FACULDADE DE ENGENHARIA DA UNIVERSIDADE DO PORTO



Correlation Between eSRT and C-levels in Cochlear Implant Users

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Master in Biomedical Engineering

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Resumo

Na história da reabilitação auditiva com implantes cocleares (IC), os critérios de indicação tornaram-se cada mais abrangentes. A eficácia e o sucesso destes dispositivos fizeram com que estas indicações se expandissem para além das tradicionais considerações audiológicas. No entanto, a dificuldade em obter respostas comportamentais fiáveis para a construção de mapas auditivos destaca a necessidade do uso de ferramentas auxiliares.

A correlação entre os níveis de conforto no IC e o limiar do reflexo estapédico eletricamente evocado (eSRT) tem sido estudada como um método objetivo para a criação desses mapas. Assim, este estudo tem como objetivo determinar se o sistema de IC da Oticon Medical é compatível com a utilização desta medida objetiva, uma vez que é a única marca de IC sem publicações neste campo.

17 indivíduos, com idades entre 34 e 75 anos, foram selecionados como participantes para este estudo. Entre eles, 9 usam um tipo reabilitação auditiva bimodal, com um IC e uma prótese auditiva, 5 utilizam um IC unilateral, 2 utilizam um IC bilateral e 1 apresenta uma surdez unilateral. Um total de 19 ouvidos foram avaliados.

O estudo avaliou a contração reflexa do músculo estapédico em ambos os lados ipsilateral e contralateral, utilizando um tom de sonda de 1000 Hz. A estimulação foi realizada através do IC, avaliando o eSRT em cinco regiões cocleares diferentes: duas apicais, duas mediais e uma basal. Diversas configurações de elétrodos foram utilizadas durante a estimulação. Os dados recolhidos foram analisados usando técnicas como a correlação linear e a informação mútua.

Além de analisar as correlações baseadas nas regiões cocleares estimuladas e no número de elétrodos utilizados, foram observadas fortes correlações tanto no lado ipsilateral (r = 0.839) quanto no lado contralateral (r = 0.804). Os valores de informação mútua foram de 4.7503 para o lado ipsilateral e 3.5367 para o lado contralateral. Estes resultados indicam um nível significativo de informação partilhada entre estas duas variáveis.

Estes resultados estabelecem condições necessárias para que os profissionais incorporem este método objetivo na sua prática clínica diária como uma ferramenta adicional no auxílio da construção de mapas auditivos, especialmente em casos em que a comunicação entre paciente e audiologista não é eficaz.

Palavras-chave: Implante coclear, eSRT, Oticon Medical, Correlação, Informação mútua

Abstract

In the history of auditory rehabilitation with cochlear implants (CI), the criteria for their use have become more comprehensive. The effectiveness and achievements of CI have expanded the indications beyond traditional audiological considerations. However, the difficulty in obtaining reliable behavioral responses for constructing auditory maps highlights the need for auxiliary tools.

The correlation between comfort levels in CI and the electrically-elicited stapedius reflex threshold (eSRT) has been studied as an objective method for creating auditory maps. This study aims to determine if the Oticon Medical CI system can utilize this type of objective measurement, as it is the only CI brand without publications in this field.

17 individuals, ranging in age from 34 to 75 years, were selected as participants for this study. Among them, 9 used a bimodal auditory rehabilitation approach with both a CI and a hearing aid, 5 used a unilateral CI, 2 used a bilateral CI, and 1 had single-sided deafness. A total of 19 ears were evaluated.

The study assessed the reflex contraction of the stapedius muscle on both the ipsilateral and contralateral sides using a 1000 Hz probe tone. Stimulation was delivered through the CI, testing the eSRT in five different cochlear regions: two apical, two medial, and one basal. Various electrode configurations were used during the stimulation. The collected data were analyzed using techniques such as linear correlation and mutual information.

In addition to analyzing the correlations based on the stimulated cochlear regions and the number of electrodes used, strong correlations were observed on both the ipsilateral side ($r = 0.839$) and the contralateral side ($r = 0.804$). The mutual information values were 4.7503 for the ipsilateral side and 3.5367 for the contralateral side. These results indicate a significant level of shared information between the two variables.

These findings establish the necessary conditions for professionals to incorporate this objective method into their daily clinical practice as an extra tool to assisting the development of auditory maps, especially in cases where patient-audiologist communication is not effective

Keywords: Cochlear implants, eSRT, Oticon Medical, Correlation, Mutual information

"You make your own luck if you stay at it long enough."

Naval Ravikant

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Abbreviations and Symbols

aSRT	Acoustic Stapedius Reflex Threshold
CI	Cochlear Implant
cU	Current Unit
eSR	Electrically-elicited Stapedius Reflex
eSRT	Electrically-elicited Stapedius Reflex Threshold
HA	Hearing Aid
mA	Milliampere
MCL	Maximum Comfort Levels
MEM	Middle Ear Muscles
OM	Oticon Medical
RMS	Root Mean Square
SR	Stapedius Reflex
SSD	Single Sided Deafness
UCL	Uncomfortable Loudness Level
WAI	Wideband Acoustic Immittance

Ω	Ohm

Chapter 1

Introduction

In the history of auditory rehabilitation using cochlear implant (CI), the establishment of eligibility criteria for potential candidates has been extremely meticulous. These criteria were primarily centered around assessing the precise characteristics and severity of an individual's hearing impairment [1]. On the other hand, at an international level, there is no standardization of these indications, with some countries adopting a broader range of criteria compared to others. These include variations in age requirements, degree of hearing loss, speech perception ability, and considerations for unilateral or bilateral hearing loss. Additionally, differences in access to rehabilitation services further contribute to the divergence in criteria across countries [2, 3].

However, given the evolution of technology in this field, currently, the indication has become increasingly comprehensive. CI and the hearing aid (HA) serve as crucial tools for auditory rehabilitation, although they differ in their approach. The CI directly stimulates the auditory nerve, while the HA amplifies sounds to compensate for the specific hearing loss. As a result, the HA is a less invasive option for auditory rehabilitation. Nevertheless, there are instances where the HA fails to provide any auditory benefit to the user, and, in such cases, the CI becomes an indispensable tool for restoring auditory function [4, 5, 6].

The effectiveness and achievement of CI have expanded the scope of indications beyond traditional audiological considerations, standardizing bilateral implantation not only at the pediatric level, but also in adults [1, 7]. These devices can now provide benefits for individuals with non-typical conditions like tinnitus, vestibular schwannoma, or neurofibromatosis [8, 9, 10]. Furthermore, coexisting conditions such as visual impairment, motor difficulties, or certain levels of cognitive impairment may be present. For these candidates, it is crucial to provide specialized attention, including counseling and follow-up appointments for proper CI programming [11].

Concerning the programming of the CI, which is the process of adjusting the settings on the device to personalize it for an individual user (see chapter 2.4.3), although there

are some guidelines of good clinical practice, there is no uniform methodology that allows distinguishing the effectiveness of programming procedures [12]. Nevertheless, it is widely agreed that the achievement and efficacy of this form of auditory rehabilitation greatly rely on its programming. It is essential to ensure that the electrical pattern transmitted in response to the captured sound maximizes speech intelligibility [12, 13]. Considering the long-lasting nature of this procedure, it is crucial to periodically review the programming strategy as changes may arise that necessitate new adjustments. For this, after the moment of implantation and subsequent activation of the sound processor, regular follow-up consultations will be essential [14].

CI programming is an individualized and exclusive procedure, even so, there are basic parameters that are commonly manipulated, regardless of the brand. The number of active electrodes, the stimulation strategy, the loudness (with reference to the amplitude and duration of the pulse) are key points that are intrinsically linked to achieving good outcomes. These aspects are predominantly refined through the assessment of behavioral responses, thereby facilitating the construction of an auditory map [12, 13, 15]. It refers to the specific way in which electrical stimulation is delivered to the auditory nerve fibers via the implanted electrode array and how different frequencies of sound are represented and perceived by the cochlear implant user.

The increase in the variability of cases that can be submitted to cochlear implantation and the difficulties associated with obtaining good behavioral responses in the construction of the auditory map, promotes the lack of auxiliary tools. In this sense, for several decades, studies have been developed using objective methods as an instrument in programming CI [13, 16, 17].

The electrically-elicited stapedius reflex threshold (eSRT) is a well-studied objective methodology. In the 1980s, Jerger et al. analyzed the contraction of the stapes muscle, by employing a conventional immittance measurement technique, as a reflex to the stimulation induced by the CI, correlating the saturation of this response with the patient's sound comfort levels [18].

In a subsequent study conducted in 1990, Hodges further supported this thesis by examining six patients with the Cochlear®Nucleus CI. The study revealed a robust correlation (r=0.91) between the eSRT and the comfort levels of the auditory map, as illustrated in Figure 1.1 [17].

Since then, numerous comparable studies have been conducted using CI from various manufacturers. Lisa Buckler et al. conducted a study involving six adults and two children utilizing the Advanced Bionics HiRes^{TM} CI, as evidenced by the graphs depicted in Figure 1.2. The correlation coefficient, denoted as r, measures the strength and direction of the relationship between these two variables. In this case, the correlation coefficient of 0.94 for adults indicates a strong positive relationship between eSRT and comfort levels. It suggests that as the eSRT increases or decreases, the comfort levels tend to follow

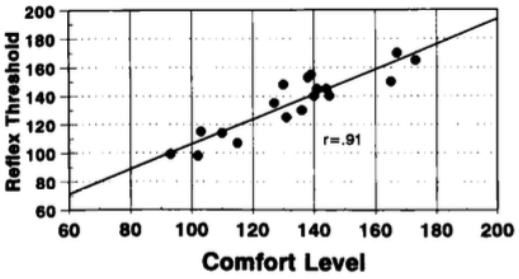


Figure 1.1: Reported correlation between the eSRT and the comfort level in 6 patients, using a Nucleus 22 channel cochlear implant from Cochlear® [17].

the same pattern. However, in the same study conducted by Lisa Bucker, the reported correlation coefficient of 1.07 for children seems to be an unusual value since correlation coefficients are generally constrained within the range of -1 to 1 [19].

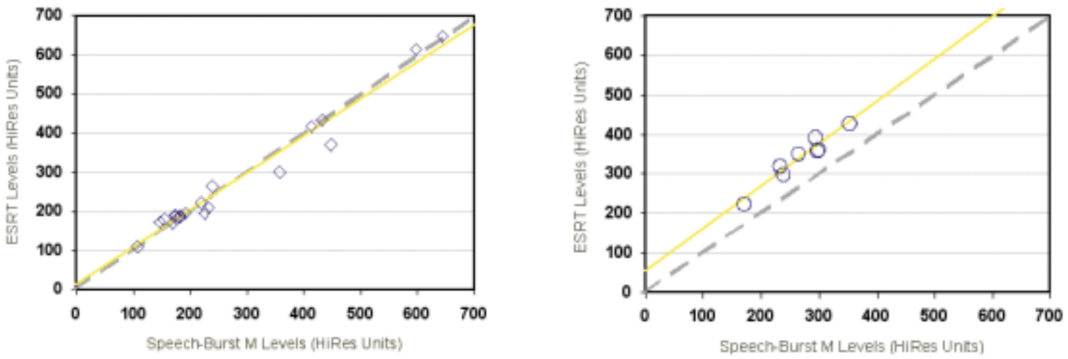


Figure 1.2: Correlation between eSRT and comfort levels in adults, at left, and children, at right, using Advanced Bionics HiRes^{TM} cochlear implant [19]

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As for the MED-EL brand, a study by Graham Brickley et al. in 22 adults, he used the COMBI 40+ implant, with different lengths and number of electrodes. Of the 22 adults tested, it was possible to obtain reliable reflexes in 13 of them (62%), of which a correlation was demonstrated between the eSRT's obtained and the MCL500 thresholds (Maximum Comfort Level using 500ms burst of stimulation pulses), r= 0.69 [20].

Since the 1960s, when the pioneering work of William House initiated the history of CI, there has been continuous development of more advanced devices aimed at enhancing the auditory experience of users. Over the years, various companies have emerged in this field, and currently, four primary brands - Cochlear® , MED-EL, Advanced Bionics and Oticon Medical (OM) - dominate the global market for CI [21]. In terms of studying the correlations between behaviorally derived comfort thresholds and eSRT outcomes with their respective implants, Oticon Medical (OM) and their cochlear implant system, Neuro System, are the only brand without published research in this area.

Considering that, the aim of this study is to determine whether the Oticon Medical CI system can utilize objective measurements, such as the response of the stapedius muscle to a comfort level stimulus, to enhance the programming of their devices. Structures such as the stapedius muscle may provide information about the sensitivity and respective auditory dynamic range not only in people with normal hearing, but also in CI users. The contraction of this muscle can be assessed through various non-invasive methods, and this study will explore its physiology, clinical applications, and evaluation techniques. In order to have a contextualization of the final objective, the field of cochlear implants will also be framed. Their indication criteria, structure, stimulation strategies and their application in programming, the different brands on the market and the usefulness of stapedius muscle reflex response in CI programming will be scrutinized.

After analyzing the implementation and respective results of some studies that share the same objectives, a study methodology was developed and adapted to the Oticon Medical device, given its differences in stimulation strategy, also contemplated throughout the study. It is intended to identify and analyze the reflex responses of the stapedius muscle electrically induced by the Neuro ZTI CI, in experienced patients. The ultimate goal is to determine whether the stapedius muscle reflex response can serve as a valuable tool in assisting CI programming, particularly in situations where behavioral responses may be inconsistent or unreliable.

This dissertation is structured into seven chapters. Following this introduction, chapter 2 provides a comprehensive overview of the fundamental principles pertaining to the anatomy and physiology of the peripheral and central auditory systems. The chapter examines the trajectory of sound from its capture in the external acoustic environment to its interpretation in the primary and secondary auditory cortex. It explores the involved structures and their respective functions throughout this auditory journey. Additionally, within a subsection of this chapter, hearing loss is discussed, along with potential methods of auditory rehabilitation, with a specific focus on CI. The influence of the eSRT on CI programming is also addressed in detail.

The chapter 3 is dedicated to outlining the study design. In this chapter, the defined objectives of the study are elaborated, along with the detailed protocol employed in conducting the research. The criteria for sample selection and the characteristics of the study participants are also described. Finally, the chapter concludes with an explanation of the data analysis methods employed in the study.

Chapter 4 presents the results of the study, organized according to the specific analyses conducted and the framing of the data. The results are systematically presented and discussed, taking into account relevant comparisons with previous studies conducted in the same field. This chapter serves to provide a comprehensive overview and interpretation of the obtained results within the context of existing research. To support and enhance the

content of these two chapters, additional complementary information is provided throughout their respective sections, presented in the appendices A.

Chapter 5 serves as the conclusion of the study, summarizing the key findings, implications, and overall significance of the research. It presents the conclusions drawn from the study's results and offers insights into their practical applications. The last chapter is dedicated to presenting the references used throughout the study, which focuses on providing an extensive literature review relevant to the study's topic.

Chapter 2

Background and Rationale

2.1 Auditory system

2.1.1 Anatomy and physiology

Hearing is one of the five senses of humans, important for awareness and essential for communication [22].

The ear, the organ responsible for conveying sound information from its capture to its transduction, is divided into three parts, as shown in Figure 2.1. The external ear, on the left side, comprises the auricle, external acoustic meatus, up to the tympanic membrane. The middle ear, in the center of Figure 2.1, where one can find the ossicular chain, consist of the three ossicles (malleus, incus and staples) and the pharyngotympanic tube, which connects the middle ear to the nasopharynx. Medially is the inner ear, presented on the right side of Figure 2.1, which is divided into two structures: the vestibule, composed of the utricle, saccule and the three semicircular canals (lateral, posterior and anterior) responsible for balance; the cochlea, a snail-shaped structure, responsible for the hearing. Both structures have distinct nerve segmentations, but they end up uniting, forming the VIII cranial nerve [22, 23].

2.1.1.1 Cochlea

The cochlea, depicted in Figure 2.2 on the left side, is the primary sensory organ responsible for hearing. It is a spiral-shaped tube that coils around the central column called the modiolus. Located in the inner ear within the petrous part of the temporal bone, it is positioned between the middle ear (laterally) and the internal acoustic meatus (medially). Within the cochlea, there are three main structures: the cochlear duct, which occupies a central position, the scala vestibuli, and the scala tympani. These structures extend throughout the cochlea until they converge at a common section called the helicotrema [23].

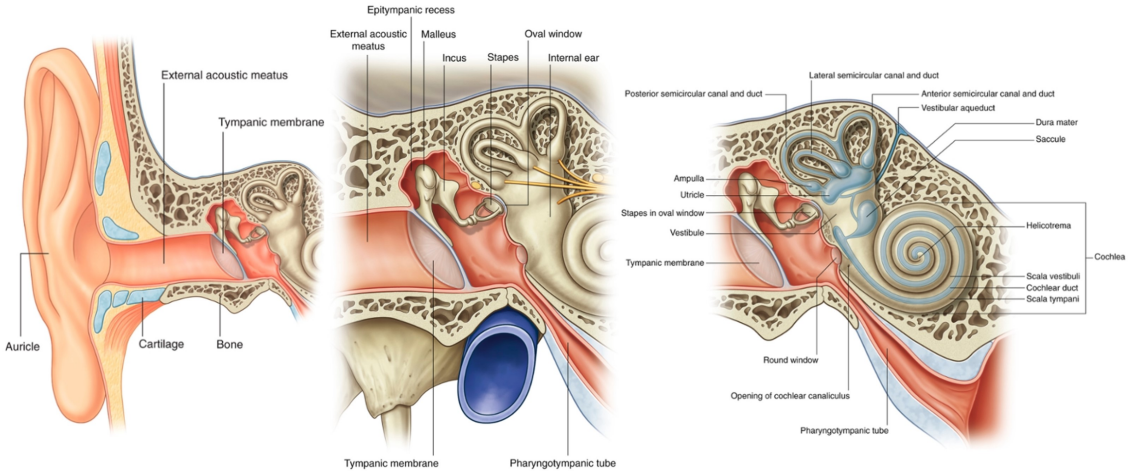


Figure 2.1: Ear's anatomy, composed of external ear (left), middle ear (middle) and internal ear (right) [23].

Located above the Organ of Corti, which rests on the basilar membrane, are two types of mechanoreceptor cells: the inner hair cells (IHCs), which are approximately 3,500 in number, and the outer hair cells (OHCs), which amount to around 12,000 units [24], are shown on the right side of Figure 2.2. These hair cells play a crucial role in converting the mechanical vibrations produced by sound waves into electrical signals. When pressure from the stapes is transmitted to the oval window, it induces a transverse displacement of the tectorial membrane and the hair cells. This displacement facilitates the transformation of sound vibrations in the perilymph into excitation of auditory nerve fibers [25].

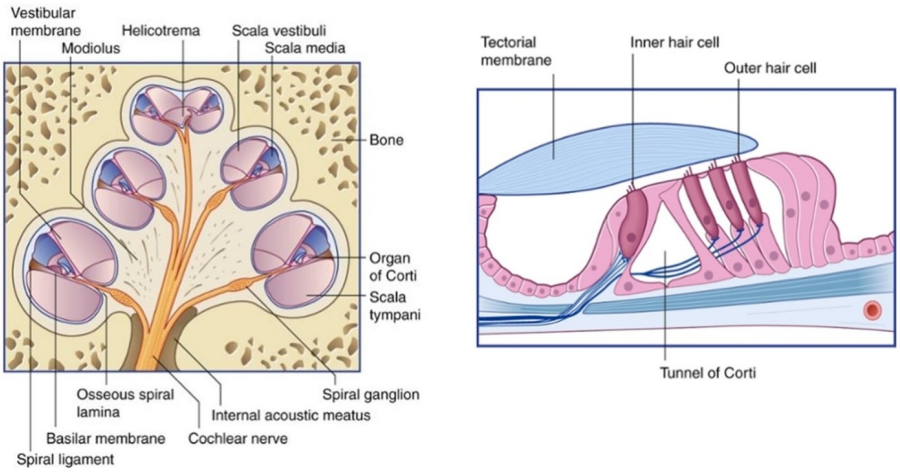


Figure 2.2: Sagittal section of the cochlea – left side; Organ of Corti with an enlarged view of the hair cells – right side [23].

Each IHC contacts an afferent peripheral axon type I, representing about 95% of afferent cochlear nerves. The remaining 5% correspond to a small population of type II

afferent nerves that contact several OHCs. The cell bodies of the auditory nerve fibers form the spiral ganglion and leave the cochlea's base as cochlear nerve. These fibers continue the ascend auditory pathway through dorsal and ventral cochlear nucleus, superior olivary nucleus, inferior colliculus, medial geniculate nucleus until reaching the primary auditory cortex, as represented in Figure 2.3. From hair cells to the primary auditory cortex, the auditory stimuli induce distinct responses depending on the frequency and intensity, being possible to represent it tonotopically, in simpler terms, the spatial organization or mapping of sound frequencies [23, 25, 26].

2.1.1.2 Cochlear nuclei

The depolarization of hair cells triggers the release of neurotransmitters, which in turn generate action potentials in the auditory nerve fibers. These nerve fibers carry the electrical signals from the cochlea to the central auditory system. Upon entering the internal acoustic meatus, this bioelectrical signal reaches the cochlear nuclei, where the fibers are distributed tonotopically, representing different frequencies of sound [28, 29].

The cochlear nuclei consist of a ventral nucleus and a dorsal nucleus. When the auditory nerve bundle enters the complex of cochlear nuclei, it bifurcates into two branches. The ascending branch extends towards the ventral nucleus, while the descending branch reaches the dorsal nucleus [30].

To provide a clearer context, the ascending branch, composed of afferent fibers is responsible for the transmission of sensory information from the periphery to the central nervous system, while the descending branch, composed of efferent fibers, transmits motor commands from the central nervous system to the periphery, facilitate the bidirectional communication [31].

Each nucleus has a crucial role in processing the temporal and spectral aspects of the auditory information received from the cochlea. Furthermore, these nuclei are responsible for transmitting the processed information to higher auditory nuclei, such as the superior olivary complex [30].

2.1.1.3 Superior olivary complex

The superior olivary complex is commonly divided into three main nuclear groups: the lateral and the medial superior olivary nucleus, and the medial nucleus of the trapezoid body, with some periolivary nuclei also being associated. Essentially, in the superior olivary complex, the auditory information received bilaterally is integrated, allowing, through temporal and spectral differences, to locate a certain sound source [30, 32, 33].

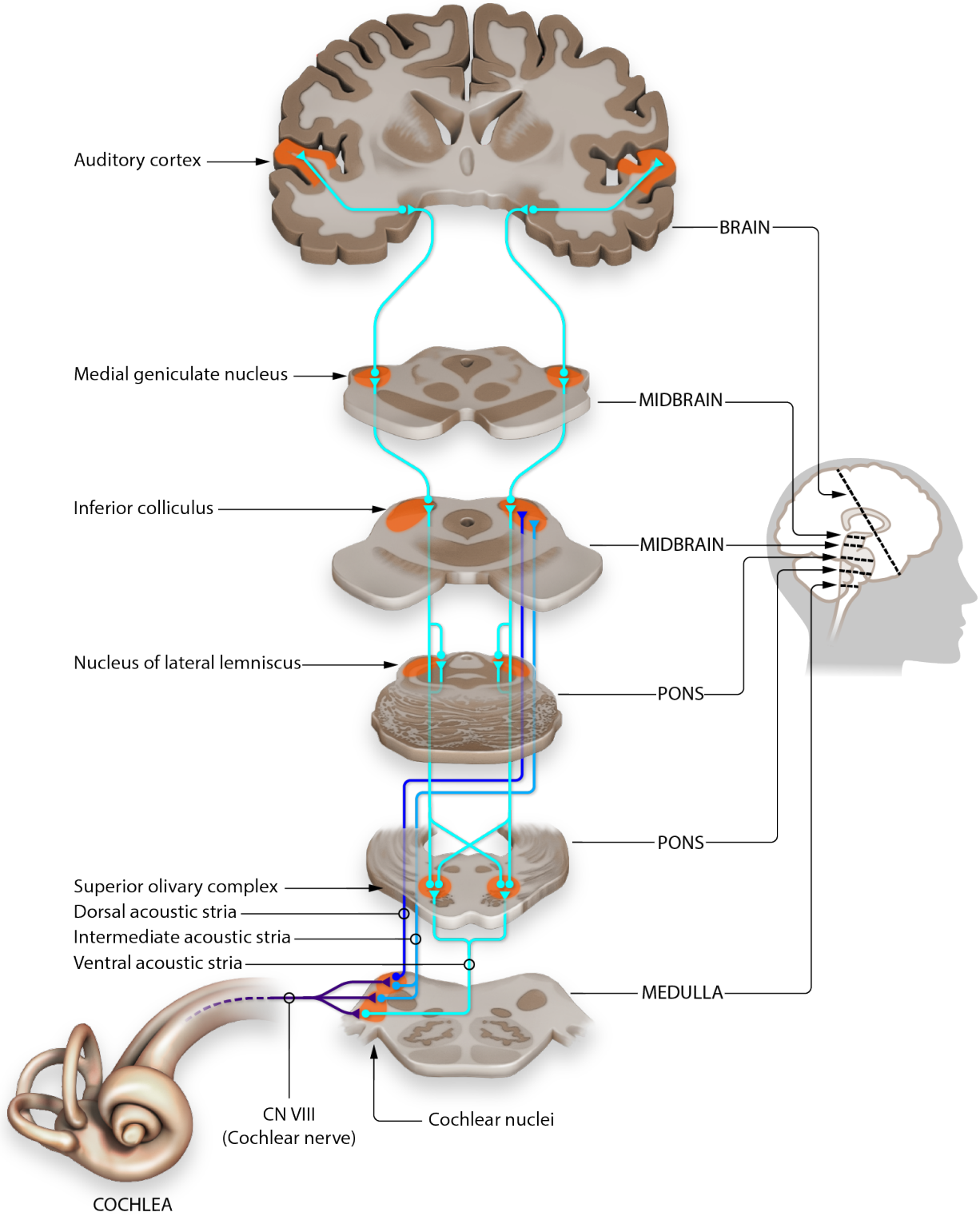


Figure 2.3: Representative scheme of the ascending human auditory system [27].

2.1.1.4 Lateral lemniscus

Axons coming from the superior olivary complex and previously from the cochlear nuclei, ventral and dorsal, join to form the nucleus of the lateral lemniscus - one of the main nerve fiber systems of the auditory pathway. It is subdivided into two different nuclei, according to their position: dorsal and ventral; [30, 34] both express different neurotransmitter, synaptic and biophysical characteristics, and most neurons in the dorsal nucleus can be activated bilaterally.

Nevertheless, in the ventral nucleus, most are only activated with contralateral stimulation. The nucleus of the lateral lemniscus, although it can be considered a less important relay station than the superior olivary complex and the inferior colliculus, plays an influential role in the modulation of the stimulus. It generates excitation and inhibition mechanisms, which allow to suppress sound reverberations, acting as a binaural temporal filter [35, 36].

2.1.1.5 Inferior colliculus

In humans, as in other mammals, the inferior colliculus, together with the superior colliculus, forms the *tectum* of the midbrain. It is the largest nucleus of the human auditory system and is subdivided into three other nuclei: dorsal, central and lateral; they are tonotopically structured concerning its response to high and low frequency stimuli. Although the central core is considered a sound processing center, the dorsal and lateral nuclei also receive descending and multi-sensory information, and may be involved in more complex cognitive functions, such as language and auditory memory. The informations processed by the inferior colliculus is subsequently sent to the medial geniculate body. This connection is essentially ipsilateral, also containing contralateral members [36, 37].

2.1.1.6 Medial geniculate body

The medial geniculate body serves as a preceding structure to the auditory perception centers in the cerebral cortex. It receives both ascending fibers from the inferior colliculus and descending fibers originating in the auditory cortex. The medial geniculate body is further divided into three segments: the dorsal division, the medial nucleus, and the ventral division[38].

The medial nucleus, also represented as the magnocellular nucleus, receives mainly information from the lateral nucleus of the inferior colliculus and does not present a tonotopically responsive cytoarchitecture, projecting itself more diffusely to the auditory cortex. The dorsal division, compared to the ventral division, is a larger and more heterogeneous structure, receiving essentially neurons from the central nucleus of the inferior colliculus. As for the ventral division, it is projected towards the primary auditory cortex,

being evidenced by the tonotopic characteristics, acquired by the identical configuration of the central nucleus of the inferior colliculus. In all these divisions, the nervous cells preserve the information of the temporal and spectral differences acquired along the aditory pathway, disseminating them in the auditory areas of the cerebral cortex [33, 36, 39].

2.1.1.7 Auditory cortex

The auditory cortex is located in the temporal lobe, more precisely in the supratemporal plane. It can be divided into three regions: the Heschl's gyrus, also known as the primary auditory cortex, the *planum polare* and *planum temporale*, considered regions of the secondary auditory cortex [40, 41]. Its tonotopic organization activates certain regions of the supratemporal plane depending on different frequency stimuli. The primary auditory cortex, as its name implies, is the first area to receive ascending information from the medial geniculate body. It is responsible for the initial processing of this information, as well as for the analysis of the most basic characteristics of the stimulus, such as intensity [40, 42]. The secondary auditory cortex, on the other hand, is responsible for more complex auditory processing such as speech and music analysis, phonemes, and the perception of tone and melody, and may even be activated by non-auditory stimuli, such as visual or somatosensory inputs [42, 43].

2.2 Middle ear muscles reflex

2.2.1 Physiology

The middle ear muscles (MEM) are composed by the stapedius muscle, attached to the stapes and innervated by the facial nerve, and the tensor tympani, innervated by the trigeminal nerve and inserted into the upper part of the malleus handle [23]. They constitute one of the main efferent feedback pathways for the peripheral auditory system, where their reflex contraction has the function of protecting the inner ear from high-level sound stimuli and reducing acoustic masking [44, 45]. It is known that this contraction of the MEM alters the acoustic impedance at the level of the tympanic membrane [46]. This reflex was first described by Lüscher in 1929, and since then, it has been extensively studied by other researchers [46, 47, 48]. This resulted in a common argument in all investigations: the reflex contraction of the MEM is a consequence of high-intensity sound stimulation. It occurs whether the stimulus is monaural or binaural, and changes in acoustic impedance in both ears can be measured [46]. As shown in the Figure 2.4, the spiral ganglion cells of the cochlea are stimulated through auditory inputs. The axons, through synaptic communication, reach the cochlear nucleus. Here, depending on the type of stimulation, there are different response properties. Motoneurons of the stapedius muscle are segregated based on their response: contralateral (in red), ipsilateral (in blue) or

bilateral (in purple). Most motoneuron axons travel in the facial nerve bundle, branching posteriorly into the fascicles of the primary stapedius nerve to the stapedius muscle. The descending projection of the motoneurons goes from brainstem to the MEM's on both sides, causing their contraction [45].

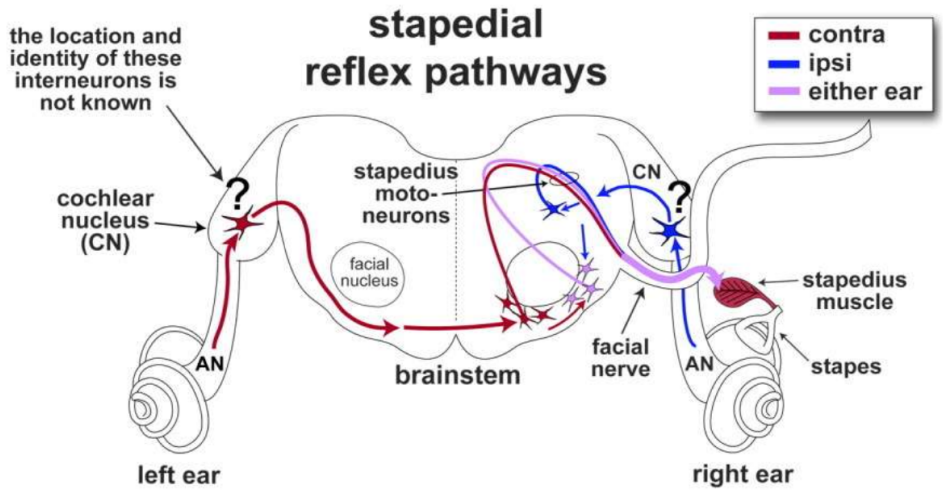


Figure 2.4: Diagram of the stapedius reflex (SR) [45].

Consequently, the MEM reflex, such as SR, results in an increase of middle ear impedance, leading to a reduction in sound transmission. This mechanism acts to attenuate the acoustic energy reaching the cochlea, thereby regulating the dynamic range of hearing as most auditory nerve fibers also have limited dynamic ranges [45].

2.2.2 Acoustic impedance concept

Impedance can be defined as the resistance to propagation in a given energy flow, in this case, resistance to propagation of sound waves. In other words, the acoustic impedance measures the opposition that a given system presents to an acoustic flow that results from an applied sound pressure [49].

Acoustic impedance is part of the battery of basic tests for hearing assessment since it is an objective method for obtaining information about the functionality of the middle ear [50]. By increasing the acoustic pressure on the external auditory canal, through a non-invasive approach, the accumulated resistance that a sound wave faces from the canal to the cochlear receptor, is measured. This resistance depends on the physical properties of the elements encountered, from the thickness and flexibility of the tympanic membrane to the mass of the three ossicles as well the stiffness of middle ear muscles [51]. The resistance of these elements is measured in cubic centimeters, and the interpretation of the resulting values may indicate the type of associated pathology in the middle ear [51, 52].

2.2.3 Measurements and clinical applications

The evaluation of the middle ear muscle reflex (MEMR) is historically used during clinical practice in defining the type of disorder, that is, if it is located in the middle ear, the cochlea or VIII for cranial. By employing either a pure tone sound stimulus of a specific frequency or a wideband probe tone, the acoustic impedance of the middle ear can be measured. This evaluation is carried out in response to the contraction of the MEM. The response can be measured in the ipsilateral ear as well as in the contralateral ear [53, 54]. When clinical assessments with a pure tone are conducted, according to the American National Standards Institute, a 226 Hz probe tone is used [54]. However, some studies indicate that the 1000 Hz probe tone - lower sound pressure level; is more effective, having a higher sensitivity and specificity in detecting middle ear disorders, particularly in children [54, 55, 56, 57].

The MEMR thresholds can be also obtained by measuring the acoustic impedances changes using a wideband probe, such as a click or chirp. This technique, inserted on wideband acoustic immittance (WAI), allows the MEMR threshold to be detected concomitantly across multiple octaves (226Hz-8000Hz). By that, the obtained thresholds are at least 8 dB lower than those obtained with the standard pure tone technique. Preventing, thus, the permanent sensorineural hearing loss induced by the sound level to elicit the reflex [54, 58, 59, 60].

As already stated, the SR is the response to a high-level sound stimulus. However, the acoustic stimulus in CI users has no effect, since, as will be explained later on, their auditory thresholds may not exist. In order to achieve the SR response, it is necessary to induce an electrical stimulus, through the CI device, obtain thus, an electrical stapedius reflex (eSR). Given that, the eSRT is defined as the minimal amount of electrical stimulation that elicits a measurable contraction of the stapedius muscle in the middle ear. Recent research focused on automatic detection of the eSR during the CI implantation, in which the movements of the stapedius tendon were recorded and analyzed by means of computer vision technique [61]. However, most of the studies focus their attention on the use of postoperative eSRTs as a determiner of maximum comfort levels (MCL) that can be measured by using acoustic impedance assessments of the middle ear.

2.3 Hearing loss and auditory rehabilitation

According to the World Health Organization [62], someone whose hearing thresholds in both ears exceed 20 dB HL is considered to have hearing loss. This may have varying degrees according to its evolution and may affect one or both ears. Hearing loss hinders the ability of sound perception and communication. In the vast majority of cases, hearing loss is a multifactorial problem with the association of a genetic component and

environmental factors [63]. With regard to acquired hearing loss, part of the causes is connected to exposure to occupational and recreational noise, as well as the treatment of other diseases with ototoxic medication as aminoglycoside antibiotics or platinum-based chemotherapeutic agents. Additionally, age-related hearing loss, or presbycusis, is an important problem that causes communication difficulties and is associated with a decrease in the quality of life of elderly people [64, 65]. There are several ways to classify hearing loss. According to its type, it can be conductive, sensorineural or mixed [66, 67]:

- Abnormalities in the outer and middle ear can cause problems in transmitting mechanical sound waves to the inner ear, resulting in a type of hearing loss called conductive hearing loss. One way to identify this condition is by using a mastoid vibrator to apply sounds to the mastoid bone. In conductive hearing loss, bone-conducted sounds are heard more efficiently compared to air-conducted sounds, as represented in Figure 2.5, which are normally perceived more effectively due to the amplifying properties of the outer and middle ear.

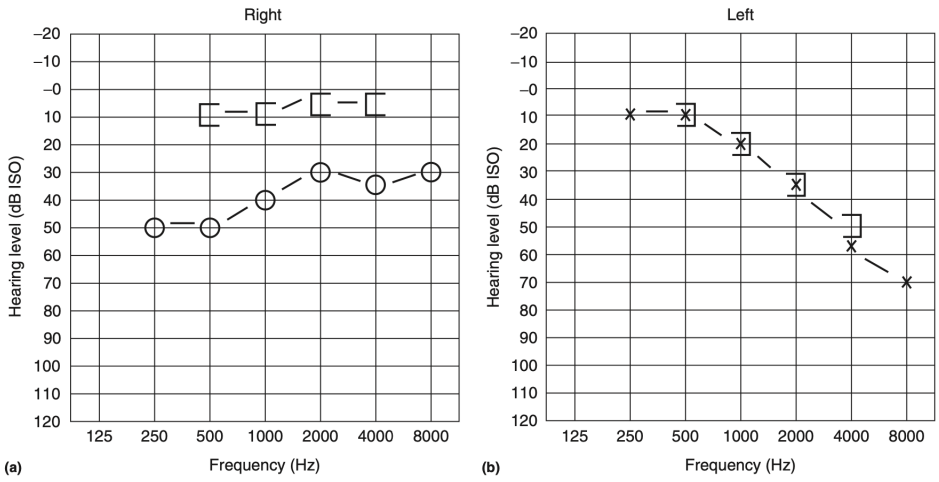


Figure 2.5: Representation of an audiometric thresholds configuration of conductive **(a)** and sensorineural hearing losses **(b)** [67].

- Issues with the inner ear and the eighth cranial nerve typically lead to sensorineural hearing loss, which affects the ability to perceive both air-conducted and bone-conducted sounds normally, as represented in Figure 2.5. This type of hearing loss not only impairs the perception of sound intensity but also affects the ability to discriminate complex sounds based on their frequencies. Sensorineural hearing loss can be further categorized as originating from the cochlea, which is part of the inner ear.

- In some cases, certain conditions such as chronic middle ear disease, otosclerosis, and physical trauma can affect both the middle and inner ear, resulting in a combination of conductive and sensorineural hearing loss. This condition is referred to as mixed hearing loss.

Additionally, hearing loss can also be classified according to its bilaterality, time of onset – pre, peri or post-lingual; audiometric configuration and also regarding its progressiveness [68]. In order to better characterize the degrees of hearing loss, after an audiological clinical evaluation and following the recommendations of the International Bureau for Audiophonology – BIAP 02/1 [69], the average hearing loss can be calculated taking into account the sum of the thresholds obtained, using pure-tone audiometry, in the frequencies of 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz, dividing by 4 and rounding to the nearest unit. After this calculation, it can be classified according to Table 2.1.

Table 2.1: Classification of hearing loss, according to thresholds average [69].

Degree of hearing loss	Average thresholds (dB HL)	Implications
Normal	Below 20 dB	No consequences
Mild	Between 21 and 40 dB	Speech is perceived if the voice is normal, difficulties may arise if the voice is distant. Most of the noises of daily life are perceived.
Moderate 1st degree Moderate 2nd degree	Between 41 and 55 dB Between 56 and 70 dB	Speech is perceived if the voice is well projected. Understanding is better with visual support. Some everyday noises are still perceived.
Severe 1st degree Severe 2nd degree	Between 71 and 80 dB Between 81 and 90 dB	Speech is perceived if the voice is well projected and close. Loud noises are noticed.
Profound 1st degree Profound 2nd degree Profound 3rd degree	Between 91 and 100 dB Between 101 and 110 dB Between 111 and 119 dB	Speech is not perceived. Only very loud noises are perceived.
Cophosis	Over 120 dB	Nothing is perceived.

To restore the normal hearing, or at least, reduce the effects of hearing loss in sound perception and oral communication, auditory rehabilitation must be considered as a fundamental procedure. Thus, the main anatomical and physiological concern is cochlear damage, which may include disruption of structures, reduced number of hair cells, or even both. These changes and their implications can be further aggravated if there is postsynaptic atrophy or other effects caused by auditory deprivation. In addition, cognitive difficulties and central auditory processing problems may still be an extra aggravating factor [70, 71]. Depending on the evaluation and subsequent characterization and

classification of the hearing loss, a certain type of auditory rehabilitation will be indicated, ranging from traditional hearing aids to cochlear implants, and there may also be a medical-surgical approach to solve the problem [72].

In some cases of conductive or mixed hearing loss, a medical-surgical approach is taken in an attempt to solve or stabilize the ear condition and its functionality. However, this type of intervention will depend on the severity of the pathology, with the possibility of reoccurrences of external and middle ear pathologies, compromising auditory functionality [73, 74]. In these cases, auditory rehabilitation is essential, and the choice of the best hearing aid system for each case is directly dependent of the hearing loss degree and ear status. In cases of conductive or mixed hearing loss, bone conduction hearing aids, bone-anchored hearing system or middle ear implantable solutions, may provide the required hearing augmentation [73, 75]. The first two solutions conduct the captured sound directly of the external environment through the bone. In a very simple way, a transducer will send sound waves that will travel through the bone until they reach the cochlea. Here, this vibration will be transmitted to the perilymph which will consequently be diffused to the hair cells [75]. The middle ear implant uses a piezoelectric or electromagnetic transducers to deliver vibrational energy to the middle ear which will then be conducted to the cochlea [73, 75].

In most peripheral sensorineural losses, a traditional hearing aid can be prescribed, which, in a very simplistic way, amplifies the sound that is captured by the microphone according to the user's audiometric configuration. This amplification, with a specific gain of frequency and compression amplitude, allows to attenuate the repercussions of hearing loss, improving sound and speech perception [72]. The device will be chosen regarding the hearing loss degree and its capability of providing the required acoustic gain. The hearing aids may have different sizes, formats, power output and between other characteristics that are dependent on the manufacturer [72, 76]. Although auditory rehabilitation with hearing aids is the most common, there are cases where hearing aids fail to provide adequate benefits as they no longer have the capacity to prescribe the necessary auditory gains. In these cases, cochlear implants present an alternative that greatly enhances hearing and, as a result, improves the quality of life for individuals affected by hearing impairment and who cannot obtain auditory benefit with traditional hearing aids [77, 78].

2.4 Cochlear Implants

2.4.1 Structure and operation

CI were a long and important step in the quest to restore the hearing of profoundly deaf people through a mechanical prosthesis. By the year 2008, CIs, as the most successful

neuroprosthesis, have helped over 120,000 people to regain their hearing sense [79, 80]. This medical device aims to restore the hearing using electrical stimuli to trigger the auditory nerve, by implanting an electrode array in the cochlea [80, 81]. The role of the CI is to mimic the function of the hair cells, via electrical stimulation. These cells, present in the organ of corti, receive the acoustic stimulus, transform it into a biosignal and forward it to the ascending path of the auditory system. In order to achieve that, the CI system is composed by two connected parts: an external part, designated as the sound processor, and an internal part composed by the implant receiver and the electrode array [82], as represented in Figure 2.6.

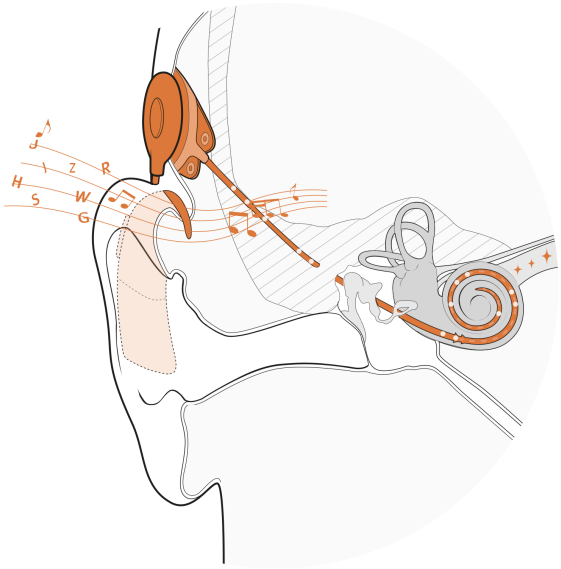


Figure 2.6: Illustration of external and internal parts of the cochlear implant system [83].

2.4.1.1 Sound processor

The external part of a CI device has a microphone system that captures the sound, transforms it into an electrical signal and then transmits it to the implant receiver. The transmission of this encoded signal is done by radiofrequency from an external transmitting coil to an internal receiving coil [82]. In order to mimic cochlear function in the best way as possible, the sound processor must convert a wideband signal with a high level of variation into multiple parallel signals with a fast data transfer rate. Nevertheless, the approximately 3500 inner hair cells in the cochlea that send information to about 32000 to 31000 myelinated nerve fibres by individual synapses, makes the mimicry a challenging task [84, 85].

The sound processor uses a process called pre-processing to reduce noise and enhance the signal-to-noise ratio. This is typically done using techniques such as filtering, compression, and gain control. The electrical signals are analyzed and break down into

different frequency bands through a process denominated feature extraction. After that, a coding strategy is applied to encode the information into a series of pulses, see Figure 2.7. This is where the different coding strategies, like place, temporal, and rate coding are applied. Place coding assigns different frequency bands to different channels, based on the place of the electrodes in the cochlea. Temporal coding refers to the method by which electrical stimulation pulses are delivered to the cochlea to convey information about the timing or temporal aspects of sound. Rate coding sends the information as a series of pulses, with the number of pulses per second representing the intensity of the sound [86, 87, 88].

Finally, the transmitting coil sends the coded information to the internal part of the implant.

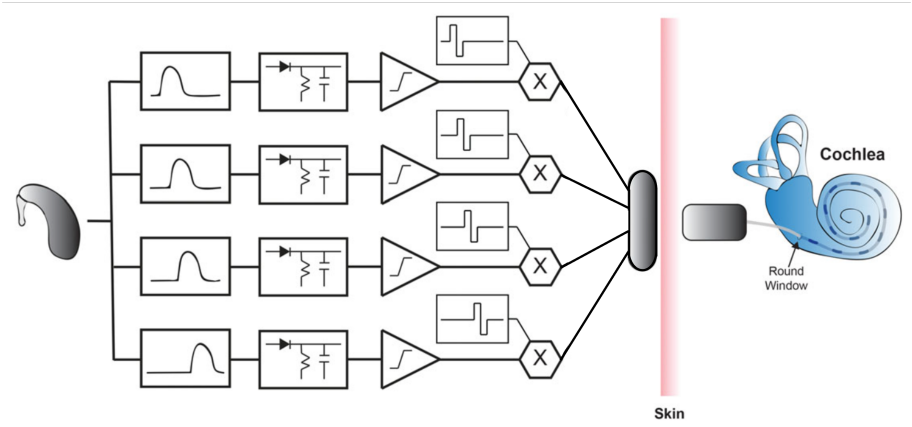


Figure 2.7: Diagram of a generic sound processing done by the CI. Transformation of the auditory input into pulses of biphasic currents [89].

2.4.1.2 Implant receiver and electrode array

The internal part of the CI system receives the coded information through the receiving coil, and depending on the signal analyses and the coding strategy, the electrodes in the cochlea will stimulate certain regions according to its tonotopic organization, as shown in Figure 2.8 [88].

Optimal performance in electrical pulse-based stimulation depends on several key factors. These factors include the pulse rate, which determines the frequency of delivering electrical pulses to the auditory nerve. The pulse amplitude represents the strength of the electrical pulses, and the pulse width signifies the duration of pulse delivery. It is important to set these values at a level that effectively activates the auditory nerve without causing discomfort or damage. Additionally, these parameters can be adjusted to encode loudness. Another factor to consider is the mode of stimulation, which can be monopolar, bipolar, or tripolar [79, 90, 91]. This default parameters, that may contribute to the

variability of performance among CI users, are common to all brands but may differ depending on the individual needs of the patient.

The electrode array is the interface between the electrical information that comes from the sound processor and the auditory neural tissue. Its design is one of the characteristics that differ more regarding the different brands [79].

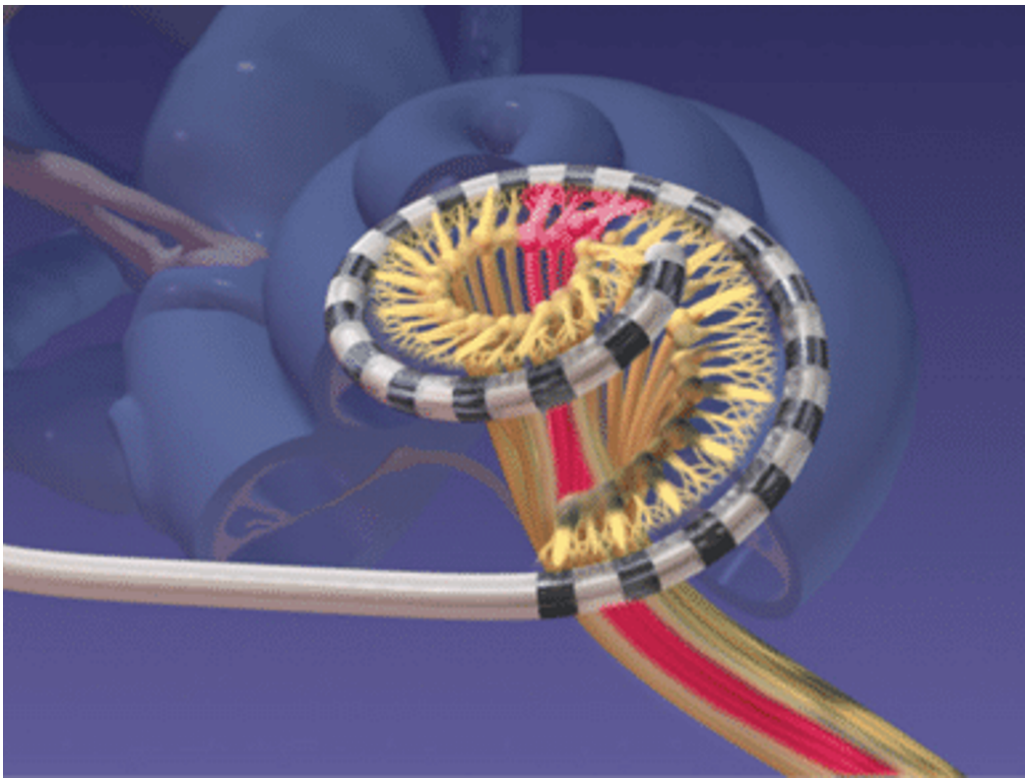


Figure 2.8: CI electrode array positioning in the cochlea [92].

CI companies typically offer multiple types of electrode arrays, each with its own characteristics. These arrays can vary in length, which determines the insertion depth into the cochlea. They may also differ in width, the number of electrodes they contain, and their stiffness or flexibility. These variations are important for facilitating the manipulation of the electrode array by the surgeon and minimizing the risk of trauma during the insertion process. Additionally, electrode arrays for CI come in three different shapes: perimodiolar, lateral wall, and mid scala. Perimodiolar arrays are preformed and positioned close to the modiolus, the central core of the cochlea. Lateral wall arrays are placed along the outer wall of the cochlea. Mid scala arrays are inserted in the middle of the scala tympani, aiming to minimize trauma to both the modiolus and the lateral wall. The choice of electrode array shape depends on factors such as surgical technique, anatomical considerations, and the desired placement within the cochlea.[91, 93].

2.4.2 Clinical indications

Before surgery, it is desirable to predict the benefit of a CI as accurately as possible in order to decide whether cochlear implantation is indicated. As stated earlier, the indication criteria for cochlear implantation has been expanded in the last years. Although in the past only profoundly deaf people were implanted, the technological evolution of these devices and the excellent performances obtained in implanted patients, make possible that, nowadays, people with residual hearing can be also submitted to a CI [94, 95].

Despite the advancements in cochlear implant technology and extensions of the indication criteria, there is still a lack of consensus within the medical community regarding the implantation of cochlear implants in patients with prelingual deafness. This is primarily due to the limited audiological outcomes observed in this population. As a result, there are two opposing positions regarding the use of cochlear implants in such cases. Some professionals advocate for cochlear implantation as an option for early intervention, aiming to provide access to sound and facilitate speech and language development [96, 97].

On the other hand, there are those who express concerns about the potential risks and uncertainties associated with the procedure, questioning its overall efficacy in improving auditory outcomes in individuals with prelingual deafness [98]. The decision to pursue cochlear implantation in these cases should be carefully considered on an individual basis, taking into account the specific circumstances, patient preferences, and available supporting evidence.

The main extensions of the indication criteria are related to age, additional handicaps in adults and children, residual hearing and special etiologies of deafness [99]. Among this special etiologies of deafness are the cochlea malformations, neurofibromatosis type 2 and tinnitus. Even though there is no consistent data in literature regarding the improvement of tinnitus after the CI procedure, a meta-analysis made by A.L.F. Borges et al. [100], showed that tinnitus perception have improved by more than 50%.

In cases of neurofibromatosis, the long-term monitoring of patients with vestibular schwannomas has demonstrated significant outcomes in terms of hearing ability. This suggests that CI should be considered as the preferred approach for restoring hearing in patients who do not retain their hearing after tumor removal, provided that the auditory nerve remains functional. CIs offer a potential solution for these individuals, allowing for the restoration of auditory perception and improved quality of life. [101].

Regarding the additional associated handicap, not only in children but also in adults, it may be included developmental delays, difficulties with learning, attention deficit/hyperactivity, visual issues, cerebral palsy, orthopedic problems, and other physical disabilities. Cochlear implantation in this population can have a significant positive impact in the patients quality of life, as well in their parents/caregivers [102].

In these particular patients, the behavioral interactions necessary to efficiently program the CI may be limited, increasing the action difficult of the audiologist in creating auditory maps.

2.4.3 Programming

Approximately one month after the surgical hospitalization for the placement of the CI, patients will have an appointment with the audiologist to activate the sound processor and program this device, which includes the configuration of personalized stimulation parameters, discussed earlier. Following the initial cochlear implant stimulation, it is common for many patients to report distorted speech sounds. However, over the course of the next few months, the sound quality gradually improves as the brain adapts to the new auditory input. The process of habituation and adjustment varies among individuals and is influenced by several factors. These factors include the age of the individual at the time of implantation, the duration of their deafness, and their previous experience with sound and speech therapy [103].

CI programming has become more intricate due to advancements in the technology. The modern implants have various advanced settings that can enhance sound quality and speech comprehension, based on the results reported by the patient. The mapping process involves making decisions such as selecting the sound coding method, determining the stimulation rate, choosing the stimulation mode, deciding on the number of electrodes used, and setting device parameters specific to the selected implant system. The CI manufacturers provide default parameter recommendations in their proprietary software [104].

Beyond that, every CI requires at least two levels for each electrode that delivers stimulation - the Threshold level, also known as T-level and the Most Comfortable Loudness level, also called C-level or MCL. The terms used and their abbreviations may differ based on its brand, but the essence of these measurements remains the same across all CIs [105, 106]. The T-levels, commonly compared to the acoustic thresholds, is the minimum of current units (cU) necessary for the patient to note the captured sounds. On other hand, the C-levels are associated to energy level perceived as a high yet comfortable sound intensity. The difference between these two levels corresponds to the electric dynamic range [104].

To create the individual auditory map, the audiologist must essentially find, beyond other mentioned parameters, the T and C-levels for each activated electrode, which will directly interfere with the individual loudness sensation. These values, measured in cU, are obtained through the patient subjective responses and changes the characteristics of the electrical pulse, more precisely, the amplitude and pulse duration [105, 107]. With the information given by the patient, the audiologist is able to create an auditory map

with the aim of enhancing auditory performance and speech understanding, balancing the loudness between electrodes [107].

However, this exchange of information between the patient and the audiologist is not always competent and successful, especially in patients with associated handicaps and in pediatric cases. These particular cases enhance the necessity of objective methods to obtain important data regarding the loudness perception and avoid stimulation levels from being under or over what is supposed for these patients. Objective methods are useful for fitting patients from whom it is not possible to obtain reliable informations and to verify results from behavioral procedures. There are two main objective measures, beyond eSRT, studied for cochlear implant fitting: the Electrically Evoked Whole Nerve Action Potential (eAP) and the Electrically Evoked Auditory Brainstem Response (eABR) [17, 104].

The eAP is used to assess the electrical responsiveness of the auditory nerve. This test helps to determine the appropriate stimulation levels for the CI. By measuring the eAP, the audiologist can ensure that the cochlear implant is set to a level that is safe and effective for the individual patient [108].

The eABR is used to assess the function of the auditory nerve and the auditory pathways in the brainstem. In this test, a small electrical current is applied by the CI, and the resulting neural activity is measured in response to the stimulation. The eABR provides information about the health and function of the auditory nerve and brainstem, and can help to determine the appropriate T-levels for the CI auditory map. [108, 109].

2.4.4 Oticon Medical CI system

Oticon Medical CI system consisting of the Neuro Zti implant and the Neuro sound processor series, with the first generation being Neuro One and the second being Neuro 2, is represented in Figure 2.9. Neuro 2 is available since 2018 and its signal processing and coding strategies are unchanged from its previous model Neuro One, launched in 2015. In both models, the Inium Sense platform includes Coordinated Adaptive Processing (CAP), which features the ability to acquire signals with a wide input dynamic range and continuously detect the environment automatically. This platform also has various signal processing options available, such as Voice Track for reducing noise and Voice Guard for compressing output [110].

The Oticon Medical Neuro Zti implant is available in the market since 2015. It is composed of a titanium flat base, a zirconia casing, and a receiver that is secured to the temporal bone with a specialized fixation system using two titanium screws, as the previous model Digisonic SP [112, 113]. The implant has two models with different electrode arrays - Classic and EVO; which differs in length and width, as shown in Figure 2.10. The Classic has 26 mm of insertion depth. Its diameter on apical part is 0.5 mm and

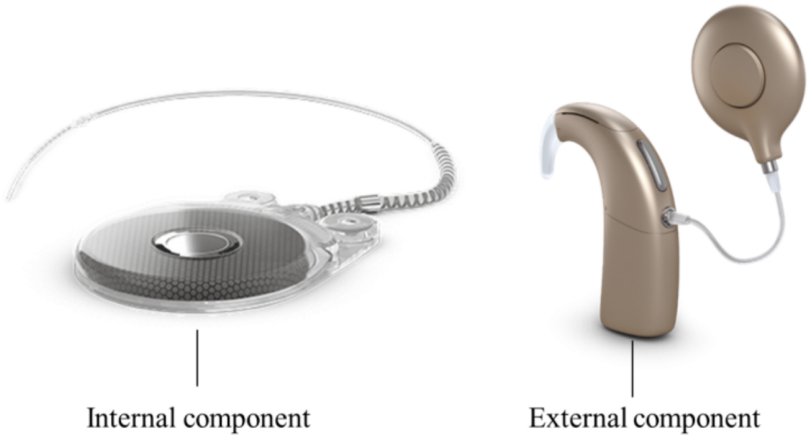


Figure 2.9: Oticon Medical CI system [111].

0.9 mm on its base. With regards to EVO, it has 25 mm of insertion depth. In the apical part its diameter is 0.4 mm and 0.5mm in its base. Both electrode arrays are composed by 20 full-band intracochlear electrodes and one extracochlear. [113, 114].

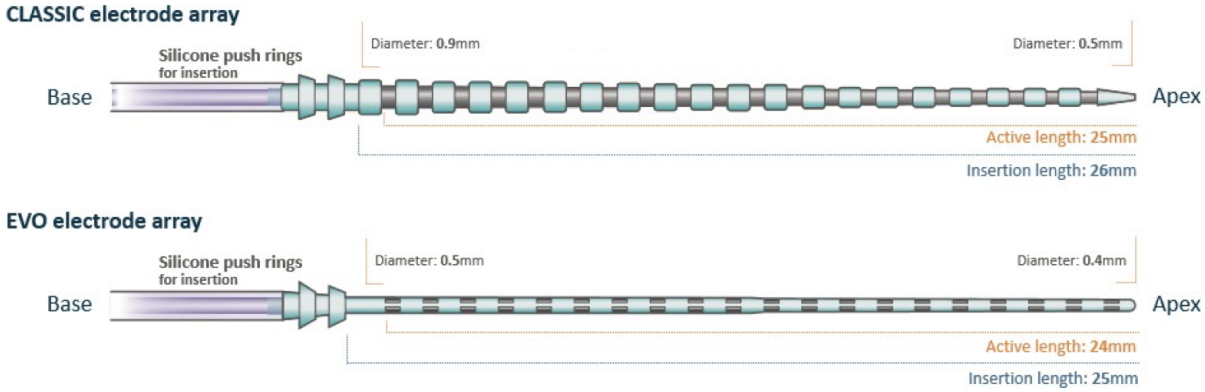


Figure 2.10: Neuro ZTI Classic and EVO electrode arrays [115].

Tippically, CI stimulation uses biphasic symmetrical pulses in a monopolar mode, where amplitude modulation is utilized to manipulate loudness. This current stimulation paradigm, although known for its effectiveness, has a energy widespread effect which leads to poor results, particularly in complicated listening situations. OM, in its implant system, utilizes a unique stimulation approach, known as Distributed All-Polar (DAP), that combines common-ground and monopolar pathways and delivers pseudo-monophasic electrical pulses with a fixed amplitude and modulated pulse duration (or width) to code for loudness [110, 113, 116]. This stimulation mode adjusts loudness by pulse duration instead of amplitude, so that loud stimuli are encoded by wide pulses rather than high current levels. Regarding the stimulation shape, the pulse waveform con-

sists of an anodic stimulation stage followed by a cathodic recovery stage. In this latter stage, the stimulating electrode and its serial capacitor are connected to ground to enable charge balancing with an exponential decay profile. This waveform only requires half the current necessary for a biphasic square pulse. This stimulation paradigm avoids device non-compliance issues by reducing the amount of extracochlear current flow in comparison to intracochlear current flow, potentially limiting facial nerve stimulation and electrode resistance. [116, 117].

2.5 Importance of eSRT to CI programming

Despite of its success, CI outcomes are known to be highly variable across patients who have received the same or highly similar cochlear implant systems [118, 119]. As mentioned earlier, the programming of multichannel cochlear implants relies on subjective feedback regarding complex sensory perceptions. If a patient lacks auditory experience or is not sensitive to subtle changes, it can be challenging to gather the required information to properly adjust the device. Age-appropriate tests can be used to measure behavioral thresholds, but determining loudness tolerance is more challenging. This is because such measurements often exhibit significant variability, and identifying a limit for loudness tolerance on a single electrode can lead to the premature conclusion of the session due to patient distress, particularly in the case of children [20]. For this reason, objectively determining the C-levels through objective methods is crucial.

Several studies have been made in order to project a relation between the MCL, or C-levels, and the eSRT:

- Lorens et al. [120] examined seven children who had an average CI experience of 1.1 years. The study compared the MCL levels, determined through either behavioral testing or eSRT measures. Subsequently, the parents were asked to provide feedback on which program they perceived as superior. The study found a strong correlation between MCL levels and no significant difference between the programs, although the eSRT program was slightly softer compared to the behavioral program.

- Andrade et al. [121] verified through a review process that the eSRT is a reliable method for guiding the activation and mapping of CI. The study concluded that the eSRT, whether measured during or after the surgery, provides an objective measurement that can assist in programming the cochlear implant device, particularly in patients with inconsistent responses. Additionally, it is recommended to utilize a combination of objective and behavioral tests when adjusting the speech processor of the cochlear implant, to prevent excessively high levels of sensation. This combined approach not only expedites and secures the process but also ensures its suitability even for infants, young children, or individuals with multiple disorders.

- A recent study looked at the relationship between two measurements, eSRT and C-level, in children with cochlear implants. The study divided the children into two groups based on their age: younger and older. The results showed that eSRT values were consistently higher than C-level values for both groups. The correlation between eSRT and C-level was moderate to very strong for the younger group and strong to very strong for the older group. This suggests that eSRT could be a useful tool for programming cochlear implants. Importantly, there was no significant difference in the correlations between the two age groups. [122].

- Regarding the detection rate of eSR, researchers have reported different values from 16% to 87% [20, 123]. The detection rate of eSR can be greatly affected by different factors such as the cochlear implant device used, the side it is placed on (ipsi or contralateral), the stimulation location (basal or apical), the probe tone frequency, and other related parameters. These factors have a significant impact on how well eSR can be detected.

- Carranco Hernandez et al. [123] investigated the eSRTs detection in unilateral Advanced Bionics CI. Out of the 19 ears that were tested, ipsilateral eSRTs were successfully measured in 16% (3 ears), 21% (4 ears), and 37% (7 ears) using probe tones of 226 Hz, 678 Hz, and 1000 Hz, respectively. Contralateral eSRT levels were measured in 58% (11 ears), 68% (13 ears), and 68% (13 ears) using the three different probe frequencies, respectively.

The documented percentages of successfully detecting the SR response thresholds to electrical stimulation from CI in both adults and children support its usefulness. Furthermore, there is a positive correlation between these thresholds and the comfort levels perceived by individual CI users in terms of loudness. This objective method can be valuable in overcoming challenges faced by audiologists when creating the auditory map, particularly when patients' collaboration is inconsistent. Moreover, it has the potential to be an effective approach in improving auditory performance and enhancing the overall quality of life for cochlear implant users.

Chapter 3

Methods

3.1 Study objectives

As explained in the previous chapter, in OM CI devices, the loudness is coded by pulse duration modulation (PDM) and not by amplitude modulation. In addition, multipolar grounding is the grounding mode that is used for the electrical stimulation. This mode provides a tradeoff between monopolar and bipolar stimulation modes in terms of current intensity in the cochlea [124]. A distinguishing factor among other CI brands, which could potentially affect the detection of eSR. Given this information, one of the main objectives of this study was to determine the success rate in detecting eSR. Additionally, it sought to evaluate whether there existed a significant difference in eSRT levels between ipsilateral and contralateral sides in patients with OM IC devices. As a final objective, it was intended to analyze the correlation between the CI comfort thresholds and the eSRT values.

3.2 Description of the protocol

3.2.1 Screening

This study resorted to tests on patients who had received cochlear implants and used the OM Neuro Zti device. The patients were selected from the implanted list of Otorhinolaryngology service at Centro Hospitalar Universitário Lisboa Norte - Hospital de Santa Maria. Two groups of patients were set up for the study: Group A and Group B. Group A consisted of patients with either unilateral or bilateral cochlear implants, while Group B included patients with bimodal hearing or single sided deafness (SSD).

Patients who had middle ear issues in either ear were not included in the study. Otoscopy, a procedure performed to examine the ear, was conducted to identify any potential outer or middle ear conditions that would make impedance testing impractical. Patients

with active problems in the outer or middle ear were excluded from the study. Tympanometry, a test to assess middle ear function, was performed to confirm that both ears had a normal middle ear status.

Background information regarding the implant insertion, middle ear condition, duration of auditory deprivation, and length of experience with cochlear implants was recorded for each patient. This information aimed to identify possible factors contributing to cases where speech recognition results were not recordable.

3.2.2 Test setup and equipment

In this study, only CE marked software and devices were utilized to conduct the tests. The GMCI fitting software was employed to establish the C-level thresholds and administer electrical stimulation through the OM CI device. Fitting mapping data was gathered for each patient.

Tympanometry and measurement of ipsilateral and contralateral SR responses were carried out using Interacoustics Titan devices (IMP440 Diagnostic + eSRT). Before recording an SR response, it was ensured that the recording probe was securely sealed and that the middle ear demonstrated peak compliance. To perform the tympanometry, probe tone of the Titan device was set to 226 Hz, since all the tested patients were adults [125, 126].

For the detection of the SR response, the specific eSRT program was selected, which provides a continuous recording window. Thus, it was possible to observe the SR response over time, upon stimulation through the CI. To ensure a valid response, a 1000 Hz probe tone was used as it is more sensitive in detecting changes in the compliance value. A valid response was considered when the compliance values had a minimum variation of 0.02 mmho [125].

Whenever possible, the study prioritized simultaneous recording of ipsilateral and contralateral SR responses for patients, rather than conducting separate recordings. The resulting SR responses, along with their raw data, were diligently stored in a dedicated data file.

3.2.3 Test procedure

3.2.3.1 Records

In the study, each participant received detailed information about the experimental procedure and the expected feedback that would be needed from them. This information was provided through an informed consent process, and participants were required to sign the consent form if they agreed to participate. An example of this informed consent is attached in appendix A.1.

If any participant experienced any discomfort from the stimuli delivered through the cochlear implant, they were instructed to promptly inform the researcher. In such cases, the stimulation would either be stopped or its intensity reduced.

For each participant, measurements of ipsilateral and contralateral SR responses were conducted for five sets of electrodes, with two sets allocated to the apical and middle cochlear regions, and one set designated for the basal cochlear region. Each set consisted of three subsets:

- 1 (a center electrode);
- 3 (a center electrode and its adjacent electrodes);
- 5 (a center electrode and its two adjacent electrodes in both sides).

There were a total of 15 different electrode groups, each of which could consist of one or more electrodes. The allocation of sets and their respective subsets was established by referring to the provided Table 3.1. This division was made when all 20 intracochlear electrodes of the OM CI device's electrode array were utilized for daily stimulation, assuming that all electrodes exhibited impedance values within the normal range.

Table 3.1: Arrangement of the 20 electrodes into 5 sets and respective subsets.

Electrode array				
Apical		Medial		Basal
20-19-18-17-16	18-17-16-15-14	14-13-12-11-10	10-9-8-7-6	5-4-3-2-1
19-18-17	17-16-15	13-12-11	9-8-7	4-3-2
18	16	12	8	3

3.2.3.2 Ipsi and contralateral eSRT measurement

The C-level values assigned to each set of electrodes (5 sets in total) followed the standard values commonly used on a regular basis. The sequence of assigning C-level values started with the subset of 5 electrodes, as the SR response becomes more prominent when a larger stimulation area is involved. This aspect will be further elaborated on in the upcoming chapter.

During this step, evaluation was conducted on all sets of 5 electrodes from different regions of the cochlea. If no SR responses were detected, the C-level values for this 5-electrode group were gradually increased until an SR response was detected or the patient's compliance limit was reached. The increase in C-level values was carried out in an ascending technique, allowing for the assessment of the amplitude of the SR response in relation to the increment of C-level values for the electrodes being tested. This relationship is illustrated in Figure 3.1. It can be seen that as the stimulus intensity rises, the

response amplitude of the SR also increases, confirming that oscillation aligns with the contraction of the stapedial muscle.

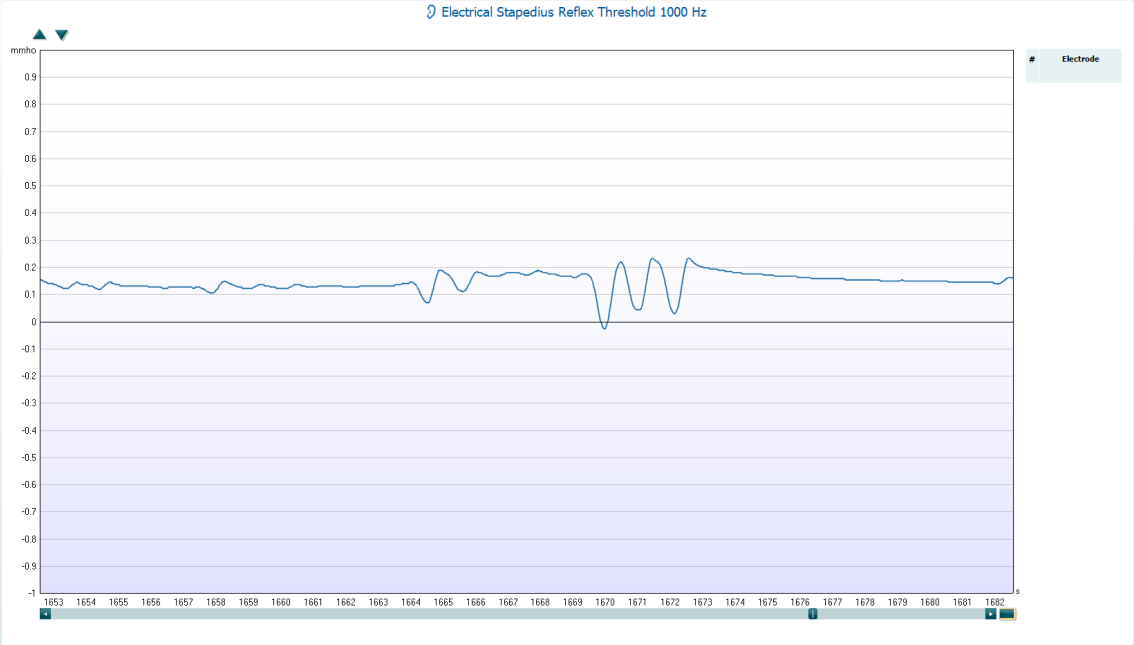


Figure 3.1: Ascending technique to acquire the eSRT.

In cases where SR was detected using the standard C-level values commonly used, the inverse technique was employed. This technique, as depicted in Figure 3.2, involved decreasing the C-level values until the SR was no longer detected, thereby obtaining the desired threshold.

Once the evaluation of all sets, consisting of 5 electrodes, was completed, the process continued with the evaluation of sets containing 3 electrodes and 1 electrode, respectively. In each case, both ascending and descending methods were utilized to determine the eSRT, depending on the specific requirements of each evaluation. If no response was detected for a specific subset, either on the ipsilateral or contralateral side, the examination of the subset(s) with the fewest number of inserted electrodes was disregarded and excluded from further analysis.

Noteworthy to mention that within the Neuro Zti implant system, 1 milliampere (mA) corresponds to 45 current units (cU). Additionally, the maximum allowable current unit can be calculated after the ratio $\frac{225}{R}$, where R represents the impedance of the stimulating electrode in kΩ [127].

Based on the obtained eSRT values, a predefined Excel worksheet was completed to record relevant information. This worksheet documented the cU that led to the detection of SR on both the contralateral and ipsilateral sides. Additionally, it included the corresponding charge values, considering the conversion to mA. The worksheet also provided

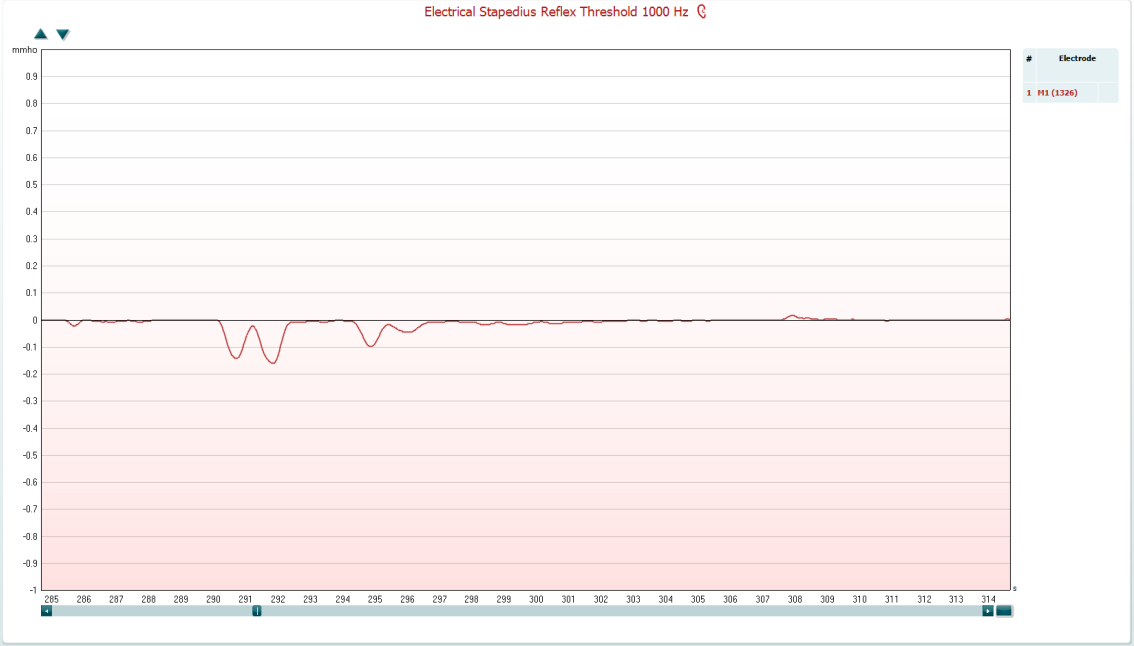


Figure 3.2: Descending technique to acquire the eSRT.

the average charge and root mean square (RMS) values for the recorded data. These details, as observed in appendix A.2, provide further visual representation of the data.

3.3 Selection criteria

3.3.1 Inclusion criteria

Criteria for inclusion in the study were as follows:

- Agreement to sign the informed consent form;
- Aged 18 years or older;
- Be a current user of the Neuro Zti EVO cochlear implant system;
- Hold a minimum of one year of experience using the OM cochlear implant.

3.3.2 Exclusion criteria

Participants who met any of the following exclusion criteria were not included in the study:

- The presence of a medical condition resulting in middle ear modifications, as detected through otoscopic examination and tympanometry;

- Individuals with psychological or linguistic limitations that prevented them from understanding the information provided;

- Participants under legal protection or deprived of liberty.

3.4 Subjects

As previously mentioned, the individuals included in this study were selected from the database of cochlear implant patients using the OM device. Subsequently, specific criteria for inclusion and exclusion were implemented to determine the eligible population for the study and uphold the credibility of the findings.

A total of 17 individuals who fulfilled all the selection criteria were chosen as participants for this study. The age of the participants ranged from 34 to 75 years, with an average age of 55.3 years. Among them, 9 individuals utilized a bimodal auditory rehabilitation approach consisting of a CI and a HA. Additionally, there were 5 participants with unilateral CI, 2 with bilateral CI, and 1 with SSD. In total, 19 ears were evaluated throughout the study.

To establish distinct groups, Group A was formed, comprising individuals with either unilateral or bilateral implants, totaling 9 ears. Group B was composed of individuals with bimodal adaptation as well as those with SSD, resulting in a total of 10 ears.

3.5 Data analysis

To achieve the predetermined objectives outlined in this study, the worksheets acquired during the sample collection phase were merged into a singular document, encompassing the data collected from all the evaluated ears.

Following that, the data underwent processing to generate customized tables that aligned with the specific needs of the planned statistical analysis. These tables were populated with the RMS value derived from all sets containing either five or three electrodes, which were previously calculated in the above mentioned Excel worksheet.

The tables encompassed three variables: the daily-utilized C-levels of each electrode that constituted the participants' auditory maps, the eSRT values obtained from evaluating the contralateral ear, and the eSRT values obtained from evaluating the ipsilateral ear.

One of the tables organized the data based on the stimulated cochlear region and the average frequency distribution used within each region, considering the electrodes comprising each set.

Individual analysis tables were also generated for each participant to facilitate a subsequent comparison between Groups A and B.

Additionally, a comprehensive table was constructed to encompass all the measurements obtained from the evaluation of the 19 ears. Given that eSR detection was performed in 15 sets and subsets for each ear, a total of 285 cases were included in this table. The aim was to calculate the percentage of eSR detection and compare the results between the responses of the contralateral and ipsilateral ears.

The MATLAB_R2023a software tool was utilized to conduct the statistical analysis of linear correlation. A significance level (α) of 0.05 was employed to determine the statistical significance. Additionally, Visual Studio Code was used to calculate the mutual information values and generate corresponding graphs and tables.

3.5.1 Linear correlation

Linear correlation, also known as Pearson correlation, is a statistical measure that quantifies the degree of linear association between two variables. It assesses how closely the relationship between the variables can be approximated by a straight line [128].

The linear correlation coefficient, denoted as r, ranges between -1 and 1. A positive value of r indicates a positive linear relationship, meaning that as one variable increases, the other variable tends to increase as well. A negative value of r indicates a negative linear relationship, where as one variable increases, the other variable tends to decrease. While r=0 indicates no association between variables [129, 130].

Considering x_i and y_i the values of two variables for a specific data point i, with n representing the sample size, and $\bar{x}$ and $\bar{y}$ the respective means of both variables, the r can be defined as [130]:

$$r = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum (x_i - \bar{x})^2 \sum (y_i - \bar{y})^2}}$$

Nevertheless, linear correlation has its limitations and potential pitfalls. It assumes a linear relationship between variables, which may not be the case for non-linear relationships. Additionally, outliers can greatly influence the correlation coefficient being important to identify and handle outliers appropriately to avoid their impact on the correlation analysis. Beyond that, correlation does not imply causation and restricted data ranges, multicollinearity, data errors, and time-related issues should also be considered for accurate interpretation of correlation results [131, 132].

3.5.2 Mutual information analysis

In addition to the conducted statistical analysis of linear correlation, an alternative measure known as mutual information was also investigated to be applied in this study.

In data analysis, it is crucial to understand the relations between variables to obtain insights and make informed decisions. Linear correlation has traditionally been used as the

primary method to measure the statistical relationship between two variables. However, mutual information analysis has gained prominence as a powerful alternative that provides several advantages over linear correlation. Mutual information offers a more comprehensive measure, capturing general dependence that includes non-linear relationships. In contrast, correlation specifically focuses on measuring linear dependence between variables [133].

Mutual information is calculated by comparing the joint distribution of the variables to their individual distributions. Mathematically, mutual information is defined as the difference between the entropy of one variable and its conditional entropy given the other variable, and, when a higher mutual information value is obtained, it is indicative to a stronger association and a greater reduction in uncertainty [134, 135]. Considering (X,Y) as two discrete random variables, if the joint distribution of these variables is represented by $P(x,y)$, and their respective marginal distributions are denoted as $P(x)$ and $P(y)$, the mutual information is defined as follows [136]:

$$I(x;y) = \sum_{i=1}^{n} \sum_{j=1}^{n} p(x_i, y_j) \log \left(\frac{p(x_i, y_j)}{p(x_i)p(y_j)} \right)$$

Mutual information has diverse applications in various fields. In neuroscience, it is employed to examine the connections between different neural signals and quantify the transfer of information between different regions of the brain. In bioinformatics, it aids in discovering interdependencies between genes or proteins. In machine learning, mutual information serves as a criterion for selecting relevant features, training models, and evaluating the importance of variables in predictive tasks. Moreover, it plays a vital role in statistical dependence analysis by assessing the relationship between variables beyond the constraints of linear correlation. [135, 137].

To perform this analysis, the Visual Studio Code software was utilized. A few lines of code were written to load the data of the two variables, see A.3.3, which in this case, were the variables used to the overall correlation for both ipsi and contralateral sides. Using the "mutual_info_score" function, the mutual information values for the respective variables were obtained and assessed.

Chapter 4

Results and discussion

4.1 eSR detection rate

Considering the evaluation of 5 cochlear zones, specifically 2 apical zones, 2 medial zones, and 1 basal zone, different sets of 5, 3, and 1 electrodes were assessed within each zone. As a result, a total of 15 evaluations were conducted for each participant. With 19 ears being observed, this accounts for a total of 285 evaluations for the contralateral ear and an additional 285 evaluations for the ipsilateral ear.

As shown in Table 4.1, the overall percentage of eSR detection in the evaluation of the contralateral side was 58.60%, whereas on the ipsilateral side, this percentage decreased to 41.05%.

Table 4.1: Overall eSR detection rate.

	Contralateral	**Ipsilateral**
Cases with eSR detection	167	117
Total cases	285	285
Detection rate	58,60%	41,05%

In the assessment of eSR detection, there was a difference of 50 fewer instances of detection on the ipsilateral side compared to the contralateral side. As indicated by previous research [138], obtaining accurate measurements of the eSRT may be more challenging when the admittance probe is positioned in an ear that has undergone implantation. This can possibly be attributed to the heightened rigidity in the middle ear, which arises due to the subtle alterations in middle ear mechanics resulting from surgical interventions or prior ear conditions [125].

When analysing the eSR detection based on the cochlear region and the frequency range allocated to the respective subset of electrodes, it became apparent that there is a variation in the occurrence of eSR response depending on the extent of the stimulation frequency bandwidth. This evidence is presented in Table 4.2.

Table 4.2: eSR detection rate and distribution of frequencies based on the cochlear region and corresponding subset.

		eSR detection rate		**Frequency distribution (Hz)**		
Cochlear region	**Subset**	Ipsi	Contra	MIN	MAX	AVG range
Apical 1	5 electrodes	57,89%	68,42%	188,0	813,0	625,0
	3 electrodes	52,63%	68,42%	313,0	688,0	375,0
	1 electrode	36,84%	42,11%	438,0	563,0	125,0
Apical 2	5 electrodes	52,63%	68,42%	438,0	1063,0	625,0
	3 electrodes	47,37%	63,16%	563,0	938,0	375,0
	1 electrode	10,53%	36,84%	688,0	813,0	125,0
Medial 1	5 electrodes	52,63%	68,42%	924,8	1859,1	934,2
	3 electrodes	52,63%	68,42%	1049,8	1563,0	513,2
	1 electrode	10,53%	42,11%	1194,6	1372,2	177,6
Medial 2	5 electrodes	47,37%	68,42%	1530,1	3641,9	2111,8
	3 electrodes	47,37%	68,42%	1819,6	2990,6	1171,1
	1 electrode	26,32%	57,89%	2076,2	2543,3	467,1
Basal	5 electrodes	47,37%	68,42%	3214,3	7760,4	4546,1
	3 electrodes	42,11%	52,63%	3845,9	6602,5	2756,6
	1 electrode	31,58%	36,84%	4740,6	5609,1	868,4

This table shows that the percentage of eSR detection increases as the stimulation frequency range expands for each cochlear region. This pattern is observed for both the ipsilateral and contralateral responses. The most significant disparity is observed when comparing the detection rates between subsets of 5 electrodes and subsets with a single electrode. In the latter case, the stimulation frequency range represents approximately 20% of the region stimulated by the 5 electrodes.

This finding suggests that the detection of the eSR response becomes more feasible with an increased number of electrodes utilized for stimulation. Figures A.6 and A.7 (appendix A.3) can be consulted for a clearer comprehension of how frequencies are distributed among the electrodes available, as they visually depict the methodology employed for this standard division within the GMCI software.

Regarding the initial division that was implemented by separating all participants into two groups, the eSRT detection rate was also assessed for each group, and a comparison was conducted between them. Table 4.3 presents the proportion of eSR detection in relation to the total number of cases for each group.

In group A, comprising 10 participants with bimodal rehabilitation and SSD, a total of 150 eSR assessments were conducted. Out of these, 50 assessments were considered valid on the ipsilateral side and 91 assessments on the contralateral side. Consequently, the calculated percentage of eSR detection was 33.33% and 60.67%, respectively.

In the case of group B, which consisted of 9 participants with unilateral or bilateral CI,

there were 135 assessments performed for each side. Among these, 67 assessments were valid in the ipsilateral ear and 75 assessments in the contralateral ear. This yielded a percentage of eSR detection of 49.63% on the ipsilateral side and 55.56% on the contralateral side.

Table 4.3: Comparison of eSR detection rates in groups A and B, considering overall rates, cochlear region and corresponding subset.

		Group A		**Group B**	
		Ipsi	Contra	Ipsi	Contra
Cases with eSR detection		50	91	67	75
Total cases		150	150	135	135
Detection rate		33,33%	60,67%	49,63%	55,56%
Cochlear region	**Subset**				
Apical 1	5 electrodes	50,00%	70,00%	66,67%	66,67%
	3 electrodes	40,00%	70,00%	66,67%	66,67%
	1 electrode	30,00%	50,00%	44,44%	33,33%
Apical 2	5 electrodes	40,00%	70,00%	66,67%	66,67%
	3 electrodes	40,00%	60,00%	55,56%	66,67%
	1 electrode	10,00%	40,00%	11,11%	33,33%
Medial 1	5 electrodes	40,00%	70,00%	66,67%	55,56%
	3 electrodes	40,00%	70,00%	66,67%	66,67%
	1 electrode	10,00%	50,00%	11,11%	33,33%
Medial 2	5 electrodes	40,00%	70,00%	55,56%	66,67%
	3 electrodes	40,00%	70,00%	55,56%	66,67%
	1 electrode	20,00%	60,00%	33,33%	55,56%
Basal	5 electrodes	40,00%	70,00%	55,56%	66,67%
	3 electrodes	30,00%	50,00%	55,56%	55,56%
	1 electrode	30,00%	40,00%	33,33%	33,33%

This comparison between the eSR responses of groups A and B also confirms a logical relation between the extent of cochlear region stimulation and the percentage of eSR detection. Hence, based on these values, it can be inferred that the higher the number of electrodes utilized for stimulation, the higher the percentage of eSR detection.

Furthermore, after examining the values presented in Table 4.3, it is possible to observe that the detection percentages on both sides, between group A and group B, exhibit similarity at 47.0% and 52.6%, respectively. However, the contralateral side of group A displays a higher percentage compared to the contralateral side of group B. Additionally, the disparity between the ipsilateral and contralateral sides is more pronounced in group A, with an approximate 27% difference, whereas in group B, the difference is approximately 6%. This dissimilarity may be due to the functionality of the contralateral ear in

cases of bimodal rehabilitation and SSD, whereas in cases of unilateral and bilateral CI, this functionality may be affected, resulting in different responses.

In CI bilateral cases, the functionality of middle ear structures may be influenced by prior surgical interventions [125], while in unilateral cases, the lack of auditory input leads to a decrease in SR thresholds, causing an increase in neural activity, strengthening excitatory responses, and reducing inhibitory responses [139]. Since MEM's contraction is an inhibitory response, the detection of eSR in the contralateral ear may be affected in these cases.

4.2 Correlation between C-levels and eSRT

Due to the significance of this topic in the study and the potential for insightful conclusions, the correlation between C-levels and the eSRT was examined from various perspectives. Each perspective was analyzed to provide additional information and complement possible deductive reasoning.

Based on the mentioned percentages of eSR detection, instances where no eSR response was observed during certain evaluations were assigned a value of 0, thereby classifying them as outliers for all correlation analyses conducted. Consequently, for all the graphs presented, cases of non-detection were excluded from the calculation of correlations, adhering to the exclusion rules. These cases are represented as red points.

4.2.1 Analysis by subsets

The correlation analysis by subsets was initiated to examine the relationship between subsets consisting of 5, 3, and 1 electrodes, and the corresponding C-levels used within each subset. This analysis resulted in the creation of six graphs, which are presented below. Three of these graphs depict the subsets of the contralateral side, while the remaining three represent the subsets of the ipsilateral side.

Figure 4.1 illustrates the correlations between the C-levels and eSRT in the subsets with 5 electrodes for both the ipsilateral and contralateral sides. A high degree of similarity is observed in the obtained r^2 values, with 0.755 on the ipsilateral side and 0.751 on the contralateral side. These values suggest that there is a favorable positive correlation between the C-levels and electrode subsets. Additionally, when comparing the r^2 values of both sides, there is a negligible disparity between them, indicating a lack of significant variation or divergence. Nevertheless, statistical significance ($p < 0.05$) was observed only for the ipsilateral side.

As the subset size decreases, there is an increase in the number of cases where eSR is not detected, as observed in the previous section that explored the relationship between the frequency distribution and the percentage of eSR detection. Furthermore, as illustrated

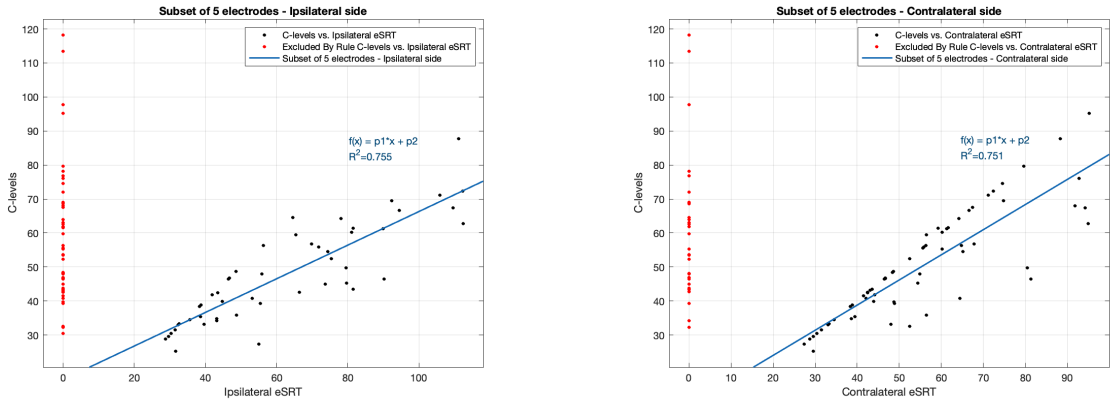


Figure 4.1: Correlation between C-levels and eSRT in subsets comprising 5 electrodes for both the ipsilateral and contralateral sides. X and Y axes are represented as RMS values of cU used.

in figure 4.2, it is apparent that the value of r^2 decreases when comparing to the subsets with 5 electrodes.

In the subsets with 3 electrodes, the obtained r^2 value was 0.638 for the ipsilateral side and 0.580 for the contralateral side, both values were found to be statistically significant ($p < 0.05$). Although they are relatively lower than those observed in the correlation analysis of the 5-electrode subsets, they still indicate a moderate to good correlation between the C-levels and the eSRT.

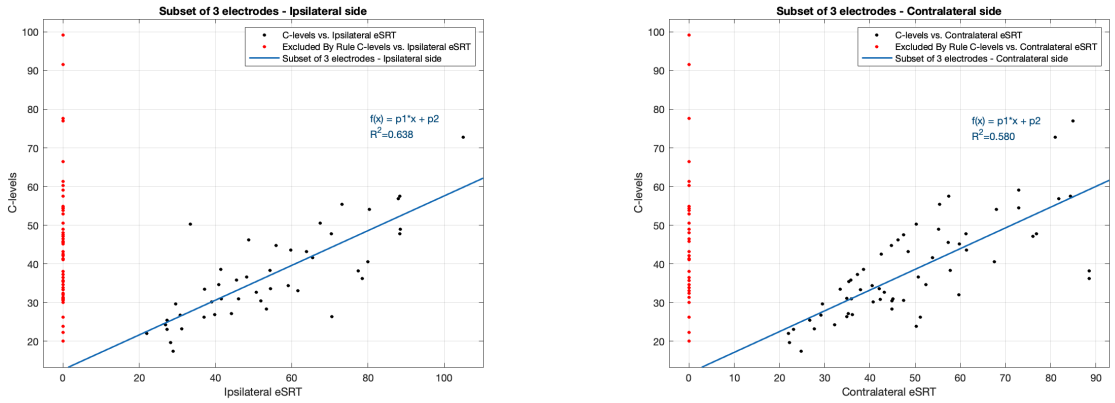


Figure 4.2: Correlation between C-levels and eSRT in subsets comprising 3 electrodes for both the ipsilateral and contralateral sides. X and Y axes are represented as RMS values of cU used.

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In the final analysis of the correlation by subsets, as observed in Figure 4.3, it was found that both the number of non-detections of eSR and the value of r^2 decrease further compared to the previous analyses. On the ipsilateral side, the r^2= 0.592, while on the contralateral side, an r^2 value of 0.544 was achieved. Both values yielded statistically significant results, as indicated by p-values less than 0.05. Despite the decrease, these

values still indicate a moderate correlation between the C-levels and the eSRT in subsets consisting of only 1 electrode.

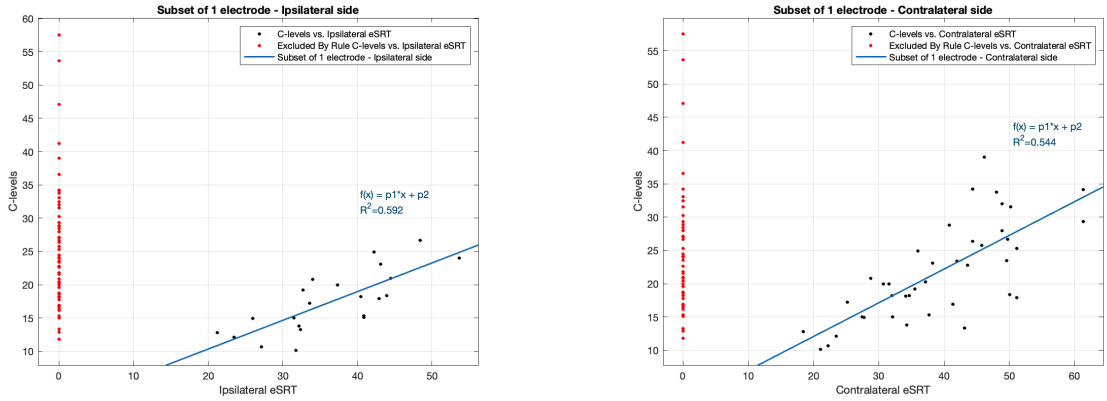


Figure 4.3: Correlation between C-levels and eSRT in subsets comprising 1 electrode1 for both the ipsilateral and contralateral sides. X and Y axes are represented as RMS values of cU used.

With this analysis, it is possible to observe that when comparing the C-levels and eSRT values by subsets, a higher number of electrodes leads to a stronger correlation between these two variables. In this case, a subset consisting of 5 electrodes highlights this increased correlation.

4.2.2 Analysis by cochlear regions

To ascertain whether there is a specific cochlear region that exhibits a higher correlation with SR contraction upon stimulation, an analysis was conducted to validate this potential hypothesis. This analysis considered the five primary divisions of cochlear zones, namely, two apical sets, two medial sets, and one basal set. Within each of these sets, the responses of the corresponding subsets with 5, 3, and 1 electrodes were combined, for both ipsi and contralateral sides.

The first two graphs depicted in Figure 4.4 illustrate the analysis conducted within the first apical zone. Observing the results, the r^2 value on the ipsilateral side is 0.526, whereas on the contralateral side, it is 0.349, both p-values were less than 0.05. These findings indicate a moderate correlation between the C-levels and the eSRT on the ipsilateral side, while the correlation on the contralateral side is moderate to low.

Regarding the second apical zone, higher values of r^2 were observed for both sides, with p<0.05. Values of r^2=0.625 and r^2=0.527 on ipsi and contralateral side were obtained, respectively, as shown in Figure 4.5.

As one move towards the middle zone of the cochlea, there is an increase in the correlation between C-levels and eSRT. This enhanced correlation is observed in both the first and second medial zones. In the preceding section, the frequency distribution shows

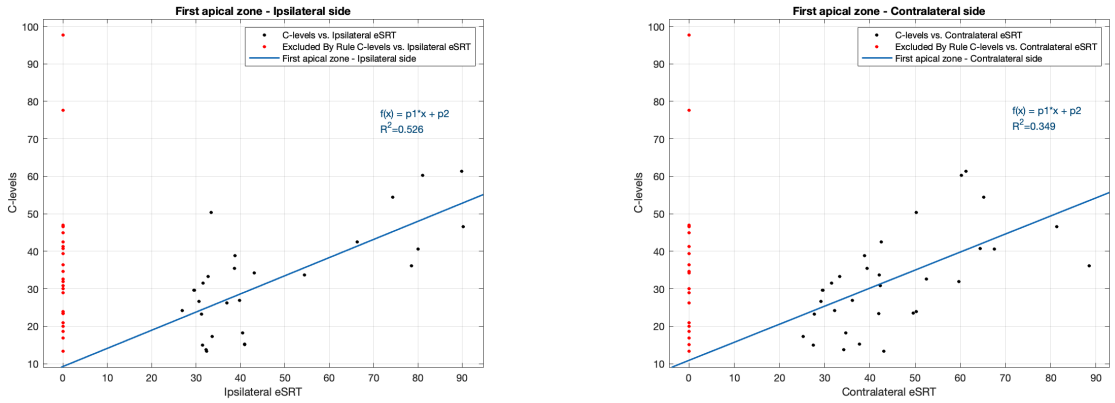


Figure 4.4: Correlation between C-levels and eSRT in first apical cochlear zone for both the ipsilateral and contralateral sides. X and Y axes are represented as RMS values of cU used.

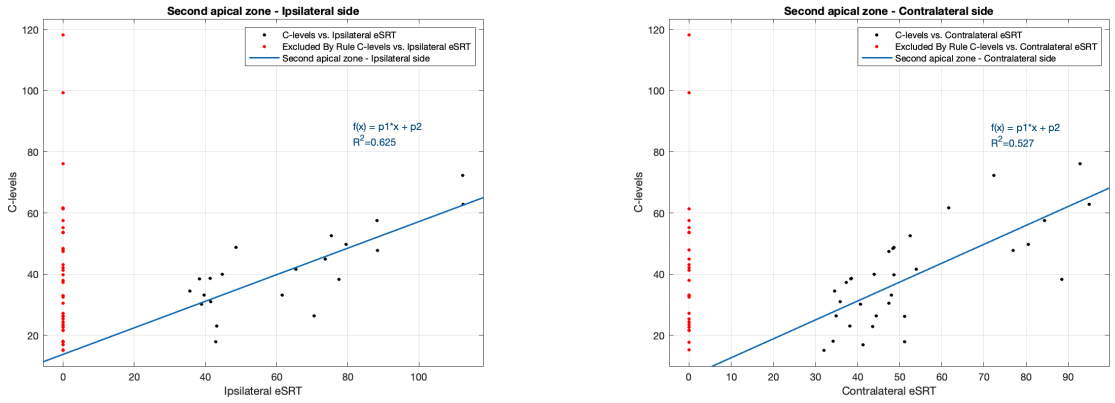


Figure 4.5: Correlation between C-levels and eSRT in second apical cochlear zone for both the ipsilateral and contralateral sides. X and Y axes are represented as RMS values of cU used.

that these medial regions of the cochlea encompass frequencies ranging from 924.6 Hz to 2543.3 Hz on average. Which means that certain consonants that play a crucial role in speech perception, are captured at these cochlear zones. Hence, the r^2 values of 0.731 and 0.625 for the first medial zone, and 0.802 and 0.729 for the second zone, on the ipsilateral and contralateral sides, respectively, demonstrate the positive and advantageous correlation in these regions. Among these four values, only the second medial zone of the contralateral side did not show statistical significance, with a p-value greater than 0.05. These values are represented in Figure 4.6 and 4.7.

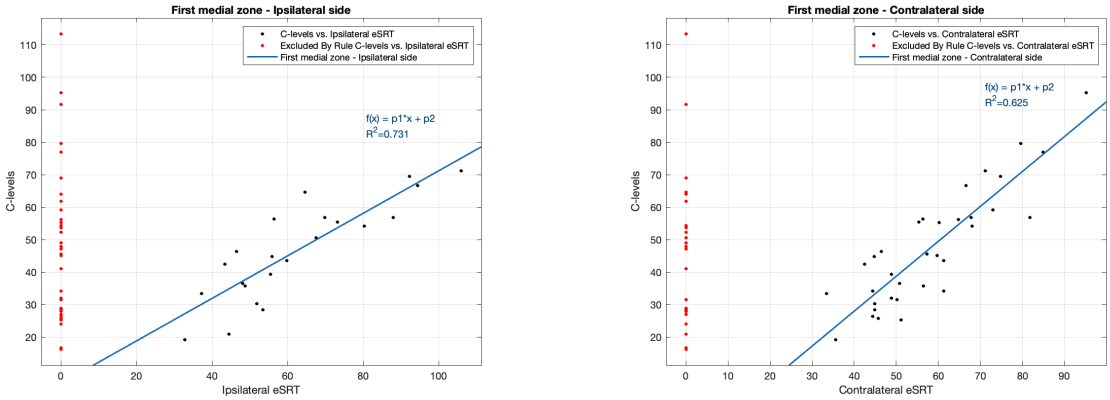


Figure 4.6: Correlation between C-levels and eSRT in first medial cochlear zone for both the ipsilateral and contralateral sides. X and Y axes are represented as RMS values of cU used.

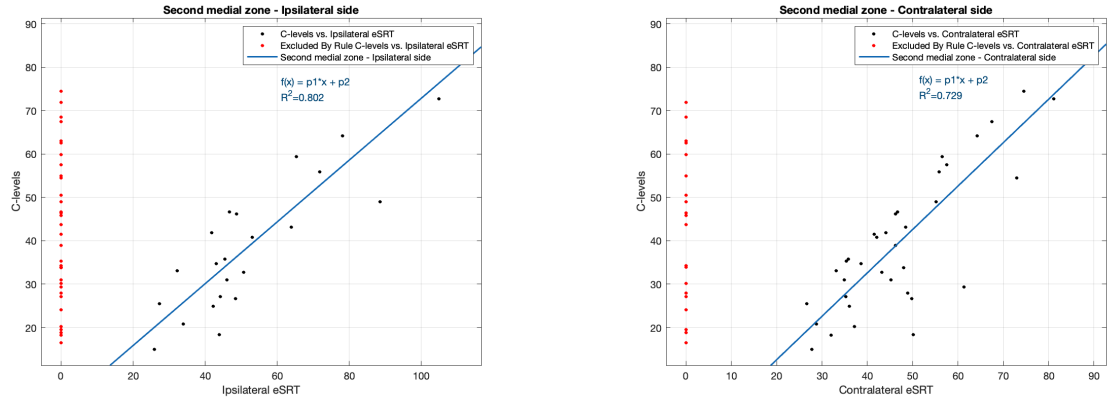


Figure 4.7: Correlation between C-levels and eSRT in second medial cochlear zone for both the ipsilateral and contralateral sides. X and Y axes are represented as RMS values of cU used.

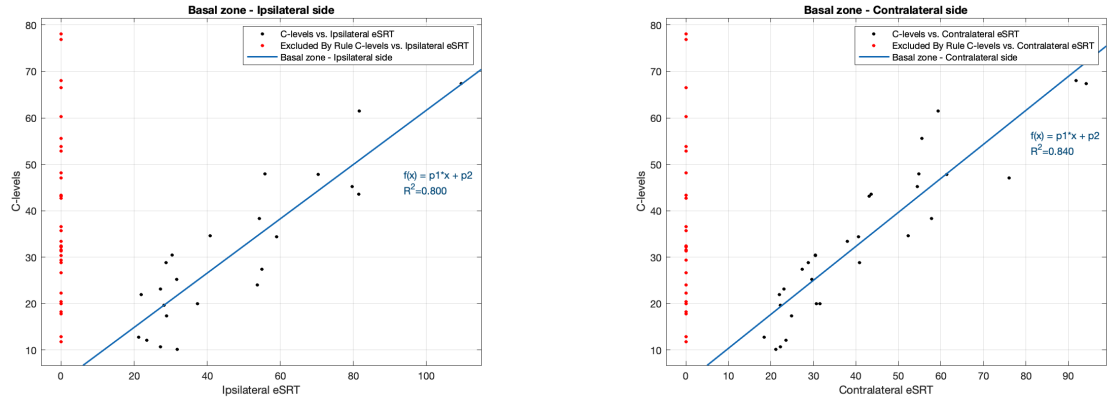


Figure 4.8: Correlation between C-levels and eSRT in basal cochlear zone for both the ipsilateral and contralateral sides. X and Y axes are represented as RMS values of cU used.

In the final assessment, the basal region of the cochlea, although there was an increase in non-detected eSR and a lower detection percentage compared to other zones, a remarkably high correlation was observed for both the ipsilateral and contralateral sides. In fact, it yielded the highest correlation among all the analyses conducted based on cochlear zone divisions. On the ipsilateral side, the correlation coefficient was 0.800, while on the contralateral side, it reached an even higher value of 0.840, as it possible to observe in the graphs of Figure 4.8. However, only the ipsilateral side was found to be statistically significant ($p < 0.05$).

By conducting these analyses based on cochlear regions, we are able to ascertain that irrespective of the specific cochlear region under evaluation, a favorable correlation between the two variables is evident. This discovery holds significant benefits, especially when contemplating the utilization of this objective measure during the development of a CI auditory map for an individual user.

4.2.3 Overall correlation

After conducting various specific analyses, including those focusing on the number of electrodes used for stimulation and the correlation with specific cochlear zones, a comprehensive analysis was performed to examine the overall relationship.

In this evaluation, the responses from all electrodes and subsets used by all participants were combined. In line with previous analyses, the C-levels were also examined for correlation with both the ipsilateral and contralateral sides, which is demonstrated in the graphs shown in Figure 4.9.

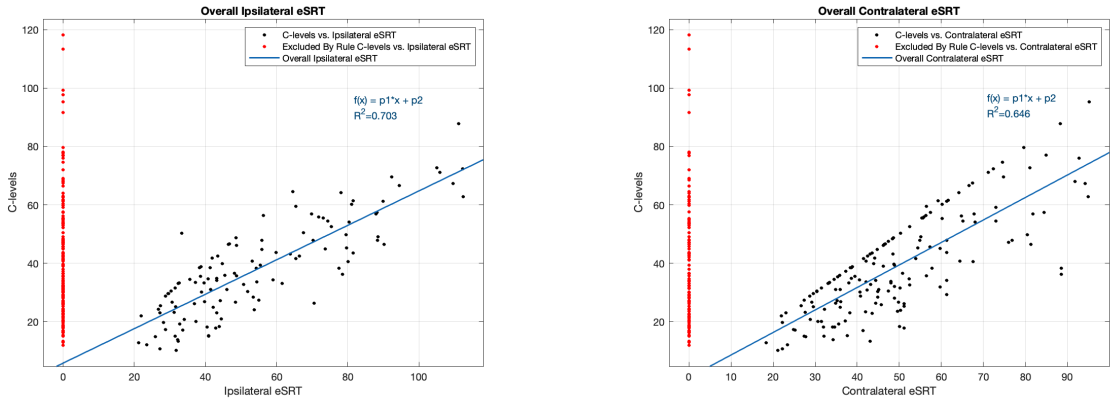


Figure 4.9: Overall correlation between C-levels and eSRT for both the ipsilateral and contralateral sides. X and Y axes are represented as RMS values of cU used.

The value obtained for the ipsilateral side was r=0.839, indicating a high correlation when assessing the detection of induced eSR within the same ear. On the contralateral side, value of r=0.804 was obtained, which, although slightly lower than the ipsilateral

side, still represents a high correlation. p-values were below the threshold of 0.05, indicating statistical significance for both values.

Based on the conducted studies in this field, which also investigated the relationship between behaviorally obtained C-level values and eSR detection thresholds, a wide range of correlation values (r values ranging from 0.43 to 0.92) was observed [16, 19, 120, 140, 141]. The values presented throughout the analyses in this study, whether more specific or more general, are within this range of values. It is also worth noting that no previous studies have compared the results obtained from assessing both the ipsilateral and contralateral sides. That, despite being more easily detectable on the contralateral side [123, 125], in this study, the highest overall correlation is related to the assessment of detection in the ipsilateral ear.

This highlights the potential for a more comprehensive and insightful interpretation of the findings in this study by examining and contrasting them with the published results of previous studies. Such a comparison could provide a deeper understanding of the similarities, differences, and possible implications across different research findings in this field.

4.3 Mutual information analysis

Given that mutual information values can range from 0 to $+\infty$, it is not possible to determine a fixed threshold to dictate the significance of an obtained value. To properly interpret the results, it is crucial to provide contextual information about the research and specific objectives of the study. This includes explaining the types of variables being analyzed, the sample size, and the field of study in which the measure is being applied, and compare with the values obtained in prior researches.

Since this study represents a pioneering attempt to use mutual information as a measure of dependence between C-levels and eSRT, a comparison with other literature was not feasible. Therefore, in order to gain a clearer understanding of the obtained values, the mutual information was calculated for C-levels vs. eSRT, considering two scenarios: one including cases of eSR non-detection and the other excluding such cases.

By examining these values and relating them to the correlation values from the same variable analysis, a more comprehensive consideration of the findings can be conducted. Table 4.4 provides a summary of this exploration.

It is evident that the mutual information analysis yields higher values when excluding cases of non-detection of the eSR compared to including those cases. The same pattern is observed when comparing linear correlation values. The high r values obtained indicate a strong correlation between C-levels, behaviorally obtained, and the eSRT, supporting the idea that the mutual information analysis demonstrates a significant amount of dependence information between these two variables.

Table 4.4: Comparison between mutual information analysis results.

	C-levels vs. Ipsi eSRT		**C-levels vs. Contra eSRT**	
	without outliers	with outliers	without outliers	with outliers
Mutual Information	4.7503	2.5718	4.9571	3.5367
Linear Correlation	0.839	0.158	0.804	0.235

However, considering that the values of mutual information are represented as $\mathbb{R}$ and the linear correlation value (r) ranges from -1 to 1, the difference observed in the ipsilateral cases (ranging from 0.839 to 0.158) and contralateral cases (ranging from 0.804 to 0.235) between the cases of detecting SR and not detecting SR would indicate, based on this reasoning, a much higher significance than what was actually indicated in the mutual information results. The differences observed in the mutual information results were from 4.7503 to 2.5718 for the ipsilateral side and from 4.9571 to 3.5367 for the contralateral side. This highlights the fact that, as mentioned in the previous section, the broader associations considered by mutual information demonstrate a stronger dependence between the two variables. This is not as apparent in linear correlation analysis, as outliers have a significant impact on the displayed r value.

When examining the same values for the ipsilateral and contralateral sides, a different relationship is observed when undetected eSR cases are excluded. Specifically, in the mutual information analysis, the value obtained for the contralateral side is higher than that for the ipsilateral side. However, this is not the case for the linear correlation analysis, where the r values are higher on the ipsilateral side compared to the contralateral side.

This suggests that there is a greater linear and non-linear dependence between these two variables on the contralateral side than on the ipsilateral side. However, when considering only the linear correlation between these variables, the opposite is observed, with the r value being higher for the ipsilateral side than for the contralateral side.

Nevertheless, mutual information only informs if there is some connection between the two random variables, without specifying the nature of their relationship. In the aforementioned case, if it is informed that C-levels and eSRT have a non-zero mutual information, it simply implies that eSRT is somehow related to C-levels, but it is not known the exact nature of this relationship. It could be a positive or negative correlation. In fact, a correlation of -1 and +1 both result in maximum value of mutual information, making it impossible to distinguish between the two scenarios based solely on mutual information.

By that, and focusing on this specific case, mutual information is an useful complementary measure for analyzing data that have been linear correlated. Bridging the pitfalls of linearity.

Chapter 5

Conclusion

After the elaboration of this study over the past few months, from the theoretical contextualization, creation of its design to the collection of the sample, analysis and obtaining of the respective results, there are some key ideas that are worth sharing. Not just for self-reflection, but also for future work to be carried out in this field by other researchers.

Audiology and its related fields, as well as other branches with interdependencies, have been extensively explored through numerous studies involving various areas. Science is not just an island, and there is always room for new and improved discoveries. However, despite the subject of this study being extensively researched over several decades, there remains a gap specifically in the publication of correlation results between C-levels, behaviorally obtained, and eSRT in CI users of Oticon Medical. This study aims to address this gap.

As noted in the reviewed literature, the objective method of constructing auditory maps has been investigated for all major CI brands worldwide, except for Oticon Medical. Considering the increasing number of patients with CI, it is crucial for professionals involved in improving their patients' hearing quality to have tools that can assist and enhance their professional practice, especially when the interaction between the professional and their patients is not effective.

The study's design was established with the same objective in mind. Initially, the goal was to assess the effectiveness of detecting SR contraction in response to electrical stimulation induced by the CI. Existing literature presents a wide range of percentages related to this detection, which is an important factor for establishing a correlation. Despite the challenge of evaluating the sample, the obtained results fall within this range, enabling a valid correlation analysis.

Once this possibility arose, multiple evaluations were conducted to determine not only an overall correlation but also more specific ones, such as evaluating correlations by cochlear region and the number of electrodes used to induce SR contraction. Obtaining more specific data was crucial to assessing the practical applicability of this objective

method in daily clinical practice. The results demonstrated favorable correlations across all studied cochlear regions, supporting its applicability.

Furthermore, determining the number of electrodes required for stimulation is vital for enhancing the accuracy of the auditory map construction. Based on the gathered information and results, it was observed that larger stimulated frequency areas exhibit better correlations between C-levels and eSRT. Specifically, a subset of five electrodes yielded the highest correlation values.

Additionally, a comprehensive analysis of all electrodes was conducted to gain a better understanding of previous studies in this field. The obtained results aligned with the range published in existing literature.

Furthermore, all the correlation analysis included detection of stapedial reflex on both the ipsilateral and contralateral sides, demonstrating similar levels of correlation. This provides an additional evaluation option when results from one side cannot be obtained for any reason.

All of these findings establish the necessary conditions for professionals to implement this objective method during their daily clinical practice, aiding in the construction of auditory maps.

To further validate this method, future steps could involve creating an auditory map solely based on the responses obtained through eSRT detection. This map could then be compared to the auditory map currently in use, and patient feedback regarding the comfort of using the eSRT-based map in everyday situations could be collected.

Appendix A

Appendices

A.1 Informed Consent

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CONSENTIMENTO INFORMADO, ESCLARECIDO E LIVRE
para Investigação Clínica

Parte Informativa

1. **TÍTULO DO PROJECTO**	**CORRELAÇÃO ENTRE *ESRT* E NÍVEIS C EM UTILIZADORES DE IMPLANTE COCLEAR.**
2. **DESCRIÇÃO DO PROJECTO, SUA NATUREZA E OBJETIVO** Metodologia, nomeadamente identificação dos procedimentos do estudo, procedimentos invasivos, consultas e seus detalhes (p ex, número e duração).	O objetivo deste estudo é comparar os limiares de conforto comportamentais em pacientes experientes com implante coclear com os resultados da avaliação do eSRT. Os pacientes serão selecionados a partir de um arquivo de dados e divididos em dois grupos: O Grupo A incluirá pacientes com implantes cocleares unilaterais ou bilaterais; O Grupo B incluirá pacientes com surdez bimodal ou unilateral. Pacientes com problemas de ouvido médio serão excluídos, e a otoscopia e timpanometria serão realizadas para confirmar a condição normal do ouvido externo e/ou médio. Serão incluídos pacientes com idade igual ou superior 18 anos, que utilizem o sistema de implante coclear Neuro Zti EVO. Serão excluídos casos onde haja condições clínicas que afetem o ouvido externo/médio, incapacidade psicológica ou linguística para entender as informações. Pacientes sob proteção legal ou privados de liberdade também serão excluídos. **Testes** Neste estudo, irá utilizar-se apenas softwares/dispositivos com marca CE. O software GMCI determinará os limiares de conforto e estimulação elétrica do implante coclear Oticon Medical. Coletaremos informações sobre o mapa auditivo de cada paciente. Utilizar-se-á o dispositivo Interacoustics Titan (IMP440 Diagnostic + eSRT) para fazer timpanometria e medir as respostas do reflexo estapédico ipsi e contralateral. Observações feitas neste estudo são seguras e não invasivas, usadas na prática clínica comum. Este teste terá uma duração de 30 a 60 min.
3. **RISCOS GRAVES E RISCOS FREQUENTES** Riscos ou incómodos previsíveis derivados do estudo	Não aplicável

Página | 1

Figure A.1: Provided informed consent - Pag. 1.

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4. **BENEFÍCIOS** Benefícios expectáveis, ou se tais benefícios não são expectáveis.	Permitirá obter mais informações no que respeita ao sucesso da criação objetiva dos mapas auditivos, já que se pretende correlacionar as respostas comportamentais com a medição objetiva dos limiares de conforto obtidos pela contração do músculo estapédico. Assim, num futuro, doentes que tenham dificuldade em colaborar com as respostas comportamentais, poderão beneficiar da criação dos mapas auditivos através das informações obtidas de modo objetivo.
5. **POSSÍVEIS ACONTECIMENTOS ADVERSOS** (de todos os procedimentos do estudo).	Não deteção da contração do músculo estapédico.
6. **APROVARAM O ESTUDO**	Comissão de Ética do Centro Académico de Medicina de Lisboa Contato – 217805405

Figure A.2: Provided informed consent - Pag. 2.

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PARTE DECLARATIVA DO PROFISSIONAL

Confirmo que expliquei à pessoa abaixo indicada, de forma adequada e inteligível, os procedimentos que o estudo envolve.

Respondi a todas as questões que me foram colocadas e assegurei-me de que houve um período de reflexão suficiente para a tomada da decisão.

Expliquei o carácter Voluntario da participação; a recusa ou a retirada do consentimento e a possibilidade de pedir para interromper ou mesmo desistir de participar caso sinta necessidade ou vontade de o fazer, sem que daí advenha qualquer prejuízo no contexto da sua assistência clínica.

Informei que se encontra assegurada a privacidade dos dados pessoais coletados mediante a pseudonimização dos mesmos, garantida pela atribuição de um código cuja chave de descodificação é restrita ao Investigador Principal do projeto ou quem ele designar para o assistir e / ou em sua substituição, bem como a se encontra acautelada a confidencialidade e a proteção dos dados pessoais de acordo com o Regulamento Geral sobre a Proteção de Dados (RGPD) entrado em vigor em 25 de Maio de 2016 e plenamente aplicável a partir de 25 de Maio de 2018, (Regulamento (UE) 2016/679 do Parlamento Europeu e do Conselho de 27/04/16), de 27 de abril, publicado no Jornal Oficial da União Europeia, no dia 4 de Maio de 2016, e na Lei n.º 58/2019, de 8 de Agosto.

Nome legível do investigador Principal _____

ASSINATURA

_____ **DATA**: _____ / _____ / _____

CONTACTO TELEFÓNICO | **E-mail**

Figure A.3: Provided informed consent - Pag. 3.

CENTRO HOSPITALAR LISBOA NORTE, EPE | HOSPITAL DE SANTA MARIA | Hospital Pulido Valente

À PESSOA/REPRESENTANTE
Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido/a. Verifique se todas as informações estão corretas. Se concordar com o acima explicado, assine este documento.

PARTE DECLARATIVA DA PESSOA QUE CONSENTE
Declaro ter compreendido os objetivos do que me foi proposto e explicado pelo profissional de saúde que assina este documento, Foi-me dada oportunidade de fazer todas as perguntas sobre o assunto e para todas elas ter obtido resposta esclarecedora, ter-me sido garantido que não haverá prejuízo para os meus direitos assistenciais se eu recusar esta solicitação, e ter-me sido dado tempo suficiente para refletir sobre esta proposta. **AUTORIZO** ☐ **NÃO AUTORIZO** ☐

Nome legível _____	
Assinatura _____	**Data**: ____ / ____ / _____

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE (se o menor tiver discernimento deve também assinar em cima)
NOME: _____
Documento de Identificação Nº: _____ **Data ou validade** ____ / _____ /_____
Grau de parentesco ou tipo de representação: _____ **ASSINATURA** _____

NOTA: Este documento é executado em duas vias – uma para o processo/estudo e outra para ficar na posse de quem consente**.**

Figure A.4: Provided informed consent - Pag. 4.

A.2 Excel worksheet

	A	B	C	D	E	F	G	H	I	J	K
1		Right Ear					Left Ear				
2	**Amplitude**	20					**Amplitude**	23			
3	**Cochlear Region**	Apical - 1	Apical - 2	Medial - 1	Medial - 2	Basal	Apical - 1	Apical - 2	Medial - 1	Medial - 2	Basal
4	**Subset 3**										
5	Electrode	20	18	14	10	5	20	18	14	10	8
6	C-Level eSRT ipsi	37	56	74	66	51	21	27	39	40	45
7	Charge eSRT ipsi	10,6889	16,1778	21,3778	19,0667	14,7333	10,7333	13,8000	19,9333	20,4444	23,0000
8	C-Level eSRT contra	37	69	86	59	48	21	27	39	42	44
9	Charge eSRT contra	10,6889	19,9333	24,8444	17,0444	13,8667	10,7333	13,8000	19,9333	21,4667	22,4889
10	Electrode	19	17	13	9	4	19	17	13	9	7
11	C-Level eSRT ipsi	43	60	78	65	40	24	31	40	37	41
12	Charge eSRT ipsi	12,4222	17,3333	22,5333	18,7778	11,5556	12,2667	15,8444	20,4444	18,9111	75,0000
13	C-Level eSRT contra	43	73	90	58	37	24	31	40	39	40
14	Charge eSRT contra	12,4222	21,0889	26,0000	16,7556	10,6889	12,2667	15,8444	20,4444	19,9333	20,4444
15	Electrode	18	16	12	8	3	18	16	12	8	6
16	C-Level eSRT ipsi	46	63	76	70	45	27	35	41	36	47
17	Charge eSRT ipsi	13,2889	18,2000	21,9556	20,2222	13,0000	13,8000	17,8889	20,9556	18,4000	24,0222
18	C-Level eSRT contra	46	76	88	63	41	27	35	41	38	46
19	Charge eSRT contra	13,2889	21,9556	25,4222	18,2000	11,8444	13,8000	17,8889	20,9556	19,4222	23,5111
20	Electrode	17	15	11	7	2	17	15	11	7	5
21	C-Level eSRT ipsi	50	64	76	67	49	31	36	43	32	56
22	Charge eSRT ipsi	14,4444	18,4889	21,9556	19,3556	14,1556	15,8444	18,4000	21,9778	16,3556	28,6222
23	C-Level eSRT contra	50	77	88	60	46	31	36	43	34	55
24	Charge eSRT contra	14,4444	22,2444	25,4222	17,3333	13,2889	15,8444	18,4000	21,9778	17,3778	28,1111
25	Electrode	16	14	10	6	1	16	14	10	6	4
26	C-Level eSRT ipsi	53	64	73	66	60	35	39	40	38	54
27	Charge eSRT ipsi	15,3111	18,4889	21,0889	19,0667	17,3333	17,8889	19,9333	20,4444	19,4222	27,6000
28	C-Level eSRT contra	53	77	85	59	57	35	39	40	40	53
29	Charge eSRT contra	15,3111	22,2444	24,5556	17,0444	16,4667	17,8889	19,9333	20,4444	20,4444	27,0889
30	Average Charge ipsi	13,2311	17,7378	21,7822	19,2978	14,1556	14,1067	17,1733	20,7511	18,7067	35,6489
31	Average Charge contra	13,2311	21,4933	25,2489	17,2756	13,2311	14,1067	17,1733	20,7511	19,7289	24,3289
32	Root Mean Square ipsi	29,5857	39,6629	48,7065	43,1511	31,6528	31,5435	38,4007	46,4009	41,8294	79,7133
33	Root Mean Square contra	29,5857	48,0606	56,4582	38,6293	29,5857	31,5435	38,4007	46,4009	44,1151	54,4010
34	**Subset 2**										
35	Electrode	19	17	13	9	4	19	17	13	9	6
36	C-Level eSRT ipsi	59	115	108	86	53	27	41	53	54	56
37	Charge eSRT ipsi	17,0444	33,2222	31,2000	24,8444	15,3111	13,8000	20,9556	27,0889	27,6000	28,6222
38	C-Level eSRT contra	52	100	91	68	45	33	43	56	53	60
39	Charge eSRT contra	15,0222	28,8889	26,2889	19,6444	13,0000	16,8667	21,9778	28,6222	27,0889	30,6667
40	Electrode	18	16	12	8	3	18	16	12	8	5
41	C-Level eSRT ipsi	62	115	106	91	58	30	45	54	53	65
42	Charge eSRT ipsi	17,9111	33,2222	30,6222	26,2889	16,7556	15,3333	23,0000	27,6000	27,0889	33,2222
43	C-Level eSRT contra	55	103	89	73	50	36	47	57	52	69
44	Charge eSRT contra	15,8889	29,7556	25,7111	21,0889	14,4444	18,4000	24,0222	29,1333	26,5778	35,2667
45	Electrode	17	15	11	7	2	17	15	11	7	4
46	C-Level eSRT ipsi	66	115	106	88	62	34	46	56	49	63
47	Charge eSRT ipsi	19,0667	33,2222	30,6222	25,4222	17,9111	17,3778	23,5111	28,6222	25,0444	32,2000
48	C-Level eSRT contra	59	104	89	70	54	40	48	59	48	67
49	Charge eSRT contra	17,0444	30,0444	25,7111	20,2222	15,6000	20,4444	24,5333	30,1556	24,5333	34,2444
50	Average Charge ipsi	18,0074	33,2222	30,8148	25,5185	16,6593	15,5037	22,4889	27,7704	26,5778	31,3481
51	Average Charge contra	15,9852	29,5630	25,9037	20,3185	14,3481	18,5704	23,5111	29,3037	26,0667	33,3926
52	Root Mean Square ipsi	31,1897	57,5426	53,3728	44,1994	28,8547	26,8532	38,9519	48,0997	46,0341	54,2966
53	Root Mean Square contra	27,6872	51,2046	44,8665	35,1927	24,8517	32,1648	40,7224	50,7555	45,1488	57,8377
54	**Subset 1**										
55	Electrode	18	16	12	8	3	18	16	12	8	5
56	C-Level eSRT ipsi	112	115	115	115	110	63	84	87	86	105
57	Charge eSRT ipsi	32,3556	33,2222	33,2222	33,2222	31,7778	32,2000	42,9333	44,4667	43,9556	53,6667
58	C-Level eSRT contra	115	115	115	115	73	67	100	115	98	115
59	Charge eSRT contra	33,2222	33,2222	33,2222	33,2222	21,0889	34,2444	51,1111	58,7778	50,0889	58,7778
60											
61	No detection - Compliance limit										

Figure A.5: Excel worksheet for data recording and analysis

A.3 Electrodes frequency distribution

A.3.1 Frequency distribution with all electrodes available

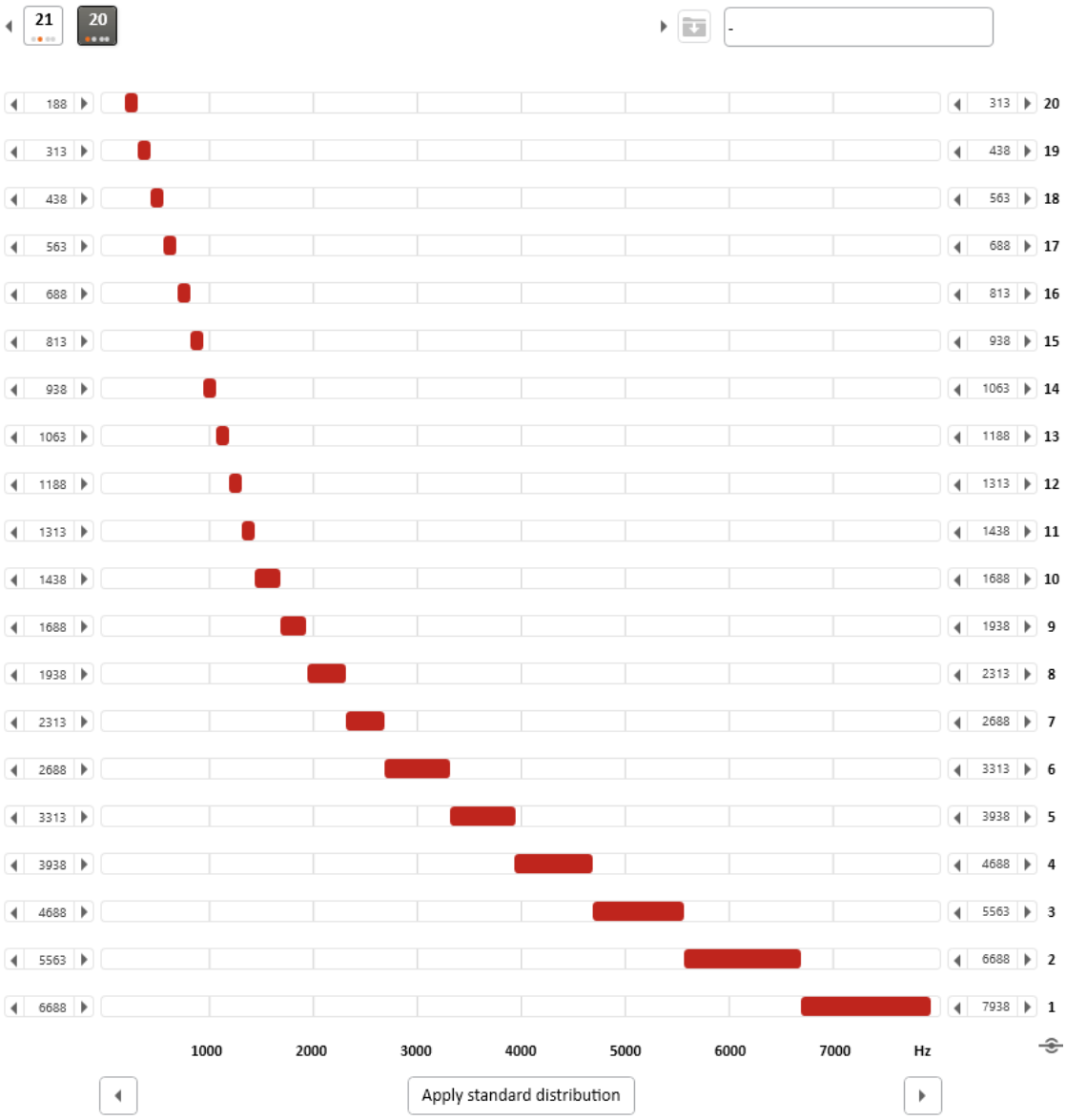


Figure A.6: 20 electrodes frequency distribution

A.3.2 Frequency distribution with 17 electrodes available

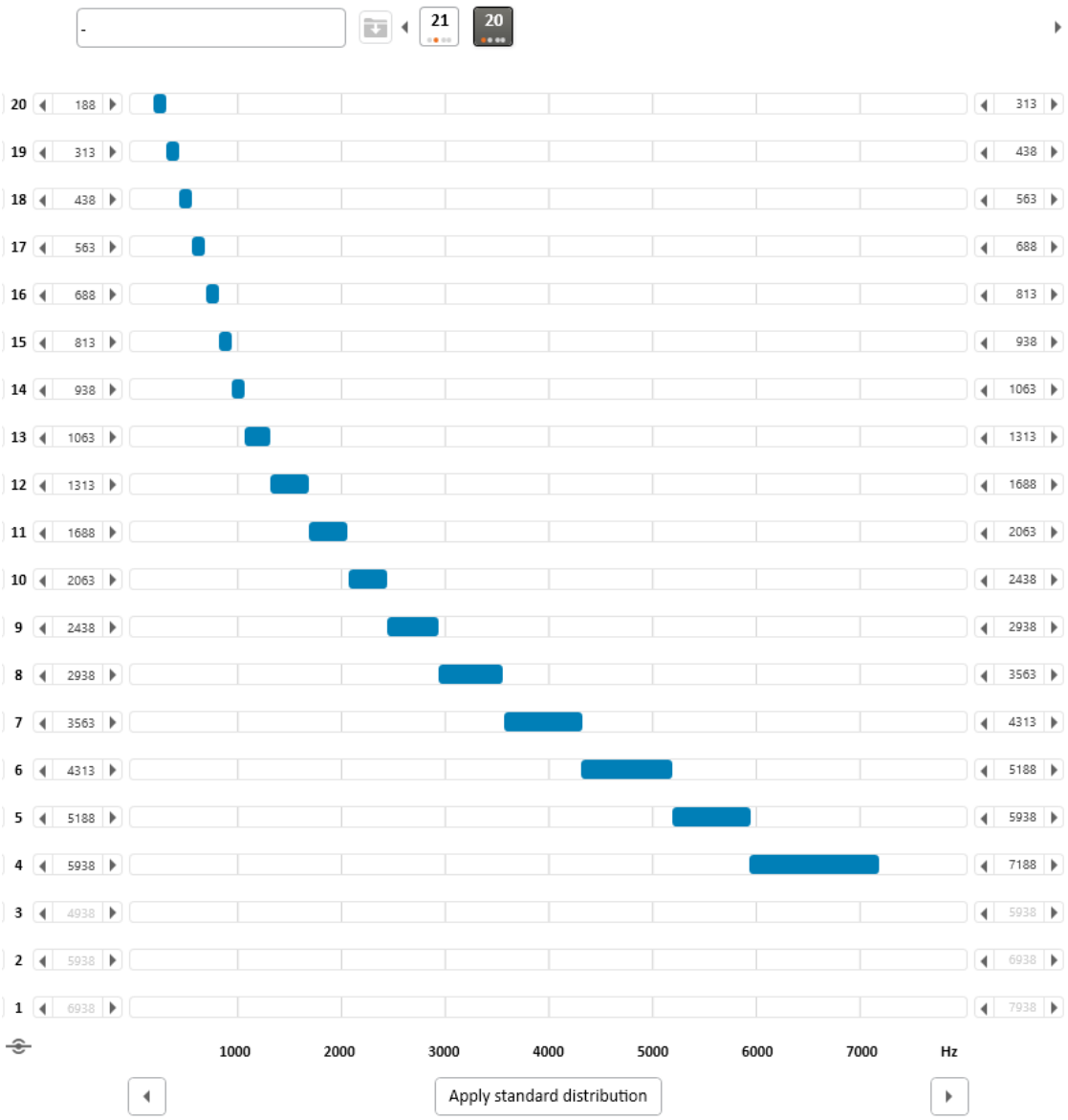


Figure A.7: 17 electrodes frequency distribution

A.3.3 Application of mutual information analysis

```
from sklearn.metrics import mutual_info_score
import pandas as pd

df = pd.read_excel('path to data file')
column_names = df.columns.tolist()
c_levels = df["C-levels"].values
c_eSRT = df["Contra eSRT"].values
i_eSRT = df["Ipsi eSRT"].values

mi_C_eSRT = mutual_info_score(c_levels, c_eSRT)
mi_C_i_eSRT = mutual_info_score(c_levels, i_eSRT)


print("Mutual Information C-levels vs. Contralateral eSRT: ", mi_C_eSRT)
print("Mutual Information C-levels vs. Ipsilateral eSRT: ", mi_C_i_eSRT)
```

Figure A.8: Code for mutual information analysis

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