Novel applications of objective measures in cochlear implants
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Chapter 7

General discussion

Cochlear implant (CI) recipients generally regain hearing such that their quality of life improves as a result of the new communication possibilities that arise from implantation. However the variability in speech perception after implantation remains substantial, and CI outcomes can range from excellent to minimal speech recognition (Holden et al., 2013; Pisoni et al., 2017). As a result, further progress in CIs is highly desired. Objective measures are widely used to serve both clinical and scientific purposes in CIs. In the present thesis, we aimed to explore new applications of objective measures of CIs. Firstly we explored the temporal firing properties of the electrically excited auditory nerve fibers (ANFs) and their potential implications of these properties for speech perception after implantation based on electrophysiological objective measures. The second goal was to develop a tool for detecting the translocation of electrode arrays using nonphysiological objective measures.

In **Chapter 2**, an iterative deconvolution model was introduced which is capable of extracting the temporal firing properties of excited ANFs underlying human evoked compound action potential (eCAP). In **chapter 3**, this model was proven to be more robust in **Chapter 3** than the convolution model proposed by Strahl et al. (2016). The result of the estimated human UR demonstrated that the unitary response (UR) of human ANFs differed from the UR previously derived from the guinea pig ANFs (Versnel et al., 1992). The CDLD model with two Gaussian components turned out to be the optimal model, such that eCAPs can be described as a combination of two separate groups of neural responses with short and long latency. With this deconvolution model, we found in **Chapter 4** that a larger number and a greater degree of synchronicity of excited ANFs revealed by CDLDs lead to better speech perception performance after implantation. **Chapter 5** demonstrated that the refractory properties revealed by the short and long-latency components of the eCAP were different from each other and differed between children and adults. Importantly, the speed of recovery as obtained by the classical RRF method using the raw eCAP did not predict speech performance, while assessing the two components of the eCAP separately proven to be indicative of speech perception performance after implantation.

In **Chapter 6**, two impedance-based methods were proposed which are capable of detecting translocation for HiFocus Mid-Scala electrode arrays without CT scan image using electrical field imaging (EFI) recording. These methods are viable to provide prompt feedback for surgeons after insertion, potentially enhancing their surgical skills and ultimately lowering the occurrence of translocations.

7.1 Application of physiological measures in cochlear implants

Over the years, cochlear implant systems have become more advanced. State-of-the-art systems are equipped with objective tools including neural response imaging/neural response telemetry that allow exploration of many factors that may provide implications for speech performance after implantation. These factors include the neuronal response of ANFs, the placement of the electrode array, among others (Fayad and Linthicum, 2006; Garadat et al., 2012).

With regard to the neural function, the temporal firing characteristics of excited ANFs were explored in this thesis based on eCAP measures. Under the UR assumption, i.e., that the action potential of each individual ANF identically contributes to the eCAP across subjects, electrode contacts and stimulus levels (e.g., Miller et al., 1990; Strahl et al., 2016; van Gendt et al., 2019), the temporal firing properties of excited ANFs in eCAPs were extracted by an iterative deconvolution model (**Chapter 2**). In this methodology, the UR plays an important role in obtaining accurate temporal firing properties of excited ANFs in eCAPs. It should be noted that the UR assumption may be an oversimplification of the actual contribution to the eCAP for all individual ANFs since this UR assumption are not completely verified yet. Differences in morphology and physiology between different species and between the cochleae of different patients and at different regions within a cochlea may result in differing URs, which in turn, affect the extraction accuracy of the temporal firing properties of excited ANFs. This speculation was supported by the results described in **chapter 3** that the eCAPs achieved with the estimated human UR were better than those achieved with a guinea pig UR reported by Versnel et al. (1992). Earlier studies also reported that for high stimulation levels the UR is unlikely to remain identical for all different ANFs (e.g., Briaire and Frijns, 2005; Westen et al., 2011). In sum, using the averaged UR across differing factors (i.e., the stimulus levels, locations along the array and different patients) might to some extent deteriorate the accuracy of the extraction of these temporal firing properties. This could be a possible reason why the temporal properties of 6% eCAPs with deviant waveforms could not be validly extracted as described in **Chapter 3**. Therefore, assuming that the UR is variable and depends on multiple factors, more accurate temporal firing properties are likely obtained when using differing URs instead of the constant UR waveform estimated in **Chapter 2** and **Chapter 3**. The use of CDLDs instead of, e.g., the eCAP amplitude-based measures, may potentially improve the prediction of speech perception outcomes after implantation in CI recipients, as reported in **Chapter 4** and **Chapter 5**. However, our modeling study can neither answer whether the estimated human UR is physiologically realistic nor how it differs across different factors as stated above. To conclusively answer this question, further anatomical and electrophysiological studies on human UR are warranted. Nevertheless, even if the UR turned out to be not constant across factors, our deconvolution model can still be applied to this situation by running the iterative deconvolution model for each condition separately.

To explain some of the variability and optimize individual speech perception performance in CI recipients, another important neural factor is formed by the refractory characteristics of the auditory nerve. The auditory refractory properties can affect the capability of accurately encoding temporal information (e.g., Brown et al., 1990; Boulet et al., 2016; He et al., 2017) and are relevant to the survival status of the ANFs as well as speech perception (e.g., Stypulkowski and van den Honert, 1984; Wilson et al., 1994; He et al., 2017). In **Chapter 2** and **3**, we demonstrated that the eCAP waveform contains a short and long-latency neural response component. With regard to the origin of the two components, they may arise from the direct excitation of the axonal process and/or the peripheral process of the auditory nerve respectively (Stypulkowski and van den Honert, 1984). Another possibility is that the two groups of neural responses originated from two different groups of excited ANFs with different degrees of degeneration and neural functionality. Thereby, the two groups of neural responses may differently affect CI outcomes. The latter hypothesis was supported by the results in **Chapter 5**, which showed the refractory properties of the two components in eCAPs were different from each other. In addition, the newly derived refractory parameters revealed differences in refractoriness between adults and children. Importantly, we found that the recovery speed of the short-latency component (S-RRF) but not the long-latency component significantly affected speech perception. Although further electrophysiological studies are warranted to completely understand the physiological mechanism of the two components in eCAPs, separately considering the refractory properties of the two separate components of eCAPs provided an additional interpretation of the variability of speech perception in CI recipients.

7.2 Application of nonphysiological measures in cochlear implants

The placement of the electrode array is an important factor that impacts the functionality of the electrode-neural interface as well as the speech understanding of patients with CIs (Usami et al., 2014; Dhanasingh et al., 2017; Liebscher et al., 2020). Unfortunately, misplacement of electrode arrays and trauma to the delicate structures within the cochlea may easily be caused as the surgeon is blind to what is happening inside the cochlea while the electrode array is being inserted. To date, electrode-array misplacements are detected commonly by analyzing postoperative (cone beam) CT images (e.g., Jia et al., 2018). However, since this radiology method requires additional work and leads to radiation exposure of patients, it is not routinely performed in many clinical practices. Therefore, an alternative, impedance-related tool for detecting electrode misplacement was developed in this thesis.

EFI measures the potential distribution through the scala tympani by recording the voltage on all electrode contacts along the electrode array when one contact is stimulated (Vanpoucke et al., 2004). With this technique, misplacements of electrode arrays can be detected, such as tip-folds over (Vanpoucke et al., 2012; Zuniga et al., 2017) and extracochlear electrodes (de Rijk et al., 2020). Moreover, based on the results described in **Chapter 6**, one can reliably detect electrode translocations intra-operatively using the electrode impedance and access resistance using EFI measures without CT scans. This method is providing surgeons with prompt feedback, which could be beneficial for future CI insertions and reduce insertion trauma (Trehan et al. 2015).

However, the EFI-based method proposed in **Chapter 6** was not directly suitable for preventing the misplacement of the arrays. It would, therefore, be desirable to develop a tool by which surgeons can intraoperatively acquire prompt feedback regarding the placement of the electrode array and eventually avoid misplacement. The EFI measured by the CI can be used as an objective measurement to detect major issues with the electrode array placement (e.g. electrode fold-over or ossification) by making use of the multidimensional scaling method (Vanpoucke et al., 2012), while the electrode array insertion depth can be detected by the tissue resistance (see Fig. 1.4) (Aebischer et al., 2021). Together with the results described in **Chapter 6**, the impedance measures presumably could be adapted to deliver real-time impedance measurements during insertion, which could provide the feedback necessary to assess the intra-cochlear placement of the electrode arrays and guide the surgeon in avoiding misplacement of the array, such as, tip fold-overs. As a tip fold-over during insertion will occur first at the tip of the electrode array, theoretically, the whole situation of the placement of the electrode could be anticipated by measuring the impedance on the first several contacts. We assumed that when a tip fold-over occurs, the physical distance between the first apical contact and other contacts will change. This change is likely to be reflected by the impedance difference between the first apical contact and other contacts. Accordingly, a tip fold-over that is developing during surgery may potentially be detected and prevented by timely intervention by the surgeon, e.g., by adjusting the speed and/or the angle of the insertion or pulling the electrode back slightly.

To test the above assumption, a pilot study to develop a real-time intraoperative monitoring system based on the dynamic measurement of electrode impedance profiles was carried out. This system simultaneously stimulated apical electrodes E1 and E3, E4 and E5 and recorded impedances from electrode E6, such that the impedance differences between E1 and E3, E4, E5, respectively were calculated ($\Delta Z1\text{-}3$, $\Delta Z1\text{-}4$ and $\Delta Z1\text{-}5$). We simulated the insertion with and without a tip fold-over in a transparent plastic cochlear model with the aid of a microscope. If the electrode array was inserted correctly, the impedance differences were expected to follow this order: $\Delta Z1\text{-}3 < \Delta Z1\text{-}4 < \Delta Z1\text{-}5$. If a fold-over begins to occur, this order will be altered. This assumption was supported by the results of the pilot study (Fig. 7.1). When a tip fold-over began, the order of the impedance differences was changed. In this tip fold-over, $\Delta Z1\text{-}5$ became the lowest one compared with $\Delta Z1\text{-}3$ and $\Delta Z1\text{-}4$ as E1 and E5 are approached each other. This alteration indicates that a tip fold-over is occurring. This pilot study proved that impedance-based measures can be used to develop a tool to prevent tip fold-over.

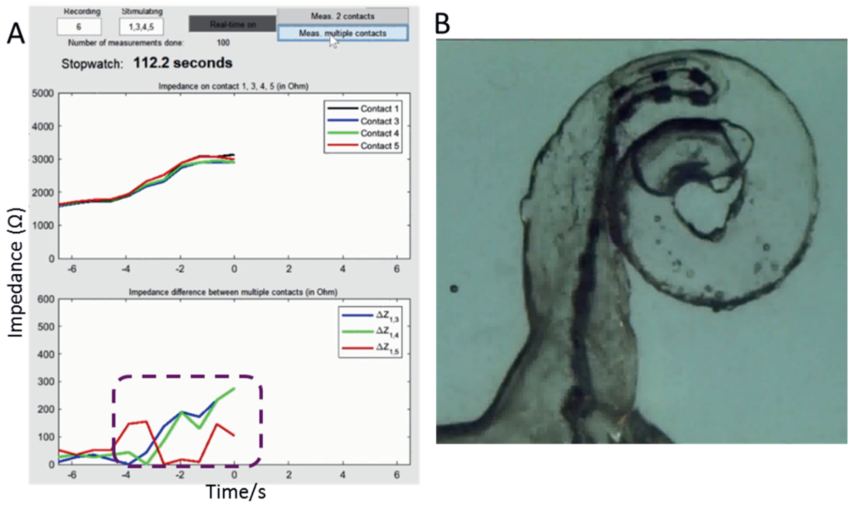

Fig.7.1 An example of electrode insertion with a tip fold-over reflected by the change of the order of the electrode impedance differences over time (A). When the fold-over is about to occur, the order of the impedance differences starts to switch (dashed square). The tip fold-over is observed in an image of the CI array in a transparent plastic dummy cochlea (B).

7.3 Clinical implications

The current research focused on the temporal firing properties of ANFs and the placement of the electrode arrays in clinical patients using objective measures. The findings regarding the temporal firing properties in the present thesis demonstrated that the eCAP waveform contains clinically valuable information: (1) the temporal properties were age-related (i.e., children tended to present greater synchronicity and a larger number of excited ANFs) which suggested children had a better survival situation of ANFs in comparison with adults (**Chapter 3**); (2) The adult patients with greater neural synchronicity and the larger number of excited ANFs on average achieved better speech performance (**Chapter 4**); (3) in children, refractory properties of the short and long-latency component in eCAPs differed from their adult counterparts (**Chapter 5**); (4) the recovery speed from the relative refractoriness of the two components in eCAPs contributed differently to speech perception (i.e., a faster recovery speed of the short-latency neural component in eCAPs is associated with a greater speech perception) (**Chapter 5**). Therefore, the temporal firing properties of ANFs and the two components of the eCAP can provide a clinical correlate of ANF survival, neural functionality and postoperative speech perception performance. Thus, it is worthwhile to integrate the CDLD and the S-RRF into eCAP measures in future clinical practice.

Our study provided a viable and non-invasive method to detect the translocation of electrode arrays based on impedance measures (**Chapter 6**). This method was capable of detecting translocation in patients immediately after CI insertion. This feedback can potentially be beneficial for surgeons in improving their skills for future CI insertions and reduce insertion trauma. Besides, another advantage of this method over radiological methods is that our method is time-saving, cheaper and safer. The findings also suggested that further development of the impedance-based tool may be useful for monitoring the insertion of electrode arrays and avoiding misplacement as stated above.

7.4 Future perspectives

The findings in this thesis provide additional clinical implications for predicting the CI performance, understanding the variability of speech perception after implantation as well as detecting the placement of the electrode arrays as mentioned above. Accordingly, new areas of interest in the field of CIs will arise.

The human UR is mathematically derived in **Chapter 2 and 3**. However, whether this estimated UR is physiologically realistic remains unknown. To address this question, biological and electrophysiological single-unit recordings studies on human ANFs are needed. With a physiologically measured UR, the accuracy of the extracted temporal firing properties can be enhanced. In turn, better interpretation and prediction of CI performance is likely achievable. As our deconvolution model has low computational complexity, it could be potentially integrated into clinical software. Such a tool could extract the temporal firing information as well as the refractory properties underlying the two components in eCAPs of CI recipients in near-real-time. As a result, these properties can provide insights into the survival status of ANFs and give an upfront prediction of speech perception performance that can be achieved by an individual CI-recipient.

The impedance measures are expected to be applicable in real-time during electrode insertion, allowing for the development of an impedance-based real-time monitoring system. This system can measure the alteration of impedances at the first several tip contacts as the insertion progresses. Any alteration in impedance can be used as an indicator for the surgeon to prevent intra-cochlear misplacement of the electrode array (e.g., tip fold-overs, translocations as well as extracochlear electrodes) and unwanted trauma to delicate structures within the cochlea in future insertions. Before such a system can be built, our findings need to be verified in temporal bones and ultimately during CI surgeries.

The preoperative residual hearing of CI candidates is found to be an important factor that affects speech performance after implantation (e.g., Gibson 2017; Chiossi et al., 2017). Thus, damage to residual hearing caused during insertion needs to be minimized. The electrocochleography (ECochG) technique was recently introduced as an objective tool to intracochlearly record electrical potentials generated by the auditory nerve in response to acoustic stimulation. ECochG has been demonstrated to be a reliable intra-operative tool for predicting postoperative hearing loss and potentially optimizing surgical technique (Mandalà et al., 2016; Dalbert et al., 2018). Researchers also found that, on average, signal amplitudes of ECochG increase with higher electrode insertion depths (e.g., Calloway et al., 2014), while a sudden decrease of its amplitude may indicate insertion trauma. These findings indicate that ECochG recordings may potentially provide real-time feedback for surgeons on whether the surgery and/or electrode insertion is inducing significant acute trauma to the cochlea and the damage to the residual hearing. In the future, such an ECochG-based real-time residual hearing monitoring system may be combined with the aforementioned real-time impedance monitoring system, capable of simultaneously monitoring ECochG and impedances of the apical contacts during the insertion.

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