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Measuring frequency discrimination and amplitude discrimination thresholds in cochlear implant users with the Acoustic Change Complex (ACC) using intracochlear stimulation

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Abstract

Objective

The main objective of the current study was to determine whether the Acoustic Change Complex (ACC) can be used to estimate auditory discrimination in cochlear implant users using direct intracochlear stimulation. The current study also investigated the correlation between the behavioral and electrophysiological frequency discrimination thresholds with the ACC in cochlear implant users. Finally, the current study investigated the correlation between the behavioral and electrophysiological amplitude discrimination thresholds with the ACC in cochlear implant users.

Method

Stimuli consisted of 12 electrode combinations (frequency changes) and 10 amplitude combinations. The control stimulus of the frequency changes was electrode 1 and had a duration of 800 milliseconds. The control stimulus of the amplitude changes was an amplitude of 0.8 (80% MCL) and had a duration of 800 ms. All other stimuli combinations consisted of the control stimulus for the first 400 ms and another electrode or amplitude for the latter 400 ms. The behavioral frequency and amplitude discrimination thresholds were determined using a single interval test, using the method of constant stimuli. The electrophysiological frequency and amplitude discrimination thresholds were determined using the ACC in a one-channel electroencephalography recording. Ten MED-EL CI users participated in the current study. The thresholds found in both behavioral and electrophysiological measurements were compared within patients to investigate the correlation between the behavioral and electrophysiological thresholds.

Results

No significant correlation was found for the behavioral and electrophysiological frequency discrimination (electrode combinations) thresholds of the CI users. The correlations between the electrode combinations and the inter-peak interval (IPI) and P-P amplitude also turned out to be non-significant. Nor was a significant correlation found for the lower amplitude discrimination threshold (decreasing amplitude change). A significant difference was found between the behavioral and electrophysiological threshold of the upper amplitude discrimination thresholds (increasing amplitude change), the results showed that the amplitude discrimination threshold for the increasing amplitude changes was significantly higher for the electrophysiological measurement than for the behavioral measurement.

Discussion and Conclusion

The usability and the effectiveness of the ACC as an objective measure of auditory discrimination cannot be evaluated properly based on the results of the current study. During the experiments, it was found that it was possible to record the electrophysiological frequency and amplitude discrimination thresholds using the ACC, but no significant results were found on the correlation between the electrophysiological and behavioral discrimination thresholds. Only a significant effect was found for the correlation between the behavioral and electrophysiological threshold of the upper amplitude discrimination thresholds (increasing amplitude change). The results differed considerably between patients, which limits the clinical value of the results about the ACC of the current study.

1. Introduction

The processing of spoken language, something that we do every minute of the day without being aware of it, is a highly complex, but also very rapid, process that we nowadays understand reasonably well thanks to research in many different disciplines such as medicine or psycholinguistics (Grosjean & Byers-Heinlein, 2013). Understanding speech requires the ability to differentiate sounds and thus the distinctions in frequency, intensity, and other parameters (Harris, Mills, He, & Dubno, 2008).

Unfortunately, this discriminatory ability is not universal. Even with conventional hearing aids or cochlear implants, individuals with hearing loss or those who are diagnosed with deafness are often unable to identify or discriminate sounds at the same level as normal hearing listeners. This has a serious effect on their perception of sounds and thus on their speech perception (Zhang et al., 2019). As a result, it's critical that, in addition to auditory detection, cochlear implant users are also assessed on their ability to discriminate different sounds. Although behavioral (subjective) measures of auditory discrimination exist, they are not per se the most credible option, especially when researching auditory discrimination in participant groups that are difficult to test such as children, elderly or patients with hearing, speech or cognitive impairments. As a result, research should be started on developing or finding metrics that are able to objectively measure auditory discrimination necessary.

Over the past few years, the Auditory Change Complex (ACC) has received a lot of research interest as a potential objective measure of auditory discrimination. The electrophysiological measured ACC discrimination thresholds have been shown to be in line with speech perception measurements in CI users (e.g., He et al., 2013).

1.1 Anatomy and Physiology of the ear

Speech perception is a part of sound perception. Sound perception mainly happens through the human ears. Sound (and thus speech) can be seen as a continuous stream of rapid and short disturbances of air pressure (Rietveld and van Heuven, 2016). These disturbances are converted into vibrations in the human ear and at their turn these vibrations are converted into electric pulses that are sent to our brain by the auditory nerve. The peripheral auditory system can be split into three sections; the outer, middle and inner ear. Each of these three sections contributes to human sound processing and perception (Rietveld and van Heuven, 2016).

1.1.1 The outer ear

The outer ear consists of the pinna and the ear canal. The pinna’s main function is to catch sound waves and transmit them to the ear canal (Rietveld and van Heuven, 2016). In addition, the pinna also assists with the localization of sound (Siekel, King & Drumright, 2015). The ear canal functions as a resonator for sounds with frequencies between 1000 and 4000 Hz (This is exactly the frequency range that is important for speech). This means that the ear canal amplifies the sounds between these two frequency boundaries (Rietveld and van Heuven, 2016).

1.1.2 The middle ear

The beginning of the middle ear is marked by the eardrum, also known as the tympanic membrane. The air pressure disturbances of sound waves make the eardrum vibrate. These vibrations of the eardrum are then transmitted to the ossicles (malleus, incus and stapes) in the tympanic cavity. The ossicles amplify the vibrations produced by the eardrum (Rietveld and van Heuven, 2016) before the vibrations are led to the oval window, which marks the end of the middle ear.

The amplifying function of the ossicles is a very important feature of the middle ear. This is not only because the sound waves are converted into vibrations, but also because the air vibrations of the outer ear are transmitted to fluid of the inner ear at the oval window. The impedance of liquids is greater than that of air, thus if the amplification of the ossicles would not be there, there would be a loss of vibrations due to the impedance difference. This would result in a loss of sound (Lamoré, 2008).

1.1.3 The inner ear

The inner consists of the vestibular system and the cochlea. The cochlea is horizontally divided in three parts by basilar and tectorial membranes. These three parts are called the Scala tympani, Scala vestibuli and Scala media. The first two parts are filled with a water-like fluid called perilymph, while the latter is filled with endolymph. The basilar membrane is stiff at the base and more flexible towards its apex. Furthermore, the basilar membrane is tonotopically organized, this implies that the base of the membrane is sensitive to high frequencies and the apex is more sensitive to lower frequencies (Ruben, 2020).

The organ of Corti is the actual receptor organ of the inner ear and is located on the basilar membrane of the Scala media. The organ of Corti is composed of sensory hair cells that transmit stimuli to the auditory nerve and auditory brainstem, which in turn transmit action potentials to the auditory cortex (Lim, 1986).

1.2 Cochlear implants

Cochlear implantation (CI) is an intervention that is among the greatest successes of modern medicine (Wilson and Dorman, 2008). CI is taken into consideration when individuals are diagnosed with moderate to severe sensorineural hearing loss or deafness. Sensorineural hearing loss often occurs when there are deficits in the cochlea, auditory nerve or higher up in the auditory system. Hearing impairments like sensorineural hearing loss can be caused by a variety of reasons such as; age, trauma, diseases, infections, exposure to loud noises or genetic predisposition (Lenarz, 2017). Cochlear implants stimulate the auditory nerve electrically which can result in (partial) restoration of a sense of hearing for cochlear implant recipients. This because acoustic stimulation is no longer possible due to their hearing impairment (Wouters, McDermott & Francart, 2015).

A modern cochlear implant system consists of an external microphone and speech processor, an internal receiver-stimulator and an electrode array (Zeng et al., 2008). The microphone and speech processor are used for sound recording, the pre-processing of sound and to convert acoustic sound waves into electrical pulses (Lenarz, 2017). These electrical pulses are transmitted to the internal receiver coil of the implant. This receiver coil sends the electrical pulses to the electrode array that transmits the electrical pulses to the auditory nerve. The number of electrodes on the electrode array is limited which results in a limited range of effective stimulation of the auditory nerve (Lenarz, 2017).

The MED-EL cochlear implant electrode array typically has 12 tonotopically arranged electrodes. Some examples of MED-EL electrodes arrays are the FLEX SOFT, FLEX28, FLEX24, FLEX20 and FLEX16 (Dhanasingh et al., 2017). The MED-EL MAESTRO CI systems consist of all The PULSARci100 and SONATAti100 Cis (Hochmair et al., 2006). Users of MED-EL Cis are given fine structural information through the MAESTRO CI software system (e.g., speech-coding strategies) during their fitting appointments (Hochmair et al., 2006). Additionally, telemetry functions are available to audiologists for clinical research and evaluations. The telemetry also enables the audiologist to streamline the fitting process in challenging circumstances and with small children (Hochmair et al., 2006).

1.3 Objective measures of auditory discrimination

Processing and perceiving speech depends on the ability of the human auditory system to discriminate changes in the spectral and temporal patterns of incoming signals (He, John & Buchman, 2012). Auditory discrimination abilities are often measured by using behavioral measures. Findings from such behavioral measurements can provide helpful information on a person's auditory perception of speech or other types of sounds.

Behavioral measurements can be carried out easily on adults, but are much more challenging when carried out on children, this because behavioral tasks often require active participation and a certain level of linguistic knowledge and cognitive ability (He, John & Buchman, 2012; Martin & Boothroyd, 1999). Overall, electrophysiological measurements might have an advantage over behavioral measurements because they do not always require active focus from the participant, which makes it easier to measure auditory discrimination abilities in infants, children or other populations that are more difficult to test, such as patients with cognitive impairments.

Another advantage of electrophysiological measurements is that they are more objective than behavioral measures are (He, John & Buchman, 2012).

1.4 Measuring auditory evoked potentials using electroencephalography

Electroencephalography makes it possible to measure spontaneously generated neuroelectric activity of the central nervous system. These neuroelectric events can be measured in a noninvasive way by placing electrodes on the scalp (Innis and Read, 2017). An advantage of EEG is that it is a neuroimaging technique that has good temporal resolution, but might have less spatial resolution (Innis and Read, 2017). Another advantage of EEG is the fact that it is relatively cheap in contrast to other neuroimaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magneto-encephalography (MEG) or functional near-infrared spectroscopy (fNIRS) (Innis and Read, 2017).

Neuroelectric responses elicited by sensory stimulation (e.g., auditory, visual or somatosensory) can be measured through EEG (Jacobson, 1994) and are called event related potentials (ERPs). The current study will mainly focus on responses evoked by auditory stimulation, i.e., auditory evoked potentials (AEPs).

1.5 Types of auditory evoked potentials

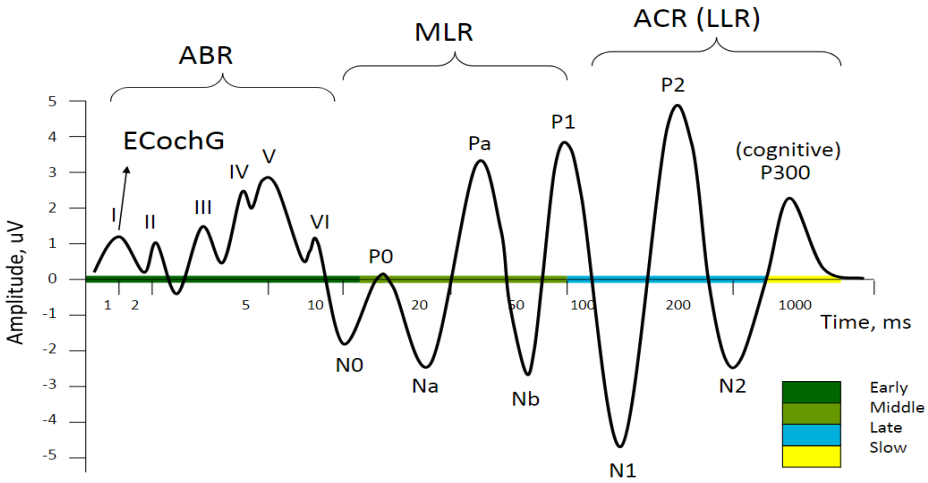


Figure 1: A visualization of all categories of auditory evoked potentials made by Beynon (2020) for the course Speech, Sound and Hearing given at Radboud University, Linguistics.

The use of AEPs has become more and more essential to the clinical practice of audiology and other professions, such as neurology (Ferraro, 1997). The ability to record rapidly occurring potentials from the human brain or human ears as a response to acoustic stimulation has resulted in multiple publications and applications for clinicians and scientists (Ferraro, 1997). AEPs can be classified in numerous ways, one type of classification is done by categorizing the AEPs based on latency (Møller, 1994): see figure 1;

1.5.1 Auditory brainstem responses (ABR)

Auditory brainstem responses (ABR) are also known as early latency potentials. ABRs appear within the first 10 milliseconds (ms) after the onset of a presented stimulus. Electrocochleographic potentials (EcochG) also belong in the auditory brainstem responses category (Møller, 1994).

1.5.2 Auditory middle latency responses (AMLR)

The auditory middle latency responses (AMLR) are also known as middle late potentials. AMLRs appear approximately 10 to 50 ms after the onset of a presented stimulus (Møller, 1994).

1.5.3 Auditory long latency responses (ALLR)

Auditory long latency responses (ALLR) are also known as late potentials or cortical auditory evoked potentials (CAEPs). ALLRs appear between 100 and 300 (- 500) ms after the onset of a presented stimulus (Møller, 1994). In contrast to ABRs, AMLRs and ALLRs elicited by an external auditory event and are therefore considered exogenous (bottom-up processing), some ALLRs are called endogenous (top-down processing), since these responses consist of a change in electrical activity of the brain that appears in response to internal higher order events such as perception, cognition or linguistic knowledge (McPherson, 1996).

1.5.4 N1-P2 Complex (SVP)

The most often used ALLR is the 'N1-P2 Complex', also known as 'Slow Vertex Potential' (SVP), resembling auditory detection of sound. This auditory evoked potential is elicited by a sudden noticeable change in the auditory environment. The potential represents a (late) cortical response with a long latency period as measured from the vertex. The N1-P2 complex appears as a negative peak (N1) around 100-150 ms after stimulus onset followed by a second positive peak (P2) around 150-200 ms. The N1-P2 complex can be used in clinical settings to e.g., objectively assess frequency-specific hearing thresholds, because the N1-P2 complex amplitude increases as the stimulus level increases (Jacobson, 1994, Ch. 8; Lightfoot, et al., 2006).

1.5.5 Acoustic Change Complex (ACC)

The Auditory Change Complex (ACC) is a variant of the SVP, resembling the detection of auditory change within a stimulus. The auditory changes that evoke the ACC can be changes such as intensity, frequency or spectral information (Martin & Boothroyd, 1999; 2000; Martin, Tremblay, & Stapells, 2007; Kim, 2015), and makes it a good candidate to be used as an objective measurement of auditory discrimination. This might be useful electrophysiological tool for investigating auditory discrimination in challenging groups, such as children or patients with cognitive or hearing impairments.

The ACC's morphological properties are also similar to those of the N1-P2 Complex for both normal hearing listeners and CI users (Martin & Boothroyd, 1999; Brown et al., 2008). This means that the first negative peak of the ACC (n1) appears around 100-150 ms

after the onset of the acoustic change in the continuous stimulus, followed by a peak (p2) around 150-200 ms after the onset of the acoustic change.

There have been several findings so far about the usability of the ACC. While some studies claim that the ACC is not as sensitive as a measuring tool as behavioral auditory discrimination tasks (Brown et al., 2017), others claim that the ACC could provide more accurate and objective evidence over behavioral auditory discrimination (Mathew et al., 2017, 2018). This last statement is not backed up by a lot of research and hence should be investigated more.

1.5.5.1 Overview of previous research on the Acoustic Change Complex

The first ever research done on the ACC was conducted by Ostroff et al. (1998.) It was found that normal hearing listeners produced a response to a change in the nucleus of a syllable. This elicited response (evoked potential) appeared to have a similar morphology as the N1-P2 Complex. Based on these findings Ostroff et al. (1998) believed that this response suggested whether auditory discrimination capacity was present, and they recognized potential clinical value in it. Soon after, Ostroff's colleagues, Martin and Boothroyd continued the research on this new found evoked potential. Martin and Boothroyd (1999, 2000) looked into the ACC in acoustic stimuli to see if changes in spectrum, amplitude, and periodicity triggered the ACC in various ways.

These three researches resulted in more interest in the ACC, which led to more research on the topic. For instance, more research has been done on the ACC responses in normal hearing listeners (e.g., Harris et al., 2008), but more recently also in patients with sensorineural hearing loss or cochlear implants (e.g., Martin, 2007; Brown et al., 2008; McGuire et al., 2021). Moreover, different strategies for stimulus presentation have been investigated to improve measurement accuracy and efficiency (e.g., Vonck et al., 2019; 2021). The relationship between behavioral measurements and electrophysiological measurements has also been investigated (e.g., He et al, 2012).

Over the past few years, research on using the ACC to measure auditory discrimination among CI users has grown. However, this is often investigated by presenting stimuli in the sound field. Little is known about the use of the ACC when the stimuli are presented directly intracochlear.

1.5.5.2 Advantages and disadvantages of the Acoustic Change Complex

The ACC has a significant advantage over behavioral measures as a measure of auditory discrimination in that it is unaffected by non-auditory characteristics such as language and cognitive aptitude (He et al., 2012).

In contrast to the P300, the ACC can be elicited even when the subject is not paying attention and it does noy need active participation (Kim, 2015). These features support the ACC’s clinical use in participants that are challenging to test when extended attention or active involvement is necessary.

When compared to the Mismatch Negativity (MMN) and P300, which have typically been used to study auditory discrimination, the ACC has a number of benefits (Kim, 2015). One notable benefit is that the ACC response may be elicited with fewer trials. Furthermore, all stimuli given (not only the aberrant stimuli) can be utilized to investigate auditory discrimination. As a result, the number of responses required to achieve a reasonable signal-to-noise ratio is reduced (Kim, 2015). Additionally, the ACC has been demonstrated to have greater amplitudes than the MMN (Martin & Boothroyd, 1999), making it less difficult to identify the ACC than the MMN.

It also has been found that the ACC has a strong test-retest reliability in both normal hearing listeners and CI users (Tremblay, Friesen, Martin, & Wright, 2003; Friesen & Tremblay, 2006).

It also needs to be mentioned that there are a few disadvantages to using the ACC. Electrophysiological measurements, such as the ACC, have a disadvantage over behavioral measures in that they require an EEG system to gather data. This can make the data gathering process more time consuming and expensive. Moreover, due to the artefact that is often included in the signal, it may be hard to distinguish between the legitimate signal and artefact.

1.5.5.3 Acoustic Change Complex in cochlear implant (CI) users

There is a difference between direct and indirect stimulation of the CI when evoking the ACC in CI users: see Figure 2. The presentation of stimuli via the sound field is known as indirect stimulation. The speech processor is bypassed and stimuli are delivered directly to the implant's electrodes, when using direct stimulation. Direct stimulation has the advantage of having more control over the electrode array's output. Secondly, speech processor settings may vary substantially between CI users, making it difficult to analyze responses from CI users. Direct stimulation can be used to avoid this (Brown et al., 2008). This is why in this thesis direct (intracochlear) stimulation will be used.

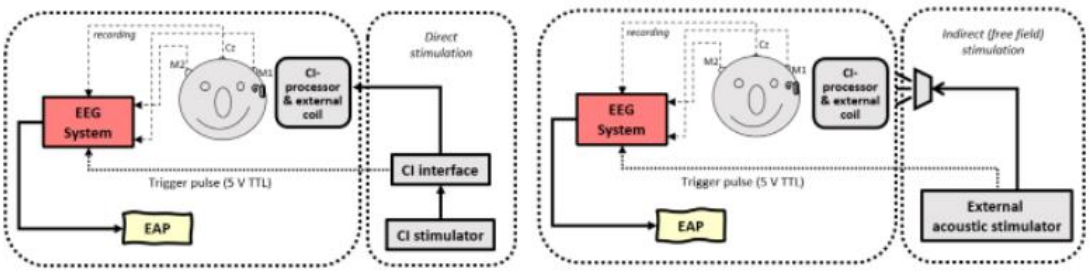


Figure 2: A Visualization of the difference between direct and indirect stimulation of CI users by Beynon et al. (2021)

1.5.5.4 Indirect stimulation of cochlear implant users with the ACC

In recent years, the amount of research into ACC among CI users has slowly increased. These investigations into ACC thresholds are often carried out by stimulating the CI users indirectly, thus via a sound field.

Recently, the ACC was used to investigate neural underpinnings of frequency change detection in cochlear implant (CI) recipients (Liang et al., 2018). The frequency change detection threshold (FCDT) in CI users was 3.79 percent, with a wide range of variability (range =0.67-9.66%). The ACC was studied by just using three magnitudes of frequency change (0, 5, and 50%), while the behavioral thresholds were determined using a two-alternative forced-choice (2AFC) approach. There was no information about the average electrophysiological threshold. Both the relationships between behavioral and electrophysiological thresholds and the relationship between ACC n1 latency and speech perception were shown to have a substantial correlation. These findings suggested that the ACC elicited by frequency changes could be used to measure frequency change detection abilities and estimate speech perception performance in CI users.

Furthermore, it has been found that CI users' ability to identify within-stimulus frequency variations may have a significant impact on their speech perception performance. For the estimation of CI speech outcomes, FCDT and Digits-in-Noise method (DIN) can be used as simple and quick tests that require no or little linguistic background (Zhang et al., 2019). Only three magnitudes of 36 Frequency change detection thresholds (FCDTs) were

behaviorally measured in 20 adult CI users utilizing a three-alternative forced-choice (3AFC) approach. The thresholds discovered by Zhang et al. (2019) (M = 5.48, 3.94, and 7.78 percent for the corresponding used frequencies of 0.25, 1, and 4 kHz) were similar to the thresholds found by (Liang et al., 2018). Moreover, Zhang et al. (2019) Zhang discovered significant connections between several speech perception metrics (such as the DIN) and frequency discrimination thresholds.

In addition, McGuire and colleagues (2021) investigated the ACC elicited by within-stimulus frequency changes in 21 adult CI users, as well as the correlation to behavioral performance in frequency change detection and speech perception. The researchers utilized the same frequencies as in their earlier publication. To establish behavioral discrimination thresholds, a 3AFC task was once again performed. For the base frequencies of 0.5, 1, and 4 kHz, the average thresholds were 8.68, 4.43, and 7.69 percent. Each frequency, was examined at three different frequency change magnitudes (0, 10, and 70%). This provides a very basic approximation of the ACC electrophysiological threshold for discriminating. The mean FCDT and speech scores were correlated with the mean N1 and P2 latencies. Using a criterion of 10% for the mean FCDT, it appeared to be possible to distinguish between good and bad CI perception with significantly different speech outcomes. The ACC amplitude was substantially higher for lower frequency bands than for higher frequency bands, indicating that cortical sensory processing is more robust in this frequency range.

1.5.5.5 Direct intracochlear stimulation of cochlear implant users with the ACC

Even though the interest for research on the ACC in CI users has increased in the past years, the ACC is rarely investigated when the CI users are stimulated intracochlear.

In 2010, Hoppe and colleagues stated that the ACC could be used to determine auditory discrimination ability. However, in their study there was no clear relationship between objective and subjective results. Hoppe and colleagues suggested that more research was needed to determine the ACC's applicability. Hoppe et al. were able to elicit the ACC at a rate of 88 percent. In most of the recordings, electrical artefacts caused by the CI stimulation can be seen. However, because of the filtering, it is primarily distinguished by a step at the start and end of the CI stimulation. When adding a 500 millisecond (ms) pre-stimulus time, ERPs were only mildly disturbed by the pulse sequence preceding the actual stimulus. Furthermore, it is suggested that ERP registration from scalp positions on the CI on the artefact's opposite side should be studied (Hoppe et al., 2010).

Earlier, a similar study was performed by Brown and colleagues (2008). Nucleus CI24 cochlear implant users had their speech processor bypassed and the output of the implanted receiver/stimulator controlled directly. The stimulating electrode was held constant in control conditions and the stimulus was a biphasic pulse train. In experimental conditions, the ACC was elicited by introducing a change in the stimulating electrode 300 msec after the onset of the stimulus. Bandpass filtering (1–100 Hz) was used to minimize contamination of the recordings by stimulus artefact. In each case, a clear onset response (P1-N1-P2) was recorded. In the experimental conditions, a second evoked potential, the ACC, was also recorded. This second response had general morphological characteristics that were very similar to those of the onset response. Increasing the separation between the two stimulating electrodes resulted in a general trend toward increased ACC amplitudes.

It has been stated that the auditory system's plasticity allows it to adapt to electrical input from cochlear implants (CI) (Mathew et al., 2017) While speech perception can improve for years after implant activation, little is understood about the changes in auditory processing that underlie them. This knowledge could aid in the development of therapies to improve hearing performance. Mathew and colleagues (2017) investigated how electrode discrimination ability changes over time in newly implanted adult CI users in this

longitudinal study. A behavioral test was used to assess electrode discrimination, as well as the ACC. The researchers showed that electrode discrimination skill improved significantly over time, albeit the pace of progress was slowed in certain individuals, accommodation was more difficult and time-consuming (Mathew et al., 2017). These findings support the plausibility of auditory processing in adult CI users. The behavioral electrode discrimination score was found to be a significant predictor of speech perception, but not the spatial ACC amplitude.

Using the ACC for assessing frequency discrimination thresholds has not been thoroughly studied in CI users. Consequently, the ACC has not been used to evaluate frequency discrimination thresholds in MED-EL CI users, only Martin (2007) used one participant for a case study with this CI brand. Therefore, more study is needed on frequency discrimination thresholds in general and in CI users of MED-EL implants.

1.6 Artefact while measuring auditory thresholds in cochlear implant users

As previously mentioned, electrical artefacts can be an issue when stimulating CI users, since they might interfere with the auditory evoked potential of interest, making it difficult to tell whether the recorded response is neural or simply a reflection of the artefact (Martin, 2007). The time-locked stimulus-related artefact is caused by the radio frequency transfer of the signal from the implant transmitter to the receiver, although other portions of the implant also contribute to the artefact.

Some research reported how to reduce the amount of artefact coming from the CI system, but not all methods have been proved to be feasible. Martin (2007) has investigated multiple ways to reduce CI system artefact in the EEG output, such as placing reference electrode placing for the EEG contralateral the CI, placing the referencing electrode on the zero iso-potential field of the artefact, alternating the polarity of the stimulus, raising the band filter of the EEG recording, or using techniques such as Principal Component Analysis (PCA) and Independent Component Analysis (ICA) (also e.g. Gilley et al., 2006; Richards, 2004; Viola et al., 2011; Firszt et al., 2002).

Martin (2007) stated that none of the attempts to reduce the artefact coming from the CI made substantial differences to the EEG recording. Even PCA and ICA could not successfully eliminate the implant artefact. Furthermore, Martin (2007) suggests that placing the reference electrode contralateral should be looked into more in future research.

1.7 Current study

Little research has been conducted on the use of the ACC to determine auditory discrimination in CI users with a MED-EL CI device via direct intracochlear stimulation. The use of ACC responses to determine auditory discrimination will be important in this thesis. In particular, the ACC will be used to measure cochlear implant users by direct intracochlear stimulation via the speech processor. Additionally, these electrophysiological evoked thresholds will be compared to behavioral responses.

1.7.1 Research questions

This thesis aims to investigate the following research questions:

1. Can the ACC be used as an objective measurement to determine discrimination thresholds when cochlear implant users are stimulated intracochlearly?
2. What is the correlation between behavioral and electrophysiological ACC frequency discrimination thresholds in cochlear implant users? (Experiment 1)
3. What is the correlation between behavioral and electrophysiological ACC amplitude discrimination thresholds in cochlear implant users? (Experiment 2)

1.7.2 Relevance of the current study

Gaining more recognition for the ACC as an objective measurement tool of auditory discrimination is one of the main objectives to why this study is necessary. It is important to determine whether the correlation between the values of behavioral and electrophysiological auditory discrimination thresholds is sufficient enough for electrophysiological measurements of auditory discrimination to be applied effectively in clinical practice.

In addition, this study is relevant because it can possibly provide predictive values of the ACC that may be useful for future use in pediatrics, on the basis of which individual capacity of auditory discrimination can be objectified. In particular for babies and young children where the adjustment of the hearing prosthesis can be optimized.

1.7.3 Hypotheses

A correlation between behavioral and electrophysiological thresholds of CI users is expected. It is expected that behavioral and electrophysiological thresholds are positively correlated, with behavioral discrimination responses being more sensitive than electrophysiological obtained responses. Even though various thresholds are predicted for individual subjects, it is believed that the findings will be comparable for all participants.

It is also expected that the ability to recognize the ACC will be more difficult when electrically-evoked auditory changes become smaller, being the result of decreasing ACC amplitudes. In addition, it is also hypothesized that ACC (n1) latencies will increase when nearing discrimination threshold.

2. Methods

2.1 Participants

10 CI users (All Med-EL users) (age range: 48-77, mean age: 66.7, 5 men; 5 women) participated in this study. All participants were recruited to participate in the experiment through the Radboud University Medical Center (Radboudumc). Informed consent was signed by all participants. More information on the participant characteristics can be seen in Table 1.

All participants completed all parts of the experiment; namely the creation of a safety map, a loudness balancing task and behavioral and electrophysiological frequency- and amplitude discrimination tasks in one session. The test session approximately takes between two and three hours. The data of the loudness balancing task are used for all behavioral and electrophysiological tasks, to avoid discomfort or painful auditory and/or vibrotactile sensations throughout the experiment. All parts of the experiment are done intracochlear, all stimuli were presented using a Med-EL speech processor (SONNET 2) in combination with the Med-EL hardware 'MAX' interface.

Patient	Gender	Age	CI side	Electrodes off
EACC001	M	72	R	11,12
EACC002	F	75	R	12
EACC003	F	61	R	NONE
EACC004	M	64	R	NONE
EACC005	M	75	L	11,12
EACC006	F	48	L	2,12
EACC007	F	65	R	12
EACC008	F	60	L	11, 12
EACC009	M	70	L	11,12
EACC010	M	77	R	11,12

Table 1: Patients demographics, including the side of the CI and which electrodes of the implant were not used during the experiments.

2.2 Experiment preparations

2.2.1 Creating a safety map

This experiment has been conducted by using the MAESTRO 9.0 (2020) and Psyworks software (MED-EL GmbH, Austria). MAESTRO 9.0 is the latest fitting software used for Med-EL cochlear implants. The Psyworks software makes it possible to do psychophysical research on CI users. With the software package clinicians and researchers are able to perform behavioral measurements such as the loudness balancing task and behavioral and electrophysiological measurements (such as frequency and amplitude discrimination).

To be able to do psychophysical research with Psyworks, it is required to check the functionality of all 12 tonotopically arranged intracochlear electrodes ('telemetry') and create a safety map with MAESTRO 9.0 first. This safety map is not the same as an audio processor's ordinary fitting map; it merely specifies the maximum and minimum charge per electrode that will be applied throughout the experiment. In this way, no stimuli can be created that will be below the hearing thresholds (THRs) of the patients, nor will there be stimuli that will be above the maximum comfortable levels (MCLs) of the patients. It also protects patients from overstimulation (i.e., beyond MCL) during all experiments. How a safety map can be created can be found in the experiment protocol in Appendix A of this thesis.

Throughout the whole experiment patients will be connected to the MAX-box from Med-EL with one of its telemetry coils or a Med-EL processor; the MAX-box is connected to a laptop with both the MAESTRO 9.0 and Psyworks software and the EEG acquisition software. The MAX-coil is placed on the patient's implant during a telemetry measurement; for the rest of the tasks, the research Med-EL processor is connected to their implant. Thus, during the tasks the patients do not use their own CI processor. See figure 3 for the setup of the MAX equipment and the laptop.

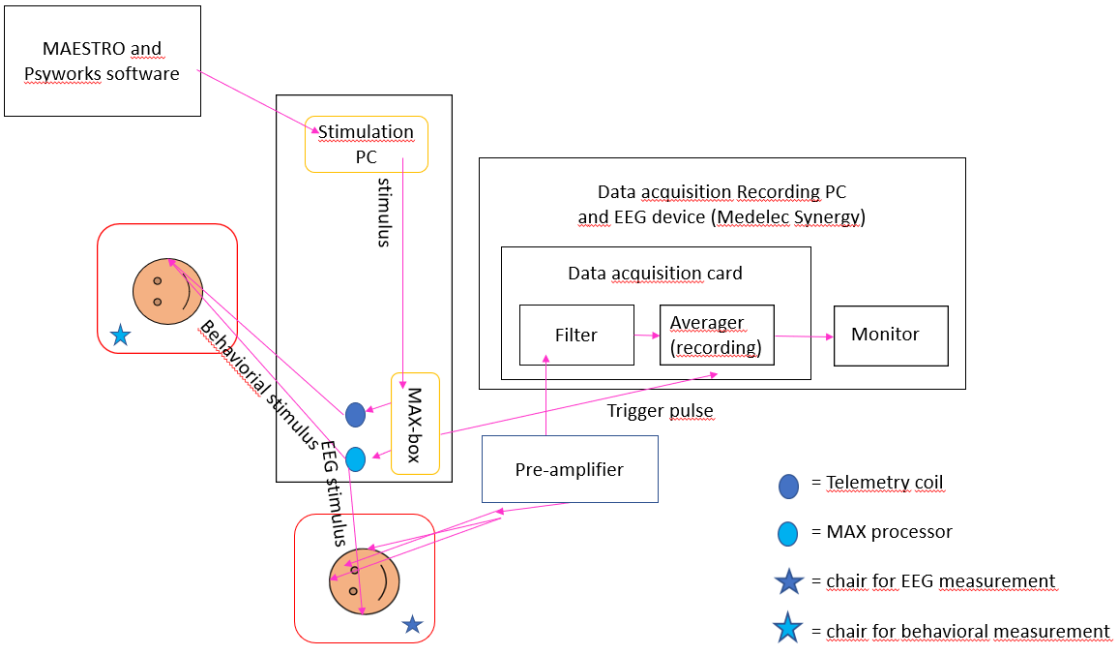


Figure 3: The setup of the behavioral and electrophysiological frequency and amplitude discrimination tasks.

2.2.2 Loudness balancing task

Before the experimental behavioral and electrophysiological tasks, patients perform a loudness balancing task after the individual safety map of the patient is uploaded in Psyworks. In this task, participants heard a stimulus pair, the first part always being the control stimulus on electrode number one (most apical electrode), presented at 80% of the MCL amplitude (based on the safety map), and the second part being one of the other electrode numbers on the electrode array (target electrode). The patients were asked to increase or decrease the loudness of the target stimulus (in a small or big step of respectively of one or five percentage point of the 80% amplitude of electrode number one) until it sounded equally loud as the control stimulus. Each stimulus pair (twelve in total, unless one of the patient's electrodes is disabled) was balanced once. The duration of the loudness balancing task was approximately between five and ten minutes. How the loudness balancing task can be programmed in Psyworks can be found in Appendix A.

2.3 Experiment 1: Intracochlear frequency discrimination (electrode combinations)

2.3.1 Behavioral measurement: frequency discrimination task

For the behavioral frequency discrimination task, 12 electrode combinations were tested. By presenting these electrode combinations, it is possible to determine subjective frequency discrimination thresholds for the patients. Electrode number 1 was chosen as the control stimulus for all active electrode combinations (1-1, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, 1-12; see table 2 for alle frequency discrimination stimuli). During the behavioral frequency discriminations task, patients were asked to confirm whether they heard a change in frequency. The stimuli consisted of a biphasic stimulus train of 800 ms, consisting of the first part of 400 ms stimulating the reference electrode (typically electrode 1) and the second part of 400 ms stimulating one of the other electrodes, including electrode 1. All electrode combinations were presented five times using the method of constant stimuli. The total duration of the behavioral test was approximately ten minutes. How the behavioral frequency discrimination task can be programmed in Psyworks can be found in Appendix A.

When the behavioral frequency task had been completed, its data is exported to an Excel file to see how many times a change was perceived in each stimulus, to determine the order of stimulus presentation in the electrophysiological frequency discrimination task. After all behavioral patient data was collected, psychometric curves were fitted in RStudio (RStudio Team, 2020) and Excel to determine if the point of 80% correct. This 80% originates from the five repetitions of each stimulus during the behavioral task, 80% means that four out of five stimulus repetitions were perceived correctly. The frequency change corresponding to the point of 80% correct was defined as the behavioral discrimination threshold.

Stimulus	Electrode combination
1	1_1
2	1_2
3	1_3
4	1_4
5	1_5
6	1_6
7	1_7
8	1_8
9	1_9
10	1_10
11	1_11
12	1_12

Table 1: All stimuli for experiment 1: Frequency discrimination (electrode combinations)

2.3.2 Electrophysiological measurement: frequency discrimination task

For the electrophysiological measurement, the same stimuli were used for the frequency discrimination as used in the behavioral task. Patients were asked to sit down in a comfortable chair and asked to sit in a relaxed manner, mainly relaxing their shoulders and neck to avoid EMG activity in the EEG. It was also asked whether patients would like to use the toilet before the EEG measurements (NB. breaks were always provided if necessary), because these are the longest tasks of both of the experiments. During the stimulus presentation, patients were instructed to close their eyes and actively listen without falling

asleep. The total duration of the EEG recording was approximately between 30 and 45 minutes.

Which stimuli were presented and in what order the stimuli were presented was determined by the results of the behavioral test and thus varied between patients.
This was also done for frequency discriminations below the behavioral thresholds to confirm the absence of an ACC. The electrophysiological task always started and ended with the presentation of the control stimulus, i.e., a continuous 800 ms pulse train without any change. The procedure for determining the electrophysiological frequency discrimination threshold(s) will be described later in the data analysis section down below.

Each stimulus was sent from Psyworks to the EEG recording with a trigger pulse of +5V TTL (sync pulse) to synchronize the time-locking between stimulation and the EEG recording. The recording window that was used was 2000 ms, including a 200 ms pre-stimulus time, with an interstimulus interval of 1000 ms with 10% jitter.

Furthermore, a 1-channel set-up was used. The electrodes that were used for this channel were placed on the patients' head at Cz (vertex; non-inverting, active), the contralateral mastoid of the CI; A1 or A2 (inverting, reference) and one electrode on the higher side of the sides of the forehead (ground). The skin of the patient was cleaned and scrubbed thoroughly before placing the electrodes on their skin with gel to obtain low impedances. The impedance of the recording electrodes was kept below 16 kΩ and checked during the EEG recording. If the impedance of the electrodes creeped up above 16 kΩ, a new electrode was placed or the skin beneath was cleaned/scrubbed again to lower the impedance.

The high and low pass filter of the EEG was set to 0.1 and 30 Hz, the notch filter was set to 50 Hz and the data of the EEG recording was acquired with a sampling rate of 25kHz with an amplifier gain of 50.000. The artifact rejection was set to 50 μV, when too much of the data was thrown away by the automatic artifact rejection (due to the signal being too noisy), it was changed to 70 μV. For each stimulus, approximately 60 responses were obtained with at least two traces and averaged during the experiment. The smallest change at which the ACC was found would be determined as the discrimination threshold for the frequency changes (electrode combinations).

2.3.3 Data analysis and statistical analysis of Experiment 1

For the current study the latency and P-P amplitude were analyzed for both the N1-P2 (onset SVP) complex and the ACC of the electrophysiological measurements. Before the data was analyzed, it was first visually determined whether the N1-P2 complex and the ACC could be identified in the raw EEG recording data. The N1-P2 complex and the ACC were determined as present when their (highest) positive and negative peaks were presented in the following latencies; The biggest negativity for the N1-P2 Complex between 90 and 200 msec post-stimulus initiation was found to be N1. Between 150 and 300 msec after the stimulus began, P2 was shown to be the most significant positive. The biggest negative between 720 and 820 msec was known as n1 for the ACC. The biggest positive between 770 and 900 msec was referred to be the p2. The lowest frequency variation that elicited the ACC was designated as the discrimination threshold. The range of latencies between which peaks and throughs required to be present in order to be recognized as a component of the SVP or ACC was enlarged (Liang et al., 2018), in order to account for potential extended latencies in CI users.

The smallest change at which the ACC was found is defined as the discrimination threshold for the electrophysiological frequency changes. Runs without any N1-P2 detection component were excluded for further analysis.

The correlation between behavioral and electrophysiological frequency discrimination thresholds was investigated by statistical analysis in RStudio (RStudio Team, 2020). The correlation between frequency changes and the inter-peak interval (IPI) of the N1-P2 Complex and the ACC was measured using linear mixed model regression. It was also determined whether the IPI of the frequency changes differed significantly from their expected inter-peak interval by using the Wilcoxon signed rank test. Moreover, linear mixed model regression was also used to investigate the correlation between the frequency changes and the P-P amplitude of the ACC. Finally, the relation between behavioral and electrophysiological frequency discrimination thresholds was investigated using both the Wilcoxon signed ranked test and Pearson's correlation.

2.4 Experiment 2: Intracochlear amplitude discrimination (Amplitude combinations)

2.4.1 Behavioral measurement: amplitude discrimination task

For the behavioral amplitude discrimination task 10 amplitude combinations were tested. Amplitude level 0.8 (80% of MCL) was the control stimulus for all amplitude combinations (0.8-0.8, 0.8-1.0, 0.8-0.9, 0.8-0.7, 0.8-0.6, 0.8-0.5, 0.8-0.4, 0.8-0.3, 0.8-0.2, 0.8-0.1, see table 3 for alle amplitude discrimination stimuli). All amplitude combinations were presented on electrode number 1 (when this electrode was disabled, then the most neighboring active electrode was used). During the behavioral amplitude discriminations task, patients were asked to confirm whether they heard a change in loudness halfway through the stimulus. The stimuli consisted of a biphasic electric stimulus pulse train of 800 ms, the first 400 ms being the amplitude of the reference amplitude (0.8), while the second 400 ms would be one of the other amplitude percentages as stated above. All electrode combinations were presented five times using the method of constant stimuli. The total duration of the behavioral test was approximately ten minutes. How the behavioral amplitude discrimination task can be programmed in Psyworks can be found in Appendix A.

When the behavioral amplitude task had been completed, its data would be exported to Excel to see how many times a change was perceived in each stimulus. According to these results the order in which the stimuli of the electrophysiological amplitude discrimination task would be presented would be determined. After all the patient data was collected, psychometric curves were fitted in RStudio (RStudio Team, 2020) and Excel to determine the point of 80% correct. The amplitude change corresponding to the point of 80% correct was defined as the behavioral discrimination threshold.

Stimulus	Amplitude combination
1	0.8-0.8
2	0.8-1.0
3	0.8-0.9
4	0.8-0.7
5	0.8-0.6
6	0.8-0.5
7	0.8-0.4
8	0.8-0.3
9	0.8-0.2
10	0.8-0.1

Table 3: All stimuli for experiment 2: Amplitude discrimination

2.4.2 Electrophysiological measurement: amplitude discrimination task

For the electrophysiological measurement the same stimuli were used for the amplitude discrimination as used in the behavioral task.

Which stimuli were presented and in what order the stimuli were presented was determined by the results of the behavioral test and thus varied for each patient. Based on the behavioral thresholds that were found, amplitude discriminations that were heard behaviorally were presented to determine if the ACC could be found as well. This was also done for amplitude discriminations below the behavioral thresholds to make sure that no ACC was found there as well. The electrophysiological task always started and ended with the presentation of the control stimulus. The procedure for determining the electrophysiological amplitude discrimination threshold(s) will be described later in the data analysis section down below.

Each stimulus was sent from Psyworks to the EEG recording with a trigger pulse of +5V TTL (sync pulse) to make sure that time-locking the stimuli and responses could be done in an exact manner. The recording window that was used was 2000 ms. This 2000 ms recording window included; 200 ms pre-stimulus time, 800 ms stimuli and an interstimulus interval of 1000 ms (with a 10% jitter; 900 ms and 1100 ms).

The EEG setup was exactly the same as described for the frequency experiment.

2.4.3 Data analysis and statistical analysis of Experiment 2

For the current study the latency and P-P amplitude were analyzed for both the N1-P2 (onset SVP) complex and the ACC of the electrophysiological measurements. Before the data was analyzed, it was first visually determined whether the N1-P2 complex and the ACC could be identified in the raw EEG recording data. The N1-P2 complex and the ACC were determined as present when their (highest) positive and negative peaks were presented in the following latencies; The biggest negative peak for the N1-P2 Complex between 90 and 200 msec post-stimulus initiation was found to be N1. Between 150 and 300 msec after the stimulus began, P2 was shown to be the most significant positive. The biggest negative between 720 and 820 msec was referred to as n1 for the ACC. The biggest positive between 770 and 900 msec was referred to be the p2. The lowest amplitude variation that elicited the ACC was designated as the discrimination threshold. The range of latencies between which peaks and throughs required to be present in order to be recognized as a component of the SVP or ACC was enlarged (Liang et al., 2018), in order to account for potential extended latencies in CI users.

The smallest change at which the ACC was found is defined as the discrimination threshold for the electrophysiological amplitude changes. Runs without any N1-P2 detection component were excluded for further analysis.

The correlation between behavioral and electrophysiological amplitude discrimination thresholds was investigated by statistical analysis in RStudio (RStudio Team, 2020). The correlation between amplitude changes and the inter-peak interval (IPI) of the N1-P2 Complex and the ACC was measured using linear mixed model regression. It was also determined whether the IPI of the amplitude changes differed significantly from their expected inter-peak interval by using the Wilcoxon signed rank test. Moreover, linear mixed model regression was also used to investigate the correlation between the amplitude changes and the P-P amplitude of the ACC. Finally, the relation between behavioral and electrophysiological amplitude discrimination thresholds was investigated using both the Wilcoxon signed ranked test and Pearson’s correlation.

3. Results

3.1 Experiment 1: Frequency discrimination (electrode combinations)

3.1.1 Behavioral results

To determine the behavioral frequency discrimination threshold. The threshold is defined as the 80% correct ratio or above 80% in the psychometric curved created for each patient. No participants were excluded due to false positives (perceiving a change in the control stimulus) or false negatives (perceiving no change in the deviant stimuli). See figure 4 for a typical example of a psychometric curve for one patient (or see Appendix B for all psychometric curves).

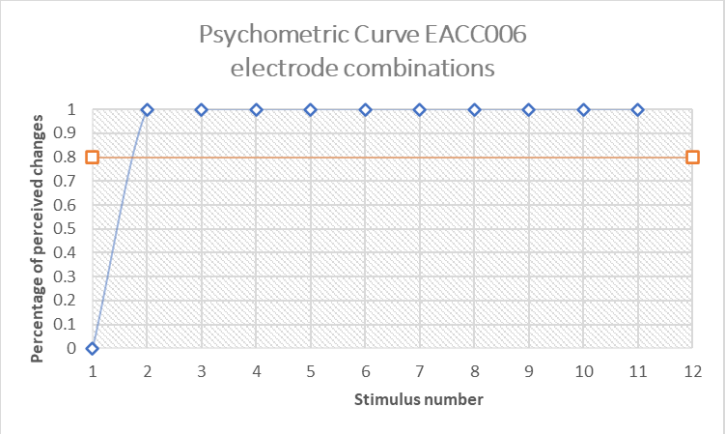


Figure 4: A psychometric curve fitted for the results of the behavioral frequency discrimination task of patient EACC006. The threshold, defined as the 80% correct ratio (orange line), for this subject is stimulus number 2 (electrode combination 1-2).

Behavioral data of two patients was excluded due to stimulation problems by Psyworks. The interpolated mean of the behavioral threshold of the frequency changes was stimulus 3.1 (SD = 2.8, range = stimulus 1 to 10, N = 8). See table 4 for the behavioral and electrophysiological frequency discrimination thresholds of all patients. The percentage of incorrect answers for the behavioral task for each patient can also be found in Appendix C.

Patient	Behavioral threshold	Electrophysiological threshold
EACC001	2	2
EACC002	*NA*	2
EACC003	3	2
EACC004	2	2
EACC005	2	4
EACC006	2	2
EACC007	2	2
EACC008	*NA*	2
EACC009	2	2
EACC010	10	2

Table 4: Both behavioral and electrophysiological thresholds of the electrode combinations for all patients.

3.1.2 Electrophysiological results

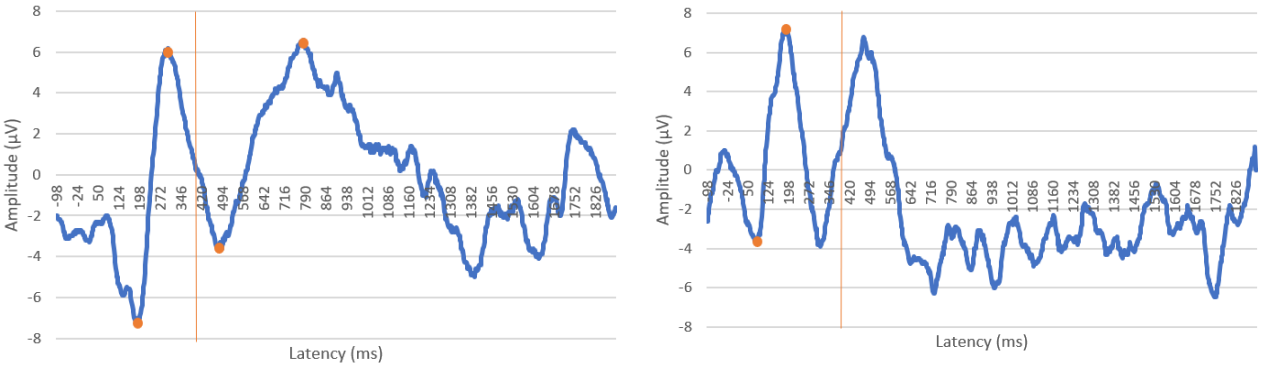
Patients were asked to keep their eyes closed during recordings of the electrophysiological responses. Any artefact of eye movements did not cause any disturbances in the N1-P2 Complex or the ACC responses. However, in some of the traces no clear p2 could be

determined in the ACC responses. Only the traces with clear a clear n1 and p2 were taken into account for the data analysis and statistical analysis of the current study.

The interpolated mean of the electrophysiological frequency discrimination threshold of the was stimulus number 2.1 (SD = 0.63, range = stimulus 2 to 4, N = 10); see table 4 for all patients' electrophysiological frequency discrimination thresholds.

In Figure 5, two examples of cortical auditory evoked responses to an electrode combination stimulus are shown; the first example shows a large difference between the electrode combinations (stimulus number 11; 1-11), the response shows the N1-P2 Complex and ACC. The second example shows the response to the control stimulus (stimulus number 1, 1-1), as can be seen no ACC response occurs, only the N1-P2 Complex can be determined.

Figure 5: Examples of a neural response (of patient EACC007) to the control stimulus (1-1, right) and to stimulus 11 (1-11,



left) (big frequency change, relatively easy to detect). Both the N1-P2 Complex and the ACC are indicated with orange dots. The moment where the change in frequency (and thus electrode) occurs in the deviant stimuli has been indicated with the orange line (400 ms).

Electrode combination	mean IPI N1-n1 (ms)
1-1	0.0
1-2	402.9
1-3	378.7
1-4	402.2
1-5	403.2
1-6	416.3
1-7	403.0
1-8	403.0
1-9	402.0
1-10	389.6
1-11	413.2
1-12	384.0

Table 5: Mean IPI of all patients for each different frequency change (electrode combinations).

3.1.2.1 Relationship between frequency change and latency n1

Based on the structure of the stimuli used in the current study it was hypothesized that the inter-peak interval (IPI) between the N1 of the N1-P2 Complex and the n1 of the ACC would be approximately 400 ms. The mean IPI of all patients for each of the frequency changes can be seen in table 5. Because not all electrode combinations were presented to each patient, it was decided to analyze only three electrode locations. i.e., one basal (stimulus 10; 1-10), one apical (stimulus 2, 1-2) and one medial (stimulus 6, 1-6).

For the correlation between the IPIs of stimulus 2, 6 and 10, a linear mixed model regression was used. The mixed model showed that the mean IPI decreases when the differences within the electrode combinations increased. Furthermore, the difference in mean IPI appeared to be smaller between stimulus 2 and 10 (est. = 13.2 ms, error = 25.3, df = 18, p = 0.60) than between stimulus 6 and 10 (est. = 26.69, error = 26.58, df = 18, p = 0.33). Post hoc, the correlation of the IPI between stimulus 2 and 6 was also determined: the mean IPI of stimulus 6 was higher than that of stimulus 2 (est. = 13.40, error = 23.50, df = 12.4, p = 0.84). Unfortunately, all the linear mixed model results and post hoc results of the IPI were not significant, so no valid generalizations can be made about the results stated above. For all the output of the statistical analysis appendix D can be consulted. Paired Wilcoxon signed ranked tests were also performed to determine whether the selected basal, apical and medial stimuli differed significantly from the expected IPI of 400 ms. The mean IPI of stimulus 2 (p = 0.860), nor stimulus 6 (p= 0.80) nor stimulus 10 (p= 0.58) differed significantly from the hypothesized IPI of 400 ms. No valid generalizations can be made about the found results.

3.1.2.2 Relationship between frequency change and P-P amplitude of the ACC

The mean P-P amplitude of both the N1-P2 Complex and ACC of all patients for all frequency changes was determined. This can be seen in table 6, this data is also visualized in figure 6.

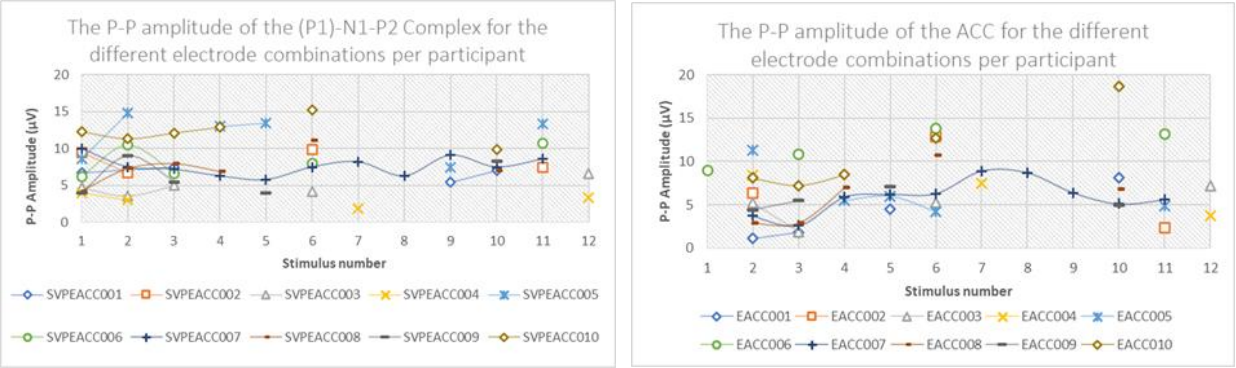


Figure 6: The P-P amplitude of both the N1-P2 Complex and ACC of each patient for the electrode combinations.

Electrode combinations	P-P Amplitude SVP (µV)	P-P Amplitude ACC (µV)
1-1	7.02	*NA*
1-2	8.08	5.72
1-3	7.41	4.67
1-4	9.78	6.73
1-4	7.77	5.95
1-6	9.32	9.40
1-7	5.05	8.20
1-8	6.30	8.70
1-9	7.33	6.40
1-10	7.94	8.74
1-11	10.00	6.50
1-12	4.95	5.45

Table 6: Mean P-P amplitude of all patients for each different frequency change (electrode combinations).

Once more, the three stimuli used for the statistical analysis of the IPI were used to examine the correlation between the P-P amplitude of a basal, apical and a medial electrode combination. The correlation between the P-P amplitude of stimulus 2, 6 and 10 a linear mixed model regression was used. The mixed model showed that the mean P-P amplitude decreases when the differences between the electrode combinations decreased. Moreover, the difference in mean P-P amplitude appeared to be smaller between stimulus 6 and 10 (est. = -0.28, error = 1.99, df = 12.45, p = 0.89) than between stimulus 2 and 10 (est. = -3.80, error = 1.69, df = 8.52, p = 0.53). Post hoc, the correlation of the P-P amplitude between stimulus 2 and 6 was also determined. The effect of the P-P amplitude of the N1-P2 Complex on the P-P amplitude was analyzed as well. The results show that when the P-P amplitude of the SVP increases, the P-P amplitude of the ACC also increases (est. = 0.46, error = 0.30, df = 11.14, p = 0.15). Overall, these results indicate that the P-P amplitude of the ACC decreased when the distance of the electrode combinations decreased, although the linear mixed model and post hoc results of the P-P amplitude were not statistically significant. For all the output of the statistical analysis appendix D can be consulted.

3.1.3 Relationship between behavioral and electrophysiological results

As can be seen in table 4, the behavioral and electrophysiological frequency discrimination thresholds are very similar for all patients. These thresholds were visualized in figure 7.

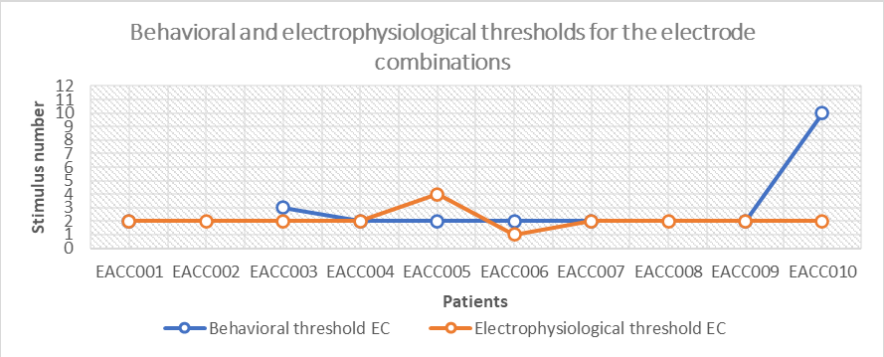


Figure 7: A visualization of both the behavioral and electrophysiological thresholds for the frequency discrimination task (electrode combinations). Patient EACC002 and EACC008 were excluded from the behavioral data.

A paired Wilcoxon signed ranked test was performed to determine whether the behavioral and electrophysiological frequency discrimination thresholds differed significantly from each other. The results of the Wilcoxon signed ranked test showed that this was not the case (p = 0.83). Moreover, a two-tailed Pearson's correlation between the behavioral and electrophysiological frequency discrimination thresholds was performed, no significant correlation between the thresholds was found (df = 8, p = 0.94).

3.2 Experiment 2: Amplitude discrimination

3.2.1 Behavioral results

To determine the behavioral amplitude discrimination thresholds, it was decided that the threshold would be defined as the 80% correct ratio or above 80% in the psychometric curved created for each patient. For the amplitude discrimination a lower and upper threshold was determined, because increasing amplitude changes (e.g., 0.8-1.0) and decreasing amplitude changes (e.g., 0.8-0.5) toward the control stimulus of 0.8-0.8 were measured. No participants were excluded due to too many false positives (perceiving a change in the control stimulus) or false negatives (perceiving no change in the deviant stimuli). See figure 8 for an example of a psychometric curve for one patient.

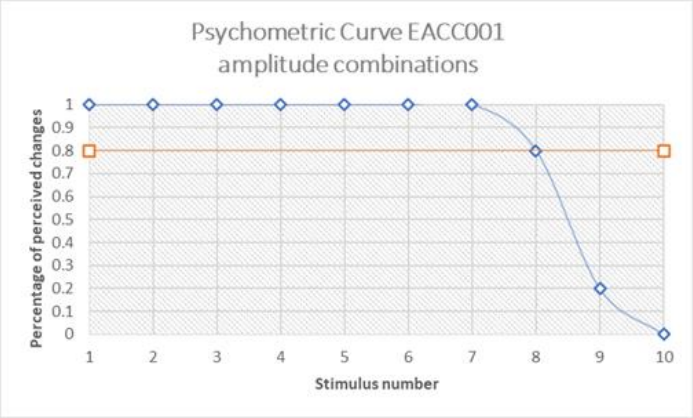


Figure 8: A psychometric curve fitted for the results of the behavioral amplitude discrimination task of CI user EACC001. The upper threshold, defined as the 80% correct ratio (orange line), for this subject is stimulus number 8 (amplitude combination 0.8 0.3). The lower threshold, defined as the 80% correct ratio (orange line), for this subject is stimulus number 3 (amplitude combination 0.8 1.0). It can be seen that this patient perceived all false positives for the control stimulus 1 (0.8 0.8).

Patient	Lower threshold (B)	Upper threshold (B)	Upper threshold (E)	Lower threshold (E)
EACC001	7	2	2	10
EACC002	*NA*	*NA*	2	10
EACC003	*NA*	3	2	7
EACC004	8	2	2	10
EACC005	10	2	2	10
EACC006	10	2	3	10
EACC007	9	2	2	10
EACC008	*NA*	*NA*	2	10
EACC009	10	2	2	8
EACC010	6	2	2	10

Table 7: Both behavioral and electrophysiological for all upper and lower thresholds of the amplitude combinations for all patients.

Behavioral data of two patients was excluded for determining the lower threshold due to stimulation problems by Psyworks. For the behavioral upper threshold an extra third patient was excluded due to inconsistent responses during the behavioral amplitude discrimination task. The interpolated mean of the lower behavioral threshold of the amplitude changes was stimulus 8 (SD = 1.6, range = stimulus 6 to 10, N = 7). The interpolated mean of the upper behavioral threshold of the amplitude changes was stimulus 2 (SD = 0.35, range = stimulus 2 to 3, N = 8). See table 7 for the behavioral and electrophysiological thresholds of all patients.

3.2.2 Electrophysiological results

The interpolated mean of the lower electrophysiological threshold of the amplitude changes was stimulus 9.5 (SD = 1.08, range = stimulus 7 to 10, N = 10). The interpolated mean of the upper behavioral threshold of the amplitude changes was stimulus 2.1 (SD = 0.32, range = stimulus 2 to 3, N = 10). See table 6 for the behavioral and electrophysiological thresholds of all patients. In figure 9 two examples of cortical auditory evoked responses to an electrode combination stimulus are shown; the first example shows a large difference between the electrode combinations (stimulus number 2; 0.8-1.0), the response shows the N1-P2 Complex and ACC. The second example shows the response to the control stimulus (stimulus number

1, 0.8-0.8), as can be seen no ACC response occurs, only the N1-P2 Complex can be determined.

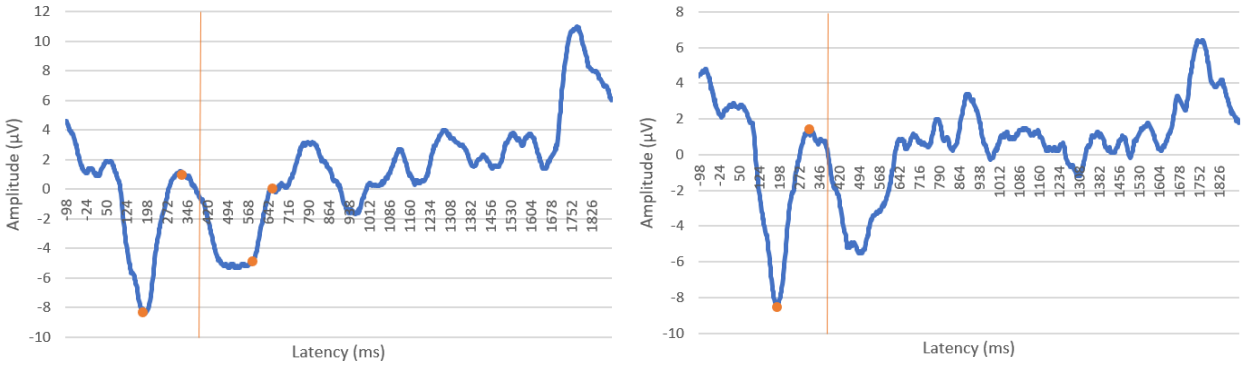


Figure 9: Examples of a neural response (of patient EACC007) to the control stimulus (0.8-0.8, right) and to stimulus 2 (0.8-1.0, left) (increasing amplitude change). Both the N1-P2 Complex and the ACC are indicated with orange dots. The moment where the change in amplitude occurs in the deviant stimuli has been indicated with the orange line (400 ms).

3.2.2.1 Relationship between frequency change and latency n1

Based on the structure of the stimuli used in the current study it was hypothesized that the inter-peak interval (IPI) between the N1 of the N1-P2 Complex and the n1 of the ACC would be approximately 400 ms. The mean IPI of the amplitude changes can be seen in table 8.

Because not all stimuli were presented to each patient it was decided to not perform a statistical analysis with all the amplitude change stimuli. Instead, one increasing amplitude change stimulus (stimulus 2; 0.8-1.0), one small decreasing amplitude change (stimulus 6, 0.8-0.5) and one big decreasing amplitude change stimulus (stimulus 10, 0.8-0.1) that were used the most over all patient were used to perform a statistical analysis on the IPI of the electrophysiological frequency discrimination task.

Amplitude combinations	**mean IPI N1-n1 (ms)**
0.8-0.8	0.00
0.8-1.0	391.63
0.8-0.9	405.80
0.8-0.7	425.00
0.8-0.6	445.50
0.8-0.5	404.25
0.8-0.4	420.33
0.8-0.3	394.00
0.8-0.2	408.00
0.8-0.1	400.43

Table 8: Mean IPI of all patients for each different amplitude change (amplitude combinations).

For the correlation between the IPIs of stimulus 2, 5 and 10 a linear mixed model regression was used. The mixed model showed that the mean IPI decreases when the differences between the electrode combinations increased. This can be seen in the difference between stimulus 5 and 10 (est. = -21.6 ms, error = 19.7, sf = 12, p = 0.53; post hoc). Furthermore, the difference in mean IPI appeared to be smaller between stimulus 2 and 10 (est. = -11.08 ms, error = 13.09, df = 17, p = 0.49) than between stimulus 2 and 5 (est. = 10.53, error = 17.49, df = 17, p = 0.55). Thus stimulus 10 was perceived easier than stimulus 2 and 5, since the IPI is

the lowest. With stimulus 5 being perceived as the most difficult.

All the linear mixed model and post hoc results of the IPI were not significant. For all the output of the statistical analysis appendix D can be consulted. Paired Wilcoxon signed ranked tests were also performed to determine whether the selected stimuli differed significantly from the expected IPI of 400 ms. The mean IPI of stimulus 2 ($p = 0.55$), nor stimulus 5 ($p= 0.75$) nor stimulus 10 ($p= 0.75$) differed significantly from the hypothesized IPI of 400 ms. No valid generalizations can be made about the found results.

3.2.2.2 Relationship between frequency change and P-P amplitude of the ACC

The mean P-P amplitude of both the N1-P2 Complex and ACC of all patients for all amplitude changes was determined. This can be seen in table 9, this data is also visualized in figure 10.

Amplitude combinations	**P-P Amplitude N1-P2 Complex (µV)**	**P-P Amplitude ACC (µV)**
0.8 0.8	7.56	*NA*
0.8 1.0	4.85	4.23
0.8 0.9	6.49	4.51
0.8 0.7	5.04	3.50
0.8 0.6	7.33	3.85
0.8 0.5	7.08	7.23
0.8 0.4	7.25	3.32
0.8 0.3	8.64	4.08
0.8 0.2	6.68	4.20
0.8 0.1	7.68	5.41

Table 8: Mean P-P amplitude of all patients for each different amplitude change (amplitude combinations).

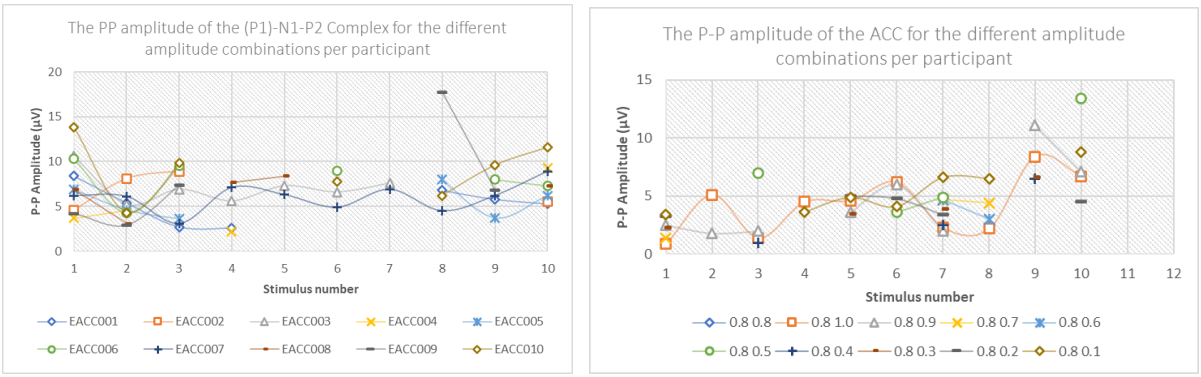


Figure 10: The P-P amplitude of both the N1-P2 Complex and ACC of each patient for the amplitude combinations.

Again, the three stimuli used for the statistical analysis of the IPI will be used to examine the correlation between the P-P amplitude of one increasing amplitude change stimulus, one small decreasing amplitude change and one big decreasing amplitude change (stimulus 2, 5 and 10).

For the correlation between the P-P amplitude of stimulus 2, 5 and 10 a linear mixed model regression was used. The mixed model showed that the mean P-P amplitude was larger when the differences within the amplitude combinations was an increasing difference, both P-P amplitudes of stimulus 10 and 5 were smaller than the P-P amplitude of stimulus 2 (est. =

2.40, error = 1.68, df = 10.12, p = 0.18) (est. = 1.73, error = 1.89, df = 8.55, p = 0.38). Post hoc the correlation of the P-P amplitude between stimulus 5 and 10 was also determined, it appeared that the P-P amplitude of stimulus 5 was larger than the P-P amplitude of stimulus 10. The effect of the P-P amplitude of the N1-P2 Complex on the P-P amplitude was analyzed as well, the results show that when the P-P amplitude increased, the P-P amplitude of the ACC also decreased (est. = -0.22, error = 0.47, df = 13.86, p = 0.64). All the linear mixed model and post hoc results of the P-P amplitude were not significant. No valid generalizations can be made about the results stated above. For all the output of the statistical analysis appendix D can be consulted.

3.2.3 Relationship between behavioral and electrophysiological results

As can be seen in table 7, the behavioral and electrophysiological of both upper and lower amplitude discrimination thresholds are very similar for all patients. These thresholds were visualized in figure 11.

Two paired Wilcoxon signed ranked tests were performed to determine whether the behavioral and electrophysiological upper and lower amplitude discrimination thresholds differed significantly from each other. The results of the Wilcoxon signed ranked test showed that this was not the case for the lower amplitude discrimination threshold (p = 0.27). In contrast, a significant difference was found between the behavioral and electrophysiological upper thresholds (p = 0.035). The increasing amplitude discrimination threshold was significantly higher for the electrophysiological measurement than for the behavioral measurement. Moreover, no statistically significant correlations between the behavioral and electrophysiological upper and lower amplitude discrimination thresholds were found: df = 8, p = 0.51, and df = 8, p = 0.59 for upper and lower threshold respectively (Pearson's correlation coefficient, two-tailed).

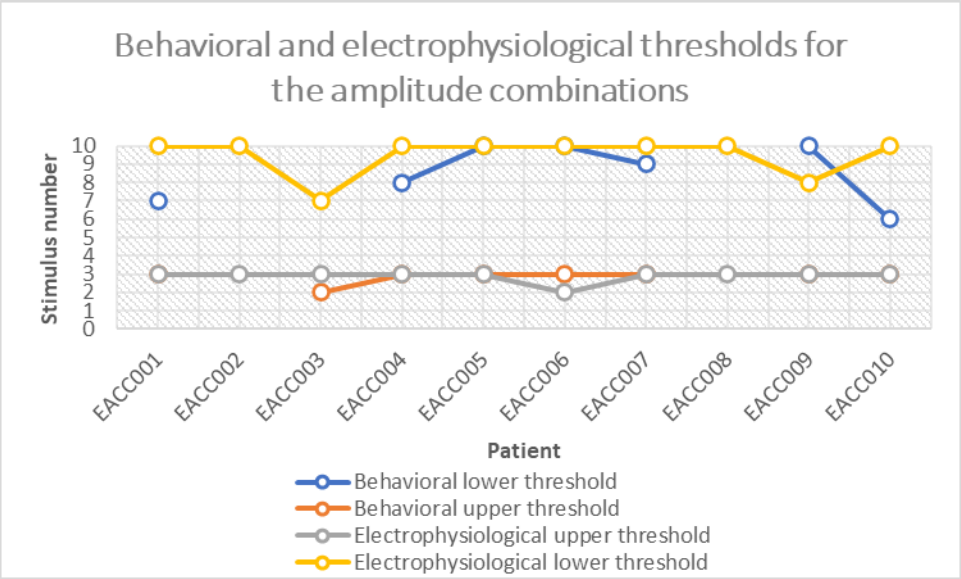


Figure 11: A visualization of both the behavioral and electrophysiological upper and lower thresholds for the amplitude discrimination task (amplitude combinations). Patient EACC002 and EACC008 were excluded from the behavioral upper and lower threshold data. Patient EACC003 was also excluded from the behavioral lower threshold data.

4. Discussion

The main objective of the current study was to determine whether the Acoustic Change Complex (ACC) can be used to estimate auditory discrimination in cochlear implant users using direct intracochlear stimulation. The current study also investigated the correlation between the behavioral and electrophysiological frequency discrimination thresholds with the ACC in cochlear implant users. To investigated these research questions two experiments were conducted. The first experiment examined the correlation between the behavioral and electrophysiological frequency discrimination thresholds with the ACC, the second experiment correlation between the behavioral and electrophysiological amplitude discrimination thresholds with the ACC. In this discussion the results of both experiments will be discussed, as well as general limitations of the current study, suggestions for future research and clinical implications.

Before conducting the experiments, the following hypotheses were made;

1. A correlation between behavioral and electrophysiological thresholds of CI users is expected;
2. It is expected that behavioral and electrophysiological thresholds are positively correlated, with behavioral discrimination responses being more sensitive than electrophysiological obtained responses;
3. Even though various thresholds are predicted for individual subjects, it is believed that the findings will be comparable for all participants;
4. It is also expected that the ability to recognize the ACC will be more difficult when electrically-evoked auditory changes become smaller, being the result of decreasing ACC amplitudes;
5. In addition, it is also hypothesized that ACC (n1) latencies will increase when approaching discrimination threshold.

4.1 Experiment 1: Frequency discrimination (electrode combinations)

4.1.1 Behavioral results

For the results of the behavioral frequency discrimination task, data of two patients was excluded from the analyses (patient EACC002 and EACC008). Their exclusion is the results of an error in the Psyworks setup during the first few patients.

While evaluating the stimuli in Psyworks it was discovered that there was a bug in the software, this resulted in the loudness balancing data not correctly being integrated in the stimuli for the behavioral task and thus no electrode combinations were made. This bug was fixed and after doing so the resulting patients of the current study did note that there were frequency changes in the behavioral stimuli.

The interpolated mean of the behavioral threshold of the frequency changes was stimulus 3.1 (SD = 2.8, range = stimulus 1 to 10, N = 8). This is higher than the mean electrophysiological frequency discrimination threshold that was found. This is contradicting since in earlier research the electrophysiological threshold tends to be less sensitive than the behavioral threshold (He et al., 2012). However, there is a chance that the problem with the Psyworks software have influenced both the behavioral and electrophysiological results. The thresholds measured in the current study are not similar to the way the thresholds were measured in previous researches. The current study measures thresholds according to electrode combinations instead of exact frequencies, thus the current study cannot be compared to earlier researches.

4.1.2 Electrophysiological results

The interpolated mean of the electrophysiological frequency discrimination threshold of the was stimulus number 2.1 (SD = 0.63, range = stimulus 2 to 4, N = 10). The thresholds measured in the current study are not similar to the way the thresholds were measured in previous researches, thus the current study cannot be compared to earlier researches. The statistical analyses that were performed on the IPI and P-P amplitude were also not significant.

During the electrophysiological tasks, electrical stimulus artefacts from the CI hampers the EEG-recording. The artefact that was found was mostly visible in the second 400 ms of the 800 ms. The artefact was also very consistent and seemed to be a 10 Hertz (Hz) sinusoid that kept appearing in most stimuli (see figure 12 for an example of the artefact). This artefact was very inconvenient for determining the ACC as it interfered with the EEG-recording where the ACC was expected to appear. Multiple possible causes of the artefact were investigated:

First, it was investigated whether the artefact would reduce if the amplitude of the stimuli would be reduced, but this solution did not help reducing the artefact. Secondly, the influence of the radio frequency (RF) of the CI was investigated. After being advised by MED-EL experts, it was concluded that the RF could not have been an influence on the EEG-recording either. Next, the influence of the 50 Hz-notch filter on the EEG-recording was also investigated. It was speculated that the ringing of the notch filter could possibly result in the sinusoid like artefact that was found. But when turning the notch filter off the sinusoid artefact did not disappear and it got even more prominent. For other studies that struggle with a lot of non-sinusoid artefact, applying a stricter notch filter (e.g., 70 Hz) might possible help reducing the artefact, as long as it does not impact the detection of both the N1-P2 Complex and the ACC.

Finally, the influence of the stimulation rate of the CI on the EEG-recording was investigated. This turned out to be the problem that resulted in the sinusoid like artefact. The stimulation rate that was used during the electrophysiological measurements was 1000 pulses per second (pps). It is possible that this (rounded) stimulation rate influenced the EEG-recording because the default rate that was chosen obviously resulted in harmonics, causing the 10 Hz sinusoid artefact that interfered with the EEG-recording. When the stimulation rate was changed to 977 pps the sinusoid artefact disappeared (see figure 12). Although an electrical artefact was still visible in the EEG-recording, it did not interfere as badly with determining the ACC as the 10 Hz sinusoid did. So, concluding, the stimulation rate used in the CI can influence the EEG-recording for MED-EL CIs. In future research it might be examined whether this is the case for other CI brands too and to investigate what artefact reduction techniques exist to reduce such artefact.

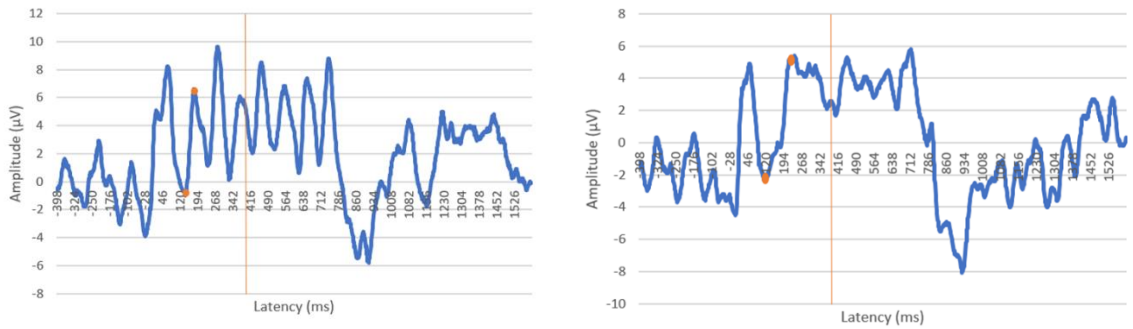


Figure 12: A typical example of the 10 Hz sinusoid artefact (left) when the control stimulus was presented. Furthermore, a typical example of the stimulation rate adjusted to 977 pps to get rid of the sinusoid artefact.

In some patients two patterns were also discovered; Firstly, it appeared that the amplitude of the N1-P2 Complex, but mostly the ACC increased when the second electrode of the electrode combination become more apical (thus the differences within the electrode combination increasing). This pattern could not be generalized to all patients, due to too much between patients' variation. This pattern also does not come forward in the mean P-P amplitude for all the electrode combinations in table 6. Similarly, the second pattern that was found was that the latency of the ACC increased when the electrode combination consisted of the control stimulus and a basal electrode (thus the difference within the electrode combination decreasing). This pattern could also not be generalized across patients, nor does it come forward in table 5. This once again might be due to too much variation between patients.

4.1.3 Relationship between behavioral and electrophysiological thresholds

The behavioral frequency discrimination thresholds differed from the electrophysiological thresholds. It was found that the electrophysiological threshold was lower, but this was not a significant difference. For almost all patients the behavioral and electrophysiological thresholds were equal. These results are better than expected for the electrophysiological thresholds using the ACC, but since no significant correlation nor difference was found between the behavioral and electrophysiological thresholds it is not possible to derive conclusions from these findings. But in future research this trend could be examined more, because more information on this could be valuable for the use of the ACC for auditory discrimination measurements in clinical practice.

4.1.4 Conclusion frequency discrimination (electrode combinations)

Experiment 1 showed that it was possible to determine objective frequency discrimination thresholds using the ACC. But no significant results were found on the correlation between the 3 electrode combinations used for the IPI nor the P-P amplitude. Furthermore, no significant different or correlation were found between the behavioral and electrophysiological frequency discrimination thresholds. It is difficult to discuss the usability and effectivity of the ACC as an objective auditory discrimination measurement without any significant results. For now, no clear statement can be made on the use of the ACC for objectively determining frequency discrimination thresholds (using direct stimulation), more research needs to be conducted to understand the usability and effectiveness of the ACC better.

4.2 Experiment 2: Amplitude combinations (amplitude combinations)

4.2.1 Behavioral results

Similar to experiment 1, also in the amplitude change experiment 2, data of two patients was excluded from the analyses (patient EACC002 and EACC008). For the behavioral lower threshold an extra third patient was excluded due to inconsistent responses during the behavioral amplitude discrimination task (patient EACC003), no clear lower threshold could be determined.

The interpolated mean of the lower behavioral threshold of the amplitude changes was stimulus 8 (SD = 1.6, range = stimulus 6 to 10, N = 7). The interpolated mean of the upper behavioral threshold of the amplitude changes was stimulus 2 (SD = 0.35, range = stimulus 2 to 3, N = 8). This is lower than the mean electrophysiological frequency discrimination threshold that was found. This is in line with the results of earlier research since in those findings the electrophysiological threshold tends to be less sensitive than the behavioral threshold. However, there still is a chance that the problem with the Psyworks software, among other issues with the methodology (see the general discussion), have influenced both

the behavioral and electrophysiological results. The thresholds measured in the current study are not similar to the way the thresholds were measured in previous researches, thus the current study cannot be compared to earlier researches.

4.2.2 Electrophysiological results

The interpolated mean of the lower electrophysiological threshold of the amplitude changes was stimulus 9.5 (SD = 1.08, range = stimulus 7 to 10, N = 10). The interpolated mean of the upper behavioral threshold of the amplitude changes was stimulus 2.1 (SD = 0.32, range = stimulus 2 to 3, N = 10). The thresholds measured in the current study are not similar to the way the thresholds were measured in previous researches, thus the current study cannot be compared to earlier researches. The statistical analyses that were performed on the IPI and P-P amplitude were also not significant.

During the electrophysiological amplitude discrimination task for the amplitude combinations the same 10 Hz sinusoid artefact was found in the EEG-recording as in experiment 1. This problem was solved in the same way as for experiment 1.

During the electrophysiological amplitude discrimination task, it was noted by patients that some stimuli appeared shorter than others. Once the researchers were alerted on this, they also found this in their electrophysiological responses. It is suggested that the stimuli with the decreasing amplitude combinations can be perceived as shorter than the other stimuli. This due to the fact that for example the amplitude 0.1 (stimulus 10) is so small that the patients simply cannot detect the second part of the stimulus, even though the differences between 0.8 and 0.1 is large. For some patients an ACC was found for stimulus 10, but in others it appeared to be more of an offset effect of the first 400 ms, because the second 400 ms were most likely not perceived. It can be discussed whether this offset effect is some form of the ACC or if it should really be considered as an offset effect.

4.2.3 Relationship between behavioral and electrophysiological thresholds

The behavioral amplitude discrimination thresholds differed from the electrophysiological thresholds. It was found that the electrophysiological threshold was higher, but this was not a significant difference for the lower amplitude discrimination thresholds (decreasing amplitude combinations). For the upper amplitude discrimination threshold (increasing amplitude combination) a significant difference was found between the behavioral and electrophysiological thresholds. The mean electrophysiological thresholds were more sensitive than the mean behavioral threshold. This once again shows the objective thresholds perform better than expected according to earlier research (Brown et al., 2008).

These results are better than expected for the electrophysiological thresholds using the ACC, but since no significant correlation nor difference was found between the lower behavioral and electrophysiological thresholds, so it is not possible to derive conclusions from these findings in a valid manner. But in future research this trend could be examined more thoroughly, because more information on this could be valuable for the use of the ACC for auditory discrimination measurements in clinical practice.

4.2.4 Conclusion amplitude discrimination (amplitude discrimination)

Experiment 2 showed that it was possible to determine objective frequency discrimination thresholds using the ACC. But no significant results were found on the correlation between the 3 electrode combinations used for the IPI nor the P-P amplitude. Furthermore, no significant different or correlation were found between the lower behavioral and electrophysiological amplitude discrimination thresholds. Only a significant difference was found for the upper amplitude discrimination thresholds, but not for their correlation. It is

difficult to discuss the clinical application and effectivity of the ACC as an objective auditory discrimination measurement without any significant results. In the general discussion possible reasons for the non-significant results are discussed. For now, no clear statement can be made on the use of the ACC for objectively determining frequency discrimination thresholds (using direct stimulation), more research needs to be conducted to understand the usability and effectiveness of the ACC better.

4.3 General discussion

4.3.1 Possible effects of the methodology on the results

4.3.1.1 Determining the ACC visually in the electrophysiological data

In this study, the occurrence of ACC was identified visually, which can be arbitrary. Naturally, the approximate latencies of each peak for both the ACC and (P1)-N1-P2 Complex were taken into account when determining their occurrence, but it might be argued that a more objective approach to detecting the occurrence of the ACC would have been preferable. This, as only an objective method guarantees that the same standards are applied across patients when estimating discrimination thresholds.

4.3.1.2 Effect of duration and active attention

When patients came in for the current study the durations of both experiments would approximately be three hours, including breaks. Nonetheless, this is quite a long time for experiments to be focused and seated for the patients. This was visible in their behavior near the end of experiment 2. Some patients started to get restless or fidgety during the EEG recording of experiment 2.

Moreover, during the electrophysiological measurements in both experiments 1 and 2 patients were asked to close their eyes while they actively listened to the stimuli. Even though the patients were warned that they were not allowed to fall asleep, some patients did get sleepy during the electrophysiological measurements and one patient almost dozed off during the last few stimuli. This might suggest that even though as many breaks as needed were provided, that the overall duration of both experiments was too long and that perhaps the tasks were asking more than expected of the patients. What is described in the above might have possibly influenced the EEG recordings of both experiments.

Furthermore, patients in this study were instructed to pay attention to the stimuli during the EEG recordings, which, as demonstrated by Martin (2007), causes ACCs to become more obvious in the EEG recording (e.g., the amplitude increases in contrast to when attention is not paid to the stimuli). Other research (such as Vonck et al., 2021) permitted participants to read or watch a quiet film to divert their attention from the stimuli being presented.

The impact of duration and active attention on ACC threshold estimate and the relationship between behavioral and electrophysiological thresholds may be further explored in future research. This is noteworthy, because it is doubtful that challenging-to-test individuals (e.g., babies, for whom the ACC is likely most useful as an objective indicator of auditory discrimination) will be able to concentrate on the task, thus discovering if attention matters while conducting ACC research is valuable information.

4.3.1.3 Effect of the explanation of the behavioral measurements

While the patients of the current study were tested it appeared that the behavioral measurements were perceived as difficult by the patients. For the first few patients this might have happened due to poor explanation of the behavioral measurements, but later on clear explanations were written for the researchers to use, including cards with explanations for the patients to tend to before/during the experiment. Thus, confusion about the behavioral tasks should have been reduced for later patients.

Unfortunately, even some of the later patients expressed confusion about the behavioral measurements. This could have possibly influenced the results of the behavioral measurements, e.g., resulting in more false positives. This cannot be stated for sure nor checked since the behavioral measurements are subjective tasks, thus answers are not per definition not right or wrong.

4.3.1.4 Effect of using a single interval test for estimating the behavioral discrimination thresholds

Instead of using the more frequently used three alternative forced choice task (3AFC task), a single-interval test (SIAM) was used to estimate behavioral threshold. The single-interval task has a number of benefits that should be mentioned.

First of all, compared to the 3AFC task, the single-interval test is believed to have less cognitive strain. Because it is a direct comparison, it is simpler and is believed to need less working memory (Kaernbach, 1990).

Secondly, when adopting a 3AFC task, the stimuli are different from those utilized in the single-interval test and the ACC EEG-recording. The thresholds determined using a single-interval test and an ACC recording are anticipated to be more closely connected than thresholds obtained using a 3AFC task and an ACC recording.

Thirdly, according to Shepherd et al., (2011) the single interval task is statistically speaking the easiest to process, as well as the least biased by the forced choice alternatives.

Finally, the single-interval test is possibly more ecologically valid than the 3AFC task since variations exist within the stimuli, making it more equivalent to auditory perception that CI users experience on a daily basis (Won et al., 2011).

4.3.1.5 Number of participants

The results of the current study could have possibly been improved with more patients. This would have increased the statistical analysis' power and shed more light on how the observed discriminating thresholds for behavioral and electrophysiological stimuli relate to one another. According to the normal distribution (Altman & Bland., 1995) that is often used in statistics, a patient group of at least 30 patients would be preferable. In the limited patient population outlier results can possibly have a significant impact on the outcomes and their variability. This significant amount of variation could probably also be apparent in larger groups of patients, raising doubts about the benefits of including more people. However, in future research having more patients would most likely be more ideal.

4.3.1.6 Intracochlear stimulation of the CI users

In this study, intracochlear stimulation of the CI users was used. This was decided to minimize inter-subject differences in the CI settings, for example in the current study the strategy in all the CIs was adjusted to HDCIS. Furthermore, because of the creation of the safety map all patients THRs and MCLs were measured before the experiment, it is assumed that the fitting of all CI users was optimal during the experiments. Another reason to use intracochlear stimulation was to possibly minimize the artefact coming from the CI in the EEG recording, but it is unclear whether this is the case.

It has to be noted that intracochlear stimulation possibly also has disadvantages, since intracochlear stimulation is not an ecologically valid method (Martin, 2007). Intracochlear stimulation is an unrealistic situation in comparison to how CI users experience sound on a daily basis; if this needs to be achieved then perhaps free field stimulation would be preferred. It appears that as of currently there is no preference for intracochlear or free field stimulation in research, because both methods have advantages and disadvantages.

4.3.2 Future research

4.3.2.1 The ACC and stimulation rate discrimination

For future research, it would be interesting to do a similar study with stimuli in which a change of stimulation rate (pulses per second, pps) occurs. This is a different way to alter the results and the effect of the stimulation rate on the ACC can possibly give new insights in the behavioral and electrophysiological discrimination thresholds of CI users and most of all the credibility of the ACC as an objective auditory discrimination measurement.

4.3.2.2 The ACC thresholds and the correlation to speech perception

It may be considered to redirect attention to the relationship between electrophysiological discrimination thresholds and speech perception (particularly in CI users) in future research. This is only possible after the relationship between behavioral and ACC electrophysiological discrimination thresholds is better understood.

Currently the majority of research examining the correlation between (in CI users) auditory discrimination thresholds and speech perception have focused on behavioral auditory discrimination (Liang et al., 2019). More research into this linkage would be helpful, because it has not been thoroughly examined yet in many studies.

4.3.2.3 The ACC in children

Once there is a clear understanding of the relationship between behavioral and ACC electrophysiological discrimination thresholds in adults, it may be considered to determine the credibility and usability of the ACC as an objective auditory discrimination measurement in children. Until now, the ACC has barely been examined in children (Martinez et al., 2013). The premise that the morphology of waveforms in children is not equal to those of adults until puberty should be taken into consideration while studying auditory evoked potentials while doing such research as stated above (Pasman, Rotteveel, Maassen, & Visco, 1999).

4.3.2.4 The use of artefact reduction techniques

In the introduction of the current study the use of artefact reduction techniques such, as ICA and PCA, was briefly discussed. As previously mentioned, electrical artefacts can be an issue when stimulating CI users, since they might interfere with the auditory evoked potential of interest, making it difficult to tell whether the recorded response is neural or simply a reflection of the artefact (Martin, 2007). With the current findings of possible influence of the stimulation rate of the stimuli on the EEG-recording (resulting in sinusoid like artefact), it might be important to continue researching ways to reduce (CI) artefact in a useful way, without losing too much information of your auditory evoked potentials.

4.3.2.5 Clinical implications

As of current, the use of the ACC as an objective measure of auditory discrimination still needs to be examined better. Currently it is unclear whether the ACC can possibly be a clinical objective auditory discrimination measurement that can be used in daily clinical practice. The current study was not able to give new insights to this question.

To possibly find useful insights the experiment duration of the current study and future research should be reduced in duration and the issues in methodology of the current study should be improved and reconsidered.

Furthermore, the linkage between behavioral and ACC electrophysiological thresholds would most likely need to be determined with explicit guidelines for thresholds for the ACC to be useful in clinical practice.

5. Conclusion

Clinical application and effectiveness of the ACC as an objective measure of auditory discrimination cannot be evaluated properly based on the results of the current study. The experiments revealed that it was possible to record the electrophysiological frequency and amplitude discrimination thresholds using the ACC, although no significant results were found on the correlation between the electrophysiological and behavioral discrimination thresholds. Only a significant effect was found for the correlation between the behavioral and electrophysiological threshold of the upper amplitude discrimination thresholds (increasing amplitude change). Moreover, the results differed considerably between patients, which limits the clinical value of the results about the ACC of the current study.

Overall, the electrophysiological results were promising for the applicability of the ACC in clinical practice, but lacks statistical significance. As of current the use of the ACC for measuring frequency discrimination and amplitude discrimination in cochlear implant users with intracochlear stimulation will need more research to investigate the clinical application of the ACC. Issues of the current methodology can be taken into consideration, as well as the future research suggestions.

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Appendices

APPENDIX A: EXPERIMENT PROTOCOL (INC. MAESTRO 9 SOFTWARE AND PSYWORKS SOFTWARE)

N.B. the general overlay of this protocol was made by Andreas Krenmayr

OVERVIEW

The generator genRib in PsyWork requires a safety map generated with MAESTRO 9. This safety map does not correspond to a regular fitting map of an audio processor, but simply defines the maximum charge per electrode that shall be applied during the experiment. The following describes how to create such a safety map in MAESTRO 9.

Global parts of the experiment:

- Preparation research
- Part A: Creating a safety map for the patient
- Part B: Loudness balancing task
- Part C: Frequency discrimination task behavioral
- Part D: Frequency discrimination task based on EEG
- Part E: Amplitude discrimination task behavioral
- Part F: Amplitude discrimination task using EEG
- Part G: Administration; think of informed consent, travel allowance, gift voucher, etc.

Preparation research

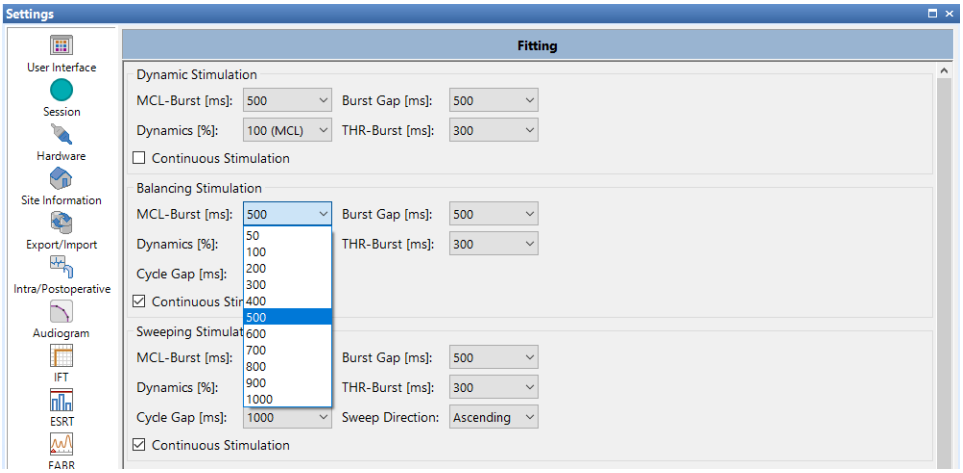
- Prepare laptop and EEG setup
- Picking up the patient in the waiting room
- Offer drink / cookie
- PLEASE NOTE wearing a mouth cap / service clothing / gloves and disinfecting the hands / setup
- Check whether the patient has brought the informed consent and if not, give a new one to sign
- **Before starting part A, ask whether the patient is ready to start, if they still want to go to the toilet, for example**
- **After each section, ask if there is a need for a break**
- **Indicate that if the research becomes uncomfortable, they must/be able to indicate this immediately and that you can always stop**

Part A: Creating a safety map for the patient

Maestro 9: (when opening MAESTRO 9, make sure to wait to log in until the program is fully loaded (see yellow loading bar), while logging in click on the correct username and fill in your password)

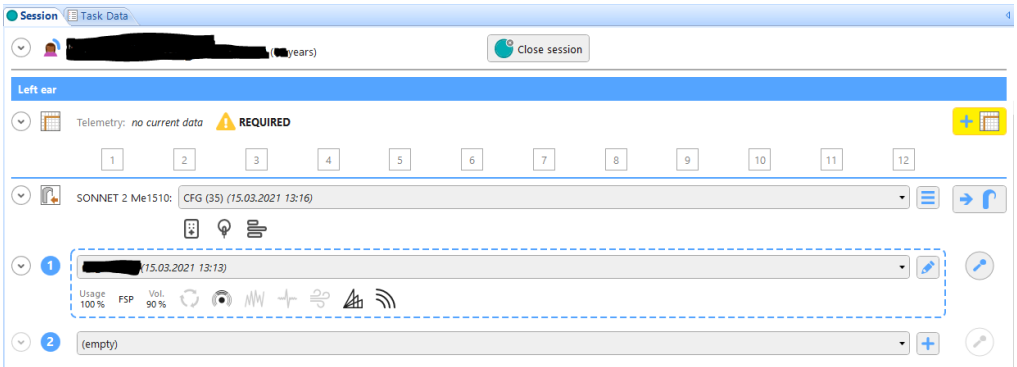
Global settings (one time only)

- Click on the menu Settings > settings management > Fitting > Dynamic & Balancing Stimulation
  set MCL Burst: 500 ms



Creating a safety map (each subject)

- Create or open the appropriate patient data for the subject or import data from the subject's audio processor.
- Connect the patient's processor to Socket 1 of the MAX box
- Connect a MAX coil or MAX-S (Synchrony implants) coil to Socket 2 on the MAX box (Telemetry socket)
- Perform an IFT > check which patients have a Synchrony so the proper coil is used for the telemetry (MAX-S coil)



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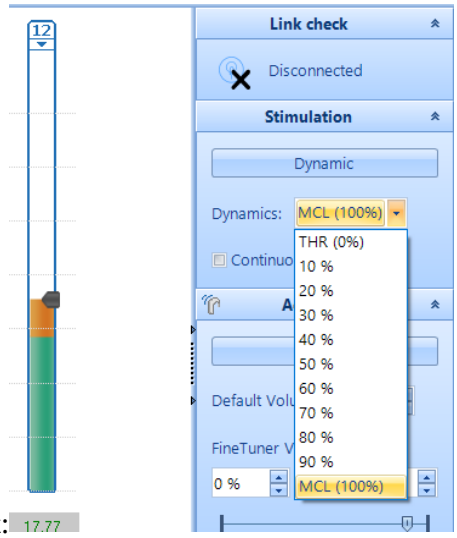
- Click save and close
- Create a new fitting MAP



- In tab *Strategy*, set: 17.77
    - *strategy* to HDCIS
    - Use *reduced stimulation rate*: an applicable rate for the study (eg 1000 pps)
- In the tab *Levels*:
    - Ensure that Stimulation > Dynamics is set to ‘MCL (100%)’
    - Measure MCL on the electrodes used in the study
    - If required, measure THR on the electrodes used in the study
- Save the fitting MAP
- Click on *Data-> Export*. Select *fitting MAP task* to export the data. Select *xml format*.
- Close Maestro

Part B: Loudness balancing task

Psyworks:

- Click menu Method selection/Method of adjustment
- Click menu Presets/Electrode loudness matching
- Click menu Presets/Settings…
- In the tab ‘Generator/player’, panel ‘Generator’ (left) specify the appropriate electrode number of the reference electrode
- save the generator preset as ‘Reference_ppnumber’ if the electrode number has changed, so the original reference electrode is not overruled and can be used as a template
    - If a preset is not saved by accident it will be saved under presetOTF by psyworks, if you want to change the name you’ll have to open the preset, change something to be able to save it and then change it back to the original that was unsaved to save it the correct way. You cannot save if you don’t change settings.
    - N.B. when psyworks is loading information or presets please wait until the progress bar states ‘loaded’ or ‘done’ if settings are changed or if programs are run while the presets or info are still loading the software might crash
- In the tab ‘Method’ ensure that all electrodes apart from the reference electrode are listed as ‘Parameter values for comparison stimuli’ the electrode parameters can be changed by typing new ones in the square where the electrodes are shown (bottom right of the screen; here you can also erase electrodes that are deactivated in the implant of the participants or type only the electrodes that you need for your study if you don’t need all 12)
- Save the method preset as ‘Electrode loudness matching _ppnumber’ , so the original reference electrode is not overruled and can be used as a template
- Click the ‘Ok’ button
- Click the ‘Start’ button and perform the measurement when you get a pop-up that asks if you want to specify extra participant information it is advised to click yes and fill in at least the experiment ID of the participant (N.B. electrodes around balanced from 1-12 but randomly, but the results are shown from 1-12. If a specific order is required for the balancing then this can be done by checking the randomize box in the method section.)
    - N.B. when a participant reaches the 100% of the MCL of the safety map while balancing 2 electrodes the + or – buttons will be deactivated so they will not be able to overstimulate or hurt themselves if this is the case it means that the safety map is not performed correctly, the charge of the electrodes is most likely incorrect in order to have good balanced electrodes please redo the safety map.
- After balancing all electrodes, a ‘save as’ dialog is displayed to save the balanced Stimulus XML file. Store it within the subject directory, it will be used in experiment 1b.
- If prompted (only after the first run) specify where to store the data file for all experiments.
- Click on the last run number

- Click 'Store as balancing file'
- Click 'Absolute values'
- Click 'All' (PsyWorks 6); Note: reference stimulus shall be included
- Store file with the subject ID in the file name it is smart if you have pre-made participant folders so you can save data of each participant separately

PART C: Experiment 1a: Electrode combination - behavioral test

- Go to the saved XML file of the patient from the loudness balancing and run this through the add on of the Psyworks program (see MEDEL directory)
- Click Menu Method selection/Method of constant stimuli
- Click Menu Presets/Electrode combination
- Click Menu Presets/Settings…
- Go to the 'Method' tab, in the section 'Stimulus XML file' click on the button 'Load file(s)' and select the updated stimulus XML file created after the loudness matching experiment in Experiment 1.
- Click on 'Save preset' remove the asterisk and overwrite the existing preset
- Click 'OK'
- Click 'Start' and run the experiment
- After the experiment export the data via menu Data/Export data.

PART D: Experiment 1b: Electrode combination – electrophysiological measurement

- Click on method of adjusment
- Click menu Extras/Present stimulus
- Click menu options and check whether Apply balancing data is checked (has to be checked), load the appropriate balancing file if prompted
- Select generator genRib (+ check if playRib has been selected)
- Select generator preset: Electrode pairs
- Specify the intended electrode pair as 'Electrode number' (e.g. 5 1)
- Note that when duration is set to 500 ms the overall stimulation is 1000 ms
- Specify the number of stimuli as 'No. Repetitions' on the top left below the 'Play stimulus button'
- Specify the 'Repetition gap (s)' as 0.9 1.1. This will ensure that there is a jitter between stimuli, if no jitter is necessary for your study, only specifying one gap duration will suffice.
- Click 'Present stimulus', N.B. if the presenting of stimuli needs to be stopped or paused press the stop button at the top of the screen
- If a warning dialog regarding the balancing file is displayed check the 'Do not show again' option and close the dialog

PART E: Experiment 2a: Amplitude combinations – behavioral measurement

- Click on method of constant stimuli
- Click Menu Extras/Create stimulus XML file
- Select generator: genRib
- Select Generator preset: Amplitude pairs
- In the section 'Parameter values' (right side) select Parameter 'Amplitude'
- In the columns 'Value X' type the amplitude pairs to be tested. Press the 'Tab' key or the 'Insert column' button to add columns to the table as required. Each cell shall contain two values.

- Example:

Parameter	Value 1		Value 2		Value 3	
amplitude	0.5	0.5	0.5	0.6	0.5	0.7

  - set the 'Multiple electrodes mode' to 'Sequential'.
    - Note: this parameter is disabled (grey) when you start the tool, but it will be enabled as soon as you enter two values for 'amplitude'. So first enter the amplitudes, then set the 'Multiple electrodes' parameter.
  - In the 'Save stimulus XML files' section click 'By column' and store the file in the subject data directory.
  - Click Quit
  - Click Menu Method selection/Method of constant stimuli
  - Click Menu Presets/Amplitude combination
  - Click Menu Presets/Settings
  - Go to the 'Method' tab, in the section 'Stimulus XML file' click on the button 'Load file(s)' and select the stimulus XML file created before.
  - Click on 'Save preset' remove the asterisk and overwrite the existing preset
  - Click 'OK'
  - Click 'Start' and run the experiment
  - After the experiment export the data via menu Data/Export data.

PART F: Experiment 2b: Amplitude combinations – electrophysiological measurement

- Click menu Extras/Present stimulus
- In the menu options/Apply balancing data check if this is unchecked, balancing data is not necessary since you'll decide what the amplitudes will be. (N.B. amplitude range is from 0-1 where 1 is the MCL of the safety map)
- Select generator genRib + check if playRib has been selected
- Select generator preset: Amplitude pairs
- Specify the intended electrode
- Specify the two amplitudes you want to use for the electrode (amplitude range 0-1)
- Note that when duration is set to 500 ms the overall stimulation is 1000 ms
- Specify the number of stimuli as 'Repetitions'
- Specify the 'Repetition gap (s)' as 0.9 1.1. This will ensure that there is a jitter between stimuli, if no jitter is necessary for your study, only specifying one gap duration will suffice.
- Click 'Present stimulus', N.B. if the presenting of stimuli needs to be stopped or paused press the stop button at the top of the screen
- If a warning dialog regarding the balancing file is displayed check the 'Do not show again' option and close the dialog

PART G: Administration; think of informed consent, travel allowance, gift voucher, etc.

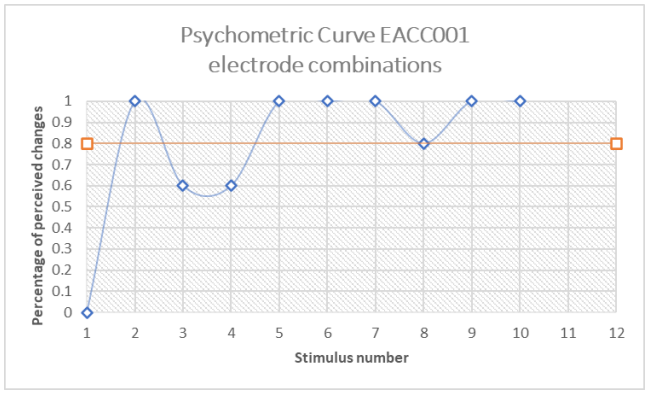
- Ask if they want to know more about this research in addition to the standard debriefing when the thesis is finished
- arrange the travel allowance → from petrol to parking fees; if necessary, give them a reply envelope for the parking costs
- Give the gift voucher as a token of appreciation for participating
- Walk with the patients to the exit / or show them the way if they want to go to the restaurant, for example

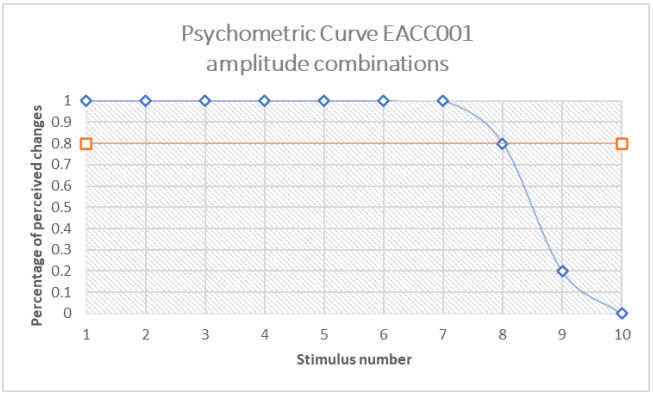
EXTRA: Experiment 3: Stimulation rate changes (not conducted yet)

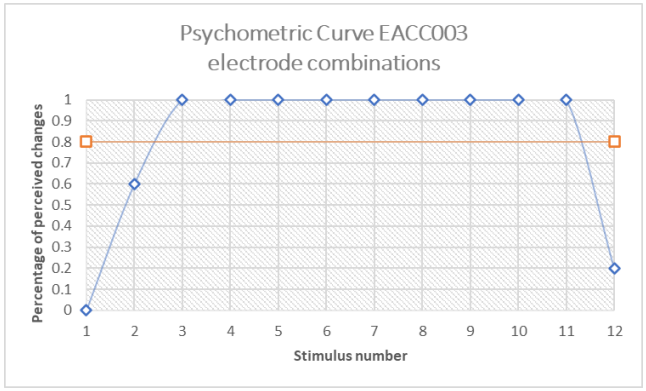
- Click menu Method selection/Method of adjustment

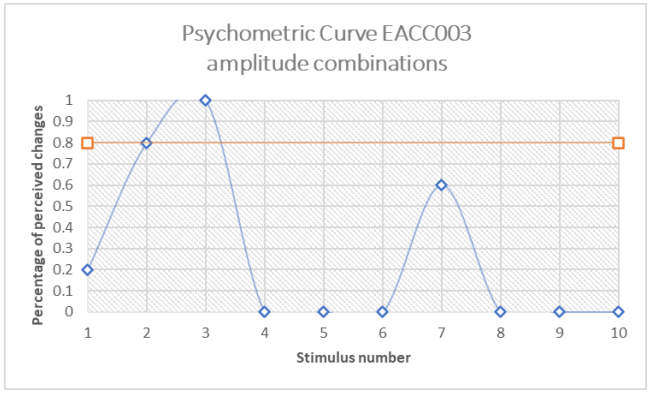
- Click menu Presets/Rate loudness balancing
- Click menu Presets/Settings…
- In the tab ‘Generator/player’, panel ‘Generator’ (left) specify the appropriate electrode number of the reference electrode
- save the generator preset as ‘reference’ if the electrode number has changed
- In the tab ‘Method’ ensure that all electrodes apart from the reference electrode are listed as ‘Parameter values for comparison stimuli’
- Save the method preset as ‘Electrode loudness balancing’
- Click the ‘Ok’ button
- Click the ‘Start’ button and perform the measurement
- Click on the last run number
- Click 'Store as balancing file'
- Click 'Absolute values'
- Click 'Yes' (PsyWorks 5) or 'All' (PsyWorks 6); Note: reference stimulus shall be included
- Store file with the subject ID in the file name
- Click menu Extras/Present stimulus
- Click menu options/Apply balancing data (has to be checked), load the appropriate balancing file if prompted
- Select generator genRib
- Select generator preset: Electrode pairs
- Specify the intended electrode pair as ‘Electrode number’ (e.g. 6 1)
- Note that when duration is set to 500 ms
- Specify the number of stimuli as ‘Repetitions’
- Click ‘Present stimulus’

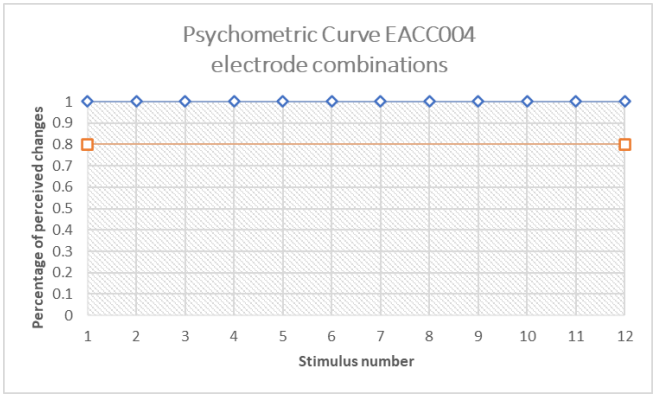
APPENDIX B: PSYCHOMETRIC CURVES FOR ALL INCLUDED PATIENTS (N = 8)

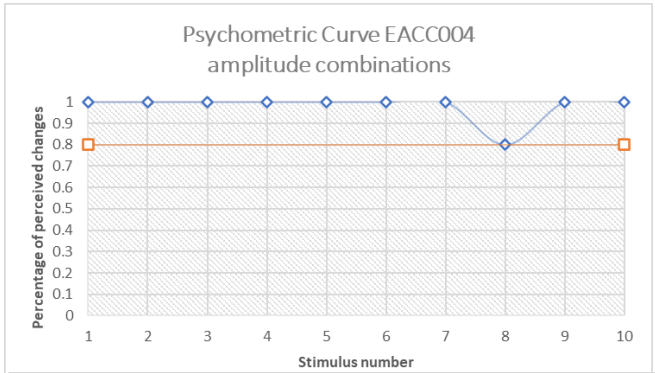


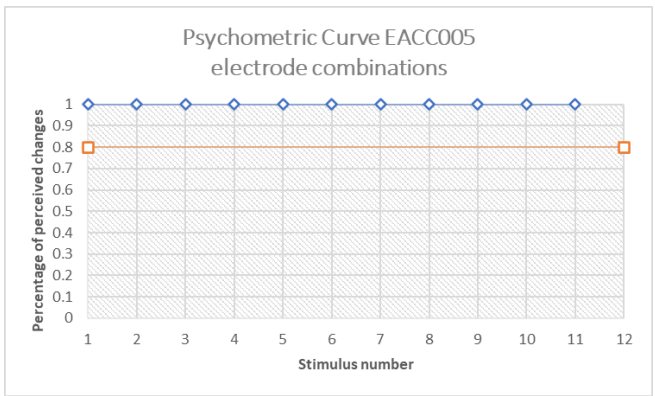


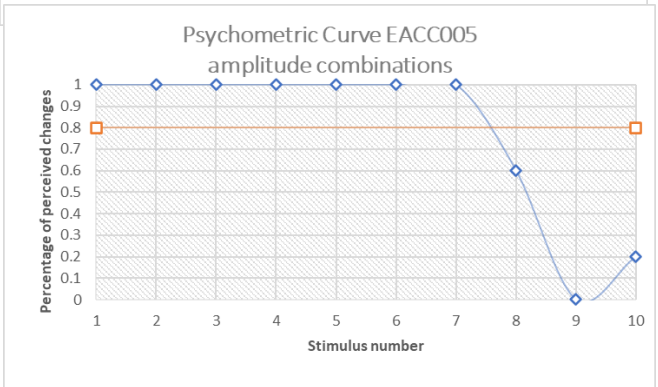


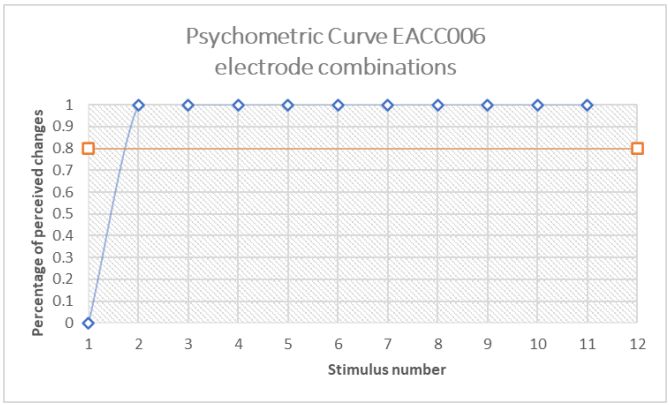


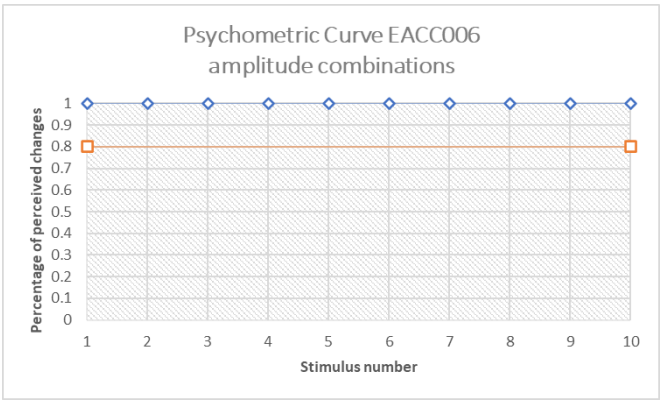


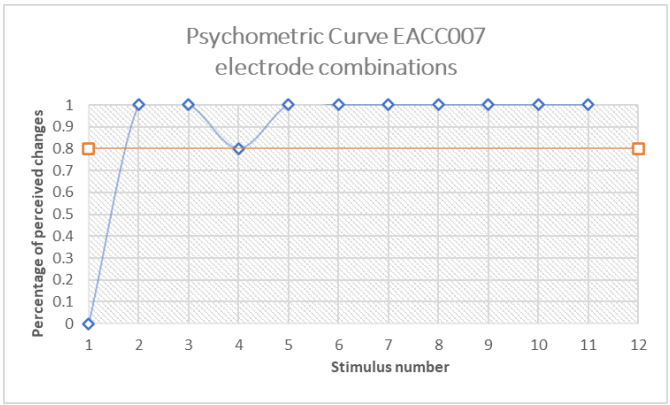


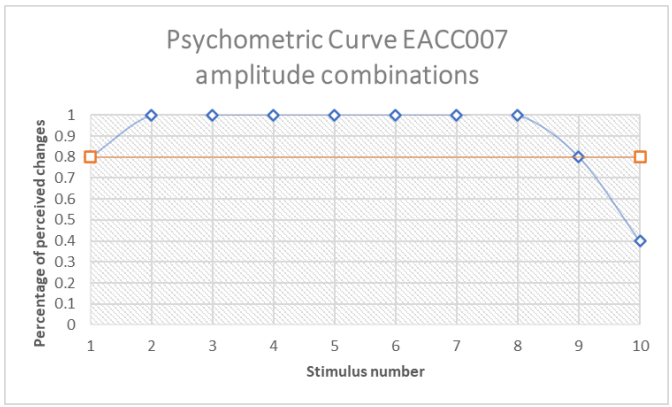


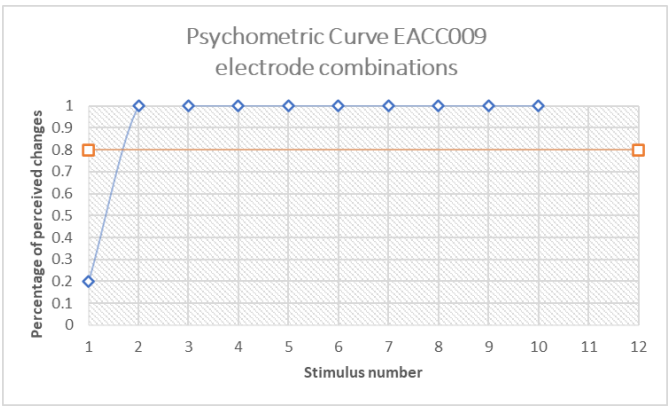


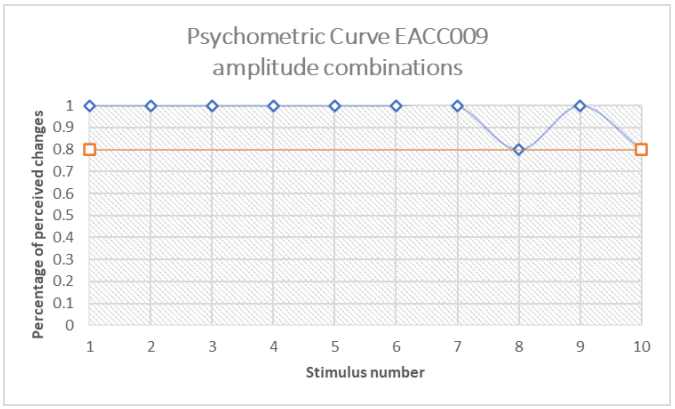

Psychometric Curve EACC006
electrode combinations
Percentage of perceived changes
Stimulus number

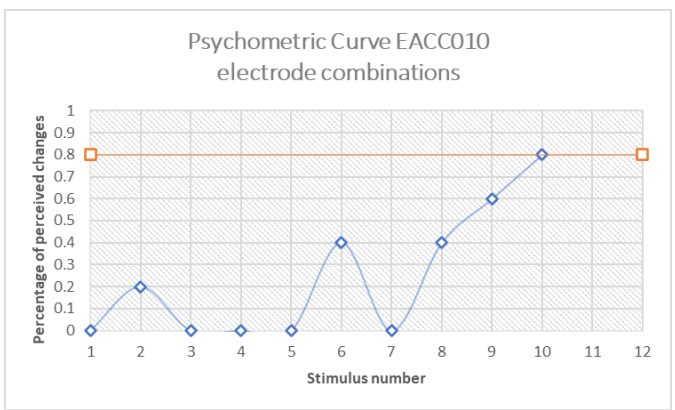

Psychometric Curve EACC006
amplitude combinations
Percentage of perceived changes
Stimulus number

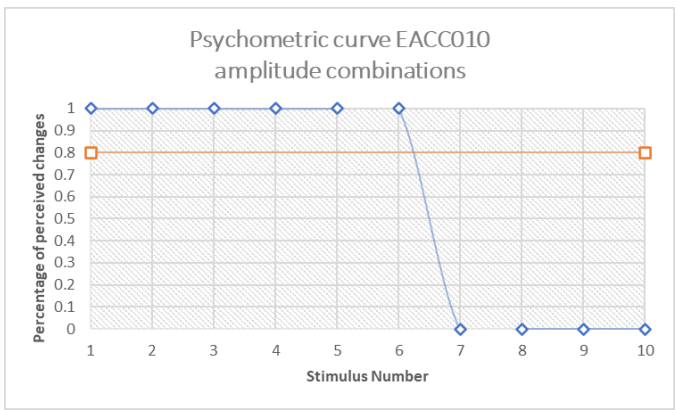

Psychometric Curve EACC007
electrode combinations
Percentage of perceived changes
Stimulus number


Psychometric Curve EACC007
amplitude combinations
Percentage of perceived changes
Stimulus number

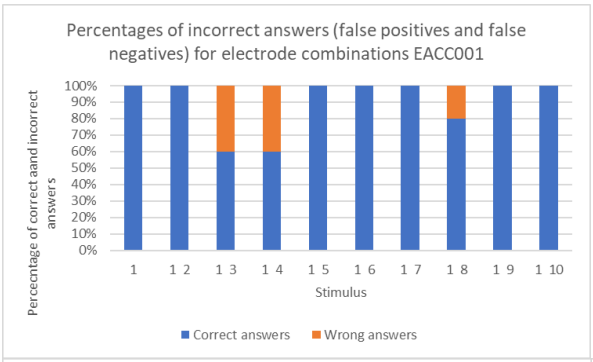

Psychometric Curve EACC009
electrode combinations
Percentage of perceived changes
Stimulus number

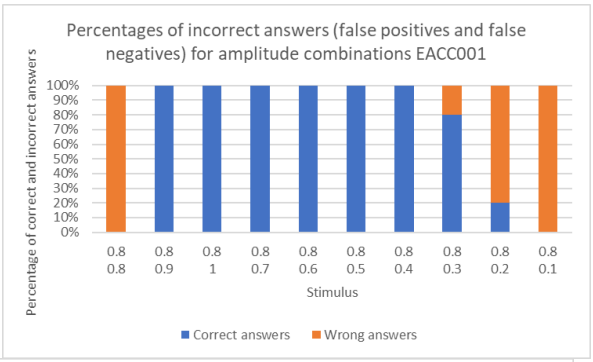

Psychometric Curve EACC009
amplitude combinations
Percentage of perceived changes
Stimulus number

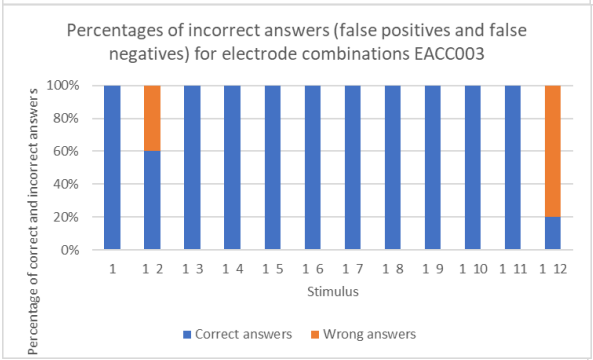

Psychometric Curve EACC010
electrode combinations
Percentage of perceived changes
Stimulus number

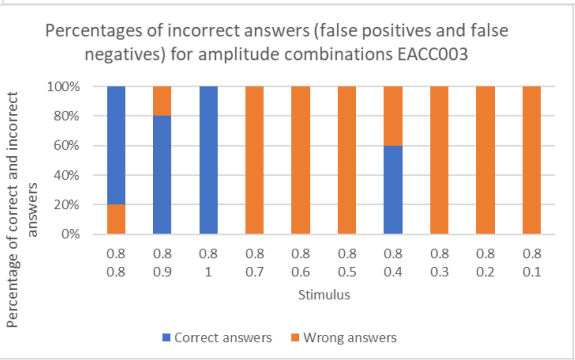

Psychometric curve EACC010
amplitude combinations
Percentage of perceived changes
Stimulus Number

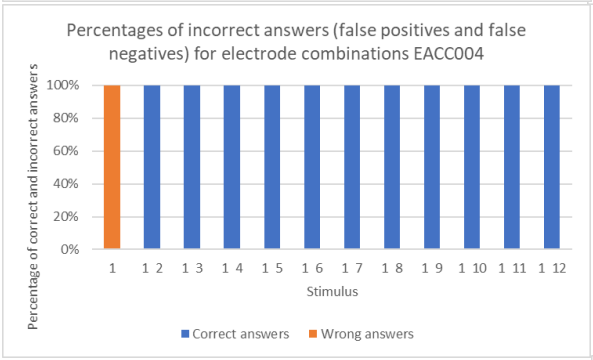
APPENDIX C: PERCENTAGES OF CORRECT AND INCORRECT ANSWERS OF THE BEHAVIORAL EXPERIMENTS FOR ALL INCLUDED PATIENTS (N = 8)

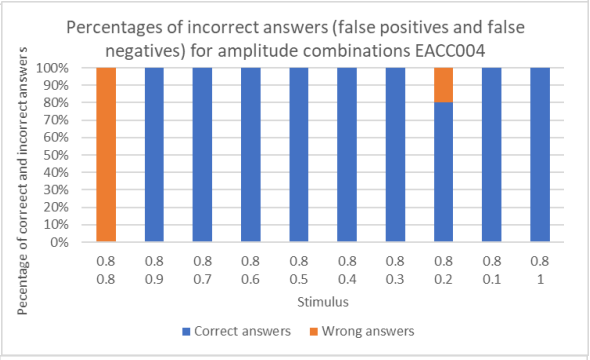


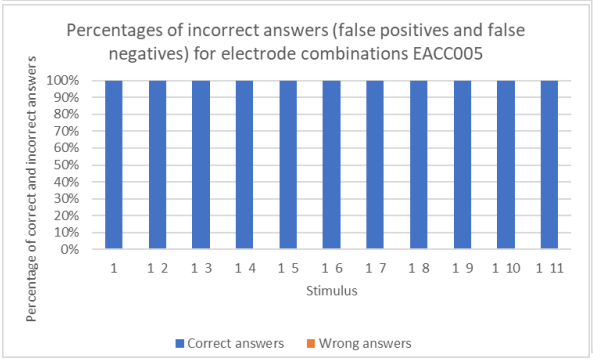


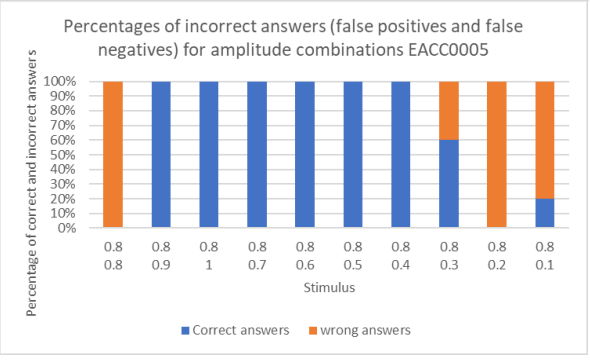


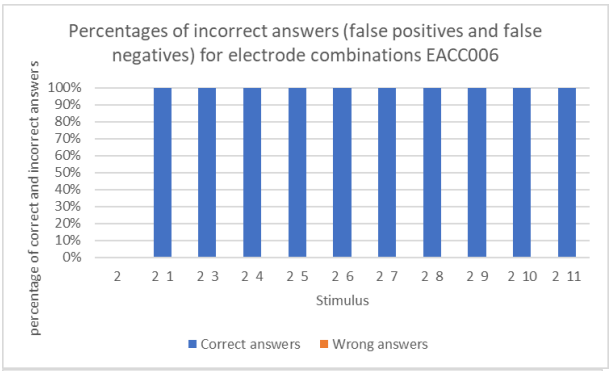


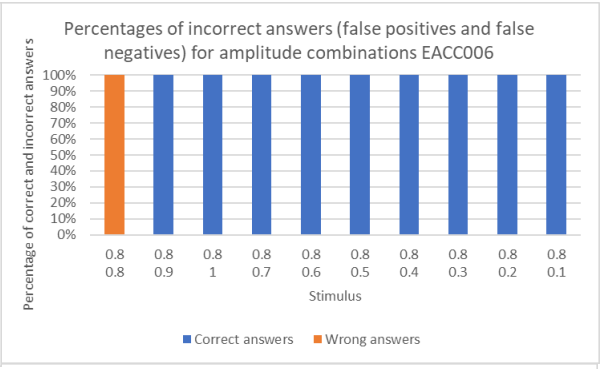


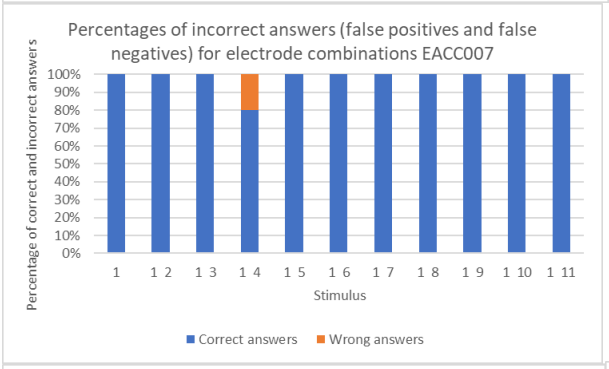


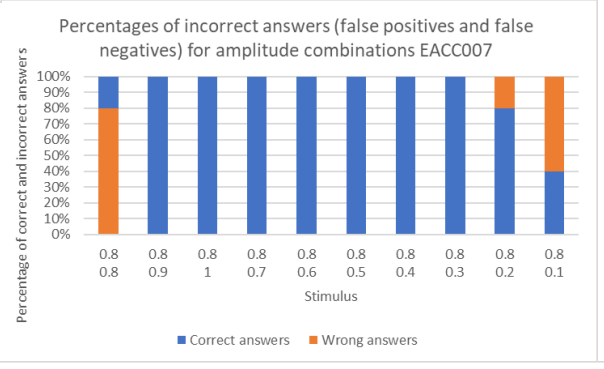


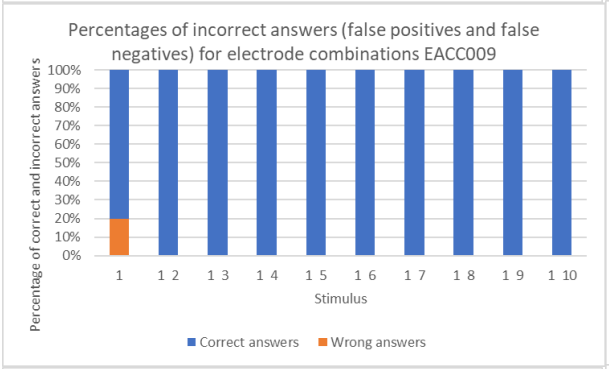



Percentages of incorrect answers (false positives and false negatives) for electrode combinations EACC006
percentage of correct and incorrect answers
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2
2 1
2 3
2 4
2 5
2 6
2 7
2 8
2 9
2 10
2 11
Stimulus
Correct answers
Wrong answers


Percentages of incorrect answers (false positives and false negatives) for amplitude combinations EACC006
Percentage of correct and incorrect answers
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0.8 0.8
0.8 0.9
0.8 1
0.8 0.7
0.8 0.6
0.8 0.5
0.8 0.4
0.8 0.3
0.8 0.2
0.8 0.1
Stimulus
Correct answers
Wrong answers


Percentages of incorrect answers (false positives and false negatives) for electrode combinations EACC007
Percentage of correct and incorrect answers
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1
1 2
1 3
1 4
1 5
1 6
1 7
1 8
1 9
1 10
1 11
Stimulus
Correct answers
Wrong answers


Percentages of incorrect answers (false positives and false negatives) for amplitude combinations EACC007
Percentage of correct and incorrect answers
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0.8 0.8
0.8 0.9
0.8 1
0.8 0.7
0.8 0.6
0.8 0.5
0.8 0.4
0.8 0.3
0.8 0.2
0.8 0.1
Stimulus
Correct answers
Wrong answers


Percentages of incorrect answers (false positives and false negatives) for electrode combinations EACC009
Percentage of correct and incorrect answers
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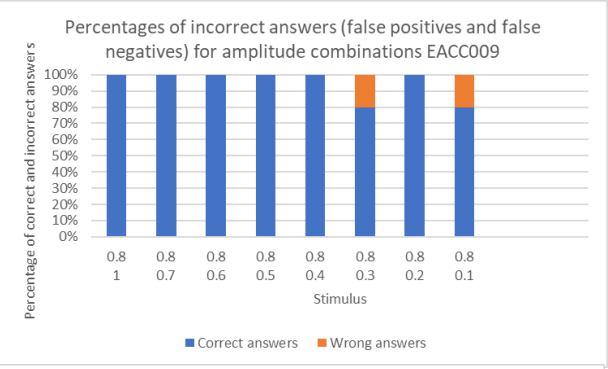
80%
70%
60%
50%
40%
30%
20%
10%
0%
1
1 2
1 3
1 4
1 5
1 6
1 7
1 8
1 9
1 10
Stimulus
Correct answers
Wrong answers


Percentages of incorrect answers (false positives and false negatives) for amplitude combinations EACC009
Percentage of correct and incorrect answers
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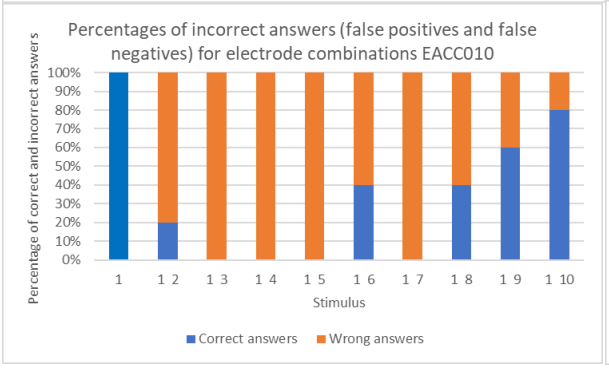
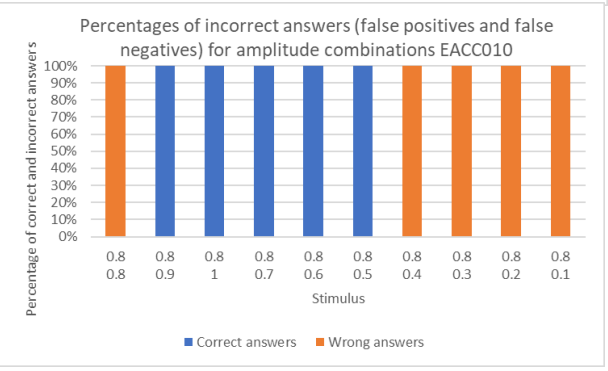
80%
70%
60%
50%
40%
30%
20%
10%
0%
0.8 1
0.8 0.7
0.8 0.6
0.8 0.5
0.8 0.4
0.8 0.3
0.8 0.2
0.8 0.1
Stimulus
Correct answers
Wrong answers


Percentages of incorrect answers (false positives and false negatives) for electrode combinations EACC010
Percentage of correct and incorrect answers
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1
1 2
1 3
1 4
1 5
1 6
1 7
1 8
1 9
1 10
Stimulus
Correct answers
Wrong answers


Percentages of incorrect answers (false positives and false negatives) for amplitude combinations EACC010
Percentage of correct and incorrect answers
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0.8 0.8
0.8 0.9
0.8 1
0.8 0.7
0.8 0.6
0.8 0.5
0.8 0.4
0.8 0.3
0.8 0.2
0.8 0.1
Stimulus
Correct answers
Wrong answers

APPENDIX D: OUTPUT OF ALL THE STATISTICAL ANALYSES OF BOTH EXPERIMENTS

Table A.1: Fixed effects the linear mixed regression model of the IPI of the electrophysiological frequency discrimination

Predictors	Estimate	Std.error	df	t value	p-value
Intercept	389.60	20.30	18.00	19.19	$p < 0.001$
1-2	13.29	25.32	18.00	0.53	0.61
1-6	26.69	26.58	18.00	1.00	0.33

Table A.2: Post hoc contrasts between the three tested electrode combinations

Predictors	Estimate	Std.error	df	t-ratio	p-value
1-10 vs. 1-2	-13.3	26.4	12.8	-0.504	0.87
1-10 vs. 1-6	-26.7	28.2	15.0	-0.946	0.62
1-2 vs. 1-6	-13.4	23.5	12.4	-0.571	0.84

Table A.3: All outputs of the paired Wilcoxon signed ranked tests for the difference between the IPI and the expected 400 ms.

Stimulus	V	p-value
1-2	20.5	0.86
1-6	16	0.80
1-10	3	0.58

Table B.1: Fixed effects the linear mixed regression model of the IPI of the electrophysiological amplitude discrimination

Predictors	Estimate	Std.error	df	t value	p-value
Intercept	405.80	8.40	17.00	48.292	$p < 0.001$
0.8-0.1	-11.09	13.10	17.00	-0.847	0.41
0.8-0.5	10.53	17.50	17.00	0.602	0.55

Table B.2: Post hoc contrasts between the three tested amplitude combinations

Predictors	Estimate	Std.error	df	t-ratio	p-value
0.8-1.0 vs. 0.8-0.1	11.1	13.3	10.8	0.832	0.69
0.8-1.0 vs. 0.8-0.5	-10.5	19.1	14.4	-0.551	0.85
0.8-0.1 vs. 0.8-0.5	-21.6	19.7	13.0	-1.095	0.53

Table B.3: All outputs of the paired Wilcoxon signed ranked tests for the difference between the IPI and the expected 400 ms

Stimulus	V	p-value
0.8-1.0	34	0.56
0.8-0.1	8.5	0.75
0.8-0.5	4	0.75

Table C.1: Fixed effects the linear mixed regression model of the P-P amplitude of the electrophysiological frequency discrimination

Predictors	Estimate	Std.error	df	t value	p-value
Intercept	6.13	2.74	14.81	2.24	$p < 0.001$
1-2	-3.79	1.69	8.52	-2.24	0.053
1-6	-0.28	1.99	12.45	-0.14	0.89
P-P N1-P2	0.46	0.30	11.14	1.53	0.15

Table C.2: Post hoc contrasts between the three tested electrode combinations

Predictors	Estimate	Std.error	df	t-ratio	p-value
1-10 vs. 1-2	3.79	1.75	9.68	2.169	0.13
1-10 vs. 1-6	0.28	2.09	13.20	0.134	0.99
1-2 vs. 1-6	-3.51	1.77	12.50	-1.980	0.16

Table D.1: Fixed effects the linear mixed regression model of the IPI of the electrophysiological amplitude discrimination

Predictors	Estimate	Std.error	df	t value	p-value
Intercept	5.32	2.46	14.47	2.158	$p < 0.001$
0.8-0.1	2.40	1.68	10.12	1.428	0.18
0.8-0.5	1.73	1.88	8.55	0.919	0.38
P-P N1-P2	-0.22	0.47	13.86	-0.479	0.64

Table D.2: Post hoc contrasts between the three tested amplitude combinations

Predictors	Estimate	Std.error	df	t-ratio	p-value
0.8-1.0 vs. 0.8-0.1	-2.40	1.79	10.41	-1.347	0.40
0.8-1.0 vs. 0.8-0.5	-1.73	1.99	8.88	-0.870	0.67
0.8-0.1 vs. 0.8-0.5	0.67	2.00	9.54	0.337	0.94

Table E.1: All outputs of the paired Wilcoxon signed ranked tests for the difference between the behavioral and electrophysiological thresholds

Threshold	V	p-value
B vs. E frequency combinations	9	0.83
B vs. E amplitude combinations (upper threshold)	2.5	0.035
B vs. E amplitude combinations (lower threshold)	1.5	0.26

Table E.2: All outputs of the two-tailed Pearson's correlation tests for the difference between the behavioral and electrophysiological thresholds

Threshold	t-value	Df	p-value
B vs. E frequency combinations	-0.076	8.00	0.94
B vs. E amplitude combinations (upper threshold)	0.689	8.00	0.51
B vs. E amplitude combinations (lower threshold)	-0.567	8.00	0.59

APPENDIX E: TABLES SHOWING INFORMATION ABOUT THE ELECTROPHYSIOLOGICAL MEASUREMENT OF BOTH EXPERIMENTS

Electrode combination	EACC001	EACC002	EACC003	EACC004	EACC005	EACC006	EACC007	EACC008	EACC009	EACC010	Succes
1_1	CI Right	CI Right	CI Right	CI Right	CI Left	CI Left	CI Right	CI Left	CI Left	CI Right	0
1_2											80
1_3											90
1_4											100
1_5											100
1_6											100
1_7											100
1_8											100
1_9											100
1_10											100
1_11											100
1_12											100

amplitude combination	EACC001	EACC002	EACC003	EACC004	EACC005	EACC006	EACC007	EACC008	EACC009	EACC010	Suc
0.8 0.8	CI Right	CI Right	CI Right	CI Right	CI Left	CI Left	CI Right	CI Left	CI Left	CI Right	
0.8 1.0											
0.8 0.9											
0.8 0.7											
0.8 0.6											
0.8 0.5											
0.8 0.4											
0.8 0.3											
0.8 0.2											
0.8 0.1											

Color	Meaning
	most likely an ACC too due to other found ACC responses
	NO ACC found
	Possible false negative
	Possible false positive
	electrodes switched off
	ACC threshold
	ACC determined
	No clear threshold found
	N.B. EACC006 reference is electrode 2