on the Workplace by choosing appropriate parameters and mathematical calculations/algorithms for the relevant organ. There are several techniques for displaying image volumes, for example, the volume rendering technique (VRT), which is used for reconstructions of the cochlea. VRT can differentiate between bone and tissue structures and display a 3D model of the inner ear.

The Syngo Workplace 3D task card can display three different slice planes through the structures. In the first three segments, the anatomical standard views are displayed as sagittal-, transversal- and coronal slices. With multiplanar reconstruction (MPR), it is possible

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to calculate secondary images of any planes from the volume. With the MPR for thick slices, the thickness can be defined from the original slice from which the image is to be reconstructed, like CT images. With parallel ranges, it is possible to generate parallel images that are a defined distance apart. It is useful to extract a small number of images of the cochlea. The greyscale values, or Hounsfield values, are chosen for the desired window and level value of the pixels in the digital image.

2.5.4 Hybrid Operating Room at Intervention Centre

The CI imaging data were gathered at OUS IVS. The operating room is equipped with a FD-CT scan and called a hybrid operating room. Figure 30 displays the set-up of the IVS hybrid operating room. The C-arm of the FD-CT scanner can rotate around the operating table. Fluoroscopy and FD-CT images can be carried out during or after surgery. In Figure 31 a CI surgery is being performed at IVS. While the surgeon inserts the electrode array into the cochlea a radiographer performs a fluoroscopy imaging to confirm proper insertion of the electrode array.

Figure 30 shows IVS's hybrid operating room equipped with a FD-CT scanner that can be used during surgery.
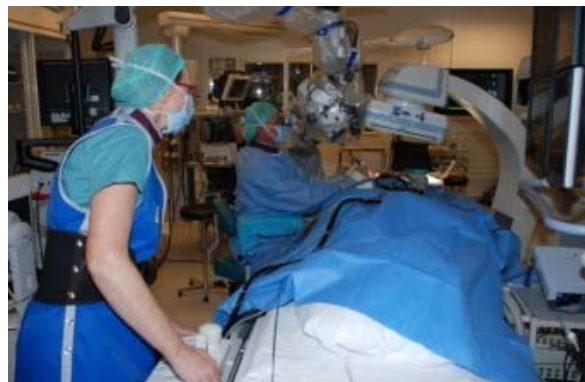
Background

Figure 31 shows a CI procedure with fluoroscopic investigation during the insertion of the electrode array. The surgeon is inserting the electrode into the cochlea with the help of a microscope. A radiographer (front) is simultaneously performing fluoroscopy.

2.6   Psychoacoustics / Programming

At OUS, when the wound has healed at between 4–6 weeks after CI surgery, the external part, the SP, can be switched on. The programming parameters need to be set for each patient individually. In most cases, the most important parameters a clinician determines when programming a recipient's CI is the magnitude of stimulation provided from the implant to the auditory nerve. The fundamental goal of programming is to restore audibility for a range of speech sounds extending from soft to loud speech. Ideally, stimulation levels are set to optimise identification of speech sounds. Finally, it is desirable to set stimulation levels so that normal loudness percepts are restored for speech in addition to environmental sounds. Sounds that are perceived as soft to a person with normal-hearing sensitivity should also sound soft to a CI implant user, while sounds that are perceived as loud for a person with normal-hearing sensitivity should also be loud, but not uncomfortable, to the user (Wolfe and Schafer, 2014). The following section will briefly explain the programming parameters used, with particular focus on those levels and parameters that were investigated in the study shown in the scientific section. The procedure is called programming the SP or finding the psychoacoustic levels. Basically, the loud and soft sound for each electrode channel needs to be found.

2.6.1   Programming Sessions

There are differences in the duration and number of programming sessions between CI clinics (Vaerenberg et al., 2014b). At our hospital first switch on of the SP is after 3 days, although this will depend on whether the patient is a child or an adult, as adult patients usually give more reliable feedback and the whole programming procedure can be shorter. There is also a difference in timing if a patient is receiving a second device sequentially and is therefore already experienced with the procedure.

For CI programming two possible methods can be used.

2.6.1.1 Feedback Method

The patient qualifies the settings in terms of loudness and frequency. This can be used most of the time for adult patients, school children, teenagers and experienced patients who had hearing before deafness or were using hearing aids. In these cases the programming vary with the precision of the information/feedback given by the patient.

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2.6.1.2 Behavioural Method

In the case of young children, multi-handicapped patients or long-term deafness, feedback from the patient cannot be expected. Here a teacher for the hard of hearing and an audiologist observe the patient's behaviour in terms of different programming parameters such as current or charge delivered to the active electrodes. This procedure can be very difficult and a good SP programming depends on many factors such as motivation, influence of the parents, clinician's experience, feedback from therapists, training, device function, parameter settings, room, toys, confidence (clinician-patient), grade of deafness/degenerated nerve fibres, success of surgery, placement of electrode, timing, age, maturation of the auditory cortex, condition of the auditory pathways, etc. Therefore, the most optimal programming of the SP can take several months or even years. During this time several adjustments are required and test results such as speech test (if possible) or questionnaires (parents judging listening experiences) are evaluated to improve the settings. During this phase valuable time can be lost as the maximum plasticity of the auditory cortex is limited and after that period improving speech listening skills is difficult. Accordingly, objective measures may help for SP programming. If an optimal programming can be found earlier, this may result in better hearing, which could lead to our youngest patients having an almost normal life (normal hearing school, normal education, etc.).

2.6.2 Lower- and Upper-Stimulation Levels

The threshold of electrical stimulation refers to the least amount of stimulation a recipient can detect when electrical signals are delivered to individual electrode contacts. In practice, the exact definition and name of the electrical threshold of stimulation varies across programming software manufacturers. For Advanced Bionics CIs, the electrical threshold is comparable to the audiometric threshold and is best defined as the lowest amount of electrical stimulation a user can detect with 50% accuracy. For Cochlear Ltd. implants, the electrical threshold is defined as the minimum amount of electrical stimulation the recipient can detect 100% of the time. In contrast, MED-EL defines electrical threshold as the highest level at which a response is not obtained. Abbreviated terms, such as "T level" for Advanced Bionics and Cochlear and "THR" or "threshold" level in MED-EL devices, are often used to describe the electrical threshold. Most commonly, recipients are instructed to give feedback when they hear the stimulation signal (Wolfe and Schafer, 2014).

The programming parameter related to the upper level of stimulation also varies by terminology and definition across manufacturers. In the Advanced Bionics system, the upper limit of electrical stimulation is set at a level the user perceives as "most comfortable." This parameter is similar to the most comfortable listening level frequently measured in hearing

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aid evaluations and, in Advanced Bionics CIs, is commonly known as the "M level." In the MED-EL system, upper-stimulation levels are known as "maximum comfort levels" (i.e., MCL) and are defined as the amount of electrical stimulation considered to be "loud, but not uncomfortable." For Nucleus implants, upper stimulation levels are known as C levels and are set to a level of stimulation the user considers to be "loud, but comfortable." A CI user's upper-stimulation levels are critically important because they influence speech recognition, sound quality and, in the case of pre-lingually deafened children, the ability to monitor one's own voice and produce intelligible speech. If upper-stimulation levels are set inappropriately, the recipient will likely experience poor outcomes. Clinicians typically set upper-stimulation levels via psychophysical loudness scaling methods or through behavioural observation (Wolfe and Schafer, 2014). Figure 32 displays a typical profile of upper- and lower-stimulation levels as an example of the Advanced Bionics system.
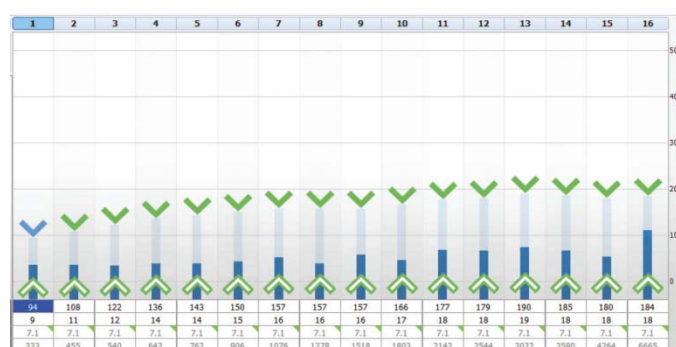
Figure 32 shows upper- and lower-programming levels for each individual channel (frequency range) for an Advanced Bionics system (image by courtesy of Advanced Bionics).

2.7 Performance/Outcome with a CI - Speech Recognition Tests

The performance or outcome of a CI can be measured or defined in several ways, for example, increased quality of life or relief of tinnitus due to the electrical stimulation of a CI. For the research work of this dissertation performance with a CI has been determined by speech recognition tests. Even though the focus of this dissertation was on objective measurements and CI imaging it is necessary to have a "measure" of performance. In article III, performance was compared with objective measurements (EABR), therefore a brief introduction of the tests and methods used will follow in this section.

In clinical practice, assessment of speech recognition abilities follows a hierarchical approach based on the patient's chronological age, hearing age, language level, communication mode, cognitive abilities, and attention span. Such behavioural tests need to be sensitive to floor and ceiling effects, where the test material may either be too difficult or too easy for the patient to tackle.

Background

These tests can broadly be categorised as either closed-set or open-set tests, which has been important for the findings of paper III, where EABRs were compared to closed-set and open-set speech recognition. Closed-set tests require subjects to choose one answer from a visually-presented list; thus, the material is high-context information. Open-set tests require the subject to respond to words and sentences without contextual information. In contrast to closed-set testing, the number of possible words or phrases to choose from is very high. The ceiling effect that results in open-set testing is usually due to the familiarity of the materials or excellent performance. The HINT test, which was originally developed for adaptive noise conditions to determine a speech-reception threshold, is used by the CI field to assess open-set sentence recognition in quiet and in speech-spectrum noise at a fixed level. Patients are asked to repeat what they hear, even if only part of the sentence. Each word repeated correctly is summed and divided by the total number of words in the sentence list to express speech understanding as the percent correct. The Norwegian HINT sentence lists are presented at 60dB SPL (Myhrum and Moen, 2008). By convention, the level of background noise is reported as a signal-to-noise ratio (SNR), in which the number of dBs above or below the presentation level is considered the SNR. For example, a presentation level of 60dB and a noise level of 50dB would be considered a +10dB SNR. Smaller SNRs indicate higher levels of noise relative to the test material presentation level and, as such, are more difficult. When the noise presentation level is louder than the test material presentation level, this is reported as a negative SNR. As an example, a presentation level of 60dB in the setting of a noise level of 70dB would be considered a -10dB SNR. Normal-hearing listeners can comprehend sentences effectively with SNRs of -3dB (Waltzman and Roland, 2014, Myhrum et al., 2016). Most implant recipients perform somewhat worse, although variability certainly exists. Our clinical experience has shown that our children with the most successful outcomes' have a SNR -1dB.

Open-set conditions for Norwegian monosyllabic word recognition are the most difficult for a listener with a CI, and are a useful test to compare outcomes in adults following implantation (Waltzman and Roland, 2014, Øygarden, 2009).

The University of Iowa developed its own battery of tests, which were translated into Norwegian. For the Norwegian IOWA test, patients sit in front of a monitor with loudspeakers. Three different options are possible: audio only, video only (here lip-reading abilities are tested, while a speaker can be seen but not heard) and finally, audio and visual conditions to simulate a real listening situation.

The Norwegian Early Speech Perception (ESP-N) test requires patients to select a word from a number of different alternatives presented. In the standard version, patients are presented

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with up to 12 picture plates from which to select their response (Niparko, 2009, Wie et al., 2007, Geers and Moog, 1990, Geers et al., 2003, Moog et al., 1990).

Chapter 3

3 Research Summary

This chapter summarises the research conducted for the thesis. First, a brief overview of the research process is given, followed by the motivation and abstract for each paper included. Finally, the publications produced during the research are listed.

3.1 Overview

The research process can be divided into several parts: First, investigation of the use and benefit of objective measurements in CI patients. Second, finding the relationship between objective measurements and patients' aetiology, such as ANSD. Third, investigation of objective measurements versus outcome (e.g. speech recognition) of CI patients. Fourth, patient's programming levels compared to patient's age. Fifth, detecting problems with the CI to help with imaging and objective measurements.

3.2 Papers

This section presents details about the motivation for, and contribution to, each paper together with the paper's abstract.

3.2.1 Paper I

Cochlear implant-evoked electrical auditory brainstem responses during surgery in patients with auditory neuropathy spectrum disorder

Paper I

This paper investigates the differences between a special patient group with ANSD and a patient group without ANSD. ANSD allows patients to hear, but not develop speech recognition. This is due to a dys-synchrony of nerve fibres that do not transfer sound signals in a synchronous manner. For many years, there was controversy about the benefits of treating ANSD patients with a CI. This study investigated the differences between non-ANSD patients and ANSD patients. Intra-operative CI-evoked electrical auditory brainstem response (impEABR) was compared to investigate if there is a difference. No difference could be found in terms of EABR eV amplitudes and latencies between non-ANSD and ANSD patients.

Research Summary

The work resulted in valuable information about the ANSD and brainstem responses with a CI. The findings of this study have resulted in EABR measurements becoming part of the clinical routine at OUS. EABR measurements are carried out during CI surgery to determine if the electrical stimulation causes a synchrony stimulation along the auditory pathways.

Abstract

Background: Our objective measurement protocol during cochlear implant (CI) surgery includes evoked compound action potential (ECAP) and electrically evoked stapedius reflex threshold (ESRT). We are evaluating the use of CI-evoked electrical auditory brainstem response (EABR) especially in patients diagnosed with Auditory Neuropathy Spectrum Disorder (ANSD) to evaluate if patients had a pre- or post-synaptic dys-synchrony of the auditory nerve. Our goal is to find out if our measurements relate to the speech recognition outcomes of a CI. We have measured more than 80 CI ears using this protocol. This group includes 13 ears with ANSD and age varies from 2 years-old to 57 years-old. **Methods:** After insertion of the CI, electrode impedance and ESRT were obtained. These measurements were followed by EABR testing of either a sweep across all the electrodes and/or threshold measurements on selected electrodes. Speech recognition testing was done before surgery and after CI fitting. For adult patients we used recorded HINT sentences and for children, the Early Speech Perception test. **Results**: To date, in all except 6 ears, we have obtained responses intra-operatively. Long-term performance tests are not available at this time. This presentation will include two ANSD cases to show the range of post-CI speech recognition performance and EABR results. All other ANSD patients have good to very good results with their CI even though there is a large variation among the patients in terms of ECAP response amplitude, ESRT threshold level, EABR latency shift and EABR wave V amplitudes. **Conclusion**: At this early stage of the study EABR measurements seem to be a promising tool that can give us a good indication about post-operative performance with a CI. So far patients with good visible waves II, III and V have good results with their CI. This study will be continued and combined with an extensive speech recognition testing battery.

3.2.2 Paper II

Cochlear implantees: Analysis of behavioral and objective measures for a clinical population of various age groups

Paper II

This paper investigated a large patient group according to their behavioural and objective measures. The different age groups under investigation showed significant differences

Research Summary

depending on their programming levels. Unfortunately, there was a poor correlation between objective measurements and programming levels.

The work resulted in a comprehensive data collection and analysis which can be used as a programming guideline for new patients according to their age. The findings of this study may improve the quality of SP programming for future patients. The data presented may be of help for patients with special needs and those who cannot give feedback as at least an indicative good starting point for SP programming.

Abstract

Introduction: As of 2014 more than 1200 patients have received a cochlear implant (CI) at Oslo University Hospital (OUS) and approximately half of them have been children. The data obtained from these patients have been used to develop a comprehensive database for a systematic analysis of several objective measurements and programming measurements. During the past 10 years, we have used an objective measurements protocol for our CI surgeries. Our intra-operative protocol includes: Evoked Compound Action Potentials (ECAP), visually observed Electrically evoked Stapedius Reflex Threshold (ESRT), and electrode impedances. Post-operative (Post-OP) programming sessions typically begin 4–6 weeks after surgery and continue on a scheduled basis. The initial programming data include threshold levels (T-levels) and comfortable levels (C-levels) for the different patient age groups. In this study, we compared initial stimulation levels and stimulation levels after at least 1 year of CI with objective measurements obtained intra-operatively. **Method:** This study focused on the development of a comprehensive database of detailed intra-operative objective measures and post-OP programming measurements from a group of 296 CI patients who received the same type of CI and electrode configuration (Cochlear® Corporation CI with Contour® electrode). This group included 92 bilateral CI patients. Measurements from 388 CI devices were studied. Patients were divided into 5 different age groups at the age of implantation: 0–2, 2–5, 5–10, 10–20, and above 20 years in order to investigate age-related differences in programming levels and objective measurements. For the comparison analysis we used T- and C-levels obtained after the last day of initial programming and also after at least 1 year implant use. These programming levels were then correlated with some of the intra-operative objective measurements. **Results:** T-levels were found to be the lowest for the youngest patient group and increased with age. C-levels varied within age groups and frequency range. Patients above 20 years of age had the highest comfort levels in the low to mid-frequencies (electrodes 22–8) and the lowest comfort levels in the high-frequency range (electrodes 1–7). Correlation coefficients between intra-operative objective measurements and programming levels were found to be in the range of no

Research Summary

correlation to moderate correlation. Adult patients had the most significant correlation coefficients between ECAP thresholds and T-levels in the low frequencies. The younger patients aged 10–20 years and 5–10 years had more significant correlations in the higher frequency channels compared to the other age groups. Intra-operative visually observed ESRTs and electrode impedances were not significantly correlated with initial or stable programming levels for the children or adults. **Conclusion:** Analyzing initial and follow-up mapping levels from previous patients is very important for a CI Center in terms of quality control. The mean T/C-levels reported in this study can provide guidance to our programming audiologists and help them determine the initial programming levels to be stored in the sound processor, especially for very young patients. Unfortunately intra-operative objective measures in our study, such as ECAP, ESRT, and electrode impedances did not provide statistically significant correlations that may help to predict the programming T- and C-levels for all patients. However, we have observed cases where the intra-operative objective measures of ESRT and TECAP profiles were very similar to an individual's MAP profile. It was not possible, however, to determine why some patients did not have an objective measures profile that was similar to their programming levels profile.

3.2.3 Paper III

Cochlear implant electrically evoked auditory brainstem responses and postoperative speech recognition in cochlear implant patients

This paper investigates if it is possible to measure which category of speech recognition scores can be achieved with a CI immediately after CI surgery. For this study patients were measured for CI EABR. The measurements were analysed in terms of EABR amplitude and latency of wave eV. The responses were compared with speech recognition scores. It emerged that there is a strong relationship between patients who had no responses and were performing poorly with the CI and patients who had EABRs and open-set speech recognition was possible. Unfortunately, it was not possible to measure exact scores of speech recognition, which means there was no correlation between larger eV amplitudes and shorter eV latencies and better speech recognition scores.

The work resulted in the possibility of an indication of speech recognition scores immediately after surgery. This can be of value in difficult procedures with, for example, malformations of the cochlea or in patients where expectations of a CI may be low. The intra-operative EABR measurements may give an indication for the outcome with a CI and suggestions for therapy may be given, such as addition of sign language because open-set speech recognition may not be possible. EABR measurements may be used in combination with test electrodes in

Research Summary

future, in order to evaluate CI candidacy intra-operatively. This could be valuable, especially in patients with cochlea malformation or a thin auditory nerve.

Abstract

Introduction: The primary aim of this study was to investigate whether intra-operative electrically evoked auditory brainstem responses (EABR) can be used to predict postoperative speech recognition in patients who receive a cochlear implant (CI). **Methods:** Patients from our Cochlear Implant Center at Oslo University Hospital (OUS), were implanted with either a Cochlear™ Corp. or a MED-EL™ device and were tested intra-operatively for EABRs on selected electrodes. These measurements were divided into three frequency areas: high, middle and low frequencies based on the stimulated regions of the cochlea, basal to apical. Results of the intra-operative EABR measurements were correlated to post-operative speech recognition testing at least 12 months after surgery. **Study Sample:** There were 53 patients, aged 1-86 years and 14 of these patients had bilateral CIs, which resulted in a total of 67 ears. **Results:** Intra-operative EABR measurements showed a wide range of response morphology. In 42 patients an EABR wave V could be measured and in 11 patients there was no response. Most patients with EABR measurements (40 out of 42) had postoperative open-set speech recognition. Patients with no EABR measurements (ten out of eleven) had poor speech recognition. **Conclusion**: This study has clearly shown that there is a significant relationship between observed intra-operative EABR measures and post-operative speech recognition. Post-operative open-set speech recognition was typical in CI patients with a measurable EABR. These results suggest that EABR responses may be of help when deciding strategies for speech and language therapy and speech processor programming.

3.2.4 Paper IV

The use of objective measurements, intraoperative fluoroscopy and flat detector CT to improve electrode array placement in difficult cochlear implant surgical cases

This paper investigates the use of objective measurements and imaging technologies, such as fluoroscopy and FD-CT scan in difficult CI surgical cases. In case of unexpected outcome with a CI imaging may help detect the origin of the problem; the idea was to investigate if it is possible to measure, for example, the displacement of an electrode array. This would make the investigation much easier because no imaging resources would be required and radiation exposure would consequently not be an issue.

Research Summary

The work resulted in an understanding of which measured objective measures may indicate a displacement of the electrode array. In addition, surgery in difficult cases such as malformations would be possible due to the per-operative information of the fluoroscopy. The information form the fluoroscopy video has increased surgical quality and has led to a much better understanding of how the electrode array moves inside the cochlea.

Abstract

Introduction: In this study we investigated, the value of Flat-panel Detector Computed Tomography (FD-CT) and fluoroscopy to verify electrode placement in cochlear implant (CI) patients. Various objective measurements were also investigated to correlate with electrode placement. These procedures were carried out in patients with technically difficult surgical issues and in patients with discomfort or unexpected poor outcomes. The primary aims of this study were to: a) to compare typical plain film x-rays with more advanced imaging techniques, b) to use intra-operative fluoroscopy as a method to assure correct electrode placement and c) correlate electrode displacement with objective measurements.

Method: The FD-CT C-arm angiography system (Artis zeego®, Siemens Healthcare®, Germany) with CT-like image reconstruction and fluoroscopy was used for scanning the cochlea with inserted electrodes. These CI patients were examined intra- or post-operatively with FD-CT scans. For patients with anatomical anomalies or known insertion difficulties, an intra-operative fluoroscopy was performed during the insertion of the electrode array. For some cases we also obtained objective measurements, such as Evoked Compound Action Potentials (ECAP) and/or Electrical Auditory Brainstem Responses (EABR).

Results: For nine of the ten patients, we obtained pre- and post-operative FD-CT scan, intraoperative fluoroscopy and objective measurements. Difficulties in the surgical procedure could be identified pre- and post-operatively. In 9 out of 10 cases an improvement of CI electrode placement was achieved.

Conclusion: Both the FD-CT scan and per-operative fluoroscopy improved the CI electrode placement during CI surgery. FD-CT shows anatomical structures and electrode placement in detail. These methods have helped us minimize poor clinical results by monitoring the exact position of the electrode array during surgery. If necessary a new device can be used. For many patients, successful surgery would not have been possible without this advanced imaging technology. ECAP and EABR measurements can also help identify in correct placement of the electrode array. These results suggest that imaging should be used in patients with technically difficult issues to verify the electrode array placement.

Discussion

Chapter 4

4 Discussion

This chapter presents the approaches followed in the thesis and summarises and discusses the results. Finally, a conclusion is given and directions for possible future work are suggested.

4.1 Discussion of Approaches and Results

The primary goal of this thesis was to improve the outcome with a CI. Many factors can influence this outcome. They can be divided into:

- **Medical/surgical** – How well was the surgery done with the proper medication and surgical technique (ideally less traumatic, to preserve the inner ear structures), how precise is the insertion of the electrode array?
- **Physiological** – The patient's physiological condition is very important for the outcome with a CI. For example, a long period of deafness, ossification of the cochlea, malformation of the cochlea, and degeneration of nerve fibres etc., are predictors for poor outcome with a CI, whereas early implantation and deafness of short duration can be seen as positive predictors.
- **Technical** – Best choice of electrode array, SP, speech coding strategy, automatic sound modification settings, etc. for individual patients may influence better outcome, but some are difficult to predict before surgery. Different types of electrode arrays cannot be tested in individual patients to find out which one gives the best results for the patient.
- **Programming** of the SP – Obviously the best programming will give the best results, and here reliable feedback is still essential, but very often not achievable, for example in small children.
- **Rehabilitation/Therapy/Training** – Adequate rehabilitation is very important and has to match the patient's needs in terms of duration and frequency.
- **Motivation** – The patient's motivation is important in training to use the SP and the more training, the better the outcome.
- **Environmental issues** – This is an important factor for children who need support from parents, teachers, therapists and carers to use the CI correctly. Sometimes simple things, such as empty batteries, SP volume levels being too soft, or a broken cable, can be stumbling block to CI rehabilitation. For adults this could be in an

Discussion

environment offering speech training possibilities, such as conversations on a regular basis; this may also improve the outcome.

These are just a few factors with some examples that describe the complexity of achievable best outcome with a CI. This thesis focuses on two aspects that may improve CI outcome:

- CI imaging
- Objective measurements

With CI imaging we can learn from the effects of a displacement and may be able to perform the surgical procedure better while gaining knowledge about what happens inside the cochlea during an electrode array insertion. Ideally, objective measurements may predict programming levels. This could be very beneficial in small children, who usually do not give reliable feedback, and where SP programming is more an estimate of good programming rather than of finding the best possible levels. The age of implantation has decreased and researchers have found that early implantation is beneficial for speech recognition (Wie, 2010). This is an increased challenge for audiologists having to treat a younger patient population and programming SPs with limited feedback. For many years researchers attempted to find correlations between programming levels and objective measures to make this task more precise (Cafarelli Dees et al., 2005, Smoorenburg et al., 2002). Obviously, the outcome is better the better the programming of the SP. Some researchers found good correlations between nerve responses (ECAP) and programming levels (Craddock et al., 2003), whilst others did not (Smoorenburg et al., 2002, Brown et al., 2000). We have analysed a large number of patients (N=377, paper II) in terms of objective measurements (ECAP, ESRT) and programming levels for different age groups, but could find only a poor correlation (Greisiger et al., 2015). Nevertheless, objective measurements (ESRTs) can be used, for example, as an upper limit for SP programming (Allum et al., 2002).

A moderate correlation was found for a range of electrodes and specific age group (paper II, (Greisiger et al., 2015)). Why are there different correlation coefficients depending on age groups? This may partly because young children are typically not able to give adequate feedback to the programming clinician. We observed different correlation coefficients for TECAP versus T-level programming for patients above age 5. There seems therefore to be better correlation coefficients for children above the age of 5 years compared to those below the age of 5 years. For the age groups above 5 years we observed that correlation coefficients were better in different frequency ranges especially at higher frequencies in younger aged children and lower frequencies in older children. The poor correlations between programming levels and objective measurements in the high-frequency range for adult patients may be explained by the different durations of deafness. These adult patients

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had relatively short or long periods with deafness. In a study, where the duration of deafness and etiology were assessed, the programming levels did not seem to be influenced by etiology (Walravens et al., 2006, Holden et al., 2013) found that there was a significant difference in performance which was dependent on electrode placement. The knowledge of such factors may be helpful for device programming. Children below 5 years of age usually do not give reliable feedback for the programming sessions. Accurate programming of the speech processor is therefore the best possible estimate when comparing results in patients aged more than 5 years with children below 5 years of age. It then appears that the frequency specific better correlation in individual age groups does get lost and overall just a poor correlation between T-levels and ECAPs can be found.

Objective measures may enable us to predict outcome with a CI. This has been confirmed by our own research work (paper III) and that of other researchers (Lundin et al., 2015, Yamazaki et al., 2015). Our studies (see paper III) have shown no statistically significant correlations between EABR eV amplitudes or latencies and monosyllable scores. However, when speech recognition scores were divided into categories of closed-set vs. open-set, those patients who had an EABR had open-set speech recognition. The primary aim of this study was to determine if intra-operative EABR measurements can be used to predict post-operative speech recognition. Speech recognition is a cortical ability and EABR measurements are responses of the first part of the auditory pathways. It is understandable that the auditory pathways, which do not have measureable responses to electro-neural stimulation, also have poor speech recognition outcomes. This was confirmed by other researchers (Kim et al., 2008).The presence of wave eV in an EABR was a good indicator for outcome prediction in this study as well as in other studies (Gibson et al., 2009, Walton et al., 2008). The amplitude of the response does not seem to be of importance provided there is a measureable response. In these patients, open-set speech recognition is very likely. Gibson and colleagues found a similar result in cases where waves eII to eV were present and their speech recognition categories higher scores (Gibson et al., 2009, Walton et al., 2008).

There are many factors that may influence speech recognition in patients with a cochlear implant. These factors include hearing loss etiology, duration of deafness and environmental factors. Intra-operative measurements can indicate if the electro-neural interface is working well and that responses along the auditory pathway can be evoked electrically (Kim et al., 2008). The patient's hearing history, therapy and patient motivation can also effect outcomes (Janeschik et al., 2013, Blamey et al., 2013, Lazard et al., 2012, Ahn and Lee, 2013, Buchman et al., 2011). The peripheral responses (EABR) measured in this study have demonstrated the potential for re-establishing neural synchrony in the auditory pathways.

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Our study confirms that a synchronous post-operative EABR appears to predict open-set or closed-set speech recognition.

Jeon et al. studied speech recognition ability using categories of auditory performance or the Infant Toddler Meaningful Auditory Integration Scale depending on post-operative EABR responses in ANSD patients (N=11). They found a similar result to ours. ANSD patients with a measureable EABR had relatively good performance after cochlear implantation, but the non-response group had variable outcomes (Jeon et al., 2013). We have more than 20 ANSD patients who have good speech recognition results with a cochlear implant (paper I, (Greisiger et al., 2011)). We studied our ANSD patients with several pre-operative measurements. We obtained ABR, tested for cochlear microphonics and oto-acoustic emissions. Magnetic Resonance Imaging was also carried out before these ANSD patients became a candidate for a CI. Our observations of ANSD patients were confirmed by a study of CI in children with ANSD which showed variable speech recognition abilities in this patient group (Teagle et al., 2010).

Placement of the CI electrode array may also have an effect on EABR responses. Case studies at our hospital have confirmed that there can be large differences in ECAP and EABR amplitude findings following scala tympani (ST) compared to Scala vestibule (SV) insertion. In one case, a bilateral CI user at our hospital had a ST insertion in one ear and on the other side a SV insertion. The eV EABR responses were three times larger following ST compared to SV insertion. This case is explained in section 2.5.1.

Objective measurements can detect, in some cases, that the electrode array has already been displaced during surgery. This has been investigated in our study (paper IV). Unfortunately, this is not always the case. For some measurements, such as ECAP measurements for testing fold-over electrodes, a sufficiently large nerve response is necessary to detect a displacement. Even though an exact displacement cannot be detected, it could be used as an indication that something is not in the normal range. Imaging is then advisable to obtain more information about the electrode placement. FD-CT imaging, intraoperative fluoroscopy and objective measurements are well established into the clinical routine in difficult cases at our hospital. For many patients, successful surgery or re-operation would be less likely without these advanced and improved imaging technologies.

FD-CT scans and fluoroscopy are not used routinely in our hospital, but have been valuable options in technically challenging surgeries such as malformations and ossifications of the cochlea. They require general anaesthesia in children and multi-handicapped patients. The use of FD-CT scan has helped in the evaluation of patients with poor performance. By

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showing the electrode position in detail, the correct position or displacement of the electrode array can be confirmed.

The use of intraoperative fluoroscopy and FD-CT during the last six years has improved the quality of the surgery at our Centre. Fluoroscopy provides an accurate view of how the electrode array moves inside the cochlea during insertion and allows the surgeon to adjust the position accordingly. Intra-operative fluoroscopy can reduce the surgical time because problem areas during insertion can be identified much earlier. Further, the use of intra-operative fluoroscopy may shorten the learning curve of the surgeon when a new electrode model is introduced. The combination of imaging and objective measurements can be of value when systematically registered in a database. In case certain patterns of measurements correspond to the same type of displacement, then such displacements may be detected and resolved. This information can also help with the post-operative programming in patients who seemingly underwent straight forward implantations.

The combination of both CI imaging and objective measurements in CIs has helped in the understanding and resolution of technical problems (see paper IV). Here, an unexpected change in ABR waveform or latency has been found as a detector for a fold-over electrode array. In another case, a delayed nerve response indicated that the electrode array was incorrectly placed.

With help of objective measurements surgical decisions may be made in future already during the surgery of the first CI. This has been raised in the first paper of this thesis (paper I, (Greisiger et al., 2011)). All ANSD children usually receive just one implant. In case the CI use is successful, the patients may receive a second implant sequentially. If a larger patient group confirms that good EABR responses correspond to good speech recognition with CI then intra-operatively the decision can be made for immediately giving the patients with ANSD two implants after good intra-OP objective measurement results with their first CI.

4.2 Conclusion

The main contributions of this thesis can be summarised as follows:

Objective measurements can be used to investigate different aetiologies; this has been performed in a patient group with ANSD. ANSD patients suffer from a dys-synchrony of the nerve fibres and have poor speech recognition. All ANSD patients investigated in our study (paper I) had synchronous stimulation due to the electrical stimulation of the CI and had similar responses to the patient group without ANSD (Greisiger et al., 2011).

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Objective measurements were investigated for predicting programming levels; unfortunately, our dataset in a large population of CI patients (paper II) did now show a satisfactory correlation between programming levels and objective measurements (Greisiger et al., 2015). A benefit of this investigation was that the results from the programming level research revealed differences in the various age groups. Patients above 20 years of age had different programming levels, especially in the high-frequency range. This is perhaps because of the longer duration of deafness in the high- as compared to the low-frequency range. The different programming profiles for the upper- and lower-stimulation levels can be used as a baseline for patients who do not give reliable feedback. In addition, the data can be used in future new electrodes for comparing differences in programming levels.

Objective measurements can be used as a predictor for speech recognition outcome (see paper III). Nevertheless, it is not possible to achieve an accurate estimate for outcome. There is no correlation between monosyllable speech recognition scores and ABR wave V amplitude. Only if there is a detectable ABR is open-set speech recognition possible and vice versa − if there is no ABR then speech recognition is usually poor.

Imaging of CI electrode placement has been found to be highly valuable. In paper IV the imaging procedures to detect the displacement of electrode arrays is explained. The imaging unit has gained important insights into how the electrode array enters the cochlea and what to do if, for example, a full insertion does not seem to be possible. In one case, pulling back, turning the electrode array and then re-inserting it was beneficial. The immediate feedback is sometimes very useful, especially where there is malformation of the cochlea, as otherwise a successful placement of the electrode array is not always possible.

4.3   Recommendation for Future Research

CI technology is still relatively young, developing in Norway in earnest in the 1980s. CI technology represents a highly successful neural prosthesis restoring hearing function to hundreds of thousands of hearing-impaired children and adults. Although implants have a proven, impressive, and extraordinary record, much work still remains to be done. Though the basic components of the implant systems have remained virtually unchanged throughout the years, changes in various aspects of technology have produced increased levels of speech understanding both in quiet and in noisy environments. The variability in performance outcome, however, still remains (Waltzman and Roland, 2014). Criteria change almost every year. A few years ago only patients with no residual hearing were candidates for a CI, but this has now changed. Patients with some residual hearing, for example, in the low-frequency range, can be candidates. This necessitates preservation of the delicate structures

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of the inner ear. The work of this thesis (e.g. paper IV) has given a very good, inside view of what happens while inserting an electrode array into the cochlea. In future, these techniques may be improved to increase preservation of residual hearing in all patients. Different aetiologies (reason of deafness) may have different outcomes. Some are identified as predictors for poor outcome (Miyagawa et al., 2016, Kraaijenga et al., 2015, Eppsteiner et al., 2012, Ahn and Lee, 2013), whereas others show no difference to the normal CI population (reference paper I). In future, aetiology may be used much more as a parameter for predicting outcome and may predict programming levels, as investigated in paper II. Auditory evoked cortical responses have been proven to be a predictor (Sharma et al., 2004), but they can only be carried out whilst awake, which is challenging in small children. The procedure described in paper III is for a method to determine outcome with ABRs. ABRs can already be carried out under anaesthesia during CI surgery. In future, methods may be found to measure cortical responses more easily and may help us to predict outcome with a CI and SP programming. The imaging part of this thesis has been found to be extremely valuable for understanding the electrode array characteristics during insertion; this has helped to significantly improve surgical technique. New projects have already begun using imaging and impedance measurements to determine the insertion angle of the electrode array. Imaging is of extreme advantage if new electrode arrays are used. In general, new electrode arrays become thinner to preserve the inner ear structures, and are more flexible than previous models, which is of benefit to the patient but is an additional challenge for the surgeon inserting more advanced electrodes into the inner ear. Here, imaging can improve the handling of new electrodes and we will continue to use this at our hospital. Radiation exposure has been a topic for every investigation being carried out. Future work must investigate how much exposure is necessary and explore new imaging technologies available that have less radiation exposure. Paper II was intended as the basis for finding algorithms to predict programming levels based on objective measures, but unfortunately, correlations were poor and the predictive power with the use of artificial intelligence was very limited. Nevertheless, there are still ongoing projects to use the gathered data for predicting programming levels. In future, more patient data and additional parameters that affect different programming levels may need to be included to develop systems that can predict programming levels. Improving the surgical procedure has been a much discussed topic at our hospital and robotic surgery may one day be an option for inserting the electrode array more precisely (Williamson et al., 2014, Anso et al., 2016, Zhang et al., 2010). During the last years many interesting research fields have entered the cochlear field. Some interesting approaches are mentioned in the following section.

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Fully implantable CIs have been a goal for many patients and have been in development for many years without reaching release status (Briggs et al., 2008). Placing the microphone under the skin is still a challenge.

Several new approaches for optimising the programming have been investigated, beginning with self-programming and/or a computer-assisted SP (Govaerts et al., 2010, Vaerenberg et al., 2014a, Buechner et al., 2014). Using artificial intelligence to help with programming has been studied by us and other authors (Vaerenberg et al., 2011). Results have been limited so far, but may be more productive with increased patient numbers. A population-based programming approach (van der Beek et al., 2014) may be possible if data from a large number of patients is collected. This could be a Scandinavian project that collects patients' programming data from all CI centres and analyses it according to age, hearing history, duration of CI use, outcome, etc.

Different types of stimulation, such as infrared stimulation, have been studied (Hernandez et al., 2014). Another group has explored the possibility of converting the energy of movement into electrical impulses with the help of piezo elements placed inside the cochlea on the basilar membrane (Inaoka et al., 2011).

Perhaps CIs do not have a future at all? Genetic mutation of hair cells may generate new hair cells and replace damaged ones. This is a regeneration mechanism observed in birds and fish, which researchers have attempted to transfer to humans (Bramhall et al., 2014, Mizutari et al., 2013). Transplantations of the hearing organ might be possible in the distant future as well.

Some of the topics mentioned will not come to fruition over the next few years and we have to work to improve the technologies and options we have to date. Evolution of the CI system is happening now in small steps rather than the giant steps of the first years of cochlear implantation. A smaller SP size and implants at lower energy consumption could be the near future targets. Electrode array placement optimisation using insertion tools may be achievable soon. New sound-coding strategies may increase speech understanding against background noise. SPs may improve with advanced signal processing to emphasise important signals and reduce noise signals. Patients with two CIs and SPs might benefit from the possibility of both processors working together to transfer important signals to both sides simultaneously (Advanced Bionics binaural VoiceStream® Technology).

Overall, the field of CIs offers much exciting study potential in the future. I hope this and my own subsequent research will benefit many CI patients in the years ahead.

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