Improving the Clinical Applicability of Electrophysiological Assessments and Cochlear Imaging in Adult Cochlear Implant Patients

Fadwa Alnafjan

B.Sc, MCAud

Audiology Section, Department of Linguistics

Faculty of Human Sciences

Macquarie University, Sydney, Australia

Thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD)

September 2017

"Improving the Clinical Applicability of Electrophysiological Assessments and Cochlear Imaging in Adult Cochlear Implant Patients"
Macquarie University, Sydney, Australia

Abstract

Cochlear implants (CI) are recognized as the most successful neural prosthesis to date. With the technology and surgical techniques for implantation continually improving, the potential for improved speech perception abilities in individuals with severe-to-profound hearing loss, also increases. While different factors which influence these outcomes have been identified, no consensus exists regarding the degree to which each factor contributes (see Holden et al., (2013)). A major challenge of using speech perception scores to evaluate cochlear implantation outcomes is that understanding degraded (such as vocoded speech from a cochlear implant) speech uses both linguistic and cognitive resources (working memory and attention). Therefore, it is not a sensitive outcome measure for assessing minor technological or surgical modifications for the implant. On the other hand, electrophysiological measures of auditory function, such as electrically evoked auditory brainstem responses (eABRs) could provide a more sensitive measure of the effects of electrode positioning, surgical outcomes, or cochlear neural integrity. However, a robust understanding of how these measures could be used to inform functional outcomes of implantation has not yet been reached.

The research reported in this thesis is based on an online questionnaire data from clinical audiologists working at the Sydney Cochlear Implant Centre (SCIC) in NSW and retrospective datasets collected from the centre, which has a long history of measuring objective responses intra-operatively during cochlear implantation surgery. This thesis firstly explores the current clinical use of these objective measures by the clinical audiologists, then investigates the potential clinical utility of imaging and intraoperative electrophysiological measures in CI to increase test battery efficiency and applicability. Further, this thesis describes a clinically viable tool of measuring cochlear length using Conebeam Computed Tomography (CBCT) with the implant array in situ, providing a more accurate method of

measuring cochlear lengths and thereby provides insights into a variable which influences final electrode placement.

The results of these investigations demonstrate that considerably greater clinical use of the intra-operative measures could be made to increase the efficiency of cochlear implant programming (or mapping) during the switch-on appointment. In particular, the results showed that electrically-evoked auditory brainstem response (eABR) measures are a sensitive tool for predicting CI mapping parameters particularly at cochlear implant "switch-on", although this is negatively affected by poor scalar placement. As such, this thesis demonstrates that CBCT can be used to identify scalar placement within the basal turn of the cochlea, thereby providing greater accuracy of predicting mapping outcomes. Finally, this thesis demonstrates the considerable inter-individual cochlear anatomical variation which highlights the need for a more individualized approach to CI for more consistent electrode placement.

Foreword and Acknowledgements

This work represents a major milestone on so many levels; academically, clinically and personally. Cochlear implants have amazed me from a very younger age and being a part of the Australian Hearing Hub still seemed like only a dream not so long ago. To be able to combine the two by conducting research on cochlear implants at Macquarie University can only be described as a dream come true.

So many have helped me make my dream a reality, and no words could possibly express my gratitude towards them. Firstly, I am profoundly grateful to my principal supervisor Associate Professor Catherine McMahon for providing me with this opportunity. Truly, since the first communication in 2012, you have been a true unwavering pillar of support throughout the whole process of putting this project together from start to finish and for that I am eternally grateful and consider myself extremely fortunate to have you as my supervisor.

This project would also have been impossible without the aid and support provided by my co-supervisor Associate Professor Melville da Cruz. This project was challenging at times, however your constant guidance, encouragement and patience has made it possible. Thank you for making me feel extremely welcome. Your patience in taking me step by step though the surgeries and sharing your immense knowledge has truly made things so much easier for me; you have truly been a source of inspiration.

I would also like to express my heartfelt thanks to my amazing mentor, Dr Isabelle Boisvert, the invaluable help, support and kindness you have provided me, particularly at the beginning of the journey when I felt lost at times and towards the end when I just simply felt like I needed to lean on someone, you were there and for that I am eternally grateful.

Thank you to my amazing daughter, Lynn, you have displayed maturity and patience throughout this process beyond your years. You definitely deserve a standing ovation for

your support. I am extremely lucky to have had the encouragement and glorious love every step of the way from my parents (Fahad and Muneerah), Abdullah, my siblings, my endless nieces and nephews (especially Salwa), and of course Macklemore.

I greatly appreciate and acknowledge the support received from the Sydney Cochlear Implant Centre and from Westmead Hospital. All of the results reported in thesis would not have been possible without their support. I would particularly like to thank Colleen Psarros for taking the time to help me with anything I needed from SCIC. Special thanks to Dr Halit Sanli, as a true mentor, you have always had the patience and time to make the most complex ideas seem so simple and easy.

To Celene and Peter, knowing you're just a phone call away was such a comfort. My gratitude of thanks will never compensate for the contribution everyone I met at the Hearing Hub has put into this project, and the support they provided me. Particularly Kelly and Heivet, you guys were always there even during the speed bumps, you kept me going!

Statement from Author

I state that this thesis has only been submitted to Macquarie University and not to any other university or institution.

The source of information for this thesis is from data collected from Sydney Cochlear Implant Centre and Westmead Hospital (Sydney, Australia).

Signed authorisation has been obtained from both centres.

Ethical review, guidance and approval have been obtained from:

- Macquarie University Human Research Ethics Review Committee.
  No. 5201400407.
- Macquarie University Human Research Ethics Review Committee.
  No. 5201400963.
- Western Sydney Local Health District Human Research Ethics Committee
  No. HREC2014/2/5.1 (3908) AU RED LNR/14/WMEAD/11.

I certify that the original idea of this thesis was to address enquiries from the Sydney Cochlear Implant Centre, in which I have taken leadership to conduct all part of this research work, including writing the content of this thesis. My two supervisors (A/Prof Catherine McMahon, A/Prof Melville da Cruz) have assisted in improving the research protocol, analyses, and interpretation of the data, as well as the quality of the written presentations. Co-authors (Supervisors, Dr. Halit Sanli, Mr Stuart M. Allan) and reviewers of the papers (Dr. Isabelle Boisvert) have helped in improving the manuscripts. I have also conducted the majority of the data collection for this project, with the support of Mr Stuart M. Allan for imaging data from Westmead Hospital.

_____

Fadwa Alnafjan

Table of Contents

List of Tables

List of Figures

Chapter 5 (Manuscript 4)

Chapter 6 (General discussion, results and conclusion)

Appendix

List of Abbreviations

BP: Bipolar

C: Comfort

CBCT: Cone Beam Computed Tomography

CI: Cochlear implant

CG: Common Ground

CT: Computed Tomography

CUNY: City University of New York

DR: Dynamic Range

E: Electrode

eABR: Electrically Evoked Auditory Brainstem Response

eCAP: Electrically Evoked Compound Action Potential

eV: Wave V

eV-NV: Peak to Trough of Wave V

IPG: Inter-phase Gap

IW: Inner Wall

kOhm: Kilohm

MP: Monopolar

MRI: Magnetic Resonance Imaging

MS: Milliseconds

µV: Micro Volts

NIII-eV: Trough to peak of Wave V

NRT: Neural Response Telemetry

OC: Organ of Corti

OW: Outer Wall

SG: Spiral Ganglion

T: Threshold

Chapter 1

Introduction

1.1 Preamble

"If I have seen further, it is by standing on the shoulders of giants." (Isaac Newton, 1675). This statement truly describes the current stages of cochlear implant (CI) technology. From the humble beginnings of placing a blade of grass into a seashell in order to configure electrodes in the cochlea (Cochlear™, n.d.), in which Graeme Clark later remarked: “In spite of the problems and criticisms, I just had to go on. A cochlear implant was their only hope of ever hearing.” Nowadays, CI’s can provide hearing to thousands of individuals with a severe hearing loss. However, while this technology has proven to be successful worldwide, and the indications for CI are constantly growing, a wide variability in speech outcomes is exhibited. As such, many attempts have been made to “stand on the shoulders” of the visionary and inspirational CI pioneer giants to refine the design of the implant and speech processing strategies and to identify the factors which affect speech outcomes. This thesis aims to examine the clinical utility of intraoperative electrophysiological measures and imaging techniques which are currently used to verify electrode placement within the cochlea.

Imaging and intraoperative electrophysiological tests that are performed to provide information on the integrity and position of the array, the integrity of individual electrodes within the array and determine whether non-auditory (i.e. facial) stimulation is present which may compromise the quality of the outcomes for the patient. However, across clinics worldwide there is no consensus to which method or combination of tests optimises the outcome for the individual. Importantly, consideration must be given to balancing the use of surgical time and resources while avoiding redundancy with the ultimate aim of predicting and/or optimizing outcomes.

While different clinics have different test batteries and protocols which are set at their discretion, this thesis addressed queries for a large clinical program which has one of the most extensive test batteries available. Through investigating the costs and the current use of these tests and finding future directions to recommend modifications and/or further training, this thesis explores an evidence-based cost-effective and clinically relevant test protocol.

1.2 Background

Since the first reports of the perception of sound through electrical stimulation by Alessandro Volta in the 18th century, in which he created a circuit by placing metallic rods into his ears which produced an unpleasant sensation with a crackling sound (Volta & Banks, 1800), the electrical stimulation of the auditory nerve for management of deafness has overcome many hurdles. From its first crude applications in the mid-19th century, in which several devices were manufactured using electrical current with the promise of remedying a wide range of pathologies including deafness (Shah, Chung, & Jackler, 1997), it was a century later that the first reports of direct stimulation of the auditory nerve emerged. In 1957, Djourno and Eyriès implanted a single electrode on the stump of the auditory nerve of a patient after cochlear removal (Eisen, 2003). That patient reported been able to discriminate high and low frequencies but could not perceive speech.

While Djourno and Eyriès's endeavours were aborted due to device failure, their attempts pioneered the development of the implant, such as the single electrode cochlear implant (CI) by William House in 1972. This was the first CI device to obtain Food and Drug Administration (FDA) approval for perception of environmental sounds and possible assistance in lip-reading in 1984 (Blume, 1999). However, it was realized that different parts of the cochlea needed to be stimulated in order to achieve robust speech discrimination, and so a multichannel array was soon after developed (Clark & Hallworth, 1976). This allowed

for stimulation of different areas of the cochlea in accordance with the tonotopic map, with which a combination of advancements in speech processing strategies, led to better speech discrimination.

Since this time, CIs have become the management of choice for profoundly deaf individuals who achieve limited benefit from hearing aids. It is the most successful neural prosthesis developed to date, with currently over 300,000 people implanted with a CI, which exceeds the number of people implanted with any other neural prostheses (e.g. spinal cord stimulator (Kumar, Caraway, Rizvi, & Bishop, 2014)). The device is comprised of a behind-the-ear sound processor and an electrode array system that is implanted within the cochlea by surgery. The electrode array is made of platinum-iridium and silicone, the electrodes are made of highly conductive, corrosion resistant material. The array consists of up to 22 electrodes, which "substitute" the function of the 3000 inner hair cells which stimulate the 30,000 primary afferent nerve endings in the inner ear (Wilson & Dorman, 2008).

Ideally, each electrode would be in close proximity with only a small number of primary afferent dendrites (proximal nerve endings) to maintain good frequency (or spectral) resolution and increase dynamic range while decreasing current consumption. However, the electrodes stimulate spiral ganglion cells rather than the dendrites which degenerate after hair cell loss, presumably due to the loss of a neurotrophic factor and electrophonic responses provided in the physiologically "normal" cochlea by the intact inner hair cells and their supporting cells (M. Sato, Baumhoff, Tillein, & Kral, 2017; Zilberstein, Liberman, & Corfas, 2012). Therefore, as the number of spectral bands is limited by the number of functioning electrodes, and the number of surviving spiral ganglion cells can affect an individual's perception of speech, it is necessary to make use of each of the electrodes to maximize the electrode-neural interface in order to optimize speech perception outcomes.

It is likely that more experienced surgeons are able to achieve complete insertion of the array and maintain array integrity. However, as the number of candidates for cochlear implant is rising, as well as the number of clinics and surgeons performing the surgery, a robust way of measuring these factors and taking into account the individual variability may guide developments in electrode design, improvements in surgical techniques, and patient counselling. Current implant arrays are designed with a "one size fits most" in terms of array length and width, which does not take into account the variability of surgical technique and cochlear anatomy that may influence the electrode placement within the cochlea and ultimately could affect speech perception outcomes. A more individualized approach may assist in limiting these variabilities and/or predicting a person's outcome and guide the best programming approach. In order to obtain a better understanding of speech perception outcomes with a CI on an individual level, a review of: (i) the individual variables that may influence their performance, (ii) along with the speech perception measures used to assess outcomes should be carried out.

1.2.1 Innovations in CI array design and surgical techniques and effects on outcomes

To improve cochlear implant outcomes, considerable work has been dedicated to maximising the positioning of the electrode array towards the modiolus to increase the electrode-neural interface and provide higher stimulation selectivity. As well as controlling for factors which may influence outcomes, such as insertion depth while reducing surgical trauma that may be caused during the array insertion process (Iso-Mustajärvi et al., 2017; Jiam, Jiradejvong, Pearl, & Limb, 2016; O'Connell et al., 2016, 2017). The electrode array is inserted in the cochlea during an intricate surgery and then evaluated upon insertion, providing information about electrode placement, integrity of the array, and the functionality

of individual electrodes. Intraoperative tests and imaging techniques provide information about insertion depth and electrode array integrity and, after the implant has been switched-on and programmed, performance is typically measured using speech perception tests. To maximise the flexibility of the electrode array in order to optimise modiolar positioning, the thin diameter of the array (which, for example, in the Cochlear Nucleus CI24RE ranges from 0.4 mm at the apex to 0.6 mm at the base) is susceptible to disruption during placement, particularly if structural abnormalities in the cochlea exist which may complicate the insertion process (e.g. cochlear ossification and malformations). This could result in a loop, bend or kink within the array itself upon insertion, or an incomplete insertion of the array in which some of the electrodes would be situated outside of the cochlea thereby reducing the spectral resolution of the array and the options for subsequent mapping (programming of the external speech processor) and rehabilitation. Further, while there are ongoing improvements in electrode array designs for optimal placement, the process requires greater surgical precision.

Several researchers have investigated different variables which may influence implantation outcomes in an attempt to maximise or better predict individual outcomes. While there is no consensus of which factors contribute, nor their level of contribution, Cosetti and Waltzman (2012) broadly grouped these into; implant-related factors (e.g. electrode design), patient-related factors (e.g. etiology of hearing loss), coexisting morbidity (e.g. autism), patient environment (e.g. socioeconomic status and family support), audiological factors (e.g. duration of hearing loss and preoperative speech perception), and anatomical factors (e.g. structural cochlear abnormalities). Poor positioning of the array within the cochlea has been identified as one of the many variables which has a negative effect on outcomes (Holden et al., 2013; Van Der Marel, Briaire, Verbist, Muurling, & Frijns, 2015). Holden et al. (2013) investigated the different factors which might influence open set

speech recognition on 114 post-lingually deaf adults, including those which could not be controlled (e.g. age at implantation, cognition) and those which might be (e.g. surgical approach, array position; insertion depth and mediolateral proximity). While Holden et al. (2013) found that all factors contributed to CI performance, after controlling for age, *only scalar position and insertion depth* were significant and, had the largest effect size. In a smaller study sample, Holden and colleagues (Holden et al., 2016) investigated similar factors in a subsequent study of 39 implanted adults, while controlling for array type (perimodiolar array) and electrode position (i.e. scala tympani placement confirmed using computed tomography). In this cohort, the mean word recognition score in quiet of 76%, which was higher than other studies, only age and spectral resolution were significantly correlated with speech recognition outcomes, whereas neither duration nor the magnitude of the pre-operative hearing loss were significant. The investigation by Holden et al. (2016) highlights the effect which electrode position has on outcomes, where the high speech recognition scores in quiet could partially be attributed to the consistent optimal positioning of the array regardless of other factors that may negatively influence outcomes.

1.2.2 Validity of the low reported rates of poor electrode positioning

Although it is recognised that surgical skills, surgical approaches and techniques for cochlear implantation are diverse, the increased reported rate of complications (Causon, Verschuur, & Newman, 2013; Tambyraja, Gutman, & Megerian, 2005) appear to be primarily the result of infection rather than structural positioning of the array, and electrode migration remains a leading indication for revision surgery apart from device failure (Wang, Wang, Psarros, & Da Cruz, 2014). Studies show the rate of surgical complications (including electrode placement) have not changed, despite the assumption that they might decrease due to developments in electrode design and surgical techniques over the past decades, or

increase due to the expanding inclusion criteria including patients with cochlear structural abnormalities. It is possible that the number of misplaced electrode arrays are under-reported in databases as these typically do not result in compromised patient safety, and only those electrode arrays placed outside the cochlea lead to poor patient-reported outcomes or unexpected sensations (Foulad & Djalilian, 2010; Ying, Lin, Oghalai, & Williamson, 2013). The Manufacturer User Facility and Distributor Experience (MAUDE) database is an example of a resource which has been used in reports of CI complications, however while it is acknowledged as a useful source for trend analyses, limitations such as mandatory reporting only in cases affecting patient's life or health could lead to unreported cases of more minor complications (Causon et al., 2013; Tambyraja et al., 2005).

Incorrect positioning of the electrode array is reported to occur in 1.2% of overall implant surgeries (Hoffman & Cohen, 1995), in 0.3% of patients implanted with Nucleus 22® (Kubo, Matsuura, & Iwaki, 2005) and in 13% of patients that required revision surgery (Lassig, Zwolan, & Telian, 2005). Yet even with postoperative imaging, techniques such as CT and X-ray are insensitive to subtle malpositioned electrode array (i.e. scalar translocation). The mismatch between the stable reported rate of surgical technical complications and current research focused on surgical techniques and electrode designs to enable more precise positioning of the electrode array, may suggest that greater refinement to imaging techniques and electrophysiological measures is required to detect more subtle disruptions to electrode position and its effect on patient outcomes.

1.2.3 Limitations in the use of speech perception measures

Certainly, the typical outcome measure for cochlear implants is open set speech recognition, and has been the main driver for the development of a multichannel array and the resultant speech coding and signal processing strategies (such as Advanced Combination

Encoder, Continuous Interleaved Sampling, Spectral Peak, and HiResolution Fidelity 120) (Choi & Lee, 2012; Chouard, 2015; Wolfe & Schafer, 2014). Speech perception measures are typically used as the primary outcome measure of CI benefit, but these are limited by ceiling effects, language effects and cognitive influences (Carlyon et al., 2005; Gifford, Shallop, & Peterson, 2008; Holden et al., 2013; Lassig et al., 2005). Speech perception tests are routinely performed at regular intervals, from the first programming session (referred to as "switch-on") throughout subsequent programming (i.e. mapping) appointments. The time needed for the client to obtain a stable map is based on subjective issues of how the client perceives the sound, their preferences and tolerance, which are determined by subjective measures, including speech perception performance.

However, while there has been rapid development in CI technology, the outcome measures used to assess benefit have not changed substantially, and this has led to individuals reaching ceiling effects within the first few months, limiting the opportunity to assess any change over time (Ebrahimi-Madiseh, Eikelboom, Jayakody, & Atlas, 2016) (Figure 1.1). The candidacy for cochlear implantation is also constantly revised and expanded to include patients who would otherwise not have met the implantation criteria due to relatively high pre-operative aided speech perception scores (Amoodi et al., 2012). Speech recognition tests are probably not sufficiently sensitive for this population. For example, Amoodi et al. (2012) reported that 30% of implantees included in their study reached a ceiling of speech perception performance, thereby underestimating the progress achieved.

Therefore, there is a need for an assessment measure that is sensitive enough to measure auditory benefit while controlling for linguistic and cognitive factors. Such a measure would prove beneficial in more accurately identifying and quantifying the variables that affect outcomes, which could lead to better individualization of the cochlear implantation process.

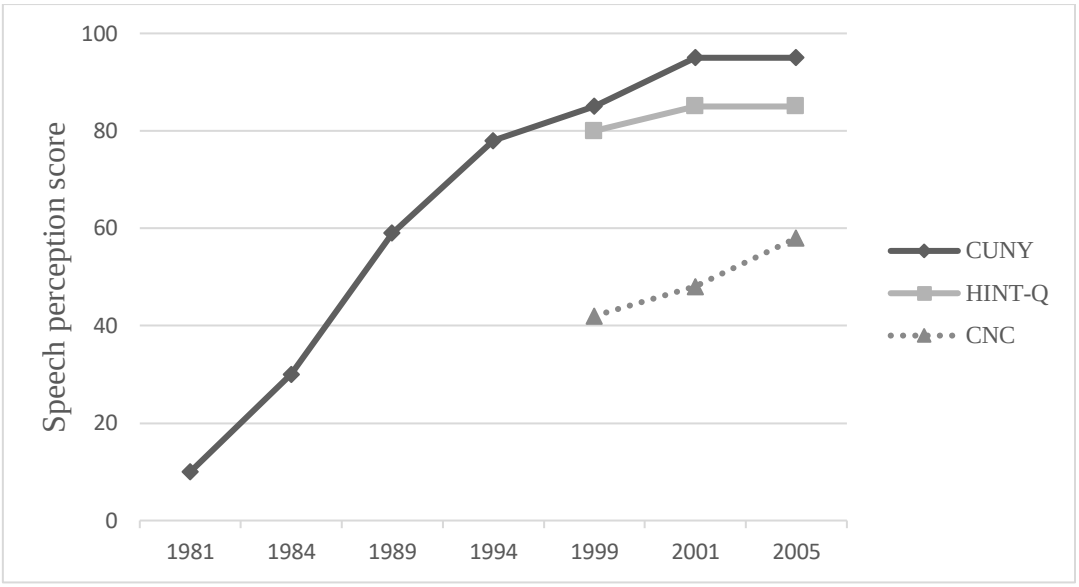


Figure 1.1. Trends towards ceiling effects on CI performance outcomes from early 1980's to 2005. This improved performance is attributed to improvements in electrode technology and signal processing over time. Mean scores for CUNY and HINT sentences in quiet, and CNC monosyllabic words (Huart & Sammeth, 2009).

1.3 Use of objective measures in evaluating CI outcomes

A current focus of cochlear implantation research using animal models of deafness is to understand how existing electrophysiological measures can be used to more sensitively quantify neural or cochlear integrity, or identify sites-of-lesion. This knowledge could ultimately be used to better predict and improve CI outcomes in humans. An example of this includes studies which have investigated the use of manipulating phase duration and inter-phase gap (IPG) on the amplitude of the electrically-evoked Compound Action Potential (eCAP) and electrically-evoked Auditory Brainstem Response (eABR) of deafened guinea pigs, as a measure of the extent of the effect of auditory deprivation on spiral ganglion integrity and correlated this with histological measures of spiral ganglion neural survival (Prado-Guitierrez, Fewster, Heasman, McKay, & Shepherd, 2006; Ramekers et al., 2014). As correlations between neural survival and changes in IPG exist, Ramekers et al. (2014)

suggested that this may have clinical applications in the future, although the high levels of electrical current required may limit this.

However, debate exists in literature regarding the current use of intraoperative electrophysiological tests, particularly in informing CI programming parameters. While there is no dispute that using an objective measure such as eCAP's is useful especially with clients whose subjective measures could not be obtained (i.e. paediatrics), there are conflicting reports as to the degree in which they can be relied on to inform on CI programming and predict outcomes. For example, Cosetti et al. (2010) found no correlation between the presence of eCAP intraoperatively and speech perception scores in both adults and children. Similarly, Brown et al. (2000) and Lo, Chen, Horng and Hsu (2004) could not find a strong correlation between objective measures and programming settings, in both children and adult populations. The authors recommended using objective measures alongside behavioural information for CI programming. Conversely, upon dichotomously categorizing intraoperative eCAP results as "present" or "absent", Guedes et al. (2007) found a strong correlation with speech perception in adults, but not in children. While there are no conclusive findings on the use of objective measures to predict CI outcomes, they provide valuable information intraoperatively regarding device integrity and the response of the auditory system to electrical stimulation. Many electrophysiological tests are clinically available, yet there is no consensus regarding the most effective test battery that should be used intra-operatively. While the inclusion of multiple tests at each CI surgery may not be time nor cost-effective, applying a minimum test battery to verify the integrity of the implant may neglect cases that require surgical adjustments leading to a negative impact on outcomes and/or leading to revision surgery.

The intraoperative tests performed during CI surgery are a battery of electrophysiological measures and imaging studies used to assess function and placement of

the device immediately after insertion of the electrodes. Different CI clinics have different test protocols during surgery as each test serves its own purpose. These tests include; impedance testing, Neural Response Telemetry (eCAP) thresholds, Electrical Auditory Brainstem Response (eABR), electrode artefact measures and cochlear view X-ray. Some of the tests used appear to give redundant information and others are based on assumptions that may not have been appropriately tested.

Electrode Impedance Testing

Electrode impedance testing shows the resistance characteristics of the electrode-tissue interface to determine the energy consumption from the implant (Guedes et al., 2005). Measuring the electrical resistance of the intra-cochlear electrodes permits the identification of short or open circuits within the array; however, it does not provide information regarding the spread of current throughout the cochlea or the physiological functioning of the auditory pathway. It may be used to compare changes over time; however, decisions solely on impedance measurement results should be made with caution. Impedances are usually low at time of surgery due to the presence of only fluids around the interface, but increases a few weeks later due to the formation of fibrous tissue around the electrodes as a reaction from the immune system (Hu et al., 2017). While this test is a commonly used method to examine device integrity, as it is rapid and allows monitoring for changes, false positive responses may occur, as an impedance measurement may be normal in a case of misplaced insertion (e.g. in the eustachian tube or the vestibule) (Ying et al., 2013) or in cases of incomplete insertion of electrodes due to the presence of fluids in the middle ear from the surgical procedure. This would postoperatively indicate an open circuit (Hughes, 2013), which may be confirmed by X-ray or eABR, if these tests are done as part of a clinical test battery. On the other hand, false negative measurements are also a possibility as 82% of intraoperative

open circuits resolve by switch-on due to presence of air bubbles at time of surgery (Hughes, 2013).

Electrically Evoked Compound Potentials

eCAP's is a bi-directional telemetry recording of the electrically evoked action potential and is the electrical correlate of Wave I of the auditory brainstem response; it is one of the most frequently used objective measurements of auditory neural activity. As eCAP's are an early latency response (wave I), it requires separation from the stimulation artefact, and therefore, each CI manufacturer has a different algorithm in order to separate the response from the stimulus. The first human neural responses were successfully obtained with Cochlear© devices in August 1996 (Lai, 1999), which the software is referred to as Neural Response Telemetry (NRT), and thus the name may be used interchangeably with eCAP for the purpose of this thesis. ECAP's are widely used to predict Threshold (T) and Comfort (C) levels of electrodes during speech processor programming (Shallop, Facer, & Peterson, 1999). However, there is no consensus as to its reliability in such predictions, Di Nardo, Ippolito, Quaranta, Cadoni, and Galli (2003) found that 72% of the eCAP's fall within the map dynamic range and suggested it is a valuable clinical tool for information on the integrity of the implant and the condition of the peripheral auditory nerves. Smoorenburg, Willeboer, and Van Dijk, (2002) and Hughes et al. (2001) showed that the contour of the eCAP's were significantly correlated with the shape of the T levels contour, but were not correlated with the shape of the C-level contour. On the other hand, Cosetti et al. (2010) found that eCAP's provided valuable intraoperative information regarding the implant function, the response of the auditory nerves to the electrical stimulation and initial programming data. However, no correlation was found between eCAP responses and speech perception outcomes and was therefore a poor predictor of performance. However, in a later investigation, Cosetti et al. (2012) reported malpositioned electrodes in 5 (1.8%) of cohort of

277 cochlear implantees, four of which presented with normal eCAP's, however tip rollover was confirmed by imaging. The fifth case reported was implanted in the superior semicircular canal and presented with an absent eCAP on one electrode, however the eCAP remained absent after correcting for placement using the backup device. The authors further report four cases with absent eCAP with optimally placed electrodes, confirmed by imaging. These findings indicate the unreliability of using eCAP as an indirect measure to verify electrode placement, which is currently a widely accepted practice in many clinics.

Electrical Auditory Brainstem Response (eABR)

eABR's reflect the functional integrity of the neurons from the cochlea to the auditory brainstem and is a measure of the synchronous neural responses (described by waves I to V) elicited by the bipolar electrical pulse, shown as a series of discrete waves. Wave I is usually obscured by the larger overlapping electrical output of the implant, however, waves II-V are typically visible following a 10 ms window of response averaging approximately 1000 to 2000 sweeps without the need for special methods to separate the artefact from the response, unlike eCAP's which require a smaller number of sweeps (50-100) as they are intra-cochlear recordings, however require processing to extract the response from the artefact. Wave V is the most robust (i.e. best signal-to-noise ratio) and is commonly used to estimate threshold, although the mode of stimulation and current level used with eABR intraoperatively can differ to the mode of stimulation and current level when a CI is used (Gibson, Sanli, Psarros, 2009). Intraoperatively, the current levels can be altered to either detect threshold (Said Abdelsalam & Afifi, 2015) for research and/or to assist with CI programming, or at higher supra-threshold levels (Pau, Parker, Sanli, & Gibson, 2005) to rapidly verify placement, exclude facial nerve stimulation with switch-on (or indicate the best stimulation mode in cases with facial nerve stimulation) and confirm auditory neural response to electrical stimulation to the level of the brainstem in a clinical setting.

Investigations have reported the use of eABR as a prognostic measure for CI performance (Gallégo, Frachet, Micheyl, Truy, & Collet, 1998; Gibson, Sanli, & Psarros, 2009; Guevara, Hoen, Truy, & Gallego, 2016; Y. Wang, Pan, Deshpande, & Ma, 2015), and indicated poor eABR traces may lead to poor CI performance outcomes (Lundin, Stillesjo, & Rask-Andersen, 2015; Walton, Gibson, Sanli, & Prelog, 2008). Yamazaki, Leigh, Briggs, & Naito (2015) found in conjunction with MRI, eABR is a valuable tool in predicting performance outcomes for patients with cochlear nerve deficiency. Other reports found a correlation between eABR and CI programming (Brown, Abbas, Fryauf-Bertschy, Kelsay, & Gantz, 1994; Ciprut & Akdas, 2007; Psarros, Bate, Berry, & Sanli, 2010).

However, as with eCAP's, there is no uniform agreement regarding the correlation between eABR and CI programming levels. Aubert and Clarke (1994), reported eABR as a poor predictor for CI programming due to the difference between the slow pulse rate used in intraoperative eABR and the faster pulse rate used with CI. Makhdoum, Snik, and van den Broek (1997) reported that there is a wide variation of the eABR thresholds within an implantee's dynamic range and should therefore be used with caution for programming of the device. Jeon et al. (2013) found variable results with the use of eABR as a prognostic tool, as subjects with poor traces showed improvement in auditory performance. Nonetheless, when comparing eCAP with eABR, Mason (2004), found eABR to be a valuable tool with comparable results to eCAP, despite only testing one electrode for eABR as opposed to various electrodes for eCAP. Mason (2004) also reported eABR is a more sensitive measure than eCAP, despite eCAP being more time efficient and not requiring external electrodes. Minami, Takegoshi, Shinjo, Enomoto, & Kaga (2015) reported advantages to eABR's over eCAP's, as eABR's can be collected from all types of implants, while eCAP's can only be measured from implants with telemetry capabilities. While the majority of modern implants have telemetry capabilities, eABR recordings can be obtained in cases in which stimulus

artifacts renders eCAP measurements unobtainable (e.g. modiolus deficiency cochlea) (Minami et al., 2015).

Electrode Artefact Measures

Stimulus current artefact measures is a test that was developed at the SCIC which has a comprehensive intraoperative test battery. There is scarce literature regarding this test which can be defined as the projection on the measurement plane of the electric fields set up by the stimulating electric current in the cochlea, in which the measurement plane is defined by the measurement electrodes (i.e. inverting input electrode, non-inverting input electrode, and the reference electrode). It is assumed to verify electrode integrity, insertion depth and identifies kinks, bends and loops in the electrode array by detecting abnormalities upon an expected pattern which results from the test.

Multi-channel CI's electrical current configuration can be directed between the intra-cochlear and the extra-cochlear electrodes, therefore different stimulation modes can be used to deliver the current to the auditory nerves (i.e. Common Ground (CG), Monopolar (MP), and Bi-polar (BP)). While the default mode for stimulation is MP1+2, different modes can be chosen taking into account the power consumption as well as the current levels required to achieve adequate loudness. In MP mode, the current runs between an activated intra-cochlear electrode and either one or both of the extra-cochlear electrodes (i.e. MP1, MP2, or MP1+2) as the return, while the current in BP stimulation mode is between two adjacent intra-cochlear electrodes (an active and a return), and in CG mode the current flows from one activated electrode while the other intra-cochlear electrodes are shorted as the return (Figure 1.2).

EABR's are measured in all three modes, however, Artefact Measures are measured only on CG and BP+2 modes, where BP+2 projects an electrical field of electrodes between two electrodes, while CG mode projects an average of the intra-cochlear electrodes. Therefore, while CG can identify if there is an abnormality along the array, BP+2 can more

accurately identify the location of the array. Artefact measures are not measured in MP1+2 mode as the area projected is much larger and therefore abnormalities along the array would be too small and would not be portrayed on the resulting projected pattern. However, as is the case with eABR, artefact measures require external electrodes and are therefore susceptible to noise and electrical artefacts.

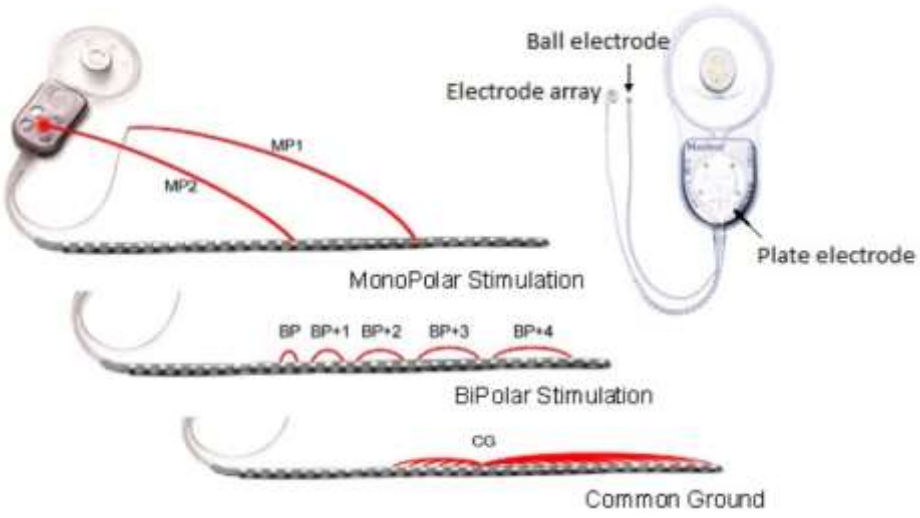


Figure 1.2. Stimulation modes of the electrical current in multichannel CI's (Seligman, 2007).

Imaging

Imaging is used in many clinics to verify electrode placement, insertion depth, and identify kinks, loops and bends within the array. While electrophysiological measures may be used to indirectly indicate array placement, imaging is a more accurate measure of placement verification. Intra-operative imaging is yet to be part of a routine clinical test battery. Several studies have explored the benefits of allowing surgeons to reposition the array intraoperatively however, this is outweighed by the increase in time and the costs associated with including it as a routine protocol. Copeland, Pillsbury and Buchman (2004) reported negligible benefit of intraoperative imaging as it has led to an intraoperative surgical decision

in only one of 79 cases. Meanwhile, Cosetti et al. (2012) concluded that imaging had the most impact on intraoperative surgical decisions.

The majority of clinics perform imaging postoperatively compared with intraoperatively; to verify placement and ensure complete insertion of the array. While in cases of displacement, performing imaging postoperatively does not allow the surgeon to alter placement without another surgery, displacements are important to identify in order to program the implant accordingly, predict outcomes and in some cases explant and reimplant.

While preoperatively CI candidates undergo computed tomography (CT) and/or magnetic resonance imaging (MRI) to rule out any middle or inner ear anomalies that may lead to an alteration in the surgical approach to avoid surgical challenges such as cerebrospinal fluid gusher or injury to the facial nerve (Vogl et al., 2015). Recent reports however debated the cost effectiveness and necessity for preoperative imaging in post-lingually deaf adults in the absence of trauma and discussed preserving pre-operative imaging to specific cases such as asymmetrical hearing loss (Choi & Kaylie, 2017). Postoperatively however, performing MRI is a relative contraindication as it carries a risk of device displacement and/or damage due to the magnetic field and is therefore not performed routinely unless indicated (e.g. cases of sequential bilateral cochlear implantation when first implant MRI is not sufficient for surgical planning, or cases where imaging of the brain is required for diagnosis of other neurological conditions) with precautions (Broomfield, Da Cruz, & Gibson, 2013). CT images are obscured by the metal artefact from the electrodes and therefore is not a straight forward procedure and would require composition to remove the artefact. Despite these limitations, visual inspection of the array *in-situ* is essential to fully understand the impact of array placement as a variable in CIs, therefore different imaging techniques have been described in literature.

Conventional X-Ray (modified Stenver's view)

While this method has been widely used due to the clarity of the images of the array within the petrous bone, it is a single image and does not provide 3D representation of the cochlea, indirectly providing information regarding the electrode placement within the cochlea from the array configuration (Arweiler-Harbeck et al., 2012). Therefore it is a useful tool for indicating insertion depth and possible tip rollovers or kinks (Cohen, Xu, Xu, & Clark, 1996; Cosetti et al., 2012; Fayad, Luxford, & Linthicum, 2000; Xu, Xu, Cohen, & Clark, 2000). Reports have indicated electrode insertion depth may affect speech perception outcomes, Yukawa et al. (2004) reported imaging is a more sensitive indicator than surgeon's perception of insertion depth, as imaging can detect angle which is the best depth related predictor of speech perception outcomes.

Xu, Xu, Cohen and Clark (2000) argued that CT scans are not used routinely, and are reserved for when complications arise due to its limitations (discussed later). Therefore Xu et al. (2000) developed a specific projection utilizing a conventional skull radiography to provide a clear and direct image of the array in order to evaluate insertion depth and electrode positioning, which may provide valuable information for CI programming, this technique was named the cochlear view x ray. Carelsen et al. (2007) argued in order to determine array placement more precisely, a 3D representation of the array *in-situ* is required, which the conventional x-ray scans do not provide. As the 2D nature of the conventional X-ray images could result in possible false positives in cases of anatomical anomalies and false negatives in cases of extra-cochlear unfolding. The authors therefore developed a technique to produce 3D images via the reconstruction of x-ray images collected intraoperatively. While this technique would overcome the main fault of this imaging procedure by providing 3D reconstructions, the radiation exposure of 225 mAs was higher than the radiation exposure using Xu et al. (2000) technique of 80 mAs, the method as well adds 15 minutes to

surgery time to apply. While this technique is associated with less cost and reduced radiation exposure, newer technologies provide clearer images in shorter durations. This is particularly important as current electrode placement studies however require more precise placement detail in relation to the cochlea structures such as scalar position which cannot be directly identified with this imaging technique.

Computed Tomography

As discussed, CT images have not yet been performed routinely due to metal artefact which affected image quality and obscured individual electrode visualization, therefore it was reserved for cases with complications. Skinner et al. (2007) developed a technique which was later validated by Teymouri, Hullar, Holden, and Chole (2011), which enabled a clear visualization of the array *in-situ*, overcoming the metal artefact created by the electrodes. The technique consisted of creating a composite image with the use of a pre-implant CT for anatomical information and a post-implant image for electrode position details. While this method has been used in many studies since then (DeVries, Scheperle, & Bierer, 2016; Holden et al., 2013, 2016; Long et al., 2014), its capacity to be used routinely in a clinical setting is limited due to high radiation concerns, therefore this method is mainly used for research and education purposes.

However, this limitation is overcome with the introduction of Cone-Beam CT (CBCT) to temporal bone imaging, as it has enabled the three-dimensional high-resolution visualization of the individual electrodes without the noise contamination from the metal and at a lower cost. The clarity of the images allows the study of the different structural dimensions of the cochlea with the array *in-situ* (e.g. cochlear length, width, electrode array position) (Lathuillière et al., 2017; Saeed et al., 2014; Würfel, Lanfermann, Lenarz, & Majdani, 2014; Zou, Lähelmä, et al., 2015).

1.4 Individualisation of cochlear implants

An individualized cochlear implant approach could take into consideration each factor that may influence outcomes on a case-by-case basis preoperatively, intraoperatively and postoperatively, and such an approach may control the large variability in CI outcomes. This wide variability could be partially due to the number of surviving spiral ganglion cells (Prado-Guitierrez et al., 2006), as the number of neurons stimulated by each electrode is influenced by the electrode-neural proximity as well as the spiral ganglion survival pattern along the cochlea (Mistrík & Jolly, 2016). While position of the electrode is recognised as a factor that influences outcomes (Holden et al., 2013; O'Connell et al., 2016, 2017; Skinner et al., 2002; Wanna et al., 2015), which can be verified by objective measures and imaging as discussed earlier, it would be of necessity to identify the factors that may influence the final placement of the array within the cochlea;

(i) The electrode design, stiffness, dimensions and length (straight vs peri-modiolar).

(ii) The anatomical variations in cochlear length and dimensions.

(iii) The surgical technique and insertion force/trauma.

While all factors are of equal importance, the anatomical variations is the only factor that cannot be controlled for, however acknowledgment of the scope of inter-individual variations could have an impact on electrode design and the surgical technique, which may lead to more individualization of the implantation process. One particular aspect of the anatomical variation of the cochlea is the length, in which existence of inter-individual variations have been documented since the 19th century by Retzius (1884) long before CIs. It has been continued to be investigated due to the wide variation in reported measurements, along with advancement in imaging technology and measurement techniques with the aim of better accuracy.

The inter-individual variability of cochlear length identifies it as a factor, As this cannot be controlled for, it should be investigated further to be considered upon electrode array selection, as the insertion of the array should aim to be deep enough to access the apical neural portions of the cochlea, while not too deep as to cause cochlear trauma and jeopardize residual hearing. This is particularly important as previous reports found a weak correlation between insertion depth and speech perception outcomes (Lee, Nadol, & Eddington, 2010), other more recent studies demonstrate the impact of insertion depth on speech perception outcomes when controlling for scalar position (Holden et al., 2013; O'Connell et al., 2016, 2017). Insertion depth is dependent on both electrode array length and cochlear length (Yukawa et al., 2004), therefore, to obtain a better understanding of cochlear length, accurate measurements at an individual level is needed to demonstrate the inter-individual variability in cochlear anatomy. This may allow it to be identified as a factor when choosing optimal electrode array length during implantation for more consistent array insertions and placement, which may lead to better speech perception outcomes. Furthermore, recent advancements in imaging technology which provide clear images and eliminate metal artefact, has enabled the development of an accurate method to measure cochlear length *in-vivo* using the array as a reference measure within the cochlea without the need to composite images from pre- and post-implant. This is particularly of importance given that majority of previous cochlear length investigations were performed *in-vitro* (Adunka, Unkelbach, Mack, Radeloff, & Gstoettner, 2005; Erixon, Ho, Wadin, & Rask-andersen, 2009; Erixon & Rask-Andersen, 2013; Koch, Elfarnawany, Zhu, Ladak, & Agrawal, 2017; Pochini Sobrinho, Lazarini, Yoo, Abreu Junior, & Meira Ade, 2009; Singla, Sahni, Gupta, Aggarwal, & Gupta, 2015; Takagi & Sando, 1989; Würfel et al., 2014).

The length of the cochlea has been extensively researched due to the implications it may have on CI outcomes. However there is a wide variability in reported lengths, which

may be influenced by the different measurement modalities (e.g. histology, plastic casts, different imaging techniques; Erixon et al., 2009; Meng, Li, Zhang, Li, & Qin, 2016; Stakhovskaya, Sridhar, Bonham, & Leake, 2007; Yu, Lee, Wan, & Peng, 2015). Individual variability may also contribute to the variability displayed between different investigations (Würfel, Burke, Lenarz, & Kraemer, 2015) which emphasizes the need for an accurate measuring technique. Therefore, the development of a method which is clinically applicable *in-vivo*, utilizing advanced imaging techniques which enabletheuse of the array in-situ as a reference point, could provide greater accuracy aboutthe maximum and minimum cochlear lengths of the human cochleae as well as their variability.

1.5 Study Rationale

Debate exists regarding the most effective test combination to confirm electrode array placement and electrode integrity while minimising surgical costs and duration of anaesthesia. Carelsen et al. (2007) stated that intra-operative neurophysiological tests are not conclusive of the electrode placement and imaging of the electrode array can facilitate its optimal placement. Viccaro, Covelli, de Seta, Balsamo, and Filipo (2009) emphasize the importance of imaging during surgery, as they found that intra-operative electrical stimulation is an indirect method of determining electrode placement and imaging is the option of choice to confirm placement. However, electrophysiological measures give an indication about the synchronous neural activity of the auditory nerve and brainstem to the stimulated arrangement of electrodes. This information may be used to guide the programming of the implant or to support counselling at switch-on. Cosetti et al. (2010) found that impedance testing and ECAP are sufficient to assess the integrity of the CI device and confirm correct intra-cochlear placement of the electrodes.

Despite the diversity of the test protocols used in different CI clinics, these test batteries are, to some degree, based on expert opinion and are set at the discretion of the

surgeon or surgical team. The intention of this research is to understand the benefits of imaging and intra-operative cochlear implant testing performed in multiple clinics from retrospective intra-operative and post-operative data from a large clinical dataset. Specifically, we aim to:

(i) Understand the clinical utility of eABR (measured using a monopolar stimulation mode with a fixed current level and pulse width) as a measure of neural integrity, and as a function of electrode array position;

(ii) Increase the accuracy of measuring cochlear length using the implanted electrode as a measuring "ruler", visualised in the basal cochlear turn using CBCT;

(iii) Make recommendations about a more streamlined test battery (i.e. to minimise the overlap of the number of electrophysiological tests performed while maximizing clinical information which may, ultimately, be used to predict functional outcomes.

This project will offer a better understanding of the current use and information provided by the intra-operative electrophysiological tests conducted during cochlear implant surgeries in order to utilize them more efficiently. This project will offer a better understanding of the current use and information provided by the intra-operative electrophysiological tests conducted during cochlear implant surgeries in order to utilize them more efficiently.

Risks and Ethical Issues

Because this project was based on retrospective data and no direct patient contact was required, there was only a low risk related to confidentiality. This risk was addressed by de-identifying patients with complete data sets and storing the information on a secure password protected database which contained no identifiable information. The study involved looking at de-identified data for population based trends and not individual results. Confidentiality of

data was strictly adhered to and maintained throughout the whole course of the study including write up and publication.

Chapter 2

Cost and reported benefits of electrophysiology testing during cochlear implant surgery

Introduction

Pre-operative radiological evaluation for cochlear implantation enables surgeons to make informed decisions about whether medical or surgical contraindications exist, the type of device and surgical approach which should be used, and the side of implantation to select, particularly for congenitally deaf candidates who are more likely to display structurally abnormal cochleae (K. J. Choi & Kaylie, 2017; Tamplen, Schwalje, Lustig, Alemi, & Miller, 2016). As such, the benefits of radiological evaluation before implantation are clear to the process of decision-making about whether to, or how to implant. During or just at the end of implantation surgery, electrophysiological evaluations can also be done to verify the position of the electrode array *in situ*, the integrity of the implant electrodes, and the electrical responsiveness of the auditory pathway. These intra-operative evaluations are suggested to provide predictive information for implantation outcomes, guide MAPping strategies (eg. identifying open or short-circuit electrodes), and help identify individuals who may require supplementary rehabilitation to gain full potential with their implants (Oghalai et al., 2009; Pau et al., 2005; Psarros et al., 2010; Raghunandhan, Ravikumar, Kameswaran, Mandke, & Ranjith, 2014; Yamazaki et al., 2015). However, it is unclear to what extent the information obtained intra-operatively is used to guide or inform clinical practice, and whether the benefits of these intra-operative assessments outweigh the time and resource costs to warrant their inclusion in a standard clinical procedure. To date, there has been little published information assessing the costs and benefits of intraoperative electrophysiological testing, which would justify the costs spent (resources and time) against the information these tests

provide. Such analyses could enable recommending the most appropriate test battery for each specific case (e.g. postlingual vs prelingual deafness or cochlear anomalies).

Measuring the costs of different procedures or interventions and weighing them against the benefits they provide is important to support hospitals and clinical settings when allocating resources and/or developing guidelines and policies. Based on the fact that the number of elective surgeries in Australia have increased by 2.4% per year from 2010 to 2015, and that 99% of ear and mastoid process related procedures performed in 2015-16 were an elective admission (The Australian Institute of Health and Welfare, 2017), it can be assumed that the number of CI surgeries, being elective, are also steadily increasing. This increase is supported by clinical data (Figure 2.1).

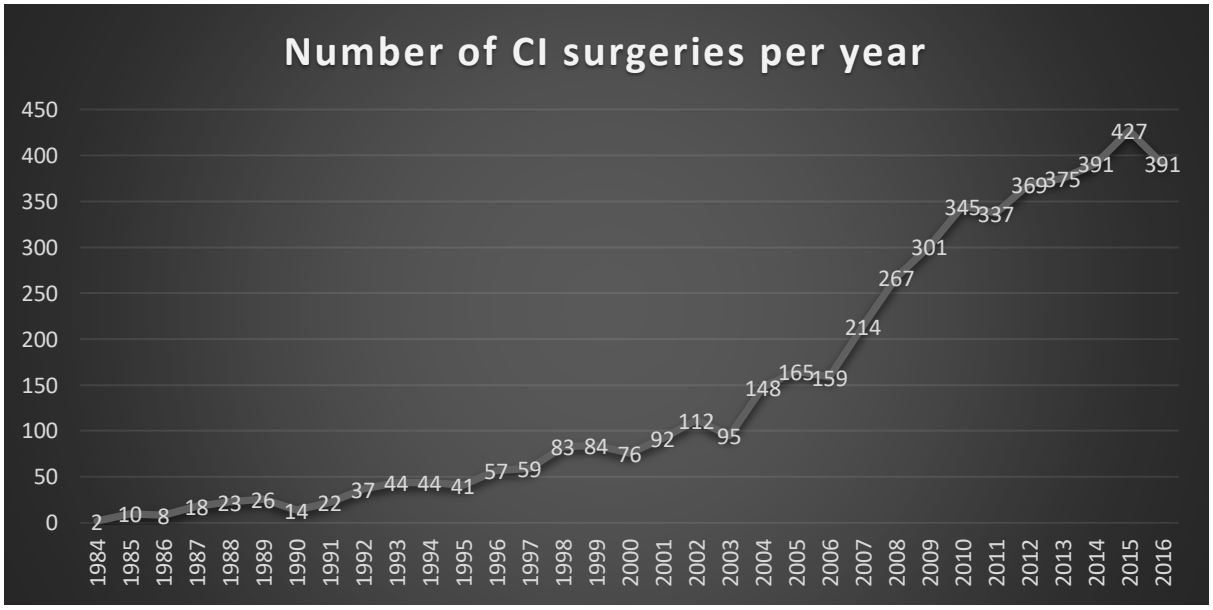


Figure 2.1. Number of CI surgeries at SCIC. Source: Data from SCIC.

In the CI published literature, there are some studies that have assessed intervention costs, for example demonstrating a cost reduction with the use of local anaesthesia in comparison to general sedation for CI surgeries (Hamerschmidt, Moreira, Wiemes, Tenório, & Tâmbara, 2013; Svrakic, Pollack, Huncke, & Roland Jr., 2014), or how alterations in the use of specific

intra-operative tests (e.g. eCAP) could reduce testing time and ultimately theatre time (Shapiro, Huang, Shaw, Roland, & Lalwani, 2008; Tavartkiladze, Bakhshinyan, & Irwin, 2015; van Dijk et al., 2007). The scientific literature, however, lacks evidence to support the best type of resources and test protocols that should be performed during CI surgery to maximize benefits while minimizing time spent in theatre. Intraoperative testing protocols are therefore established at the discretion of each clinic with no uniform test battery.

Operating theatres costs per minute vary greatly based on the country and the surgical procedure being performed. While the average expenses per minute of operating theatres in NSW has never been precisely characterized (NSW Agency for Clinical Innovation [ACI], n.d.), it was estimated in 2013 that operating theatre cost an average of AUD$42 per minute, which are covered by the Australian Government and private health insurance funds (Hamilton & Oorloff, 2014; NSW Health, 2013). Despite not clearly stated, this estimate appears to exclude surgeon and anaesthetists costs, given that an older report from USA (Shippert, 2005) found that per minute operating theatres cost an average of US$62 and an additional US$4 for anaesthesiologist professional fee (total of US$66) excluding surgeon costs. Shippert (2005) found that this figure had inflated 210% over 14 years since 1991, which suggests that the figure provided above for NSW's is only an estimate which may have increased over the past four years given that the overall cost of surgery in Australia has increased from AUD$19,030 in 1991 (AUD$ 17,030 device cost and AUD$2000 procedure cost) (Lea, 1991) to AUD$30,000 in 2016 (approximately AUD$26,000 device cost and AUD$4000 procedure cost) (WSLHD, 2016). Foteff et al. (2016) reported a cost of AUD$34,621 for a unilateral CI surgery (AUD$25,000 device cost and AUD$9,621 for surgery and direct costs including imaging, hospital bed, pharmacy, nursing, ect.). While the majority of the cost relates to the CI device, an estimate of theatre costs per minute in Australia for a surgery without complications (approximately 105 minutes) with a complete

objective test battery amounts to $AUD38 (calculations based on AUD$4000 procedure cost). Given that 391 implant surgeries were performed at SCIC in 2016, this would amount to $AUD14,858 per year for every minute of surgical time. In other words, a reduction of 5 minutes of testing during theatre time could equate to savings of approximately $AUD75,000 yearly for that clinic.

CI intraoperative testing protocols are also usually performed under general anaesthesia, for which the risks and outcomes, affected by patient's age and general health, should not be neglected (Dietz, Wüstefeld, Niskanen, & Löppönen, 2016; Holman MA, Carlson ML, Driscoll CLW, Grim KJ, Petersson RS, Sladen DP, 2013; Strøm & Rasmussen, 2014). A search for costs of anaesthesia in NSW showed that there is no standard scale of fees for anaesthetists (Australian Society of Anaesthetists, 2016). However, while other international reports show that the price of the anaesthesia is relatively small compared to the overall price of surgery, reducing the amount of time a patient is under anaesthesia without affecting the quality or effectiveness of care could only be beneficial.

The quality of health care should never be compromised, however it should also not be valued by the quantity of services provided (Porter, 2010). An analysis of the intraoperative electrophysiological tests should consider first and foremost the outcomes of these tests (i.e. information they provide and how they are used), as any procedural policy changes that occur as a result should primarily be to eliminate any redundancy or unused material provided by these tests. This outcome focus would benefit the patient by reducing anaesthesia time while maintaining health care quality and efficiency, and any cost reduction as a result would be secondary.

Mason (2004) emphasized the importance of developing a scientifically valid evidence-based electrophysiological (EP) test protocol to use in conjunction with experienced technical skills

to maximize the clinical effectiveness of implants, however that suggestion has resource and cost implications. A number of electrically-evoked potential measures, as well as electrode impedance measures (used to assess the resistance to electrical current flow) have been used intra-operatively and post-operatively for over 25 years at SCIC as part of a standard clinical test protocol. Specifically, the typical CI intraoperative test battery at this clinic during these years included impedance measures, electrode artefact measures using two different CI stimulation modes (common ground [CG], and bipolar [BP]+1), electrically-evoked compound action potential (eCAP), and electrically-evoked auditory brainstem response (eABR) in three different modes (CG, BP+1 and monopolar [MP1]+2), followed by imaging post-operatively to assess the position of the implant in the cochlea.

INTRAOPERATIVE ELECTROPHYSIOLOGY TESTS	DURATION (MINUTES)
IMPEDANCE	0.5
NRT	5
EABR MP1+2 MODE	3
EABR AND AM IN CG MODE	3
EABR AND AM IN BP+2 MODE	3
TOTAL	14.5

Table 2.1. Estimates of time required to conduct each test intraoperatively for Cochlear® implants (reported by the principal biomedical engineer conducting the tests at this clinic). NRT, neural response telemetry; AM, artefact measures; CG, common ground; BP+2, bipolar; eABR, electrically evoked auditory brainstem response; MP1+2, monopolar (durations exclude setup time).

Given the time needed to complete these tests (Table 2.1), it appears appropriate to assess the extent to which the results are used, or could be used, to guide surgical decisions (e.g. immediate explant of a faulty device and re-implantation with a new device) and the later programming of the CI. While a systematic cost-benefit analysis of this protocol is warranted to inform future practices, the limited scale of the data currently available provides only an opportunity to address clinical research questions potentially encountered globally in CI clinics. As a first step in that direction, the aim of this study was to gain a better

understanding of how clinical audiologists presently interpret and use the intra-operative electrophysiological tests results, post-operatively.

Methods

A 13-item questionnaire designed to investigate the perceived benefits as well as the extent to which audiologists utilize intra-operative electrophysiological data in their clinical practice post-operatively, was sent to all clinical audiologists at SCIC (N=20). The questionnaire classified the audiologists into two groups; those who use the information from electrophysiological tests and those who did not. We aimed to gain knowledge from those who used the data in their clinical sessions to determine: (i) which tests are used most often; (ii) the type of information that is derived from these test results and how that information is used; and (iii) whether there is any specific information that they would like to know more about in relation to these tests (see Questionnaire in the appendix).

From the audiologists who reported not using the intra-operative test data, we aimed to understand: (i) the primary reasons behind their lack of use of the test results; and (ii) what information they would like to know about these tests, particularly in cases where a shortage of training is indicated. Approval was obtained through the Faculty of Human Sciences Ethic Committee at Macquarie University.

Survey Results

Response rate

A return rate of 85% was achieved with 17 clinical audiologists responding to the questionnaire. All respondents reported they used at least one of the intraoperative EP tests to some degree, however 35% (n=6) used the information only at the initial CI switch-on session, while 65% (n=11) used the information at subsequent appointments (Figure 2.2).

While a set of questions were addressed to clinicians who reported not using EP tests, none of the respondents reported within that group, therefore the results displayed in this section are of the questions addressed to those who do use EP test results.

Figure 2.2. Proportion of clinicians who reported using the information from intra-operative test results only at time of switch on (Yes) and clinicians who reported using results at subsequent appointments (No).

Tests used

Audiologists were asked to select all the tests results that they use from a list of 7 intraoperative EP tests available at their clinic: impedance, neural response telemetry (NRT – measuring the eCAP), artefact measures in CG mode, artefact measures on BP+2 mode, eABR in CG mode, eABR in BP+2 mode and eABR in MP1+2 mode. One audiologist reported only using one test results (NRT), while 41% (7 audiologists) reported using all 7 tests, the remaining nine reported using varying combinations of the test results.

The majority (94%) reported using impedance and NRT measures, that is, only one audiologist reported not using impedances, and only another audiologist reported not using NRT measures (Figure 2.3). Both measures combined were reported by 88% of the respondents. Following this, the two most common measures reported to be used were eABR's on MP1+2, and on CG modes, both at 59%.

Twenty-nine percent of the respondents reported using only impedance and NRT data. Two audiologists (12%) reported using eABR results without using the artefact measure results, however none of the respondents reported using the artefact measure results without using the eABR data.

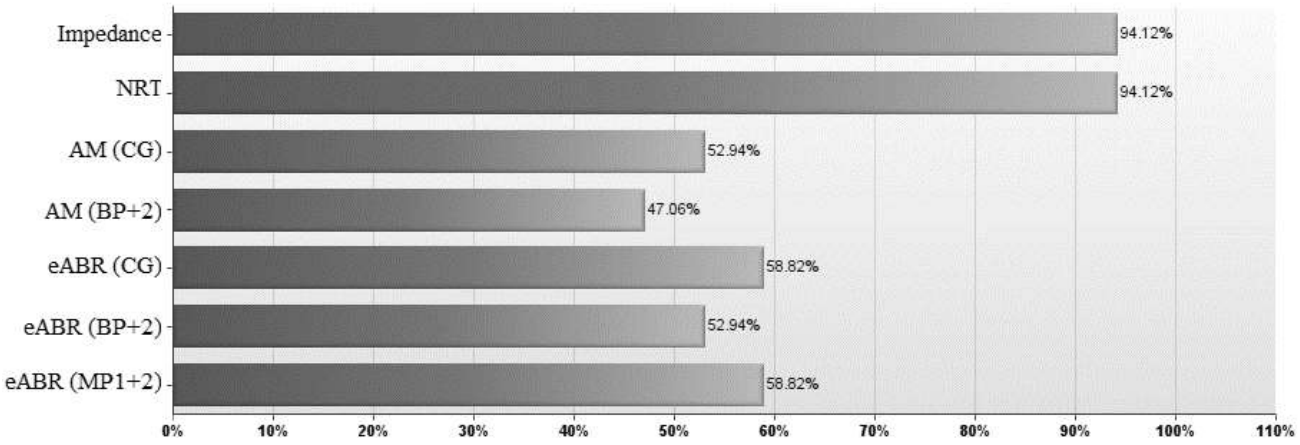


Figure 2.3. Percentage of clinicians reporting the use of each test. NRT, neural response telemetry; AM, artefact measures; CG, common ground; BP+2, bipolar; eABR, electrically evoked auditory brainstem response; MP1+2, monopolar.

Test usefulness

Respondents were asked to rate each test based on their opinion of its clinical usefulness on a scale of 1 (very useful) to 5 (not at all useful). NRT obtained the highest score with 70.6% of audiologists giving it a score of one, followed by eABR MP1+2. NRT was also the only test that was not scored below three, while other test scores varied from one to five (Table 2.2). One respondent did not score the tests at all, while 23% only scored impedances and NRT's. The usefulness between the different modes of eABR results differed as well, with 29% allocating MP1+2 a score of one (very useful), while BP+2 and CG were given a score of one by a smaller proportion of respondents (18% and 12% respectively). Artefact measures in

both modes scored the lowest in perceived usefulness, as only one respondent gave it a score of one, and the majority gave it a score of three.

POST-OPERATIVE CLINICAL USEFULNESS
RANKING OF INTRA-OPERATIVE TEST RESULTS

TEST/SCORE	1	2	3	4	5	Mean Score	SD
NRT	12 (70.6%)	2 (11.8%)	1 (5.9%)	0	0	1.27	0.6
IMPEDANCE	9 (53%)	2 (11.8%)	2 (11.8%)	2 (11.8%)	1 (5.9%)	2.00	1.4
EABR (MP1+2)	5 (29.4%)	2 (11.8%)	4 (23.5%)	0	1 (5.9%)	2.17	1.3
EABR (BP+2)	3 (17.6%)	2 (11.8%)	4 (23.5%)	2 (11.8%)	1 (5.9%)	2.67	1.3
EABR (CG)	2 (11.8%)	3 (17.6%)	4 (23.5%)	2 (11.8%)	1 (5.9%)	2.75	1.2
AM (CG)	1 (5.9%)	3 (17.6%)	4 (23.5%)	2 (11.8%)	2 (11.8%)	3.08	1.2
AM (BP+2)	1 (5.9%)	2 (11.8%)	5 (29.4%)	2 (11.8%)	2 (11.8%)	3.17	1.2

Table 2.2. Audiologists' ranking of the usefulness of electrophysiological tests using a scale of 1 (very useful) to 5 (not at all useful). NRT, neural response telemetry; AM, artefact measures; CG, common ground; BP+2, bipolar; eABR, electrically evoked auditory brainstem response; MP1+2, monopolar.

Clinical utility of tests

Of the 17 respondents, 12 reported using EP tests to verify implant integrity and electrode placement. Respondents were asked to select from a list all the uses that applied to the EP test results, and were also given the option to write other uses. Only 4 of the 17 audiologists reported using EP test results to predict client speech perception outcomes (Table 2.3). While 59% of respondents reported using the results for counselling, one clinician commented:

"*Very rarely use in counselling or expectations - only when electrophysiology has been extremely poor and have used to explain and prepare client for difficult/disappointing SO*"

Other uses reported by the audiologists were:

"*Verify measured T levels and decide whether to alter them (usually lower them).*"

"*MAP verification ONLY if unable to repeat NRT at switch on*."

"*Compare modes of stimulation for non-auditory responses to guide programming options*."

"*I use NRT at switch on to make an objective offset map and then do a behavioural map at week 1, I use artefact measurements to get general idea if how CI is placed in the cochlea, I use MP1+2 to assess general response to electrical stimulation and how this may affect their outcomes.*"

REPORTED USAGE OF TEST RESULTS	NUMBER OF RESPONSES (%)
COUNSELING	10 (59%)
PREDICT CLIENT SPEECH PERCEPTION OUTCOMES	4 (23.5%)
CREATE THE CLIENT MAP - ESTIMATE T AND C LEVELS	13 (76.5%)
SETTING REALISTIC CLIENT EXPECTATIONS	10 (59%)
VERIFY IMPLANT INTEGRITY AND ELECTRODE PLACEMENT	12 (70.6%)
OTHER	3 (17.7%)

Table 2.3. Post-operative usage of intra-operative test results as reported by audiologists.

Further training

The majority (94%) reported they would use the tests more if they had a wider knowledge about their applicability. One clinician commented: "*I don't have a good understanding of the eABR and artefact measures. However, the report summary often gives a poorer indication of outcomes than are actually achieved.*" The comments generally indicated that while there is a report included with the EP results, its usefulness to support clinical practice was questioned, and the lack of knowledge about the clinical usefulness and interpretation of eABR and artefact measures could act as a barrier for using the results to their full potential. These results suggest that increasing clinical knowledge about these tests could further support clinicians during programming sessions.

Discussion

While intra-operative EP tests may be more relevant to surgeons than to clinicians by providing information on electrode integrity and position, this study suggests that audiologists find these results clinically applicable during post-operative clinical sessions. Different combinations and/or uses of the information provided by these tests were reported. When developing a minimal intra-operative test battery, care should be taken to minimize redundancy in the information provided, which would unnecessarily prolong surgery time, while maximizing the tests' clinical utility by providing adequate training to the audiologists using them post-operatively.

Overall, all respondents reported using EP test results at switch on and over half reported using them at subsequent programming sessions, which indicates that the perceived clinical utility of these tests expands beyond the surgical setting. While all respondents reported using these tests in varying combinations, the majority (94%) use NRT and impedance measures. If taking into consideration the amount of time required intraoperatively to conduct each test at this clinic (Table 2.1), over half of the time taken to perform these tests were for results not used beyond surgery by over a quarter of the clinical audiologists.

The amount and combination of tests that are conducted intra-operatively differ from clinic to clinic and sometimes within the same clinic, as shown in Table 2.4, due to time restraints and/or protocol. At this clinic, the protocol suggests that when artefact measures are not conducted, the test battery usually only consists of measuring impedance, NRT's and eABR's in MP1+2 mode as it is the default mode used for cochlear implants (personal communication with Dr H. Sanli, biomedical engineer at SCIC). Without measuring the electrical artefacts, the EP testing protocol time can be reduced by a minimum of 6 minutes. Considering that

nearly half of the respondents reported not using the artefact measures post-operatively, an assessment of their clinical utility is warranted.

INTRA-OPERATIVE TEST BATTERIES	DURATION (MINUTES)	ESTIMATE COST PER SURGERY	ESTIMATE COST PER YEAR (2016)
1) IMPEDANCE + NRT	5.5	AUD$209	AUD$81,719
2) IMPEDANCE + NRT + EABR (MP1+2 MODE)	8.5	AUD$323	AUD$126,293
3) IMPEDANCE + NRT + EABR WITH ARTEFACT MEASURES (3 MODES)	14.5	AUD$551	AUD$215,441

Table 2.4. Different intra-operative test batteries with estimated clinical costs per year based on average cost of $38 per minute and number of surgeries per year at SCIC.

CI Electrical artefact measures have been developed and used at this clinic to provide an indirect method to verify the placement of the CI electrode array in the cochlea. Analysing the pattern of electrical artefacts created by stimulating each individual electrode is suggested to be helpful to rule out the presence of any loops, kinks or tip-over folds within the implanted array. This can be done before completing the surgery and waking up the patient. However, immediate surgical revision is not performed routinely in such cases due to the risk of further cochlear trauma, as opposed to more severe array misplacement positions (i.e. vestibule, Eustachian tube, semicircular canal) which may have a more serious impact on outcomes and can be detected by impedances, NRT and/or eABR (Pau et al., 2005; Ying et al., 2013). In cases where CI electrical artefacts are not measured intra-operatively, loops, kinks or tip-over folds would only be detected with imaging techniques used post-operatively. This technique was developed to provide information about electrode array placement during surgery while minimizing exposure to radiation that accompanies more widespread imaging techniques such as Stenver's projections.

While this study suggests that intra-operative test results are not utilized to their maximum clinical potential, 15 of the 17 respondents indicated they would use the information more if more advanced training was provided on their clinical applicability. Clinicians mostly commented regarding the applicability of the artefact and eABR measures and how to read the traces, while the only comment on NRT was to imply that further training may identify cases that require the complete test battery or a subset of the tests. While the majority of clinicians reported using the test results for counselling and to estimate threshold (T) and comfort (C) levels, some mentioned relying only on the EP report summary. Others however, indicated that the EP report was not an accurate indication, and requested more training in reading the eABR and artefact measures' original traces to be able to combine their interpretations of the traces with the report summary. Only one clinician indicated using the results for counselling in cases in which traces were poor, to prepare the client and adjust their expectations. Insight on accurate result interpretation could lead to a broader and more routine use of the information, for example providing guidance even if traces are not clearly absent.

Despite the small number of participants included in this study, it captured the responses of the majority audiologists in one of the largest CI centres in the world, where reportedly, the most extensive intra-operative EP test battery is performed. From this study, it is clear that there are inconsistencies in the use of the test results and that different clinicians have different opinions about their applicability. Only one clinician commented that the results could be used to guide programming when non-auditory responses (i.e. neural facial stimulation) are present in the traces with the MP1+2 mode. Detecting non-auditory stimulation intra-operatively and using this information to guide programming could reduce the amount of time to stabilize the CI MAP and accelerate the client's acclimatization to the sound provided by the device. A large proportion of questions provided by the clinicians

regarded the correlation of these tests with outcomes, for example how these tests could help predict performance with the CI, particularly for clients with compromised nerves, and the difference in intraoperative test results and applicability for clients with and without congenital deafness.

Because the original scope of this study regarded the use of the EP test results post-operatively, this survey only targeted clinical audiologists. It would however, be informative to conduct a similar survey with CI surgeons to further understand their use and interpretation of the intra-operative EP tests results. While it is commonly known that these tests provide information on placement and function of the implant, and that these can provide reassurance on the surgical success for the surgeon as well and the patient and their family, there is conflicting reports as to the test protocol that should be used and the extent to which the results would influence surgical decisions at time of surgery (Khater, Moustafa, said, & Fahmy, 2015; Mason, 2004; Page et al., 2017).

There is a need for the implementation of an intra-operative test battery across clinics within an evidence-based framework. However, this is complicated by the lack of consensus in literature as to the best test battery, with clinics setting testing protocols based on the needs of each particular clinic (i.e. availability of professionals to conduct detailed testing, amount of theatre time allocated to each surgery, and equipment availability).

This study indicates that a greater and more efficient utilization of the information provided by these tests is possible. A directly implementable solution would be to eliminate redundancy and provide more practical training for clinicians to further understand the results and their applicability. To do this effectively, however, further studies are required to fully assess, validate, cost and compare the information provided by the clinically available intra-operative EP tests. This would support the design of a more appropriate test battery based on

normative data, and the development of evidence-based guidance in order to interpret and apply the results in a more consistent manner.

Chapter 3

Developing a method for assessing the integrity of electrically-evoked auditory brainstem response (eABR) measures

Fadwa F. Alnafjan, MCAud*[1,2,3,4], Catherine M. McMahon, PhD[1,2], Halit Sanli, PhD[4,5], Melville Da Cruz, FRACS MSc MD[3,4];

[1]Macquarie University, Sydney, Australia, [2]HEARing Cooperative Research Centre, Melbourne, Australia, [3]Dept. of Otolaryngology, Westmead Hospital, University of Sydney, Sydney, Australia, [4]SCIC Cochlear Implant Centre – a service of RIDBC, Sydney, Australia, [5]Royal Prince Alfred Hospital, Sydney, Australia.

Abstract

Electrically-evoked auditory brainstem responses (eABRs) is an objective measure of neural response that is widely used peri-operatively in cochlear implantation surgery, although its clinical utility is yet to be fully explored. This study aimed to compare the effects of using different methods of calculating wave eV amplitude (a common marker of the eABR response) while controlling for stimulation pulse width and amplitude. Further, this study assessed whether the eV amplitude is affected by the stimulus artefact, structural/neural integrity, and whether it is associated with subsequent cochlear implant mapping parameters.

Study Design: Fifty "normal" adult eABR waveforms collected intraoperatively were analysed retrospectively to obtain normative amplitude values for the apical (electrode 20), mid (electrode 11) and basal electrodes (electrode 3) of the cochlear implant array, using three different methods of measuring wave eV amplitude. Amplitudes were analysed for the influence of artefacts (electrical and facial nerve) and neural excitation (i.e. the distance between the electrode array and neural elements as related to the use of straights versus peri-modiolar electrode arrays). Amplitudes were correlated with mapping T and C levels as a functional outcome. To evaluate the influence of neural integrity on the eABR response, 37 eABR waveforms of adults with diagnosed Large Vestibular Aqueduct Syndrome (LVAS) were compared to the 50 waveforms from structurally normal cochleae.

Results: No significant difference was found between the different methods used to calculate eV amplitude. A significant difference was found for modiolor proximity at the mid electrode only. A significant difference was found between the eV amplitude of the LVAS and the control group at the apical region. A strong correlation was found between eV amplitude measured intra-operatively and the mapped T- and C- levels at switch-on. The strength of this relationship decreased at subsequent test times.

Conclusion: Intra-operative eABRs can provide a sensitive measure of neural integrity and a sufficiently accurate estimation of mapped T- and C-levels at switch-on, regardless of the method used to measure eV amplitude.

Introduction

Multiple factors can affect auditory performance in post-lingually deaf adults after cochlear implantation (see Blamey, Arndt, Bergeron, & Bredberg, 1996 for a review). As technology evolves with the development of new implant arrays and electrical stimulation paradigms, and pharmacological therapies with cochlear implants are combined and evaluated in animal models and human clinical trials (Auris Medical AG, 2015; Konerding et al., 2017; Plontke, Götze, Rahne, & Liebau, 2017), greater precision in assessing neural integrity and enhanced imaging techniques are needed to evaluate the benefits of such interventions. Auditory performance is typically assessed using speech perception tests and, while this remains an important clinical measure, both linguistic and cognitive ability can influence the outcomes (Best, Keidser, Freeston, & Buchholz, 2016; Cox & Xu, 2010), thereby reducing the sensitivity of the measure for cochlear interventions. Certainly, considerable individual variability in speech performance outcomes continues to be observed that is yet to be fully understood. On the other hand, focal electrical stimulation of the auditory neurones from the intra-cochlear electrodes of the implant could provide information about the integrity of the spiral ganglion neural population (Hall, 1990; Pfingst, Zhou, et al., 2015; Ramekers et al., 2014), the distance between the cochlear implant and the neural elements (Runge-Samuelson, Firszt, Gaggl, & Wackym, 2009; R. K. Shepherd, Hatsushika, & Clark, 1993; Telmesani & Said, 2015), and neural refractoriness (Pfingst, Hughes, et al., 2015; Ramekers, Versnel, Strahl, Klis, & Grolman, 2015). However, the clinical utility of intraoperative electrically-evoked auditory brainstem responses (eABRs) has yet to be fully explored.

Yamazaki, Leigh, Briggs, & Naito (2015) explored the diagnostic utility of combining eABR with magnetic resonance imaging (MRI) to predict outcomes immediately after cochlear implantation for cases of cochlear nerve deficiency (CND, i.e. hypoplasia and aplasia of the cochlear nerve). Within this study, the current level and pulse width was systematically

varied until a distinguishable eABR waveform was identified (specifically wave V > 0.15μV and 3.8-5.0 ms latency) which demonstrated characteristic behaviour of a neural response with increases in current. Other studies have demonstrated the role of eABR with an intracochlear "test" electrode in cases of CND to determine whether to implant a cochlear implant or auditory brainstem implant (Cinar et al., 2017). Similar stimulation protocols in adults (Kubo et al., 2001) and children (Mittal et al., 2015; Y. Wang et al., 2015), obtaining eABR thresholds and an amplitude growth curve, have shown significant correlations between eABR thresholds and measures of auditory performance in children, eABR thresholds and psychophysically obtained thresholds (T-levels) in children and adults, as well as amplitude growth curves with speech reception scores measured 1 month after implantation in adults.

eABR is an objective measure which is used clinically to evaluate the integrity of the auditory pathway from the cochlea to the inferior colliculus (Hughes, 2013) and remains a long established tool with thresholds more sensitive than eCAP thresholds (Mason, 2004). Its uses have been extensively researched. These include assessing cochlear integrity and cochlear response to electrical stimulation (neural integrity) before implantation, as well as evaluating intra-operatively electrode integrity, the effectiveness of the implant in situ and determining whether facial nerve stimulation occurs. Further, the intra-operative responses could also indirectly indicate correct positioning of the array and facilitate the monitoring of potential post-surgical changes and provide preliminary device programming data. eABR measures have already been established as a useful tool in the process of programming the cochlear implant device as it can be used to estimate the magnitude of electrical current necessary when programming particularly for young children or individuals for whom behavioural testing is not possible (Brown et al., 1994; Ciprut & Akdas, 2007; Raghunandhan et al., 2014). Both waveform morphology and magnitude are important in these evaluations,

as any abnormality along the auditory pathway may cause latency delay or amplitude decrease, yet no consensus for assessing these factors have been defined in the literature, as different studies have calculated the amplitude of wave V (eV) differently (Gordon, Papsin, & Harrison, 2007; Walton et al., 2008; Yamazaki et al., 2015).

Comparisons between the eABR amplitude, using a fixed current level and pulse width, and speech perception ability in children has been assessed previously (Gibson et al., 2009; Walton et al., 2008). Specifically, a grading method, based on the amplitude of the eABR waveform (either wave eII, III or IV/V) was developed and compared with functional performance after 1 or 2 years post-implant. In that study, functional performance was assessed using a scale from 1-7 which broadly categorises children's speech perception ability from detection of speech sounds only through to good open set speech perception ability (>50% phonemically scored Phonetically-Balanced Kindergarten words). However, the limitations of this method are two-fold. First, the Gibson et al. method graded each of the 22 electrodes based on a fixed amplitude of 0.5 μV, whereas it has been demonstrated that the amplitude of the eV is dependent on the position along the cochlea whereby, at least in children, more apical electrodes have a larger amplitude compared with basal electrodes. For example, Gordon et al. (2007) demonstrated that eV amplitudes measured at initial device activation from the apical electrodes showed a mean amplitude of 1.18μV (SD 0.56) compared with a mean amplitude from basal electrodes of 0.81μV (SD 0.42). Therefore, more subtle differences in neural integrity may not be observable using this paradigm. Second, scores across each of the 22 electrodes are added, however, neural integrity can be affected differently across the cochlea and may have differing effects on speech perception outcomes. Lundin, Stillesjo, & Rask-Andersen (2015), modified this classification method to grade each waveform by wave V latency only and not amplitude. The authors justified the modification to better reflect location within the cochlea, as latency changes are smaller than

amplitude changes across the array. However, unlike Gibson et al., no correlations were found with this classification and speech perception outcomes.

As wave eV amplitudes are relatively large at the apical end and systematically decrease in size towards the basal end (Gordon et al., 2007), it is necessary to evaluate the impact of using different methods of calculating eV amplitude while controlling for electrode site within the cochlea (apical vs mid vs basal), stimulation pulse width and current level. Establishment of normative data would allow the further study of the electrophysiological responses in known pathologies in order to better explain and/or predict outcomes.

This study aims to further refine such a grading method using specific electrodes along the implant array, corresponding to an apical, mid and basal position, and to obtain normative data for further classification of eABR waveforms. Further, this study aims to investigate the extent to which artefacts affect waveforms, as one disadvantage of eABR reported in literature is the requirement of external electrodes, which makes measurements susceptible to stimulus based electrical artefacts (Guedes et al., 2005). Finally, the study aims to investigate the amount to which intra-operative eABR contributes to predict functional performance for cochlear implant users. To do this, this study compares responses obtained from subjects with structurally normal inner ears, with responses obtained from subjects with large vestibular aqueduct syndrome (LVAS). While gross structural abnormalities of the cochlea (such as Mondini's dysplasia) can lead to the use of different electrode arrays and surgical procedures to position the array. It was assumed that more subtle abnormalities of the cochlea such as isolated LVAS present with post lingual hearing losses, are implanted with comparable electrode arrays, and rehabilitated in the same way as anatomically normal inner ears, as LVAS is associated with normal development of auditory skills and better pre-operative pure tone thresholds (Chen et al., 2011). The only difference between the two groups is a subtle intracochelar neurological rewiring in the membranous elements of the cochlea in the LVAS

group, therefore it was assumed that the neural integrity of LVAS would differ to subjects with normal inner ears and eABR would be sensitive to such factors which would reflect on eV amplitudes.

Specifically, this study aims to determine: (i) a method of evaluating eABR eV amplitude which provides the least amount of variance across a normative population and is sensitive to factors which can influence neural excitation (i.e. the distance between the electrode array and neural elements) and which might influence neural integrity (i.e. LVAS); (ii) whether the methodologies of assessing eV amplitude are affected by the stimulus artefact; and (iii) whether functional outcomes are associated with eV amplitude (as a measure of neural integrity).

Materials and Methods

Participants

Fifty adult eABR waveforms (29 females, 21 males) with structurally normal inner ears were analysed retrospectively from subjects aged 18 to 89 years (mean age = 49 years) who underwent cochlear implant surgery at Sydney Cochlear Implant Centre (SCIC) between 2005 and 2014. All subjects had a severe or greater hearing loss and were implanted with either a Cochlear™ Nucleus® slim straight electrode array (n=8), a Cochlear™ Nucleus® full band straight electrode array (n=17), or a Cochlear™ Nucleus® peri-modiolar electrode array (n=25) (Cochlear Corp., Sydney, Australia). An experienced biomedical engineer selected 50 typical eABR records based on visual identification and all showed unremarkable MRI and CT scans (i.e. excluded cases showed neural atrophy, signs of cytomegalovirus (CMV) and Mondini deformity). For comparison, 37 eABR waveforms from 35 participants (24 females, 11 males) with LVAS, aged 18 to 87 (mean age = 35 years) were selected. Subjects with LVAS were implanted with a Cochlear™ Nucleus® slim straight electrode

array (n= 7), or a Cochlear™ Nucleus® full band straight electrode array (n= 14), or a Cochlear™ Nucleus® peri-modiolar electrode array (n=16) (Cochlear Corp., Sydney, Australia).

eABR Measurement

The electrode montage used for eABR recording is shown in Figure 3.1. Software from Cochlear ™ was used to deliver the intracochlear electrical current and the recordings were made with a Medelec Synergy apparatus which is designed to measure auditory evoked potentials coupled with software with a custom-designed pre-amplifier. Waveforms were measured intraoperatively, immediately after implantation, as part of the SCIC cochlear implantation intraoperative test protocol. Monopolar current pulses using extra-cochlear electrodes as parallel return pathways (MP1+2) were delivered to each electrode independently, using a pulse width (PW) of 25 μs, repetition rate of 31 pulses per second, a current level of 228 (26.9 μA). Neural responses were averaged across 200-400 sweeps, the number which was determined by visualisation of the presence of the signal by an experienced biomedical engineer. While the test protocol includes three stimulation modes: monopolar, bipolar (BP +2; from one electrode to the second consecutive electrode) and common ground (CG; where current flows from one electrode with a return to all other intracochlear electrodes), data for the current study used eABR waveforms using the MP1+2 stimulation mode, which is the default mode for Cochlear Ltd implants at “switch on”. Three electrodes were selected to represent different regions of the cochlea; the basal region represented by electrode 3, mid-region by electrode 11 and apical region by electrode 20.

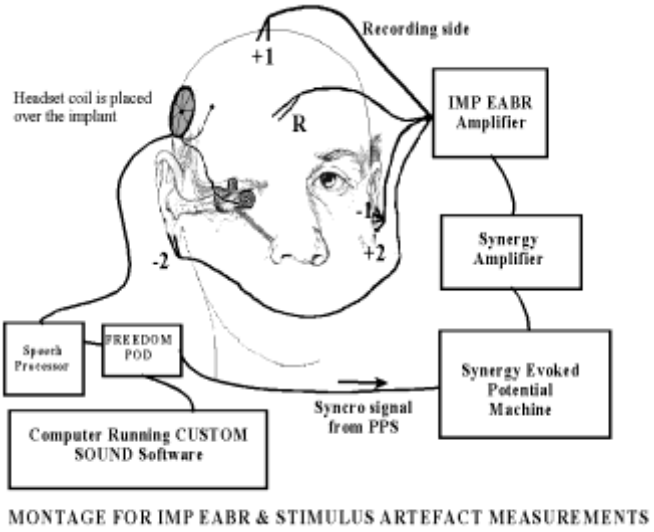


Figure 3.1. Montage for intra-operative eABR measurements.

Three methods (M) of assessing eV amplitude were compared (see Figure 3.2), which include those that have previously been mentioned in the literature; M1 is the amplitude of NIII-eV, M2 is the average of NIII-eV and eV-NV. A third method (M3) was developed for this study in which the absolute value of eV is compared to a baseline average at 9 to 9.98ms as traces stabilized in the 10 ms sweep duration in the absence of facial nerve stimulation, allowing comparison to the absolute amplitude of wave V.

Cochlear implant mapping parameters

Mapping threshold (T), comfort (C) and dynamic range (DR) were collected retrospectively from Cochlear Custom Sound® suite software for both the control and the LVAS group at the following time intervals: at time of switch-on, four weeks and twelve weeks post CI activation, in the MP1+2 stimulation mode.

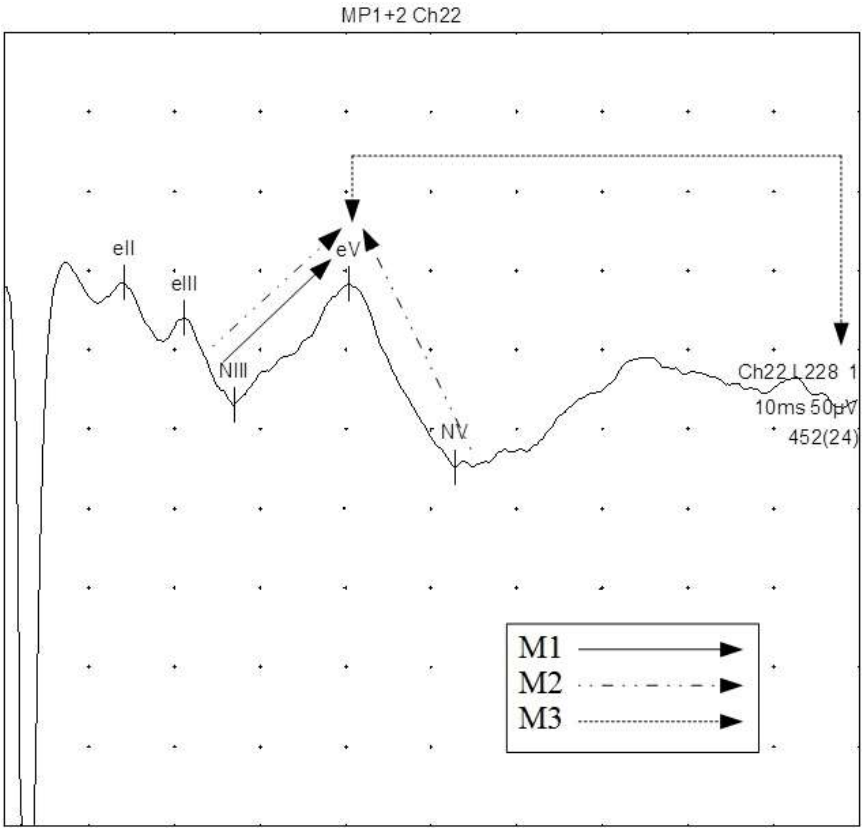


Figure 3.2. Comparison of three methods of calculating intra-operative EABR eV amplitude; (i) M1: trough to peak NIII-eV; (ii) M2: the average of trough to peak NIII-eV and peak to trough eV-NV; and (iii) M3: absolute amplitude of eV compared to a baseline between 9 to 10ms.

Participants included in the analyses were mapped with a stimulation rate of 900 pulses per second and a PW of 25 µs. Implants programmed with a rate other than 900 pulses per second, were excluded. While the effect of rate on loudness perception is complex to calculate, those implants with a stimulation PW of 37 µs, were converted to a 25 µs for analysis purposes according to the following (personal email communication from Cochlear® [based on data from the systems engineering team and verification with A. Schindhelm]):

(i) Stimulus (T and C levels) were converted to charge units with the following formula:

Q37=lcl(µA) = 0.0175*100^(CL/255) µA*37 µs

(ii) The charge of the 25 µs pulse was determined with the following formula:

Q25 = ϕratio * Q25

In which: ϕratio = 10^.1262ln(ϕ/37)

(iii) Reverse calculation of the T and C levels:

Q25= lcl*PW Therefore: lcl= Q25/25

(iv) Calculation of the final current level with 25 μs PW:

CL = 255*LN(lcl/0.0175)/LN(100)

Data Analysis

eABR eV amplitude was measured on Medelec Synergy software and subject data was collected and compiled into a Microsoft Excel spreadsheet. Different analysis measurements were made to compare the different methods of wave V estimation:

(i) Data were exported to Python to fit an exponential function to waveforms to cancel the electrical artefact that obscures wave I and sometimes wave II in eABR measurements as described by Undurraga et al. (2013) (see Figure 3.3 for an example).

(ii) Data were exported to the SPSS version 24.0 statistical package (SPSS, Inc., Chicago, IL) for statistical analysis.

Results

Comparing eV amplitudes across methods and electrode site

Three methods of evaluating eV of eABR waveforms from structurally normal implanted cochleae (n=50) were first analysed. The mean amplitude of eV, depending on electrode location (basal, mid and apical) and the method use (M1-M3), were compared using General Linear Modelling with Bonferroni corrected ad-hoc pairwise comparisons. Because eABR recordings are contaminated by large stimulus-based electrical artefacts, the original traces containing large artefacts were first compared to the traces after removal of the artefacts using exponential fitting (see Figure 3.3). As there was no significant difference between the

eV amplitude for each method at each electrode site before and after artefact removal, as well as when comparing traces with and without facial nerve stimulation ($p > .05$), all further data analyses were conducted on the original waveforms.

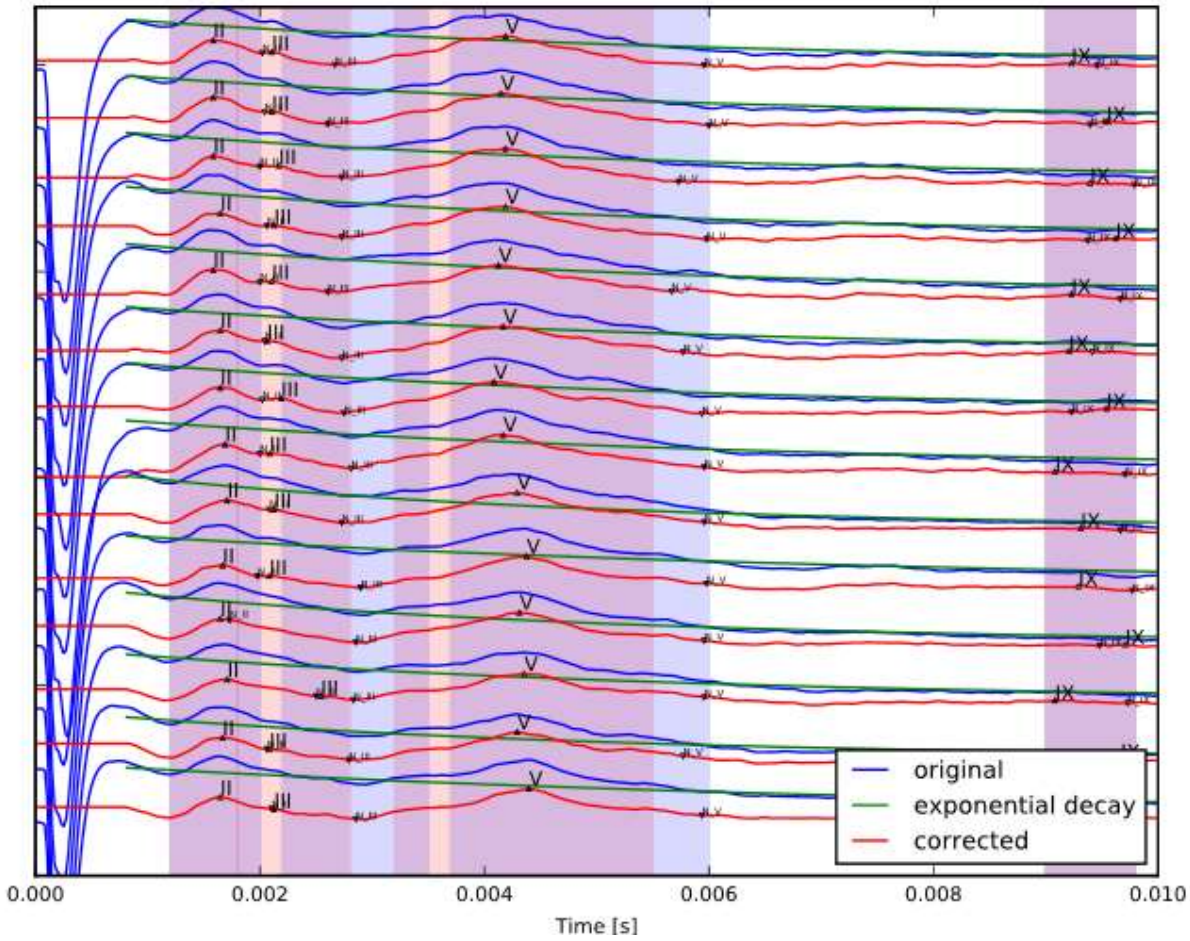


Figure 3.3. eABR traces from one participant for 14 electrodes from the apical region (top traces) to the basal region (bottom traces) of the cochlear, shown before (blue) and after (red) exponential subtraction to remove the stimulus artefact. The green curve shows the exponential curve used to remove the artefact.

As expected, the amplitude of eV was significantly different ($p< .05$) across the three electrode sites, increasing from the basal to mid to apical electrode sites, for each method (Figure 3.4). The different methods used to measure eV yielded no significant difference in pattern of results for the basal electrode location ($F_{3, 141}= 0.837$, $p=.476$). However, significant differences were found between methods for mid ($F_{3, 123}= 8.184$, $p < .001$) and apical ($F_{3, 96}= 11.733$, $p< .001$) electrode sites. Ad-hoc Bonferroni corrected pairwise

comparisons showed a significant difference in eV amplitude ($p < .05$) between M1 and M2 in the apical region as well as between M2 and M3 in the mid and apical regions (see Table 3.1). As the M2 method has previously been described in the literature (Gibson et al., 2009), and showed similar variance for each electrode site (basal, mid and apical) to M1 (see Table 3.2), this has been selected and used throughout the rest of the data analysis.

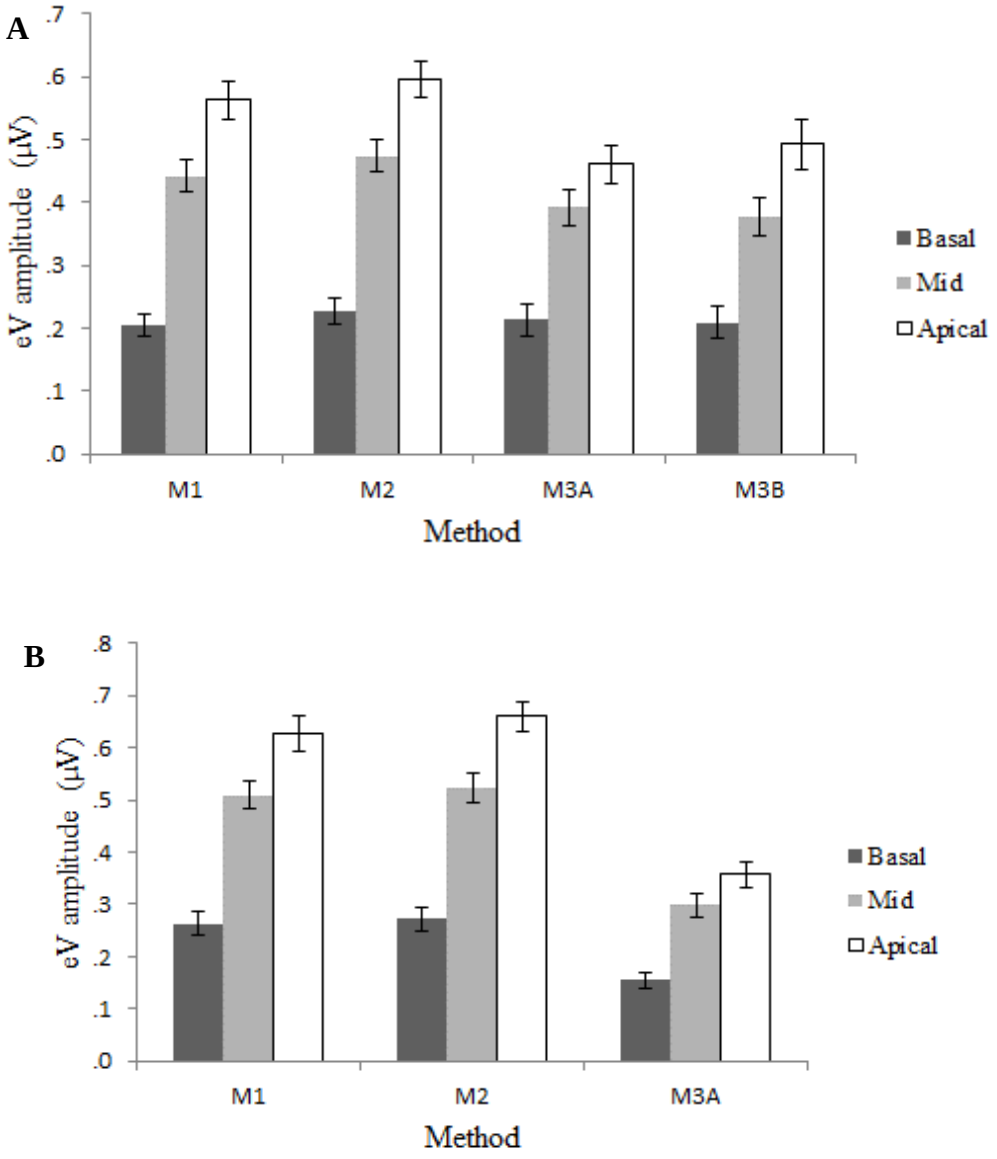


Figure 3.4. Mean eV amplitude for method 1-3 generated by electrical stimulation using an MP1+2 paradigm from basal (electrode 3; dark bars), mid (electrode 11; grey bars), and apical (electrode 22; white bars) electrodes shown (A) before after (B) after fitting traces to an exponential function to remove the stimulus artefact.

Electrode location	Methods	Significance
Basal	M1 – M2	.004
	M1 – M3a	1.000
	M1 – M3b	1.000
	M2 - M3a	1.000
	M2 - M3b	1.000
	M3a - M3b	.
Middle	M1 - M2	.076
	M1 - M3a	.133
	M1 - M3b	.133
	M2 - M3a	.014
	M2 - M3b	.014
	M3a - M3b	.
Apical	M1 - M2	.004
	M1 -M3a	.068
	M1-M3b	.068
	M2-M3a	.002
	M2-M3b	.002
	M3a-M3b	.

Table 3.1. Difference between methods of measuring eV amplitude at each location within the cochlea.

		Min	Max	Mean	Std. D	Var.
M1	Basal	0.05	0.65	0.2052	0.13249	0.018
	Medial	0.17	0.98	0.4421	0.18561	0.034
	Apical	0.15	1.10	0.5623	0.21644	0.047
M2	Basal	0.06	0.68	0.2278	0.14057	0.020
	Medial	0.21	1.08	0.4736	0.18236	0.033
	Apical	0.20	1.19	0.5956	0.21368	0.046
M3a	Basal	0.04	1.01	0.2131	0.17780	0.032
	Medial	0.14	1.28	0.3921	0.20080	0.040
	Apical	0.13	1.19	0.4605	0.21712	0.047
M3b	Basal	0.04	1.01	0.2095	0.17806	0.032
	Medial	0.14	1.28	0.3770	0.19903	0.040
	Apical	0.14	1.19	0.4921	0.22407	0.050

Table 3.2. Range for each method at each location

Comparison between eV amplitudes and CI programming levels

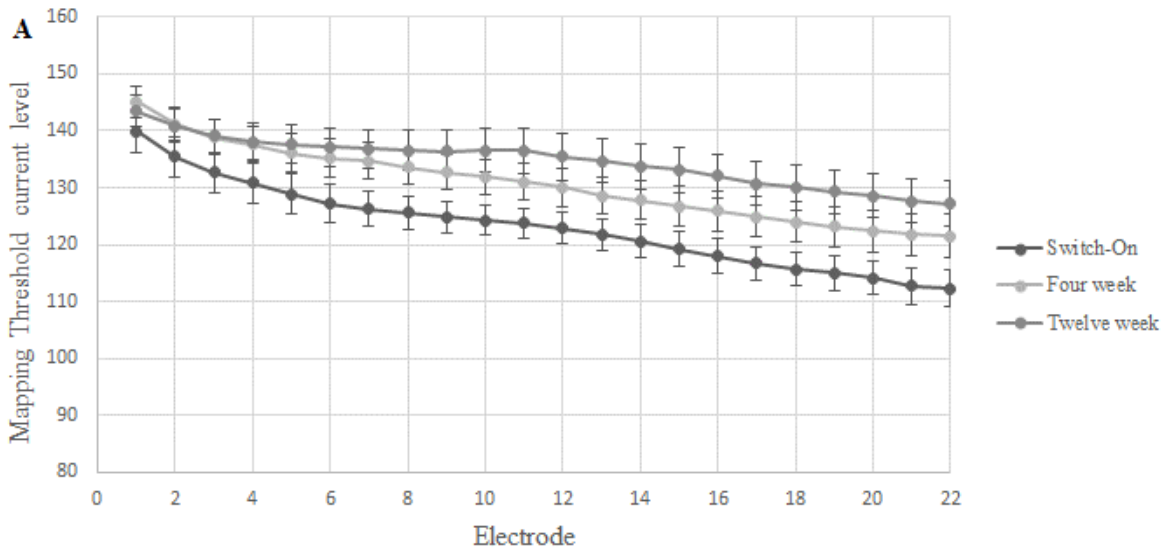
The mean (+/- SE) T- and C- levels at each electrode site at the initial "switch-on", four weeks and twelve weeks after switch-on are presented in Figure 3.5. With the group with structurally normal cochleae, a linear regression analysis was used to determine whether the eV amplitude was significantly associated with the mapped T- and C-levels. At switch-on, a significant negative regression equation was found for T ($F_{(1, 20)}$=464.94, p <.05 ; R^2 = 0.96) and C levels ($F_{(1, 20)}$= 207.45, p <.05; R^2=0.91).(Figure 3. 6), whereby;

T-levels = 145.94 – 52.34*(eV amplitude) current levels

With eV amplitude measured in µV. That is, T-levels decreased 52 current levels for each 0.1 µV of intraoperatively-measured eV amplitude. The relationship with C-levels was;

C-levels = 174.09 - 44.27*(eV amplitude) current levels

With eV amplitude measured in µV. C-levels decreased 44 current levels for each .1 µV of eV amplitude measured intraoperatively.



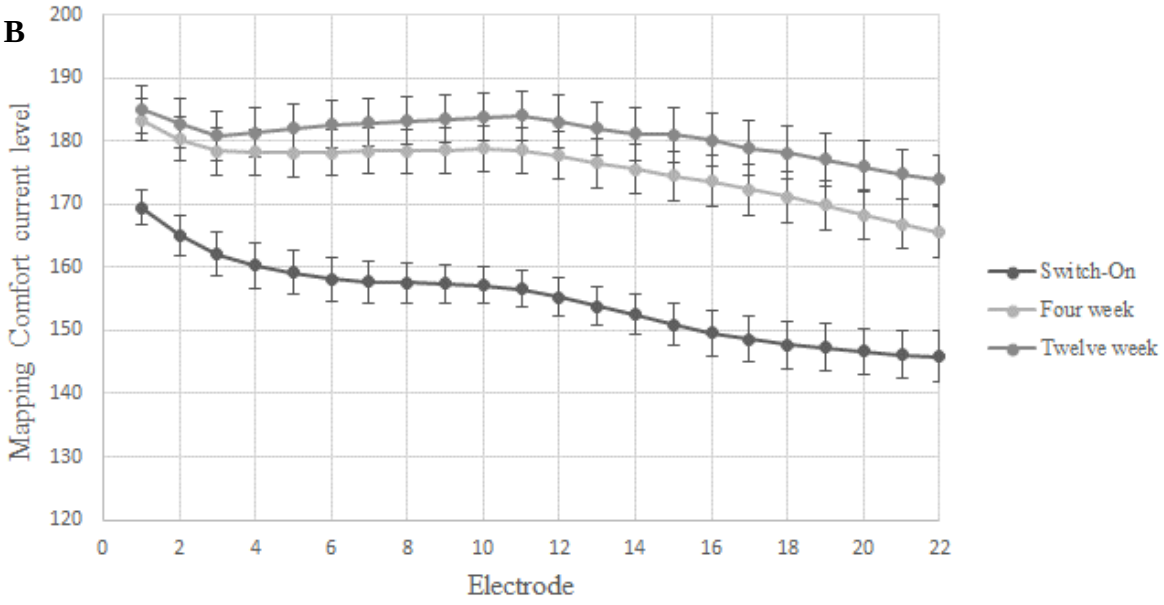
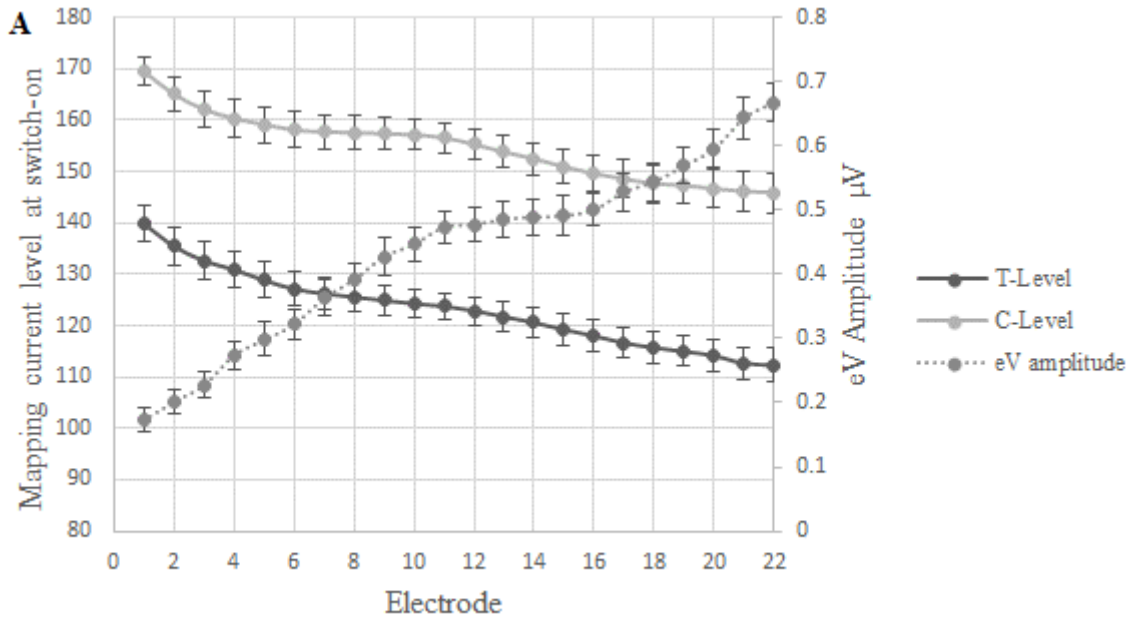


Figure 3.5. Average (+/-SE) MAP T-levels and C-levels at device switch-on (black curve), four weeks (light grey curve) and twelve weeks (dark grey curve) post activation.

However, while the significant correlation with the mapping parameters also remained after switch-on, the proportion of variance explained decreased over time, particularly for the C-levels (at four weeks, T: ($F_{(1, 20)}$ =461.73, p <.05; R^2 = 0.96), C: ($F_{(1, 20)}$= 62.62, p <.05; R^2=0.76); at twelve weeks, T: ($F_{(1, 20)}$ =177.39, p <.05; R^2 = 0.90), C: ($F_{(1, 20)}$= 22.07, p <.05; R^2=0.52).



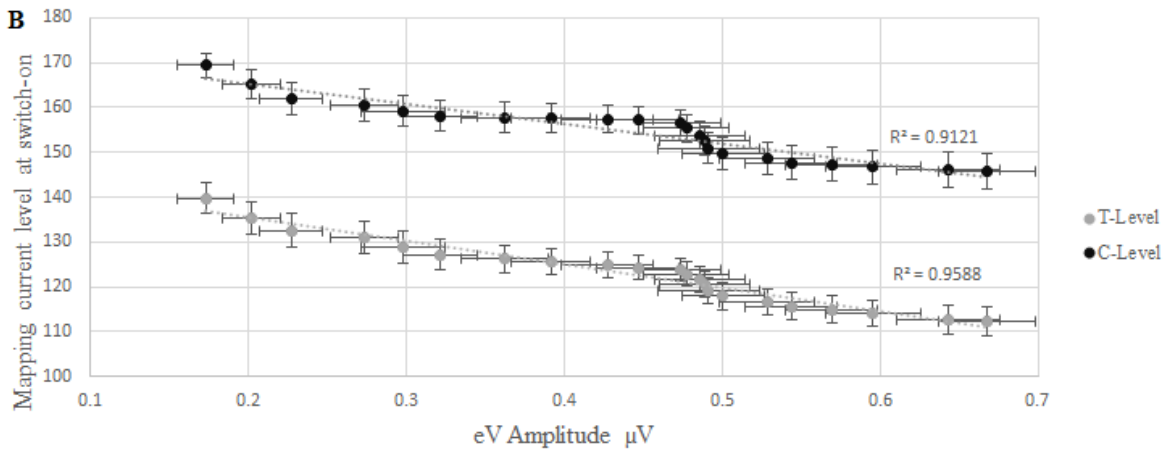


Figure 3.6. A. Relationship between mean (+/- SE) eV amplitude (dashed line) measured intra-operatively and MAP T-levels (solid grey line) and C-levels (solid black line) for all electrodes from base-apex (1-22) at switch-on. B. Correlation between eV amplitude and T-levels (light grey dashed regression line) and C-levels (dark grey dashed regression line) at switch-on.

Comparison between mean eV amplitude for straight and peri-modiolar electrode arrays

To determine the sensitivity of the eV amplitude in evaluating the proximity of the electrode array to the spiral ganglion cells (or modiolus), in individuals with structurally normal cochleae, the eV amplitude in the apical, mid, and basal region was compared for those implanted with a straight array (n=25) and with a peri-modiolar array (n=25). It was assumed that, on average, the peri-modiolar electrode array would be located closer to the modiolus in structurally normal cochleae. However, when comparing at electrodes 3, 11 and 20, a significant difference was found between the peri-modiolar and straight arrays in the mid region electrode (E11) ($p < .05$) (see Figure 7). Contrary to expectations, the straight array showed a larger average eV amplitude than the peri-modiolar array. This suggests that, on average, either; (i) the straight array was closer to the spiral ganglion cells in the modiolus; (ii) those participants implanted with a straight array had a greater residual neural population or better neural integrity than those with the peri-modiolar array; or (iii) the impedance of the straight array is less than the peri-modiolar array.

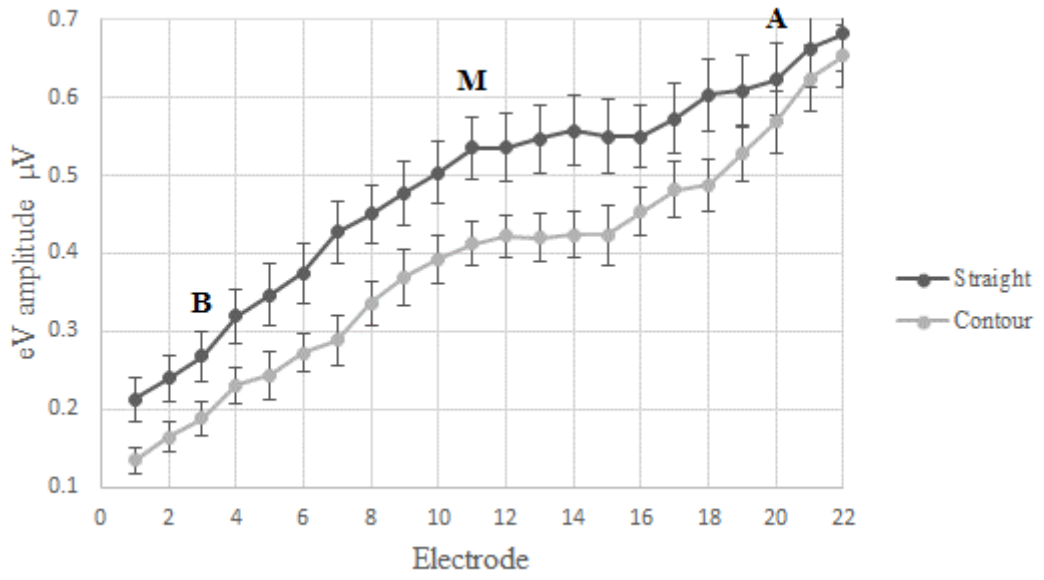


Figure 3.7. Mean eV amplitude (+/- SE) measured intraoperatively for peri-modiolar (grey line) and straight (black line) arrays. Electrodes used for comparison; B (basal E3), M (mid E11), and A (apical E20).

Comparison between mean eV amplitude and CI programming parameters for structurally normal and abnormal (LVAS) cochleae

A comparison between the mean eV (+/-SE) amplitudes for participants with structurally normal cochleae (n=50) and those characterised with a large vestibular aqueduct syndrome (i.e. LVAS; n=37) was made to determine whether the eV amplitude was sufficiently sensitive in identifying minor structural inner ear abnormalities (see Figure 3.8). An independent-samples t-test with Bonferroni correction suggested that the eV amplitude was significantly higher in the apical region for subjects with LVAS (M = .86, SD = .68) compared to those with structurally normal cochleae (M = .59, SD = .21), t(40) = -2.2, p = .03. The magnitude of the differences in the means was medium (eta squared = .06). There was no significant difference in eV amplitude between the two groups in the mid and basal regions.

A significant difference was found in the age distribution between the structurally normal cochleae group (M = 49, SD = 2.5) and the LVAS group (M = 35, SD = 2.7), t(81) = 3.8, p = 0.00.

Using repeated-measures ANOVA via GLM, no significant difference in T-levels and C-levels (p > 0.05) was found between subjects with LVAS compared with those with structurally normal cochleae at switch on, four weeks and 12 weeks after switch-on, across the basal, mid, and apical electrodes (LVAS-Norm T-levels mean difference: -5.147 (apical), 2.764 (mid), and .860 (basal); LVAS-Norm C-levels mean difference: -5.698 (apical), 1.011 (mid), and .2.529 (basal)). It should be noted that because LVAS is typically associated with only a mild structural change, cochlear implantation in this population at this clinic is usually done with standard implant arrays.

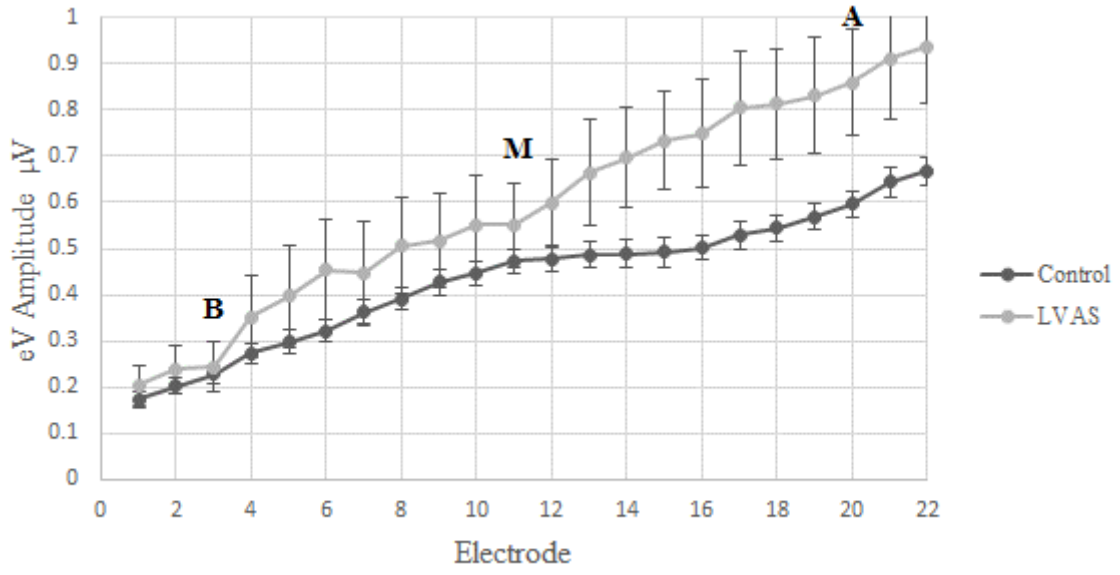


Figure 3.8. Mean (+/- SE) eV amplitude measured intraoperatively for control (black curve) and LVAS (grey curve) groups. Electrodes used for comparison; B (basal E3), M (mid E11), and A (apical E20).

Discussion

The results of this study demonstrate that across a population of post-lingually deafened adults who were implanted within structurally normal cochleae, of three methods of calculating eV amplitude, no single method of evaluating eV amplitude appeared superior across each of the three electrode sites selected (basal, mid and apical). Further, artefact removal using exponential fitting showed no significant differences in eV amplitude at these electrode sites. As M2 averages both NIII-eV and eV-NV, it is reasonable to consider it to better represent the eV amplitude, particularly in traces where there is electrical and myogenic contamination, therefore this method was selected for the remaining analyses. A significant negative correlation was found between the mean eV amplitude and T- and C-levels, which was greatest for the mapping levels at switch-on compared with 4- and 12-weeks later. Further, when stratifying between those implanted with straight compared with peri-modiolar electrode arrays, the mean amplitude of eV was greater in the mid electrode for those with a straight electrode. Finally, when comparing those with structurally normal cochleae and those with structurally abnormal inner ear (LVAS), a significant difference was found in the apical electrode region. This suggests that the eV amplitude measured intra-operatively using a fixed current amplitude and pulse width may be a useful tool in programming of the implant at switch-on, differentiating between proximity to the modiolus and identifying differences in structural or neural integrity of the cochlea.

Selection of method of measuring eV amplitude

Across all methods, the amplitude of eV was significantly different from one location to the other (largest at the apical and smallest at the basal). This is similar to findings reported by Firszt, Chambers, Kraus, and Reeder (2002), however, in their study, this did not reach statistical significance. Other reports showed a significant difference based on electrode site (Gordon et al., 2007). As the present study was done retrospectively, eABR threshold data

was not obtained, however when controlling for current level, the larger eV amplitude suggests a lower threshold (Runge-Samuelson et al., 2009). Therefore, it can be assumed that the higher eV amplitude of the apical region when compared to the basal region suggests a lower threshold in the apical end than the basal end, as found in other reports (Gordon, Papsin, & Harrison, 2004). This pattern of neural activation may have resulted from the monopolar (MP 1+2) stimulation paradigm used within the current study, whereby electrical stimulation was delivered through each electrode and the return current retrieved from the two extracochlear electrodes. This paradigm means that the electrical current delivered to the basal electrodes travels the least distance before returning to the extracochlear electrodes. On the other hand, electrical current delivered to the apical electrodes travels across the cochlea, presumably stimulating a broader population of neurones before being returned through the extracochlear electrodes.

While electrical artefact and facial nerve interference can affect the waveform morphology, the extent to which it affects eV amplitude has been investigated in this study. As eABR responses require external recording electrodes, it is susceptible to both the stimulus artefact which obscures wave I (eCAP response), myogenic artefact and electrical interference, these can affect waveform morphology and/or cause a baseline shift in the recorded response. Electrical artefact was addressed by fitting traces to an exponential function to cancel the electrical artefact and variances did not change significantly from the original traces. The facial nerve interference was also addressed by comparing amplitudes with normal traces and no significance was found. This confirmed the appropriateness of using the original traces obtained intraoperatively for further analysis, increasing the clinical applicability of the results.

When comparing between methods of evaluating eV amplitude, statistically there was no clear answer to the best method, as the variance was small in all methods. However, as M1

and M2 showed similar variance across the basal, mid and apical electrodes, M2 which is the average of the trough to peak NIII to eV and the peak to trough eV to NV provides a more accurate representation of the eV and was therefore chosen for further comparisons.

Correlation between eV amplitude and CI programming

Intraoperative eV amplitude showed a high negative correlation with CI T and C levels at switch-on (R^2 = 0.96 and 0.91 respectively) while controlling for eABR current level and pulse width and map level stimulus rate and pulse width. This indicates eABR may be a more sensitive measure of predicting mapping levels than eCAP's, as Cafarelli Dees et al. (2005) found a lower correlation between T and C-levels and eCAP thresholds when controlling for the mapped stimulus rate (i.e. R = 0.44 to 0.58). This is also supported by findings of Brown et al. (2000) who found a correlation of R = 0.5 between eCAP thresholds and C- and T-levels when only using objective measures, leading the authors to suggest introducing subjective measures of one electrode to improve utilization of eCAP to predict CI programming levels.

While there is a strong correlation in the current study population between intraoperative eV amplitudes and T and C levels at each time point tested, the correlation slightly lessens at subsequent T and C measurements of 4- weeks then 12 weeks post switch-on.

Changes in T- and C-levels after switch-on has previously been described as has been attributed to the increases in impedance levels during the first weeks of implantation caused by fibrosis and immune cell formation (Hu et al., 2017; Tykocinski, Cohen, & Cowan, 2005).

Correlation between eV amplitudes and array type

A significant difference was found between the peri-modiolar and straight array for both the control group in the mid region electrode. While the mean eV amplitudes were expected to be higher for the peri-modiolar array compared to the straight array consistent with a closer proximity to the spiral ganglion cells, which has previously been shown through imaging

(Davis et al., 2016) and behavioural studies (Jeong et al., 2015), this was not the findings of the current study. That is, the amplitude of eV was smaller for the modiolus-hugging peri-modiolar array than the straight array which should assume a more lateral position due to difference in the design of each. It is assumed that a smaller eV amplitude is consistent with an increased eABR threshold. This is in contrast to another investigation that found that the threshold of eV is lower in the apical and basal region for peri-modiolar electrodes which use a positioner to place the array closer to the modiolus (Firszt, Wackym, Gaggl, Burg, & Reeder, 2003).

While this finding was only significant for the mid array, this finding may be attributed to several factors such as the projection in which the peri-modiolar array and the straight array presumes within the cochlea. As the peri-modiolar array may deviate away from the modiolus in the mid region as it curves around the cochlea (Balkany, Eshraghi, & Yang, 2002), the straight array may deviate away from the lateral wall in the mid region , however this could only be confirmed by imaging. Another factor is the electrode design, as impedance increases with a decrease in the geometric area of the electrode (Saunders et al., 2002). That is, in the current study, 17 of the 25 straight array implants were full band electrodes, compared with all 25 peri-modiolar array implants, which were half band electrodes. As such, the increase in impedance of the peri-modiolar array may explain the decrease in eV amplitude.

As no significance was found between eV amplitude and array type for the basal and apical region, other studies investigating the effect of modiolar proximity on objective neural response (eCAP) showed no significance across all three areas of the cochlea (basal, mid and apical) (van Weert, Stokroos, Rikers, & van Dijk, 2005).

The amplitude of eV for the apical electrode was significantly higher in the LVAS group when compared with the structurally normal cochleae, although the LVAS group exhibited a larger variability. It is possible that the difference is a result of the assumed greater neural

integrity in the LVAS group, in which LVAS pathology exists in the vestibular aqueduct after controlling for cochlear deformities (i.e. Mondini). As the pathology of the control group on the other hand originates from the cochlea despite the normal structure, it can be assumed there is an element of neural deficiency. The limitation in this assumption is that both groups are most likely heterogeneous with a variety of intracochlear changes causing hearing loss. Defining these subtle differences within each group is a job for future research. This finding may be further influenced by the age distribution between the two groups, as the mean age of the LVAS group was significantly lower than the control group.

In conclusion, intra-operatively obtained eABRs can provide a sensitive measure of neural integrity and a sufficiently accurate estimation of mapping T- and C-levels at switch-on. This finding has applicability in clinical settings without further processing of the original traces, due to the non-significant differences found between traces with and without electrical and facial nerve artefacts. While there is no consensus in the literature as to the most appropriate method to use to measure eV amplitude, this study has shown there is no significant difference between methods. This suggests that the method of eV measurement did not contribute to the conflicting reports in previous studies.

Chapter 4

A clinically feasible technique of assessing scalar location of cochlear implant basal electrodes using Cone Beam Computed Tomography

Fadwa F. Alnafjan, MCAud*[1], Stuart M. Allan, BAppSc[2], Catherine M. McMahon, PhD[1], and Melville da Cruz, FRACS MSc MD[3].

[1]Macquarie University, Sydney, Australia, [2]Castlereagh Imaging, Westmead, Sydney, Australia , [3]Dept. of Otolaryngology, Westmead Hospital, Sydney, Australia.

Abstract

Cone Beam Computed Tomography (CBCT) can be utilized to inspect different aspects of the placement of cochlear implant electrode arrays in order to better understand factors that may influence the programming of the device. By eliminating metal artefact contamination, CBCT provides sufficient image clarity to identify the scalar position of the basal electrodes. This study aimed to investigate the functional effects on mapping parameters that may occur when structural damage by scalar translocation is present.

Study Design: Basal turn Insertional trauma was assessed in 108 adult cochlear implant recipients by visual inspection of post-operative CBCT images by two independent trained raters. Impedance, electrically evoked auditory brainstem response (eABR) and mapping T and C levels were compared, controlling for the type of array implanted, and across three groups: scala tympani insertions, scala vestibuli insertions and translocations from scala tympani to vestibuli.

Results: Peri-modiolar arrays had a higher rate of scalar translocation (14.7%) compared to straight arrays (5%). eABR eV amplitude was significantly higher in the scala tympani group and showed a high correlation with impedance (R^2= 0.79) and mapping T and C levels (R^2= 0.91), this correlation weakened with implants that had translocated (R^2= 0.49 and 0.45 respectively) and weakened even further for implants in which the basal electrodes were situated completely in the scala vestibuli (R^2= 0.00 and 0.25 respectively).

Conclusion: This study provides a clinically applicable method of identifying scalar translocation through the use of CBCT images, and comparing this with electrode impedance and mapping level outcomes. Comparing CBCT images with intra-operative electrophysiological test results enables us to obtain a better understanding of their clinical utility in assisting with the estimation of mapping parameters.

Introduction

Despite considerable surgical and technological advances since the multichannel cochlear implant was introduced, wide variability in speech perception outcomes in implanted adults with late-onset (or post-lingual) hearing loss remain. Much research has sought to identify the sources of this variability and the degree to which each contributes (for examples see Holden et al., 2013, 2016; Kraaijenga et al., 2016; Mosnier et al., 2014; Wanna et al., 2017). One example is the intracochlear positioning of the electrode array and its relationship to the remaining functional elements (e.g. basilar membrane, organ of Corti and residual functioning spiral ganglion cells) (Dalbert, Huber, Veraguth, Roosli, & Pfiffner, 2016; De Seta et al., 2017; Van Der Beek, Briaire, Van Der Marel, Verbist, & Frijns, 2016), whereby the effects of electrode design, insertion depth, wrapping factor, and scalar position on clinical outcomes have been evaluated (Finley et al., 2008; Hilly et al., 2016; Holden et al., 2013, 2016; Huang, Reitzen, Marrinan, Waltzman, & Roland, 2006; Lathuillière et al., 2017; Lazard et al., 2012; Nordfalk, Rasmussen, Hopp, Greisiger, & Jablonski, 2014; Rebscher et al., 2008; Skinner et al., 2002; Van Der Marel, Briaire, Verbist, Muurling, & Frijns, 2015; Wanna et al., 2014, 2015). Aligned with this, in the past two decades, refinements in surgical techniques, imaging of anatomical variations and innovations in electrode design have aimed to improve the consistency of electrode array positioning within scala tympani and its proximity to the modiolus, minimising cochlear damage and reducing cochlear fibrosis (Avci, Nauwelaers, Hamacher, & Kral, 2017; Gu et al., 2016; Hoskison, Mitchell, & Coulson, 2017; Jiam et al., 2016; Torres et al., 2017). Certainly, translocation of the array across the basilar membrane or complete dislocation into scala vestibuli is associated with poorer speech perception outcomes, higher levels of electrical current required to stimulate the neurones, and/or lower hearing thresholds after implantation (Aschendorff, Kromeier, Klenzner, & Laszig, 2007; Finley et al., 2008; Fischer et al., 2015). This may be the result of damage to

the structural or neural elements from translocation or from damage to the electrode array itself.

Identifying scalar position can be achieved with electrophysiological and/or other imaging techniques, such as Computed Tomography (CT). However, most techniques used compromise image quality and/or have a high radiation exposure. For example, CT images have been used extensively in research, however image clarity is contaminated by metal artefact by the implanted electrode array, which reduces visualization of individual electrodes, rendering the information obtained as inaccurate. While methods to overcome the metal artefact have been validated, the technique requires a composition of pre- and post-implant images in which radiation exposure may become a concern in a routine clinical setting. However, more recently Cone Beam Computed Tomography (CBCT) has been used as it overcomes the disadvantages of CT, providing visualization of each electrode while exposing the patient to significantly less radiation. The clarity of the images due to the elimination of the artefact contamination with CBCT permits to clearly identify the scalar position of the basilar electrodes. CBCT images can be utilized to inspect different aspects of the placement of the array in order to better understand the factors which may influence an individual's performance with a cochlear implant.

While imaging provides a clear visualization of electrode position and the structural damage caused by translocation of the array, it provides no information about the functional effects that such displacement may have. Studies investigating electrophysiological response patterns to electrical stimulation (e.g. eCAP) in cases of translocation have reported a 92% reliability between the eCAP responses and CT-images (Mittmann, Todt, et al., 2015). Other studies suggest that speech perception outcomes after implantation can be predicted by intraoperatively measured eABR responses (Gibson et al., 2009).

Therefore, in this study, we have combined electrophysiological and imaging (CBCT) measures to better understand how incorrect positioning of the implant array, either in scala vestibuli or translocation across the basilar membrane (from scala tympani to scala vestibuli) can affect neural activation (measured using eABR), electrode impedances, and cochlear implant mapping (measured using threshold (T) and comfort (C) levels at switch-on).

Materials and Methods

This retrospective case series reviewed 119 CBCT scans conducted after CI surgery by a single surgeon using the cochleostomy technique, between 2008-2016, no inner ear abnormalities or intraoperative difficulties such as kinks or fold overs were noted in the surgical reports for any surgeries included in this study. Three scans were excluded due to compromised image quality related to movement artefact (i.e. clear images require patients to sit still and breathe held for the CBCT acquisition time of 12 seconds). Eight scans were further excluded as they related to the implantation of different CI systems that would bring additional variability to the study analyses due to a different number of electrodes implanted. After this initial review, the analyses included 108 CBCT scans from 95 subjects (45 females, 50 males; 13 subjects had a CI in each ear), aged 18 to 95 years with a mean age of 57. All subjects had a bilateral severe to profound hearing loss and were implanted with either a Cochlear™ Nucleus® slim straight electrode array (n=81), or a Cochlear Nucleus® Contour™ advance electrode array (n=27) (Cochlear Corp., Sydney, Australia).

Imaging

Cone-beam computed tomography (CBCT) was carried out a day after surgery via a Carestream CS9300 CBCT scanner. Using a cylindrical volume field of view (FOV) of 545 x545 x 545/bits, and a high resolution isometric 90µm x90um x 90um voxel size. Exposure

factors of 90kV, 10mA and 12second scan time were used. The effective X-ray total dose received by patients was 873 mGy.cm² +/- 30%.

Reconstructed images of the raw data projection images were examined using OnDemand3DApp Project Viewer CD Viewer (Cybermed Inc., Seoul, Korea). Multiplanar reconstructions were obtained to enable the examination of the cochlea and labyrinth through the coronal, axial and sagittal planes using 1mm slices with no overlap. Using the software, the images were rotated in the coronal plane. This plane of view enabled visualization of the anatomy of the round window region and each individual electrode of the implanted array in one plane inserted into the cochlea, as well as the identification of any kinks along the array.

eABR Measurement

The electrode montage used for eABR recordings is shown in Figure 4.1. Software from Cochlear ™ was used to deliver the intracochlear electrical current and the recordings were made with a Medelec Synergy apparatus which is designed to measure auditory evoked potentials coupled with software with a custom-designed pre-amplifier. Waveforms were measured intraoperatively, immediately after implantation, as part of the SCIC cochlear implantation intraoperative test protocol. Monopolar current pulses using extra-cochlear electrodes as parallel return pathways (MP1+2) were delivered to each electrode independently, using a pulse width (PW) of 25 μs, repetition rate of 31 pulses per second, a current level of 228. Neural responses were averaged across 200-400 sweeps, the number which was determined by visualisation of the presence of the signal by an experienced biomedical engineer. While the test protocol includes three stimulation modes: monopolar, bipolar (BP +2; from one electrode to the second consecutive electrode) and common ground (CG; where current flows from one electrode with a return to all other intracochlear electrodes), data for the current study used eABR waveforms from MP1+2, which is the default mode for Cochlear Ltd implants at “switch on”. Some data points for the eABR were

extrapolated for analysis purposes. As this study was done retrospectively, some electrodes may not have been tested in the clinical setting as part of a standard clinical protocol.

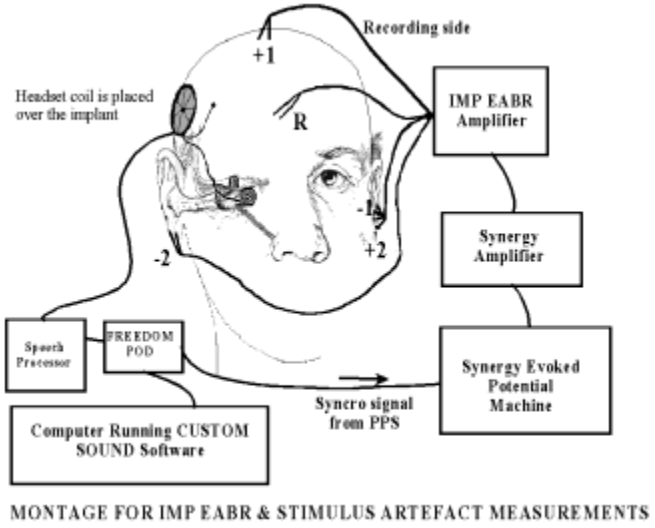


Figure 4.1. Montage for intra-operative eABR measurements

Impedance measurements

Impedance measures were collected for all electrodes intraoperatively and, while measurements were made in the common ground (CG), monopolar 1 (MP1), monopolar 2 (MP2), and monopolar 1+2 (MP1+2) modes, all data was analysed in the MP1+2 stimulation mode for comparison with eABR intraoperative data and cochlear implant mapping.

Cochlear implant mapping parameters

Mapping threshold (T) levels, comfort (C) levels, and dynamic range (DR) were collected retrospectively from Cochlear Custom Sound® suite software at switch on and all devices were programmed in the MP1+2 stimulation mode. The speech processors of participants included in analyses were mapped with a stimulation rate of 900 pulses per second and a PW of 25 µs. Implants programmed with a rate other than 900 pulses per second were excluded. While the effect of stimulation rate on loudness perception is not simple to estimate, those

implants with a stimulation PW of 37 µs, were converted to a 25 µs for analysis purposes according to the following calculations (personal email communication from Cochlear® [based on data from the systems engineering team and verification with A. Schindhelm]):

(v) Stimulus (T and C levels) were converted to charge units with the following formula:

Q37=lcl(µA) = 0.0175*100^(CL/255) µA*37 µs

(vi) The charge of the 25 µs pulse was determined with the following formula:

Q25 = ϕratio * Q25

In which: ϕratio = 10^.1262ln(ϕ/37)

(vii) Reverse calculation of the T and C levels:

Q25= lcl*PW Therefore: lcl= Q25/25

(viii) Calculation of the final current level with 25 µs PW:

CL = 255*LN(lcl/0.0175)/LN(100)

Scalar position assessment

CBCT scans were visualized by two independent raters to identify intra-cochlear membranous trauma and associated translocation in the region of the basal electrodes. Only the basal electrodes (1-5) were identified as being sufficiently reliable to identify electrode position (Mittmann, Ernst, & Todt, 2015; Saeed et al., 2014). As shown in Figure 4.2, images were classified on the location of the basal electrodes into the following 4 categories: (a) scala tympani (optimal placement; n=97); (b) translocated (from scala tympani to scala vestibuli; n=3); (c) scala vestibuli (n=5); and (d) undetermined (n=3). The three scans for which the raters could not reach consensus on the exact position of the array based on the available CBCT were excluded for the purpose of this study. Ethical guidance and approval for this study was obtained from the Western Sydney Local Health District's Human Research Ethics Committee (HREC) in NSW, Sydney.

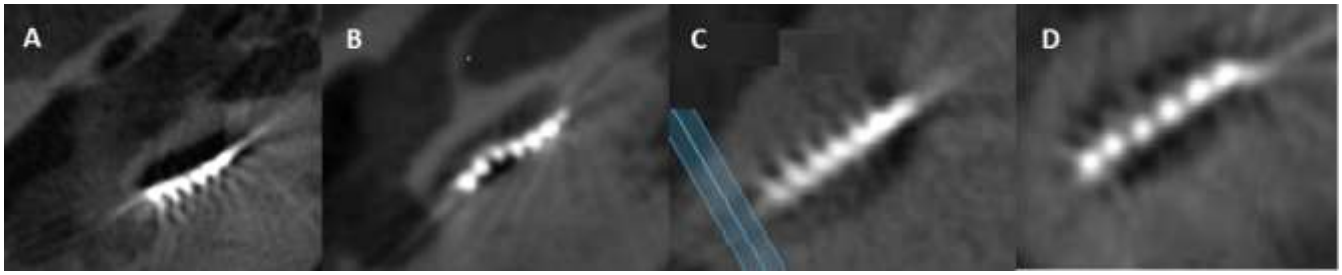


Figure 4.2. Cone-beam computed tomography (CBCT) image of the basal turn of the cochlea with an implanted electrode array showing the four categories based on location of basal electrodes: (a) scala tympani, (b) translocated, (c) scala vestibuli, and (d) undetermined.

Results

Scalar position

Scalar position was determined in 81 cochleae implanted with a slim straight electrode array and 27 cochleae implanted with a peri-modiolar electrode array. In four images the individual electrodes could not be clearly visualized, however they were included based on the general position of the array within the cochlea. The inter-rater reliability to determine electrode position was 88% (n =95), raters came to consensus on 9% (n=10) and the remaining 2% (n=3) were excluded as scalar position could not be detected with available CBCT images. The majority of the CBCT scans reviewed showed the position of the basal electrodes in the scala tympani. However, the basal electrodes were positioned in scala vestibuli for two of the straight array implants (2.5%), and for three of the peri-modiolar array implants (11%), while translocation from the scala tympani into the scala vestibuli was observed in two of the straight array implants (2.5%), and one on the peri-modiolar array implants (3.7%) (Table 4.1).

	ST (%)	*SV (%)*	*Translocated (%)*	*Undetermined (%)*	*Total*
Straight	75 (92.6%)	2 (2.5%)	2 (2.5%)	2 (2.5%)	81
Perimodiolar	22 (81.5%)	3 (11%)	1 (3.7%)	1 (3.7%)	27

Table 4.1. Location of basal electrodes; in scala tympani (ST), scala vestibuli (SV), translocated or undetermined by the two independent raters.

Correlation between eV amplitude and electrode position

A comparison between the mean eV (+/-SE) amplitudes for the group identified as having basal electrodes in scala tympani and the eV amplitudes for arrays in which translocation has occurred was made to determine whether the eV amplitude was sufficiently sensitive in identifying scalar dislocation. A one-way ANOVA yielded no significance across all groups when comparing individual electrodes and across the whole array ($F_{2,95}$= .863, p = .43; Figure 4.3).

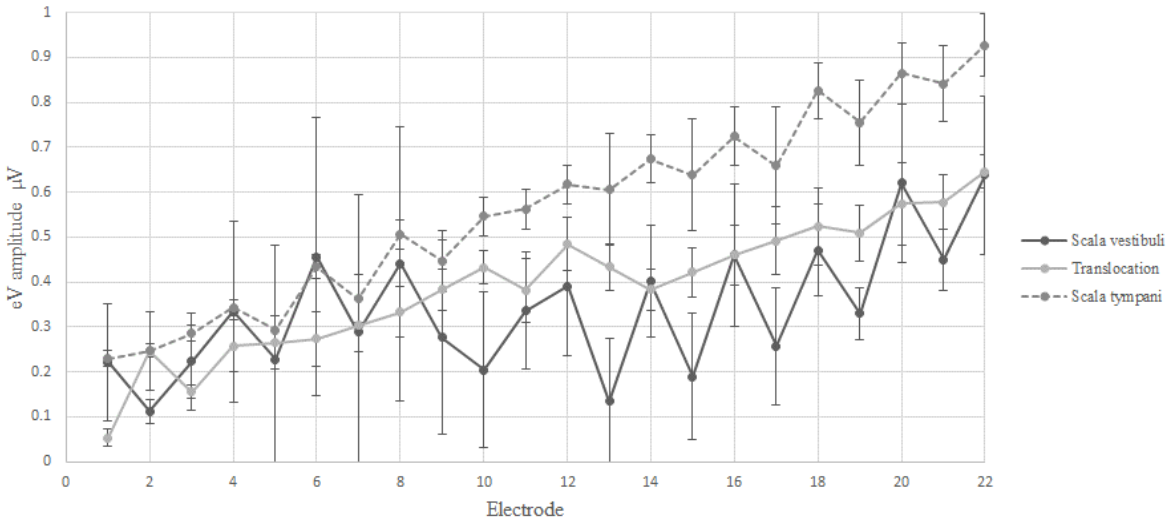


Figure 4.3. Mean eV amplitude (+/- SE) measured intraoperatively for electrodes located in scala tympani, translocated from scala tympani to scala vestibuli, and scala vestibuli.

Correlation analyses via linear regressions were used to assess the relationship between eV amplitude and impedance levels (see Figure 4.4). For those arrays positioned in scala tympani, a significant correlation was found intraoperatively ($F_{(1,20)} = 75.67$, $p < .05$; $R^2 = 0.79$). With the electrode arrays partly translocated into scala vestibuli, impedance levels and eV amplitude remained significantly correlated although the variance explained decreased ($F_{(1,20)} = 19.4$, $p < .05$; $R^2 = 0.49$). However, no significant relationship was found between intraoperative eABR and impedances for electrode arrays fully placed in the scala vestibuli ($F_{(1,20)} = 0.002$, $p > .05$; $R^2 = 0.00$).

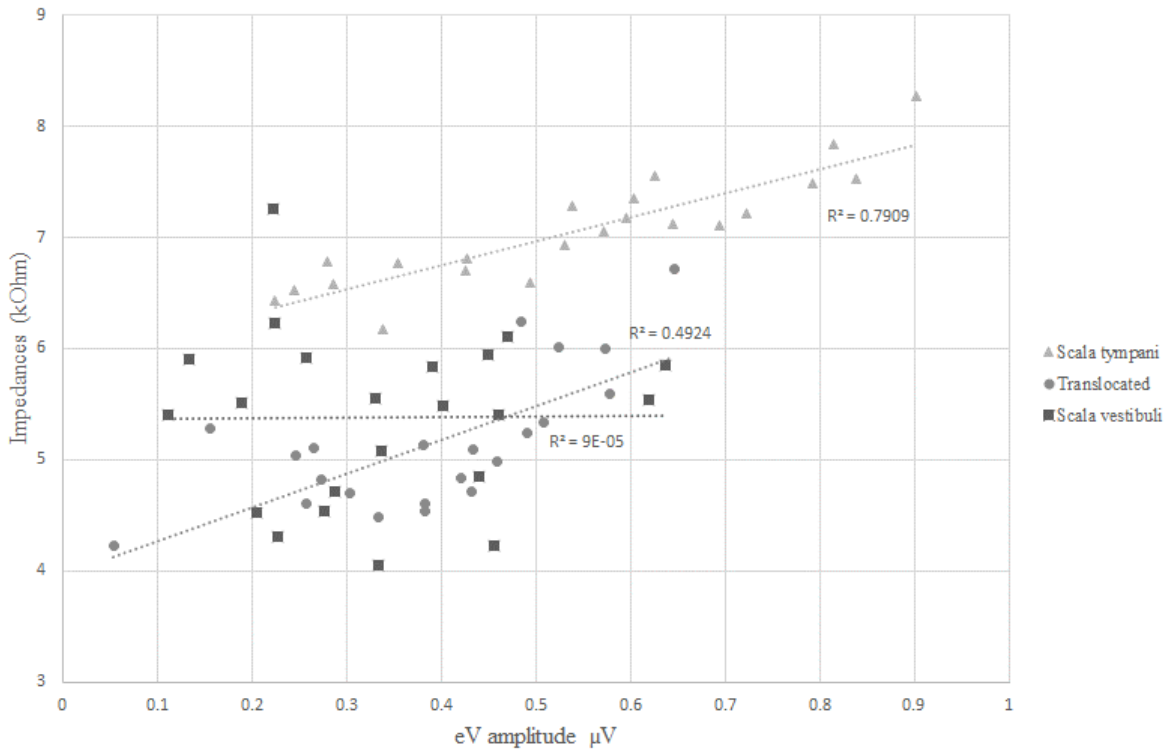
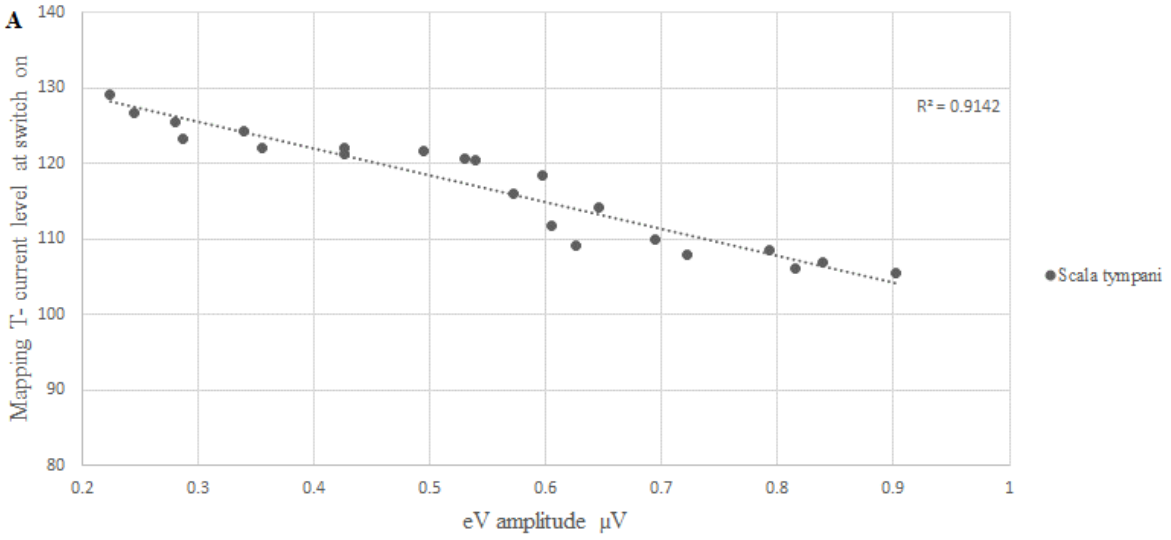


Figure 4.4. Correlation between eV amplitude and intraoperative impedances for electrodes located in scala tympani, translocated from scala tympani to scala vestibuli, and scala vestibuli.

Correlation between eV amplitude and mapping levels for three types of array position

A linear regression analysis for the scala tympani group was conducted to verify whether the eV amplitude was correlated with T- and C- levels mapped at switch-on. A significant negative regression equation was found for T- ($F_{(1, 20)}$ =213.09, p <.05 ; R^2 = 0.91) and C-levels ($F_{(1, 20)}$= 156.06, p <.05; R^2=0.89). However, while the linear regression analysis of the translocated group also showed a significant correlation between eV amplitude and switch-on mapped T- ($F_{(1, 20)}$ =16.58, p <.05 ; R^2 = 0.45) and C-levels ($F_{(1, 20)}$= 8.01, p <.05; R^2=0.29), the explained variance was reduced. A weaker correlation was found for the scala vestibuli group for T- ($F_{(1, 20)}$ =6.69, p <.05 ; R^2 = 0.25) and C-levels ($F_{(1, 20)}$= 5.69, p <.05; R^2=0.22; Figure 4.5).



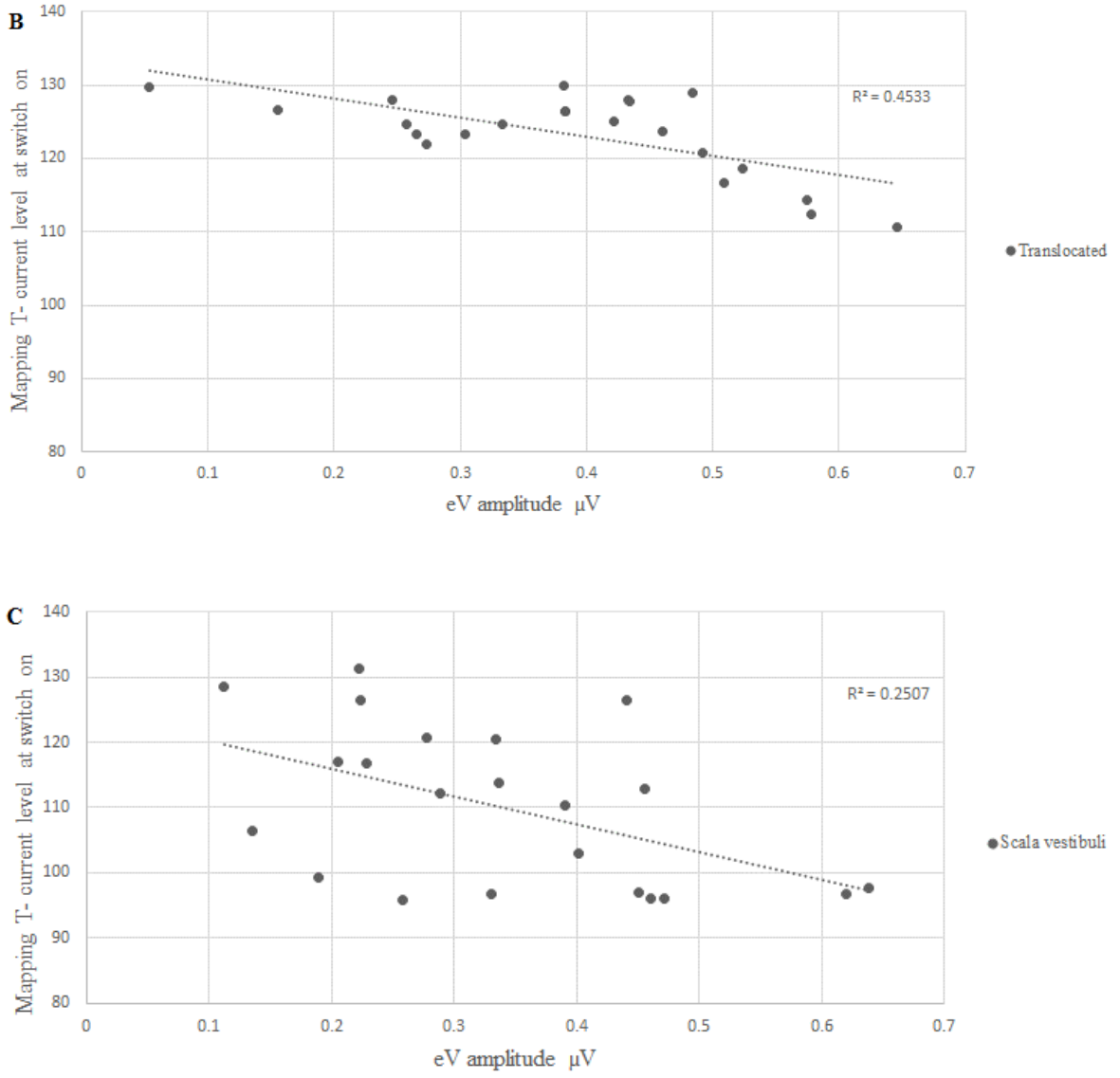


Figure 4.5. Correlation between eV amplitude and T-levels and C-levels at switch-on for (A) electrodes located in scala tympani, (B) translocated from scala tympani to scala vestibuli, and (C) scala vestibuli.

Discussion

The following exploratory study demonstrated that scalar positioning of the implant array affects the ability for the eV to predict CI mapping. A significant negative correlation was found between eV amplitudes and T- and C- levels at switch on for electrodes placed in the scala tympani. However the correlation was weaker for implants that were shown by imaging

to have translocated into the scala vestibuli, and the correlation was further weakened for electrodes placed completely in the scala vestibuli. This indicated this method is sensitive to scalar placement, which should be verified through imaging, which highlights the importance of imaging in confirming electrode placement due to its implications on programming and ultimately outcomes.

Scalar position has been previously identified as a variable that has an effect on speech perception outcomes (Aschendorff et al., 2007; Holden et al., 2013). This may be caused by the trauma to cochlear structures as the array dislocates from the ST to the SV which may reduce chances of preserving residual hearing (Nordfalk et al., 2014; Tien & Linthicum, 2002; Todt, Basta, & Ernst, 2008).

Therefore, 108 CBCT scans were viewed in order to determine basal scalar position, with the aim to compare how placement of the electrode array may affect electrode impedances. The position of the basal electrodes only were evaluated due to the difficulty to identify the electrode position in the middle and apical turns as reported by Saeed et al. (2014) who noted that, using CBCT, identification of scalar position was more reliable at the basal turn than the apical turn. This issue has also been identified when utilizing other imaging techniques, as Mittmann, Ernst and Todt (2015) found the reliability of identifying scalar position using flat panel tomography to be 68% for the electrodes in the apical region as opposed to 100% for electrodes in the basal region. This can be expected, as the fine structures within the cochlea cannot be clearly identified with the resolution of CBCT, and as the dimension of the scala reduces towards the apex in a non-linear manner (Biedron, Prescher, Ilgner, & Westhofen, 2010), scalar classification based on general position within the cochlear duct would be more reliable towards the basal region, where the diameter is largest.

While surgical approach and electrode design have both shown to influence scalar position (Fischer et al., 2015; Rebscher et al., 2008). This data yielded a higher rate of suboptimal

scala placement for the peri-modiolar array (14.7%), than for the straight array (5%). This finding is supported by Boyer et al. (2015), that found a 26% rate of scalar dislocations with the peri-modiolar array as opposed to 3% for the straight array. Fischer et al. (2015), also reported a low dislocation rate for straight arrays (7.9%), although they were not compared to any peri-modiolar arrays in the study. Wanna et al. (2014, 2015), also found a larger proportion of translocations with the peri-modiolar array when compared to the straight array. Lane et al. (2007) found the opposite effect, however image quality and the small sample size of straight arrays included in which scalar position could be determined (n=4, in which two (50%) were identified as scalar vestibuli) may have influenced this finding.

Impedance measures were taken at time intervals of intraoperatively and postoperatively at switch on, four weeks, twelve weeks and six months post CI activation, in order to determine whether a change in pattern can be seen when the array is situated within the SV or if translocation occurs. While the impedance levels of the scala tympani group appeared to have higher impedance levels intraoperatively when compared with the scala vestibuli and translocated groups, this difference did not reach statistical significance. Similar findings were reported by Lathuillière et al. (2017), in which, as in this study, the authors attributed the non-significant finding to the low number of translocations investigated. All three groups followed the same pattern over time, in which impedances were lowest intraoperatively, and raised at switch on followed by a plateau from four weeks. This pattern was also found in previous studies that found significant changes in impedances up to the fourth week, in which impedances stabilized (Hu et al., 2017). Hu et al. (2017) has also reported a decrease in intraoperative impedances from the apical electrodes towards the basal, which was also found in the current study, this is attributed to the decrease in the geometric area of the electrodes towards the apex in Cochlear ® arrays which increases impedance (Cochlear®, 2014a, 2014b).

eABR amplitudes showed no significant difference when comparing the scala tympani group with the translocated and scala vestibuli groups. This finding may be attributed to the low number of cases identified with translocation and scala vestibuli electrode placement. Mittmann, Ernst, et al. (2015), found eCAP thresholds to be higher in the apical region for dislocated arrays, however they reported lower thresholds in the basal region which they attributed to the projection of the basal electrodes towards the modiolus when translocation occurs higher in the array. Mittmann et al. (2015) however reported the reliability of identifying dislocation with imaging in the apical region is less than the basal region, which may have influenced their findings of the basal region.

It was expected that the increased distance from the spiral ganglion cells that occurs with the displacement affects amplitude of eV. Which further influences the neural-electrode interface and has implications on mapping of the CI. This is exhibited by the correlation found between eABR eV amplitudes and intra-operative impedance levels and between eABR eV amplitudes and T and C programming levels at switch on for the scala tympani group. The correlation for the translocated group is less and the variance explained decreased for both the intraoperative impedances and the switch on T and C levels. However as the basal electrodes are placed completely in the scala vestibuli and therefore further away from the spiral ganglion cells, the correlation between eV amplitude and impedances becomes non-significant and weak with mapping T and C levels. It is possible that the increased variance and weaker correlation between eV amplitude and T-levels found for scalar dislocation may result from the small number of participants with translocations included in this study. Therefore, further study is needed in this area. Nonetheless, it seems reasonable that a greater distance between the stimulating electrode array and the neural population that is activated could also explain part of this variance.

Therefore, the application of intra-operative eABR amplitudes to predict T and C levels should be used with caution in cases of electrode scalar dislocation.

In conclusion, CBCT is a useful and feasible tool that allows to validate the utility of electrophysiological measures to further understand how structural changes within the cochlear may cause functional changes. These results provide insight to how electrode placement can affect and predict mapping parameters, as well as provide quality feedback data to implanting surgeons.

Chapter 5

Assessing cochlear length using Cone Beam Computed Tomography in adults with cochlear implants.

Fadwa F. Alnafjan, MCAud*[1], Stuart M. Allan, BAppSc[2], Catherine M. McMahon, PhD[1], Melville Da Cruz, FRACS MSc MD[3].

[1]Macquarie University, Sydney, Australia; [2]Castlereagh Imaging, Westmead, Sydney, Australia; [3]Dept. of Otolaryngology, Westmead Hospital, University of Sydney, Sydney, Australia.

Abstract

Developing a clinically viable technique for measuring cochlear length could enhance future electrode design of cochlear implants and surgical skills to improve clinical outcomes. While Computed Tomography (CT) has been used, metal artefact and the exposure to higher levels of radiation limits its use. More recently, Cone Beam CT (CBCT) has been used to assess the integrity of the implant array *in situ*, exposing implantees to lower levels of radiation while retaining image quality. The current study aims to develop a technique for measuring cochlear length in implanted adults, using CBCT images combined with known dimensions of implant arrays and lengths of cochlear structures from cadaveric human temporal bones.

Study Design: 100 CBCT temporal bone images of ears implanted with Cochlear^{TM} straight or peri-modiolar arrays were reviewed by two independent examiners.

Results: Outer-wall length, based on the position of the straight array within the cochlea and the reported average length of the organ of Corti, was 27.44 to 35.91 mm (mean = 32.24 mm). Inner-wall length, based on the position of the peri-modiolar array and the reported average length of the spiral ganglion, ranged from 17.8 to 22.24 mm (mean = 19.43 mm).

Conclusion: A novel method for calculating outer- and inner-wall cochlear length using CBCT images has been developed which is feasible in clinical settings.

Introduction

Cochlear implants are the treatment of choice for individuals with severe to profound hearing impairment. As technology improves, clinical guidelines for implantation have evolved to include a wider range of hearing loss degrees and configurations. However, while this treatment has greatly advanced over time, variability in speech perception outcomes remain broad(Firszt et al., 2004), and are not always predictable with existing clinical or surgical information.

Multiple factors influence variability in speech perception outcomes, including patient factors (duration of deafness, age of implantation, residual ganglion cell population)(Kraaijenga et al., 2016), surgical factors (depth of insertion, degree of insertional trauma, electrode scala position)(Finley et al., 2008; Van Der Marel et al., 2015), and technical factors (electrode characteristics: length diameter and stiffness)(Huang et al., 2006; Rebscher et al., 2008). However, it is less clear how surgical or technical factors influence this variability, particularly the length of the cochlear scalae, which in turn, affects the depth of insertion of an electrode array of fixed length. Currently, accurate measurements of cochlear length can only be gleaned from post mortem temporal bone studies(Avci, Nauwelaers, Lenarz, Hamacher, & Kral, 2014; Erixon et al., 2009; Erixon & Rask-Andersen, 2013; Escudé et al., 2006; Johnston et al., 2016; Pelliccia et al., 2014; Rask-Andersen et al., 2011; Shin et al., 2013; Singla et al., 2015; Würfel et al., 2014) (Table 5.1), and no reliable technique exists for *in vivo* measurements.

Measurement of cochlear length with the electrode *in situ* using standard Computed Tomography (CT) imaging is compromised by metal artefact from the implant array, rendering estimates of insertion depth inaccurate. To overcome these limitations, techniques such as ‘Cochlear view’ X-rays utilizing plain radiographs(Escudé et al., 2006) enable *in-situ*

visualization of electrodes, (though this technique is limited to measuring insertion depth in terms of angle of rotation and not absolute length), or the use of a 3-dimentional reconstructed cochlear image(Skinner et al., 2007; Teymouri et al., 2011) from CT utilizing pre- and post-operative images(Chole, Richard A, Hullar, Timothy E, Potts, 2014; DeVries et al., 2016; Holden et al., 2013, 2016; Long et al., 2014), have been investigated. Despite the benefits of detecting cochlear dimensions with the array *in-situ*, such methods expose subjects to higher levels of radiation than alternatives, such as Cone Beam Computed Tomography (CBCT)(Razafindranaly et al., 2016). Additionally, concern has increased over radiation toxicity associated with spiral CT(Brenner & Hall, 2007; Pearce et al., 2012).

Previous descriptions of cochlear length were performed *in vitro* (Table 5.1) using methods such as electron microscopy sections of human cadaveric cochlea(Adunka et al., 2005) or temporal bone cast moulds(Erixon & Rask-Andersen, 2013). Histological studies provide useful information for understanding cochlear-length distributions within a population, assessing post-implantation types of cochlear trauma, and identifying the proximity of an electrode array to underlying neural structures. However, by their very post mortem nature, no understanding of relationships between electrode array placement and interactions between array length and speech perception outcomes for clinical decision-making is possible. Accordingly, a need for a clinically feasible method to assess cochlear length remains.

CBCT both overcomes challenges associated with metal artefact contamination, and exposes individuals to significantly lower doses of radiation than traditional CT scans. However, the majority of studies evaluating this method for placement validation have been performed *in vitro*, comparing findings to gold standard histological controls(Marx et al., 2014; Saeed et al., 2014; Zou, Hannula, et al., 2015). The aim of this study is to develop a clinically feasible technique to measure cochlear length using CBCT imaging, combined with previously known

data from human temporal bone studies(Stakhovskaya, Sridhar, Bonham, & Leake, 2007) and known dimensions of commonly used cochlear implant electrodes(Cochlear®, 2014a, 2014b). Applications might contribute to improved electrode design (in terms of electrode length), and surgical skill training, for more consistent and ideal placement of electrodes.

Materials and Methods

One hundred Conebeam CT scans were obtained retrospectively from 94 subjects (45 females, 49 males), aged 18 to 95 years, of mean age 57. All subjects had bilateral severe-to-profound hearing loss, and had been implanted with a Cochlear™ Nucleus® slim straight electrode array (n=77), or Cochlear Nucleus® Contour™ advance electrode array (n=23) (Cochlear Corp., Sydney, Australia). Measurements were based on the radiologically visible length of the electrode, the length from the first to the last electrode[1].

A single surgeon performed all surgeries between October 2012 and June 2016. The cochleostomy technique was used on all subjects. No intraoperative difficulties, such as partial insertions, kinks and fold overs, were reported in any surgery included for this study.

CBCT was performed one day post-surgery using a Carestream CS9300 CBCT scanner, with a cylindrical volume field of view (FOV) of 545 x 545 x 545/bits, and a high resolution isometric 90 x 90 x 90µm voxel size. Exposure factors of 90kV, 10mA and 12second scan time were used; the effective X-ray total dose received by patients was 873 mGy.cm² +/- 30%.

[1] The CI422 and CI522 have a radiologically visible length of 19.1 mm. The two radiolucent white markers on the array indicate insertion depth at 20 and 25 mm. The CI24RE and CI512 have a visible length of 14.25 mm with a radiolucent marker ring at 19 mm.

Reconstructed images of the raw data projection images were examined using OnDemand3DApp Project Viewer CD Viewer (Cybermed Inc., Seoul, Korea). Multiplanar reconstructions were obtained for examination of the cochlea and labyrinth through coronal, axial and sagittal planes using 1mm slices with no overlap. Using the software, all images were rotated in the coronal plane to enable visualization of the anatomy of the round window region and individual electrodes in the implanted array in one plane inserted into the cochlea. This permitted measurement of the angle of rotations, in addition to identification of any kinks along the array.

Human Research Ethics approval for this study was obtained from Western Sydney Local Health District in NSW, Sydney (ref # LNR/14/WMEAD/11).

Measurements

Using CBCT, four landmarks were identified to measure cochlear length: the bony lip of the round window, the modiolus, outer wall, and the most apical electrode. These landmarks were used to estimate the number of electrodes (i.e. to estimate the percentage of the array) inserted at 360 degrees, and the remaining length between this point and the bony lip of the round window (Figure 5.1). The centre of the cochlea was visually identified, and a line drawn from it to the most apical electrode and the aligned basal electrode on which the line fell, which was equivalent to the 360-degree point.

Stakhovskaya et al. (2007) found a high correlation and lower intersubject variability when measuring the required percentage distance of cochlear structures to reach specific angles of rotation as opposed to absolute distances. Therefore, percentage of cochlear structure lengths at 360° of rotation obtained were derived from histological studies by Stakhovskaya and colleagues. It was assumed the organ of Corti (OC) and spiral ganglion (SG) measured histologically approximate the outer wall and inner wall length respectively. While it is

acknowledged that both assumptions may have some deficiencies, there is no other available technique to provide accuracy with these measurements in-vivo. The percentage of length of the OC was used to calculate the outer wall length for subjects implanted with a straight array, given the straight array's preferred position along the outer wall of the cochlea. The percentage of length of the SG was used to calculate the length of the inner wall for subjects implanted with a peri-modiolar array, as the array sits in a perimodiolar position. The 360-degree angle of insertional rotation accounted for 81.47% of the cochlea length for the peri-modiolar array and 61.46% for the straight array(Stakhovskaya et al., 2007). Using the electrode array as a measuring tool for its known dimensions(Cochlear®, 2014a, 2014b), an equation was developed based on the number of electrodes inserted at 360 degrees.

The length of the cochlea was calculated as: [(the number of electrodes inserted at 360°/total number of electrodes)*visible length*(100/the percentage of length corresponding at 360°)] + the remaining length up to the bony lip of the round window (Figure 5.1).

In which:

- The number of electrodes inserted at 360° was manually counted (20 electrodes in the example shown in figure 5.1),
- Total number of electrodes was 22 for all the arrays used in this study,
- Visible length from the first electrode to the last electrode however changed from 19.1 mm for the straight arrays to 14.25 mm for the peri-modiolar arrays as specified by manufacturer.
- Percentage of length corresponding at 360° was 81.47% for the peri-modiolar array and 61.46% for the straight array as specified by Stakhovskaya and colleagues (2007).
- Calibrated measure on the radiology work station was used for linear measurement of the distance from the round window lip to the 360° rotation angle in the array.

Using the length of the clearly visible cochlear implant array and comparing the data across two raters, allowed more accurate assessment of cochlear length.

We define cochlear length in terms of outer- and inner-wall length. We calculate outer-wall length based on the percentage of length of the OC at 360°, and the visible length of the slim straight electrode. Due to the highly flexible nature of the slim straight electrodes, we assumed they followed the path of least resistance within the scala tympani, rarely deviated from the lateral wall(Verberne, Risi, Campbell, Chambers, & O'Leary, 2016). Inner-wall length was based on the percentage of length of the SG at 360 degrees and the visible length of the peri-modiolar electrode, which we assume consistently occupied a perimodiolar position due to its preformed coiled shape.

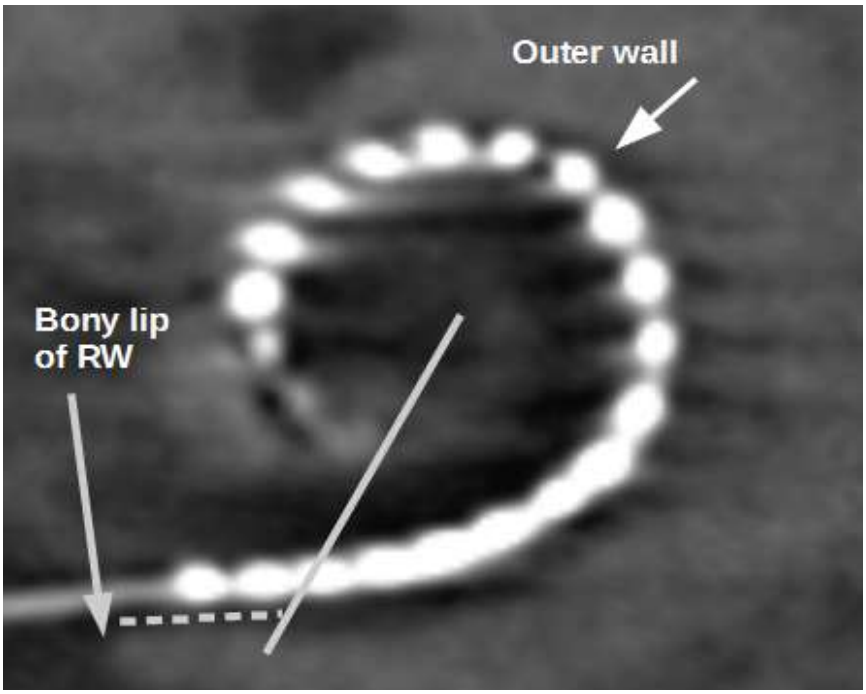


Figure 5.1. Cone-beam computed tomography (CBCT) image of implanted electrode array (Slim Straight Electrode) showing four landmarks for measurement of cochlear length: (i) bony lip of round window (RW), (ii) outer wall, (iii) modiolus, and (iv) most apical electrode (#22). These are used to calculate the number of electrodes inserted at 360° (solid line) and length between this point and the RW bony lip (dashed line). See text for details.

Results

A sequential case series approach was employed consisting of 119 CBCT images. Eleven subjects were excluded due to poor image quality related to movement artefact, and a further eight subjects' implant arrays were excluded from the study; i.e. not Cochlear™ Nucleus® slim straight or contour advance electrode array. Therefore, cochlear length was measured in 77 cochleae implanted with a slim-straight array, and 23 cochleae implanted with a contour-advanced array. Inter-rater reliability to determine cochlear length between two raters had a high level of agreement with a correlation coefficient of 0.97.

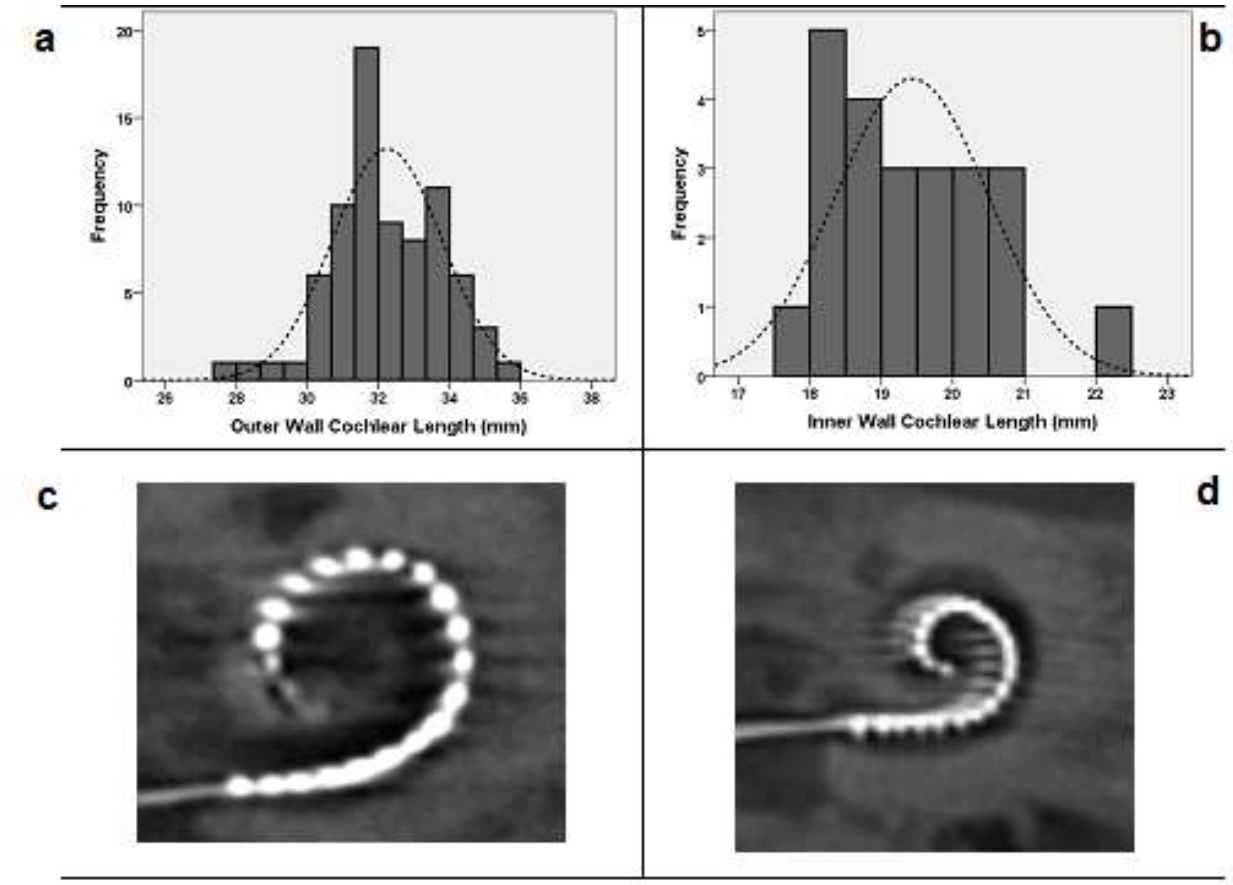


Figure 5.2. a. The distribution of cochlear length for 77 ears with a straight array (CI422 and CI522). The dashed curve shows a normal distribution. b. The distribution of cochlear length for 23 ears with a peri-modiolar array (CI24RE and CI512). The dashed curve shows a normal distribution. c. Cone-beam computed tomography (CBCT) image of an implanted straight electrode array (CI422) sitting along the outer wall and/or floating mid-array. d. CBCT image of an implanted peri-modiolar array (CI512) sitting along the inner wall of the cochlea.

The outer wall length based on ears implanted with a straight array ranged 27.44–35.91 mm, with a mean of 32.24 mm (Figure 5.2a, c). Inner wall length based on ears implanted with a peri-modiolar array ranged 17.8–22.24 mm, with a mean of 19.43 mm (Figure 5.2b, d). The Shapiro-Wilk test confirmed the normal distribution of implanted straight array and the peri-modiolar array data (Figure 5.2a and 2b respectively; $p = .354$ and $p = .327$), distribution of the raw data shown in figure 5.3.

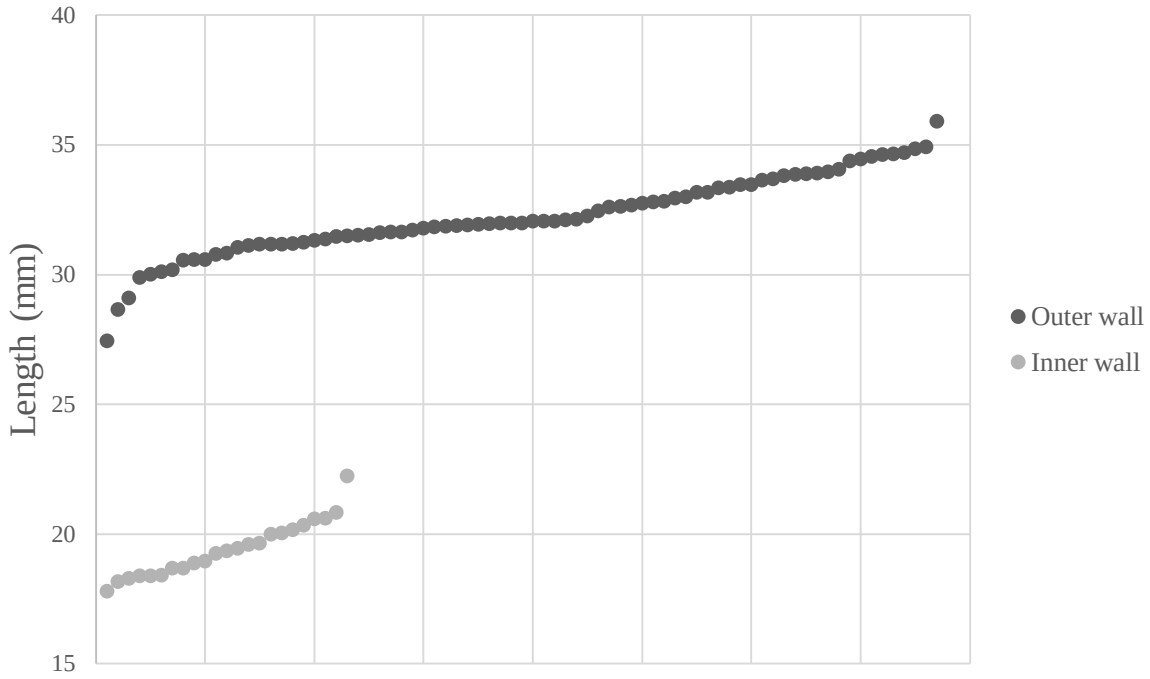


Figure 5.3. Distribution of cochlear length raw data.

No gender differences were found between mean cochlear lengths of males (n=39) and females (n=38) implanted with a straight array ($t(75) = 1.616$, $p = .110$). No significant difference was found between the side of implantation and the mean cochlear length for subjects implanted with a straight array ($t(75) = -.136$, $p = .892$).

Discussion

Previous detailed examinations of cochlear length have yielded variable measurements, in part depending on the techniques used (see Table 5.1). Their clinical usefulness has been limited by the post mortem nature of investigation and the requirement for specialized laboratory based techniques. In ante mortem studies using spiral CT, the image quality is often degraded by metal artefact, with the added concern of relatively high dosage radiation exposure to patients. There is a need for a more practical method to determine cochlear length with the knowledge that this has diverse implications, for future electrode design, surgical skills development and cochlear implant mapping. As it provides surgeons with in-sight to variability of the cochlea structure and further feedback for quality control and documentation. A greater understanding of these aspects of cochlear implantation is likely to have a positive impact on future cochlear implantation outcomes.

Previous research has found angle of rotation to be correlated with cochlear length, from which length can be derived from a mathematical spiral function based on the length from the centre of the round window to the lateral wall of the basal turn through the modiolus (Escudé et al., 2006; Ketten et al., 1998; Skinner et al., 2002). However, this remains an indirect method of cochlear length calculation in which significant inter-observer variability has been reported as opposed to a more direct method of measuring length (Rivas et al., 2017). We have described a novel and clinically viable method for measuring cochlear length based on the clarity of CBCT images of the implanted cochlea. Using the implanted electrode array lengths, assumed positions of which lie within the scala tympani, and the known relationship between percentage length and angle of rotation gleaned from human cadaveric temporal bones(Stakhovskaya et al., 2007), we have estimated cochlea lengths of the *in-vivo* implanted cochlea. While Cone-beam CT does not eliminate the metal artefact completely, it does so sufficiently to enable visualization of each electrode individually *in-situ*, it is assumed the

low electrode artefact does not have implications on the results as the calculations were based on: (i) the number of electrodes inserted at 360 degree points which the clarity of images was sufficient to identify as seen in figure one, and (ii) the remaining distance using the calibrated measure on the radiology workstation to measure from the round window lip (which is uninterrupted by artefact due to its distance from the first electrode) to the 360° rotation angle.

We have developed a formula that considered the percentage length of each structure at the 360° point and the number of electrodes inserted at that point, making use of the known dimensions of the array as a "measuring tape" within the cochlea. A previous single-observer CBCT study on cochlear length of the un-implanted cochlea(Würfel et al., 2014) disregarded potential inter-rater variability, which was recognised to be a limitation. Moreover, while providing an understanding of outer-wall length, no internal reference to validate dimensions was used and estimate inner wall lengths were not estimated. The distribution of length produced by this method assumed a normal distribution, yet mean lengths were overestimated 14.9% compared to our study using implanted electrodes as a calibration reference.

Our measurements of inner and outer wall length are very likely to be accurate and representative of the true dimensions, because: (i) they follow a normal distribution, with outer- and inner-wall average lengths of 32.24 mm (SD=1.55) and 19.43 mm (SD=1.07), respectively. (ii) Inner wall mean length was 40% shorter than outer wall, consistent with the findings of other measurement techniques such as electron microscopy histology (Stakhovskaya et al., 2007), wherein the SG was 40 to 43% shorter than the OC. Outer-wall length, based on the length of the array at 360°, represented 50% of the total length of measured cochleae, similar to findings from cast studies (Erixon et al., 2009), wherein the 360° point was equivalent to 53% of the total outer-wall length. Percentage of inner-wall length in our study, based on measurements calculated from the length of the array at the

360° point, represented 65% of the total inner-wall length. This is supported by the findings of Stakhovskaya et al.(Stakhovskaya et al., 2007) in which the SG length at 360° represented 81% of total SG length, with a 40-43% difference between SG OC. We assume the percentage of inner wall length at 360° would be less than the SG, but greater than outer wall length, therefore our reporting of a 20% difference between inner and outer wall lengths is reasonable.

Outer wall length in our study was normally distributed (Figure 5.2a), similar to other studies, despite considerable variation in lengths(Alexiades, Dhanasingh, & Jolly, 2015; Würfel et al., 2014). Though more variable (Figure 5.2b) — likely a function of lower sample size — measurements of inner wall length were also normally distributed. As for other studies(Hardy, 1938; Würfel et al., 2014; Yu, Lee, Wan, & Peng, 2015), we recognise no significant differences between right and left cochlear length. However, in contrast to other studies(Hardy, 1938; Meng, Li, Zhang, Li, & Qin, 2016; Miller, 2007; H. Sato, Sando, & Takahashi, 1991; Würfel et al., 2014), we report no significant gender-related difference in cochlear length.Yu et al.(Yu et al., 2015) measured cochlear length using MRI, and though differences between right and left cochlear lengths were not significant, right ear measurement standard deviation (1.30 cm) was much greater than that of the left (0.33) (see Figure 5.4), which was not addressed by the authors.

Since cochlear lengths were first reported(Retzius, 1884),(Hardy, 1938), considerable inter-individual variation has been demonstrated, regardless of measurement technique. That we report similar variation reinforces the need for individualization of implant arrays. A more tailored approach to choosing correct electrode length for cochlear size is important for consistent insertional depth and pitch masking. The implications of knowing the implantable cochlear length could inform future surgical techniques as well as electrode design to reduce the trauma caused by insertion, ultimately improving hearing preservation and outcomes. As

current electrode designs do not take individual variability into consideration, negative performance outcomes due to under- or over-insertion of the array might be experienced.

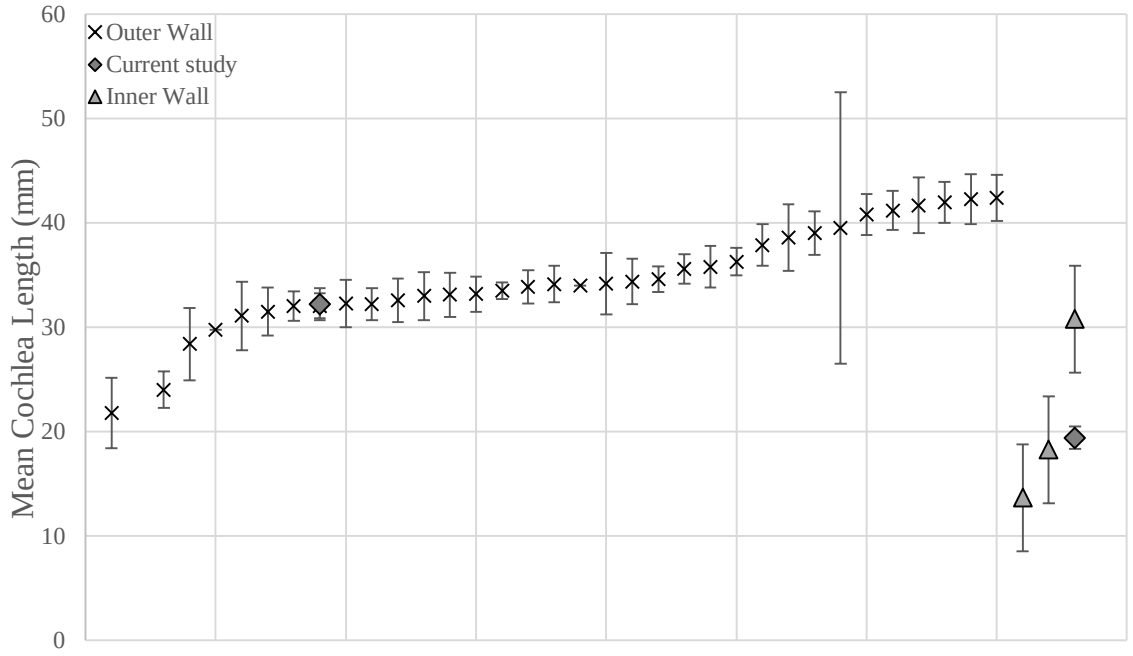


Figure 5.4. Mean inner- and outer-wall length (previous and current study).

Our results using CBCT were generally consistent with others reporting outer-wall lengths using a variety of different methods, such as histology, casts and CT (Figure 5.4). Nonetheless, discrepancies exist which may in part be explained by the limitations of the different techniques. For example, although small, the shrinkage rate of 0.6–1% in plastic casts reported when this technique was used to measure cochlear dimentions(Dimopoulos & Muren, 1990; Erixon et al., 2009) has been considered a possible cause of variation. *In vitro* histological fixation artefacts(de Groot, Veldman, & Huizing, 1987; Desciak & Maloney, 2000), metal artefact on measurements performed with CT scans, different reference points, measurement methods (angular vs length measurements), and terminology and/or the anatomical structure that was measured (e.g. cochlear duct vs bony lateral wall), in addition

to possible single rater study validation inaccuracies, may all contribute to observed differences. The shortest cochlear lengths (Figure 5.4) thus-far reported (Pochini Sobrinho et al., 2009) were possibly caused by computer alteration of cochlear images.

Alexiades et al. (2015) reported on discrepancies between cochlear length studies, which was attributed to the level at which measurements were taken in each study (OC vs OW). This discrepancy emphasizes the need for developing an accurate method to measure the implantable length of the cochlea, given implications it may have on electrode array length.

Conclusion

The complexity of measuring cochlear length necessitates various assumptions and utilization of a variety of modalities, which has resulted in a large variability between previous reports. Advances in imaging technology that enable clear visualisation of individual electrodes *in situ* provide new opportunities to study cochlear dimensions with greater accuracy. With CBCT, measuring cochlear length using known array length might reduce variability and increase accuracy in length measurements, given metric references are provided within the cochlea. Our data demonstrates the inter-individual variability in cochlear length and therefore the need for a more individualized approach in implant design and selection.

Techniques that facilitate measurement of structures within the cochlea using fixed metric references could inform on the implications of these inter-individual differences on performance outcomes. Further studies will investigate the use of CBCT measurements with an *in-situ* array to inform on other dimensions of the cochlea such as height, depth and (coiling) rotation. We did not consider cochlear width or other implant types, both of which could influence implantable length of the cochlea and further inform potential effects of electrode diameter and position on performance outcomes.

Authors	**Technique**	**Measured structure**	***n***	**Mean length (mm)**	**Range (mm)**	**SD**
Retzius et al. (1884)	Histology	Cochlear duct	5	33.5	32–34	0.8
Hardy (1938)	Histology	OC	68	31.52	25.26–35.46	2.3
Bredberg et al. (1965)	Histology	OC	-	34	-	-
Walby (1985)	Histology	OC and ST	20	OC 32.6 ST 24.03	30.1–36.4 20.8–27.6	2.1 1.74
Hinojosa et al. (1985)	Histology	CL and SG	16	CL 32.88 SG 13.69	29.34–37.52 12–16.14	2.17 1.14
Pollak et al. (1987)	Histology	OC	9	28.4	24–33.5	3.44
Wright et al. (1987)	Histology	OC	10 18 14 14	33.5 34.7 32.9 34.25	- - - -	2.9 1.1 1.9 3.1
Úlehlová et al. (1987)	Histology	Cochlear duct	50	34.2	28–40.1	2.93
Takagi & Sando (1989)	Histology	OW	1	30.8 in 2D 36.3 in 3D	-	-
Ariyasu et al. (1989)	Histology	OC and SG	2	32 OC 12 SG	-	-
Sato et al. (1991)	Histology	OW and IW	18	OW 38.6 IW 30.8	32.7–43.2 26.4–34.5	3.19 2.7
Kawano et al. (1996)	Histology	OC, ST OW and ST IW	8	OC 35.58 ST OW 40.81 ST IW 18.29	34.15–37.9 37.93–43.81 16.99–21.17	1.41 1.97 1.47
Ketten et al. (1998)	CT	Cochlear canal	20	33.01	29.07–37.45	2.31
Skinner et al. (2002)	CT	Cochlear canal (with hook)	13	With hook 34.62 Without hook 32.07	32.94–36.57 30.43–33.97	1.22 1.19
Adunka et al. (2005)	Histology	Basal cochlear length	8	20.3	18.8–22	-
Escudé et al. (2006)	CT	OW	42	34.4	30.76–37.41	2.2
Stakhovskaya et al. (2007)	Histology	OC and SG	9	OC 33.13 SG 13.69	30.5–36.87 12.54–14.62	2.11 0.8
Erixon et al. (2009)	Plastic cast	OW	58	42	38.6–45.6	1.96
Sobrinho et al. (2009)	Histology +MRI	Spiral canal	6	21.8	17–26.5	3.39
Lee et al., (2010)	Histology	Cochlear duct, inserted length and depth of insertion	27	CDL 30.8 IL 15.1 DI 18.7	25.5-35.1 7.9-21 9-24	2.6 3.3 3.9
Erixon & Rask-Andersen (2013)	Plastic cast	OW	51	41.2	37.6–44.9	1.86
Würfel et al. (2014)	CBCT	OW	436	37.9	30.8–43.2	1.98
Singla et al. (2015)	Histology	OW of basal turn	40	20.42	15.6–24.6	2.15
Yu et al. (2015)	MRI	Cochlear canal	4 (L) 8 (R)	31.1 39.5	28.1–35.5 18.2–59.6	3.3 13

Würfel et al. (2015)	Histology	CL	9	Histological serial grinding imaging 41.7 microCT 42.3 fpVCT 42.4	38.7-45.3 39.3-46.1 39.8-45.8	2.68 2.38 2.21
Johnston et al. (2016)	CT	Preimplant OW and OC (incomplete (II) and full (FI) insertions)	(II)22 (FI) 41	OW (II) 32.3 OC (II) 28.7 OW (FI) 33.2 OC (FI) 29.6	- - - -	2.27 - 1.68 -
Meng et al. (2016)	CT	OW	310	35.8	30.7–42.2	2
Rivas et al. (2017)	CT	Cochlear duct	276	*A*-value measure 33.87 Direct measure 34.14	- -	1.61 1.75
Koch et al. (2017)	Histology	OC, LW and EL	10	OC 32.05 LW 39.04 EL 36.28	30.45-35.1 33.58-41.68 34.43-38.63	1.4 2.06 1.32
Thong et al. (2017)	CT	Basal cochlear length	157	-	19.71-25.09	-
Grover et al. (2018)	CT	Cochlear duct	104	29.8	28-34.3	-
This study 2017	CBCT	OW	77	32.24	27.44–35.91	1.55
This study 2017	CBCT	IW	23	19.43	17.80–22.24	1.07

Table 5.1. Summary of cochleae length reports (previous and current study)

Chapter 6

General discussion and results

The development of any medical device begins with an idea and develops into crude prototypes that are refined and developed through research and trial-and-error. Cochlear implants are no exception, from the development of the idea to the failure of two out of three prototypes, there are currently over 350,000 implantees worldwide. Through research, the CI has been in the refinement stages for the past 40 years to improve electrode array design and placement, signal processing strategies and stimulation paradigms to ultimately optimise performance outcomes and improve quality of life for those with permanent severe hearing loss.

Refining CIs should take into account individual variability, and address this using both good clinical skills and evidence-based measures and decision-making. Good clinical skills, using a person-centred model of care, can foster higher motivation and adherence to rehabilitation after implantation and can lead to improved outcomes of an intervention (Bennett, Jayakody, Eikelboom, Taljaard, & Atlas, 2016; Grenness, Hickson, Laplante-Lévesque, & Davidson, 2014). However, evidence-based measures, such as objective assessments, self-report scales and standardised questionnaires, enable researchers to evaluate and compare the effects of innovations in technologies and therapies. Objective measures in particular, can provide more granular information about how an intervention has influenced a particular outcome.

While individualizing the CI for each candidate is attempted routinely intra-operatively (e.g. medical and surgical technique modifications for each patient as necessary), technically (e.g. selection of the type of implant array), and post-operatively (e.g. programming of the CI), it can be assumed that the right combination of these could lead to the best outcomes. However, with ongoing advancements in technology and surgical techniques, along with the many

variables that could influence speech outcome measures, there is no clear paradigm for the best combination. If a central focus is placed on the surgery, there are three major predictors of outcomes which interact at varying degrees: (i) pre-surgery factors, such as demographic information including age and duration of deafness (Holden et al., 2013); (ii) peri-surgery information, including electrophysiological tests (impedance, NRT, EABR, and artefact measures) as well as imaging (Ruivo et al., 2009; Saeed et al., 2014); and (iii) post-surgery information, involving active clinical mapping parameters (T- and C-levels, stimulation mode and rate, pulse width, and number of activated channels) and data logging information (Busch, Vanpoucke, & van Wieringen, 2017; Vaerenberg et al., 2014; Zwolan & Stach, 2016).

This thesis examined the clinical utility of imaging and intraoperative electrophysiological measures in adults with CIs. Specifically, it addressed the following questions: (i) What is the current use of intraoperative electrophysiological objective measures of CI by clinical audiologists?; (ii) Can we use intra-operative eABR waveforms generated with a fixed current level to estimate neural integrity, electrode placement and predict mapping levels?; (iii) How does poor electrode placement effect electrode impedances, intra-operative eABR waveforms, and CI mapping?; and (iv) can CBCT with the CI *in situ* be used to better calculate the length of the cochlea to understand the anatomical variability and inform new designs of implant arrays? The findings of these as well as future directions of research are each discussed below.

What is the current use of intraoperative electrophysiological objective measures of CI by clinical audiologists?

Electrically-evoked potentials and impedance measures have been measured intra-operatively and post-operatively for over 25 years at the Sydney Cochlear Implant Centre (SCIC) in

NSW. While an extensive test battery is completed, a thorough cost-benefit analysis has not yet been undertaken. Given the time needed to complete these tests, which includes an increase in the duration of anaesthesia as well as an increase in staff and theatre time, it is unclear what extent these electrophysiological test results are used to guide surgical decisions, in the programming of the cochlear implant and in the counselling and rehabilitation given to patients post-operatively. To understand the way that these test results are used by clinical audiologists after CI surgery, a questionnaire was developed and administered online to SCIC audiologists. The results indicated that, although the applicability of these tests apply for both surgeons and clinicians, there are inconsistencies in the use of the data and in the views expressed regarding their applicability.

The use of electrophysiological and imaging data should take into account eliminating redundancy while maximizing clinical utility. Certainly, the results of this thesis indicate that the clinical utility of these tests should be improved given the cost and time of conducting these tests per year; that is, test results that take over 50% of the intraoperative test battery time were not used by over 25% of the clinicians in the current study. The reason for this result is unclear but could include the following possibilities; redundancies exist in the information gathered by the test battery, more training is required for clinicians to effectively utilise the objective information within their clinical practice, and/or there is a paucity of information about their clinical utility. While the majority of clinicians expressed willingness for training, the order in which these questions should be addressed is important. That is, a full understanding of the clinical utility and applicability of the intra-operative test battery needs to be conducted first to increase its efficiency, thereby making training possible to maximize the clinical utility and provide a more individualized level of patient care. To address this, the clinical utility of eABR and imaging was investigated across a retrospective patient dataset.

Can we use intra-operative eABR waveforms generated with a fixed current level to estimate neural integrity, electrode placement and predict mapping levels?

The spiral ganglion survival rate can affect the efficacy of the CI, as they transmit the electrical stimuli to the central nervous system, therefore an increased survival rate could lead to better electrical transmission. While studies have investigated the effect of chronic electric stimulation and/or applying exogenous neurotrophins on spiral ganglion cell survival rate, these studies were confined to animal models and *in-vitro* human studies (Konerding et al., 2017; Seyyedi, Eddington, & Nadol, 2013; Robert K. Shepherd, Coco, & Epp, 2008). On the other hand, studies that have investigated the spiral ganglion survival rate with speech perception outcomes have contradicting results. For example, Seyyedi, Viana and Nadol (2014) reported better word recognition scores in subjects with a higher spiral ganglion survival rate, however, Blamey (1997) argued that only a 15% spiral ganglion survival rate is required for adequate CI performance and did not find a strong correlation between spiral ganglion survival rate and speech perception. The variability across studies may indeed result from the insensitivity of speech perception outcomes, which are influenced by the perception of the auditory signal as well as linguistic and cognitive abilities (which are often not assessed or accounted for within clinical CI studies).

On the other hand, the amplitude of wave V of the eABR (eV) elicited with a fixed current level and pulse width from individual electrodes can provide information about integrity of the neurones or the effectiveness of electrical current reaching the spiral ganglion cells (which could be affected by proximity to the neural elements or changes in electrode impedance). As such, inter-individual variability and the integrity of the neural population can be more precisely accounted for, which could be combined with other techniques such as CBCT to evaluate modiolar proximity and the electrode-neural interface. In this case, the combination of CBCT and eABR could be used to validate the effects of pharmaceutical

interventions on the prevention and/or reduction of spiral ganglion degeneration. While different studies have investigated eABR waveforms for this purpose, there is no clear consensus to its applicability and prediction of outcomes. This lack of consensus may have existed due to the different methodologies used to measure eV amplitude, confounds of stimulus and facial-nerve artefacts on the measurement of the neural response, and the unaccounted for linguistic and cognitive factors which are known to confound speech outcome measures (which is used across many studies as a standard outcome measure). To address these factors, manuscript 2 compared different methods of calculating eV amplitudes for discrete electrode locations (i.e. basal, mid, and apical). The only significant difference was found when comparing electrode placement within the cochlea (i.e. apical, mid and basal; as shown previously by Gordon, Papsin, & Harrison (2007), however no single method appeared superior, suggesting that this may not have significantly contributed to the variability in the literature. The second point was addressed by comparing eABR waveforms with and without facial nerve artefact, as well as comparing eABR waveforms before and after exponential fitting to remove electrical artefact form the stimulus. In both conditions, no significant difference was found which also suggests that these artefacts generally are not a major cause of variability. The final point was addressed by correlating the amplitudes to mapping levels collected at different intervals. While a significant correlation existed at all time-points tested (i.e. switch-on, 4 weeks and 12 weeks), the correlation was strongest at switch-on, indicating the clinical utility of eABR eV amplitude in programming the implant once the implant has been activated. A future prospective study could be to investigate speech outcomes for implantees who were programmed based on intraoperative eABR eV amplitudes. Our retrospective dataset in manuscript 2 was limited by the relatively small proportion of individuals who had speech perception tests completed (in some cases due to having English as a second language). Therefore, there was insufficient statistical power to

show a correlation between speech perception outcomes and eV amplitudes. Nonetheless, if only a limited dataset is used, when comparing across specific electrode sites and dividing the recipients into good (>75%) and poor (<75%) sentence perception scores using CUNY sentences presented in quiet, the basal area showed a trend (which did not reach significance across methods) from preoperative scores to 12 months post-implant (see Figure 6.1). That is, the amplitude was eV was larger as the amount of change in the scores increased. DeVries, Scheperle and Bierer (2016), in a cohort of 10 adults, found higher eCAP amplitudes correlated with better speech perception scores, therefore a further exploration of this trend with eABR with sufficient statistical power in a prospective study could be of interest.

Manuscript 2 also showed significant differences between array types. That is, the amplitude of eV was significantly lower for the peri-modiolar array compared to the straight array (in the mid-region of the array); an unexpected result due to the widely accepted view that the peri-modiolar array is located more proximally to the modiolus which should have increased the magnitude of neural stimulation. It is possible that this may be due to the broad stimulation mode used for this study (MP1+2), compared with a more focused stimulation mode (BP+2) which may be more sensitive to smaller changes in the electrode-neuron interface. However, by investigating MP1+2 mode, the clinical applicability is increased as it is the default stimulation mode for CI programming, which questions whether the broad stimulation mode of MP1+2 reduces the effectiveness of positioning the electrode array close to the modiolus. Alternatively, this questions whether simply the choice of array type (peri-modiolar versus straight) and its proximity to the modiolus is sufficient to influence the electrical excitation of the neurones, or whether differences in impedance from different designs of the electrode arrays could negate the usefulness of its positioning. Certainly this is an area which is worth developing a greater understanding as it may influence future designs of electrode arrays.

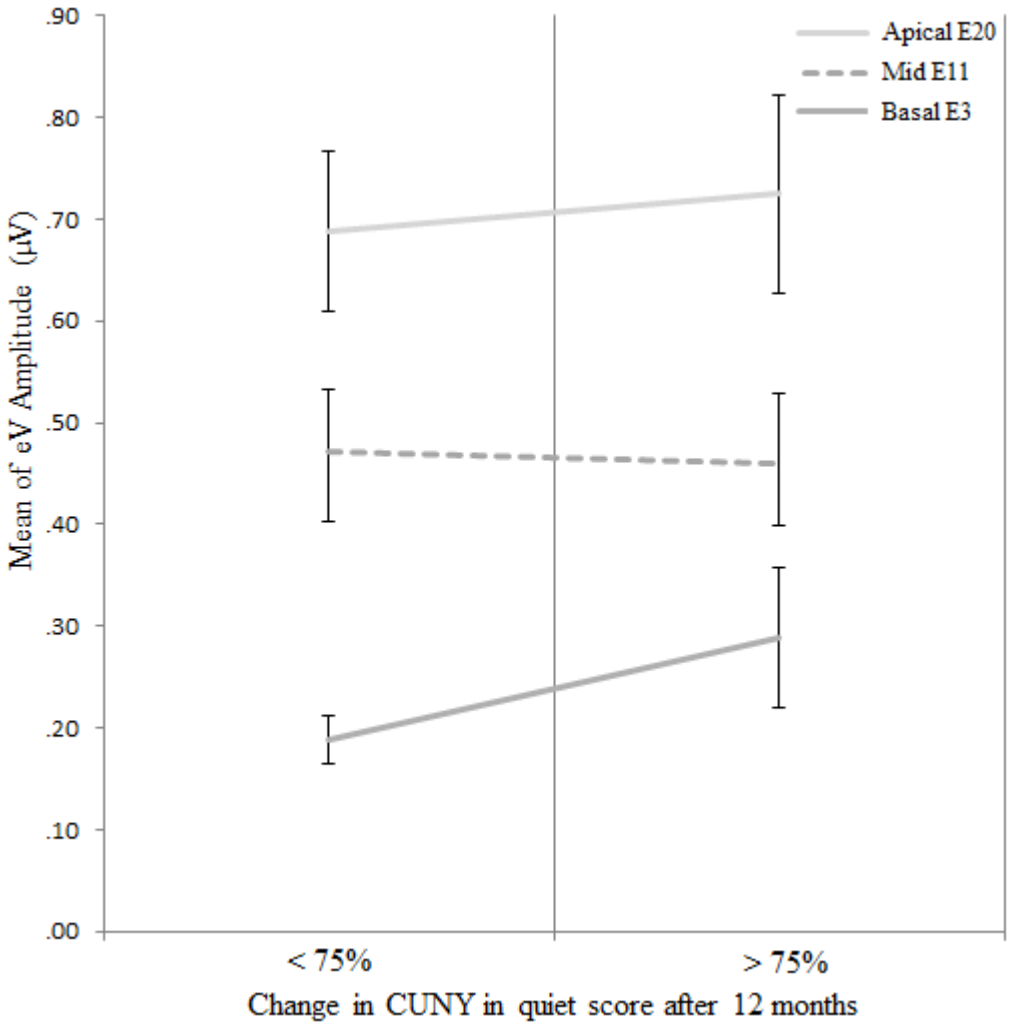


Figure 6.1. Mean change in CUNY sentences presented in quiet scores divided into good (>75%) and poor (<75%) plotted according to mean eV eABR amplitude.

By investigating eABR amplitudes in MP1+2 mode while controlling for pulse width and current level, in both manuscripts, 2 and 3 on two separate cohorts (n=50, n=97 respectively) a strong correlation with eV amplitude and mapping T- and C-levels was found when the electrode array was (correctly) placed in the scala tympani, which reinforces the applicability of eABR as a sensitive tool for predicting T- and C-levels.

How does poor electrode placement effect electrode impedances, intra-operative eABR waveforms, and CI mapping

eABR eV amplitude was shown to predict T- and C- levels as exhibited in manuscripts 2 and 3 when electrodes are placed in the scala tympani. While this correlation has been shown previously, threshold levels and smaller cohorts were used in such studies. The larger numbers in the current study in manuscript 3, while controlling for eABR stimulation parameters and its combination with imaging, enabled a greater understanding of the limitations of the clinical utility of using eABR amplitudes to estimate mapping parameters. That is, the strength of the correlation between eV amplitudes and both impedance and mapping T levels at switch on decreased considerably in cases of translocation of the electrode array, and was not present when all basal electrodes were shown to be in scala vestibuli. This indicates that while only placement of basal electrodes can be reliably validated by imaging, as discussed in manuscript 4, it is sufficient, for clinical purposes. This is evident by the findings of weaker correlations between eABR amplitudes and mapping T levels, as more basal electrodes were detected into the scala vestibuli. As such, scalar placement should be validated with imaging prior to using eV amplitudes to predict switch on T and C levels.

While eV amplitude by itself was not sensitive enough to detect scalar placement as discussed in manuscript 3, this finding may result from the small sample size of scalar misplacements, or it may indicate eABR is not a sufficiently sensitive measure to detect scalar placement, particularly in the broad stimulation mode MP1+2 as discussed earlier.

Can we develop a technique to better calculate the length of the cochlea to better understand the anatomical variability and possibly inform new designs of implant array?

As wide variability remains in CI speech outcomes as discussed earlier in this thesis, the investigation of the source of variability remains a widely researched topic. This is complicated further due to the multiple interactions of these variables at varying degrees at an individual basis. Therefore, as manuscript 2 and 3 have shown, the clinical utility of eABR in predicting mapping T- and C- levels has shown to be conditional of correct array placement. While this finding highlights the importance of verifying electrode array placement with imaging, it also puts forward the major role electrode placement may have in the variability of CI outcomes.

Although electrode placement is identified as one of many variables which may affect CI outcomes, this is further complicated as the placement cannot be investigated on its own without looking at the multiple variables which can affect it. Such factors include surgical factors, array design and inter-individual anatomical cochlear variations. As the size of the cochlea presumably affects the electrode array's position, it can be assumed it can partially account for the intra-cochlear trauma caused in some cases. Therefore, this thesis aimed to explore the variability of cochlear length by developing a technique to measure cochlear length. Acknowledgment of this variability might contribute to improved electrode design (in terms of electrode length) and may provide surgeons with insight and feedback for quality control, surgical skill training and documentation which may lead to more consistent and ideal placement of electrodes. While cochlear length has been explored previously, the inconsistencies between the reported ranges can be attributed to a range of factors, described in manuscript 4. Therefore, the technique developed took into account the possible source of these discrepancies to provide a more accurate measure of cochlear length. That is, the method described was conducted *in vivo*, to control for possible artefacts caused by *in vitro* measurements. It also used an imaging modality that eliminates metal artefact and provides clarity without the need for composition of pre- and post- implant images and enabled the use

of the known dimensions of the electrode array as a physical measurement tape within the cochlea. Finally, measurements were compared across two raters to control for possible single rater inaccuracies.

Considerable inter-individual variation has been shown in previous studies, regardless of measurement technique. The data reported in this thesis fell with a range that has been previously demonstrated, which highlights the need for individualization of implant arrays. As insertion depth is dependent on both electrode array length and cochlear length (Yukawa et al., 2004), a more individual approach to choosing correct electrode length for cochlear size is important for consistent insertional depth, pitch masking and inform future surgical techniques to reduce insertion trauma. This may ultimately lead to control for under- or over-insertion of the array on an individual basis, which may impact performance outcomes.

Intraoperative test battery recommendations

While eCAP may be more routinely used in a clinical setting due to the advantages as discussed earlier in this thesis, eABR proves to be a more accurate and useful tool, particularly in cases in which eCAP measurements may not be recorded (e.g. inner ear malformations), or in cases that require a more comprehensive overview of the integrity of the auditory pathway up to the brainstem (e.g. auditory neuropathy). In such cases, eABR can be used to predict mapping of switch on T- and C-levels where scalar placement of the basal electrodes has been confirmed with imaging. Viccaro, Covelli, de Seta, Balsamo and Filipo (2009) emphasize the importance of imaging during surgery, as they found that intra-operative electrical stimulation is an indirect method of determining electrode placement and imaging is the option of choice to confirm placement. Carelsen et al. (2007) argued that while intra-operative neurophysiological tests are not conclusive of the electrode placement and that imaging of the electrode array can facilitate the optimal placement of the array, Stenver's

view scans could result in possible false positives in cases of anatomical anomalies and false negatives for example extra-cochlear unfolding. Imaging however is usually restricted to post-surgery in most clinical settings, thus limiting the surgeon's ability intra-operatively to make any clinical decisions regarding repositioning or extraction / reimplanting.

However, this thesis has shown limitations of using eABR test results to predict mapping levels at switch on in cases of scalar displacement, and the insensitivity of current test measures of indicating scalar location when compared to the accuracy imaging provides. Therefore, postoperative imaging utilizing modalities that provide image quality sufficient to indicate scalar position (e.g. CBCT) would be recommended as standard protocol in any clinical setting.

However, this thesis has provided evidence to recommend two different set batteries:

(i) Utilizing the information in a more effective way by providing clinical training for a more cost effective approach, while limiting eABR testing to MP1+2 testing in which would reduce theatre time by approximately six minutes. This could amount to savings of up to $89,000 per year (cost of two CI surgeries including device) based on the number of surgeries from which the data for this thesis was collected. This recommendation is made based on reducing redundancy, as the applicable clinical utility of the MP1+2 for mapping while imaging is a gold standard for electrode placement. While performing imaging postoperatively would limit the ability to adjust array placement intraoperatively, there are conflicting reports as to the extent to which this can be done without causing further intra-cochlear trauma.

(ii) As there has been shown somewhat limited use of intraoperative eABR data beyond CI surgery when compared with eCAP, a more basic test battery (eCAP

and impedances) could be recommended, complemented with imaging for cases of normal cochlear morphology. However, a more comprehensive test battery could be recommended for cases of cochlear malformation or complicated cases which require predicting mapping. While this test battery amounts to a reduction of nine minutes of surgery time (approximately $133,500 savings per year), it would not provide an accurate indication of best mode of stimulation for cases with facial nerve interference, as eABR would.

Limitations and future research

This thesis examined the use of intra-operative electrophysiological tests and imaging to detect electrode placement and the effects it may have. While the scale of the data available at SCIC provided an opportunity to gain a better understanding of how clinical audiologists currently interpret and use information from intra-operative electrophysiological tests (as aimed with the survey) and allowed us to address specific clinical research questions, Addressing the survey to only one clinic is acknowledged as a limitation as a systematic cost-benefit analysis across various practices is warranted to generalize and inform other practices which may not have an extensive test battery.

Furthermore, the results obtained provide insight and highlights the importance of imaging in a test battery and accounting for the inter-individual variability in cochlear length, however the retrospective nature of the study leaves many questions unanswered, particularly as this study was restricted in the available speech outcomes measures. Further research is needed to more effectively measure CI outcome performance which is sensitive to the ceiling effects current speech outcome measures achieve, as well as control for the variability linguistic and cognitive factors provide. In addition, further research is needed to accurately identify the

inter-individual variability of other aspects of cochlear dimensions. Gaining a better understanding of the contribution inter-individual variability provides on CI electrode placement is necessary to inform on surgical techniques and electrode design which could ultimately lead to more consistent placement into the scala tympani.

References

Adunka, O., Unkelbach, M. H., Mack, M. G., Radeloff, A., & Gstoettner, W. (2005). Predicting basal cochlear length for electric-acoustic stimulation. *Archives of Otolaryngology--Head & Neck Surgery*, *131*(6), 488–92.

Alexiades, G. B., Dhanasingh, A., & Jolly, C. (2015). Method to estimate the complete and two-turn cochlear duct length. *Otology & Neurotology*, *36*, 904–907.

Amoodi, H. a., Mick, P. T., Shipp, D. B., Friesen, L. M., Nedzelski, J. M., Chen, J. M., & Lin, V. Y. W. (2012). Results with cochlear implantation in adults with speech recognition scores exceeding current criteria. *Otology & Neurotology*, *33*(1), 6–12.

Ariyasu, L., Galey, F. R., Hilsinger, R., & Byl, F. M. (1989). Computer-generated three-dimentional reconstruction of the cochlea. *Otolaryngology-Head and Neck Surgery*, *100*(2), 87–91.

Arweiler-Harbeck, D., Mönninghoff, C., Greve, J., Hoffmann, T., Göricke, S., Arnolds, J., … Schlamann, M. (2012). Imaging of electrode position after cochlear implantation with flat panel CT. *ISRN Otolaryngology*, *2012*.

Aschendorff, A., Kromeier, J., Klenzner, T., & Laszig, R. (2007). Quality control after insertion of the nucleus contour and contour advance electrode in adults. *Ear and Hearing*, *28*(2 Suppl), 75S–79S.

Aubert, L. R., & Clarke, G. P. (1994). Reliability and predictive value of the electrically evoked auditory brainstem response. *British Journal of Audiology*, *28*(3), 121–124.

Auris Medical AG. (2015). Auris medical and cochlear to collaborate on clinical trial with AM-111 for otoprotection during cochlear implant surgery. Retrieved from

https://globenewswire.com/news-release/2015/06/25/747480/10139762/en/Auris-Medical-and-Cochlear-to-Collaborate-on-Clinical-Trial-with-AM-111-for-Otoprotection-during-Cochlear-Implant-Surgery.html#sthash.bxgNwD2N.dpuf

Australian Society of Anaesthetists. (2016). Health insurance rebates for anaesthesia procedures. Retrieved from http://www.asa.org.au/UploadedDocuments/Policy/ASA Billing information sheet 2016 Version FINAL.pdf

Avci, E., Nauwelaers, T., Hamacher, V., & Kral, A. (2017). Three-dimensional force profile during cochlear implantation depends on individual geometry and insertion trauma. *Ear and Hearing*, *38*(3), e168–e179.

Avci, E., Nauwelaers, T., Lenarz, T., Hamacher, V., & Kral, A. (2014). Variations in microanatomy of the human cochlea. *Journal of Comparative Neurology*, *522*(14), 3245–3261.

Balkany, T. J., Eshraghi, A. a, & Yang, N. (2002). Modiolar proximity of three perimodiolar cochlear implant electrodes. *Acta Otolaryngol*, *122*(4), 363–369.

Bennett, Jayakody, D. M. P., Eikelboom, Taljaard, D. S., & Atlas. (2016). A prospective study evaluating cochlear implant management skills: development and validation of the Cochlear Implant Management Skills survey. *Clin. Otolaryngol*, *41*, 51–58.

Best, V., Keidser, G., Freeston, K., & Buchholz, J. M. (2016). A dynamic speech comprehension test for assessing real-world listening ability. *Journal of the American Academy of Audiology*, *27*(7), 515–526.

Biedron, S., Prescher, A., Ilgner, J., & Westhofen, M. (2010). The internal dimensions of the cochlear scalae with special reference to cochlear electrode insertion trauma. *Otology & Neurotology*, *31*(5), 731–737.

Blamey, P. (1997). Are spiral ganglion cell numbers important for speech perception with a cochlear implant? *The American Journal of Otology*, *18*(6 Suppl), S11-2.

Blamey, P., Arndt, P., Bergeron, F., & Bredberg, G. (1996). Factors affecting auditory performance of postlinguistically deaf adults using cocjlear implants. *Audiology & Neuro-Otology*, *1*, 293–306.

Blume, S. S. (1999). Histories of cochlear implantation. *Social Science and Medicine*, *49*(9), 1257–1268.

Boyer, E., Karkas, A., Attye, A., Lefournier, V., Escudé, B., & Schmerber, S. (2015). Scalar localization by cone-beam computed tomography of cochlear implant carriers: a comparative study between straight and periomodiolar precurved electrode arrays. *Otology & Neurotology*, *36*(3), 422–429.

Bredberg, G., Engstrom, H., & Ades, H. W. (1965). Cellular pattern and nerve supply of the human organ of corti-a preliminary report. *Arch Otolaryngologica*, *82*, 462–469.

Brenner, D. J., & Hall, E. J. (2007). Computed tomography--an increasing source of radiation exposure. *The New England Journal of Medicine*, *357*(22), 2277–2284.

Broomfield, S. J., Da Cruz, M., & Gibson, W. P. R. (2013). Cochlear implants and magnetic resonance scans: A case report and review. *Cochlear Implants International*, *14*(1), 51–5.

Brown, C. J., Abbas, P. J., Fryauf-Bertschy, H., Kelsay, D., & Gantz, B. J. (1994). Intraoperative and postoperative electrically evoked auditory brain stem responses in nucleus cochlear implant users: implications for the fitting process. *Ear and Hearing*, *15*(2), 168–176.

Brown, C. J., Hughes, M. L., Luk, B., Abbas, P. J., Wolaver, A., & Gervais, J. (2000). The relationship between EAP and EABR thresholds and levels used to program the nucleus 24 speech processor: data from adults. *Ear and Hearing*, *21*(2), 151–163.

Busch, T., Vanpoucke, F., & van Wieringen, A. (2017). Auditory environment across the life span of cochlear implant users: insights from data logging. *Journal of Speech, Language, and Hearing Research : JSLHR*, *60*(5), 1362–1377.

Cafarelli Dees, D., Dillier, N., Lai, W. K., Von Wallenberg, E., Van Dijk, B., Akdas, F., … Smoorenburg, G. F. (2005). Normative findings of electrically evoked compound action potential measurements uing the neural response telemetry of the nucleus CI24M cochlear implant system. *Audiology and Neurotology*, *10*(2), 105–116.

Carelsen, B., Grolman, W., Tange, R., Streekstra, G. J., Van Kemenade, P., Jansen, R. J., … Fokkens, W. J. (2007). Cochlear implant electrode array insertion monitoring with intra-operative 3D rotational X-ray. *Clinical Otolaryngology*, *32*(1), 46–50.

Carlyon, R. P., Van Wieringen, A., Deeks, J. M., Long, C. J., Lyzenga, J., & Wouters, J. (2005). Effect of inter-phase gap on the sensitivity of cochlear implant users to electrical stimulation. *Hearing Research*, *205*(1–2), 210–224.

Causon, A., Verschuur, C., & Newman, T. a. (2013). Trends in cochlear implant complications: implications for improving long-term outcomes. *Otology & Neurotology*, *34*(2), 259–265.

Chen, X., Liu, B., Liu, S., Mo, L., Liu, H., Dong, R., … Zhang, L. (2011). The development of auditory skills in infants with isolated Large Vestibular Aqueduct Syndrome after cochlear implantation. *International Journal of Pediatric Otorhinolaryngology*, *75*(7), 943–947.

Choi, C. T. M., & Lee, Y. (2012). A review of stimulating strategies for cochlear implants. In *Cochlear Implant Research Updates* (pp. 77–90). InTech.

Choi, K. J., & Kaylie, D. M. (2017). What is the role of preoperative imaging for cochlear implants in adults with postlingual deafness? *Laryngoscope*, *127*(2), 287–288.

Chole, Richard A, Hullar, Timothy E, Potts, L. G. (2014). Conductive component after cochlear implantation in patients with residual hearing conservation. *American Journam of Audiology*, *23*, 359–364.

Chouard, C. H. (2015). The early days of the multi channel cochlear implant: Efforts and achievement in France. *Hearing Research*, *322*, 47–51.

Cinar, B. C., Yarali, M., Atay, G., Bajin, M. D., Sennaroglu, G., & Sennaroglu, L. (2017). The role of eABR with intracochlear test electrode in decision making between cochlear and brainstem implants: preliminary results. *European Archives of Oto-Rhino-Laryngology*, *274*(9), 3315–3326.

Ciprut, A., & Akdas, F. (2007). Electrically evoked auditory brainstem responses in cochlear implant patients. *The Mediterranean Journal of Otology*, *3*, 6–11.

Clark, G. M., & Hallworth, R. J. (1976). A multiple-electrode array for a cochlear implant. *The Journal of Laryngology and Otology*, *90*(7), 623–627.

Cochlear®. (2014a). *Contour Advance ® Electrode (CI512)*.

Cochlear®. (2014b). *Slim Straight Electrode (CI522)* (Vol. 382660).

Cohen, L. T., Xu, J., Xu, S. A., & Clark, G. M. (1996). Improved and simplified methods for specifying positions of the electrode bands of a cochlear implant array. *The American Journal of Otology*, *17*, 859–865.

Copeland, B. J., Pillsbury, H. C., & Buchman, C. A. (2004). Prospective evaluation of intraoperative cochlear implant radiographs. *Otology and Neurotology*, *25*, 295–297.

Cosetti, M. K., Shapiro, W. H., Green, J. E., Roman, B. R., Lalwani, A. K., Gunn, S. H., … Waltzman, S. B. (2010). Intraoperative Neural Response Telemetry as a Predictor of Performance. *Otology & Neurotology*, *31*(7), 1095–1099.

Cosetti, M. K., Troob, S. H., Latzman, J. M., Shapiro, W. H., Roland, J. T., & Waltzman, S. B. (2012). An Evidence-Based Algorithm for Intraoperative Monitoring During Cochlear Implantation. *Otology & Neurotology*, *33*(2), 169–176.

Cox, R. M., & Xu, J. (2010). Short and long compression release times: speech understanding, real-world preferences, and association with cognitive ability. *Journal of the American Academy of Audiology*, *21*(2), 121–138.

Dalbert, A., Huber, A., Veraguth, D., Roosli, C., & Pfiffner, F. (2016). Assessment of Cochlear Trauma During Cochlear Implantation Using Electrocochleography and Cone Beam Computed Tomography. *Otology & Neurotology*, *37*(5), 446–453.

Davis, T. J., Zhang, D., Gifford, R. H., Dawant, B. M., Labadie, R. F., & Noble, J. H. (2016). Relationship between electrode-to-modiolus distance and current levels for adults with cochlear implants. *Otology & Neurotology*, *37*(1), 31–37.

de Groot, J. C., Veldman, J. E., & Huizing, E. H. (1987). An improved fixation method for guinea pig cochlear tissues. *Acta Oto-Laryngologica*, *104*, 234–242.

De Seta, D., Torres, R., Russo, F. Y., Ferrary, E., Kazmitcheff, G., Heymann, D., … Nguyen, Y. (2017). Damage to inner ear structure during cochlear implantation: Correlation between insertion force and radio-histological findings in temporal bone specimens. *Hearing Research*, *344*, 90–97.

Desciak, E. B., & Maloney, M. E. (2000). Artifacts in frozen section preparation. *Dermatologic Surgery*, *26*(5), 500–504.

DeVries, L., Scheperle, R., & Bierer, J. A. (2016). Assessing the electrode-neuron interface with the electrically evoked compound action potential, electrode position, and behavioral thresholds. *JARO - Journal of the Association for Research in Otolaryngology*, *17*(3), 237–252.

Di Nardo, W., Ippolito, S., Quaranta, N., Cadoni, G., & Galli, J. (2003). Correlation between NRT measurement and behavioural levels in patients with the Nucleus 24 cochlear implant. *Acta Otorhinolaryngologica Italica*, *23*(5), 352–355.

Dietz, A., Wüstefeld, M., Niskanen, M., & Löppönen, H. (2016). Cochlear implant surgery in the elderly: The feasibility of a modified suprameatal approach under local anesthesia. *Otology and Neurotology*, *37*(5), 487–491.

Dimopoulos, P., & Muren, C. (1990). Anatomic variations of the cochlea and relations to other temporal bone structures. *Acta Rodiologico*, *31*(5), 439–444.

Ebrahimi-Madiseh, A., Eikelboom, R. H., Jayakody, D. M., & Atlas, M. D. (2016). Speech perception scores in cochlear implant recipients: An analysis of ceiling effects in the CUNY sentence test (Quiet) in post-lingually deafened cochlear implant recipients. *Cochlear Implants International*, *17*(2), 75–80.

Eisen, M. D. (2003). Djourno, Eyries, and the first implanted electrical neural stimulator to restore hearing. *Otology & Neurotology*, *24*(3), 500–506.

Erixon, E., Ho, H., Wadin, K., & Rask-andersen, H. (2009). Variational anatomy of the human cochlea : implications for cochlear implantation. *Otology & Neurotology*, *30*(1), 14–22.

Erixon, E., & Rask-Andersen, H. (2013). How to predict cochlear length before cochlear implantation surgery. *Acta Oto-Laryngologica*, *133*, 1258–1265.

Escudé, B., James, C., Deguine, O., Cochard, N., Eter, E., & Fraysse, B. (2006). The size of the cochlea and predictions of insertion depth angles for cochlear implant electrodes. *Audiology and Neurotology*, *11*(Suppl. 1), 27–33.

Fayad, J. N., Luxford, W., & Linthicum, F. H. (2000). The Clarion electrode positioner: temporal bone studies. *The American Journal of Otology*, *21*(2), 226–229.

Finley, C. C., Holden, T. A., Holden, L. K., Whiting, B. R., Chole, R. a, Neely, J. G., … Skinner, M. W. (2008). Role of electrode placement as a contributor to variability in cochlear implant outcomes. *Otology & Neurotology*, *29*(7), 920–8.

Firszt, J. B., Chambers, R. D., Kraus, N., & Reeder, R. M. (2002). Neurophysiology of cochlear implant users I: effects of stimulus current level and electrode site on the electrical ABR, MLR, and N1-P2 response. *Ear and Hearing*, *23*(6), 502–515.

Firszt, J. B., Holden, L. K., Skinner, M. W., Tobey, E. A., Peterson, A., Gaggl, W., … Wackym, P. A. (2004). Recognition of speech presented at soft to loud levels by adult cochlear implant recipients of three cochlear implant systems. *Ear Hear*, *25*(4), 375–387.

Firszt, J. B., Wackym, P. A., Gaggl, W., Burg, L. S., & Reeder, R. M. (2003). Electrically evoked auditory brain stem responses for lateral and medial placement of the Clarion HiFocus electrode. *Ear and Hearing*, *24*(2), 184–190.

Fischer, N., Pinggera, L., Weichbold, V., Dejaco, D., Schmutzhard, J., & Widmann, G. (2015). Radiologic and functional evaluation of electrode dislocation from the scala tympani to the scala vestibuli in patients with cochlear implants. *American Journal of*

Neuroradiology, *36*, 372–377.

Foteff, C., Kennedy, S., Milton, A. H., Deger, M., Payk, F., & Sanderson, G. (2016). Cost-utility analysis of cochlear implantation in Australian adults. *Otology and Neurotology*, *37*(5), 454–461.

Foulad, A., & Djalilian, H. (2010). Analysis of cochlear implant complications. *Otolaryngology - Head and Neck Surgery*, *143*(2), P222–P222.

Gallégo, S., Frachet, B., Micheyl, C., Truy, E., & Collet, L. (1998). Cochlear implant performance and electrically-evoked auditory brain- stem response characteristics. *Electroencephalography and Clinical Neurophysiology*, *108*, 521–525.

Gibson, W. P. R., Sanli, H., & Psarros, C. (2009). The use of intra-operative electrical auditory brainstem responses to predict the speech perception outcome after cochlear implantation. *Cochlear Implants International*, *10*(SUPPL. 1), 53–57.

Gifford, R. H., Shallop, J. K., & Peterson, A. M. (2008). Speech recognition materials and ceiling effects: Considerations for cochlear implant programs. *Audiology and Neurotology*, *13*(3), 193–205.

Gordon, K. A., Papsin, B. C., & Harrison, R. V. (2007). Auditory brainstem activity and development evoked by apical versus basal cochlear implant electrode stimulation in children. *Clinical Neurophysiology*, *118*(8), 1671–1684.

Gordon, K. A., Papsin, B. C., & Harrison, R. V. (2004). Toward a battery of behavioral and objective measures to achieve optimal cochlear implant stimulation levels in children. *Ear and Hearing*, *25*(5), 447–463.

Grenness, C., Hickson, L., Laplante-Lévesque, A., & Davidson, B. (2014). Patient-centred

care: A review for rehabilitative audiologists. *International Journal of Audiology*, *53*(sup1), S60–S67.

Grover, M., Sharma, S., Shashank, ·, Singh, N., Kataria, T., Rajendra, ·, … Sharma, P. (2018). Measuring cochlear duct length in Asian population: worth giving a thought! *European Archives of Oto-Rhino-Laryngology*, *275*, 725–728.

Gu, P., Jiang, Y., Gao, X., Huang, S., Yuan, Y., Wang, G., … Dai, P. (2016). Effects of cochlear implant surgical technique on post-operative electrode impedance. *Acta Oto-Laryngologica*, *136*(7), 677–681.

Guedes, M. C., Neto, R. V. B., Gomez, M. V. S. G., Sant'Anna, S. B. G., Peralta, C. G. O., Castilho, A. M., & Bento, R. F. (2005). Neural response telemetry measures in patients implanted with Nucleus 24®. *Brazilian Journal of Otorhinolaryngology*, *71*(5), 660–667.

Guedes, M. C., Weber, R., Goffi Gomez, M. V. S., Neto, R. V. D. B., Peralta, C. G. O., & Bento, R. F. (2007). Influence of evoked compound action potential on speech perception in cochlear implant users. *Brazilian Journal of Otorhinolaryngology*, *73*(4), 439–445.

Guevara, N., Hoen, M., Truy, E., & Gallego, S. (2016). A cochlear implant performance prognostic test based on electrical field interactions evaluated by eABR (Electrical Auditory Brainstem Responses). *PloS One*, *11*(5), e0155008.

Hall, R. D. (1990). Estimation of surviving spiral ganglion cells in the deaf rat using the electrically evoked auditory brainstem response. *Hearing Research*, *49*, 155–168.

Hamerschmidt, R., Moreira, A. T. R., Wiemes, G. R. M., Tenório, S. B., & Tâmbara, E. M. (2013). Cochlear implant surgery with local anesthesia and sedation: comparison with

general anesthesia. *Otology & Neurotology*, *34*(1), 75–8.

Hamilton, V., & Oorloff, J. (2014). Using information technology to improve operational efficiencies and achieve efficiency targets in the operating theatre [Powerpoint Slides]. Retrieved from https://patientsafe.files.wordpress.com/2016/03/cost-per-minute-for-an-operating-theatre-a421.pdf

Hardy, M. (1938). The length of the organ of Corti in man. *American Journal of Anatomy*, *62*(2), 291–311.

Hilly, O., Smith, L., Hwang, E., Shipp, D., Symons, S., Nedzelski, J. M., … Lin, V. Y. W. (2016). Depth of cochlear implant array within the cochlea and performance outcome. *Annals of Otology, Rhinology & Laryngology*, *125*(11), 886–892.

Hoffman, R. A., & Cohen, N. L. (1995). Complications of cochlear implant surgery. *Annals of Otology, Rhinology & Laryngology*, *104*(9 II SUPPL.), 420–422.

Holden, L. K., Finley, C. C., Firszt, J. B., Holden, T. A., Brenner, C., Potts, L. G., … Skinner, M. W. (2013). Factors affecting open-set word recognition in adults with cochlear implants. *Ear Hear*, *34*(3), 342–360.

Holden, L. K., Firszt, J. B., Reeder, R. M., Uchanski, R. M., Dwyer, N. Y., & Holden, T. A. (2016). Factors affecting outcomes in cochlear implant recipients implanted with a perimodiolar electrode array located in scala tympani. *Otology & Neurotology*, *37*(10), 1662–1668.

Holman MA, Carlson ML, Driscoll CLW, Grim KJ, Petersson RS, Sladen DP, F. R. (2013). Cochlear implantation in children 12 months of age and younger. *Otology & Neurotology*, *34*(2), 251–8.

Hoskison, E., Mitchell, S., & Coulson, C. (2017). Systematic review: Radiological and histological evidence of cochlear implant insertion trauma in adult patients. *Cochlear Implants International*, *18*(4), 192–197.

Hu, H. C., Chen, J. K. C., Tsai, C. M., Chen, H. Y., Tung, T. H., & Li, L. P. H. (2017). Evolution of impedance field telemetry after one day of activation in cochlear implant recipients. *PLoS ONE*, *12*(3), 1–11.

Huang, T. C., Reitzen, S. D., Marrinan, M. S., Waltzman, S. B., & Roland, J. T. (2006). Modiolar coiling, electrical thresholds, and speech perception after cochlear implantation using the nucleus contour advance electrode with the advance off stylet technique. *Otology & Neurotology*, *27*(2), 159–66.

Huart, S., & Sammeth, C. (2009). Identifying cochlear implant candidates in hearing aid dispensing practice. Retrieved from http://www.hearingreview.com/2009/05/identifying-cochlear-implant-candidates-in-the-hearing-aid-dispensing-practice/

Hughes, M. L. (2013). *Objective measures in cochlear implants*. Plural Publishing.

Hughes, M. L., Werff, K. R. Vander, Brown, C. J., Abbas, P. J., Kelsay, D. M. R., Teagle, H. F. B., & Lowder, M. W. (2001). A longitudinal study of electrode impedance, the electrically evoked compound action potential, and behavioral measures in Nucleus 24 cochlear implant users. *Ear and Hearing*, *22*(6), 471–486.

Iso-Mustajärvi, M., Matikka, H., Risi, F., Sipari, S., Koski, T., Willberg, T., … Dietz, A. (2017). A new slim modiolar electrode array for cochlear implantation. *Otology & Neurotology*, *38*(9), e327–e334.

Jeong, J., Kim, M., Heo, J. H., Bang, M.-Y., Bae, M. R., Kim, J., & Choi, J. Y. (2015). Intraindividual comparison of psychophysical parameters between perimodiolar and

lateral-type electrode arrays in patients with bilateral cochlear implants. *Otology & Neurotology*, *36*(2), 228–234.

Jiam, N. T., Jiradejvong, P., Pearl, M. S., & Limb, C. J. (2016). The effect of round window vs cochleostomy surgical approaches on cochlear implant electrode position. *JAMA Otolaryngology–Head & Neck Surgery*, *142*(9), 873–880.

Johnston, J. D. A., Scoffings, D., Chung, M., Baguley, D., Donnelly, N. P., Axon, P. R., … Tysome, J. R. (2016). Computed tomography estimation of cochlear duct length can predict full insertion in cochlear implantation. *Otology & Neurotology*, *37*(3), 223–8.

Kawano, Atsushi; Seldon, H. Lee; Clark, G. M. (1996). Computer-aided three-dimensional reconstruction in human cochlear maps: measurement of the lengths of organ of Corti, outer wall, inner wall, and Rosenthal's canal. *Annals of Otology and Laryngology*, *105*(9), 701–709.

Ketten, D. R., Skinner, M. W., Wang, G., Vannier, M. W., Gates, G. A., & Neely, J. G. (1998). In vivo measures of cochlear length and insertion depth of nucleus cochlear implant electrode arrays. *Annals of Otology, Rhinology and Laryngology*.

Khater, A. M., Moustafa, M. F., said, A. E., & Fahmy, H. S. (2015). An evidence-based guide for intraoperative cochlear implant backup use. *International Journal of Pediatric Otorhinolaryngology*, *79*(9), 1500–1504.

Koch, R. W., Elfarnawany, M., Zhu, N., Ladak, H. M., & Agrawal, S. K. (2017). Evaluation of cochlear duct length computations using synchrotron radiation phase-contrast imaging. *Otology and Neurotology*, *38*(6), e92–e99.

Konerding, W. S., Janssen, H., Hubka, P., Tornøe, J., Mistrik, P., Wahlberg, L., … Scheper, V. (2017). Encapsulated cell device approach for combined electrical stimulation and

neurotrophic treatment of the deaf cochlea. *Hearing Research*, *350*, 110–121.

Kraaijenga, V. J. C., Smit, A. L., Stegeman, I., Smilde, J. J. M., van Zanten, G. A., & Grolman, W. (2016). Factors that influence outcomes in cochlear implantation in adults, based on patient-related characteristics - a retrospective study. *Clinical Otolaryngology*, 585–592.

Kubo, T., Matsuura, S., & Iwaki, T. (2005). Complications of cochlear implant surgery. *Operative Techniques in Otolaryngology-Head and Neck Surgery*, *16*(2), 154–158.

Kubo, T., Yamamoto, K., Iwaki, T., Matsukawa, M., Doi, K., & Tamura, M. (2001). Significance of Auditory Evoked Responses (EABR and P300) in cochlear implant subjects. *Acta Otolaryngol*, *121*, 257–261.

Kumar, K., Caraway, D. L., Rizvi, S., & Bishop, S. (2014). Current challenges in spinal cord stimulation. *Neuromodulation*, *17*(SUPPL. 1), 22–35.

Lane, J. I., Witte, R. J., Driscoll, C. L. W., Shallop, J. K., Beatty, C. W., & Primak, A. N. (2007). Scalar localization of the electrode array after cochlear implantation: clinical experience using 64-slice multidetector computed tomography. *Otology & Neurotology*, *28*(5), 658–62.

Lassig, A.-A. D., Zwolan, T. a, & Telian, S. a. (2005). Cochlear implant failures and revision. *Otology & Neurotology*, *26*(4), 624–634.

Lathuillière, M., Merklen, F., Piron, J.-P., Sicard, M., Villemus, F., Menjot de Champfleur, N., … Mondain, M. (2017). Cone-beam computed tomography in children with cochlear implants: The effect of electrode array position on ECAP. *International Journal of Pediatric Otorhinolaryngology*, *92*, 27–31.

Lazard, D. S., Vincent, C., Venail, F., van de Heyning, P., Truy, E., Sterkers, O., … Blamey, P. J. (2012). Pre-, Per- and Postoperative Factors Affecting Performance of Postlinguistically Deaf Adults Using Cochlear Implants: A New Conceptual Model over Time. *PLoS ONE*, *7*(11), 1–11.

Lea, A. R. (1991). *Cochlear implants*. Canberra: Australian Government Publishing Service.

Lee, J., Nadol, J. B., & Eddington, D. K. (2010). Depth of electrode insertion and postoperative performance in humans with cochlear implants: A histopathologic study. *Audiology and Neurotology*, *15*(5), 323–331.

Lo, T. S., Chen, Y. S., Horng, M. J., & Hsu, C. J. (2004). Efficacy of EABR and ECAP in programming children with Nucleus-24 cochlear implants. *Cochlear Implants International*, *5*(SUPPL. 1), 47–49.

Long, C. J., Holden, T. A., McClelland, G. H., Parkinson, W. S., Shelton, C., Kelsall, D. C., & Smith, Z. M. (2014). Examining the electro-neural interface of cochlear implant users using psychophysics, CT scans, and speech understanding. *JARO - Journal of the Association for Research in Otolaryngology*, *15*(2), 293–304.

Lundin, K., Stillesjo, F., & Rask-Andersen, H. (2015). Prognostic value of electrically evoked auditory brainstem responses in cochlear implantation. *Cochlear Implants International*, *16*(5), 254–261.

Makhdoum, M. J. A., Snik, A. F. M., & van den Broek, P. (1997). Cochlear implantation: a review of the literature and the Nijmegen results. *The Journal of Laryngology and Otology*, *111*(11), 1008–1017.

Marx, M., Risi, F., Escudé, B., Durmo, I., James, C., Lauwers, F., … Fraysse, B. (2014). Reliability of cone beam computed tomography in scalar localization of the electrode

array: A radio histological study. *European Archives of Oto-Rhino-Laryngology*, *271*(4), 673–679.

Mason, S. (2004). Electrophysiologic and objective monitoring of the cochlear implant during surgery: implementation, audit and outcomes. *International Journal of Audiology*, *43*(Suppl 1), S33–S38.

Meng, J., Li, S., Zhang, F., Li, Y., & Qin, Z. (2016). Cochlear size and shape variability and implications in cochlear implantation surgery. *Otology & Neurotology*, *37*, 1307–1313.

Miller, J. D. (2007). Sex differences in the length of the organ of Corti in humans. *The Journal of the Acoustical Society of America*, *121*(4), EL151-EL155.

Minami, S. B., Takegoshi, H., Shinjo, Y., Enomoto, C., & Kaga, K. (2015). Usefulness of measuring electrically evoked auditory brainstem responses in children with inner ear malformations during cochlear implantation. *Acta Oto-Laryngologica*, *0*(May 2017), 1–9.

Mistrík, P., & Jolly, C. (2016). Optimal electrode length to match patient specific cochlear anatomy. *European Annals of Otorhinolaryngology, Head and Neck Diseases*, *133S*, S68–S71.

Mittal, R., Panwar, S. S., Nair, S., Sinha, V. R., Ramesh, A. V., Nilkanthan, A., & Raj, P. (2015). Mapping of paediatric cochlear implant recipients using EABR as a tool. *Journal of Otology & Rhinology*, *4*(2), 2.

Mittmann, P., Ernst, A., & Todt, I. (2015). Intraoperative electrophysiologic variations caused by the scalar position of cochlear implant electrodes. *Otology & Neurotology*, *36*(6), 1010–1014.

Mittmann, P., Todt, I., Wesarg, T., Arndt, S., Ernst, A., & Hassepass, F. (2015). Electrophysiological detection of scalar-changing perimodiolar cochlear electrode arrays : A six-month follow-up study. *Otology & Neurotology*, *36*(7), 1166–1171.

Mosnier, I., Bebear, J.-P., Marx, M., Fraysse, B., Truy, E., Lina-Granade, G., … Sterkers, O. (2014). Predictive factors of cochlear implant outcomes in the elderly. *Audiology & Neuro-Otology*, *19 Suppl 1*(1), 15–20.

Nordfalk, K. F., Rasmussen, K., Hopp, E., Greisiger, R., & Jablonski, G. E. (2014). Scalar position in cochlear implant surgery and outcome in residual hearing and the vestibular system. *International Journal of Audiology*, *53*(2), 121–127.

NSW Auditor General. (2013). New South Wales Auditor-General's report: Performance audit. Managing operating theatre efficiency for elective surgery. Retrieved from https://www.audit.nsw.gov.au/ArticleDocuments/278/01_Managing_Operating_Theatre_Efficiency_Full_Report.pdf.aspx?Embed=Y

O'Connell, B. P., Cakir, A., Hunter, J. B., Francis, D. O., Noble, J. H., Labadie, R. F., … Wanna, G. B. (2016). Electrode location and angular insertion depth are predictors of audiologic outcomes in cochlear implantation. *Otology & Neurotology*, *37*(8), 1016–1023.

O'Connell, B. P., Hunter, J. B., Haynes, D. S., Holder, J. T., Dedmon, M. M., Noble, J. H., … Wanna, G. B. (2017). Insertion depth impacts speech perception and hearing preservation for lateral wall electrodes. *Laryngoscope*, *127*(10), 2352–2357.

Oghalai, J. S., Tonini, R., Rasmus, J., Emery, C., Manolidis, S., Vrabec, J. T., & Haymond, J. (2009). Intra-operative monitoring of cochlear function during cochlear implantation. *Cochlear Implants International*, *10*(1), 1–18.

Page, J. C., Murphy, L., Kennett, S., Trinidade, A., Frank, R., Cox, M., & Dornhoffer, J. L. (2017). The influence of intraoperative testing on surgical decision-making during cochlear implantation. *Otology & Neurotology*, *38*(8), 1092–1096.

Pau, H., Parker, A., Sanli, H., & Gibson, W. P. R. (2005). Displacement of electrodes of a cochlear implant into the vestibular system: intra- and postoperative electrophysiological analyses. *Acta Oto-Laryngologica*, *125*(10), 1116–1118.

Pearce, M. S., Salotti, J. A., Little, M. P., McHugh, K., Lee, C., Kim, K. P., … De González, A. B. (2012). Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: A retrospective cohort study. *The Lancet*, *380*, 499–505.

Pelliccia, P., Venail, F., Bonafé, A., Makeieff, M., Iannetti, G., Bartolomeo, M., & Mondain, M. (2014). Cochlea size variability and implications in clinical practice. *Acta Otorhinolaryngologica Italica : Organo Ufficiale Della Società Italiana Di Otorinolaringologia E Chirurgia Cervico-Facciale*, *34*(1), 42–9.

Pfingst, B. E., Hughes, A. P., Colesa, D. J., Watts, M. M., Strahl, S. B., & Raphael, Y. (2015). Insertion trauma and recovery of function after cochlear implantation: Evidence from objective functional measures. *Hearing Research*, *330*, 98–105.

Pfingst, B. E., Zhou, N., Colesa, D. J., Watts, M. M., Strahl, S. B., Garadat, S. N., … Zwolan, T. A. (2015). Importance of cochlear health for implant function. *Hearing Research*, *322*, 77–88.

Plontke, S. K., Götze, G., Rahne, T., & Liebau, A. (2017). Intracochlear drug delivery in combination with cochlear implants. *Hno*, *65*(1), 19–28.

Pochini Sobrinho, F., Lazarini, P. R., Yoo, H. J., Abreu Junior, L., & Meira Ade, S. (2009). A method for measuring the length of the cochlea through magnetic resonance imaging.

Braz J Otorhinolaryngol, *75*(2), 261–267.

Pollak, A., Felix, H., & Schrott, A. (1987). Methodological aspects of quantitative study of spiral ganglion cells. *Acta Oto-Laryngologica*, *104*(suppl 436), 37–42.

Porter, M. (2010). What is value in health care? *The New England Journal of Medicine*, *363*(26), 2477–2481.

Prado-Guitierrez, P., Fewster, L. M., Heasman, J. M., McKay, C. M., & Shepherd, R. K. (2006). Effect of interphase gap and pulse duration on electrically evoked potentials is correlated with auditory nerve survival. *Hearing Research*, *215*(1–2), 47–55.

Psarros, C., Bate, K., Berry, K. G., & Sanli, H. (2010). Electrophysiology revisited — implications for paediatric maps. *Cochlear Implants International*, *11*(2), 454–460.

Raghunandhan, S., Ravikumar, A., Kameswaran, M., Mandke, K., & Ranjith, R. (2014). A clinical study of electrophysiological correlates of behavioural comfort levels in cochlear implantees. *Cochlear Implants International*, *15*(3), 145–160.

Ramekers, D., Versnel, H., Strahl, S. B., Klis, S. F. L., & Grolman, W. (2015). Recovery characteristics of the electrically stimulated auditory nerve in deafened guinea pigs: Relation to neuronal status. *Hearing Research*, *321*, 12–24.

Ramekers, D., Versnel, H., Strahl, S. B., Smeets, E. M., Klis, S. F. L., & Grolman, W. (2014). Auditory-nerve responses to varied inter-phase gap and phase duration of the electric pulse stimulus as predictors for neuronal degeneration. *JARO - Journal of the Association for Research in Otolaryngology*, *15*(2), 187–202.

Rask-Andersen, H., Erixon, E., Kinnefors, A., Löwenheim, H., Schrott-Fischer, A., & Liu, W. (2011). Anatomy of the human cochlea--implications for cochlear implantation.

Cochlear Implants International, *12*(Suppl 1), S8–S13.

Razafindranaly, V., Truy, E., Pialat, J.-B., Martinon, A., Bourhis, M., Boublay, N., … Ltaïef-Boudrigua, A. (2016). Cone beam CT versus multislice CT: radiologic diagnostic agreement in the postoperative assessment of cochlear implantation. *Otology & Neurotology*, *37*(9), 1246–1254.

Rebscher, S. J., Hetherington, A., Bonham, B. H., Wardrop, P., Whinney, D., & Leake, P. A. (2008). Considerations for design of future cochlear implant electrode arrays: electrode array stiffness, size, and depth of insertion. *Journal of Rehabilitation Research and Development*, *45*(5), 731–747.

Retzius, G. (1884). Das Gehörogan der Wirbeltiere, II. Das Gehörorgan der Reptilien, der Vogel und der Saügetiere. *Stockholm: Samson and Wallin*.

Rivas, A., Cakir, A., Hunter, J. B., Labadie, R. F., Geraldine Zuniga, M., Wanna, G. B., … Noble, J. H. (2017). Automatic cochlear duct length estimation for selection of cochlear implant electrode arrays. *Otology and Neurotology*, *38*(3), 339–346.

Runge-Samuelson, C., Firszt, J. B., Gaggl, W., & Wackym, P. A. (2009). Electrically evoked auditory brainstem responses in adults and children: effects of lateral to medial placement of the Nucleus 24 contour electrode array. *Otology & Neurotology*, *30*(4), 464–470.

Saeed, S. R., Selvadurai, D., Beale, T., Biggs, N., Murray, B., Gibson, P., … Boyd, P. (2014). The use of cone-beam computed tomography to determine cochlear implant electrode position in human temporal bones. *Otology & Neurotology*, *35*(8), 1338–44.

Said Abdelsalam, N. M., & Afifi, P. O. (2015). Electric auditory brainstem response (E-ABR) in cochlear implant children: Effect of age at implantation and duration of implant

use. *Egyptian Journal of Ear, Nose, Throat and Allied Sciences*, *16*(2), 145–150.

Sato, H., Sando, I., & Takahashi, H. (1991). Sexual dimorphism and development of the human cochlea. Computer 3-D measurement. *Acta Oto-Laryngologica*, *111*(6), 1037–40.

Sato, M., Baumhoff, P., Tillein, J., & Kral, A. (2017). Physiological mechanisms in combined electric–acoustic stimulation. *Otology & Neurotology*, *38*, e215–e223.

Saunders, E., Cohen, L., Aschendorff, A., Shapiro, W., Knight, M., Stecker, M., … Cowan, R. (2002). Threshold, comfortable level and impedance changes as a function of electrode-modiolar distance. *Ear and Hearing*, *23*(1 Suppl), 28S–40S.

Seyyedi, M., Eddington, D. K., & Nadol, J. B. (2013). Effect of monopolar and bipolar electric stimulation on survival and size of human spiral ganglion cells as studied by postmortem histopathology. *Hearing Research*, *302*, 9–16.

Seyyedi, M., Viana, L. M., & Nadol, J. B. (2014). Within-subject comparison of word recognition and spiral ganglion cell count in bilateral cochlear implant recipients. *Otology & Neurotology*, *35*, 1446–1450.

Shah, S. B., Chung, J. H., & Jackler, R. K. (1997). Lodestones, quackery, and science: electrical stimulation of the ear before cochlear implants. *The American Journal of Otology*.

Shallop, J. K., Facer, G. W., & Peterson, A. (1999). Neural response telemetry with the nucleus CI24M cochlear implant. *Laryngoscope*, *109*(11), 1755–1759.

Shapiro, W. H., Huang, T., Shaw, T., Roland, J. T., & Lalwani, A. K. (2008). Remote intraoperative monitoring during cochlear implant surgery is feasible and efficient.

Otology & Neurotology, *29*(4), 495–8.

Shepherd, R. K., Coco, A., & Epp, S. B. (2008). Neurotrophins and electrical stimulation for protection and repair of spiral ganglion neurons following sensorineural hearing loss. *Hearing Research*, *242*(1–2), 100–109.

Shepherd, R. K., Hatsushika, S., & Clark, G. M. (1993). Electrical stimulation of the auditory nerve: The effect of electrode position on neural excitation. *Hearing Research*, *66*(1), 108–120.

Shin, K.-J., Lee, J.-Y., Kim, J.-N., Yoo, J.-Y., Shin, C., Song, W.-C., & Koh, K.-S. (2013). Quantitative analysis of the cochlea using three-dimensional reconstruction based on microcomputed tomographic images. *The Anatomical Record*, *296*(7), 1083–1088.

Shippert, R. D. (2005). A study of time-dependent operating room fees and how to save $100 000 by using time-saving products. *The American Journal of Cosmetic Surgery*, *22*(1), 25–34.

Singla, A., Sahni, D., Gupta, A. K., Aggarwal, A., & Gupta, T. (2015). Surgical anatomy of the basal turn of the human cochlea as pertaining to cochlear implantation. *Otology & Neurotology*, *36*(2), 323–328.

Skinner, M. W., Holden, T. A., Whiting, B. R., Voie, A. H., Brunsden, B., Neely, J. G., … Finley, C. C. (2007). In vivo estimates of the position of advanced bionics electrode arrays in the human cochlea. *Annals of Otology, Rhinology and Laryngology*, *116*(4_suppl), 1–24.

Skinner, M. W., Ketten, D. R., Holden, L. K., Harding, G. W., Smith, P. G., Gates, G. A., … Blocker, B. (2002). CT-derived estimation of cochlear morphology and electrode array position in relation to word recognition in nucleus-22 recipients. *JARO - Journal of the*

Association for Research in Otolaryngology, *3*(3), 332–350.

Smoorenburg, G. F., Willeboer, C., & Van Dijk, J. E. (2002). Speech perception in nucleus CI24M cochlear implant users with processor settings based on electrically evoked compound action potential thresholds. *Audiology and Neuro-Otology*, *7*(6), 335–347.

Stakhovskaya, O., Sridhar, D., Bonham, B. H., & Leake, P. A. (2007). Frequency map for the human cochlear spiral ganglion: Implications for cochlear implants. *JARO - Journal of the Association for Research in Otolaryngology*, *8*(2), 220–233.

Strøm, C., & Rasmussen, L. S. (2014). Challenges in anaesthesia for elderly. *Singapore Dental Journal*, *35*, 23–29.

Svrakic, M., Pollack, A., Huncke, T. K., & Roland Jr., J. T. (2014). Conscious sedation and local anesthesia for patients undergoing neurotologic and complex otologic procedures. *Otology & Neurotology*, *35*(10), e277–e285.

Takagi, A., & Sando, I. (1989). Computer-aided three-dimensional reconstruction: A method of measuring temporal bone structures including the length of the cochlea. *Annals of Otology, Rhinology and Laryngology*, *98*(7), 515–522.

Tambyraja, R. R., Gutman, M. A., & Megerian, C. A. (2005). Cochlear implant complications. *Archives of Otolaryngology–Head & Neck Surgery*, *131*, 245–250.

Tamplen, M., Schwalje, A., Lustig, L., Alemi, A. S., & Miller, M. E. (2016). Utility of preoperative computed tomography and magnetic resonance imaging in adult and pediatric cochlear implant candidates. *Laryngoscope*, (126), 1440–1445.

Tavartkiladze, G., Bakhshinyan, V., & Irwin, C. (2015). Evaluation of new technology for intraoperative evoked compound action potential threshold measurements. *International*

Journal of Audiology, *54*, 347–352.

Telmesani, L. M., & Said, N. M. (2015). Effect of cochlear implant electrode array design on auditory nerve and behavioral response in children. *International Journal of Pediatric Otorhinolaryngology*, *79*(5), 660–665.

Teymouri, J., Hullar, T. E., Holden, T. A., & Chole, R. a. (2011). Verification of computed tomographic estimates of cochlear implant array position: a micro-CT and histologic analysis. *Otology & Neurotology*, *32*(6), 980–986.

The Australian Institute of Health and Welfare. (2017). *Admitted patient care 2015–16*.

Thong, J. F., Low, D., Tham, A., Liew, C., Tan, T. Y., & Yuen, H. W. (2017). Cochlear duct length–one size fits all? *American Journal of Otolaryngology - Head and Neck Medicine and Surgery*, *38*(2), 218–221.

Tien, H. C., & Linthicum, F. H. (2002). Histopathologic changes in the vestibule after cochlear implantation. *Otolaryngology - Head and Neck Surgery*, *127*(4), 260–264.

Todt, I., Basta, D., & Ernst, A. (2008). Does the surgical approach in cochlear implantation influence the occurrence of postoperative vertigo? *Otolaryngology - Head and Neck Surgery*, *138*(1), 8–12.

Torres, R., Mamelle, E., Seta, D. De, Sterkers, O., Ferrary, E., & Nguyen, Y. (2017). Influence of electrode array stiffness and diameter on hearing in cochlear implanted guinea pig. *PloS One*, 1–15.

Tykocinski, M., Cohen, L. T., & Cowan, R. S. (2005). Measurement and analysis of access resistance and polarization impedance in cochlear implant recipients. *Otology & Neurotology*, *26*(5), 948–956.

Úlehlová, L., Voldřich, L., & Janisch, R. (1987). Correlative study of sensory cell density and cochlear length in humans. *Hearing Research*, *28*(2), 149–151.

Undurraga, J. A., Carlyon, R. P., Wouters, J., & Van Wieringen, A. (2013). The polarity sensitivity of the electrically stimulated human auditory nerve measured at the level of the brainstem. *JARO - Journal of the Association for Research in Otolaryngology*, *14*(3), 359–377.

Vaerenberg, B., Smits, C., DeCeulaer, G., Zir, E., Harman, S., Jaspers, N., & Govaerts, P. (2014). Cochlear implant programming: A global survey on the state of the art. *The Scientific World Journal*, *2014*, 1–14.

Van Der Beek, F. B., Briaire, J. J., Van Der Marel, K. S., Verbist, B. M., & Frijns, J. H. M. (2016). Intracochlear position of cochlear implants determined using CT scanning versus fitting levels: Higher threshold levels at basal turn. *Audiology and Neurotology*, *21*(1), 54–67.

Van Der Marel, K. S., Briaire, J. J., Verbist, B. M., Muurling, T. J., & Frijns, J. H. M. (2015). The influence of cochlear implant electrode position on performance. *Audiology and Neurotology*, *20*(3), 202–211.

van Dijk, B., Botros, A. M., Battmer, R.-D., Begall, K., Dillier, N., Hey, M., … Offeciers, E. (2007). Clinical results of AutoNRT, a completely automatic ECAP recording system for cochlear implants. *Ear and Hearing*, *28*(4), 558–570.

van Weert, S., Stokroos, R. J., Rikers, M. M. J. G., & van Dijk, P. (2005). Effect of peri-modiolar cochlear implant positioning on auditory nerve responses: a neural response telemetry study. *Acta Oto-Laryngologica*, *125*(7), 725–731.

Verberne, J., Risi, F., Campbell, L., Chambers, S., & O'Leary, S. (2016). The effect of scala

tympani morphology on basilar membrane contact with a straight electrode array: a human temporal bone study. *Otology & Neurotology*, *38*, 47–53.

Viccaro, M., Covelli, E., de Seta, E., Balsamo, G., & Filipo, R. (2009). The importance of intra-operative imaging during cochlear implant surgery. *Cochlear Implants International*, *10*(4), 198–202.

Vogl, T. J., Tawfik, A., Emam, A., Naguib, N., Nour-Eldin, A., Burck, I., & Stöver, T. (2015). Pre- , intra- and post-operative imaging of cochlear implants. © *Georg Thieme Verlag KG*, *187*(11), 980–989.

Volta, A., & Banks, J. (1800). I. *On the electricity excited by the mere contact of conducting substances of different kinds*. *Philosophical Magazine Series 1*, *7*(28), 289–311.

Walby, A. P. (1984). Scala tympani measurement. *The Annals of Otology, Rhinology, and Laryngology*, *94*(4 Pt 1), 393–397.

Walton, J., Gibson, W. P. R., Sanli, H., & Prelog, K. (2008). Predicting cochlear implant outcomes in children with auditory neuropathy. *Otology & Neurotology*, *29*(3), 302–309.

Wang, J. T., Wang, A. Y., Psarros, C., & Da Cruz, M. (2014). Rates of revision and device failure in cochlear implant surgery: A 30-year experience. *Laryngoscope*, *124*(10), 2393–2399.

Wang, Y., Pan, T., Deshpande, S. B., & Ma, F. (2015). The relationship between EABR and auditory performance and speech intelligibility outcomes in pediatric cochlear implant recipients. *American Journal of Audiology*, *24*(2), 226–234.

Wanna, G. B., Noble, J. H., Carlson, M. L., Gifford, R. H., Dietrich, M. S., Haynes, D. S., …

Labadie, R. F. (2014). Impact of electrode design and surgical approach on scalar location and cochlear implant outcomes. *Laryngoscope*, *124*(S6), S1–S7.

Wanna, G. B., Noble, J. H., Gifford, R. H., Dietrich, M. S., Sweeney, A. D., Zhang, D., … Labadie, R. F. (2015). Impact of intrascalar electrode location, electrode type, and angular insertion depth on residual hearing in cochlear implant patients: preliminary results. *Otology & Neurotology*, *36*(8), 1343–8.

Wanna, G. B., O'Connell, B. P., Francis, D. O., Gifford, R. H., Hunter, J. B., Holder, J. T., … Haynes, D. S. (2017). Predictive factors for short- and long-term hearing preservation in cochlear implantation with conventional-length electrodes. *Laryngoscope*, 1–8.

Wilson, B. S., & Dorman, M. F. (2008). Cochlear implants: a remarkable past and a brilliant future. *Hear Res.*, *242*, 3–21.

Wolfe, J., & Schafer, E. C. (2014). *Programming cochlear implants*. *Plural Publishing*.

Wright, A., Davis, A., Bredberg, G., Ülehlová, & Spencer, H. (1987). Hair cell distributions in the normal human cochlea: a report of a european working group. *Acta Oto-Laryngologica*, *104*(436), 15–24.

Würfel, W., Burke, W. F., Lenarz, T., & Kraemer, R. (2015). Cochlear length determination in temporal bone specimens using histological serial Micro grinding imaging, micro computed tomography and flat-panel volumetric computed tomography. *Otolaryngology Online Journal*, *5*(2).

Würfel, W., Lanfermann, H., Lenarz, T., & Majdani, O. (2014). Cochlear length determination using Cone Beam Computed Tomography in a clinical setting. *Hearing Research*, *316*(2014), 65–72.

Xu, J., Xu, S. a, Cohen, L. T., & Clark, G. M. (2000). Cochlear view: postoperative radiography for cochlear implantation. *Am J Otol*, *21*(1), 49–56.

Yamazaki, H., Leigh, J., Briggs, R., & Naito, Y. (2015). Usefulness of MRI and EABR testing for predicting CI outcomes immediately after cochlear implantation in cases with cochlear nerve deficiency. *Otol Neurotol*, *36*, 977–984.

Ying, Y. L. M., Lin, J. W., Oghalai, J. S., & Williamson, R. A. (2013). Cochlear implant electrode misplacement: incidence, evaluation, and management. *Laryngoscope*, *123*(3), 757–766.

Yu, J.-F., Lee, K.-C., Wan, Y.-L., & Peng, Y.-C. (2015). Curvature measurement of human bilateral cochleae. *The Journal of Laryngology & Otology*, *129*(11), 1085–1090.

Yukawa, K., Cohen, L., Blamey, P., Pyman, B., Tungvachirakul, V., & O'Leary, S. (2004). Effects of insertion depth of cochlear implant electrodes upon speech perception. *Audiology and Neuro-Otology*, *9*(3), 163–172.

Zilberstein, Y., Liberman, M. C., & Corfas, G. (2012). Inner hair cells are not required for survival of spiral ganglion neurons in the adult cochlea. *Journal of Neuroscience*, *32*(2), 405–410.

Zou, J., Hannula, M., Lehto, K., Feng, H., Lähelmä, J., Aula, A. S., … Pyykkö, I. (2015). X-ray microtomographic confirmation of the reliability of CBCT in identifying the scalar location of cochlear implant electrode after round window insertion. *Hearing Research*, *326*, 59–65.

Zou, J., Lähelmä, J., Koivisto, J., Dhanasingh, A., Jolly, C., Aarnisalo, A., … Pyykkö, I. (2015). Imaging cochlear implantation with round window insertion in human temporal bones and cochlear morphological variation using high-resolution cone beam CT. *Acta*

Oto-Laryngologica, *135*(5), 466–72.

Zwolan, T. A., & Stach, C. J. (2016). Diagnosis and management of cochlear implant malfunctions. In Y. N. & I. K. K. (Eds.), *Pediatric cochlear implantation*. New York: Springer.

Appendix: 1

Questionnaire addressed to clinical audiologists (manuscript 1)

Do you use the intra-operative electrophysiological tests results in your clinical practice? (Impedance, NRT, Artefact Measures, and EABR)

If yes to Q1:

1. Which of these intra-operative tests results do you use? (Choose all that apply)
2. On a scale of 1 (very useful) to 5 (not at all useful) please rate each EP test based on your opinion of its clinical use.
3. Do you use these results only at switch-on?
4. How do you personally use these test results? (Choose all that apply)
5. (a) If you had wider knowledge about the applicability of these tests would you use them more? Y/N and please comment.

   (b) Please list any questions you have about these tests.

   (c) Please list any questions you have about how these tests might be used in clinical practice.

If no to Q1:

1. Do you believe any of these tests could be useful to your clinical practice?
2. List the reasons and/or barriers for why you do not use them.
3. (a) If you had wider knowledge about the applicability of these tests would you use them more? Y/N and please comment.

   (b) Please list any questions you have about these tests.

   (c) Please list any questions you have about how these tests might be used in clinical practice.

MACQUARIE University

FHS Ethics <fhs.ethics@mq.edu.au>

RE: HS Ethics Application - Approved (5201400407)(Con/Met)

Fhs Ethics <fhs.ethics@mq.edu.au> 30 April 2014 at 13:44
To: Dr Isabelle Boisvert <isabelle.boisvert@mq.edu.au>
Cc: Associate Professor Cath McMahon <cath.mcmahon@mq.edu.au>, Dr Erik Lundmark <erik.lundmark@mq.edu.au>, Ms Fadwa Fahad AlNafjan <fadwa.alnafjan@students.mq.edu.au>, Ms Jennifer Clemesha <jennifer.clemesha@students.mq.edu.au>

Dear Dr Boisvert,

Re: "Clinical decision-making and health economics in Audiology"(5201400407)

Thank you for your recent correspondence. Your response has addressed the issues raised by the Faculty of Human Sciences Human Research Ethics Sub-Committee and approval has been granted, effective 30th April 2014. This email constitutes ethical approval only.

This research meets the requirements of the National Statement on Ethical Conduct in Human Research (2007). The National Statement is available at the following web site:

http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e72.pdf.

The following personnel are authorised to conduct this research:

Associate Professor Cath McMahon
Dr Erik Lundmark
Dr Isabelle Boisvert
Ms Fadwa Fahad AlNafjan
Ms Jennifer Clemesha

Please note the following standard requirements of approval:

1. The approval of this project is conditional upon your continuing compliance with the National Statement on Ethical Conduct in Human Research (2007).

2. Approval will be for a period of five (5) years subject to the provision of annual reports.

Progress Report 1 Due: 30th April 2015
Progress Report 2 Due: 30th April 2016
Progress Report 3 Due: 30th April 2017
Progress Report 4 Due: 30th April 2018
Final Report Due: 30th April 2019

NB. If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. If the project has been discontinued or not commenced for any reason, you are also required to submit a Final Report for the project.

Progress reports and Final Reports are available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

3. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report and submit a new application for the project. (The five year limit on renewal of approvals allows the Sub-Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).

4. All amendments to the project must be reviewed and approved by the Sub-Committee before implementation. Please complete and submit a Request for Amendment Form available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

5. Please notify the Sub-Committee immediately in the event of any adverse effects on participants or of any unforeseen events that affect the continued ethical acceptability of the project.

6. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University. This information is available at the following websites:

http://www.mq.edu.au/policy

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/policy

If you will be applying for or have applied for internal or external funding for the above project it is your responsibility to provide the Macquarie University's Research Grants Management Assistant with a copy of this email as soon as possible. Internal and External funding agencies will not be informed that you have approval for your project and funds will not be released until the Research Grants Management Assistant has received a copy of this email.

If you need to provide a hard copy letter of approval to an external organisation as evidence that you have approval, please do not hesitate to

contact the Ethics Secretariat at the address below.

Please retain a copy of this email as this is your official notification of ethics approval.

Yours sincerely,

Dr Simon Boag
Acting Chair
Faculty of Human Sciences
Human Research Ethics Sub-Committee

Faculty of Human Sciences - Ethics
Research Office
Level 3, Research HUB, Building C5C
Macquarie University
NSW 2109

Ph: +61 2 9850 4197
Fax: +61 2 9850 4465

Email: fhs.ethics@mq.edu.au

http://www.research.mq.edu.au/

Health
Western Sydney
Local Health District

Our ref: ***HREC2014/2/5.1 (3908) AU RED LNR/14/WMEAD/11***

29 May 2014

A/Prof Melville da Cruz
Department of Surgery
Westmead Hospital

Dear A/Prof da Cruz

LNR Research Project: 'The evaluation of intra-operative electrophysiological measurements in adult cochlear implant users'

Your request to undertake the above protocol as a Low and Negligible Risk (LNR) research project was reviewed by a subcommittee of members of the Scientific Advisory Committee and the Human Research Ethics Committee. We are satisfied that your protocol meets the criteria for an LNR research project and does not require review by the full HREC.

This HREC has been accredited by the NSW Department of Health as a lead HREC to provide the single ethical and scientific review of proposals to conduct research within the NSW public health system. This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise that the HREC has granted ethical approval of this LNR research project to be conducted by you at:

- Westmead Public Hospital
- Westmead Private Hospital (MoU in place)
- Sydney Cochlear Implant Centre – Gladesville and Macquarie University Clinics (MoU in place)

The following documentation has been reviewed and approved by the HREC:

- LNR Application Form AU/6/FE36111
- Protocol version Jan 2014
- Data Collection Sheet

T:\RESEARCH OFFICE\ETHICS\COMMITTEES\HREC\CORRESPONDENCE\2014\1405 CORRESPONDENCE\140529 - 3908 da Cruz - LNR.doc

HUMAN RESEARCH ETHICS COMMITTEE

Research Office, Room 1072, Level 1, Education Block
Westmead Hospital, Hawkesbury & Darcy Roads, Westmead NSW 2145
Telephone 02 9845 8183 Facsimile 02 9845 8352
Email: WSLHD-ResearchOffice@health.nsw.gov.au

WESTERN SYDNEY LOCAL HEALTH DISTRICT
ABN 48 702 394 764
WSLHD Office, Westmead Hospital Campus
Institute Road, Westmead NSW 2145
PO Box 533, Wentworthville NSW 2145
Telephone 02 9845 5555

Please note the following conditions of approval:

- The coordinating investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- The coordinating investigator will immediately report any protocol deviation / violation, together with details of the procedure put in place to ensure the deviation / violation does not recur.
- Proposed amendments to the protocol or conduct of the research which may affect the ethical acceptability of the project, must be provided to the HREC to review in the specific format. Copies of all proposed changes must also be provided to the research governance officer.
- The HREC must be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.
- The coordinating investigator must provide an annual report to the HREC and a final report at completion of the study, in the specified format. HREC approval is valid for 12 months from the date of final approval and continuation of the HREC approval beyond the initial 12 month approval period is contingent upon submission of an annual report each year.
- It should be noted that compliance with the ethical guidelines is entirely the responsibility of the investigators.

You are reminded that this letter constitutes *ethical approval only*. You must not commence this research project until separate Governance authorisation from the Chief Executive or delegate has been obtained. Copies of this letter, together with any approved documents as enumerated above, have been forwarded to the WSLHD Research Governance Officer. For Governance authorisation at sites outside WSLHD you must forward a copy of this letter and any approved documents to the Research Governance Office at each additional site.

In all future correspondence concerning this study, please quote approval number ***HREC2014/2/5.1 (3908) AU RED LNR/14/WMEAD/11.*** The HREC wishes you every success in your research.

Yours sincerely

Mrs Patricia Fa
Secretary
WSLHD Human Research Ethics Committee

cc Ms Margaret Piper, Research Governance Officer

T:\RESEARCH OFFICE\ETHICS\COMMITTEES\HREC\CORRESPONDENCE\2014\1405 CORRESPONDENCE\140529 - 3908 da Cruz - LNR.doc

Study Number	***HREC2014/2/5.1 (3908) AU RED LNR/14/WMEAD/11***
Principal Investigator	A/Prof Melville da Cruz
Study Title	The evaluation of intra-operative electrophysiological measurements in adult cochlear implant users

Please complete the boxes below and return a copy of <u>this page only</u> to the WSLHD Research Office:

☐ *I acknowledge and accept the conditions of ethical approval listed above*

☐ *I will not commence this project at any site until separate written authorisation from the Chief Executive or delegate of that site has been obtained*

Melville Da Cruz	Melville da Cruz	2.6.2014
Chief Investigator (Print Name)	*Signature*	*Date*

T:\RESEARCH OFFICE\ETHICS\COMMITTEES\HREC\CORRESPONDENCE\2014\1405 CORRESPONDENCE\140529 - 3908 da Cruz - LNR.doc

MACQUARIE University

FADWA ALNAFJAN <fadwa.alnafjan@students.mq.edu.au>

External Approval Noted - McMahon (Ref: 5201400963)

Ethics Secretariat <ethics.secretariat@mq.edu.au> Thu, Apr 30, 2015 at 12:41 PM
To: FADWA ALNAFJAN <fadwa.alnafjan@students.mq.edu.au>
Cc: Catherine McMahon <cath.mcmahon@mq.edu.au>

Dear Associate Professor McMahon,

Thank you for your email advising the Human Research Ethics Committees (HRECs) of your involvement in the following application approved by the 'Western Sydney Local Health District Human Research Ethics Committee'

RE: The evaluation of intra-operative electrophysiological measurements in adult cochlear implant users

In accordance with ch 5.3 of the *National Statement on Ethical Conduct in Human Research* (2007) the Macquarie University HRECs note your authority to proceed under this external approval.

No further action is required. Any amendments must be submitted to the approving HREC.

The HRECs wish you the very best for your research.

Regards

Michelle Thorpe

--

Ethics Secretariat
Research Office
Level 3, Research Hub, Building C5C East
Macquarie University
NSW 2109 Australia
T: +61 2 9850 4459
F: +61 2 9850 4465
http://www.mq.edu.au/research

MACQUARIE University
SYDNEY·AUSTRALIA