Novel applications of objective measures in cochlear implants

Dong, Y.

Chapter 1

Introduction and outline of the thesis

1.1. Physiology of hearing

Hearing, or auditory perception, begins when the auditory system transduces sound vibrations into nerve impulses and forwards them to the brain, where they are perceived as sounds. The sense of hearing plays a crucial role in maintaining connections with the world around us. Our external ears capture this mechanical signal, the middle ear transmits it to the receptor organ, the cochlea, which transduces it into neural signals to the central nervous system (Figure 1.1A). The external ear consists of the auricle and the external ear meatus, which ends at the tympanic membrane (eardrum). In the air-filled middle ear, three tiny connected auditory ossicles are located, namely the malleus, the incus, and the stapes. The stapes is placed on the oval window, which separates the middle ear from the inner ear, or cochlea. The cochlea is a coiled tube, divided into three liquid-filled compartments: the scala tympani, scala media, and scala vestibuli (Figure 1.1B). The base of the scala vestibuli is closed by the oval window. The base of the scala tympani ends in the round window, a thin, flexible membranous structure. Both scalae are filled with perilymph. The scala vestibuli and scala tympani communicate with each other at the apical helicotrema.

Between the scala media and the subjacent scala tympani lies the basilar membrane along the length, which supports the organ of Corti (Figure 1.1B). In the process of hearing, sound waves are captured and converged to the external meatus by the auricle. Then sound waves stimulate the tympanic membrane to vibrate, such that the connected ossicular chain starts to vibrate and simultaneously amplify the vibration pressure. Because the stapes connects to the cochlea via the oval window, the action of the stapes produces a travelling wave that propagates along the length of the basilar membrane. As the travelling wave pushes up on the basilar membrane, the hair cells of the organ of Corti are excited resulting in the release of neurotransmitters, which causes the auditory nerve fibers (ANFs) to generate action potentials (Pickles, 1988). These action potentials can be transmitted along the brainstem to the auditory cortex where sound waves are ultimately interpreted as meaningful sounds (Rizzolatti and Kalaska, 2013).

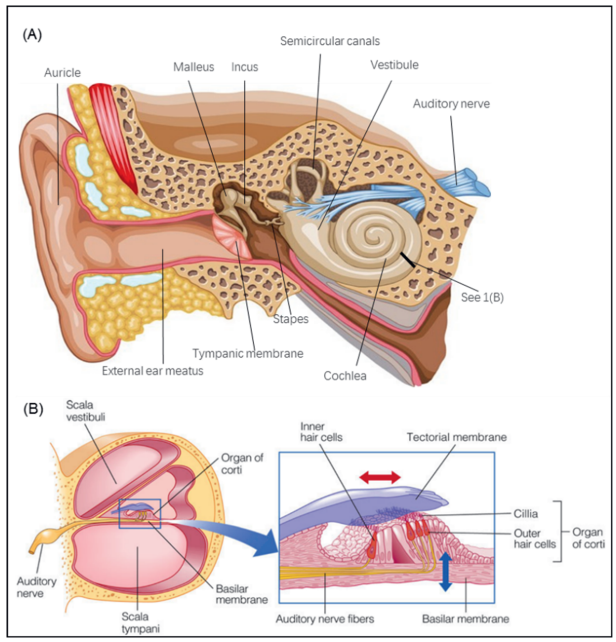

Fig. 1.1. Graphical representation of the basic anatomy of the human ear.

Hearing loss can arise from both physiological and structural defects in the auditory system and can be roughly classified as conductive and sensorineural hearing loss. Conductive hearing loss occurs in the outer and/or middle ear when sound waves cannot be carried through to the cochlea. Sensorineural hearing loss results from damage to the neural structures in the cochlea, auditory nerve or central auditory system (Hartmann and Kral, 2004). In recent decades, remarkable advances in the capability to treat deafness have been achieved. For the majority of patients who have significant residual hearing, such as patients with conductive hearing loss, hearing aids are typically recommended which can amplify sound to activate the residual hair cells. When greater degrees of hearing loss has occurred, the benefit of hearing aid may become insufficient. However, severe hearing loss can be restored with a cochlear implant (CI), which can bypass the hair cells and the whole preceding normal route of sound conduction.

1.2. Cochlear implant

A CI is an implantable electronic prosthesis that can restore a part of the hearing abilities of patients by directly applying electrical stimulation to the auditory nerve fibers (ANFs). In the last decades, CI has become a standard method of rehabilitation for patients with severe to profound hearing loss (stated by WHO, https://www.who.int/en/news-room/fact-sheets/detail/deafness-and-hearing-loss). Although CI designs differ in appearance across manufacturers and generations of technology, all CIs share the same basic components and functions. A CI system is composed of two basic parts. The externally worn part, the sound processor, has microphones, electronics, a battery and a headpiece. The surgically implanted internal component contains a coil to receive signals, electronics and an array of electrode contacts which is typically placed into the scala tympani. A microphone captures sound waves and converts them to electrical signals which are processed in a sound processor. The auditory signals are decoded into a number of frequency bands and the temporal envelope of each band is extracted. The amplitudes of the various frequency bands are forwarded to the receiving antennas implanted in the temporal bone across the skin by radio frequency transmission. The information is further decoded into an electrical current in the internal electronics. Like the basilar membrane and hair cells, the ANFs are tonotopically organized. That is to say, nerve fibers in the basal turn of the cochlea process higher frequencies and lower frequencies in the apical region. Due to this tonotopic organization, electrode contacts are arranged near ANFs along the scala tympani to code specific frequencies. Lead wires carry the electrical signals from the internal electronics to appropriate electrode contacts placed at various locations. Activation of the electrodes evokes action potentials in the nearby auditory nerves and thus produces a different auditory percept.

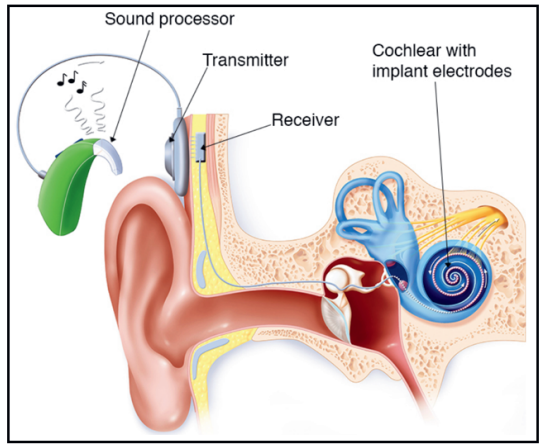

Fig. 1.2 Schematic representation of the basic components of a cochlear implant system. Picture adapted from healthdirect (https://www.healthdirect.gov.au/cochlear-implant#backToTop).

To date, cochlear implantation is the most successful treatment for severe sensorineural hearing loss through developments in speech processing strategies, surgical techniques and electrode designs. As of December 2019, over 736 thousand registered devices worldwide have implanted since their development in the 1970s (stated by NIH, https://www.nidcd.nih.gov/health/cochlear-implantsCochlear). Most patients demonstrate improved speech performance when compared to their pre-implant abilities. However, the outcomes of the population of CI recipients still differ greatly between implanted patients and ears. This makes it difficult to predict post-implantation speech performance before implantation. A multitude of related factors may potentially contribute to the variability, including patient-related characteristics, device designs, and neurophysiological properties. More specifically, factors that attribute to variation in speech outcomes across patients include the degree of nerve degeneration (Shepherd et al., 1983; He et al., 2017), characteristics of the auditory nerve like the capability to recover from the refractory state (Stypulkowski & van den Honert, 1984; Brown et al., 1990; Abbas et al., 1996), age at implantation, duration of deafness, spatial and temporal resolution abilities (Shannon,1983; Zeng & Shannon, 1994), the extent of residual hearing (Miller et al., 2008), the placement of electrode arrays and the integrity of the central auditory nervous system (Oviatt et al., 1991; Micco et al., 1995). Up to now, however, variability in speech perception is not completely understood.

1.3 Objective measures of cochlear implant function

State-of-the-art CIs usually provide multiple objective measures for both clinical and scientific research purposes that can aid in verifying the device function in CI recipients. Objective measures encompass two general measuring techniques, namely physiological measures and nonphysiological measures.

Physiological measures are tools for recording neural responses from different levels of the auditory system in response to electrical stimulation through a CI device. They are usually applied to assess the physiological functioning of the auditory pathway (Botros and Psarros, 2010) and device functionality (Gantz et al., 1988). Although there are some potential clinical applications of physiological measures, the most immediate is to determine if the outcome responses are useful for facilitating the programming of the CI processor so as to achieve better speech perception. The commonly used physiological measures in CI research are electrically evoked stapedial reflexes (ESRs), electrically evoked auditory brainstem responses (EABRs) and electrically evoked compound action potentials (eCAPs).

The scope of physiological measures in this thesis is to apply eCAP measurements involved in CIs. ECAP measures are widely used in clinical practice and represent a synchronous physiological response produced by depolarization of an aggregate population of electrically evoked activity in ANFs (e.g., DeVries et al., 2016; He et al., 2017). Modern CI devices incorporate a reverse telemetry system that allows for eCAPs to be recorded using the intra-cochlear electrode array. In contrast to the acoustically evoked CAP, eCAPs are immune to dampening by the anaesthesia effect and to muscle artefacts (e.g., Stronks et al., 2010; Hughes 2012). As a result, patients do not have to keep still or be asleep or sedated during recording. In sum, the eCAP recording is an easy and quick method to obtain clinically, and they are ideal for use with pediatric or other difficult-to-test patients (van Dijk et al., 2007). Despite the eCAPs recording has been extensively used in clinical practice, the eCAPs are not variable to determine

the behavioural threshold and maximum comfortable hearing levels (e.g., De Vos et al., 2018). The eCAP is usually characterized by the main peak, namely, a negative deflection (N1), followed by a positive peak or plateau, P2 (Fig 1.3) (Stypulkowski & van den Honert,1984; Abbas et al., 1999; Cullington et al., 1997). Earlier studies have used eCAP recordings to objectively assess the performance of CIs, such as the eCAP amplitude growth functions and the refractory recovery function (Abbas et al., 1999; Kim et al., 2010; Walker et al., 2010; He et al., 2017). These eCAP-based studies have mainly focused on the magnitude characteristics of eCAPs rather than temporal firing properties. The morphology of eCAP waveforms is dependent on both the number of action potentials and the degree of synchronicity of neural responses (namely, the temporal firing properties) in the ANF population. As the onsets of speech segments are encoded by the synchronous response of a large number of ANFs, the temporal firing properties may potentially affect CI outcomes. Given that the eCAP amplitudes alone do not provide synchronical information, it is worthwhile to investigate whether the temporal features underlying eCAPs can be indicative of CI outcomes after implantation.

To investigate the temporal firing properties of excited ANFs underlying eCAP, it has been simplified to assume that the neural response of each single ANFs is identical to the so-called unitary response (UR) and that all URs contribute equally to the eCAP (e.g., Versnel et al., 1992a; Strahl et al., 2016; van Gendt et al., 2019). Accordingly, the eCAP can be mathematically described as the convolution of this UR with a compound discharge latency distribution function (CDLD) across all fibres (Goldstein and Kiang 1958; de Sauvage et al., 1987; Versnel et al., 1992b). The CDLD reflects both the weights of all URs of each excited ANF over time as well as the neural synchronicity that the eCAP waveform does not show directly. Strahl et al. (2016) have extracted CDLDs from human eCAP recordings using a convolution model with the guinea pig UR reported by Versnel et al. (1992a). Although this is an interesting approach, it has some serious limitations which will be improved in Chapter 2 of this thesis.

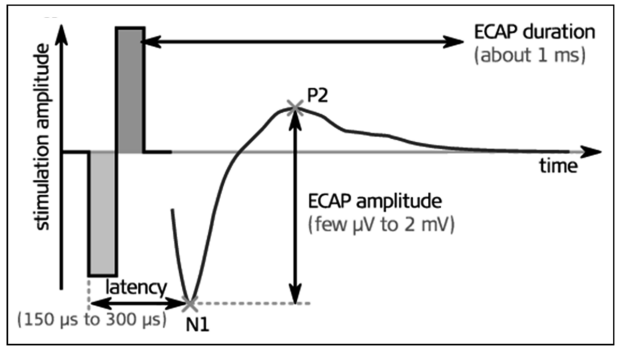

Fig. 1.3 Example of an electrically evoked compound action potential (eCAP) response for a current pulse. The horizontal axis shows time from stimulus onset. The difference between the negative peak N1 and the second positive peak P2 is defined as the eCAP amplitude.

Nonphysiological measures, such as the electrode impedance, and electric field imaging (EFI) are typically applied to evaluate the function of the internal device. These measures can be used to obtain insight into the characteristics of the surrounding tissue, the electrode-tissue interface and the path of current flow.

Electrode impedance depends on the static electrical impedances of the elements involved, but also on dynamic electrochemical processes at the level of this electrode-tissue interface (Fig. 1.4). Electrode impedance consists of the resistance component and the reactance component (Clark et al. 2003; Tykocinski et al. 2001, 2005; Hughes 2012). The resistance component refers to the access resistance which depends on the size and type of metal in the electrode contact and lead wire, and the resistivity of the surrounding fluid and tissue in cochlear implants (e.g., perilymph, fibrous tissue, bone; Clark et al. 2003). The reactance component arises from the electrode-tissue interface, involving mechanisms of charge transfer. The first is capacitive, indicating that a capacitor stores electrons ("C" in Fig. 1.4A). The second is the faradic ("Rf" in Fig. 1.4A), which transfers electrons through chemical reactions (Clark, 2004). Electrode impedance measures are incorporated into clinical software by all four manufacturers (i.e., Advanced Bionics, Cochlear, MED-EL and Oticon) (Hughes 2012; Dang et al. 2015). Electrode impedance has been used for some clinical practices, such as identifying the electrode failures, monitoring impedances over time and verifying voltage compliance.

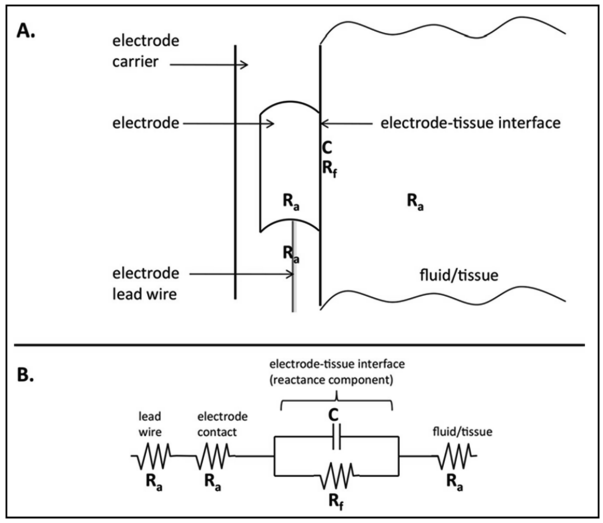

Fig. 1.4 Graphical presentation of the components of electrode impedance. A. Schematic of electrode contact on a carrier. R_a represents the access resistance; C represents the capacitance (reactance component) at the electrode-tissue interface; R_f represents potential faradic resistance. B. Corresponding electrical circuit for panel A. Adapted from Hughes, M. L., (2012) with permission.

EFI represents an intracochlear potential (or impedance) map which is measured by consecutively stimulating each contact from apex to base (e.g., Vanpoucke et al., 2004, 2012; Mens 2007). The intracochlear potential is recorded at all contacts, including the stimulating contact and thereby a picture of the distribution of electrical current in a cochlea is provided. The difference between electrode impedance and EFI recording is that voltages in the EFI mode are recorded across the whole electrode array for each single stimulated electrode pair. For electrode impedance, the voltage across only the stimulated electrode pair is recorded. Previous studies have found that the field distributions may be a feasible measure to evaluate the placement of the electrode array, such as tip fold-over (Vanpoucke et al., 2004, 2012) within the cochlea and the nature of the tissue in the cochlea (e.g., Hughes 2012). However, to date, neither the electrode impedance nor EFI yet has been deployed for the detection of electrode translocation, namely, the shift of an electrode array from the scala tympani to the scala vestibuli through the basilar membrane, which is the most common type of electrode misplacement in patients with CIs

(Finley et al. 2009; Holden et al. 2013).

1.4 Overview of the current thesis

1.4.1 Aims

The research goal of the present thesis is to explore the novel applications of objective measures in cochlear implants. The first aim is to extract the temporal firing properties of excited ANFs underlying eCAPs and examine the possible implications in terms of neural survival and refractory properties of ANFs and, ultimately, speech perception. To do this, a deconvolution model of neural responses to electrical stimulation of the ANFs was developed. The second aim of this thesis is to develop a novel tool to detect translocations of the electrode array using EFI recordings.

1.4.2 Outline of the current thesis

In **chapter 2** we propose an iterative deconvolution model for estimating the human evoked unitary response (UR) and then extract the temporal firing properties of ANFs underlying human eCAPs. In **chapter 3**, we validate this iterative deconvolution model using a relatively large data set of human eCAP recordings, consisting of 4982 eCAPs recorded from 111 CI recipients at the Leiden University Medical Center. This validation process encompasses the verification of the estimation of the human UR, the extraction of CDLDs and finding the optimal CDLD model for each eCAP waveform. From the CDLDs the temporal firing properties of excited ANFs underlying the eCAPs can be obtained. To investigate whether the temporal firing properties between children and adults are different, CDLDs derived from the two groups are compared. To further investigate the association between the CDLD extracted from eCAPs and speech perception performance in CI recipients, **chapter 4** conducts a prospective study on a group of 134 adult patients in our center. The relationship between the number and the temporal firing properties of ANFs underlying eCAPs and speech perception is evaluated. **Chapter 5** describes

a retrospective study evaluating to what extent the refractory properties of the short and long-latency components of the eCAP differed from each other and their potential clinical relevance.

In **Chapter 6** we attempt to detect translocation of the Hi-Focus Mid-Scala electrode array (Advanced Bionics, Valencia, CA) using the electrode impedance and access resistances recorded preoperatively in CI recipients.

Finally, **chapter 7** presents an overall discussion and conclusions of the studies reported in this thesis. Practical implications in clinics and future perspectives are presented.

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