Temporal information transfer by electrical stimulation in auditory implants

Zeitliche Informationsübertragung durch elektrische Stimulation bei Hörprothesen

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Section Neuroscience

submitted by:

Sabrina H. Pieper

from:

Oldenburg

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Submitted on: ____________________

Members of the Thesis Commitee:

Chairperson: Prof. Dr. Matthias Gamer

Primary Supervisor: PD Dr. rer. nat Dr. med. habil. Dr. rer. med. Dipl.-Phys. Andreas Bahmer

Supervisor (Second): Prof. Dr.-Ing. Mario Cebulla

Supervisor (Third): Prof. Dr. rer. nat. Erhard Wischmeyer

Supervisor (Fourth): Prof. Dr. Sarah Verhulst

Date of Public Defence: ____________________

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Abstract

In deafness, which is caused by the malfunctioning of the inner ear, an implantation of a cochlear implant (CI) is able to restore hearing. The CI is a neural prosthesis that is located within the cochlea. It replaces the function of the inner hair cells by direct electrical stimulation of the auditory nerve fibers. The CI enables many deaf or severe hearing-impaired people to achieve a good speech perception. Nevertheless, there is a lot of potential for further improvements. Compared to normal-hearing listeners rate pitch discrimination is much worse. Rate pitch discrimination is the ability to distinguish the pitch of two stimuli with two different pulse rates. This ability is important for enjoying music as well as speech perception (in noise). Further, the small dynamic range in electrical hearing (compared to normal-hearing listeners) and therefore the small intensity resolution limits the performance of CI users. Both, rate pitch coding and dynamic range were investigated in this doctoral thesis. For the first issue, a pitch discrimination task was designed to determine the just-noticeable-difference (JND) in pitch with 200 and 400 pps as reference. Additionally to the default biphasic pulse (single pulse) the experiment was performed with double pulses. The double pulse consists out of two biphasic pulses directly after each other and a small inter-pulse interval (IPI) in between. Three different IPIs (15, 50, and 150 μs) were tested. The statistical analysis of JNDs revealed no significant effects between stimulation with single-pulse or double-pulse trains. A follow-up study investigated an alternating pulse train consisting of single and double pulses. To investigate if the 400 pps alternating pulse train is comparable in pitch with the 400 pps single-pulse train, a pairwise pitch comparison test was conducted. The alternating pulse train was compared with single-pulse trains at 200, 300 and 400 pps. The results showed that the alternating pulse train is for most subjects similar in pitch with the 200 pps single-pulse train. Therefore, pitch perception seemed to be dominated by the double pulses within the pulse train. Accordingly, double pulses with different amplitudes were tested. Based on the facilitation effect, a larger neuronal response was expected by stimulating with two pulses with a short IPI within the temporal facilitation range. In other studies, this effect was shown to be maximal in CIs of the manufacturer Cochlear, with first pulse amplitudes set at or slightly below the electrically evoked compound action potential (ECAP) threshold. The second pulse amplitude did not influence the facilitation effect and therefore could be choose at will. Similarly, this effect was tested in this thesis with CIs of the manufacturer MED-EL. Nevertheless, to achieve a proper signal-to-noise ratio, technical issues had to be addressed like a high noise floor, resulting in incorrect determination of the ECAP threshold. After solving this issues, the maximum facilitation effect was around the ECAP threshold as in the previous study with Cochlear. For future studies this effect could be used in a modified double pulse rate pitch experiment with the first pulse amplitude at ECAP threshold and the second pulse amplitude variable to set the most comfortable loudness level (MCL). The last study within this thesis investigated the loudness perception at two different loudness levels and the resulting dynamic range for different interphase-gaps (IPG). A larger IPG can

reduce the amplitude at same loudness level to save battery power. However, it was unknown if the IPG has an influence on the dynamic range. Different IPGs (10 and 30 μs) were compared with the default IPG (2.1 μs) in a loudness matching experiment. The experiment was performed at the most comfortable loudness level (MCL) of the subject and the amplitude of half the dynamic range (50%-ADR). An upper dynamic range was calculated from the results of MCL and 50%-ADR (therefore not the whole dynamic range was covered). As expected from previous studies a larger IPG resulted in smaller amplitudes. However, the observed effect was larger at MCL than at 50%-ADR which resulted in a smaller upper dynamic range. This is the first time a decrease of this dynamic range was shown.

Zusammenfassung

Bei einer Taubheit, welche durch eine Schädigung des Innenohres hervorgerufen wird, ist es möglich das Gehör mittels eines Cochlea-Implantates (CI) wieder herzustellen. Das Implantat befindet sich innerhalb der Hörschnecke und ist in der Lage, die Funktion der inneren Haarzellen zu ersetzen. Dies geschieht durch direkte elektrische Stimulation der auditorischen Nervenfasern. Dadurch ermöglicht das CI Ertaubten oder stark Schwerhörigen, ein gutes Sprachverstehen zu erlangen. Dennoch gibt es weiterhin Verbesserungspotential. Im Vergleich zu Normalhörenden ist unter anderem die Tonhöhenunterscheidung stark eingeschränkt. Die Unterscheidung von Tonhöhen ist sowohl für den Musikgenuss als auch für das Sprachverstehen (im Störgeräusch) wichtig. Ebenso verfügen CI Träger über einen vergleichsweise kleinen Dynamikbereich und einer daraus resultierenden geringen Auflösung der Intensitäten. Dies kann zu einer Beeinträchtigung des Hörens führen. Sowohl die Fähigkeit der Tonhöhenunterscheidung als auch der Dynamikbereich werden in der vorliegenden Doktorarbeit untersucht. Hierfür wurde zunächst ein Tonhöhenunterscheidungs-Experiment entworfen, bei welchem der kleinste wahrnehmbare Unterschied zweier Pulsraten ermittelt wurde. Die Pulsraten 200 und 400 pps dienten als Referenzwert. Neben dem standardmäßig verwendeten Biphasischen Puls, wurden Doppelpulse genutzt. Diese bestehen aus zwei aufeinander folgenden biphasischen Pulsen gleicher Amplitude, welche durch ein kurzes interpuls Intervall (IPI) separiert sind. In dem Experiment wurden drei unterschiedliche IPIs getestet (15, 50 und 150 μs). Die Analyse des kleinesten wahrnehmbaren Tonhöhenunterschieds ergab keine signifikanten Unterschiede zwischen dem einfachen Puls und den Doppelpulsen. Ein Folgeexperiment beschäftigte sich mit einer alternierenden Pulsfolge bestehend aus dem einfachen und dem Doppelpuls. In einem paarweisen Vergleichsexperiment wurde die alternierende Pulsfolge bei 400 pps mit einem Einfachpuls bei 200, 300 und 400 pps in ihrer Tonhöhe verglichen. Es zeigte sich, dass die alternierende Pulsfolge bei 400 pps mehrheitlich mit dem Einzelpuls bei 200 pps vergleichbar war. Demzufolge scheint die Tonhöhenwahrnehmung der alternierenden Pulsfolge von dem Doppelpuls dominiert zu werden. Auf beide Experimente aufbauend, wurden Doppelpulse mit unterschiedlichen Amplituden untersucht. Basierend auf den Bahnungseffekt (Facilitation-Effekt), kann eine

größere neuronale Antwort hervorgerufen werden, indem mit Doppelpulsen mit kurzem IPI stimuliert wird. In einer anderen Studie konnte anhand von CIs der Firma Cochlear gezeigt werden, dass dieser Effekt maximal war, wenn die Amplitude des ersten Pulses nahe der Schwelle zum elektrisch evozierten Summenaktionspotential (ECAP) liegt. Die Amplitude des zweiten Pulses dagegen hatte keinen Einfluss auf den „Facilitation“ -Effekt und konnte beliebig gewählt werden. Dieser Effekt wurde mit CIs der Firma MED-EL in der vorliegenden Doktorarbeit nachgestellt. Es zeigte sich, dass auch hier der größte „Facilitation“-Effekt auftrat, wenn die Amplitude des ersten Pulses nahe der ECAP-Schwelle lag. In zukünftigen Studien könnte dieser Effekt für einen modifizierten Doppelpuls genutzt werden, um mit diesem das ursprüngliche Tonhöhenunterscheidungs-Experiment zu wiederholen. Dabei würde die Amplitude des ersten Pulses der ECAP-Schwelle entsprechen, während die zweite Pulsamplitude variiert wird, um den größten, möglichst angenehmen, Lautheitspegel zu erhalten. In einer letzten Studie wurde das Lautheitsempfinden bei zwei unterschiedlichen Lautheiten bei unterschiedlichen Interphasen-Gaps (IPG) untersucht und der daraus resultierende Dynamikbereich. Eine Vergrößerung des IPGs führt bei gleich bleibendem Lautheitsempfinden zu geringeren Stimulations-Amplituden und ist dadurch in der Lage die Batterie schonen. Allerdings ist der Einfluss auf den Dynamikbereich bisher unbekannt. In einem Lautheits-Experiment wurden Pulse mit verschiedenen IPGs (10 und 30 μs) mit dem standardmäßig verwendeten IPG (2.1 μs) in ihrer Lautheit angeglichen. Dieses Verfahren wurde bei MCL und der Amplitude des halben Dynamikbereichs (50%-ADR) durchgeführt. Aus den ermittelten Werten konnte ein „oberer“ Dynamikbereich zwischen MCL und 50%-ADR ermittelt werden. Es zeigte sich, dass sich die Amplituden mit größerem IPG, wie erwartet, verringerten. Jedoch zeigte sich ein stärkerer Effekt bei MCL, was eine Verringerung des Dynamikbereichs zur Folge hat. Dies ist das erste Mal, dass eine Verringerung des Dynamikbereichs gezeigt wurde.

Content

List of abbreviations

ADR	amplitude dynamic range
AFC	alternative forced choice
ANOVA	analysis of variances
BDR	behavioral dynamic range
CI	cochlear implant
CU	current unit
dB	decibel
ECAP	electrically evoked compound action potential
EABR	electrically evoked auditory brainstem response
(E)ASSR	(electrically) auditory steady-state response
IFC	interval forced choice
IPG	interphase gap
IPI	interpulse interval
ITD	interaural time difference
JND	just noticeable difference
MCL	most comfortable level
MPI	masker-probe interval
NH	normal-hearing
pps	pulses per second
relMCU	relative masker current unit
relPCU	relative probe current unit
RIBII	research interphase box II
SDT	signal detection theory
SGC	spiral ganglion cell
SNR	signal to noise ratio
SP	single pulse
SPL	sound pressure level

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1 Introduction

Humans uses different senses to navigate through the environment. The five most prominent senses are sight, taste, smell, touch, and hearing, although there are even more senses the human relies on. All these senses help us in everyday situations and can prevent us from risky situations. The auditory system enables us to communicate with other people and therefore take part in social life. It is a warning system (also in combination with several other senses), e.g. hearing the sound of a car when crossing the street, hearing the alarm of a smoke detector in case of fire or an ambulance crossing our way. In case of a severe hearing impairment or even deafness, we are losing one of our important senses. Nowadays, the complete loss of hearing due to a malfunctioning inner ear can be restored by auditory prostheses. The cochlear implant (CI) induces auditory sensations by electrically stimulating the auditory nerve. However, the CI is not able to restore hearing perfectly. Because of that, a lot of effort was put in the investigation of improvement of auditory prostheses. The improvement of auditory prostheses is also the topic of the thesis. In particular, the thesis is concerned with the improvement of temporal information transfer in CI users. In the following, the auditory system and CIs are introduced. Subsequently, new strategies are presented that may enhance the rate pitch discrimination in CI users and that may influence loudness perception as well as the dynamic range of CI users.

1.1 The auditory system

The auditory system is a complex system that translates acoustic signals into auditory sensations. It can be roughly divided into two main parts (Zwicker and Fastl, 2013): the peripheral region and the neural processing region. Within the peripheral region, oscillations of the sound wave travel from the outer ear through the middle and inner ear (cochlea) to the sensory cells (located within the cochlea, Figure 1.1). In the sensory cells acoustic stimuli are encoded into electrical action potentials. The second part comprises the neural processing which finally leads to an auditory sensation in the cortex.

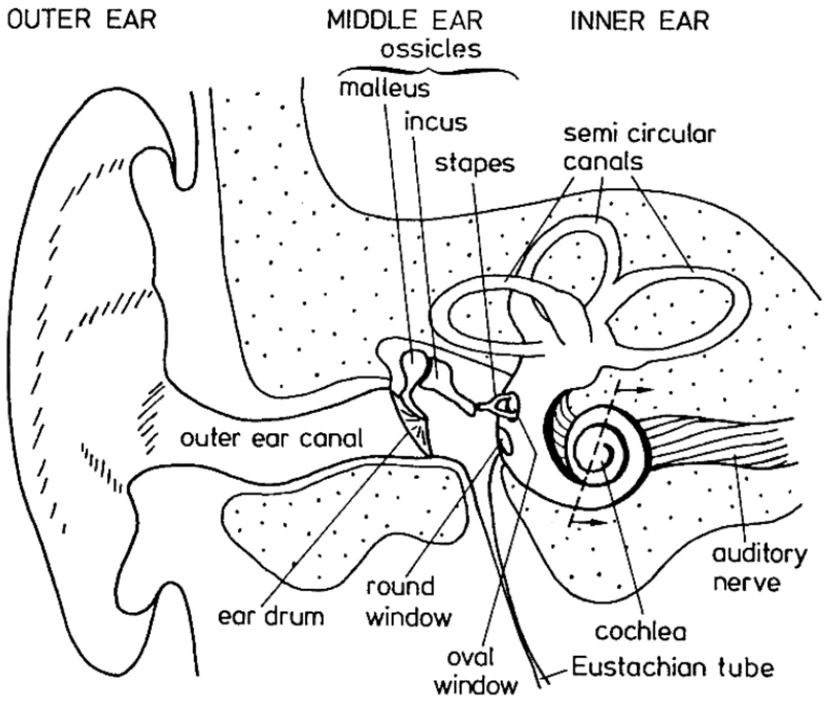


Figure 1.1: The outer, middle and inner ear as schematic drawing (Figure from Zwicker and Fastl, 2013).

1.1.1 Structure and functionality of the cochlea

The cochlea is embedded into the temporal bone. It is coiled in 2 1/2 turns like a snail's shell (Figure 1.1). It is separated from the middle ear by the oval and the round window. The cochlea is divided into the scala tympani, the scala vestibuli and the scala media (Figure 1.2a). All these structures range from the base (oval window) of the cochlea to the apex. At the apex the scala tympani and the scala vestibuli are connected (helicotrema). All three scalae are filled with fluid. The scala vestibuli and the scala tympani are filled with perilymph containing a high sodium concentration, whereas the scala media is filled with endolymph containing a high potassium concentration and a high positive potential (Zwicker and Fastl, 2013). The scalae are separated from each other by thin membranes: The reissner's membrane between the scala vestibuli and the scala media and the basilar membrane between the scale media and the scala tympani (Figure 1.2a). The basilar membrane has a total length of about 33 mm, is narrow, thick and stiff at the base while approximately five times wider, thin and floppy at the apex (Kandel et al., 2000). The organ of corti is located on the basilar membrane and covered by the tectorial membrane with the sensory cells (outer and inner hair cells,

Figure 1.2b). On the inner side of the organ of corti, one row of approximately 3,500 inner hair cells is located, while three rows of approximately 12,000 outer hair cells are located at the middle of the organ of corti (Kandel et al., 2000). The hair cells are connected to the auditory nerve by several afferent (to the brain) and efferent (from the brain) nerve fibers. More than 90 % of the 30,000 afferent, myelinated nerve fibers are connected to the inner hair cells, where each fiber makes contact to only one hair cell and each hair cell makes contact with around 10 afferent fibers (Kandel et al., 2000). The remaining 10 % afferent fibers are unmyelinated and innervate the outer hair cells (Kandel et al., 2000). The cell bodies of the afferent fibers, the spiral ganglion cells (SGC), are located in the cochlear ganglion or spiral ganglion. In contrast to the afferent nerve fibers, the around 500 efferent nerve fibers are mostly connected to the outer hair cells and only a few inner hair cells (Zwicker and Fastl, 2013).

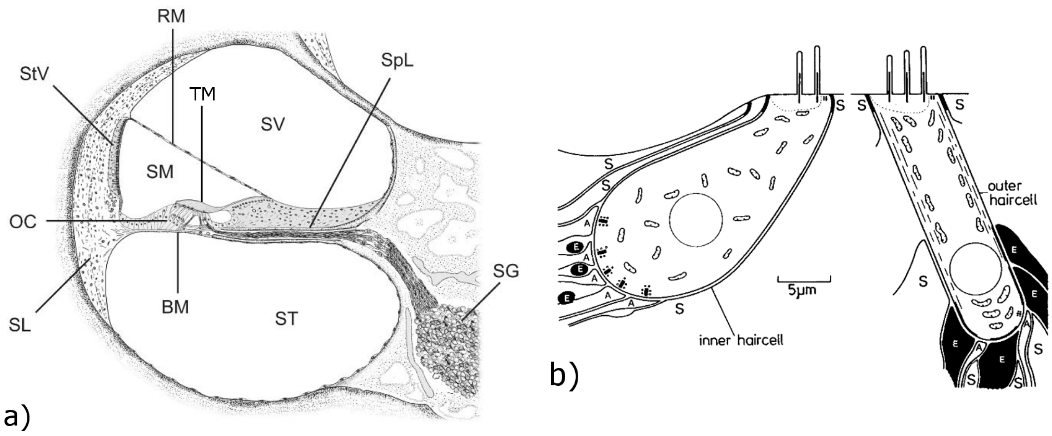


Figure 1.2: a) The cross section of the cochlea shows the following structures: scala vestibuli (SV), scala media (SM) scala tympani (ST), Reissner's membrane (RM), basilar membrane (BM), tectorial membrane (TM), Organ of Corti (OC), spiral ganglion (SG), spiral ligament (SL), spiral lamina (SpL), and stria vascularis (StV). b) Scheme of the hair cells with it's stereocilia, the supporting cells (S), and the connected afferent (A) and efferent (E) nerve fibers (Figure a from Clark, 2004 and figure b from Zwicker and Fastl, 2013).

The acoustic sound travels through the outer ear canal into the middle ear. In the middle ear the impedance between the air and the fluid inside the cochlea is matched by the ossicular chain (lever ratio) and due to the different ratios of the large tympanic membrane and the small oval window (transformation ratio, Zwicker and Fastl, 2013). Otherwise the most amount of acoustic sound would be reflected at the mediums barrier. The sound wave enters the inner ear through the oval window. As neither the fluid nor the surroundings are compressible, the round window at the base of the scala tympani compensates for the incoming pressure fluctuations. The fluctuations are transmitted by the fluid to the basilar membrane. leading to a displacement of that membrane (Zwicker and Fastl, 2013). The basilar membrane is displaced strongest at the resonance sites specific to the frequency components of the acoustic signal (Clark, 2004). Due to the previous described decrease in stiffness of the basilar membrane along the cochlea, the lower frequencies respond strongest at the apical part of the cochlea and the high frequencies at the base (tonotopic organization, Kandel et al., 2000). In the organ of corti, the mechanical displacements of the basilar membrane and the tectorial membrane are transduced into electrical signals (Purves et al., 2004). The mechanical displacement of both membranes leads to a movement of the stereocilias, that are located on top of the hair cells. This movement induces an influx of the endolymphic potassium (K^+)-ions depolarizing the hair cells by opening channels near the tips of the stereocilias (Purves et al., 2004). In the inner hair cells the depolarization leads to opening of the calcium channels (Ca^{2+}) in the cell soma (Purves et al., 2004). Thereupon, an influx of Ca^{2+}-ions occurs, leading to the release of neurotransmitter, the glutamate, which initiates the action potential in the auditory nerve fibers (Purves et al., 2004). In the outer hair cells the depolarization of the cell leads to an amplification of the basilar membrane displacements (Kandel et al., 2000). The information flows from the hair cells to the auditory nerve and finally to the auditory cortex.

1.1.2 Cochlea malfunctions

Due to malfunctioning of different parts of the auditory system, different types of hearing disorders are possible. One of the most common hearing disorders that can lead to severe hearing loss or deafness is the sensorineural hearing loss (Shepherd and Javel, 1999). Typically, the sensorineural hearing loss is associated with the loss of the sensory hair cells within the cochlea. As the hair cells in humans (and in general in mammals) are not able to regenerate, a loss of hair cells is permanent and thus the corresponding hearing impairment (Shepherd and McCreery, 2006). A loss of the outer hair cells leads to a lack of amplification of soft sounds. Therefore, especially soft sounds are hard to be detected. Contrary, a loss of the inner hair cells prohibits the initiation of action potentials in the nerve fibers. If fewer inner hair cells are intact, fewer fibers can respond to the incoming sounds. Therefore, hearing loss can increase up to deafness. A rapid reduction of the unmyelinated SGCs in the organ of corti follows the loss of (outer) hair cells (Clark, 2004). Additionally with the loss of inner hair cells, the myelinated SGCs begin to degenerate gradually, while the surviving myelinated SGCs may be demyelinated (Clark, 2004). The degeneration process is ongoing. It is slower in human than in animals, and it is depending on etiology and the pathology that is underlying the deafness (Shepherd and McCreery, 2006).

The reason of a sensorineural hearing loss is manifold. The structures of the cochlea are sensitive to acoustic trauma (e.g. explosions), ototoxic drugs, viral or bacterial infects (e.g. rubella, measles, labyrinthitis followed by meningitis), head injuries (e.g. fracture of the temporal bone) and aging (Clark, 2004). All these factors can lead to an acquired hearing loss/deafness in children or adults. This kind of hearing loss can be sudden or progressive over time. Another type than the acquired hearing loss is the congenital deafness. It refers to a deafness before (prenatal) or during the birth (perinatal) and can be genetic e.g. due to chromosomal abnormalities or can be caused by diseases that affected the mother during the pregnancy (Clark, 2004). Deafness that occurs after birth (postnatal) is mostly the result of injuries during the birth or diseases but also can happen due to delayed genetic effects (delayed hearing loss, Clark, 2004). It is assumed, that genetic deafness has the highest prevalence in children (about two third) who have a severe hearing loss before developing language (prelingualistic, Clark, 2004).

1.2 The cochlear implant

In case of profound hearing loss due to a loss of functioning (inner) hair cells hearing aids often reach their limit in restoring hearing. As there are not enough inner hair cells left to initiate action potentials in the nerve fibers, the amplification of the hearing aid is not helpful any longer. However, with a CI it is possible to restore auditory sensations by replacing the malfunctioning inner ear with direct electrical stimulation of the auditory nerve fibers. Hence, a prerequisite for the CI to function properly is an intact auditory nerve.

1.2.1 Configuration of the cochlear implant

The CI consists of two parts. The speech processor and transmitter are the outer part and the implanted electrode array within the cochlea and the receiver are the inner part (Figure 1.3). Both parts are connected via coils inducing an electromagnetic field. The transmitter is held in place by magnet force on the outside against the receiver, which is placed directly under the skin.

The function of the CI is as follows (Clark, 2004). The incoming sound is received by microphones positioned on the processor. Depending on the manufacturer, an additional microphone may be positioned on the transmitter coil. The speech processor processes the signal in several stages. First, the sound wave is AD converted and afterward filtered into its frequency bands. Thereafter, the electrical signal is processed by the manufacturers coding strategy. The CI user's individual map defines voltages of hearing threshold and maximum comfort level (MCL) for each electrode, as well as stimulus parameters of the electric signal such as phase duration and interphase gap (IPG). The default IPG in CIs depending on manufacturer range from 2.1 (MED-EL, Innsbruck, Austria) to 8 μs (Cochlear, Sydney, Australia). The manufacturer Advanced Bionics (Valencia, California) does not use IPGs per default for their coding strategy. Additional algorithms regulate e.g. the noise cancellation and the microphone settings for omnidirectional or directional sound.

The processed signal is transmitted from the sending coil of the speech processor via electromagnetic connection to the receiving coil of the implant. The receiver and the reference electrode is surgically embedded in the mastoid bone. The receiver generates a pattern of electrical stimuli in the electrode array. The electrode array is placed in the first turns of the cochlea in the scala tympani, close to the SGCs and peripheral nerve fibers. The auditory nerve is stimulated by electrical pulses from the electrode array and a pattern of hearing nerve activity is generated in response to electrical stimulation. After the excitation of nerve fibers, the neural information is processed up to the auditory cortex.

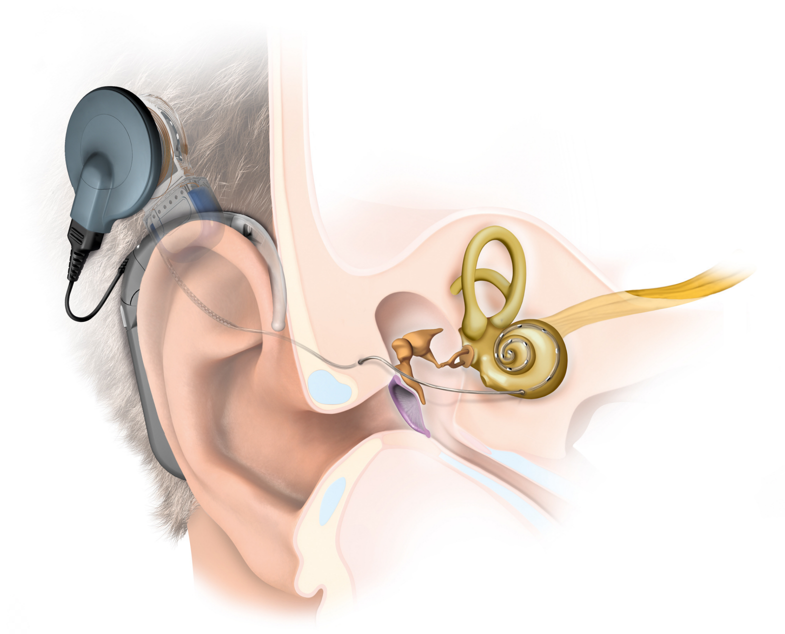


Figure 1.3: The CI system from the manufacturer MED-EL with the speech processor behind the ear and the electrode array placed within the cochlea (Figure from MED-EL, Innsbruck).

The effectiveness of the electrical stimulation depends on the pulse charge. Charge is a product of the electrical current and the duration of stimulation. Neurons are sensitive to changes in amplitude as well as stimulus duration (Shepherd and McCreery, 2006). Therefore, loudness can be controlled by the variation of current and pulse duration. In contrast to statistically independent firing of nerve fibers in acoustical hearing, electrical stimulation leads to a synchronous firing of the fibers (Shepherd and McCreery, 2006). This synchronous firing pattern is one reason for the perceptional differences of electrical hearing compared to acoustical hearing (Shepherd and McCreery, 2006).

1.2.2 The electrode array

Depending on the manufacturer, the electrode array consists of different numbers of electrodes (MED-EL: 12 electrodes, Cochlear: 22 electrodes, Advanced Bionics: 16 electrodes, Oticon Medical: 20 electrodes). Depending on the patient's anatomy of the cochlea, the surgeon can choose between different types and lengths of electrode arrays that are offered by the manufacturers. For instance, the manufacturer MED-EL offers the FORM series, designed for malformed cochleae, the FLEX series, an electrode array with flexible tip for atraumatic insertions and the CLASSIC series (Med-el, 2020). Subjects within the described studies in this thesis are implanted with the 31.5 mm long standard electrode array (CLASSIC series) or with electrode arrays from the FLEX series (FlexSoft: 31.5 mm; Flex28: 28 mm; or Flex24: 24 mm). It is possible to stimulate the contacts of the electrode array sequentially (one electrode at a time) or simultaneously (several electrode contacts at the same time). In coding strategies of current CIs sequential stimulation is the default strategy to avoid channel interaction effects (Shepherd and McCreery, 2006). The electrode array may stimulate the nerve fibers in monopolar or bipolar mode. In the bipolar mode, two electrodes that are located within the cochlea are stimulated and generate a pattern of excitation. One negative effect of the bipolar mode is that the thresholds may be relatively high if the electrodes are not located close enough to the nerve (Shepherd and McCreery, 2006). In the monopolar mode, one electrode located in the cochlea is stimulated against the reference electrode outside of the cochlea. This electrode configuration shows lower thresholds than bipolar stimulation, with place-pitch perceptions according to the tonotopic organization of the cochlea (Shepherd and McCreery, 2006). The CI system from the manufacturer MED-EL stimulates only in the monopolar mode.

1.2.3 Safety and bio-compatibility of cochlear implants

Safety is an important issue for neuroprostheses like cochlear implants. Already the selection of the implant housing and electrode material is critical. Toxic chemicals from using the wrong material can cause inflammation, foreign body reactions or a hypersensitivity in the patient's body (Clark, 2004). Therefore, only proved bio-compatible materials are used for the implant case (e.g. ceramic or titanium), electrode array (e.g. silicone) and the electrode contacts (e.g. platinum). Similar to the material, the physical shape and dimensions of the implanted device can lead to unwanted reactions (Clark, 2004). Therefore, it is necessary to have a proper follow-up of the patients' recovery after implantation.

Another important factor for a successful long term stability of the implant is to avoid neural damage by electrical stimulation. The delivery of unbalanced charge or over-stimulation can release harmful electrochemical products and thereby lead to damages of the surrounding tissue (Shepherd and McCreery, 2006). Avoiding over-stimulation and careful selection of stimulus parameter assures a safe electrical stimulation. Hence, the phase duration should be within a range below 300 μs and the charge density for electrodes that are located within the cochlea should be below 60 μCcm^{-2} geometric/phase (Shepherd and McCreery, 2006). One of the most important factors to avoid toxic effects on the surrounding tissue are therefore charge balanced stimuli (Brummer et al., 1983; Merrill et al., 2005). In most cases, CIs stimulate the nerve fibers by pulse trains consisting of biphasic pulses. A biphasic pulse has two opposing phases (anodic/cathodic or cathodic/anodic) with identical amplitude and phase duration to ensure a balance in charge between negative and positive phase (Figure 1.4 top right). Within the first phase, an electrochemical reaction is caused by the electrical stimulation (Clark, 2004). During the second phase, this reaction is reversed (Clark, 2004).

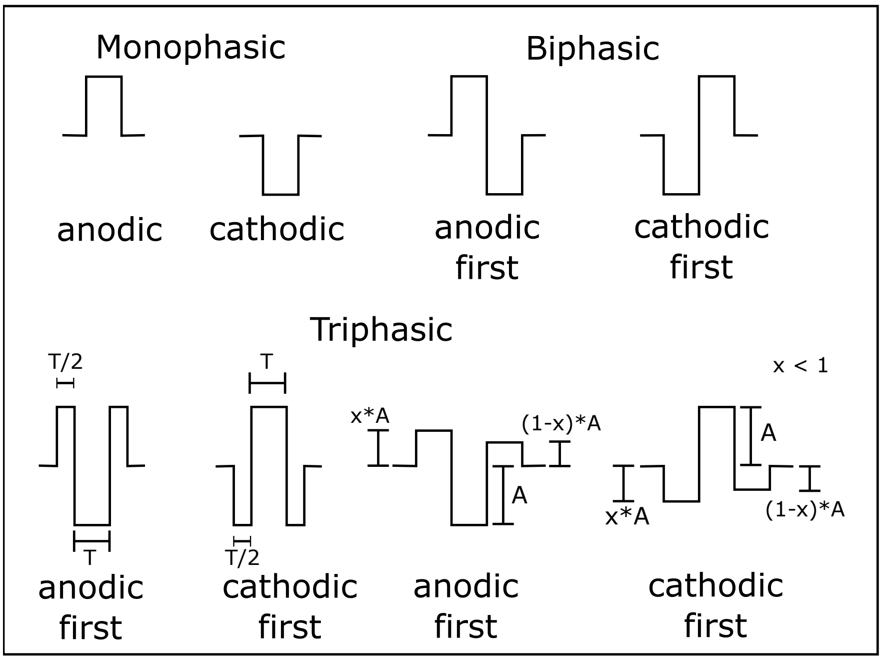


Figure 1.4: Different types of pulse forms for electricals stimulation. Depicted are the monophasic pulse with either anodic or cathodic phase, the biphasic pulse, with anodic first or cathodic first phase, and the triphasic pulse with anodic first or cathodic first phase. For balanced charge for the triphasic pulse, either the phase duration (T) or the amplitude (A) of the first and third phase are adjusted to the second phase. The factor x to adjust the charge balancing of the amplitudes has to be smaller than one.

A stimulation with triphasic pulses can also ensure charge balancing. A triphasic pulse consists of three phases (anodic/cathodic/anodic or cathodic/anodic/cathodic) with a fixed amplitude and phase duration of the second phase. The first and third phase are either adjusted in phase duration or in amplitude to match in sum either the phase duration or amplitude of the second phase, whereas the factor to adjust the amplitude has to be smaller than one (Figure 1.4 bottom). Both cases ensure a balance in charge between anodic and cathodic phases. Contrary to the biphasic and triphasic pulses, a monophasic pulse stimulates the surrounding tissue solely with an anodic or a cathodic phase and therefore does not guarantee charge balancing (Figure 1.4 top left). Accordingly, monophasic long-term stimulation has to be avoided in humans, although monopolar stimulation had been shown to be more effective than biphasic pulses in single-cell experiments in animals (Shepherd and Javel, 1999). Compared to biphasic pulses, the monophasic pulses were able to reduce the threshold in single-cell recordings up to 4 dB (Shepherd and Javel, 1999).

1.2.4 Coding strategies of the cochlear implant

In normal hearing (NH) listeners, sound information is transferred in a covariation of spatial and temporal coding. The spatial information is provided by the tonotopic projection of sound in the cochlea, the auditory nerve, and auditory cortex (Lyon, 2017). Temporal information is encoded via the nerve fibers by firing in phase with the period of the sound wave. This principle is called phase locking. Not every individual nerve fiber is able to fire at each cycle, but a group of nerve fibers is able to represent the sound waves fine structure (Kandel et al., 2000). The phase locking is strong in the low frequencies up to 1.5 to 3 kHz and deteriorates afterward (Clark, 2004). While the phase locking decreases with frequency, the stochastically firing induced jitter around each peak of firing neurons increases (Clark, 2004).

In CIs spatial and temporal information can be coded separately. The place coding can be partially reproduced, by stimulating a certain place within the cochlea with the electrodes on the array (Clark, 2004). Depending on the place of the stimulated electrode, different fibers are firing and carry the place information along the auditory system. The temporal coding can be addressed separately by stimulation of one single electrode and the variation of temporal information (i.e. pulse sequences in time). In sensorineural hearing loss, often the temporal coding is affected as the demyelination of nerve fibers reduces temporal resolution (Shepherd and McCreery, 2006). Despite implantation, limitations in temporal coding still exist (Clark, 2004). Especially at high pulse rates (above 200 to 500 pulses per second (pps) or higher), it was shown that the electrical stimulation with CIs is not able to reproduce the same firing patterns than the acoustic stimulation at the same frequency (Clark, 2004). It is assumed, that the neurons are not able to respond to the higher pulse rates, as the "electrical stimulation produced strong inhibition that suppressed neural activity" (Clark, 2004). The limitation in temporal coding is i.a. reflected in the poor pitch rate discrimination at low and high pulse rates (see chapter 1.4.1).

1.2.5 Deficits using cochlear implants

Since the development of the first CIs, large progress was achieved regarding the patients performance. Speech processing strategies were enhanced as well as quantity and quality of the auditory input. In general, the CI users benefit from the implant in different ways. One main aspect is the speech and environmental sound perception and consequently the ability to develop speech and language. There are also other effects, like a change in quality of life, caused by i.a. enjoying social or music events, a reduction in tinnitus, or a general well-being (Cooper, 2006).

However, there is still room for improvements. For example, the performance of speech perception differs strongly between CI users. Especially in complex situations such as background noise or competing speakers many CI users have difficulties to properly understand speech. One aspect that could affect speech perception (in noise) is the ability to perceive and discriminate pitch, as pitch perception helps to segregate the different sound streams (Oxenham, 2012). Additionally, the encoding of prosody which carries semantic information in tonal languages is supported by pitch perception (Oxenham, 2012). The ability to distinguish between pitch and therefore analyze auditory information is not only important in speech perception. Also other aspects of hearing are influenced by pitch perception, e.g. the melody recognition and music appreciation (Oxenham, 2012). As CI users have more difficulties to discriminate pitch compared to NH listeners, the improvement of temporal pitch perception in electrical hearing is crucial for further improvements. NH listeners are able to observe small pitch differences which depends on the presented frequency. Up to 1 kHz, NH listeners have a just-noticeable-difference (JND) in frequency of approximately 1 Hz, while above 1 kHz, the JND is about 0.2% of the presented frequency (Zwicker and Fastl, 2013). For a better comparison between NH listeners and CI users Macherey and Carlyon (2014) developed stimuli, that consisted of harmonic complex tones with harmonics that were summed up in either sine, alternating sine-cosine, or pulse-spreading phase. These harmonic complex tones consist of the same spectrum but due to their temporal structure they differ in pitch and therefore allow to investigate the pitch perception in NH listeners solemnly relying on temporal coding. NH listeners performed a pitch-ranking test with these stimuli and were able to discriminate the temporally structured stimuli up to 700-800 pps. Some CI users are able to discriminate rate pitch up to 700-800 pps or higher as well (Kong and Carlyon, 2010; Goldsworthy and Shannon, 2014). However, in most CI users the upper limit of rate pitch discrimination is about 300-400 pps (Townshend et al., 1987; Zeng, 2002). As described, the upper limit of rate pitch discrimination is usually worse than in NH listeners and the variability of rate pitch discrimination thresholds for base rates up to 300 pps among CI listeners is huge. However, a correlation between upper limit of pitch and the performance in rate pitch discrimination was not yet found. As examples for the variability in rate pitch discrimination, at a base rate of 200 pps, previous studies revealed JNDs in rate pitch of 5.4% (McDermott and McKay, 1997), 20% (Baumann and Nobbe, 2004; Bahmer and Baumann, 2013) and 50% (Townshend et al., 1987). The JND deteriorates further with increasing pulse rate (Baumann and Nobbe, 2004). Although training can significantly improve the pitch discrimination in CI users, the gap between CI users and NH listeners remains (Goldsworthy and Shannon, 2014).

Another aspect which is important to consider for the speech perception is the small dynamic range in electrical hearing. The behavioral dynamic range (BDR) is defined as the difference between hearing threshold and either the most comfortable loudness level (MCL) or the loudness discomfort level. Normal-hearing listeners are able to use an acoustically dynamic range of more than 100 dB (Viemeister, 1988). Because of this wide dynamic range of around 120 dB, the NH listeners benefit from a high intensity resolution that allows them to discriminate between up to 200 intensity steps (Zeng and Galvin III, 1999). Additionally, the high intensity resolution helps in speech recognition, as it leads to a high speech intelligibility with background noise (Viemeister, 1988). In contrast, the electrically dynamic range of CI users is about 6-20 dB and therefore shows a much lower resolution than NH listeners (Zeng et al., 2002). The discriminable intensity steps of CI users range from 6.6 to 45.2 across the electrical dynamic range (Nelson et al., 1996).

1.3 Psychophysics in the auditory system

One way to investigate the previous described differences in performance between NH listeners and CI users is the usage of psychophysical methods. Therefore, these methods are a basic measure for the experiments of this thesis. Before the methodical concept of different test procedures is described in chapter 2.1, the theory of psychophyic in general is described in this section. Psychophysics describes the quantification of the human sensation by measuring psychological correlations to physical stimuli (Hansen, 2012). Part of the term psychophysic is the topic psychoacoustic. In psychoacoustics sensations are investigated which are induced by acoustic stimuli. Accordingly, the psychoacoustic does not question, how hearing works, but quantifies the sensation of sound (Hansen, 2012). To investigate sensation by acoustical stimulation, specific experiments were designed that aim to answer specific questions. These questions address the presence (detection) or discrimination of stimuli, how the properties of a stimuli could be described (e.g. loud/soft, low/high, rough/sharp) or if a stimulus sounds comfortable/uncomfortable. Another type of question addresses effects that can be measured by comparing different types of stimuli, if they are reproducible, if they appear due to subjective/objective factors, if they are dependent on the attention of the subject or if learning effects occur. The experiments are designed to overcome subjective attention or learning effect. An advantage of a psychoacoustic measurement is, that the subject can offer additional information - more subjective and describing - about the sensation. Electrical stimulation in CI does not match the term psychoacoustic properly (as no acoustic signal but an electrical signal is present). Therefore, the more general term "psychophysics" is used throughout the later chapters.

In psychophysics, the signal detection theory (SDT) is applied. The concept of the SDT based on the examination of two different types of stimuli, namely the signal and the noise. The signal may describe the presence of a sound but also the presence of a difference between two sounds. Therefore, it is possible to apply the SDT in detection as well as in discrimination experiments (Hartmann, 2004). The noise comprises the stochastic character of the subjects decision process and may describe an external noise, e.g. an acoustical background noise (Hartmann, 2004). Even without the presence of an external noise, at least the presence of an internal noise is assumed. The internal noise describes the spontaneous firing of the neurons that leads to a variability in the subjects' responses. Sometimes presenting the same tone repeatedly may lead to a perception or not (Hansen, 2012). Especially near detection or discrimination threshold, this effect can be observed. The aim of the SDT is the mathematical description of the subjects perception ability and the decision process (Hansen, 2012). Therefore, it "can serve as an interface between psychophysical observations and neural models of perception" (Hartmann, 2004).

In the SDT, each perception results in a response "r" on an internal continuous coordinate. Hence, a weak or even no signal results in a low r and a pronounced signal results in a large r. The decision process is based on that. As an example an experiment with two possible responses is described in the following (Hansen, 2012). One interval contains the signal with noise (SN) and the other one only noise (N). The subject has to decide which interval contains the signal (random presentation of SN and N). It is assumed, that none of the two intervals are preferred by the subject leading to the possibility of a correct response between 50% (guessing) and 100%. For both intervals (N and SN) a variate r is generated with the normal distribution f_N and f_{SN} (Figure 1.5). In the SDT f_N has a mean value of 0, while the distribution f_{SN} is identical to f_N (both normal distributed with same standard deviation σ) but shifted by the mean value μ relative to f_N. Depending on the overlap of both distributions, the interval N may lead to a higher r than for the interval SN. If the subject will always decide for the interval with the larger r, the question arises to which probability P_c the response of the subject is correct. This probability of a correct answer is equal to the probability, that the larger r (the pronounced signal) is from the distribution f_{SN} and the smaller r (the weak signal) from the distribution f_N (Equation 1.1).

$$P_c = P(r_{SN} > r_N) = P(r_{SN} - r_N > 0) = P(\Delta r > 0) \tag{1.1}$$

Additionally to the score P_c giving the percentage of correct responses, an additionally quantitative value describes the reliability of the result: the sensitivity index d' that is defined as μ/σ. A d' at zero would suggest, that the subject is only able to guess the answer (e.g. because of the difficulty of the assignment due to small differences in reference and target, Hansen, 2012). In case of a negative d' it can be assumed, that the subject misunderstood the assignment and constantly gives the wrong interval as answer (Hansen, 2012). The higher the d', the easier the reference and target can be distinguished from each other, as the distributions of reference and target are widely separated from each other.

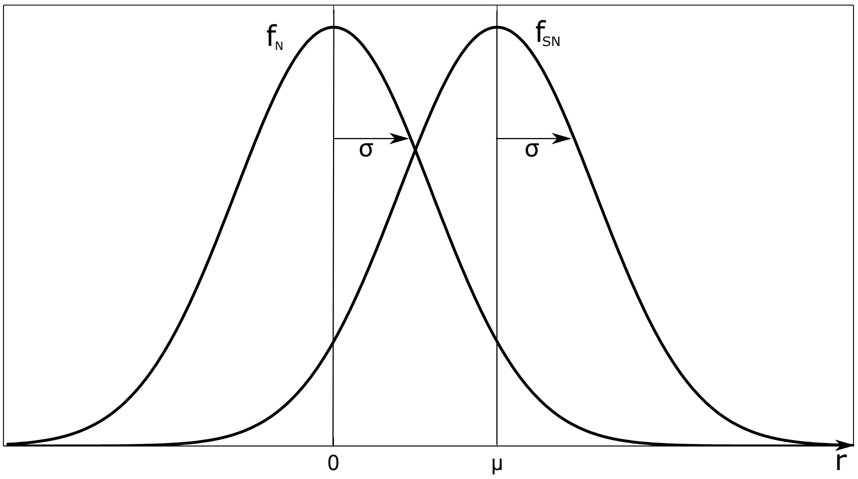


Figure 1.5: In the signal detection theory (SDT), the distributions of f_N (normal distribution of noise) and f_{SN} (normal distribution of the mixture signal and noise) are identical in form and standard deviation σ, with f_{SN} shifted by the mean value μ.

1.4 Motivation

1.4.1 Improving rate pitch perception in CI users

An approach to improve rate pitch discrimination in CI users originates from studies in sound localization with CIs. Interaural time differences (ITD) are used to localize sound for frequencies up to 1 kHz. Similar as for pitch discrimination, ITD sensitivity of CI users is worse than for NH listeners. Both - ITD and rate pitch sensitivity - get worse with increasing pulse rate and therefore may be related to insufficient temporal encoding of the incoming signals (Majdak et al., 2006). Ihlefeld et al. (2015) investigated the hypothesis that the deterioration in ITD and pitch discrimination has a common neural basis. They compared within the same subjects pitch discrimination in the worse ear with binaural ITD discrimination. The performance in ITD and pitch discrimination both deteriorated between 100 and 500 pps with increasing pulse rate. Additionally, the results correlated significantly with each other, supporting the hypothesis, that ITD and pitch sensitivity are partly influenced by a common mechanism. Laback and Majdak (2008) introduced jitter to pulse trains that were presented to synchronized bilateral CIs to improve the sound localization in CI users. The jitter was applied to the pulse trains with a certain time lag between the left and right implant, which defined the ITD. With this approach, they were able to improve the ITD sensitivity especially at the high pulse rates between 800 and 1600 pps. The effect of jitter was further investigated by Hancock et al. (2012). The neural activity was measured in the inferior colliculus in cats with bilateral CIs. They found higher firing rates of the neurons tuned to the ITD after introducing jitter to the pulse train. They also found that the main effect of improved sound localization was because of double pulses with short interpulse intervals (IPI) that were introduced by applying the jitter. Therefore, it seems to be reasonable to use double-pulse trains instead of jittered pulse trains for improvement of temporal resolution in CI. Because of their common mechanism this approach may be beneficial in pitch discrimination as well, which was already suggested by Laback and Majdak (2008).

1.4.1.1 Hypothesis on pitch discrimination

Based on the observations in the studies of Laback and Majdak (2008), Hancock et al. (2012), and Hey et al. (2017), it was hypothesized in this thesis that it may be possible to improve rate pitch discrimination by using double pulses with short IPIs instead of the standard used single pulses. Therefore, in the first experiment, rate pitch JNDs are estimated using pulse trains containing either single pulses or double pulses. The double pulses have short IPIs within the facilitation range (see chapter 1.4.2). The maximum facilitation effect was found by Hey et al. (2017) at an IPI/masker-probe interval (MPI) of 13 μs. Nevertheless, three different IPIs were tested within the psychophysical experiment, assuming that the best IPI for pitch discrimination may differ along CI users depending on their cochlea health status. This assumption is also reflected in the temporal coding characteristics of electrically evoked compound action potentials (ECAPs) that are influenced by spiral ganglion density, the marker of cochlea health status, which was shown by Ramekers (2014) in an animal model. Babacan et al. (2010) already pursued the idea of individual parameter fitting. Based on neuronal refractory time (refractory state coding) they implemented a coding strategy that was individually fitted to CI users. Additionally to the hypothesis on effects on pitch discrimination, a loudness summation effect was expected in double-pulse trains. By investigating double-pulse trains, Karg et al. (2013) was able to find loudness summation due to temporal interaction of the two pulses. The effect decreased with increasing the IPI between the two pulses of the double pulse complex. Therefore, a second hypothesis of the first experiment is, that the amplitudes of the double-pulse trains are lower compared to the single-pulse trains to achieve the same loudness level.

1.4.1.2 Hypotheses on pitch perception

In the case of an application of jitter to a pulse train, the relevant double pulses with short IPI for a performance improvement appear only occasionally (Laback and Majdak, 2008; Hancock et al., 2012). Rate pitch discrimination may also be improved by this occasionally occurring double pulses. Yet, it is unclear if double pulses with the same amplitude as single pulses may dominate the pitch perception in a mixed pulse train due to the temporal interaction effects. Therefore, a pulse train consisting of double and single pulses may lead to a different pitch perception than a single pulse with same pulse rate. This possible difference in pitch perception was evaluated in a second experiment, comparing a pulse train consisting of alternating double pulses with short IPIs and single pulses at equal amplitudes with single-pulse trains. Three possible scenarios of pitch perception in this alternating pulse train may occur: (A) The perceived pitch may be half of the stimulation rate in comparison to a single-pulse train with identical pulse rate, if the repetition rate of the double pulses dominates the pitch perception. Due to the loudness summation within the double pulse complex, a loudness difference between double and single pulse within the pulse train occurs, as both types have identical amplitudes. This may lead to the fact, that the double pulse dominates the pitch perception. (B) The perceived pitch may be equal to the stimulation rate, if the repetition rate of both, single and double pulses, determine the pitch perception. The loudness difference between double and single pulse may not influence the pitch perception and therefore the pitch is identical to a single-pulse train with same pulse rate as the alternating pulse train. (C) The perceived pitch may be between the pitch that would be perceived in a single-pulse train and half the pitch (a combination of case A and B), if a mixture of the repetition rate of double and single pulses determines the pitch perception. In this case, the double pulse complex would influence the pitch perception but does not determine the pitch alone. The single pulse would interfere with the double pulse complex which could lead to a perceived pitch that neither represents the expected pitch in case A nor in case B but a pitch in between.

1.4.2 Facilitation effect in recording auditory nerve potentials

The acoustical stimulation and the stimulation with electrical pulses leads to the generation of an action potential. After successfully initiating an action potential, a certain time period has to pass, before the same nerve fiber is able to fire again. This time period is called the refractory time. The refractory time is split up in the absolute and the relative refractory time. Within the absolute refractory time it is not possible to initiate another action potential (Kandel et al., 2000). In CI users, this period was found to last until approximately 400 μs (Morsnowski et al., 2006). Afterward, the relative refractory time starts. Within this time period, which lasts until 5-10 ms after initiation of the action potential, it is possible to initiate a new action potential under certain prerequisites (Kandel et al., 2000). Within the relative refractory time, the stimulus has to be stronger than in the non-refractive status to reach the threshold for initiating an action potential. With progression of the relative refractory time, the threshold for nerve firing decreases. The other way round, if the stimulation amplitude stays constant, the probability of firing nerves is nearly zero at the beginning of the relative refractory time and increases with longer duration within the refractory time (Hey et al., 2017). This can also be observed in the response of the ECAPs (Figure 1.6).

The so-called facilitation range falls within the absolute refractory period. The term facilitation describes in CI the enhancement of the neural response by pairing two electrical pulses within a short period of time and can be observed in ECAP recordings (Hey et al., 2017, Figure 1.6). It is assumed, that the facilitation effect occurs due to a "residual subthreshold depolarization of neurons in which the masker did not generate an action potential. The depolarization is short lasting and temporarily lowers the threshold and facilitates the probability of firing to the probe" (Hey et al., 2017). This effect may improve the amount of temporal information transfer as more nerves are able to fire stochastically and therefore may be beneficial in pitch perception. The stochastical firing of the neurons is present in acoustic stimulation but destroyed in electrical hearing by strong temporal and spatial synchronization from the pulses (Shepherd and McCreery, 2006).

By applying double pulses to improve pitch discrimination a twofold interaction may occur due to the double pulse stimulation. Depending on amplitude and IPI, the first pulse of the double pulse complex may have a masking or a facilitation effect on the following second pulse. The short IPI within the study of Laback and Majdak (2008) and Hancock et al. (2012) falls into the facilitation range. The facilitation effect was investigated by Hey et al. (2017) in CI users recording ECAPs. In their study, compared to single pulse stimulation, higher ECAP amplitudes could be recorded in response to double pulses with short IPIs. The effect could be found for IPIs up to 200 μs. However, the first pulse amplitude had to be set at or slightly below ECAP threshold level to get the maximum effect. Further increase of the first pulse amplitude led to a decrease in ECAP amplitude as the neural response to the second pulse was masked by the first pulse.

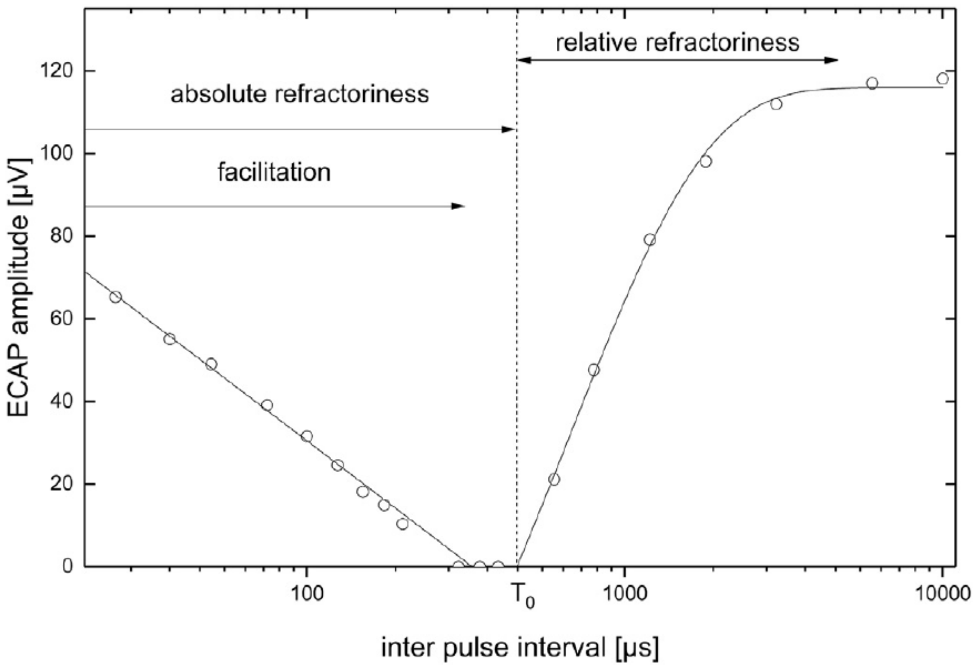


Figure 1.6: A schematic drawing of the amplitude of an electrically evoked compound action potential when stimulating within the refractory time as a function of the masker probe interval. At T_0, the estimated absolute refractory time ends and the relative refractory time starts (Figure from Hey et al., 2017).

1.4.2.1 Investigation of the facilitation effect

The first experiment aimed to improve the rate pitch perception by using double pulses in pulse trains. Similar as in Laback and Majdak (2008) and Hancock et al. (2012), identical amplitudes for each pulse within the double pulses were used. The idea to benefit from the facilitation effect was applied by using short IPIs. However, the potential facilitation effect was not verified. Also a suppression effect due to double pulses may occur, if the applied amplitude level (of the first pulse) would be larger than the ECAP threshold at this electrode and thereby masking the neural response to the second pulse instead of facilitate it. So far, a documentation of the facilitation effect depending on masker level (first pulse) was only performed using CIs from the manufacturer Cochlear (Sydney, Australia) by Hey et al. (2017). Therefore, the third experiment aims to investigate the facilitation effect depending on masker level in CI systems of MED-EL (Innsbruck, Austria) similar as in Hey et al. (2017). It was expected to find the maximum facilitation effect around the ECAP threshold similar to the findings with the CI systems of Cochlear (Hey et al., 2017).

1.4.3 Improving the effectiveness of stimulation due to different interphase gaps

As discussed in chapter 1.2.3, the stimulation with biphasic pulses is not as effective as the stimulation with monophasic pulses. However, it is even possible to increase the effectiveness of biphasic pulses by prolonging the IPG of the biphasic pulse. In animal experiments, prolonging the IPG more than 100 μs and therefore delaying the second phase leads to a reduced threshold similar to the threshold obtained with monophasic stimulation (Shepherd and Javel, 1999). Below an IPG of 100 μs, the biphasic pulse is less effective than a monophasic pulse because "increasing the rate of delivering the hyperpolarizing charge within this 100 μs window would reduce the probability of action potential generation" (Shepherd and Javel, 1999). In humans with a CI, variation of the IPG also effects loudness. Increasing the IPG led to a higher loudness at a constant stimulation level (for detailed references see chapter 1.4.3.1). Therefore, the utilization of pulse trains with large IPG in CI users, could potentially reduce the battery power consumption. Saving battery power is important for the development of fully implantable CIs because they have limited access to battery power. A prerequisite for a successful usage of larger IPGs for saving battery power is the loudness dynamic range which has to be still in the same range or even increases. As mentioned in chapter 1.2.5 the dynamic range in CI users is already limited compared to NH listeners. This limited dynamic range leads to a lower intensity resolution, whereas a high intensity resolution leads to a high speech recognition in background noise (Viemeister, 1988). Therefore, a further decrease in dynamic range due to IPGs is critical, as it would further decrease the intensity resolution and thus may hinder the speech recognition in background noise. Consequently, the fourth experiment of this thesis aims to investigate the effect of IPG variation on loudness perception at different amplitude levels as well as the arising dynamic range. This loudness perception was assessed with a psychophysical loudness matching procedure at different pulse rates. The change in dynamic range was calculated and compared.

1.4.3.1 Hypothesis on loudness perception varying the IPG

The effect of IPG on loudness perception was investigated in several studies in humans (e.g. McKay and Henshall, 2003; Carlyon et al., 2005; Schvartz-Leyzac and Pfingst, 2016) as well as in animals (e.g. Prado-Guitierrez et al., 2006; Ramekers et al., 2014). Lower amplitude levels were found when psychoacoustic measurements with CI users were performed at hearing threshold with increasing IPG (from 8 to 3000 μs, Carlyon et al., 2005). Schvartz-Leyzac and Pfingst (2016) also found an effect of IPG in bilateral implanted CI users by investigating ECAP recordings at supratheshold levels up to MCL. The analysis of their data revealed an increase in peak amplitude (N1-P2 amplitude, for details about ECAP see chapter 2.2) and slope of the amplitude growth function with increasing the IPG (7 and 30 μs) at equal stimulation level at each electrode. Therefore, for the fourth experiment it was hypothesized in this thesis, that an increase of IPG results in a decrease of amplitude level for similar loudness.

1.4.3.2 Hypotheses on dynamic range varying the IPG

Although different studies investigated the influence of the IPG on loudness perception in CI, only one study investigated the influence by IPGs on the BDR in CI users (McKay and Henshall, 2003). They increased the IPG (8.4, 45, and 100 μs) at two different pulse rates. They found a decrease in amplitude level at hearing threshold as well as at c-level (relates to MCL in CIs from the manufacturer Cochlear). The decrease in amplitude at hearing threshold was larger than at c-level, resulting in an increase of dynamic range. The largest decrease in amplitude at both amplitude levels was between 8.4 and 45 μs. They assumed, the increase of IPG resulted in a higher efficiency of the neural excitation.

In contrast, the animal experiment by Ramekers et al. (2014) revealed a constant dynamic range for normal hearing and 2-week deafened animals. Yet, in 6-week deafened animals an increase in dynamic range was observed as well. They obtained their data from implanted guinea pigs about the influence of IPG (2.1, 10, 20, and 30 μs) by measuring ECAP threshold and ECAP 50 % level (current level to achieve 50% of the maximum peak amplitude). A dynamic range in animals based on ECAP data and the BDR in humans is obviously not the same. Therefore, a comparison between experiments with animals and humans has to be conducted cautiously. However, they used similar pulse parameters as in the loudness matching experiment of this thesis.

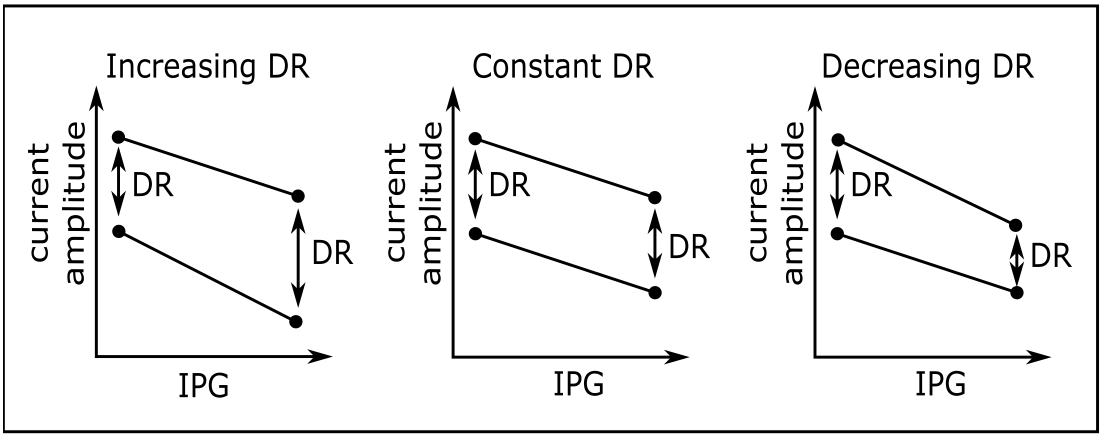


Figure 1.7: The assumed influence of the interphase gap (IPG) on current amplitude and dynamic range (DR). Left panel: The lower boundary is influenced stronger by the IPG then the upper boundary, what leads to an increase of the DR. Middle panel: The lower and upper boundary of the DR are influenced equally by the IPG, what leads to a constant DR. Right panel: The upper boundary is influenced stronger by the IPG then the lower boundary, what leads to a decrease of the DR.

Accordingly, in the fourth experiment of the thesis, subjects performed a loudness matching experiment. The upper boundary of the BDR was defined as MCL to avoid uncomfortable loudness during the time of testing. Additionally, it was intended to use equal adaptive tests for lower and upper boundary. Therefore, it was decided to determine a suprathreshold level as lower boundary instead of the hearing threshold (see chapter 3.5.2 for details). Based on the findings from McKay and Henshall (2003) and Ramekers et al. (2014) three different hypotheses regarding the dynamic range are made in this thesis. First, the dynamic range may increase with increasing IPG. This would be the case if the effect of the IPG is stronger at the lower than at the upper boundary of the dynamic range (Figure 1.7 left). Second, the dynamic range may stay constant, if the IPG effects both stimulation levels equally (Figure 1.7 middle). However, a third scenario may occur: The dynamic range may decrease if the effect of the IPG is stronger at the upper boundary than at the lower boundary of the dynamic range (Figure 1.7 right).

1.4.3.3 Hypothesis on loudness perception varying the pulse rate

In the fourth experiment of the thesis, the influence of IPG on loudness perception should be investigated at different pulse rates. Therefore, the impact of the pulse rate on loudness perception will also be analyzed. In the study of McKay and Henshall (2003) investigating different IPGs, they found no impact of stimulation rate (1 and 4 kHz) on loudness at both amplitude levels and therefore not in BDR. This differs from the results of Carlyon et al. (2005). They were able to report significant differences in loudness perception between pulse rates but at much lower rates (20 and 100 pps). From the results of both studies, it can be suggested, that loudness perception is less affected at higher pulse rates than at lower pulse rates. This suggestion is confirmed by Kreft et al. (2004). They were able to find three effects when investigating the influence of pulse rate on amplitude level. First, the loudness perception increased with increasing pulse rate, leading to a lower amplitude level at hearing threshold and MCL. Second, the BDR increased as well with increasing pulse rate. Third, the influence of pulse rate on loudness perception decreased at higher pulse rates, leading to smaller changes of amplitude level at higher pulse rates.

Consequently, as a result of the discussed studies, it was hypothesized in this thesis that the variation of pulse rates change loudness perception and therefore may impact the results regarding the influence of IPG and thus the calculated BDR.

2 Methodical Concept

For the experiments with CI subjects in this thesis, psychophysical and electrophysiological measurements were used. The psychophysical measurements were used to evaluate the ability of CI users to perform tasks like pitch discrimination or loudness matching. The electrophysiological tests provide information about the hearing system without a necessary active participation of the CI user. Detailed information about subjects, stimuli, materials and the test procedures of the experiments can be found in chapter 3.

2.1 Psychophysical tests

Depending on the research question, different appropriate kinds of psychophysic experiments were selected. In this thesis, to investigate rate pitch discrimination and loudness differences between pulse trains with different properties, an adaptive alternative forced choice (AFC) design was chosen.

2.1.1 Alternative Forced Choice Test

The AFC is a psychophysical method which is also known as interval forced choice (IFC) test. For an AFC the subject has to detect the target signal in N number of signals (N-AFC). The stimuli are presented after each other (one target/test signal and N-1 masker/reference signals) with a certain inter-stimulus interval between the stimuli. Dependent on the experiment the signals can be either presented in a random or in a fixed order. A random order is mostly used in detection (e.g. detecting a hearing threshold) or discrimination (e.g. discriminate between rate of a stimuli) experiments, where the subject has to decide which of the given intervals contained the target signal. In a properly implemented AFC test a subject does not favor one of the intervals. "The experiment is symmetrical and independent of the subject's a priori inclination to claim that a signal is present or not present" (Hartmann, 2004). In a fixed order paradigm, the subject does not need to indicate the position of the target, rather than the relation between target and reference, e.g. if the second tone was louder or softer than the first. Therefore, depending on the experimental design, the fixed order paradigm could be appropriate for a matching experiment. In addition, AFC tests can be performed either with constant stimuli or with an adaptive procedure. The term constant stimuli means that the parameters of target and masker are not changed and they are presented repeatedly (e.g. 10 times) during one run. After each run the score of correct identifications of the target signal ($P_{correct}$) is calculated. The score can be between chance level and 100%. The chance level is defined by the number of alternatives N (2-AFC: 50%, 3-AFC: 33%, 4-AFC: 25%). By using the adaptive procedure, a detection threshold or JND is determined. One parameter of the target is varied (e.g. pulse rate) after each presentation, while the parameters of the masker remain constant. Thereby, the score is defined by the selected adaptive procedure (for more details see section 2.1.2). In all presented psychopysical experiments in this work, 2-AFC procedures were selected.

2.1.2 Adaptive procedure

Adaptive procedures are commonly used in AFC experiments because of the short time that is required to determine a perception threshold. For example, adaptive procedures are used in the clinical routine for speech recognition tests in noise to determine a signal-to noise ratio (SNR) with whom the subject understands a certain percentage (e.g. 50%) of speech in noise. One parameter of the target signal (e.g. loudness or pitch) is varied for the adaptive test. The variation of the parameter depends on the response of the subject and is changed automatically by the algorithm. In the case of a correct answer the difference between masker and target is set smaller, thereby the task to discriminate between target and masker gets more difficult. In the case of an incorrect answer, the difference between masker and target is set larger, thereby the task to discriminate between target and masker gets easier. Additionally, the step size of the parameter change (a certain value or percentage) can alter during an experiment. At the beginning of the measurement, the step size is set larger to force a faster convergence of the procedure, during the experiment, the step size is set smaller automatically to increase the precision in determination of the threshold until a defined minimum step size is reached. The change in step size may be dependent on the subjects' responses. For example, the step size may be set smaller each time when an incorrect answer is followed by a correct answer. Different criterion can be defined for the termination of a measurement. The criterion may be a defined number of presented sentences in a speech recognition test or a defined number of reversals between increasing and decreasing the target parameter in the AFC experiment after reaching the minimum step size. At the end of a successful experiment, the difference of the target and masker converges to a certain value which defines a JND between masker and target or a threshold.

As a common example for an adaptive procedure, the staircase or up-down procedure by Levitt (1971) will be described in the following. In an 1up-2down procedure, the subject has to give two correct answers after each other for the parameter value to go down (decrease), while the parameter value goes up (increase) after one incorrect answer. Consequently for a 1up-3down procedure, three answers have to be correct in a sequence to decrease the parameter value. The typical test progress of the up-down procedure and the convergence around a certain threshold is depicted in figure 2.1.

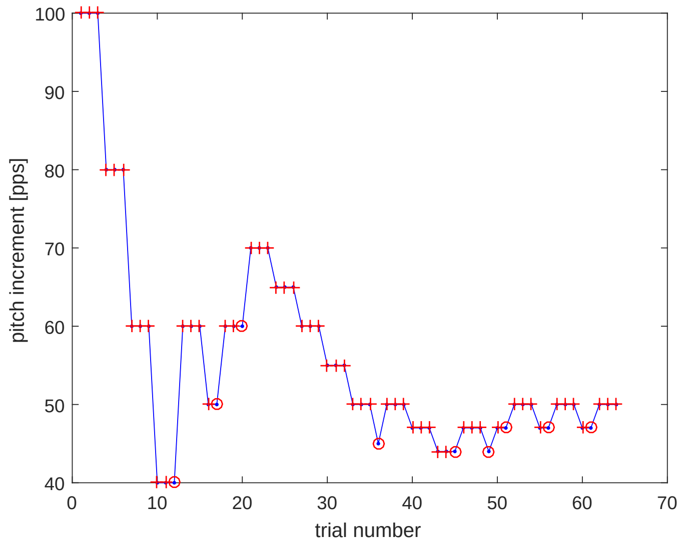


Figure 2.1: An exemplary 1up-3down adaptive staircase test of a subject. The crosses indicate correct answers, while the circles indicate incorrect answers. After each incorrect answer, the difference (e.g. rate increment) increases between masker and target, while three correct answers decrease this difference. If an incorrect answer is followed by three correct answer, the step size decreased. After reaching minimum step size, the procedure ends after eight reversals and converges around a certain value.

Dependent on the up-down procedure, a certain $P_{correct}$ or P_c at the end of the measurement can be reached (Levitt, 1971). The higher the number of correct answers that is required in a sequence to decrease the parameter value, the higher the P_c. The respective P_c for each up-down procedure is given by equation 2.1.

$$P_{down} = P_{up} \tag{2.1}$$

The equation describes that the probability at threshold/JND to go up is equal to the probability to go down. In case of the 1up-2down procedure, the probability of one incorrect answer or one correct answer followed by an incorrect answer is equal to the probability of two correct answers:

$$\underbrace{P_{correct} \cdot P_{correct}}_{\text{two times correct}} = \underbrace{(1 - P_{correct})}_{\text{one time incorrect}} + \underbrace{P_{correct}(1 - P_{correct})}_{\text{one time correct and one time incorrect}} \quad (2.2)$$

$$\rightarrow 2P^2_{correct} = 1 \quad (2.3)$$

$$\rightarrow P_{correct} = 1/\sqrt{2} = 0.707 \quad (2.4)$$

The values of $P_{correct}$ for different up-down procedures and the sequences for the parameter value to go up or down are depicted in table 2.1.

Table 2.1: Sequences of correct (C) and incorrect (I) answers for different up-down procedures for the parameter value to go up or down and the respective P_c (Data from Hartmann, 2004).

procedure	Sequence to go up	Sequence to go down	P_c
1up-1down	I	C	50 %
1up-2down	I CI	CC	70.71 %
1up-3down	I CI CCI	CCC	79.37 %
1up-4down	I CI CCI CCCI	CCCC	84.09 %

Combining an N-AFC test with a certain up-down procedure does not only result in a certain score but also in a certain sensitivity index d', rating the reliability of the result. The N-AFC test and up-down procedure should be combined in a way, to achieve an acceptable score as well as sensitivity index. The commonly used 2-AFC measurement in combination with an 1up-2down procedure has a d' of 0.77. This value can be increased to 1.16, using the same measurement with an 1up-3down procedure. Likewise the d' can be increased to 1.26 by combining the 3-AFC instead of the 2-AFC measurement with the 1up-2down procedure. In that case it is possible to increase the reliability of the result, although the desired P_c stays the same (Table 2.2, Hartmann, 2004).

Table 2.2: Depending on the $p_{correct}$ and the intervals of the AFC, a certain sensitivity index d' exists. The higher d' the more reliably the stimuli can be distinguished (Data from Hartmann, 2004).

procedure	$p_{correct}$	d'		
		2AFC	3AFC	4AFC
1up-1down	50 %	0	0.56	0.84
1up-2down	70.71 %	0.77	1.26	1.52
1up-3down	79.37 %	1.16	1.62	1.87
1up-4down	84.09 %	1.41	1.86	2.09

2.1.3 Psylab

The pychoacoustic measurements were conducted using a software in Matlab called "Psylab" (Version 2.6, Jade Hochschule, Oldenburg, Germany). Psylab enables to perform N-AFC detection and discrimination tasks (up to N=4) as well as 2-AFC matching experiments (Hansen, 2006). The up-down procedure described in Levitt (1971) can be combined with AFC procedures in Psylab for an adaptive control of the test variable as described in section 2.1.2. Different conditions can be investigated with Psylab by employing sequences of single runs (one run per condition) or performing interleaved tracks (Hansen, 2006). In an interleaved track, several runs with different conditions are nested into one run. Then all conditions are presented in a random order, while each condition is treated as a single run. Additionally, Psylab offers the option to use a graphical user interface for the subject to response (Figure 2.2). An experiment is designed in Psylab by editing the main, set and user script-files (see 7.1 Hansen, 2016).

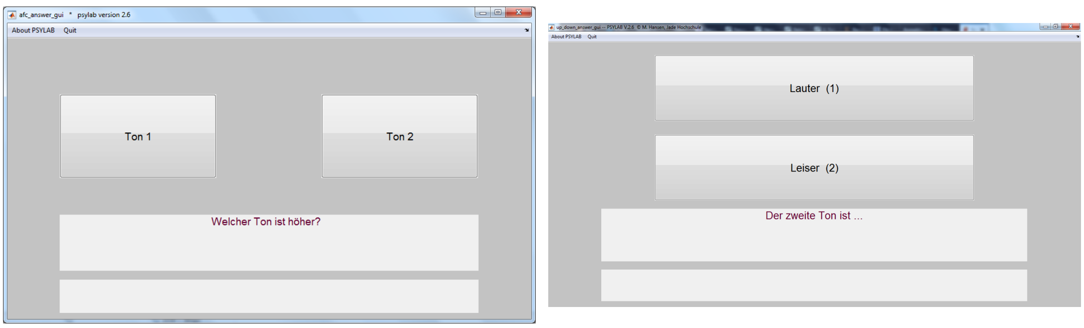


Figure 2.2: The graphical user interface for AFC measurements in Psylab with task and button labeling in german. Left panel: An example of a discrimination task to determine a just noticeable difference of rate pitch. Right panel: An example of an experiment for loudness matching of two different signals.

In general, Psylab was primarily designed to be used for acoustical stimulation. To perform the psychophysic tests with CI users, an electrical stimulation script was required. To be able to use electrical stimulation via Psylab, the software environment had to be modified. For this, Psylab was combined with a cochlear implant research interface (see section 2.1.4).

2.1.4 Research Interface

CI users wear a sound processor behind the ear or attached to the head that is wirelessly connected with the implant that resides under the skin of the head. The sound processor converts the acoustic signals to electrical stimulation. However, the clinical fitted sound processor has limitations for research. The characteristics of the processor and the performance of the patient after defined electrical stimulation is tested together and cannot be disentangled (e.g. due to patients individual clinical map, Litovsky et al., 2017). To investigate only the performance of the patient, it is necessary to use a research processor or another interface instead. The research processor is very similar to the normal clinical sound processor and can be worn behind the ear. Identical maps for each subject can be used and additional features such as gain control or noise reduction can be disabled (Litovsky et al., 2017). Another option to be even more flexible in stimulus control is a research interface without any speech processor. It can be used for testing fundamental capabilities of the subject without the limitations of a processor implementation and controls the implant via a personal computer (Litovsky et al., 2017).

The Research Interface Box II (RIBII, University of Innsbruck, Austria) can control the entire range of implants of the manufacturer MED-EL. The RIBII software works with different programming languages such as C++, Phython or Matlab. The latter is used in all experiments of the following chapters. With the newest version it is possible to use the RIBII software via the MAX-Box, the clinical fitting interface of MED-EL, instead of custom hardware. The RIBII provides charge balanced biphasic and triphasic pulses for uni- or bilateral stimulation. To prevent damage to the cochlea and the electrodes of the implant the charge is limited to 283 nC (Litovsky et al., 2017). No sound coding strategy algorithms are provided by the RIBII. Instead, it is possible to pre-render stimulus patterns from audio signals to present them via RIBII (Litovsky et al., 2017). Since the first implant of the I100 series (Pulsar), it is possible to record intracochlear potentials via the electrode array and the RIBII (intracochlear potentials: see chapter 2.2). For implants of the type I100 (Pulsar, Sonata, Concerto and Synchrony) the RIBII offers an amplitude scale between 0 and 127. Depending on the given range (0 to 3) a certain change in current per amplitude value is applied. The lower the range, the higher the accuracy by making small current steps (in current unit [CU], with 1 CU approximately 1 μA) between amplitude values but at the same time the possible maximum current is limited to low values. To be able to reach a higher maximum current with the RIBII, the range can be increased but at the same time the accuracy decreases, with larger current steps (Table 2.3). In older CI implants (C40 and C40+) the current steps and therefore the maximum amplitude differ from the I100 series.

Table 2.3: Current steps and current at maximum amplitude of the RIBII depending on the chosen range. This current steps and maximum current are valid for data streams with implants of the I100 series.

Range	current step	current at maximum amplitude
0	1.18 CU	150 CU
1	2.36 CU	300 CU
2	4.72 CU	600 CU
3	9.45 CU	1200 CU

In the following experiments, the RIBII software was programmed with Matlab 2016a (The Mathworks, Nattick). Within Matlab, an exchange streaming media file (stm-file) is built by creating, open and write a file (for sourcecode example see 7.2). The stm-file defines the pulse train the implant generates. The following details are part of the stm-file: implanttype, pulse properties (phase duration, gap, distance, amplitude), type of stimulation (sequential or parallel stimulation), range (from 0 to 3, change in current per step depending on given range), pulse form (biphasic or triphasic), number of stimulated electrodes, and electrodenumber. The stm-file may be build up as the follwing example:

```
Implanttype Synchrony
Default Pulsar Phase 30 Gap 2.1 Sequential
Ranges 3 3 3 3 3 3 3 3 3 3 3 3
Biphasic Distance 5000 Number 1 Channel 4 Amplitude 43.5
```

To finally stimulate the implant with the defined pulse train the stm-file is load into Matlab, where it is processed (for an example sourcecode see chapter 7.2).

2.2 Electrically Evoked Compound Action Potentials

To elucidate the neural health status of the auditory nerve, recordings of the nerve neural response may be helpful. The measurement of ECAPs provides a possibility to record the nerve response after electrical stimulation. The ECAP consists of combined responses of electrically activated auditory nerve fibers. The ECAP response consists of a prominent negative peak (N1) which appears within a time-window of about 0.2-0.4 ms after the stimulus onset (Abbas et al., 1999). The N1 peak is followed by a weaker positive peak (P2) within around 0.6-0.8 ms (Figure 2.3, Cullington, 2000). Depending on the stimulation level, the N1-P2 amplitude of the ECAP response can be 1-2 mV large (He et al., 2017).

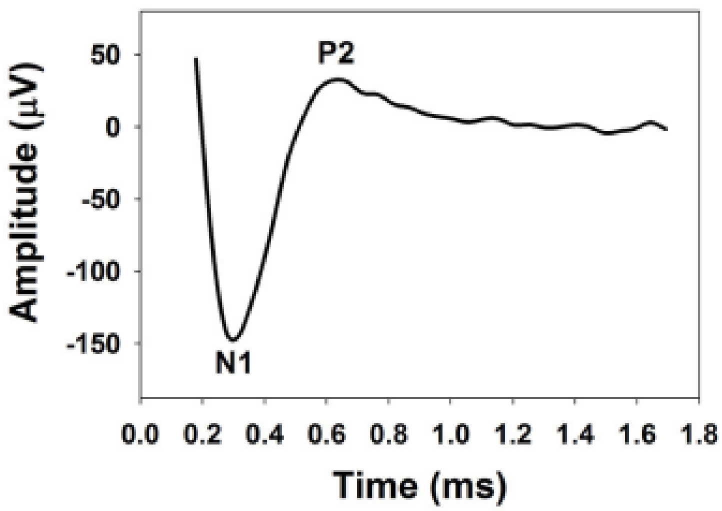


Figure 2.3: Exemplary data of an electrically evoked compound action potential (ECAP). The prominent negative peak (N1) after 0.2 ms as well as the weaker positive peak (P2) after 0.6 ms are visible in the response. (Figure modified from He et al., 2017)

The measurement of ECAPs in CI patients is easy to perform as no additional electrodes or software are necessary. Instead, the intra-cochlear electrodes of the implant are used for the ECAP measurement which allows a measurement close to the nerve (Hughes, 2010). One of these electrodes serves as a stimulation electrode, on a second (neighbored) electrode the neural response to the stimulation is recorded. In current CIs, the ECAP can be measured in patients via the telemetry function of the implant and the fitting software of the manufacturer. Compared to the electrically evoked auditory brainstem responses (EABR), the relatively large response to the stimulation is more robust and not affected by muscle activity due to the electrode position in the cochlear instead of on the scalp (Miller et al., 2000). On the other hand, the close position to the nerve fibers and the fact that the ECAP is an early evoked potential has also a negative impact on the measurement, as they lead to large stimulus artifacts that overlap with the neural response (Hughes, 2010). To reduce these artifacts, different techniques can be used. Two of these artifact reduction techniques that were used within this thesis are introduced in the following sections.

2.2.1 Alternating polarity paradigm

To measure the ECAP thresholds in this thesis, the fitting software of MED-EL (Maestro 7, MED-EL Innsbruck, Austria) was used. The Maestro software offers the "auditory nerve response telemetry (ART)" tool, which is a tool to record ECAPs at each electrode of the implant. To reduce artifacts, the software uses the alternating polarity method. With the alternating polarity method, the ECAPs were measured with both cathodic- (C) and anodic-leading (A) biphasic pulses (Figure 2.4 left). The response of these two pulses were averaged ($R = (C + A)/2$). Due to reversing the polarity of the pulse, the artifact is also reversed, while the polarity of the neural response following the pulses is constant (Hughes, 2010). It is assumed, that the amplitude of the artifact and the ECAP as well as the latencies are equivalent for both polarities (Hughes, 2010). Thereby averaging the responses would cancel out the artifact, while the neural response remains. But studies showed, that the assumption of identical latencies and amplitudes is not always true (Miller et al., 1998). Therefore, averaging the responses often leads to ECAP responses with reduced amplitudes compared to other artifact reduction methods (Baudhuin et al., 2016).

2.2.2 Masked response paradigm

The second artifact reduction method used within this thesis is the masked response paradigm. Based on the forward masking paradigm (Brown et al., 1990), the masked response paradigm was developed by Miller et al. (2000). To obtain the ECAP response from the artifact of the probe pulse, a subtraction technique is used. Therefore, the ECAP is recorded under different conditions using two pairs of masker and probe pulses and two masker-only stimuli (2.4 right). First a forward-masked response at a masker probe interval (MPI) outside the relative refractory time is recorded (A). The relative refractory time ends at 3 to 4 ms (Hey et al., 2017) and therefore the MPI in A (MPI1) should be about 4 ms or larger. Second, a fully masked probe, with a delayed masker pulse is recorded, with a short MPI (MPI2) in absolute refractory time (B) and subtracted from A to eliminate the probe artifact. The absolute refractory time lasts up to 500 μs, therefore the MPI2 should be shorter than 500 μs (Hey et al., 2017). Now the response from the two masker pulses in A and B have to be eliminated. Therefore, first the masker alone is recorded (C) and subtracted to eliminate the influence of the masker in A. Second, the delayed masker alone is recorded (D). This time the recording of D has to be added to eliminate the influence of the masker in B, which as subtracted before. The ECAP response without artifacts finally results in $R = A - B - C + D$. Despite four recordings (A, B, C, and D), the neural response to the probe stimulus is recorded only once (A).

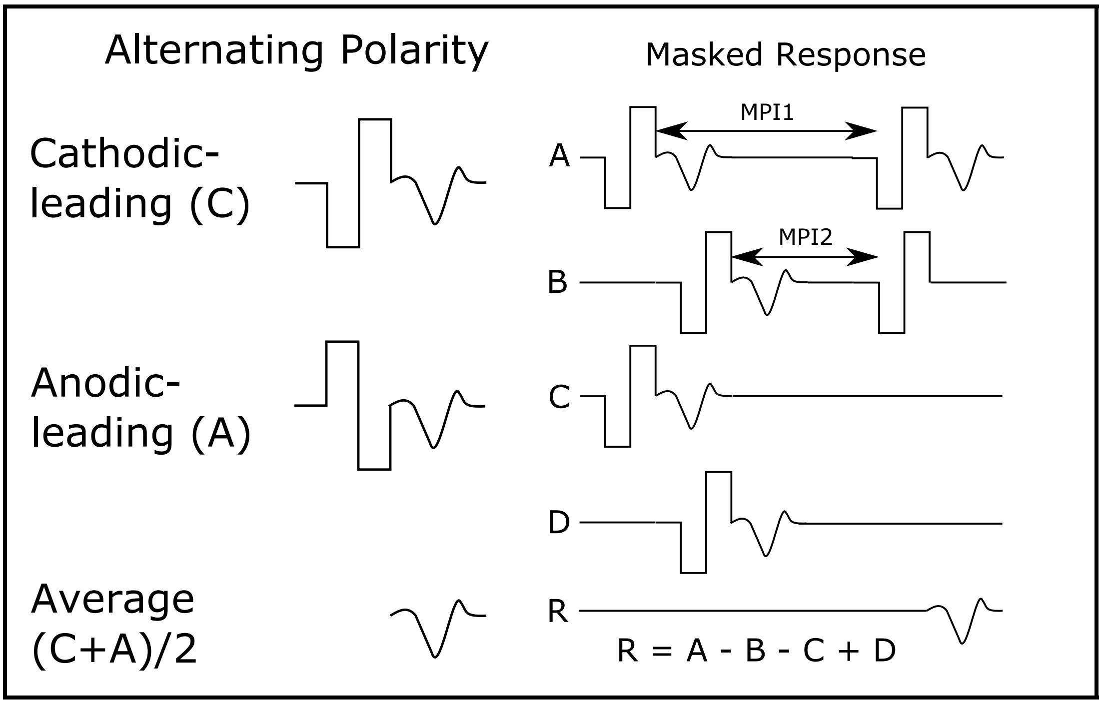


Figure 2.4: In this thesis, two different artifact reduction methods to record electrically evoked compound action potentials (ECAPs) were used. Left panel: The alternating polarity paradigm; Right panel: The masked response paradigm.

3 Material and Methods

A pitch discrimination experiment (PD), a pitch comparison experiment (PC), a loudness matching experiment (LM) and a facilitation effect experiment (FE), were conducted to investigate the effect of double pulses on rate pitch, the amount of facilitation effect in MED-EL implants as well as the effect of interphase gaps and pulse rate on loudness perception and dynamic range. To perform the experiments, two different concepts were used. For the experiments PD, PC and LM psychophysical tests were used (see chapter 2.1), for the experiment FE an electrophysiological test measuring ECAPs was used (see chapter 2.2). All experiments were performed under the authorization of the Ethics Committee of the University of Würzburg (31/15).

The following software and hardware was used throughout the experiments:

- Standard laptop (2.3 GHz Intel Core, 8 GB RAM, 64-Bit operation system)
- Matlab 2016a (The Mathworks, Natick, Massachusetts)
- Research Interface Box II (RIBII) software (University of Innsbruck, Austria)
- MAX Programming Interface with transmitting coil (MED-EL, Innsbruck, Austria) which contains RIB II
- MED-EL cochlear implant, I100 electronic platform (MED-EL, Innsbruck, Austria)
- Touchscreen monitor (Experiment PD, PC and LM)
- Maestro 6 and 7.0.3 system software (MED-EL, Innsbruck, Austria)
- IBM SPSS statistics 24 and 25 (IBM, Armonk, New York)
- RIB Detector Box I100 for control of the stimuli (MED-EL, Innsbruck, Austria)
- Tektronix TDS 5054 Digital Phosphor Oscilloscope (Tektronix, Beaverton, Oregan)

3.1 Subjects

37 subjects (27 to 84 years old) participated in the four experiments (Table 3.1). All subjects were recruited from the clinical routine and therefore a limited test time was available. Thus, different subjects participated in the four experiments (PD: S01-S23,

PC: S24-31, LM: S24-S32, FE: S33-S43). Additionally, the pitch discrimination experiment was split up in experiment A (PDA) with base rate 200 pps (S01-S11) and experiment B (PDB) with base rate 400 pps (S12-S23) to reduce the duration of testing for each participant. Also the facilitation experiment was split up in two experiments: the first approach (FE1, S33-S38) and the revised approach (FE2, S38-S43).

Table 3.1: Subject demographic data. S01-S11 participated in pitch discrimination experiment A (PDA), S12-S23 in pitch discrimination experiment B (PDB), S24-32 in the pitch comparison experiment (PC) and the loudness matching experiment (LM, except S32: only LM), and S33-43 in the facilitation experiment (FE1 and FE2).

Subject	Age [years]	Sex	CI experience [months]	monosyllable recognition in quiet @ 80 dB SPL	Device	Experiment
S01	68	f	67	83.00%	Sonata Standard	PDA
S02	46	m	113	82.50%	Sonata Standard	PDA
S03	68	f	79	73.75%	Pulsar Standard	PDA
S04	71	f	80	86.67%	Sonata Standard	PDA
S05	62	f	24	55.00%	Sonata FlexSoft	PDA
S06	75	m	134	76.67%	Pulsar Standard	PDA
S07	60	m	50	81.25%	Sonata FlexSoft	PDA
S08	34	m	28	57.50%	Sonata FlexSoft	PDA
S09	27	m	21	52.50%	Sonata Flex24	PDA
S10	59	m	22	73.33%	Sonata FlexSoft	PDA
S11	41	f	20	77.50%	Sonata FlexSoft	PDA
S12	50	m	11	84.00%	Synchrony FlexSoft	PDB
S13	55	f	73	60.00%	Sonata Standard	PDB
S14	71	m	16	79.19%	Synchrony FlexSoft	PDB
S15	72	m	24	68.33%	Sonata FlexSoft	PDB
S16	69	f	18	72.50%	Synchrony FlexSoft	PDB
S17	55	m	16	90.00%	Synchrony FlexSoft	PDB
S18	69	f	72	53.33%	Sonata Standard	PDB
S19	61	m	24	68.75%	Sonata FlexSoft	PDB
S20	36	f	98	83.33%	Sonata Standard	PDB
S21	60	m	50	86.25%	Sonata FlexSoft	PDB
S22	55	f	90	62.50%	Sonata Standard	PDB
S23	67	m	36	83.75%	Sonata Flex28	PDB
S24	54	m	91	82.50%	Sonata Standard	PC& LM
S25	67	m	24	67.50%	Synchrony Flex28	PC& LM
S26	54	f	42	62.50%	Sonata FlexSoft	PC& LM
S27	60	m	58	87.50%	Sonata Standard	PC& LM
S28	36	m	14	65.00%	Synchrony FlexSoft	PC& LM
S29	70	f	31	73.75%	Synchrony FlexSoft	PC& LM
S30	68	m	32	81.25%	Synchrony FlexSoft	PC& LM
S31	30	f	12	56.25%	Synchrony Flex28	PC& LM
S32	57	f	54	68.30%	Sonata Flex28	LM
S33	56	f	110	62.50%	Sonata Standard	FE1
S34	42	f	166	51.25%	Pulsar Standard	FE1
S35	38	f	123	65.00%	Pulsar Standard	FE1
S36	84	f	132	70.00%	Pulsar Standard	FE1
S37	79	m	29	50.00%	Synchrony Flex28	FE1
S38	59	m	16	72.50%	Synchrony Flex28	FE1& FE2
S39	62	m	20	65.00%	Synchrony FlexSoft	FE2
S40	27	m	136	82.50%	Pulsar Standard	FE2
S41	62	m	78	86.25%	Sonata Standard	FE2
S42	32	f	95	unknown	Concerto FlexSoft	FE2
S43	63	m	50	68.33%	Sonata FlexSoft	FE2

The subjects were implanted with CIs from MED-EL on the basis of the I100 electronic platform (Pulsar, Concerto, Sonata, Synchrony) and had at least 11 months of listening experience with the CI. Before testing, the impedance of the electrodes were checked as well as the programming of the processor for possible deactivated electrodes with the fitting software Maestro 6 (experiment PD, PC and LB) and 7 (experiment FE). Both checks were performed for the safety of the subject to ensure no deactivated electrodes were stimulated during the experiment. As speech recognition and pitch perception are related (Oxenham, 2012, see chapter 1.2.5), subjects were recruited, that scored at least 50% in the Freiburg monosyllabic word recognition test (averaged from their last four speech tests conducted at routine clinical follow-up visits). Merely, for subject S42 the speech score was unknown. It was expected that the performance in pitch discrimination in experiment PDA and PDB may be better with a higher score. A good speech perception is also important for an easy and fast explanation of the test procedure.

3.2 Pitch discrimination experiment

The pitch discrimination experiment aimed to determine the rate pitch JND at different test conditions. It was analyzed if a pulse train consisting of double pulses leads to a better rate pitch discrimination than the standard pulse train.

3.2.1 Stimuli

The stimuli were generated with a custom-designed software in Matlab 2016a (The Mathworks, Natick) and streamed to the implant via the RIBII software (University of Innsbruck, Austria), the MAX Programming Interface (MED-EL, Innsbruck, Austria) and the transmitting coil (Figure 3.1). For all tests of the pitch discrimination experiment, a biphasic pulse with a phase duration of 26.7 μs, an interphase gap of 2.1 μs, and a leading cathodic phase was used. At one single apical electrode contact (# 2), the signal with a duration of 0.5 s was presented at MCL of each subject. Depending on the test condition, the signals pulse train consisted of either standard biphasic pulses (single pulse, Figure 3.2a) or two biphasic pulses with same amplitude and a short IPI (double pulse, Figure 3.2b). Three double pulse conditions with different IPIs (15, 50 and 150 μs) were tested, whereas the IPIs were within the facilitation range (below

200 μs). Additionally, the single pulse condition and the three double pulse conditions were tested at two base rates: 200 pps (Experiment PDA) and 400 pps (Experiment PDB). As pointed out in the introduction (see chapter 1.2.5), the typical limit of rate pitch discrimination in CI users is at about 300 pps without training. Therefore, the base rates were chosen to represent rate values below and above this limit. It was assumed, that the achieved results above the typical limit may show a stronger effect using double pulse as stimulation compared to single pulses.

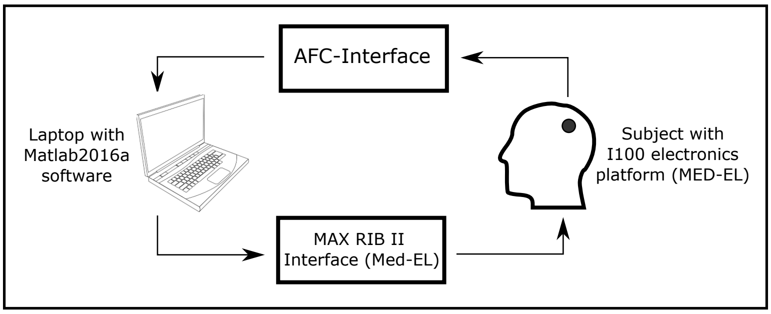


Figure 3.1: Setup of the experiments. The signal is generated by a custom-designed software in Matlab and streamed via the RIBII software, the MAX Programming Interface (MED-EL, Innsbruck, Austria) and the transmitting coil to the subjects CI. Via the grapical user interface on the touchscreen, the subject can reply to the presented stimuli (figure from Pieper and Bahmer, 2019).

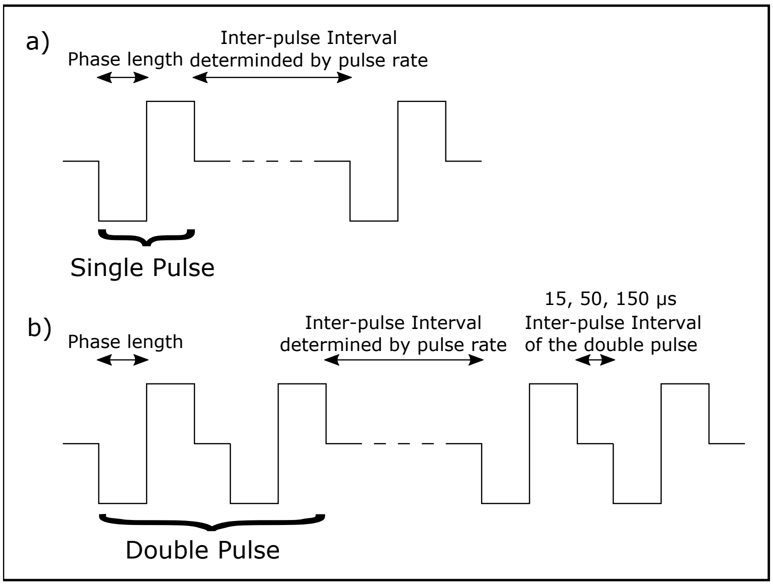


Figure 3.2: Illustration of the stimuli: a) biphasic single-pulse train b) biphasic double-pulse train with short IPI (figure from Pieper and Bahmer, 2019).

3.2.2 Test procedure

The test procedure consisted of two parts. Before the pitch discrimination procedure, a loudness balancing procedure was performed. This ensured equal loudness levels within and between test conditions for a comparison of the test conditions.

3.2.2.1 Loudness balancing procedure

To ensure equal loudness between pulse trains of the test conditions, a loudness balancing procedure adapted from (Landsberger and McKay, 2005) was performed. Therefore, the base rate of the single pulse stimulus (Exp. PDA: 200 pps, Exp. PDB: 400 pps) was adjusted to the MCL of the individual subject. During the loudness balancing procedure the single pulse stimulus at the base rate served as reference signal. Within the pitch discrimination procedure a constant loudness over a range of pulse rates had to be provided. Therefore, two additional pulse rates below and above the base rate per test condition (single pulse, double pulse with IPIs of 15, 50 and 150 μs) were balanced in loudness to the reference signal (Exp. PDA: 100 and 300 pps, Exp PDB: 283 and 566 pps). The pulse rates below the base rate were required because of the base roving of the pitch discrimination procedure, which could result in a rate below 200 and 400 pps, respectively (see chapter 3.2.2.2). The loudness of each stimulus was balanced to the reference by a pairwise comparison. In total, 11 loudness adjustments to the reference stimulus were performed. The reference and the test signal were presented pairwise in repetition for a direct comparison. The test signal was adjusted in amplitude until the subject reported equal loudness to the reference signal. Each pair of stimuli was balanced in loudness two times. First, the reference signal was presented followed by the test signal with its amplitude adjusted. Second, the order of presentation was reversed, i.e. the test signal was presented first with its amplitude adjusted, followed by the reference signal. The amplitude differences between reference and test signal of both adjustments were averaged and subtracted from the amplitude of the reference signal to obtain the amplitude of the test signal used in the following pitch discrimination procedure.

3.2.2.2 Pitch discrimination procedure

To determine the JND in rate pitch perception, which reflects the pitch discrimination threshold, an adaptive 2-AFC staircase procedure was used. The 2-AFC procedure was designed by means of the previously described Matlab script library Psylab (see chapter 2.1.3) and expanded to interface the MED-EL CIs via RIBII. The reference and test stimuli were presented in random order with an inter-stimulus interval of 0.3 s. In each of the four test conditions (single pulse, double pulse with IPIs of 15, 50 and 150 μs), the base rate stimulus served as reference condition, whereas the test stimulus contained the same test condition but with a higher pulse rate. After each presentation of both intervals, the subject had to decide which interval contained the signal with higher pitch and had to respond via touchscreen or mouse. Using the 3down-1up method by (Levitt, 1971), the point of 79.4% percent correct was tracked. Prior to the actual test procedure, each subject performed one training run to familiarize the subject with the stimuli, the task and the procedure itself. The training run was performed with the single-pulse train stimuli. In case the subjects failed to finish the training run, they were excluded from the experiment. In case the subjects successfully finished the training run, the test procedure was performed with one run per test condition in a random order. In experiment PDA, the reference stimulus was fixed at a base rate of 200 pps. The start value of the test signal was set to 300 pps and was varied in pulse rate following the 3down-1up adaptive staircase procedure. From the literature it was assumed, that subjects should be able to discriminate pitch differences of around 100 pps (Baumann and Nobbe, 2004; Bahmer and Baumann, 2014; McDermott and McKay, 1997; Townshend et al., 1987). Therefore, a maximum value of 350 pps (which allows a pitch difference up to 150 pps) was set. If a subject reached this limit five times during the test run, the adaptive procedure was stopped. In experiment PDB, the reference stimulus was fixed at a base rate of 400 pps. The standard deviation between the subjects JND was expected to be high (Baumann and Nobbe, 2004). To cover the high standard deviation, the start value of the test signal could be set as high as necessary to enable a proper pitch discrimination in each subject. However, to reduce measurement time, the start value was set individually for each subject depending on the JND of their training run. Due to unknown limits of discrimination thresholds, no additionally abortive criterion was set. In both experiments, the initial step size was set to 20 pps. At each reversal point, the step size was decreased by a factor 2 until the final minimum step size of 3 pps was reached (step sizes: 20, 10, 5, 3 pps). After obtaining the minimum step size, the test run ended after eight reversals, whereby the final JND in rate pitch was calculated by taking the median of the rates from the last six reversals. An adaption effect to the base rate as well as the loudness should be prevented by applying a base rate and an amplitude roving. The base rate and the amplitude were adjusted in each new presentation of test and reference signal within the AFC procedure by $\pm$ 10 pps (base rate) and $\pm$ 5% (amplitude). Thereby, both presented signals changed in the same direction and value. Additionally, linear inter- and extrapolation was applied to calculate the amplitudes for pulse rates other than the ones within the loudness balancing procedure. The inter- and extrapolation was applied to ensure equal loudness within one run of stimuli presentations despite different pulse rates of reference and test signal.

3.2.3 Statistical analysis

A possible statistical effect on pitch discrimination between IPIs as well as on amplitude between MCLs was tested by a one-way repeated-measures ANOVA. Therefore, the data was tested for normal distribution with the Kolmogorov-Smirnov test, a prerequisite for the repeated measures ANOVA. Another prerequisite is the sphericity (variances of differences between the tested conditions). The sphericity was tested with the Mauchley's test. If the sphericity was violated, the one-way repeated-measures ANOVA could be applied by using a Greenhouse-Geisser correction. In case of a significant effect, a post-hoc analysis (paired t-test with Bonferroni correction) was performed to determine differences between the conditions. Additionally a correlation analysis was performed between the pitch discrimination results and speech recognition threshold in quiet and the time after implantation, respectively. The correlation analysis calculates Pearson's linear correlation coefficient and the corresponding p-value using a two-tailed t-test. In all cases, significance was accepted for $p < 0.05$. While the Kolmogorov-Smirnoff test and the correlation analysis was performed using Matlab 2016a (The Mathworks, Natick), the remaining statistical analysis were performed using IBM SPSS statistics 24 (IBM, Armonk).

3.3 Pitch comparison experiment

In the pitch discrimination task, a pitch JND was determined, i.a a difference in rate pitch that is necessary to just be able to detect a difference between two pulse trains in rate pitch. Differently, in the pitch comparison task, two pulse trains are compared if in general a difference in pitch is detectable or if the two pulse trains are similar in pitch. For the pitch discrimination experiment above, each pulse train consisted of either single pulses or double pulses. In contrast, in the pitch comparison experiment, the pulse train consisted of alternating single and double pulses that were compared to single-pulse trains. Despite that the pulse trains may have the same pulse rate, the subjects had to indicate if they perceive any pitch change between the pulse trains.

3.3.1 Stimuli

To generate the stimuli the same setup as described in chapter 3.2.1 was used (Figure 3.1). For all test conditions within this experiment a biphasic pulse with a phase duration of 26.7 μs, an interphase gap of 2.1 μs, and a leading cathodic phase was used as in experiment PD. The signal was presented with a duration of 0.5 s at one single apical electrode contact (# 2) and at the subjects' MCL. Depending on the test condition the signal pulse train consisted of either standard biphasic pulses at pulse rates 200, 300, or 400 pps or an alternating pulse train consisting of single and double pulses with equal amplitudes (Figure 3.3) at a pulse rate of 400 pps. The IPI of the double pulses within the alternating pulse train was 50 μs. The alternating pulse train served as reference and the single-pulse trains were compared regarding pitch to that reference.

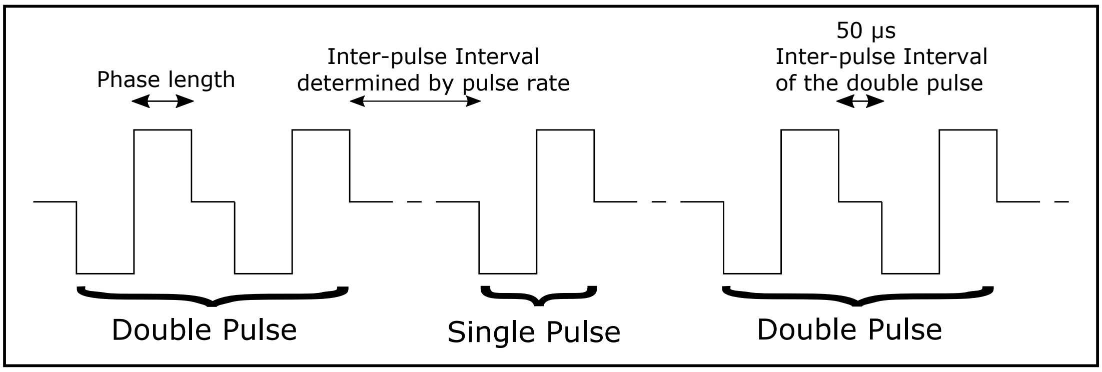


Figure 3.3: Illustration of the stimulus. Alternating single and double pulses with short IPI (figure from Pieper and Bahmer, 2019).

3.3.2 Test procedure

The test procedure consisted of a loudness balancing between test conditions and the actual pitch comparison procedure. The loudness balancing was necessary to ensure equal loudness levels between test conditions. Otherwise, a comparison of test conditions would not have been possible.

3.3.2.1 Loudness balancing procedure

The amplitude of the alternating pulse train was set to the MCL of each subject. The alternating pulse train served as reference condition in the subsequent pitch comparison experiment. Therefore, the single-pulse trains (test stimuli) were balanced in loudness to the reference. To balance the test stimuli to the reference signal, the same loudness balancing procedures as described in chapter 3.2.2.1 was used. Therefore, loudness adjustments of the test signals were done by repeatedly presenting the reference signal and one of the test signals for direct comparison. That allowed to modify the amplitude of the test stimulus until equal loudness to the reference signal was reported by the subject.

3.3.2.2 Pitch comparison procedure

The reference signal (alternating pulse train) and one of the test signals (single-pulse trains) were presented pairwise. The task of the subject was, to decide whether the pitch of both presented signals is (nearly) equal or differs from each other. These pairwise comparisons were performed for each of the test signals to judge which of the three test signals matched the alternating pulse train best in pitch. A repetition of each pair was possible for the subject by pressing a software button.

3.4 Facilitation effect experiment

The facilitation effect describes the potentiation of a neural response after pulse stimulation by a sub-threshold pre-pulse of an electrical stimulus. A potential facilitation effect was probably present in the pitch discrimination experiment, because of the short IPIs of the double pulses. However, no verification for an actual facilitation effect within the measurements was done. Therefore, the following experiment investigated the determination of a maximal facilitation effect with CIs from MED-EL. A similar test was already successfully performed with CI from the manufacturer Cochlear (Hey et al., 2017, see chapter 1.4.2).

3.4.1 Stimuli

To generate the stimuli the same setup as described in chapter 3.2.1 was used (figure 3.1), except for the graphical interface. As in experiment PD and PC, a biphasic pulse with an interphase gap of 2.1 μs and a leading cathodic phase was used for all test conditions within this experiment. The phase duration was set to 30 μs. The facilitation effect was determined at an IPI of 15 μs. A single apical electrode contact (#2) was stimulated, the neighboring electrode was recording (#1). The double pulses were separated by a distance of 12.38 ms, resulting in a repetition rate of approximately 80 pps.

3.4.2 Test procedure

The test procedure consisted of two parts. In the first part, the ECAP threshold had to be determined and in the second part an amplitude growth function was measured to determine the facilitation effect. Two different approaches (FE1 and FE2) were performed to measure the ECAP threshold and the facilitation effect and are described in the following.

To record ECAPs the fitting software from MED-EL only offers the possibility recording with an alternating polarity paradigm. This paradigm does not enable the possibility to conduct facilitation measurements. A prerequisite to objectively estimate a potential facilitation effect is a masker and probe paradigm. Therefore, in a first run of the experiment with six subjects (FE1), a custom made software was used to perform both measurements. The software was developed in Matlab by David Herrmann, M.Sc. (PhD student in the lab of Dr. Bahmer). It can address the RIBII to communicate with the subjects' implant. The software measured ECAPs with the masked response paradigm (Miller et al., 2000, see chapter 2.2.2), allowing the determination of ECAP threshold and facilitation effects via visual inspection. The MPI of trace A (MPI1) was set to 10 ms, to ensure a stimulation by the probe pulse outside the refractory time (figure 3.4. The MPI of trace B (MPI2) was set to 400 μs, within the absolute refractory time. The amplitudes of masker and probe were set to be equal. To obtain the final ECAP response, several ECAP responses derived from the masked response paradigm were averaged (50 repetitions). To determine the ECAP threshold several ECAP responses were measured at different amplitudes. The amplitude was increased from an amplitude below threshold until an ECAP response with a clear N1-P2 amplitude was observable or the subject responded that the loudness gets uncomfortable. Within this individually defined range (below threshold up to clear N1-P2 amplitude) the loudness was increased in steps of five amplitude levels on the RIBII scale (range 3, see chapter 2.1.4). After this screening, the measurement was repeated using a finer sampling of one amplitude level on the RIBII scale (range 3) and optimized amplitude levels as start and end point of the measurement. The ECAP threshold was determined as the stimulation level where a weak N1-P2 amplitude was still observable in the ECAP response.

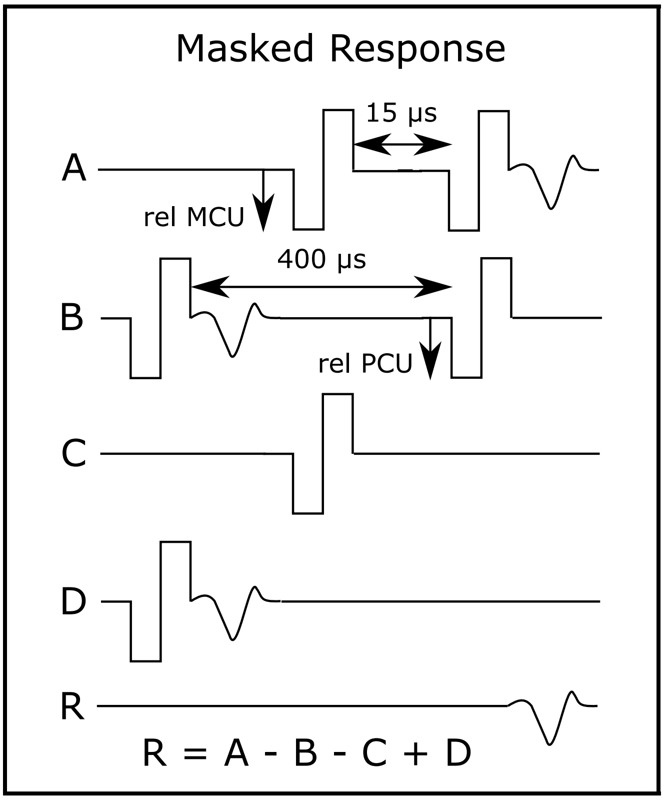


Figure 3.4: Illustration of the modified masked response paradigm to record the facilitation effect. For inducing a facilitation effect, the MPI in trace A was shortened to 15 μs.

After the determination of the ECAP threshold, the facilitation effect was further investigated. Therefore, an amplitude growth function was measured with the masker level varying around the ECAP threshold. The masker level was defined relative to the ECAP threshold (relative masker current unit [relMCU] of 0 CU := ECAP threshold in CU). The amplitude growth function was measured from relMCU = - ECAP Threshold up to relMCU = 94.50 CU in varying steps. The amplitude steps were larger in the beginning, got as small as possible around the ECAP threshold and got larger at levels larger the ECAP Threshold (-ECAP threshold, -283.5, -189, -113.4, -94.5, -75.6, -56.7, -37.8, -18.9, -9.45, 0, 9.45, 18.9, 28.35, 37.8, 47.25, 56.7, 75.6, 94.5 relMCU). Depending on the subjects ECAP threshold additional steps within the first recordings may be added (e.g. -378 relMCU or lower).

During the recording of the amplitude growth function, the probe pulse level was held constant. As for the masker level, a relative probe level was defined (relative probe current unit of 0 CU [relPCU] := ECAP threshold in CU). To measure the facilitation effect, the MPI1 of trace A was set to 15 μs instead of an MPI longer than the relative refractory time (Figure 3.4). The MPI2 in trace B was not changed.

The analysis of the data (see chapter 4.3.1) revealed that the custom made software showed a high noise floor. This high noise floor lead to a poor SNR and therefore to inaccurate measurements of the ECAP threshold. The inaccurate ECAP threshold in turn led to inaccurate amplitude growth functions to determine the facilitation effect. To enable the best possible determination of the ECAP threshold, in a revised test method with six subjects (FE2), the ART-tool of MED-EL's fitting software Maestro was used. The ART measures ECAP curves using the alternating polarity paradigm (see chapter 2.2.1). The ECAPs were measured from zero to 500 CU (500 CU is a security limit using the ART to prohibit uncomfortable loudness) with 50 iterations in 20 amplitude value steps. Additionally to the plotted ECAP curves for each amplitude level, the N1-P2 amplitude from each of these ECAP responses was plotted as an amplitude growth function. The ECAP threshold is determined by applying a linear regression to the amplitude growth function. In the case that no clear ECAP responses were visible the maximum amplitude was set higher (up to 700 CU) with the subjects' approval. If ECAP responses were still not observable, the data of the subject was excluded from the experiment. In case that ECAP responses were measured successfully, the measurement was repeated with optimized amplitude values as starting and ending point of the measurement that were selected based on the first ART to allow a higher resolution in 20 amplitude value steps.

Similar to the primary determination of the ECAP threshold with the custom made software, the determination of the facilitation effect was affected by a high noise level. By increasing the number of iterations, the noise floor could be substantially reduced. The higher the number of iterations was set, the better the noise was averaged out and therefore the remaining noise floor decreased. Therefore, the number of iterations was increased from 50 to 200. Additionally, more amplitude steps at suprathreshold ECAP levels were measured to be able to observe the decrease in N1-P2 amplitude (94.50, 189, 283.5 relMCU). If the subject declared uncomfortable loudness, the measurement was stopped. The remaining settings and procedure were set to the same values as in the first test procedure (MPI1: 400 μs, MPI2: 15 μs). However, in three subjects (S41, S42, S43) a ECAP measurement was recorded at a suprathreshold level with two different MPI1 (350 and 400 μs). This was similar as described in Hey et al. (2017) to determine which MPI1 leads to the better ECAP response (the higher N1-P2 amplitude).

During the whole test procedure no active participation of the subject was necessary despite reporting uncomfortable loudness.

3.5 Loudness matching experiment

In the loudness matching experiment, subjects had to detect changes in loudness. Pulses with larger IPGs to a pulse with the default IPG (2.1 μs) were presented and had to be compared by the subject. The measurement was performed at MCL and a level above hearing threshold. From the amplitude values of these loudness levels the dynamic range could be calculated for different rates.

3.5.1 Stimuli

To generate the stimuli, the same setup as described in chapter 3.2.1 was used (Figure 3.1). As in experiment PD, PC and FE, biphasic pulses with a leading cathodic phase were used for all test conditions of this experiment. The phase duration was set to 30 μs. The signal with a duration of 0.5 s was presented at one single electrode contact close to the middle of the electrode array (# 4), at three different pulse rates (200, 400, and 600 pps), and two different loudness levels. Altogether, three different pulse trains were generated using three different IPGs (Figure 3.5): 2.1 μs which was the reference condition as well as 10 and 30 μs which were the test conditions.

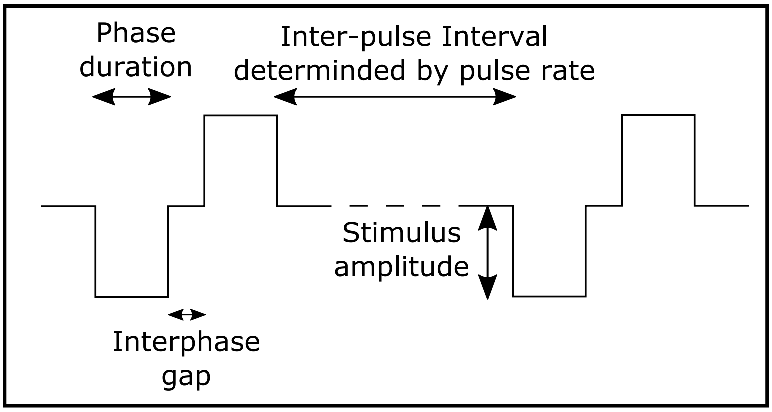


Figure 3.5: Illustration of the biphasic pulse train stimulus with different IPG (figure from Pieper et al., 2020).

3.5.2 Test procedure

An adaptive loudness matching procedure was conducted to determine the lower and upper bound of the subjects' dynamic range for each IPG. Thereby, the pulse trains with different IPGs were matched in loudness to pulse trains with the smallest IPG of 2.1 μs. Identical test procedures to obtain amplitude levels for lower and upper boundary of the dynamic range were used. This enabled the best possible comparison of methods when analyzing the results. However, to determine the absolute threshold (hearing threshold), which would be the optimal lower boundary to gain the complete BDR of each subject, an adaptive loudness matching procedure would be crucial. The loudness matching procedure aims to compare the stimuli in loudness. Thereby the amplitude of the test stimulus is varied around the reference signals loudness level, following the staircase paradigm. As a consequence of the staircase paradigm, the test signal may be softer than the reference during some point of the measurement procedure. Yet, no audible stimulus below hearing threshold exists and therefore no loudness matching procedure could be used. To be able to use the loudness matching procedure for the lower and upper boundary, an alternative, still audible, lower boundary was used. The lower boundary was set to the amplitude level representing 50% of the dynamic range on the amplitude scale between hearing threshold and MCL (from now on referred to as 50% amplitude dynamic range, ADR). Consequently, the complete BDR was not covered using 50%-ADR as lower boundary instead of hearing threshold. Still, the major part of the BDR was covered by the "upper" dynamic range from 50%-ADR to MCL as in CI users the loudness growth is not linear to the increase in amplitude

(Figure 3.6, compare Chatterjee et al., 2000). Especially the "upper" dynamic range covers the loudness range for speech perception in everyday situations as well as for most speech perception tests in the clinic at 65 or 80 dB SPL.

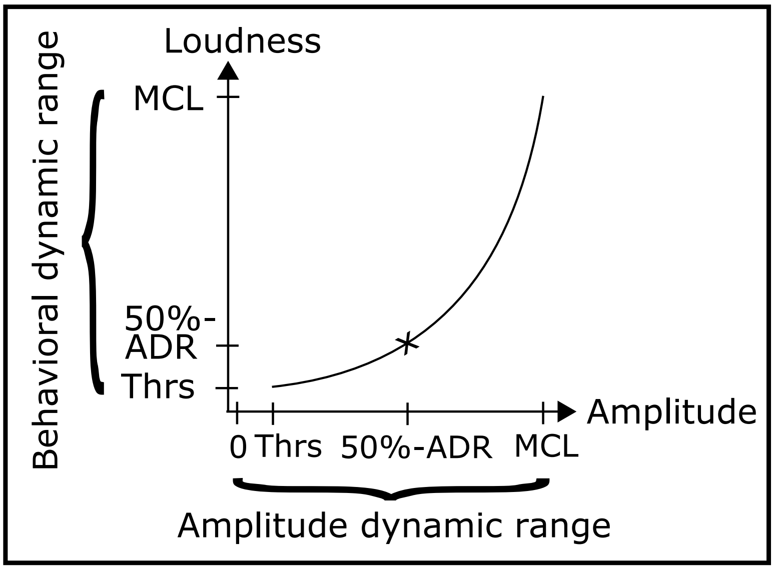


Figure 3.6: Schematic non-linear relation between stimulus amplitude and loudness at 50%-amplitude dynamic range (ADR) in most speech processors (figure from Pieper et al., 2020).

The test procedure consisted of two parts. First, the amplitude values for 50%-ADR and MCL for pulse trains with an IPG of 2.1 μs were determined. Therefore, the amplitude value was increased from zero until the subject stated that MCL was reached. Afterwards, the amplitude value was decreased until the subject was not able to detect a sound anymore. This procedure was repeated for each pulse rate (200, 400, and 600 pps) and hearing threshold and MCL was noted. The amplitude value for 50%-ADR was calculated from MCL and hearing threshold as 50%-ADR was used in the following matching experiment. Second, an adaptive 2-AFC procedure with 1down-1up method was performed to match the loudness between stimuli with various IPGs. The AFC test was designed using the Matlab script library Psylab which was expanded to interface MED-EL CIs via the RIBII. The pulse train with an IPG of 2.1 μs was the reference signal, whereas the pulse trains with an IPG of 10 and 30 μs was the test signal. Separated by an inter-stimulus interval of 0.3 s, the reference signal was presented first, followed by the test signal. Both stimuli were presented at the same pulse rate. The amplitude level of the reference signal was fixed at the beforehand determined level. The amplitude level of the test signal with either 10 or

30 μs IPG started 28.35 CU above the amplitude level of the reference tone. During one test run, this amplitude level was varied according to the adaptive procedure and the RIBII range 3 setting. The subjects' task was to decide via touchscreen display whether the second tone (test singal) was softer or louder than the first tone (reference tone). All test conditions (IPG, pulse rate) were nested into one test run which meant that each condition was randomly presented within one test run. In total the subjects performed two test runs, one per loudness level (MCL and 50%-ADR). Half of the subjects started with MCL and half of the subjects with 50%-ADR. The initial step size of amplitude change was set to 56.7 CU. At each reversal point, the step size was decreased by factor 2 until the final minimum step size of 9.45 CU was reached (step sizes: 56.7, 28.35, 14.18, 9.45 CU). The minimum step size was defined by the current step of the RIBII range 3 setting. After obtaining the minimum step size, the test run ended after eight reversals. The estimated amplitude of the test signal by the test was calculated by taking the median of the amplitudes from the last six reversals.

3.5.3 Statistical analysis

A potential statistical effect on amplitude of IPG and pulse rate was tested by a two-way repeated-measures ANOVA for MCL, 50%-BDR and dynamic range. As for the pitch discrimination experiment, the data was tested for normal distribution and sphericity (see 3.2.3). In case of a significant interaction effect between the two factors (IPG, pulse rate) an additional one-way repeated-measures ANOVA was performed for each level of both factors. Without interaction effect, no further ANOVA was required. To determine differences between the conditions, a post-hoc analysis (paired t-test with Bonferroni correction) was performed. In all cases, significance was accepted for $p < 0.05$. All statistical data was analyzed using IBM SPSS statistics 25 (IBM, Armonk).

3.6 Validation of the setups

Before the subjects performed the test, the setup of each experiment within this thesis had to be validated for feasibility and security reasons (e.g. avoiding charge inbalanced pulses or in controlled pulse amplitudes). Therefore, the transmitting coil was positioned on the RIB detector box with an embedded I100 CI system. The detector box was connected to an oscilloscope. The stimulus was visible on the oscilloscope screen after starting the experimental procedure, and the pulses could be checked for its correct amplitude, phase duration, IPG, IPI, pulse rate, pulse form, and the correct duration of stimulus presentation.

4 Results

4.1 Rate pitch discrimination with double pulses

The presented data within this chapter was originally published and discussed in Pieper and Bahmer (2019). It was investigated if the application of double pulses within a pulse train leads to a improvement of rate pitch discrimination.

4.1.1 Loudness perception with single and double pulse stimulation

Loudness cues may influence pitch perception, which would confound a comparison between test conditions. Therefore, possible loudness cues were eliminated by balancing the stimuli in loudness. It was hypothesized in this thesis that the application of pulse trains consisting of biphasic double pulses with a short IPI may influence the loudness perception compared to pulse trains consisting of biphasic single pulses.

In experiment PDA, the loudness was balanced between a single-pulse train and three different double-pulse trains (IPI: 15, 50, and 150 μs) at MCL with pulse rate 200 pps. The corresponding amplitude levels after balancing of each subject are depicted in figure 4.1 (left) according to test condition with the single pulse condition as reference (S01: no IPI of 15 μs). Despite of high variability of amplitude levels between subjects, it is clearly visible, that the single-pulse train required the highest amplitude for each subject. In contrast, the double pulse train with an IPI of 15 μs required the lowest amplitude level in most subjects. However, subject S01 showed the lowest amplitude at an IPI of 150 μs and subject S11 at 50 and 150 μs (identical amplitudes). In subject S08, similar to S11, the amplitude remained constant between 50 and 150 μs and in subject S09 the amplitude remained constant between 15 and 50 μs. For a better visualization, the amplitudes in CU were normalized according to equation 4.1 for each subject between conditions. $x(i)$ represents the subjects' amplitude level of one test condition, x_{max} and x_{min} the maximal and minimum amplitude value of the four test conditions of the particular subject.

$$x(i)_{norm} = \frac{x(i) - x_{min}}{x_{max} - x_{min}} \tag{4.1}$$

The normalized data is depicted in figure 4.1 (right). Similar as for the individual data it can be observed that the amplitude has to be decreased for all double pulse conditions for equal loudness (MCL) to the single pulse condition. An increase in IPI requires an increase in amplitude to ensure a match in loudness. The analysis of the data with a one-way ANOVA revealed a significant effect of amplitude level on test condition ($F(1.54,11.56) = 62.24$, $p < 0.001$). Between single pulse condition and all double pulse conditions, the amplitude had to be reduced around 10 to 25% (up to 200 CU) for each subject for equal loudness perception. The pairwise post-hoc analysis confirmed, that each double pulse condition differs significantly in amplitude compared to the single pulse (SP) condition (SP vs. 15 μs: $p < 0.001$; SP vs. 50 μs: $p < 0.001$; SP vs. 150 μs: $p = 0.001$). In two of three comparisons between double pulse conditions, significant changes in amplitude could be observed (15 μs vs. 150 μs: $p = 0.008$; 50 μs vs. 150 μs: $p = 0.013$), whereas one comparison revealed a non-significant change in amplitude (15 μs vs. 50 μs: $p = 0.204$).

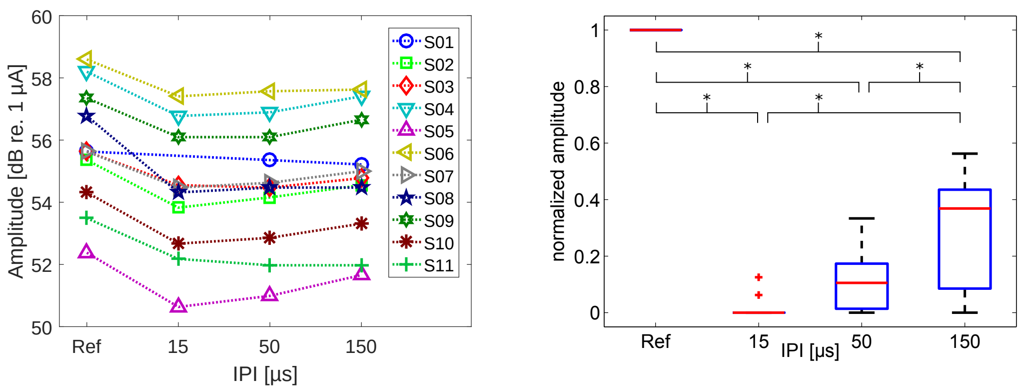


Figure 4.1: Left panel: MCL amplitudes (in dB) at equal loudness for the single-pulse reference (Ref) and for double-pulse stimuli with IPI of 15, 50, or 150 μs. The stimulation rate was 200 pps. Right panel: Boxplots of normalized amplitude for the single-pulse reference (Ref) and double-pulse stimuli. The red lines show the median and the asterisks indicate significant differences (p <0.05, figure from Pieper and Bahmer, 2019).

In experiment PDB loudness was balanced between a single-pulse train and three different double-pulse trains (IPI: 15, 50, and 150 μs) at MCL with pulse rate 400 pps. The corresponding amplitude levels of each subject are depicted in figure 4.2 (left) according to the test condition with the single pulse condition as reference. Despite the high variability of amplitude levels between subjects, it is clearly visible that the single-pulse train required the highest amplitude for each subject. For seven out of twelve subjects, the lowest amplitude level is required for double-pulse trains with an IPI of 15 μs. However, five subjects (S13, S14, S17, S20, S23) showed the minimal amplitude at an IPI of 50 μs and two subjects (S12 and S18) had their minimal amplitude at an IPI of 15 and 50 μs (identical amplitudes). Towards an IPI of 150 μs this amplitude increased in all subjects. As in experiment PDA the amplitudes in CU were normalized according to equation 4.1 for each subject between conditions. The normalized data is depicted in figure 4.2 (right) and confirms, that the amplitude has to be decreased for all double pulse conditions compared to the single pulse condition and that an increase in IPI leads to an increase in amplitude. The analysis of the data with a one-way ANOVA revealed a significant effect of amplitude level on test condition ($F(1.73,19.01) = 149.3$, $p < 0.001$). Between single pulse condition and all double pulse conditions, the amplitude had to be reduced about 10 to 20% (up to 100 CU) for each subject to provide the same loudness perception. The pairwise post-hoc analysis confirmed, that each double pulse condition differs significantly in amplitude compared to the single pulse condition (SP vs. 15 μs: $p < 0.001$; SP vs. 50 μs: $p < 0.001$; SP vs. 150 μs: $p < 0.001$). Also in two of three comparisons between double pulse conditions, significant changes in amplitude could be observed (15 μs vs. 150 μs: $p < 0.001$; 50 μs vs. 150 μs: $p < 0.001$), whereas one comparison revealed a non-significant change in amplitude (15 μs vs. 50 μs: $p > 0.99$).

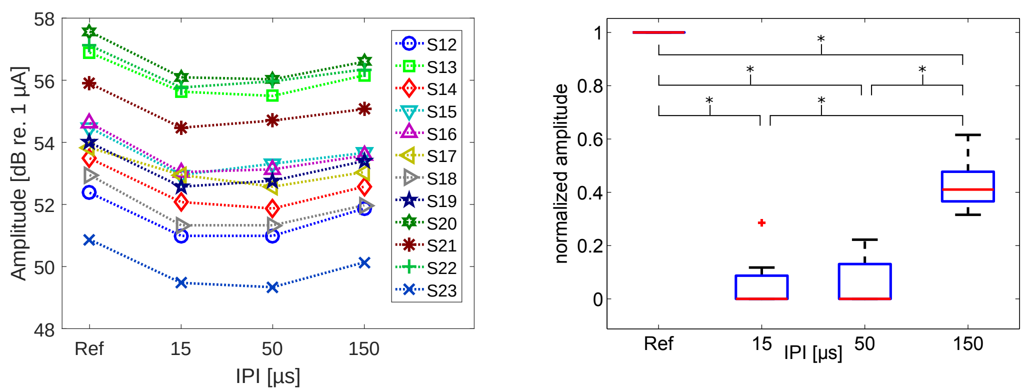


Figure 4.2: Left panel: MCL amplitudes (in dB) at equal loudness for the single-pulse reference (Ref) and for double-pulse stimuli with IPI of 15, 50, or 150 μs. The stimulation rate was 400 pps. Right panel: Boxplots of normalized amplitudes for the single-pulse reference (Ref) and double-pulse stimuli. The red lines show the median and the asterisks indicate significant differences (p <0.05, figure from Pieper and Bahmer, 2019).

None of the subjects in experiment PDA and PDB reported differences in pitch between the single- and double pulse train with identical pulse rate and with loudness balanced stimuli.

4.1.2 Pitch discrimination procedure

The pitch discrimination was performed with loudness balanced stimuli for single-pulse trains and double-pulse trains with different IPIs (15, 50, 150 μs). It was expected that all subjects were able to discriminate pitch at a base rate of 200 pps (exp. PDA). In contrast, the ability of the subjects to discriminate pitch at a base rate of 400 pps (exp. PDB) was expected to deteriorate.

The performance of the subjects in experiment PDA is depicted in figure 4.3 (left). The JND in rate pitch (discrimination threshold) is shown for each test condition. The JND of the single-pulse train stimulation was set as reference and should be compared with the results of the three double-pulse conditions. Two subjects (S04 and S05) were excluded from the experiment as they reached the limit of 150 pps rate increment already during the training run. Only three test conditions were measured in one subject (S01), who did not perform a test run with a double-pulse train at an IPI of 15 μs. The subjects S06 and S11 reached the rate increment limit of 150 pps in one double pulse condition (S06: 15 μs, S11: 150 μs) leading to an abortion of the particular test run. Therefore, only three data points could be determined for both subjects. The results of the pitch discrimination procedure revealed a high inter-subject variability. The best performers had a JND between 20 and 40 pps rate increment (around 10 to 20% relative rate increment). Though, some subjects barely reached a discrimination threshold of 150 pps rate increment, which was set as the limit to stop the experiment (around 80% relative rate increment). The individual data did not reveal a trend for one specific IPI condition. The statistical analysis with the one-way repeated-measures ANOVA confirmed the observation. No significant effect could be found between test conditions ($F(3,15) = 0.202$, $p = 0.893$). Because of the missing data for three subjects (S01, S06 and S11), the ANOVA rejects the complete data set of these subjects within the analysis process. Therefore, an additional statistical analysis was calculated by means of the general estimation equation to include the incomplete data sets. The general estimation equation confirmed the result of the ANOVA ($p = 0.495$).

The values of the discrimination performance of the subjects in experiment PDB is depicted in figure 4.3 (right). The JND in rate pitch is shown for each test condition. The JND of the single-pulse train stimulation was set as reference and is compared to the results of the three double-pulse conditions. Three subjects (S15, S17, and S20) were not able to perform the discrimination task and therefore were excluded from the experiment. Two of these subjects (S17 and S20) had a reversed pitch perception and consistently judged the higher pulse rate to be lower in pitch and vice versa. As for base rate 200 pps, the results of the pitch discrimination procedure revealed again a high inter-subject variability. The best performers had a discrimination threshold between 100 and 200 pps rate increment (around 25 to 50% relative rate increment). Nevertheless, most subjects had a JND between 400 and 600 pps rate increment (around 100 and 150% relative rate increment). The discrimination threshold of one subject (S19) exceeded even 600 pps and required extremely high rate increments (rate increment > 1000 pps; not shown in figure 4.3 (right) for better visualization of the remaining data) to finish the pitch discrimination test. The individual data of the subjects did not reveal a trend favoring one specific IPI condition. As in experiment PDA, the statistical analysis with the one-way repeated-measures ANOVA confirmed no significant effect between test conditions (F(1.08,8.63) = 0.919, p = 0.372).

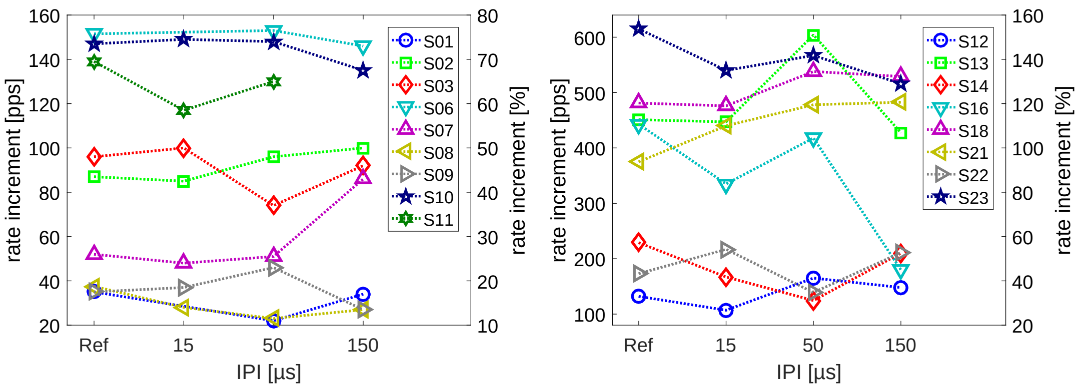


Figure 4.3: Individual rate pitch JNDs of each subject for each measurement condition with single pulse condition as reference at a base rate of 200 pps (left) and at a base rate of 400 pps (right). As the rate increment of subject S19 is higher than 1000 pps, the data is not shown to allow a better visualization of the remaining data (figure from Pieper and Bahmer, 2019).

4.1.3 A best double pulse for each subject?

It seemed that for every subject at least one double pulse IPI condition could be determined with a better pitch discrimination than the single pulse condition. This double pulse condition is denoted as "best double pulse". The individual best double pulses were grouped and compared to the single pulse condition for pitch discrimination results at both investigated pulse rates (200 and 400 pps, Figure 4.4).

In experiment PDA, three subjects (S02, S07, and S11) benefited from an IPI of 15 μs, three subjects (S01, S03, and S08) had their best pitch discrimination at 50 μs IPI and the remaining three subjects (S06, S09, and S10) at 150 μs IPI. In experiment PDB one subject (S21) did not benefit from any of the three double pulse conditions. His best pitch discrimination result was with single pulse stimulation. From the remaining subjects two subjects (S12 and S18) had their best pitch discrimination result at 15 μs IPI, for two subjects (S14 and S22) the best result was at 50 μs IPI, and for four subjects (S13, S16, S19, and S23) it was at 150 μs IPI.

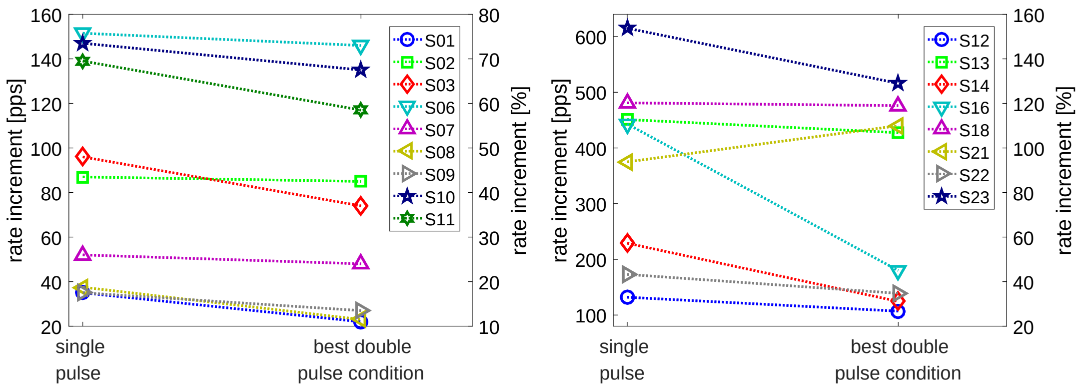


Figure 4.4: Comparison between single pulse train stimulation and the individually best IPI condition with double pulse train stimulation for rate pitch JNDs at 200 pps (right) and rate pitch JNDs at 400 pps (left).

A pairwise comparison analysis of the rate pitch JND at the best IPI of each subject would bias the analysis and therefore lead erroneously to a significant result. Instead, by calculating the differences between the single pulse condition and each double pulse condition a potential best IPI could be tested with the one-sample Wilcoxon signed-rank test. No significant effect could be found for each median of the generated differences for both pulse rates (200 pps: Difference 15 μs-IPI to SP: p = 0.348; Difference 50 μs-IPI to SP: p = 0.373; Difference 150 μs-IPI to SP: p = 0.674; 400 pps: Difference 15 μs-IPI to SP: p = 0.678; Difference 50 μs-IPI to SP: p = 0.859; Difference 150 μs-IPI to SP: p = 0.515).

4.1.4 Correlation of pitch discrimination with speech and time of implantation

As pointed out in the introduction, pitch perception can be related to speech perception (Oxenham, 2012). Therefore, it was expected that subjects with good speech perception might discriminate rate pitch better than subjects with low speech perception values. Thus, the JND in rate pitch discrimination were correlated with speech perception scores (Freiburger monosyllables in quiet at 80 dB SPL) derived from routine clinical testing in a sound-proof booth. Additionally, the pitch discrimination was correlated with the time of implantation. The assumption was, that with a longer listening experience subjects are more experienced/trained in pitch perception, as it was shown in Goldsworthy and Shannon (2014).

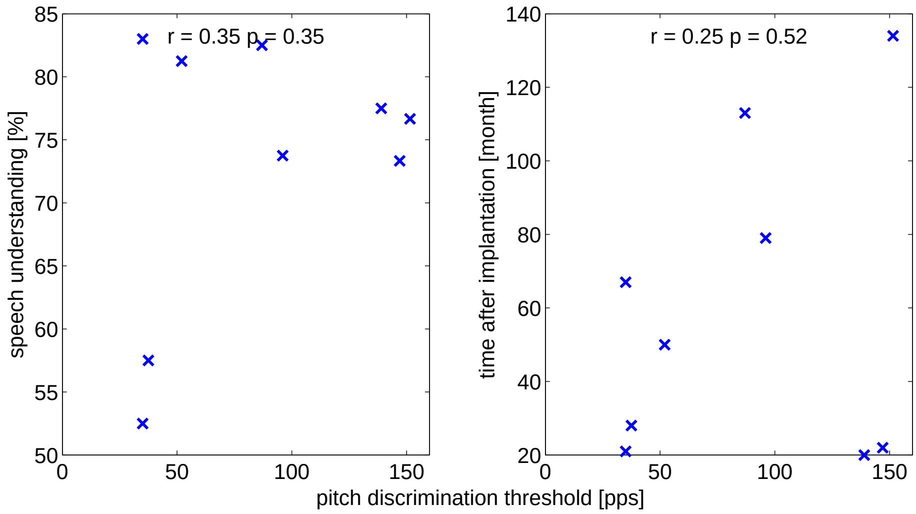


Figure 4.5: Correlation analysis between pitch discrimination threshold at 200 pps and speech recognition score of Freiburger monosyllabic words in quiet (left) and time after implantation (right). No correlation could be observed.

Figure 4.5 depicts the correlation analysis for a base rate of 200 pps (exp. PDA). No correlation between rate pitch discrimination and speech perception ($r = 0.35$, $p = 0.35$) nor between rate pitch discrimination and CI listening experience was observed ($r = 0.25$, $p = 0.52$). Similarly, for base rate 400 pps (exp. PDB) no correlation was found between speech reception and pitch discrimination (r = -0.15, p = 0.7) nor between listening experience and rate pitch discrimination (r = -0.19, p = 0.63, Figure 4.6).

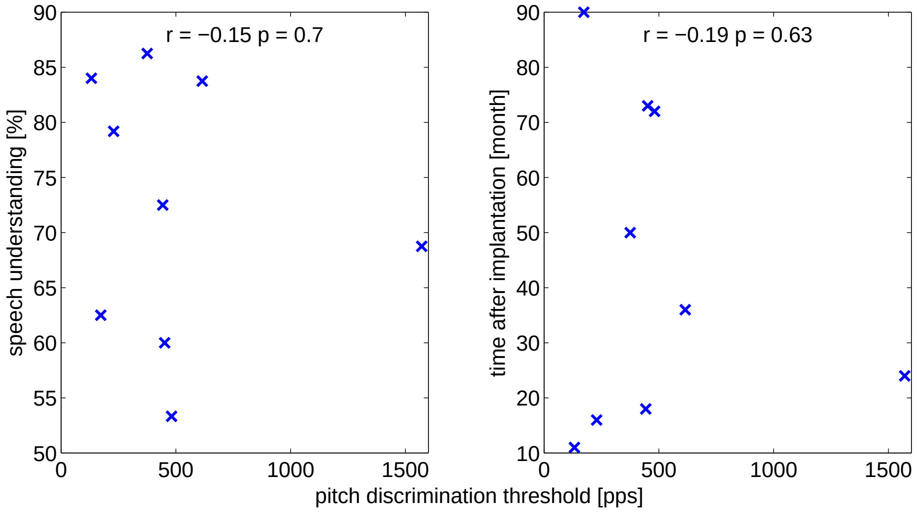


Figure 4.6: Correlation analysis between pitch discrimination threshold at 400 pps and speech recognition score of Freiburger monosyllabic words in quiet (left) and time after implantation (right). No correlation could be observed.

4.2 Pitch comparison with an alternating single- and double-pulse train

The presented data within this chapter was originally published and discussed in Pieper and Bahmer (2019).

The loudness was balanced at MCL between the alternating single- and double-pulse train and the single-pulse train conditions (200, 300, and 400 pps). The corresponding amplitude levels of each subject are depicted in figure 4.7 (left) according to test condition with the alternating pulse train as reference. Despite the high variability of amplitude levels between subjects, it is clearly visible that the alternating pulse train is lowest in amplitude compared to the single-pulse trains in each subject. In most subjects, amplitude levels of the single pulse conditions are similar at different pulse rates. An exception is S28 with a distinct and visible decrease in amplitude level with increasing pulse rate. The analysis of the data with a one-way ANOVA revealed a significant effect of amplitude level on test condition (F(1.41,9.85) = 42.393, p < 0.001).

Between alternating single- and double-pulse train and all single pulse conditions, the amplitude had to be increased for each subject for equal loudness perception. The pairwise post-hoc analysis (Bonferroni correction) confirmed that each single pulse condition differs significantly in amplitude compared to the alternating pulse train (Alternating vs. 200 pps: $p < 0.001$; Alternating vs. 300 pps: $p < 0.001$; Alternating vs. 400 pps: $p = 0.002$). However, between amplitudes of single puls-trains with different pulse rate no significant changes were found (200 vs. 300 pps: $p > 0.99$; 200 vs. 400 pps: $p > 0.99$; 300 vs. 400 pps: $p > 0.99$).

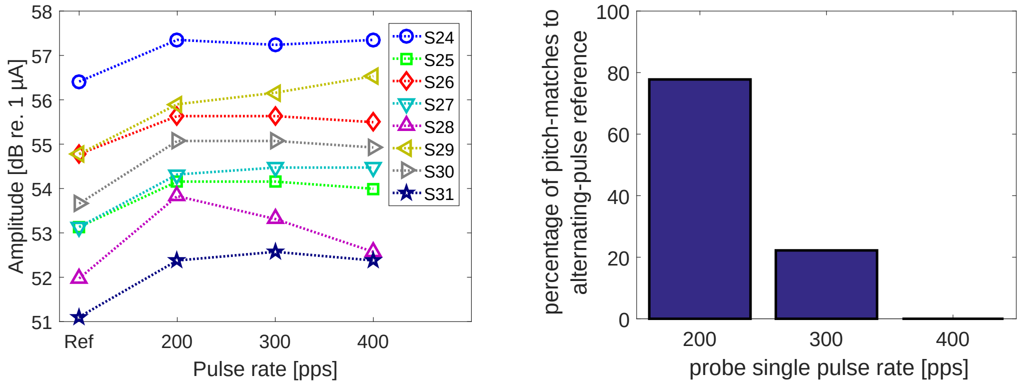


Figure 4.7: Left panel: Amplitudes for MCL of different pulse trains. The three single pulse stimuli with 200, 300, and 400 pps were loudness balanced to the alternating pulse train at 400 pps which served as a reference. Figure from Pieper and Bahmer (2019). Right Panel: Pitch comparison of alternating pulse train at pulse rate 400 pps with single-pulse train at pulse rates 200, 300 and 400 pps (Figure from Pieper and Bahmer, 2019). Most of the subjects rated the alternating pulse train similar in pitch as the 200 pps single-pulse train.

The results of the pitch comparison are depicted in figure 4.7 (right). The bar chart shows the number of subjects (in percentage) that estimated the 400 pps alternating pulse train similar in pitch with either the 200, 300, or 400 pps single-pulse train. Nearly all subjects estimated the alternating pulse train to be similar in pitch with the 200 pps single-pulse train. However, subject S25 assessed the alternating pulse train to be similar in pitch with the 300 pps single-pulse train. One subject (S30) was not able to distinguish pitch between 200 and 300 pps and therefore assessed the alternating pulse train to be similar in pitch with both single-pulse trains. None of the subjects reported that the alternating pulse train was similar to the 400 pps single-pulse train. Although the subjects were able to match the alternating pulse train to one of the presented single-pulse trains, they commented that the pitch quality of both stimuli types were not completely identical.

4.3 Recording of the facilitation effect

The facilitation describes the enhanced neural response that is induced by a pair of electrical pulses that are separated by a short IPI, similar to a masker and a probe. To investigate the facilitation effect, ECAP responses were measured with the masked response paradigm. This paradigm based on the masker and probe principle and therefore is appropriate to record facilitation.

4.3.1 Primary test procedure

In a first test procedure, ECAP thresholds and facilitation measurements were performed with a custom-made software. Based on the recorded data, ECAP thresholds and facilitation effect were determined by visual inspection.

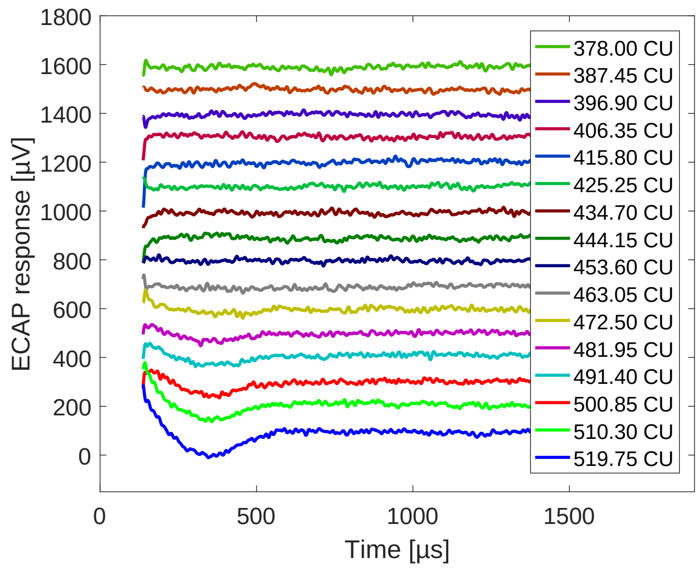


Figure 4.8: Measurement of the ECAP responses with fine level resolution for subject S38 (current levels between 378 and 520 CU). The ECAP threshold value was estimated 482 CU. ECAPs were recorded with a custom made software in Matlab.

4.3.1.1 Determination of ECAP thresholds

The ECAP measurements shown in figure 4.8 and figure 7.1 to 7.6 are highly interfered by noise. Because of this noise, a correct determination of the ECAP threshold was nearly impossible. In the first screening over a wide range of current levels some subjects showed only weak ECAP responses even at MCL (e.g. S34, figure 7.2). Despite poor SNR in some subjects, ECAP thresholds were determined for all six subjects (range 482 to 624 CU).

4.3.1.2 Determination of the maximum facilitation effect

To determine the maximum facilitation effect, the N1-P2 peak amplitude of the ECAP responses was recorded for several masker levels relative to the estimated ECAP threshold (relMCU). The N1-P2 amplitude of each ECAP response was plotted against relMCU (amplitude growth function, figure 4.9). After measuring subject S33 it was decided, to set smaller level steps, for a better resolution of the curve. Nevertheless, in three of six subjects (S34, S36, S37) no distinct facilitation effect was visible.

Additionally, the amplitude growth function of subject S34 was affected by a huge artifact at a relMCU of - 548.1 CU (- ECAP threshold), resulting in a inaccurate N1-P2 amplitude (not shown in figure 4.9 for better visualization of the remaining data points). For subjects S33, S35, and S38 a facilitation effect was observed. For subjects S33 and S38 the maximum facilitation effect was at a relMCU of -94.5 CU and -37.8 CU. Only subject S35 had a maximum facilitation at -9.45 CU which was in the expected range near ECAP threshold. The amount of the facilitation effect was around 50 μV (S33 and S38) and 150 μV (S35).

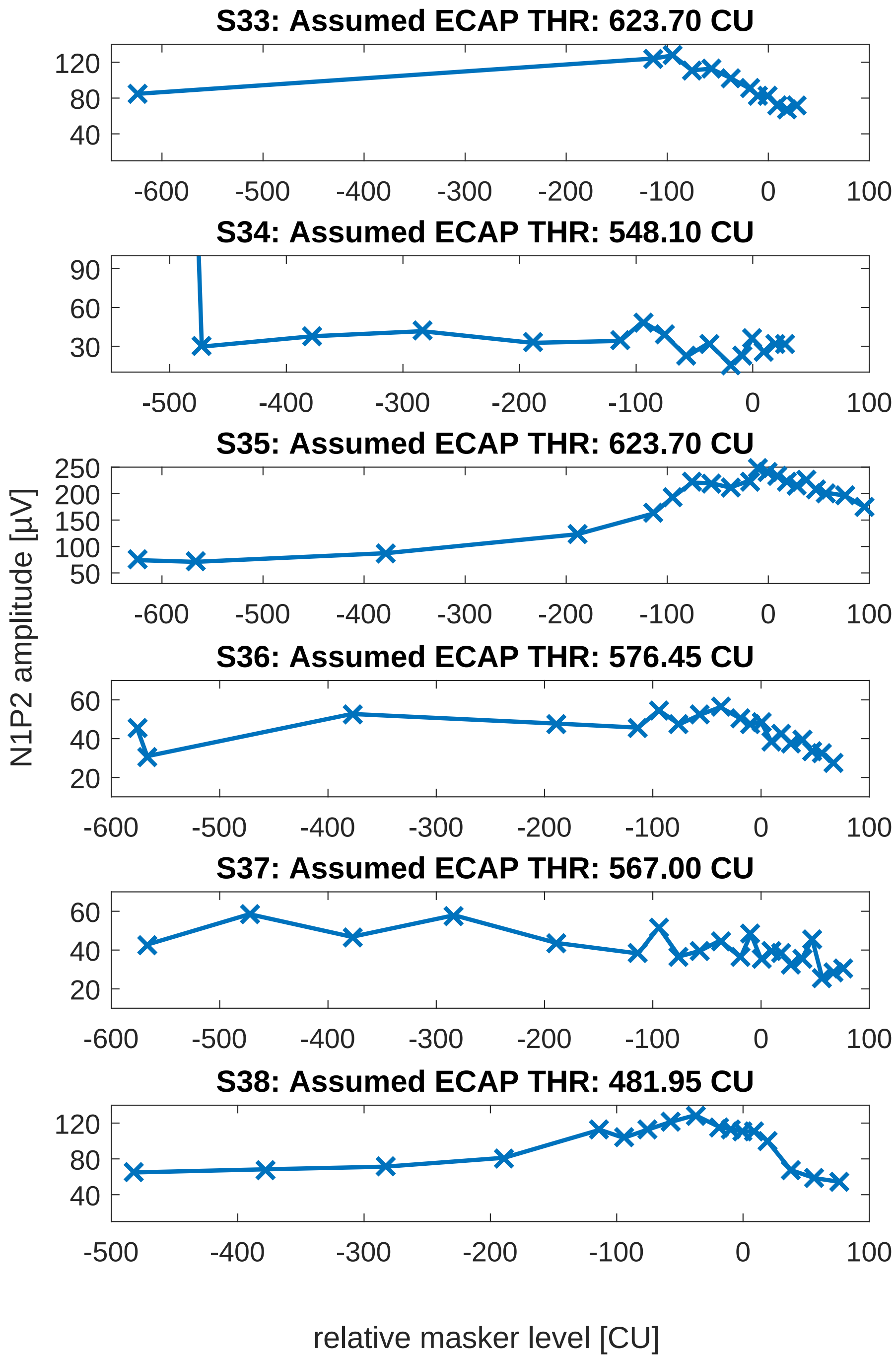


Figure 4.9: Amplitude growth function of each subject showing the ECAP response depending on the relative masker level (relMCU, MPI : 15 μs). The relative probe level (relPCU) was fixed at 0 CU. A facilitation effect could not be observed for subject S34, S36 and S38. Because of a huge artifact, the N1-P2 amplitude at relMCU = - ECAP threshold of subject S34 is not shown for better visualization of the remaining data points.

4.3.2 Revised test procedure

To optimize the ECAP determination and the measurement of the facilitation effect the first test procedure was revised. Therefore the ECAP measurement was determined via the ART-tool from MED-EL's fitting software Maestro. As in the first test procedure, the facilitation effect was recorded using the custom-made software. However, to optimize the noise floor in the custom-made software and therefore to receive a better SNR, in this revised test procedure the number of iterations for averaging was increased from 50 to 200. Using this revised test procedure, the determination of the ECAP threshold and the facilitation effect was repeated.

4.3.2.1 Determination of ECAP thresholds

With the ART-tool it was possible to determine ECAP thresholds for each subject. Subject S38 already participated in the test with the first test procedure and therefore a direct comparison was possible. By the automatic linear regression of the ART tool, the ECAP threshold was determined to be 394 CU (Figure 4.10). This value is 92 CU lower compared to the ECAP threshold that was determined with the first procedure (482 CU). This shows, that a more accurate ECAP measurement is possible via ART-tool of the Maestro. The ECAP thresholds of the remaining subjects (Figure 7.7 to 7.11) were in a range of 267 and 739 CU, whereby four out of six subjects had an ECAP threshold within the range of 390 and 490 CU. Except for subject S38 a direct comparison between ECAP thresholds recorded with the custom-made software and the ART tool was not possible.

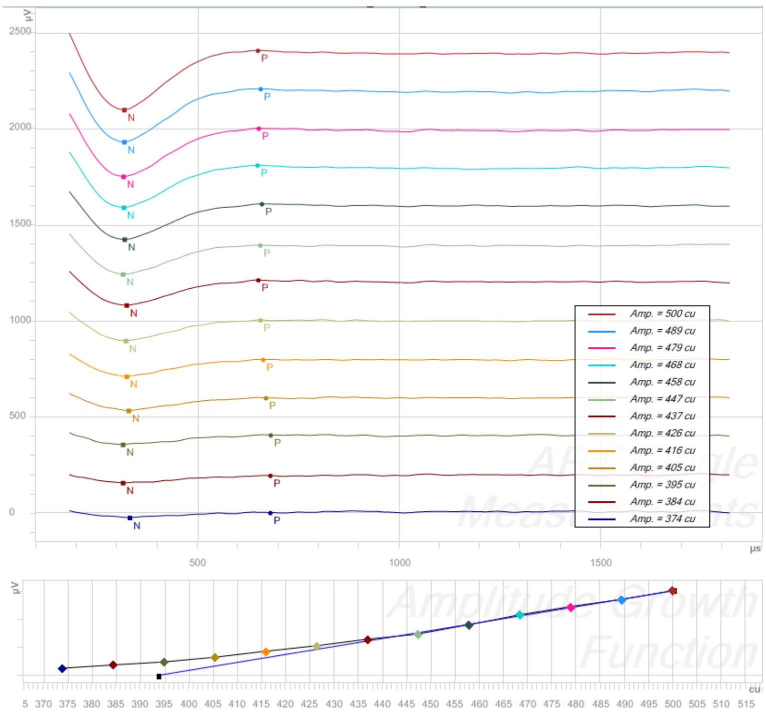


Figure 4.10: Upper panel: ECAP responses recorded of subject S38 for current levels between 374 and 500 CU. Lower Panel: Amplitude growth function of the recorded ECAP responses from subject S38. The N1-P2 peak amplitude is plotted for each current level. The ECAP threshold of 394 CU was estimated by a linear regression. ECAPs were recorded with the ART-tool of the fitting software Maestro.

To determine which MPI leads to the best ECAP response (higher N1-P2 amplitude) and therefore can optimize the following facilitation measurement, an ECAP measurement was assessed for three subjects (S41, S42, S43) with an MPI1 of either 350 or 400 μs using the custom-made software. In all three subjects, the MPI1 of 400 μs led to the larger ECAP response (Table 4.1). Therefore the MPI1 of 400 μs was used in the following facilitation measurements.

Table 4.1: Comparison of N1-P2 peak amplitude with an MPI of 350 and 400 μs at suprathreshold ECAP measurements.

Subject	amplitude level [CU]	N1-P2 amplitude [μV]	
		MPI = 350 μs	MPI = 400 μs
S41	70	72	78
S42	64	209	240
S43	70	57	64

4.3.2.2 Determination of the maximum facilitation effect

Similar as in the first test procedure, the maximum facilitation effect was determined by plotting the N1-P2 peak amplitude against relMCU (amplitude growth function). The results of each of the six subjects are depicted in figure 4.11. In two of six subjects (S39 and S43) no distinct facilitation effect was visible. Although a local maximum around ECAP threshold can be observed for both subjects, the maximum does not stand out from the remaining data points (S39: several maxima; S43: similar amplitude to several data point with relMCL below ECAP threshold). Therefore the maximum may appear due to noise instead of the facilitation effect. For the remaining four subjects (S38, S40-S42) a facilitation effect was observable with the maximal facilitation for masker levels around ECAP threshold (Table 4.2). The maximal facilitation effect is around 50 to 60 μV (S38, S40, and S41) and 240 μV (S35). The noise floor was reduced compared the first test procedure by around 30 μV (from approx. 50 to approx. 20μV) due to the increased averaging of 200 measurements instead of 50 averages. In the revised test procedure, the curve progression before and after passing the maximum was observed. The N1-P2 amplitude increased for a relMCU below the ECAP threshold. With a further increase of relMCU after passing the maximum around ECAP threshold the N1-P2 amplitude decreased steeply.

Table 4.2: Relative masker current unit (relMCU) for each subject that led to the maximum facilitation effect. For S39 and S43, no relMCU is documented because of the missing facilitation effect.

Subject	S38	S40	S41	S42
relMCU [CU]	9.45	18.9	9.45	9.45

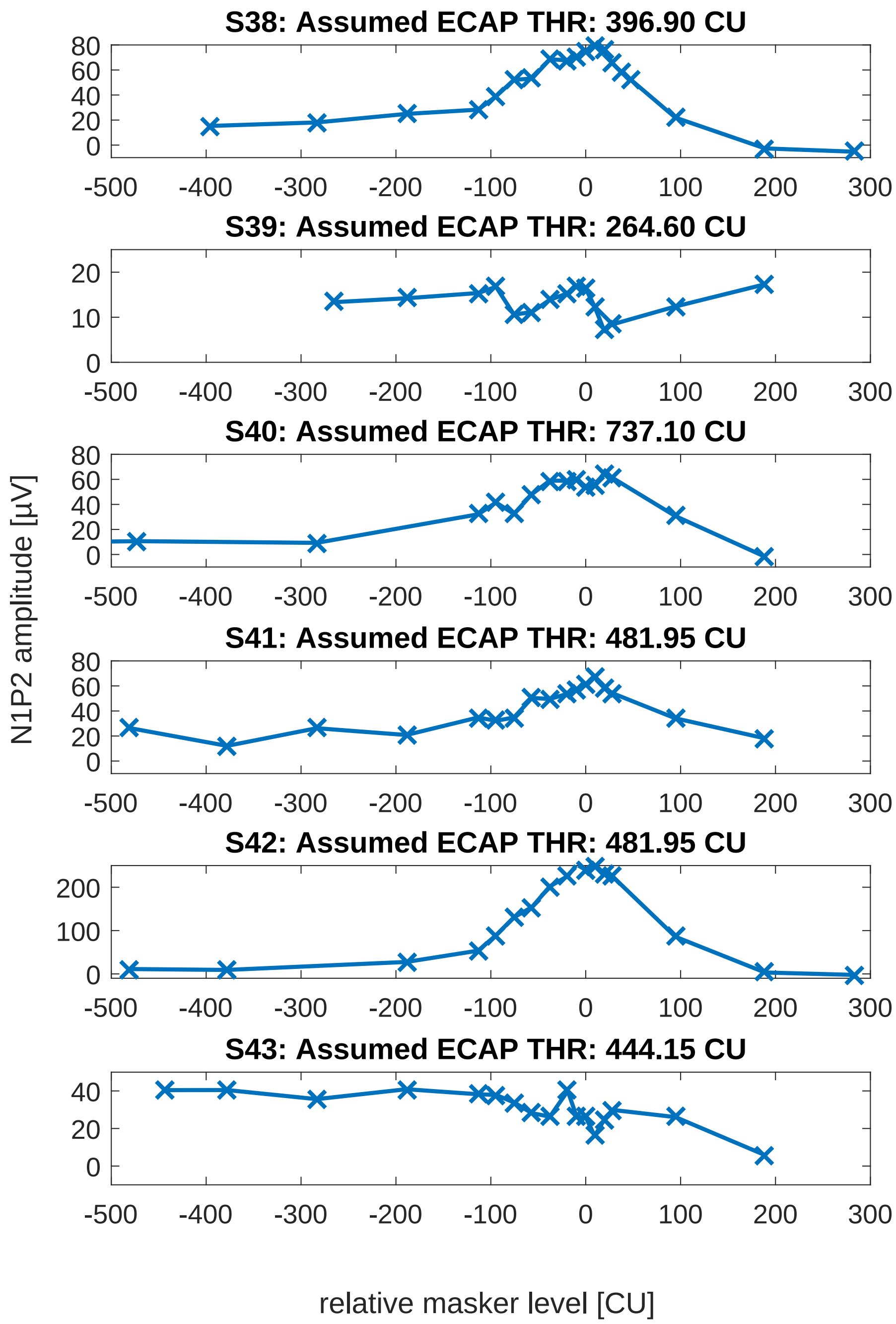


Figure 4.11: Amplitude growth function of each subject showing the ECAP response depending on the relative masker level (relMCU, MPI : 15 μs). The relative probe level (relPCU) was fixed at 0 CU. For all subjects except S39 and S43 a clear facilitation effect could be observed.

4.4 Loudness perception and dynamic range by variation of the interphase gap

The presented data within this chapter was originally published and discussed in Pieper et al. (2020). For two different loudness levels (50%-ADR and MCL) and at three different pulse rates (200, 600 and 1000 pps), the loudness was matched between pulse trains with IPGs of either 2.1 and 10 μs or 2.1 and 30 μs.

4.4.1 Loudness perception at hearing threshold

The hearing threshold was determined at each pulse rate (200, 600, and 1000 pps) for pulse trains with an IPG of 2.1 μs. The determination of the hearing threshold was necessary to calculate the 50%-ADR amplitude value. In most subjects, the hearing threshold decreased in amplitude level with increasing the pulse rate (individual data: Table 7.1). In one subject (S30) the hearing threshold was the same for all pulse rates. For another subject (S25) the hearing threshold showed a slight increase from 600 to 1000 pps but from 200 to 1000 pps a decrease in hearing threshold could be observed. For subject S26 the hearing threshold only decreased from 600 to 1000 pps but was constant between 200 and 600 pps. An increase in hearing threshold could be observed in subject S31 between 200 and 600 pps. With a further increase of the pulse rate (1000 pps) the hearing threshold decreased to an amplitude level below the hearing threshold of 200 pps.

Table 4.3: Averaged data with standard deviation from all subjects at hearing threshold with an interphase gap (IPG) of 2.1 μs (Data from Pieper et al., 2020).

Pulse rate	Mean Threshold [dB re 1 μA]	Standard deviation [dB re 1 μA]
200 pps	48.38	2.09
600 pps	47.28	2.49
1000 pps	46.09	2.04

On average, the decrease of amplitude level at hearing threshold from 200 to 1000 pps is about 2.28 dB re 1 μA (compare table 4.3). This decrease was shown to be significant (one-way repeated-measures ANOVA: $F(2,16) = 9.94$, $p = 0.002$).

4.4.2 Loudness perception at 50% amplitude dynamic range

The matched amplitude levels at 50%-ADR are depicted in figure 4.12 as a function of IPG. The change in amplitude according to IPG is shown for the three investigated pulse rates (200, 600, and 1000 pps). A general trend towards lower amplitudes with increasing IPG at all three pulse rate can be observed (individual data: Table 7.1). The strongest decrease in amplitude level with increasing the IPG can be observed at 200 pps (1.42 dB re 1 μA on average between 2.1- and 30-μs IPG). The stimulation at the higher pulse rates (600 and 1000 pps) revealed an increase in amplitude between 2.1 and 10 μs. However, between 10 to 30 μs the amplitude level decreased further. On average, the overall decrease in amplitude between 2.1- and 30-μs IPG add up to 0.58 dB re 1 μA at 600 pps and 0.62 dB re 1 μA at 1000 pps. The two factors pulse rate and IPG were statistically analyzed using a two-way repeated-measures ANOVA. Both factors were found to be significantly affecting the amplitude level (IPG: $F(1.148,16) = 11.595$, $p = 0.006$; pulse rate: $F(1.156,16) = 10.249$, $p = 0.009$). Additionally, a significant interaction effect of IPG and pulse rate on amplitude was found ($F(1.951,32) = 10.021$, $p = 0.002$). The significant interaction effect did not allow an interpretation of the effects of IPG and pulse rate on amplitude.

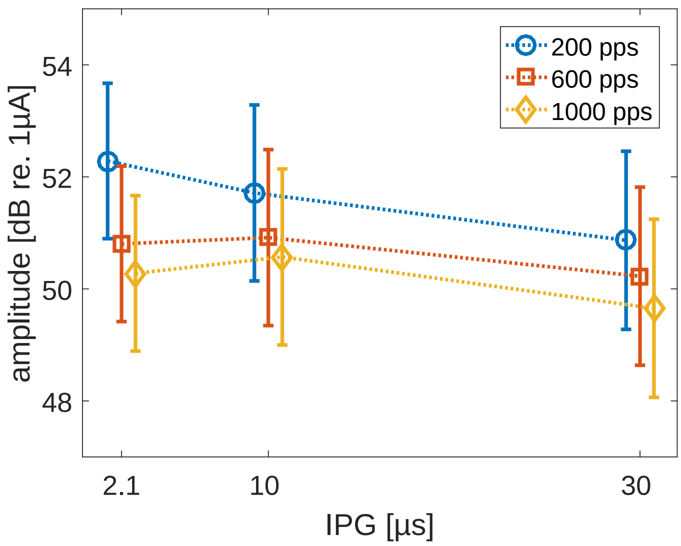


Figure 4.12: Pulse stimulus amplitudes (in dB) for equal loudness at 50%-amplitude dynamic range (ADR) with different interphase gaps (IPGs; 2.1, 10, and 30 μs) at different stimulation rates (200, 600 and 1000 pps, figure from Pieper et al., 2020).

Therefore, an additional one-way repeated-measures ANOVA with a post-hoc pairwise comparison (Bonferroni correction) was performed separately for each factor. The analysis revealed a significant effect of IPG on amplitude for stimuli with a pulse rate of 200 pps ($F(2,16) = 44.995$, $p < 0.001$). Also all three pairwise comparisons to investigate the different IPG combinations were significant (2.1- vs. 10-μs IPG: $p = 0.037$; 2.1- vs. 30-μs IPG: $p < 0.001$; 10- vs. 30-μs IPG: $p < 0.001$). A significant effect was found as well for the effect of IPG on amplitude level at 1000 pps ($F(1.047,16) = 5.473$, $p = 0.045$). However, in the pairwise comparison significant differences in amplitude were only found between 10- and 30-μs IPG ($p < 0.001$) but no significance could be found between 2.1- and 10-μs IPG ($p = 0.793$) as well as between 2.1- and 30-μs ($p = 0.377$). Different to the stimulation condition at 200 and 1000 pps, the decrease in amplitude level according to increasing the IPG was not significant at 600 pps ($F(1.168,16) = 13.297$, $p = 0.063$). The same analysis for the effect of pulse rate on amplitude level showed a significant effect for pulse trains with an IPG of 2.1 μs ($F(1.215,16) = 16.553$, $p = 0.002$). In two of three pairwise comparisons, the post-hoc test found significant differences in amplitude (200 vs. 600 pps: $p = 0.042$; 200 vs. 1000 pps: $p = 0.002$). Hence, a comparison between pulse trains with pulse rates of 600 and 1000 pps did not result in significant differences in amplitude ($p = 0.056$). In pulse trains with an IPG of 10 μs, the amplitude level was influenced significantly by pulse rate ($F(1.143,16) = 5.040$, $p = 0.048$). However, the post-hoc pairwise comparison did not show significant differences in amplitude between pulse rates (200 vs. 600 pps: $p = 0.347$; 200 vs. 1000 pps: $p = 0.098$; 600 vs. 1000 pps: $p = 0.07$). Similarly, the pulse trains with an IPG of 30 μs were significantly influenced in amplitude level by pulse rate ($F(1.143,16) = 6.231$, $p = 0.031$) but the post-hoc pairwise comparison showed significant differences in amplitude level merely between pulse rates of 600 and 1000 pps ($p = 0.011$). The remaining pairwise comparisons were not significant (200 vs. 600 pps: $p = 0.389$; 200 vs. 1000 pps: $p = 0.075$).

4.4.3 Loudness perception at most comfortable level

The matched amplitude levels at MCL are depicted in figure 4.13 as a function of IPG. The change in amplitude according to IPG is shown for the three investigated pulse rates (200, 600, and 1000 pps). A general trend towards lower amplitudes with increasing IPG at all three pulse rate can be observed. The strongest decrease in amplitude level with increasing the IPG can be observed at 200 pps (1.68 dB re 1 μA on average between 2.1- and 30-μs IPG). The stimulation at the higher pulse rates (600 and 1000 pps) as well revealed a decrease in amplitude level with increasing IPG (on average between 2.1- and 30-μs IPG: 0.96 dB re 1 μA at 600 pps; 0.87 dB re 1 μA at 1000 pps). The decrease in amplitude at all pulse rates could be observed in the individual data of most subjects (Table 7.1). However, subjects S26 and S29 had an increase at 600 and 1000 pps in MCL towards an increasing IPG. The factors pulse rate and IPG were analyzed statistically by using a two-way repeated-measures ANOVA. Both factors were found to be significantly affecting the amplitude level (IPG: $F(1.193,16) = 31.48$, $p < 0.001$; pulse rate: $F(1.086,16) = 10.847$, $p = 0.006$). Additionally, a significant interaction effect of IPG and pulse rate on amplitude was found ($F(1.381,32)$ 8.262, $p = 0.01$). The significant interaction effect did not allow an interpretation of the effects of IPG and pulse rate on amplitude.

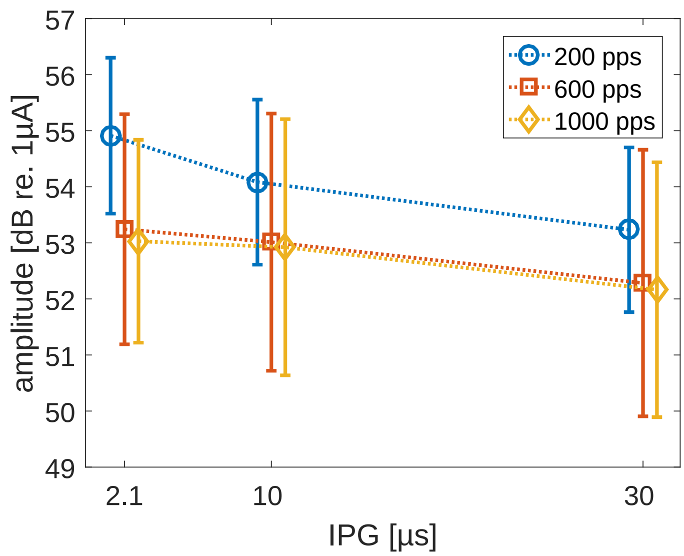


Figure 4.13: Pulse stimulus amplitudes (in dB) for equal loudness at the most comfortable level (MCL) with different interphase gaps (IPGs; 2.1, 10, and 30 μs) at different stimulation rates (200, 600 and 1000 pps, figure from Pieper et al., 2020).

To overcome that issue, an additional one-way repeated-measures ANOVA with a post-hoc pairwise comparison (Bonferroni correction) was performed separately for each factor. The analysis revealed a significant effect of IPG on amplitude for stimuli with a pulse rate of 200 pps ($F(1.092,16) = 53.825$, $p < 0.001$). Also, all three pairwise comparisons to investigate the different IPG combinations were significant (2.1- vs. 10-μs IPG: $p = 0.005$; 2.1- vs. 30-μs IPG: $p < 0.001$; 10- vs. 30-μs IPG: $p < 0.001$).

The influence of IPG on amplitude level at 600 pps was significant as well ($F(1.168,16) = 13.297$, $p < 0.001$). The pairwise comparisons revealed significant differences in amplitude between 2.1- and 30-μs ($p = 0.014$) and 10- and 30-μs IPG ($p < 0.001$) but no significance was found between 2.1- and 10-μs IPG ($p > 0.99$). Likewise, the effect of IPG on amplitude level at 1000 pps was significant ($F(1.241,16) = 6.546$, $p = 0.024$) with a significance within the pairwise comparison between 10- and 30-μs IPG ($p = 0.001$), whereas the remaining two pairwise comparisons of the IPG were not significant (2.1- vs. 10-μs IPG: $p = 0.99$; 2.1- vs. 30-μs IPG: $p = 0.056$). The influence of pulse rate on amplitude level was investigated with the one-way repeated-measures ANOVA as well. It showed a significant effect for pulse trains with an IPG of 2.1 μs ($F(1.105,16) = 16.475$, $p = 0.003$). In two of three pairwise comparisons the post-hoc test showed significant differences in amplitude (200 vs. 600 pps: $p = 0.024$; 200 vs. 1000 pps: $p = 0.003$). Hence, a comparison between pulse trains with pulse rates of 600 and 1000 pps did not lead to significant differences in amplitude ($p = 0.441$). In pulse trains with an IPG of 10 μs, the amplitude level was influenced significantly by pulse rate ($F(1.116,16) = 6.682$, $p = 0.027$). Yet, the post-hoc pairwise comparison was not able to reveal significant differences in amplitude between pulse rates (200 vs. 600 pps: $p = 0.104$; 200 vs. 1000 pps: $p = 0.08$; 600 vs. 1000 pps: $p > 0.99$). Similarly, the pulse trains with an IPG of 30 μs were significantly influenced in amplitude level by pulse rate ($F(1.118,16) = 5.095$, $p = 0.048$). Again, the post-hoc pairwise comparison did not reveal any significant differences in amplitude between pulse rates (200 vs. 600 pps: $p = 0.245$; 200 vs. 1000 pps: $p = 0.09$; 600 vs. 1000 pps: $p = 0.818$).

4.4.4 Influence of IPG and pulse rate on dynamic range

The dynamic range was calculated by using the previous measured amplitudes for 50%-ADR and MCL as lower and upper boundary. The amplitude value at 50%-ADR does not represent the lowest possible boundary. Therefore, not the complete BDR is covered. Instead, the range between 50%-ADR and MCL represents the upper part of the whole BDR. In the following, the calculated dynamic range is referred to as the "upper dynamic range". The development of the dynamic range with increasing IPG depends on the amplitude behavior at 50%-ADR and MCL. If increasing the IPG resulted in a similar decrease of amplitudes at both loudness levels, the upper dynamic range would not be affected by the IPG. However, as shown in the analysis of 50%-ADR and MCL, the amplitude decreased by a larger amount at MCL than at 50%-

ADR. This implies, that the upper dynamic range may decrease as well with larger IPG. Indeed, a decrease of upper dynamic range can be observed as a function of IPG (figure 4.14).

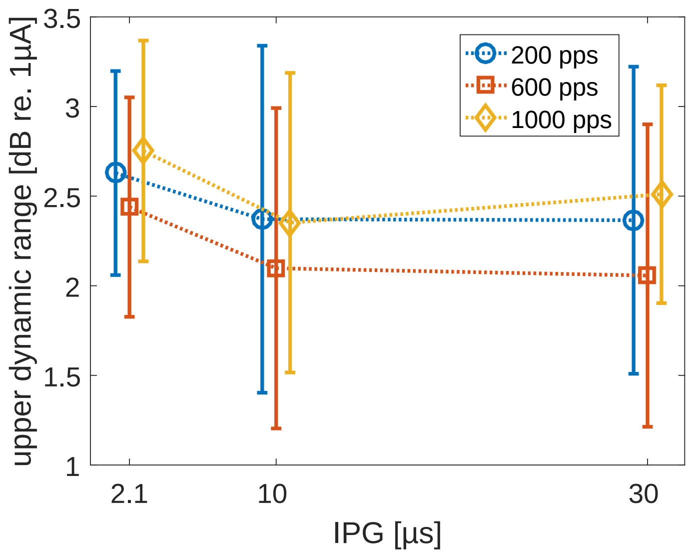


Figure 4.14: Upper dynamic range (in dB) of different interphase gaps (IPGs; 2.1, 10, and 30 μs) at different stimulation rates (200, 600, and 1000 pps). The upper dynamic range does not represent the whole BDR and is calculated by subtracting the amplitude level at 50%-ADR from MCL (figure from Pieper et al., 2020).

Especially the increase in IPG from 2.1 μs to 10 μs resulted in a decrease of upper dynamic range. No further decrease can be observed between 10- and 30-μs IPG for pulse rates of 200 and 600 pps, whereas there is a slight increase for 1000 pps towards an IPG of 30 μs. On average, the upper dynamic range decreased 0.26 dB at 200 pps, 0.38 dB at 600 pps and 0.24 dB at 1000 pps. The decrease of upper dynamic range could be observed in the individual data of the subjects (Table 7.1). An exception was subject S29, who had an increase in upper dynamic range at all three pulse rates. Similarly to the analysis of amplitudes at 50%-ADR and MCL, the upper dynamic range was analyzed for significant effects caused by pulse rate and IPG with the two-way repeated-measures ANOVA. The IPG as well as the pulse rate were found to influence the upper dynamic range significantly (IPG: $F(2,16) = 7.121$, $p = 0.006$; Pulse rate: $F(2,16) = 6.838$, $p = 0.007$). Different to the previous analyzed loudness levels, there is no interaction effect of IPG and pulse rate for the upper dynamic range ($F(2,32) = 1.047$, $p = 0.398$). Therefore, only a post-hoc pairwise comparison was applied as no further data analysis with a one-way repeated-measures ANOVA was necessary. These post-hoc analysis showed a significant difference in upper dynamic range between 2.1 and 30 μs for the factor IPG (p = 0.021). The remaining two pairwise comparisons of the factor IPG were not significant (2.1 vs. 10 μs: p = 0.175; 10 vs. 30 μs: p = 0.631). For the factor pulse rate, the post-hoc test revealed a significant difference in upper dynamic range between 200 and 600 pps (p = 0.02). Again, the remaining two comparisons were not significant (200 vs. 1000 pps: p = 0.284; 600 vs. 1000 pps: p = 0.304).

5 Discussion

5.1 Rate pitch discrimination

The aim of using double pulses with a short IPI was to improve the temporal coding of pitch and therefore allow a better pitch discrimination ability in CI users. To investigate if the application of double pulses leads to the desired effect, a pitch discrimination task was performed. Stimuli consisted of pulse trains with either double pulses with different IPIs or single pulses. Additionally, the pitch perception was investigated for combined pulse trains. These pulse trains consisted of alternating single and double pulses. They were compared in a pairwise pitch comparison task with single-pulse trains at different pulse rates.

5.1.1 Rate pitch discrimination with single and double pulses

Applying double pulses with short IPI in a pulse train may improve the pitch discrimination ability in CI users. However, the results showed no significant effects when comparing pitch discrimination thresholds for double-pulse trains with several IPIs (15, 50, and 150 μs) at 200 and 400 pps with single-pulse trains. As no specific IPI led to better pitch discrimination, the hypothesis could not be confirmed. However, it may be possible that an individual "best IPI" is existing. This individual best IPI leading to better pitch discrimination may exist due to subject specific variations in the spiral ganglion density. This would lead to the assumption that a "one solution fits all"-approach may not be true for further improvement in pitch discrimination. This potential effect may be masked in this study due to the high inter-subject variability. Especially after averaging the data, a possible best IPI for pitch discrimination cannot be detected. A better way to conduct a statistical analysis may be to repeat the single pulse versus double pulse (with the best IPI) condition several times. This would enable a balanced statistical analysis and can be addressed in a future "individual best IPI" study. The idea of individualized optimization of stimulus parameters in CI users was already suggested by Babacan et al. (2010). They developed a coding strategy that takes channel interaction and refractory properties of the neural population into account. They measured the spread of excitation within the cochlea and the recovery function of neurons with ECAPs. Their aim was to generate a more physiological neuronal activity pattern of neurons.

In this thesis, the JND results showed a high inter-subject variability for double-pulse trains as well as for single-pulse trains. At a base rate of 200 pps, the best performers achieved a rate pitch JND of about 20 pps (10% rate increment). At a base rate of 400 pps, the rate pitch JND for best performers was around 200 pps (50% rate increment). These results are in line with previous studies (e.g. Baumann and Nobbe, 2004; Bahmer and Baumann, 2013; Carlyon et al., 2010). In these studies pitch discrimination ability in CI users was evaluated with pulse trains consisting of single pulses. Similar to the experiment in this thesis, the rate pitch JND deteriorated with increasing pulse rate. Carlyon et al. (2010) investigated the pitch discrimination ability by measuring the performance in %-correct at different pulse rates (100, 200, 300, 400 and 500 pps). With the test tone always 35% higher in pulse rate than the base rate of the reference signal they found a decrease in performance with increasing pulse rate. This is in line with the experiment in this thesis, were the pitch discrimination at 400 pps is worse compared to the performance at 200 pps.

The idea to investigate if double pulses with short IPI enhance the pitch discrimination based on the study from Laback and Majdak (2008). They observed an improvement of ITD sensitivity with jittered stimuli. This observation led to their suggestion that jittered pulse trains may also improve rate pitch perception. In a previous study, pitch discrimination with jittered pulse trains was already investigated by Chen et al. (2005). They did not find an improvement in pitch discrimination with pulse trains jittered with small standard deviations compared to pulse trains without jitter. Contrary, the pitch discrimination deteriorated at a frequency of 100 Hz. Bahmer and Baumann (2014) investigated pitch discrimination with jittered pulse trains as well, applying jitter with high standard deviations. This jittered pulse trains did also deteriorate pitch discrimination ability in CI users. Therefore, both studies demonstrated that the application of a certain amount of jitter can lead to a decrease in pitch discrimination ability and therefore may degrade temporal information. Based on the study of Laback and Majdak (2008), Hancock et al. (2012) investigated the improvement of ITD sensitivity due to jitter in animal experiments. They showed that this improvement is due to double pulses with short IPI within the applied jittered pulse train. Exactly these double pulses with short IPI lead in this thesis neither to an improvement nor to a deterioration of pitch discrimination. Luckily, an application of these double pulses for a better sound localization will therefore not change pitch discrimination. In a recent study, Lindenbeck et al. (2020) investigated the pitch effect of double pulses with short IPI in amplitude modulated pulse trains. They investigated five different modulation depths, two carrier frequencies and two typical fundamental frequencies F0 for speech. The double pulse was inserted either at each maximum of the envelope (full rate) or at each second maximum of the envelope (half rate), representing either F0 or F0/2 in a high frequency carrier, respectively. Different to the approach in this thesis using low pulse rates without modulation, Lindenbeck et al. (2020) found an improved sensitivity to temporal pitch at low modulation depths for the full rate condition.

5.1.2 Rate pitch perception with alternating double pulses

A pulse train with alternating double and single pulses may change pitch perception due to a domination of pitch information from the double pulse or single pulse component. In the previous experiment which investigated pitch discrimination using double pulses, subjects did not report any changes in pitch perception between single-pulse trains and double-pulse trains. Contrary, a pulse train consisting of alternating double and single pulses with equal amplitude for all double and single pulses led to a change in pitch compared to a homogeneous single-pulse train. At same pulse rate, subjects reported that the alternating pulse train had a lower pitch than the single-pulse train. Consequently, the 400 pps alternating pulse train matched best in pitch with the 200 pps single-pulse train. In summary, the pitch of the alternating pulse train seems to be mainly influenced by the double pulse component within the alternating pulse train. As single and double pulses have equal amplitudes, they may differ in loudness due to a temporal loudness summation effect for double pulses. The loudness difference may be the reason for the domination of the double pulse in pitch perception. To compensate for the loudness difference the double pulse complex has to be adjusted to the single pulse. Accordingly, the next step in a possible future study would be an additionally loudness balancing between single and double pulses within the alternating pulse train for further comparative tests with single pulse trains. After subsequent loudness balancing between alternating and single pulse trains, a rate pitch discrimination task with the alternating pulse train could be performed to determine the rate pitch JND.

5.1.3 Correlation of rate pitch discrimination with speech performance and listening experience

Rate pitch discrimination may correlate with speech performance of the subject. This assumption based on the fact that pitch perception is one important cue for speech comprehension (see chapter 1.2.5). Pitch perception can be encoded in tonotopic and temporal information. In this study, only the encoding of temporal information of pitch was investigated. This was accomplished by testing rate pitch discrimination tests in CI users at a single electrode. In speech perception the fundamental frequency is encoded in temporal information which corresponds partly to pitch perception. The fundamental frequency "is the prime acoustic correlate of the perception of voice pitch" (Rosen, 1992). Other components are the patterns of voice pitch such as intonation and tone. They "play important roles in accenting syllables in words and sentences" (Rosen, 1992). This clear link between rate pitch and speech perception triggered the analysis of a potential correlation between speech recognition scores (Freiburg monosyllabic word recognition test, without noise) and the JND in pitch discrimination. However, no statistical significant correlation was found. As mentioned in chapter 1.2.5, a proper pitch perception helps to segregate different sound streams from each other. Accordingly, rate pitch discrimination and speech recognition in noise was investigated by Zhou et al. (2019). Different to the test without noise in this thesis, Zhou et al. (2019) found a significant correlation between speech in noise and pitch discrimination. Thus, further investigations to improve rate pitch discrimination ability should correlate rate pitch discrimination scores with speech in noise as well.

The duration of time after implantation may also correlate with rate pitch discrimination. A particular rate pitch training can significantly improve rate pitch discrimination (Goldsworthy and Shannon, 2014). Therefore, already a duration of listening experience may lead to a better rate pitch discrimination. However, the correlation between rate pitch discrimination and subjects' time after implantation in this thesis was found to be not significant. This implies that a longer listening experience in everyday situations may not necessarily train rate pitch perception.

5.2 Facilitation effect

The facilitation effect describes the enhanced neural response in electrical hearing by pairing two electrical pulses that are separated by a short IPI. This effect may improve the temporal information transfer and thereby the pitch discrimination ability. A potential facilitation effect in CI users can be objectively determined by recording ECAPs Hey et al. (2017). ECAPs can be recorded by means of different paradigms to reduce the distortion induced by the electrical artifact. One of these paradigms employs intervals between pulses. These intervals can be in a facilitation effect range. According to Hey et al. (2017) the maximum facilitation effect occurs for masker levels (level of the first pulse) at or slightly below ECAP threshold. They investigate the variation of the masker level on the facilitation while the probe level (level of the second pulse) was set constant. In this thesis' experiment, the maximum N1-P2 peak amplitude and therefore the maximum facilitation effect was at a relMCU slightly above their ECAP threshold for all subjects with an observable facilitation. The small difference in masker level between the study of this thesis and Hey et al. (2017) may be due to the different artifact reduction methods that were used to determine the ECAP threshold. While Hey et al. (2017) used the masked response paradigm that was introduced by Miller et al. (2000), the ART-tool of the Maestro software (Clincal fitting sofware from the company MED-EL) that was used in this thesis employs the alternating polarity paradigm and a subsequent linear regression to determine the ECAP threshold. Comparing different artifact reduction methods, Baudhuin et al. (2016) showed, that the application of the alternating polarity paradigm to reduce artifacts differs from other artifact reduction methods and leads to smaller ECAP amplitudes and therefore different ECAP thresholds. Another reason for the slightly different results may be noise. Especially in the first test measurements in this thesis, the facilitation effect and the ECAP threshold determination as well were strongly influenced by noise. Comparing the ECAP threshold of the first approach with the revised test method in subject S38 showed, that the ECAP threshold in the first approach was overestimated in this subject. After repeating the ECAP threshold determination with the ART-tool of the Maestro, the estimated ECAP threshold dropped nearly 90 CU. This comparison let assume, that due to the noise, the ECAP thresholds of the subjects in the first approach were overestimated. The increase of the number of recordings to 200 for averaging, improved clearly the responses in the revised approach. Still, the unsuccessful measurement of a facilitation effect in two subjects with the revised version of the setup might be a clear hint that improvements of the custom-made software are still necessary.

Similarly as in the study of Hey et al. (2017) the study results of this thesis showed an increase of N1-P2 amplitude up to its maximum around ECAP threshold, with a steep decrease of N1-P2 amplitude with further increase of relMCU above ECAP threshold. In regard to pitch discrimination with double pulses this may imply, that the application of double pulses may only be beneficial if the first pulse amplitude of the double pulse complex is around the ECAP threshold. Otherwise the effect of double pulses might be disadvantageous as the neural response declines with higher amplitude levels. According to Hey et al. (2017) the second pulse, the probe pulse, does not affect the curve progression but can increase the N1-P2 amplitude in general. This was not investigated in the study of this thesis.

Further investigations should aim to investigate the influence of the probe pulse in MED-EL implants. In addition, it could be interesting to compare the neural response of a single pulse to a double pulse at same loudness. The first pulse of the double pulse should represent an amplitude level that leads to the maximum facilitation effect. The comparison of the N1-P2 peak amplitude at the maximum facilitation of the double pulse with the N1-P2 peak amplitude of the single pulse (both at equal loudness, e.g. MCL) might already give a hint if double pulses that show a facilitation effect are beneficial for pitch discrimination. In case of a larger neural response for double pulses than for the single pulse, the double pulse may be beneficial for pitch discrimination. Afterward, a repetition of the pitch discrimination test might give more insight about a possible better pitch discrimination ability. Investigating the facilitation effect might also allow to screen subjects for their best IPI. Thereby the pitch discrimination task does not have to be performed for several IPIs but only the best IPI, limiting the test time for the subject. However, in the study of Hey et al. (2017) the strongest facilitation effect was found for the shortest tested IPI of 13 μs.

5.3 Loudness perception

The loudness perception of a pulse train is modified by various parameters of the pulse train and the pulses. For example, the increase of pulse amplitude increases the perceived loudness. However, temporal parameters like pulse rate can also influence loudness by temporal integration effects. Accordingly, the variation of IPI in double pulses and IPG leads to a change in loudness. The results of the studies in this thesis evaluating the effect of IPI in double pulses and the effect of IPG in single pulses on loudness perception are discussed in the following chapters.

5.3.1 Effect of double pulses with short IPI on amplitude at MCL

In this thesis it was hypothesized, that the application of double pulses with short IPI within a pulse train might result in a decrease of amplitude level at MCL. This hypothesis could be confirmed for double-pulse trains at a tested base rate of 200 and 400 pps. It was shown, that the amplitude level decreased significantly in a range of 10-20% for all tested double pulses with short IPIs (15, 50, 150 μs) compared to the amplitude level of a single-pulse train. The increase of the IPI resulted in a decrease of amplitude level at MCL. Comparing the change of amplitude at different IPIs, it could be observed that larger changes in IPI (between 15 and 150 μs as well as between 50 and 150 μs) lead to a significant change in amplitude. In contrast, smaller changes in IPI (between 15 and 50 μs) did not significantly influence the amplitude level. Also the alternating pulse train resulted in significantly lower amplitude levels at MCL than a single-pulse train. While the amplitude levels at MCL between single-pulse trains with different pulse rate did not differ significantly, a decrease in amplitude of about 10-20% was observed for the alternating pulse train compared to the single-pulse train to achieve MCL.

Both findings are consistent with a study by Karg et al. (2013). They measured the temporal interaction effect of double pulses. The temporal interaction effect was measured by stimulation of the same neural population using the same electrode with a double pulse. Thereby the spatial interaction component was eliminated. The first pulse amplitude of their double pulse complex was 80% of the required amplitude to reach the hearing threshold (estimated with a single-pulse train). The second pulse amplitude of the double pulse was varied in a hearing threshold task. They found decreasing amplitudes for double pulses with same polarity (both pulses cathodic first or anodic first) with decreasing IPI from 20 ms to 20 μs (double pulses with an IPG of 30 μs and a repetition rate of 4 double pulses per second with single electrode stimulation). The conclusion of their study was, that the first pulse (pre-pulse) leads to a pre-conditioning of the neurons. Due to the non-linearity of the auditory nerve fibers, the pre-condition of the neurons allows the following second pulse to activate a larger neural population (temporal integration). The non-linearity results in a potential shift due to the first phase of the pre-pulse. This potential shift is not completely neutralized by the second phase leading to a threshold shift for the second pulse. They showed that this effect can be increased using double pulses with alternating polarities (first pulse anodic first phase, second pulse cathodic first phase and vice versa) as for different polarities the non-linearity led to different time-courses. The application of alternating polarity double pulses may be also interesting for future rate pitch studies.

Temporal integration can also be induced by dual electrode stimulation. In the study of Landsberger and Galvin (2011), two adjacent electrodes were stimulated sequentially with a short IPI. Consistent with our findings at one single electrode, they found higher amplitudes for comfortable loudness levels when increasing the IPI from 0 to 1.8 ms at a pulse rate of 250 pps.

McKay et al. (2001) did not investigate different IPI in one electrode but an increasing electrode separation with sequential dual electrode stimulation that can be translated to IPI. They did not detect significant loudness summation effects with increasing electrode separation at C-level (corresponding to MCL) and mid-range level (comparable to 50%-ADR in the loudness matching experiment of this thesis). The non-existing loudness summation effect may be explained by a presentation of the second pulse beyond the facilitation range (0.8 ms after first pulse). Only at the smallest electrode separation (adjacent electrodes), effects of level and pulse rate were found. With higher pulse rate a higher adjustment of the amplitude level was required at mid-range loudness levels. They compared the results with a loudness model. In their model, they observed two effects. First, the neural refractoriness reduced the neural excitation at the overlapping regions of the two stimulated electrodes. Second, in a temporal integration window, the neural excitation of each stimulated position along the cochlear is summed up. This temporal integration counters the first effect leading to a minimal effect of loudness summation due to electrode separation. The later effect may be similar to the applied double pulses at one single electrode in the experiment of this thesis. Different to the study of McKay et al. (2001), the second pulse of the double pulse complex was presented within the facilitation range instead of the refractory time, leading to a significant loudness summation effect. Instead of applying double pulses with short IPI, another possibility to reduce amplitude levels at equal loudness is the increase of the IPG between the two opposing polarity phases of a biphasic pulse. The effect of IPG on loudness perception (in single pulses) is discussed in the following chapters 5.3.2 and 5.3.3.

5.3.2 Effect of IPG on amplitude level at different loudness levels

The variation of the IPG has a clear impact on the required amplitude level for different loudness levels. The effect of different IPGs (2.1, 10, and 30 μs) on amplitude level was measured at three pulse rates (200, 600, and 1000 pps) in an adaptive procedure. The adaptive procedure was applied for 50%-ADR and MCL. The results showed a significant amplitude level decrease for 50%-ADR and MCL. This is consistent with several other studies (e.g. McKay and Henshall, 2003; Carlyon et al., 2005; Schvartz-Leyzac and Pfingst, 2016). Carlyon et al. (2005) investigated the influence of IPG on amplitude level at hearing threshold. In contrast to the study in this thesis, the threshold was detected with an adaptive 2-IFC procedure in subjects with implants from the manufacturer Cochlear. They also used slightly different stimulus properties, such as a phase length of 100 μs, pulse rates at 20 and 100 pps and larger IPGs (8, 100, 300, and up to 3000 μs). Similarities with this thesis were the monopolar mode and the biphasic pulses with cathodic first phase. Despite the methodical differences, they found a significant effect of IPG as well. Lower amplitude levels at hearing threshold were required with increasing IPG. The effect was larger at 100 pps than at 20 pps. Next to the hearing threshold, McKay and Henshall (2003) additionally investigated the effect of IPG (8.4, 45, 100 μs) at a comfortable loudness in monopolar mode at 1000 and 4000 pps pulse rate (phase length: 26 and 52 μs). The subjects were implanted with CIs from Cochlear. Different to the experiment in this thesis, they used two different methods to determine the amplitudes at the two desired loudness levels. To determine the amplitude of the comfortable loudness level they performed a loudness balancing test between two stimuli with different IPGs using a toggle button to increase/decrease the loudness of one of the signals. In the experiment of this thesis, always the second tone had to be adjusted, whereas in the study of McKay and Henshall (2003) the tone that was adjusted alternated in position. The loudness balancing procedure was performed four times for each pair. The final amplitude level was averaged over the results of the four trails. At hearing threshold they used a threshold determination task similar to Carlyon et al. (2005) by performing an adaptive 4-IFC task with 2down-1up procedure. Therefore, they did not asked for a comparison of two signals as in the experiment of this thesis. Instead, the interval that contained an audible signal had to be identified. Despite the methodical differences, they found a significant decrease in amplitude level with increasing the IPG at hearing threshold and comfortable loudness level, which is in line with the findings in the experiment of the thesis.

The effect of IPG can also be observed with ECAP responses. Increasing the IPG leads to an increase of peak amplitude and slope of suprathreshold ECAP recordings in CI users (Schvartz-Leyzac and Pfingst, 2016) as well as in animals (Prado-Guitierrez et al., 2006; Ramekers et al., 2014). Similar to the IPG parameters in this thesis, Ramekers et al. (2014) investigated IPGs between 2.1 and 30 μs (phase length: 20 and 50 μs, pulse rate: 50 pps) in implanted guinea pigs. They observed the effect of IPG at ECAP threshold as well as at suprathreshold level (50% of the maximum N1-P2 amplitude). Thereby they found a decrease of stimulation level at suprathreshold level and lower ECAP threshold levels with increasing IPG. By measuring ECAPs and EABRs with different IPGs, Prado-Guitierrez et al. (2006) found similar results in guinea-pigs. The influence of IPG were studied in several groups of CI implanted animals (Prado-Guitierrez et al., 2006, : 1 week, 4 weeks, and 12 weeks deafened); (Ramekers et al., 2014, : NH, 2 week and 6 week deafened). Both studies reported a decrease in effect size of increasing IPG over the length of deafness. They found, that the amount of surviving SGCs seemed to influence the effect size of increasing IPG, as the density of surviving SGCs decreased with duration of deafness. An investigation of CI users with regard to their performance (poor performers vs. good performers) or CI users with specific pathology may be interesting to determine whether the IPG effect in humans is influenced by these factors. Additionally, the influence of the duration of deafness could be investigated with a larger study population similar to the animal experiments of Prado-Guitierrez et al. (2006) and Ramekers et al. (2014). However, as the group of CI users in the experiment of this thesis was relatively small and homogeneous (speech performance between 55 and 88%), no differentiation between subjects was made.

5.3.3 Effect of IPG on loudness dynamic range

Compared with NH listeners, the dynamic range in CI users is known to be very limited (Zeng et al., 2002). This can be a critical point in speech performance, because it leads to a coarse mapping of the high resolution of acoustical level information to electrical stimulation. Therefore, an increase of electrical dynamic range is associated with a better representation of acoustical level information, while a decrease of electrical dynamic range would further limit the available bandwidth and reduce the resolution of sound information. A lower level resolution could cause a severe discomfort in electrical hearing for CI users and can make the fitting process of the CI challenging.

In the same experiment investigating the influence of IPGs on amplitude at different loudness levels (50%-ADR and MCL), different hypothesis were made concerning the influence of the IPG on the dynamic range. One scenario claims that the IPG may have an effect on the dynamic range and leads to a decrease of the dynamic range. This hypothesis could be confirmed, as for all three pulse rates (200, 600, and 1000 pps), a significant change of dynamic range was observed: An increase of the IPG (2.1, 10, and 30 μs), led to a decrease of the upper dynamic range (from 50%-ADR to MCL). The decrease is caused by a larger IPG effect size at MCL than at 50%-ADR. These findings are in contrast to the study of McKay and Henshall (2003). They reported an increase of dynamic range with increasing the IPG. The amplitude level at hearing threshold decreased on average about 2 dB between 8.4 and 45 μs IPG, while the amplitude level at comfort level decreased on average about 1.3 dB between 8.4 and 45 μs IPG. This resulted in an increase of dynamic range of about 0.7 dB in their study. However, in the experiment of this thesis the decrease in upper dynamic range was found in each of the participating subjects, except for subject S29 (increase in dynamic range at all three pulse rates). This general trend, leading to the significant effect, indicates that the results of the subjects are reliable despite the different findings to McKay and Henshall (2003). However, each subject performed solely one test run per test condition because of the limited time of testing what may have an influence on the subjects' result (see chapter 5.4.1). Another reason for the different findings may be the different choice of the lower boundary of the dynamic range. While McKay and Henshall (2003) measured amplitude levels at hearing threshold and therefore the whole BDR, in this thesis the 50%-ADR amplitude level was chosen as lower dynamic range boundary, covering the upper part of the dynamic range. However, for the sake of better methodical testing, it seems reasonable to use a suprathreshold level as lower boundary instead of hearing threshold. Also, the important levels for everyday situations in CI users (e.g. speech) are covered by the upper dynamic range. Nevertheless, it may be interesting to repeat the experiment of this thesis and measuring the hearing threshold at different IPGs additionally to 50%-ADR and MCL. Thereby, next to the upper dynamic range, the whole BDR would be covered and a better comparison with the data of McKay and Henshall (2003) would be possible. If this additional measured BDR would be in line with the findings of McKay and Henshall (2003), it would suggest that the benefit of a larger BDR occurs due to benefit in the lower part of the dynamic range (hearing threshold to 50%-ADR).

Different to McKay and Henshall (2003), Ramekers et al. (2014) reported in the animal study a constant dynamic range in ECAP measurements (between ECAP threshold and 50% of the maximum N1-P2 amplitude) over IPG for implanted normal hearing and 2-weeks deafened guinea-pigs. Similar to McKay and Henshall (2003) the dynamic range increased with larger IPG in implanted 6-weeks deafened guinea-pigs. Ramekers et al. (2014) suggested that a higher excitation threshold of the SGCs leads to the increased dynamic range in 6-weeks deafened guinea-pigs. As this increase is only found in the 6-week deafened animals, this could also correspond to the degeneration of SGCs over time of deafness. However, the dynamic range in ECAP measurements in animals and the BDR of humans are not identical. Therefore, a comparison of data is difficult. However, it could be interesting to investigate if the dynamic range in CI users is influenced by the duration of deafness as well. Because of the small number of participants in this study (nine subjects), a differentiation of subjects concerning the duration of deafness was not reasonable. Nevertheless, this could be addressed in future studies.

5.3.4 Effect of pulse rate on amplitude level and dynamic range

For the loudness matching experiment of this thesis it was hypothesized that the pulse rate has an impact on loudness perception and may as well influence the dynamic range. Accordingly, a significant effect of pulse rate (200, 600, and 1000 pps) on stimulation level was found, confirming the first part of the hypothesis. The amplitude level had to be decreased with increasing pulse rate for hearing threshold (only 2.1 μs measured), 50%-ADR, and MCL. The results are consistent with the findings from Kreft et al. (2004). In the study from Kreft et al. (2004), amplitude levels decreased at hearing threshold and maximum acceptance level for pulse rates between 200 and 6500 pps. At pulse rates above 3500 pps a decrease of effect size was observed. They made the assumption that the effect size decreases further up to a complete saturation at higher pulse rates above 6500 pps. The comparison of the amplitude level decrease between 200 and 600 pps and between 600 and 1000 pps in the experiment of this thesis revealed a decrease in effect size already at lower pulse rates (between 600 and 1000 pps) than described in Kreft et al. (2004). Similarly a significant effect of pulse rate on dynamic range was found as well, confirming the second part of the hypothesis. The results are only partially consistent with the findings of Kreft et al. (2004). They found an increase of dynamic range with higher pulse rates. Also, the results of the experiment of this thesis revealed an overall increase in upper dynamic range between 200 and 1000 pps. However, increasing the pulse rate from 200 pps to 600 pps, led to a decrease of the upper dynamic range. A further increase of the pulse rate to 1000 pps led to an increase of the upper dynamic range. To allow a better comparison between these two studies, it would have been necessary to measure amplitude levels and dynamic range higher than 1000 pps in the experiment of this thesis.

5.3.5 Interaction effect of pulse rate and IPG

The statistical analysis of both loudness levels (50%-ADR and MCL) revealed an interaction of the two investigated factors pulse rate and IPG. The interaction of pulse rate and IPG can be seen in the curve progression in figure 4.12 and 4.13. At 50%-ADR as well as at MCL differences in curve progression depending on pulse rate can be observed. At the lower pulse rate (200 pps), the amplitude level drops between 2.1 and 10 μs IPG for both loudness levels. Contrary to the curve progression at 200 pps, there is a slight rise in amplitude level at the higher pulse rates (600 and 1000 pps) between 2.1 and 10 μs for the loudness level of 50%-ADR. At MCL, only a slight drop can be observed at the higher pulse rates (600 and 1000 pps) between 2.1 and 10 μs compared to 200 pps. Without interaction of pulse rate and IPG, the curve progression of the different pulse rates would be similar, as the change in amplitude over IPG would not be affected by pulse rate. The interaction effect seems to disappear when calculating the upper dynamic range, as no significant interaction of pulse rate and IPG could be found. Still, it can be observed in figure 4.14 that the curve progression of the three pulse rates is similar but not equal. While the upper dynamic range at 1000 pps pulse rate increases between 10 and 30 μs IPG, this increase cannot be observed at 200 and 600 pps pulse rate. Both, Carlyon et al. (2005) and McKay and Henshall (2003), investigated the effect of the IPG at different pulse rates. However, they did not investigate the interaction of pulse rate and IPG on amplitude level. Therefore, a comparison with the studies regarding the interaction effect is not possible.

5.4 General discussion

5.4.1 Selection of psychoacoustic measurement procedures

To investigate the IPG effect, a loudness matching procedure was selected to determine the amplitude levels for a certain loudness. By means of this loudness matching procedure the test signal was compared with the reference signal in an adaptive procedure. This procedure uses amplitude level bracketing to approach the desired value iteratively. The desired value is the amplitude level inducing equal loudness (e.g. MCL) as the reference signal. As mentioned in chapter 3.5.2, during the test procedure the amplitude level bracketing leads to test signals that are softer than the reference signal. Therefore, it was not possible to use the test procedure at absolute threshold as no audible stimulus exists below absolute threshold. As an alternative, a threshold detection task could have been performed using an AFC procedure to determine the amplitude level at absolute threshold for each IPG. A threshold detection with the AFC procedure uses an inaudible signal (e.g. a pulse train with an amplitude level of zero) as reference signal. Although loudness matching and threshold detection both are based on the AFC procedure the methodical concept is slightly different. The loudness matching compares the test signal with the reference signal in loudness, while the threshold detection aims for the audibility of the test signal (reference signal is always inaudible). Therefore, slightly different methods would have been used to determine the lower and upper boundary of the dynamic range. Instead, a suprathreshold level was chosen as lower boundary of the dynamic range, the 50%-ADR level. This enabled the usage of identical test methods for both loudness levels. On the other hand, this resulted in a substitute of the whole BDR by the upper dynamic range from 50%-ADR to MCL. It is unknown if the upper dynamic range is a good representative of the BDR. However, the upper dynamic range represents the necessary range to understand speech in everyday life condition (except pauses in the speech signal). Therefore, it is assumed, that the upper dynamic range is an appropriate measure for the sake of a better testing with identical adaptive procedures.

A weak spot in the test procedure in the performed psychophysic experiments may be that no repetitions of measurement conditions were done. As psychophysical measurements are subjective measurements, it is common to perform several runs of one test condition. Afterward, the trails are averaged to represent the final value. By repeating the test condition it is possible to investigate the reliability of the result of one subject. The smaller the standard deviation among the trails from one test condition, the more reliable is the received data from the subject. In the experiments of this thesis, only one trail per test condition was performed. This is motivated by the fact that the measurement time was limited. Especially for the pitch discrimination experiment it may have been helpful to perform additional trials of one test condition to verify the subjects results, because of the high variability between subjects where no trend in favor of one test condition could be observed. Nevertheless, also with performing one trial per test condition a certain reliability of the result can be achieved. The result of one trail is achieved by taking the median over a certain number of the final reversals (defined beforehand) and its corresponding standard deviation. Depending of the dimension of this standard deviation one is able to rate the reliability of the achieved data (the larger the standard deviation, the more questionable the result). Also, by combining the 2-AFC procedure with the 3down-1up paradigm in the pitch discrimination task, a good reliability (d' = 1.16) of the result can be achieved, as the subject had to confirm the perceived difference several times after each other. This tracks the reliably of the subject. Also in the loudness matching procedure, one run per test condition seems to be reasonable as the achieved results as a distinct influence of IPG on amplitude level could be observed in each subject.

In the rate pitch discrimination task it would have been possible to perform a 3-AFC instead of a 2-AFC procedure to determine the rate pitch JND. This would enable to perform a 2down-1up procedure. As the subject only has to make two correct answers in a sequence instead of three in a 3down-1up procedure, this would be more time efficient. Despite the lower p_c (70.71% instead of 79.37%), the result of a 3-AFC with 2down-1up would still be reliable (d' = 1.26) due to the lower guessing probability (33%). However, the 3-AFC enables the subject to find the interval that "sounds different" instead of the interval with the higher pitch. Therefore, to eliminate other cues in the decision process than rate pitch it was decided to perform the 2-AFC procedure.

5.4.2 Consequences for CI fitting

The results of the effect of double pulses with short IPI on pitch discrimination may suggest a best IPI for each subject. Additionally, taking advantage of the maximum facilitation effect may be also beneficial. The latter can be achieved in clinical routine by determining the ECAP threshold with the companies fitting software relatively easily and fast. Setting the first pulse at ECAP threshold, the second pulse has to be adjusted to reach the desired loudness. The identification of each subjects' best IPI by psychoacoustic testing, may be too time consuming in clinical routine. Therefore, a fast objective measurement to determine this best IPI would be preferred to optimize the fitting process. It may also result in a lower variability of the results and therefore outperform the subjective measurement. A possibility to measure the transfer of temporal information in rate pitch coding with objective measurements may be by using the electrically evoked auditory steady-state responses (EASSRs). The possibility to record EASSRs in CI users was shown by Hofmann and Wouters (2010) and Bahmer et al. (2018). Furthermore, it was already shown, that with recording ASSR the loudness growth in NH and hearing-impaired listeners can be measured, which is mostly determined using psychoacoustic measurements (Van Eeckhoutte et al., 2016). Another setup, combining psychoacoustic with ASSR by measuring the ability to detect temporal signal modulation, was successfully technically tested (Bahmer and Baumann, 2015). Yet, it has to be evaluated with NH listeners. Both studies showed, that it is possible to establish objective measurements in the near future for evaluating coding strategies to reduce the time of testing. The latter ASSR setup transferred to EASSR would enable to measure the temporal signal modulation transfer using different IPIs to determine an optimal IPI for pitch discrimination. Another possibility to determine the best IPI may be facilitation measurements using ECAP recordings. Varying the IPI, the best IPI would be the one with the strongest facilitation effect. However, as already mentioned, Hey et al. (2017) reported the strongest facilitation effect with IPIs of 13 μs. When applying double pulses in the clinical fitting process, another effect that has to be taken into account is the prolonging of the overall pulse duration. Presenting two biphasic pulses separated by a short IPI compared to one single pulse prolongs the effective pulse duration. This, in turn, limits the maximal possible pulse rate for CI stimulation.

The application of increased IPGs in the fitting process to reduce amplitude levels is straightforward, as the fitting software already allows a variation of the IPG. Similarly to the application of double pulses, a prolonging of the IPG would lead to a limitation of the maximal possible pulse rate for CI stimulation. Another factor that has taken into account is the dynamic range when applying prolonged IPGs. Compared to NH listeners, CI users have a small dynamic range. As the experiment of this thesis revealed, the upper dynamic range decreased significantly with larger IPG, leading to an even stronger limitation. The upper dynamic range is clinically relevant, as it covers the speech dynamic range. However, additionally to the reduced amplitude levels at MCL and 50%-ADR, the application of increased IPGs may have a positive effect for CI users suffering from facial nerve costimulation. An increase of IPG may lead to a reduction of the facial nerve costimulation (Alexander Möltner, personal communication, Nov 14, 2018).

6 Conclusion

Different aspects of coding temporal information in cochlear implants were investigated in this thesis and described in the following.

- Rate pitch discrimination

  To increase the ability of rate pitch discrimination biphasic pulse trains were modified. Instead of one biphasic pulse as part of the pulse train, two biphasic pulses with a short IPI were used in this paradigm. The hypothesis (that was already mentioned in another study showing advantageous effects for sound localization) is that temporal information is increased by using the additional biphasic pulse and therefore enhance rate pitch discrimination. The reason is the lower amplitude and therefore a smaller saturation effect on auditory nerve fibers. However, the analysis of the experimental results showed no improved rate pitch discrimination thresholds using double pulses at 200 and 400 pps with different short IPIs (15, 50, and 150 μs). Nevertheless, the pitch discrimination threshold did not deteriorate using single-pulse trains or double-pulse trains but remained more or less constant which is important when employing these pulse for a better sound localization.

- Rate pitch comparison

  A subsequent pitch discrimination experiment was designed to test perceived pitch by pulse trains containing double pulses. Each of the double pulses is alternating with single pulses. Double and single pulse within the alternating pulse train had equal amplitudes. The study revealed that the pitch perception between this alternating pulse train and the standard single-pulse train differed systematically. Instead, the alternating pulse train at 400 pps was equal with the 200 pps single-pulse train, showing a domination in pitch perception of the double pulse. Further research should address pitch perception of alternating pulse trains with loudness balanced amplitudes between single and double pulses within the alternating pulse train.

- Facilitation effect

  A facilitation effect is the enhancement of the neural response due to pairing two electrical pulses within a short time period up to 200 μs. It may help in rate pitch discrimination by enhance the amount of temporal information transfer due to a higher number of nerve fibers that fire stochastically. The occurrence of the maximum facilitation effect at masker levels (first pulse level) at ECAP threshold was shown by Hey et al. (2017) in CIs of the manufacturer Cochlear. The question behind the experiment in the thesis was, if the determination of the facilitation effect can be achieved with CIs from MED-EL. The goal was to determine the level of the masker pulse with the largest facilitation effect. It could be confirmed that similar to the investigations of Hey et al. (2017), the largest facilitation effect is around the ECAP threshold of a biphasic pulse. To confirm their finding that the maximum facilitation effect does not shift with increasing the probe level and therefore is independent of the probe level, additional measurements are necessary. For further pitch discrimination experiments "individual adapted" double pulses could be used with the first pulse amplitude level around ECAP threshold to use the maximum facilitation effect. The second pulse amplitude level may be varied to reach MCL.

- Loudness perception

  To investigate the possibility of saving battery power, the change in loudness perception was evaluated when the IPG of each pulse within the pulse train was prolonged. The modified pulse train with prolonged IPG was matched in loudness to the standard pulse train with the default IPG of 2.1 μs. The results showed a decrease in amplitude for larger IPGs for same loudness perception. This decrease could be observed at different pulse rates (200, 600, and 1000 pps) and at a soft as well as at a loud perception level (50%-ADR and MCL). As the decrease in amplitude towards larger IPGs was larger at MCL than at 50%-ADR, the upper dynamic range (defined from 50%-ADR to MCL) was decreasing as well. As not the complete dynamic range was investigated in this study additional psychophysic experiments could be performed, e.g. to additionally investigate amplitude behavior at hearing threshold at prolonged IPGs. This could help to get further insight into the underlying mechanisms that are responsible for the findings (Pieper et al., 2020). Another aspect to investigate the influence of IPG is by reproducing the findings using models for loudness perception with electrical hearing.

7 Appendix

7.1 Psylab

To design an adaptive AFC experiment with psylab, three script files - main, set and user file - have to be edited:

- main script: The purpose of the main script is to define all necessary parameters and variables with name and unit to design the experiment. This includes the number of experimental parameters, the adaptive method, the minimum step size, the number of forced choice intervals, and the number of reversals (stop criterion). Additionally, the subjects' task is set (e.g. which presented tone was higher in pitch?) and it can be selected if the subject provides feedback (correct or incorrect answer). Within a loop, the conditions of the experimental parameters are selected and the command for starting the single or interleaved run is set. The main script is only executed once per experimental run.

- set script: At the beginning of each run, the set script is executed once, before the first stimulus presentation has started. The aim of the set script is to assign proper start values for the target signal and the initial step size with whom the target value is changed. Additionally, every other variables and calculations that only needed to be performed once should be put here. This could be the inter-stimulus interval or even the reference signal, if it stays constant during the whole run (e.g. no base rate roving).

- user script: After each response of the subject, adjustments of the target signal are set. The target signal is defined in the user script and therefore it is executed before each new trail of the run. Every other variable that is affected by the subjects' response or e.g. is changed by base rate roving before a new trial should be calculated in the user script.

7.2 Research Interface

With the help of the RIB2, a stimulus can be generated and presented to MED-EL CIs. An example to generate a stm-file which contains the stimulus information and an example to present the stimulus to the implant is provided in the following.

```
%% generate stm-file
initializeRIB;
default.l1 = 'Implanttype Synchrony';
default.l2 = 'Default' ;
rate = 200; %pulses per second
distance = round((1/rate)*1e6); %convert rate into distance
gap = 2.1; %interphase gap
phaseduration = 30; %mikroseconds
tdur = 0.5; %seconds
amplitude = 43.5; %0-127
electrode = 4;

fid = fopen('rate_ref_normal.stm','w');
header = {default.l1 ; [default.l2 ' Pulsar' ' Phase ' num2str(phaseduration) ' ' 'Gap ' num2str(gap) ' Sequential' ' Ranges 3 3 3 3 3 3 3 3 3 3 3 3'] ;};
string = ['Biphasic Distance ' num2str(distance) ' Number 1 Channel ' num2str(electrode) ' Amplitude ' num2str(amplitude)];

fprintf(fid,'%s\n',char(header(1))); %default command
fprintf(fid,'%s\n',char(header(2))); %default command
fprintf(fid,'%s\n',string); %Pulse information
fclose(fid);
HandleFGref = [];
```

```
%% Play file
n = round((tdur*1e6)/distance);
pathFG = 'rate_ref_normal.stm';
HandleFGref = LoadStimulationSequence(pathFG, 10);
for z=1:n
    if ~isempty(HandleFGref)
        AddFgStimulation(HandleFGref, 1, 1); % Zeitlich begrenzt abspielen
```

```
        end
end
SwitchStimulation(2,2,0,0);
```

7.3 Loudness matching experiment (individual data)

In the loudness matching experiment (see 4.4) for each subject the amplitude levels at 50%-ADR and MCL were measured for several IPGs and pulse rates as well as the hearing threshold for 2.1 μs IPG at several pulse rates. These individual data and the corresponding upper dynamic range is shown in table 7.1.

Table 7.1: Individual results of each subject participating in the loudness matching experiment. The table shows amplitude levels for hearing threshold (Thres), 50%-amplitude dynamic range (50%-ADR), most comfortable level (MCL) and the upper dynamic range (upper DR) according to the interphase gap (IPG) at three different pulse rates.

Subject	IPG [μs]	2.1	2.1	10	30	2.1	10	30	2.1	10	30
	Rate [pps]	Thres [dB re 1 μA]	50%-ADR [dB re 1 μA]			MCL [dB re 1 μA]			upper DR [dB re 1 μA]		
S24	200	50.87	53.91	53.49	52.48	56.16	55.43	54.63	2.25	1.94	2.15
	600	50.14	53.31	52.95	52.48	55.63	55.21	54.24	2.32	2.26	1.76
	1000	47.11	52.18	52.86	51.97	55.36	54.70	54.16	3.18	1.84	2.18
S25	200	48.45	52.57	51.21	50.39	55.36	53.49	52.48	2.78	2.27	2.09
	600	43.03	46.93	47.47	4.29	49.61	49.34	48.45	2.68	1.87	1.16
	1000	43.59	47.97	47.47	46.55	50.87	49.75	49.47	2.90	2.28	2.92
S26	200	49.33	53.04	53.40	52.28	55.63	54.24	53.40	2.59	0.84	1.12
	600	49.33	51.97	53.83	52.67	53.99	54.39	53.99	2.02	0.57	1.33
	1000	48.45	51.33	53.57	52.38	53.48	54.55	53.99	2.16	0.98	1.62
S27	200	49.61	52.57	52.46	51.87	54.78	54.39	53.49	2.20	1.92	1.62
	600	48.14	51.22	51.97	51.33	53.48	53.66	52.86	2.27	1.69	1.53
	1000	45.08	50.27	50.87	50.14	53.48	53.66	52.86	3.22	2.78	2.72
S28	200	47.81	51.76	50.99	50.51	54.47	54.16	53.40	2.71	3.17	2.89
	600	45.95	49.61	49.05	48.76	52.18	51.76	50.87	2.57	2.71	2.11
	1000	44.12	48.45	48.30	47.64	51.33	51.10	50.39	2.88	2.81	2.75
S29	200	49.05	53.74	52.95	52.08	56.78	56.47	55.70	3.03	3.52	3.62
	600	48.45	52.67	53.40	52.28	55.50	56.16	55.63	2.83	2.76	3.35
	1000	47.47	52.08	53.22	52.18	55.07	56.35	55.36	3.00	3.12	3.18
S30	200	44.61	51.33	50.27	49.74	55.07	54.08	53.04	3.74	3.81	3.30
	600	44.61	51.10	50.27	49.61	54.78	53.91	53.13	3.67	3.65	3.52
	1000	44.61	50.75	50.27	49.48	54.32	53.83	52.67	3.56	3.56	3.19
S31	200	45.53	49.34	48.76	47.47	51.97	51.10	50.39	2.64	2.35	2.92
	600	45.95	48.76	47.97	47.11	50.87	50.01	49.19	2.12	2.04	2.08
	1000	45.08	48.14	47.47	46.16	50.39	49.88	48.61	2.25	2.41	2.45
S32	200	50.14	52.28	51.87	50.99	53.99	53.40	52.57	1.72	1.53	1.58
	600	49.88	51.66	51.33	50.51	53.13	52.67	52.18	1.48	1.34	1.66
	1000	49.34	51.33	51.10	50.39	52.95	52.48	51.97	1.62	1.37	1.58

7.4 ECAP responses - Primary test procedure

The ECAP recordings to predict the ECAP threshold of subject S33 to S38 that participated in the primary test procedure (see chapter 4.3.1) are shown in the following figures.

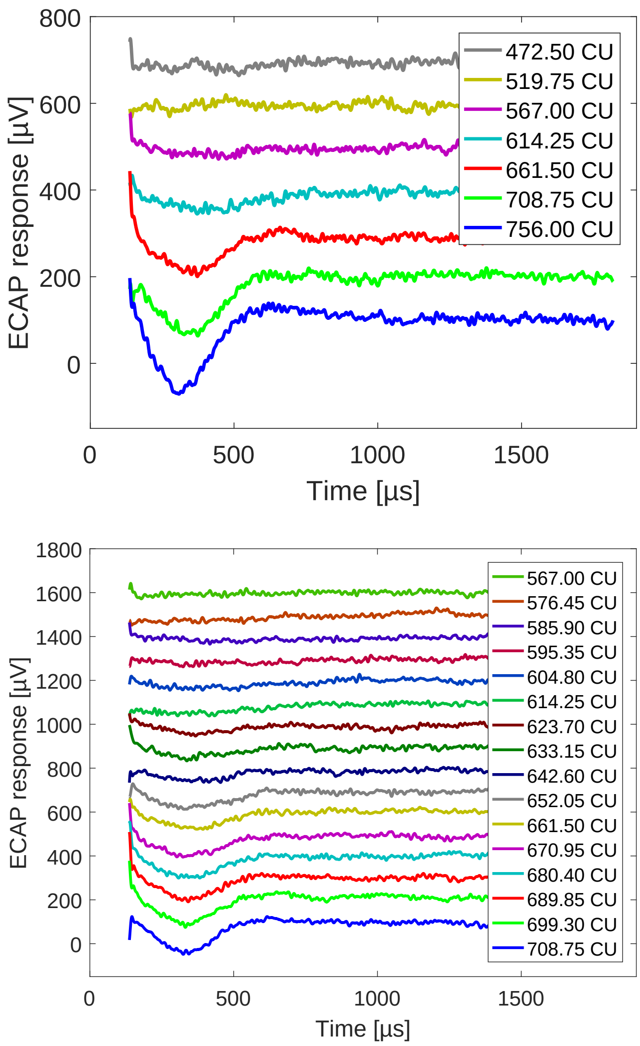


Figure 7.1: Upper panel: First screening measurement of the ECAP responses with low level resolution for subject S33 (current levels between 472 and 756 CU). The ECAP threshold was predicted between 567 CU and 662 CU. Lower Panel: Second measurement of the ECAP responses with fine level resolution for subject S33 (current levels between 567 and 709 CU). The ECAP threshold value was estimated 624 CU. ECAPs were recorded with a custom made software in Matlab.

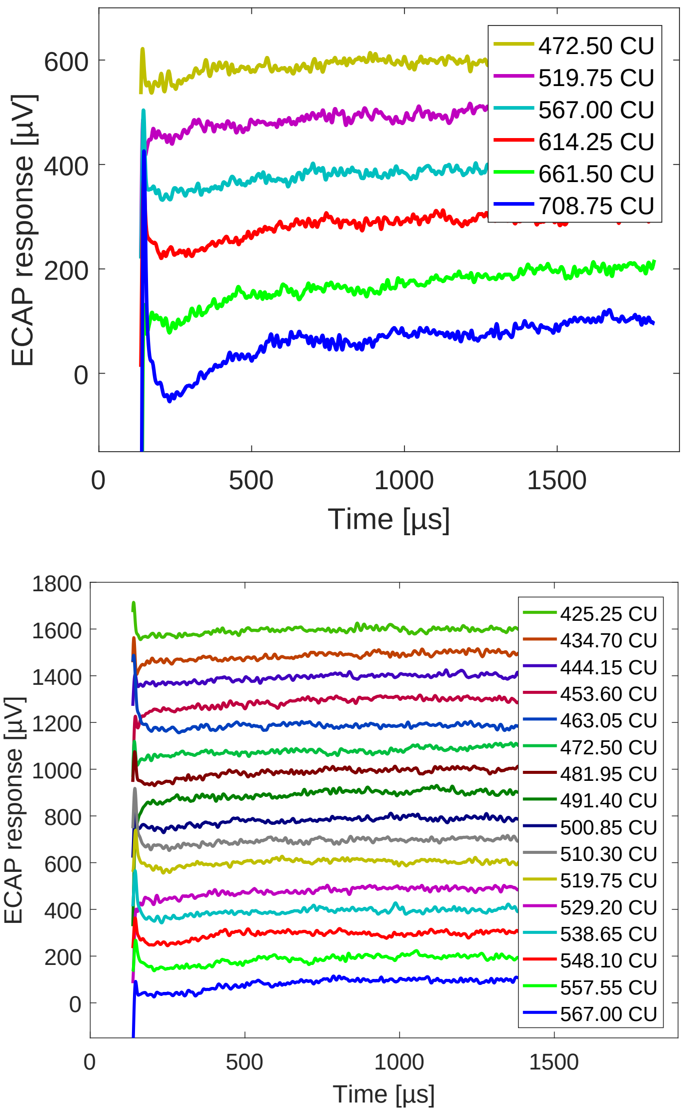


Figure 7.2: Upper panel: First screening measurement of the ECAP responses with low level resolution for subject S34 (current levels between 472 and 709 CU). The ECAP threshold was predicted between 519 CU and 576 CU. Lower Panel: Second measurement of the ECAP responses with fine level resolution for subject S34 (current levels between 425 and 567 CU). The ECAP threshold value was estimated 548 CU. ECAPs were recorded with a custom made software in Matlab.

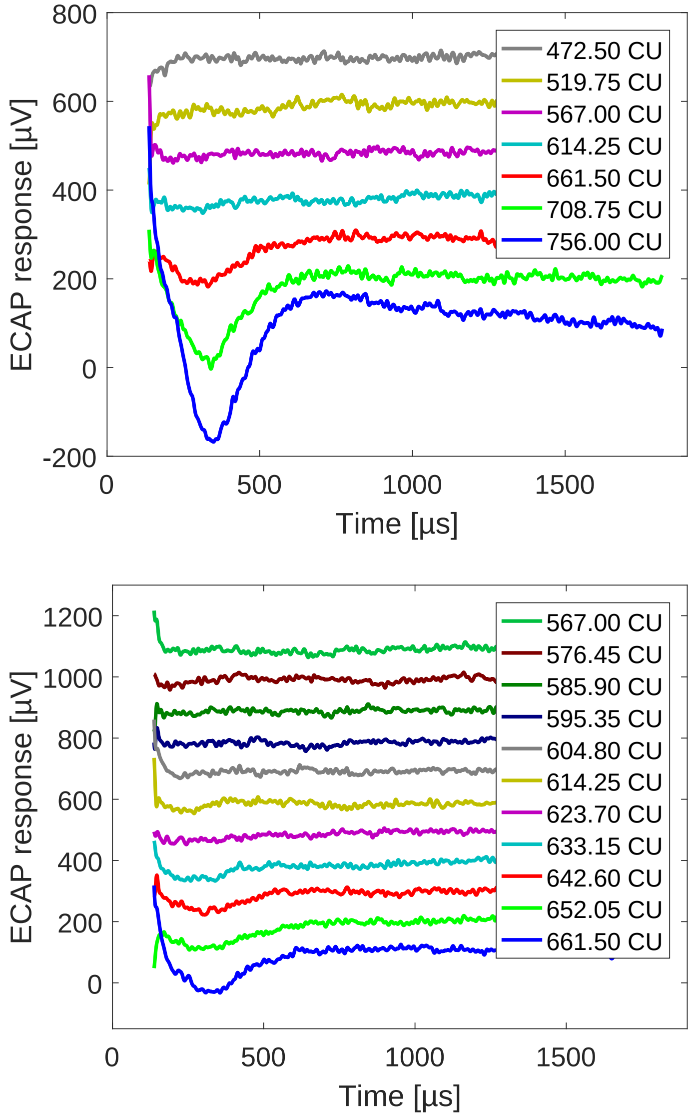
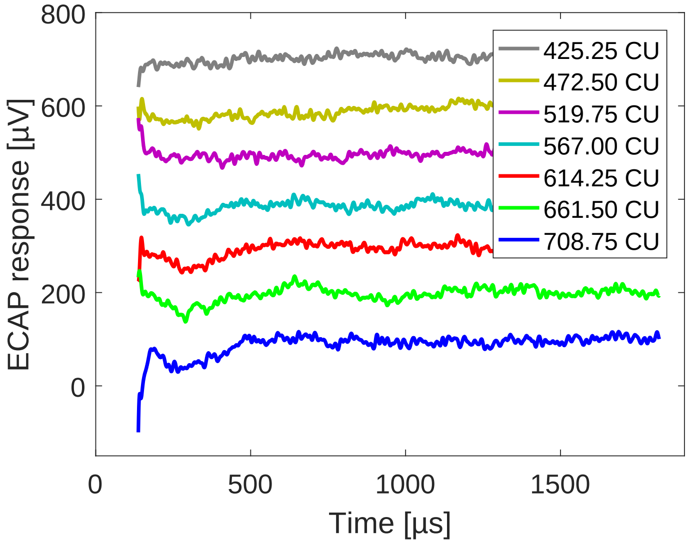


Figure 7.3: Upper panel: First screening measurement of the ECAP responses with low level resolution for subject S35 (current levels between 472 and 756 CU). The ECAP threshold was predicted between 567 CU and 662 CU. Lower Panel: Second measurement of the ECAP responses with fine level resolution for subject S35 (current levels between 567 and 662 CU). The ECAP threshold value was estimated 623 CU. ECAPs were recorded with a custom made software in Matlab.



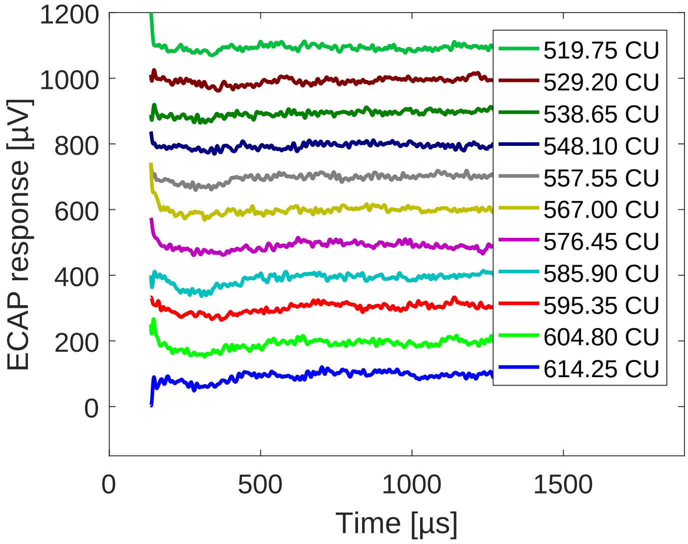


Figure 7.4: Upper panel: First screening measurement of the ECAP responses with low level resolution for subject S36 (current levels between 425 and 709 CU). The ECAP threshold was predicted between 520 CU and 614 CU. Lower Panel: Second measurement of the ECAP responses with fine level resolution for subject S36 (current levels between 520 and 614 CU). The ECAP threshold value was estimated 576 CU. ECAPs were recorded with a custom made software in Matlab.

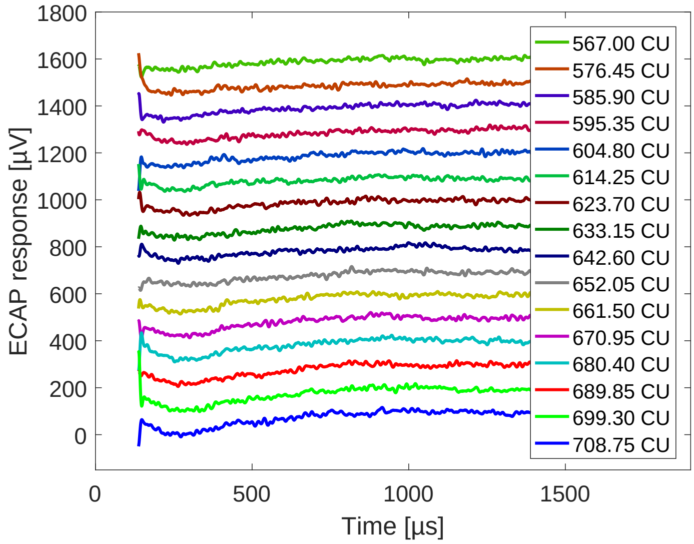


Figure 7.5: Measurement of the ECAP responses with fine level resolution for subject S37 (current levels between 567 and 709 CU). The ECAP threshold value was estimated 567 CU. ECAPs were recorded with a custom made software in Matlab.

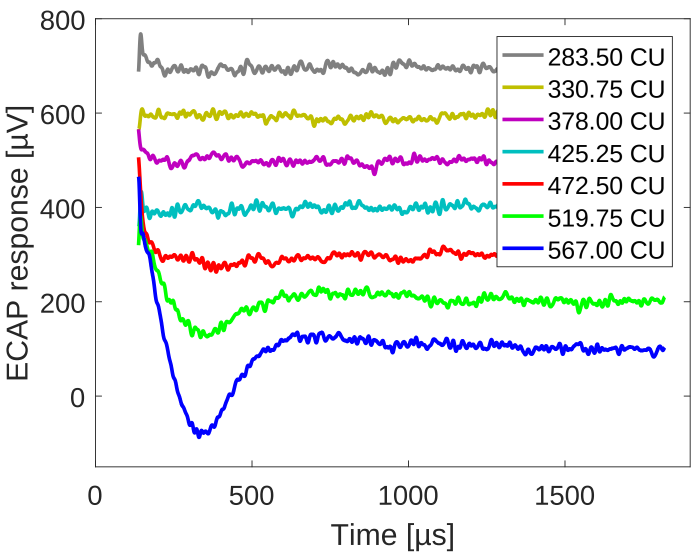


Figure 7.6: First screening measurement of the ECAP responses with low level resolution for subject S38 (current levels between 283 and 567 CU). The ECAP threshold was predicted between 425 CU and 520 CU. ECAPs were recorded with a custom made software in Matlab.

7.5 ECAP responses - Revised test procedure

The ECAP recordings to predict the ECAP threshold of subject S38 to S43 that participated in the revised test procedure (see chapter 4.3.2) are shown in the following figures.

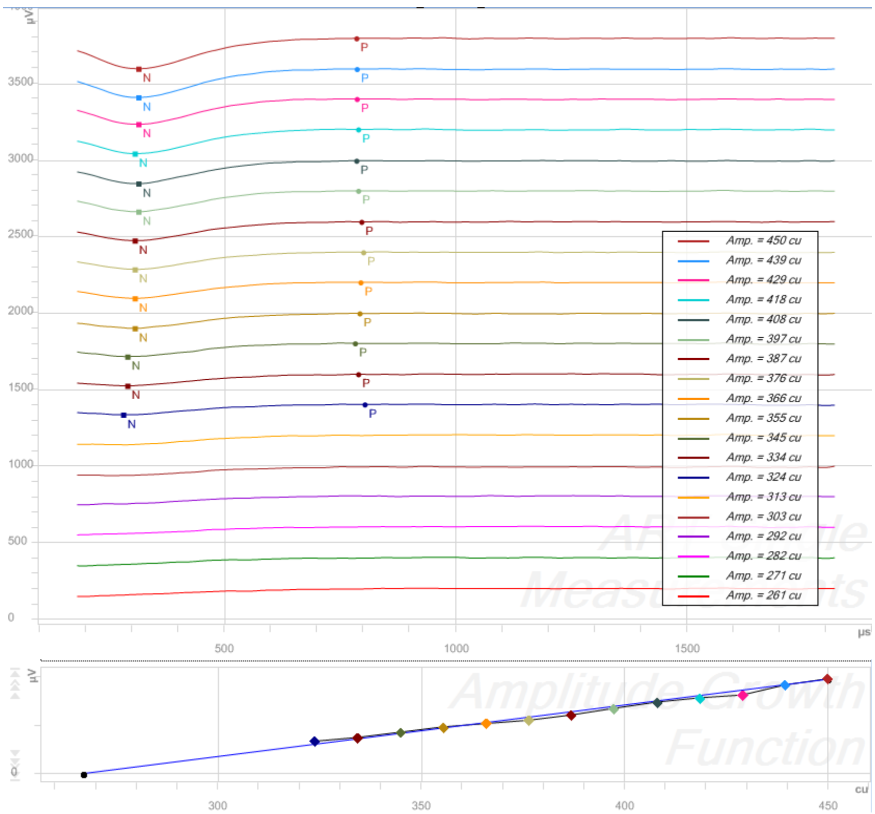


Figure 7.7: Upper panel: ECAP responses recorded of subject S39 for current levels between 281 and 450 CU. Lower Panel: Amplitude growth function of the recorded ECAP responses from subject S39. The N1-P2 peak amplitude is plotted for each current level. The ECAP threshold of 267 CU was estimated by a linear regression.

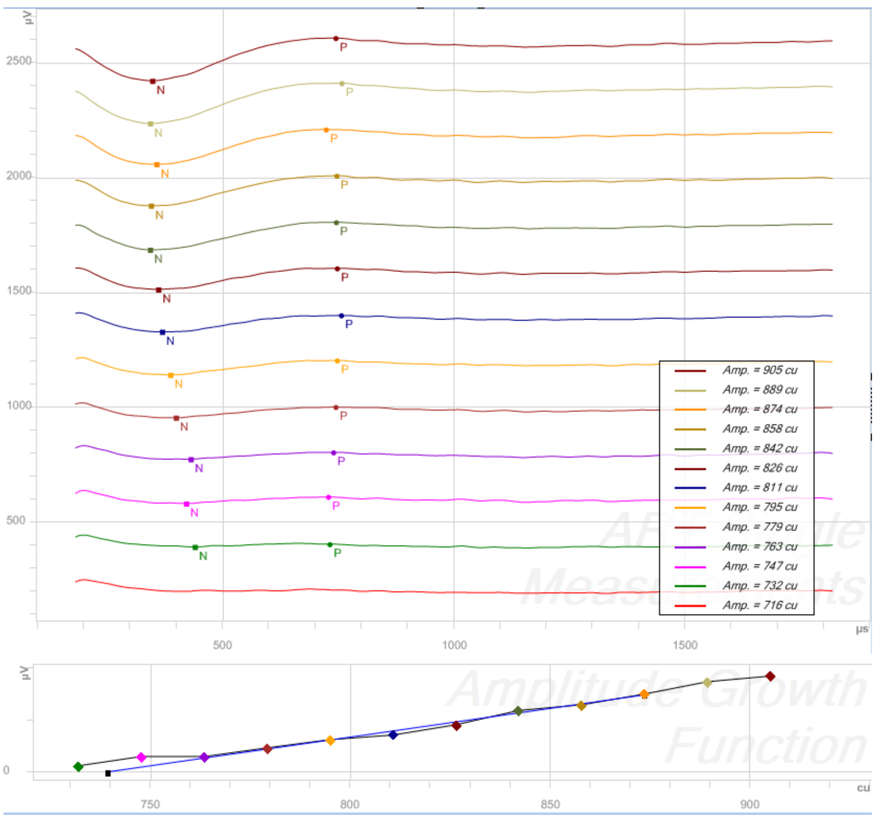


Figure 7.8: Upper panel: ECAP responses recorded of subject S40 for current levels between 716 and 905 CU. Lower Panel: Amplitude growth function of the recorded ECAP responses from subject S40. The N1-P2 peak amplitude is plotted for each current level. The ECAP threshold of 739 CU was estimated by a linear regression. ECAPs were recorded with the ART-tool of the fitting software Maestro.

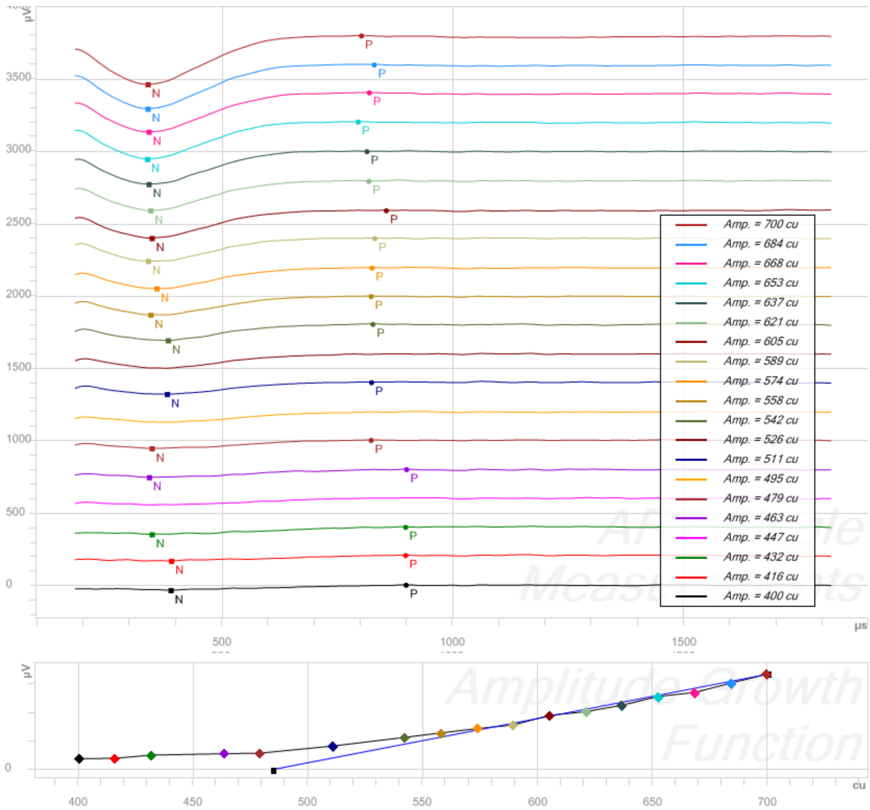


Figure 7.9: Upper panel: ECAP responses recorded of subject S41 for current levels between 400 and 700 CU. Lower Panel: Amplitude growth function of the recorded ECAP responses from subject S41. The N1-P2 peak amplitude is plotted for each current level. The ECAP threshold of 485 CU was estimated by a linear regression. ECAPs were recorded with the ART-tool of the fitting software Maestro.

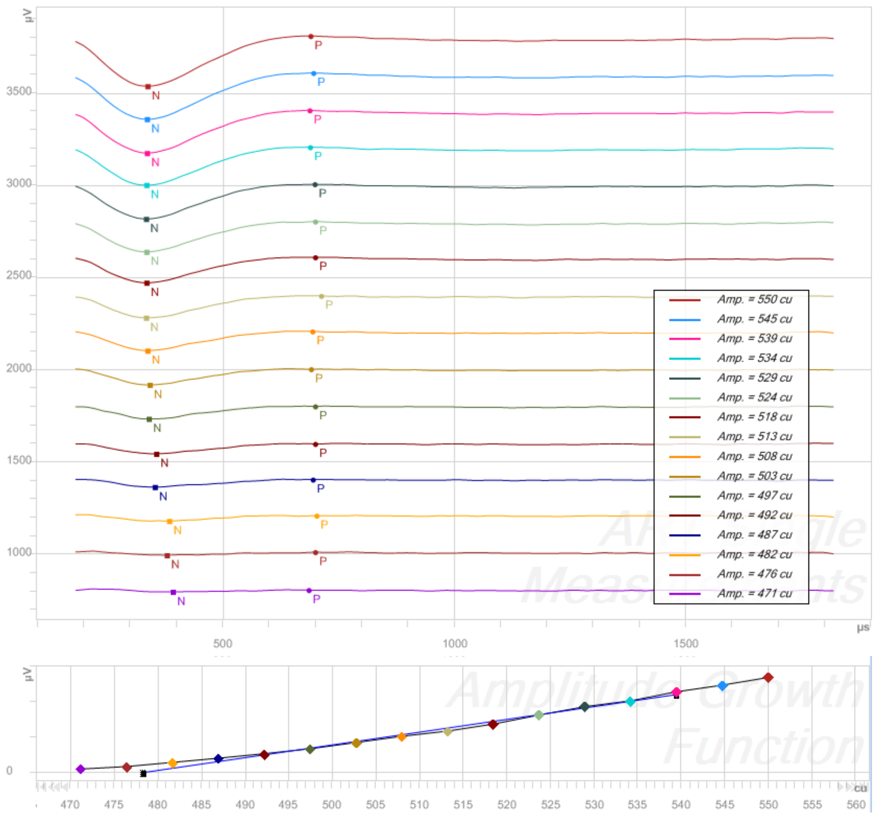


Figure 7.10: Upper panel: ECAP responses recorded of subject S42 for current levels between 471 and 550 CU. Lower Panel: Amplitude growth function of the recorded ECAP responses from subject S42. The N1-P2 peak amplitude is plotted for each current level. The ECAP threshold of 478 CU was estimated by a linear regression. ECAPs were recorded with the ART-tool of the fitting software Maestro.

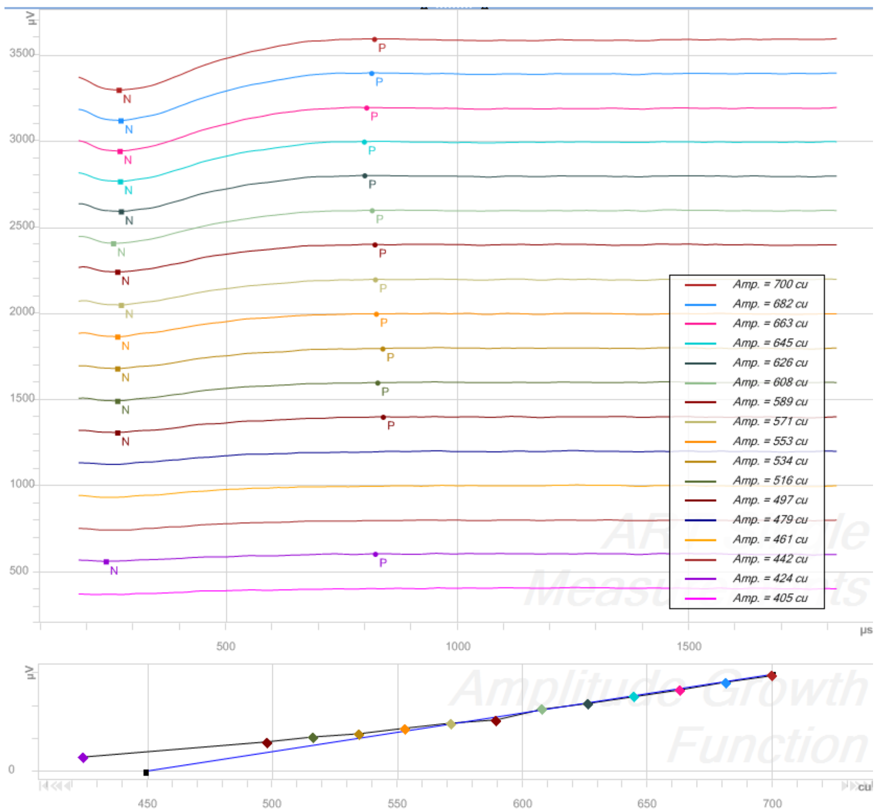


Figure 7.11: Upper panel: ECAP responses recorded of subject S43 for current levels between 405 and 700 CU. Lower Panel: Amplitude growth function of the recorded ECAP responses from subject S43. The N1-P2 peak amplitude is plotted for each current level. The ECAP threshold of 449 CU was estimated by a linear regression. ECAPs were recorded with the ART-tool of the fitting software Maestro.

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Publisher: Wolters Kluwer Health, Inc.
Date: Feb 10, 2020

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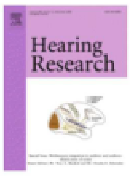

Facilitation and refractoriness of the electrically evoked compound action potential

Author: Matthias Hey,Joachim Müller-Deile,Horst Hessel,Matthijs Killian

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***Correspondence:** Shuman He, Shuman.He@boystown.org

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Declaration

I hereby confirm that my thesis entitled "Temporal information transfer by electrical stimulation in auditory implants" is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor similar form.

Würzburg, September 22, 2020

Sabrina H. Pieper

Hiermit erkläre ich an Eides statt, die Dissertation „Zeitliche Informationsübertragung durch elektrische Stimulation bei Hörprothesen“ eigenständig, d.h. insbesondere selbstständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Würzburg, den 22. September 2020

Sabrina H. Pieper