Accepted Manuscript

Development and validation of a method to record electrophysiological responses in direct acoustic cochlear implant subjects

Hanne Deprez, Robin Gransier, Michael Hofmann, Jan Wouters, Nicolas Verhaert

PII: S0378-5955(18)30136-9

DOI: [10.1016/j.heares.2018.08.004](https://doi.org/10.1016/j.heares.2018.08.004)

Reference: HEARES 7606

To appear in: *Hearing Research*

Received Date: 11 April 2018

Revised Date: 30 July 2018

Accepted Date: 14 August 2018

Please cite this article as: Deprez, H., Gransier, R., Hofmann, M., Wouters, J., Verhaert, N., Development and validation of a method to record electrophysiological responses in direct acoustic cochlear implant subjects, *Hearing Research* (2018), doi: 10.1016/j.heares.2018.08.004.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

- Electrophysiological responses could confirm DACI coupling intra-operatively.
- RF artifacts are dominant and can be modeled based on the RF encoding protocol.
- Electrophysiological responses could be obtained intra-operatively.

Development and validation of a method to record electrophysiological responses in direct acoustic cochlear implant subjects

Hanne Deprez^{a,*}, Robin Gransier^a, Michael Hofmann^a, Jan Wouters^a,
Nicolas Verhaert^{a,b}

^a*ExpORL, Dept. of Neurosciences, KU Leuven, Herestraat 49, 3000 Leuven, Belgium*

^b*University Hospitals Leuven, Department of Otolaryngology, Head and Neck Surgery, 3000 Leuven, Belgium*

Abstract

Acoustic hearing implants, such as direct acoustic cochlear implants (DACIs), can be used to treat profound mixed hearing loss. Electrophysiological responses in DACI subjects are of interest to confirm auditory processing intra-operatively, and to assist DACI fitting post-operatively. We present two related studies, focusing on DACI artifacts and electrophysiological measurements in DACI subjects, respectively. In the first study we aimed to characterize DACI artifacts, to study the feasibility of measuring frequency-specific electrophysiological responses in DACI subjects. Measurements of DACI artifacts were collected in a cadaveric head to disentangle possible DACI artifact sources and compared to a constructed DACI artifact template. It is shown that for moderate stimulation levels, DACI artifacts are mainly dominated by the artifact from the radio frequency (RF) communication signal, that

*Corresponding author

Email address: `hanne.deprez@kuleuven.be` (Hanne Deprez)

URL: (Hanne Deprez)

can be modeled if the RF encoding protocol is known. In a second study, the feasibility of measuring intra-operative responses, without applying the RF artifact models, in DACI subjects is investigated. Auditory steady-state and brainstem responses were measured intra-operatively in three DACI subjects, immediately after implantation, to confirm proper DACI functioning and coupling to the inner ear. Intra-operative responses could be measured in two of the three tested subjects. Absence of intra-operative responses in the third subject can possibly be explained by the hearing loss, attenuation of intra-operative responses, the difference between electrophysiological and behavioral threshold, and a temporary threshold shift due to the DACI surgery. In conclusion, RF artifacts can be modeled, such that electrophysiological responses to frequency-specific stimuli could possibly be measured in DACI subjects, and intra-operative responses in DACI subjects can be obtained.

Keywords: Acoustic hearing implant, Intra-operative objective measures, Radio frequency (RF) artifact modeling, Auditory steady-state response (ASSR), Auditory brainstem response (ABR)

Highlights

- Electrophysiological responses could confirm DACI coupling intra-operatively.
- RF artifacts are dominant and can be modeled based on the RF encoding protocol.
- Electrophysiological responses could be obtained intra-operatively.

⁰ABR: auditory brainstem response, AC: air conduction, ASSR: auditory steady-state

1. Introduction

Middle ear implants exist as treatment options for patients with severe to profound mixed hearing loss (MHL) if conventional middle ear surgery or hearing aids do not suffice. Active middle ear implants mechanically vibrate either the middle ear, when coupled to the ossicular chain, or the inner ear fluids, when coupled to the round window. However, the output power delivered by acoustic middle ear implants is limited [1, 2]. A direct acoustic cochlear implant (DACI) delivers mechanical vibrations directly to the inner ear [3]. The powerful Cochlear CodacsTM, has specifically been designed to deliver an equivalent sound pressure level of 125 dB SPL between 125 and 8.000 Hz [4]. Therefore it presents the potential to exploit the remaining cochlear reserve. The CodacsTM external part consist of two microphones, a sound processor and a radio frequency (RF) link. The CodacsTM internal part contains a receiver, and an electromagnetic actuator that is coupled to the oval window via an artificial incus and conventional stapes prosthesis. Good speech perception outcomes have been achieved in subjects with severe to profound mixed HL implanted with the CodacsTM system [1]. Cochlear implants (CI), that stimulate the auditory nerve electrically, could also be used. In general terms, CI fitting can be regarded as more challenging because of the risk of facial nerve stimulation and a longer rehabilitation is required. Interestingly, DACI sound is based on mechanical vibrations dif-

response, BC: bone conduction, CI: cochlear implant, DACI: direct acoustic cochlear implant, EEG: electro-encephalogram, LDV: laser Doppler vibrometry, LI: linear interpolation, MHL: mixed hearing loss, OR: operating room, PTA: pure tone average, RF: radio frequency, RQ: research question.

ferent to the well-known electrical CI stimulation. Studies have shown that patients achieved better word recognition and speech recognition in noise with a DACI compared to a CI [5], to a hearing aid [6, 7] and to the unaided condition [8]. Long term studies show stable results, without the need to convert to cochlear implantation [9].

Electrophysiological measures obtained in DACI patients could possibly be used for intra-operative feedback about the inner ear coupling, or to assist fitting in hard to fit subjects. Recently, reliable auditory brainstem (ABR) and auditory steady-state (ASSR) responses to click stimuli have been measured post-operatively in three DACI subjects [10]. The RF link between the DACIs internal and external parts creates an electrical RF artifact that distorts the EEG measurements. In the previous study, the RF artifact was removed by linearly interpolating the EEG samples affected by RF artifact. The RF artifact is effectively removed, without response distortion, as the number of EEG samples affected by RF artifact is limited for click stimuli [10].

In the following, two related, yet separate, studies are presented. First, DACI artifacts are characterized to study the feasibility of measuring ABRs and ASSRs to narrow-band stimuli, such as tonebursts. Interestingly, narrow-band stimuli can provide information about frequency-specific threshold levels, e.g., to assist DACI fitting. This would result, for the first time reported in literature, into a frequency-specific measure provided directly by an acoustic hearing implant. However, toneburst stimuli typically have longer stimulus durations than click stimuli, resulting in RF artifacts that are more difficult to remove through linear interpolation, and therefore requiring alter-

native RF artifact suppression methods. In this study, cadaveric head measurements were obtained to disentangle possible electrical artifact sources, and to investigate the possibility of modeling the electrical artifacts based on prior knowledge.

Second, the feasibility of measuring ABRs and ASSRs intra-operatively is investigated. Although the DACI has shown its clinical success [5, 6, 7], the coupling to the inner ear is still a challenge for the surgeon. Hearing improvement is highly dependent on the coupling efficiency. An efficient coupling is required to achieve adequate hearing results and avoid revision surgeries. To improve the outcome of the surgery, the need to develop an objective perioperative electrophysiological measure is obvious. Currently, in the ideal situation, the movement of the actuator is verified intra-operatively using laser Doppler vibrometry (LDV), requiring specific technical skills. Furthermore, LDV movement measurements at the actuator rod do not confirm correct DACI coupling or adequate auditory processing and cannot be obtained post-operatively. The presence of ABRs or ASSRs detected intra-operatively indicates that the eliciting sounds are transmitted well to the inner ear and processed in the auditory brainstem or higher structures of the auditory pathway. However, intra-operative ABR and ASSR measures may be more difficult to obtain compared to postoperative measures, because (1) responses may be attenuated due to the general anesthesia compared to when subjects are awake [11, 12, 13, 14], and (2) the electrical environment is less controlled in the operating room (OR) compared to when subjects are tested in an electrically shielded EEG cabin. In this study, intra- and postoperative ABR and ASSR measurements were obtained and compared in three sub-

jects implanted with the CodacsTM system. The RF artifact modeling of the first study was not used here, since the stimuli, and thus the resulting DACI artifacts, were not the same for both studies.

The novelty of the current study is twofold. We first show that electrical artifacts in DACI subjects are mainly dominated by RF artifacts that can be modeled, in particular for frequency-specific stimuli, such as tonebursts. Second, we show that intra-operative measurements can be obtained in DACI subjects, although intra-operative responses are generally smaller than post-operative responses, and that threshold levels can be estimated from these measurements, however, with slightly elevated thresholds in intra-operative measurements. Ultimately, the current study aims to provide a generic method to create an objective measure to assess the functioning of several types of acoustic hearing implants.

2. Materials and methods

2.1. Study I: Characterization of DACI artifacts

The RF link between the DACI's external and internal parts causes electrical artifacts, obscuring the ABR and ASSR. The actuator possibly also causes electrical artifacts, obscuring the EEG, although it was shown in [10] that the actuator did not cause visible artifacts in a simple bench set-up.

In each RF frame, the stimulation parameters for the next stimulation frame are encoded. The RF artifact duration is therefore related to the stimulus duration. It was shown in [10] that RF artifact durations for 200 μs click stimuli are always less than 300 μs before, and less than 1.4 ms after filtering. The RF artifacts were suppressed by applying a linear interpolation

(LI) over the RF artifact duration. The LI does not obscure the ABR peaks or the ASSR, since click RF artifacts have decayed before the neural responses occur. RF artifacts are also related to the energy of the corresponding RF frames, as shown in [10].

To assess frequency-specific thresholds, toneburst stimulation is considered. Because toneburst stimuli are longer than clicks, RF artifacts for toneburst stimuli overlap temporally with the neural response peaks. More advanced RF artifact suppression methods are thus needed to analyze ABRs and ASSRs elicited by toneburst stimulation. As a first step in the development of more advanced RF suppression methods, the DACI artifacts, elicited by click and toneburst stimuli, were further examined. The aim of this study was twofold: (1) examining which parts of the DACI system and the stimulation set-up contribute to the electrical artifacts seen in the EEG, and (2) investigating the feasibility of modeling RF artifacts based on the energy of the RF frames.

For this purpose recordings were obtained in a cadaveric head with various stimulation conditions. Measuring DACI artifacts in a cadaveric head has several advantages: (1) it is a realistic set-up, (2) no neural background noise or auditory evoked responses are present, and (3) it is possible to disentangle the DACI artifacts from either the RF coil, the actuator or the trigger pulses using various stimulation conditions.

The following research questions were formulated:

1. How do DACI artifact shape and amplitude vary with recording electrode position (contralateral mastoid vs inion vs ipsilateral mastoid) and with time in a realistic set-up? (RQ1)

2. Which parts of the DACI stimulation (RF communication link, actuator, trigger pulses) contribute to the electrical artifacts seen in EEG measurements? (RQ2)
3. For realistic DACI artifacts, can DACI artifact templates be made, based on prior knowledge, i. e., the energy of RF frames? (RQ3)

2.1.1. Human cadaveric head preparation

A standard CodacsTM implantation was performed on a full cadaver head to simulate the in vivo set-up [8, 15]. Microscopic visual inspection was carried out to verify temporal bone integrity and quality, as well as the absence of otologic disease, as recommended in the ASTM F2504-05 standard practice [16]. Through a posterior tympanotomy, a stapes prosthesis was crimped to the CodacsTM actuator and coupled to the inner ear's perilymph. During this step the middle ear was immersed with saline fluid to avoid the entrance of air bubbles in the cochlea. As in living human subjects, the implant was inserted in an implant bed behind the mastoidectomy. Finally, the wound was closed with sutures in a double-layer technique.

Using a separate actuator and implant's receiver, different stimulation conditions could be investigated. Measurements took place in the wet lab space, so additional Faraday caging was not present. The head was firmly held in a soft holding block. An external coil and receiver were coupled for a standard RF link.

The use of human cadaveric heads was done under approval of the Medical Ethics Committee of University Hospital Leuven. The head was acquired by the Anatomy department (Vesalius Institute) and remains were processed according to their verified standards.

2.1.2. Stimulation and recording set-up

Stimuli were generated in *RBA*, an in-house developed stimulation and recording environment [17], running on a measurement laptop. The amplified recorded signals were digitized at 32 kHz with an external RME Hammerfall DSP Multiface II sound card, and either analyzed online in *RBA* or saved on the laptop for offline analysis.

Trigger stimuli, synchronous with the click or toneburst stimuli, were sent directly from the stimulation set-up, that is described in more detail further on in this section, to the sound card recording channel 1. During each measurement, two recording channels were used with non-inverting electrode on the high forehead, and ground electrode in the neck. As shown in Figure 2, the inverting electrode was placed on the contralateral mastoid (channel 2), and either on the inion or on the ipsilateral mastoid (channel 3). Commercially available monopolar needle electromyographic penetrating electrodes were placed subdermally, and inter-electrodes impedances were checked to be below 5 $k\Omega$ at 30 Hz at the start of the measurement session. Two SR560 medical pre-amplifiers were used with the internal band pass filter (6 dB/octave) set to 0.3 Hz to 30 kHz. In most measurements a gain of 10.000 was applied, but in some measurements a lower gain of 1.000 was used.

Four different stimulation conditions were tested, see also Figure 1: (1) complete implant, (2) actuator alone, (3) RF and implant, and (4) only triggers.

[Please insert Figure 1 here.]

In the first condition (complete implant: RF, implant and actuator (R+I+A)), stimuli were generated in *RBA*. The digital stimuli were sent to a program-

ming device (POD), which is an interface between a computer and the subject's processor [18], connected to an L34 research processor [19]. RF packets encoding the stimuli were sent over the RF link between the CodacsTM implant's external and internal part. The packets were decoded at the receiving side, and the actuator, that was coupled to the inner ear, was driven based on the decoded electrical signal. In this condition, the recorded electrical signals may consist of RF artifacts, actuator artifacts, trigger artifacts, and electrical background noise.

In the second condition (actuator alone (A)), the implant was removed and the actuator was driven with an audio signal provided via an audio cable. Stimuli were generated in *RBA*, and sent to an implant-in-a-box via a POD and L34. The implant-in-a-box, consisting of a DACI receiver [18], outputs an audio signal that was used to drive the actuator. In this condition, the recorded electrical signals may consist of actuator artifacts, trigger artifacts, and electrical background noise.

In the third condition (RF and implant (R+I)), the implant was put back in place, but the actuator was kept outside of the head, and electrically shielded. In this condition, the recorded electrical signals may consist of RF artifacts, trigger artifacts, and electrical background noise.

In the fourth condition (only triggers, no RF, implant, or actuator (T)), no implant parts were implanted in or connected to the cadaver head. This condition was used to investigate whether the stimulation set-up itself (e. g., the triggers) was generating electrical artifacts, aside from the expected RF and actuator artifacts. In this condition, the recorded electrical signals may consist of trigger artifacts and electrical background noise. Stimulation and

recording leads were repositioned, to investigate whether the relative positioning of both may have an influence on the recorded trigger artifacts.

In the four conditions, click and tonebursts stimuli with various stimulation levels were used. Stimulation levels are expressed in dBpeFS, i. e., the level of a sinusoid with the same peak level as the click or toneburst stimulus, relative to the maximum-amplitude sinusoid generated with direct stimulation [10]. The maximum-amplitude sinusoid that can be generated with direct stimulation is at 0 dBpeFS. A click stimulus at -x dBpeFS is then x dB below this maximum output level. High stimulation levels could be used, as there is no risk for over-stimulation in a cadaveric head.

200 μ s click stimuli were presented at various low-rate repetition frequencies. 500 Hz tonebursts with a total duration of 6 ms and rise/fall times of 3 ms without plateau, gated with a Blackman window, were presented at a repetition rate of 30 Hz. 1000 Hz tonebursts with a total duration of 4 ms and a rise/fall times of 2 ms without plateau, gated with a Blackman window, were presented at a repetition rate of 33 Hz. Recording durations varied between 30 s and 5 min, and are specified in the results section.

[Please insert Figure 2 here.]

2.1.3. *Recording analysis*

A notch filter with cut-off frequency 50 Hz and quality factor 35 was applied to the recorded EEG signal to remove line interference. The filtered EEG signals were split into epochs, based on the trigger signal. In order to keep signal processing similar to the processing used in living subjects, 5% of epochs was rejected, based on their peak-to-peak amplitude to remove the most noisy epochs. The remaining epochs were then averaged for each

recording channel, resulting in the average epoch.

One of the aims of this study was to examine whether an artifact template could be constructed, e. g., based on the energy in the RF frames. The RF stimulation sequence was determined based on the stimulation parameters, and was further filtered and down sampled to create an RF artifact template. The procedure is described in further detail in Section 3.1.3.

2.2. Study II: Intra-operative electrophysiological responses

Intra-operative measures confirming DACI functioning and auditory processing are of interest, to ensure that surgery has been successful when the subject is still under anesthesia. The presence and thresholds of ABRs or ASSRs confirms that the DACI has effectively been coupled to the inner ear, which is reassuring for both the medical team and the patient. Ideally, absence of ABRs or ASSRs, even at high stimulation levels, could indicate that cochlear reserve is too small, such that even powerful DACI stimulation does not lead to auditory percepts.

Intra-operative ABRs and ASSRs may be more difficult to obtain than postoperative measures. First, ASSRs, elicited by lower stimulation frequencies in the 40 Hz range, may be attenuated or absent due to the general anesthesia. In [11], 40 Hz ASSRs were obtained in 10 subjects under general anesthesia with isoflurane. ASSR amplitudes were significantly reduced during unconsciousness, such that the ASSRs were no longer detectable, and increased only during emergence and recovery. In [13], enflurane was used as an anesthetic agent. ASSR amplitudes were again significantly reduced during anesthesia and surgery, compared to baseline, but ASSRs could still be detected based on phase coherence. Propofol sedation, used in [12], initially

caused 40 Hz ASSR disappearance, but the ASSR reappeared afterwards, regardless of whether consciousness was regained or not. In the same study, the ASSR amplitude could not be related to the return of consciousness. In [20], significant 40 Hz ASSRs were present in 24 experiments in 13 subjects under general anesthesia with propofol. In [21], ASSR thresholds could be determined in infants anesthetized using propofol using chirp stimuli. In [22], ASSR thresholds were measured intra-operatively in patients receiving a VSB to determine the most optimal coupling of the floating mass transducer. No details about anesthetic agents were given in the study. In summary, many studies have shown attenuation of 40 Hz range ASSR amplitudes during general anesthesia [11, 12, 13, 14], although significant ASSRs could still be detected in some cases [12, 13, 14, 20, 21]. Measurement of 90 Hz range ASSRs are probably less affected by general anesthesia, as 90 Hz range ASSR generators are believed to be located in the brainstem [23]. 90 Hz range ASSRs are therefore less susceptible to cortical arousal than ASSRs elicited by lower stimulation frequencies. 90 Hz range ASSRs could indeed be measured intra-operatively in [24].

A second challenge for intra-operative EEG measurements is the uncontrolled electrical environment in the OR, that may lead to more electrical artifacts and interference. In [10] and in this study, postoperative measurements were obtained while the subjects were sitting in a sound attenuated electrically shielded Faraday cage, while manipulations of the electrical environment are restricted in the OR. Prior to the intra-operative measurements in DACI subjects, we obtained EEG measurements in the OR in three subjects without DACI, who were under general anesthesia, to check whether

reliable ABRs and ASSRs could be obtained in the OR environment. The subjects underwent an ear surgery on the opposite ear. The investigated ear was normal hearing. The tests were briefly performed and all subjects gave their written approval. Electrical interference was indeed present, but was mostly dominant at 50 Hz and its harmonics, and at high frequencies above 1 kHz. Significant ABRs and ASSRs could be detected at suprathreshold stimulation levels in all three subjects.

In this study, ABR and ASSR measures were obtained intra-operatively and post-operatively in three DACI subjects. The following two research questions were formulated:

1. Can ABRs and ASSRs be measured intra-operatively in DACI subjects? (RQ4)
2. How do responses obtained intra-operatively compare to responses obtained postoperatively? (RQ5)

We hypothesize that general anesthesia may lead to attenuated 40 HZ range ASSRs, compared to postoperative measures. Ideally, ABR and ASSR attenuation due to general anesthesia is limited, such that absence of ABRs and ASSRs at high stimulation levels indicates inadequate DACI coupling. However, ABR and ASSR attenuation may be large such that ABRs and ASSRs may no longer be detectable, even if the subject has auditory perception at these stimulation levels postoperatively. This may mainly be apparent for subjects with profound hearing losses.

2.2.1. Subjects and test sessions

Three subjects with severe to profound mixed hearing loss were implanted with a Codacs™ DACI at the University Hospitals Leuven. A standard Codacs™ implantation was performed, no surgical complications occurred. Subject details are included in Table 1. Because of the specific indication criteria and because DACIs are not reimbursed in Belgium, only a limited number of subjects received a DACI in the University Hospitals Leuven. All three subjects that were implanted between October 2015 and June 2017 participated in this study.

The surgical details have been discussed above and in literature [8]. Stapedotomy was performed through the posterior tympanotomy. In subject S3, the procedure was more laborious because of the extensive character of the obliterative otosclerosis with facial nerve dehiscence, overhanging of the nerve over the oval window niche and obliterative focus on the stapes footplate. All subjects received general anesthesia and a single dose of corticosteroids. All subjects showed postoperatively stable BC thresholds and no complications were noted. Currently all subjects are daily satisfied DACI users.

Electrophysiological responses were acquired in all subjects, both intra- and post-operatively. The postoperative measurements were obtained 3 to 5 months post implant activation, and also included some behavioral measurements to determine threshold and comfort levels for the stimuli used during the electrophysiological tests. The UZ Leuven/KU Leuven Medical Ethics Committee gave approval for the experiments (approval number B322201112184). All subjects gave their written informed consent.

[Please insert Table 1 here.]

2.2.2. Stimulation set-up

The in-house developed software platform *RBA* was used both for stimulation and recording [17]. As in [10] stimuli were generated in *RBA* and sent to a programming device (POD) connected to an L34 research speech processor.

In general, monophasic positive 200 μs clicks were used with repetition rates of 33, 80 and 95 Hz, which are similar stimuli to the ones used in [10] where reliable post-operative measurements could be measured. As the first study, concerning RF artifact modeling for toneburst stimuli based on cadaveric head measurements, was still going on at the moment of testing in DACI subjects, toneburst stimuli were not used in these measurements.

For all experiments, the stimulation level is expressed as *dBpeFS*: “the level of a sinusoid with the same peak amplitude as a the stimulus clicks, relative to the levels of a maximum-amplitude sinusoid generated with direct stimulation” [10].

2.2.3. Postoperative behavioral measurements

In the postoperative sessions, the minimum audible and maximum comfortable stimulation levels, further called T and C levels respectively, were determined for monophasic 200 μs clicks with stimulation frequencies of 33, 80 and 95 Hz. Rough T and C levels were determined based on an adjustment procedure. Stimulation started at a level of -80 dBpeFS, and was increased in steps of 5 dBpeFS until the subject reported auditory sensation or “very soft” loudness was perceived. Next, the stimulation level was further increased in steps of 3 dBpeFS until the subject reported that the loudness was “good”. After that, steps of 1 dBpeFS were used until a “hard”

stimulation level was reported by the subject, after which stimulation level was decreased in steps of 1 dBpeFS until “good” loudness was reported. This level was noted down and defined as the C level. A stimulation level in the “soft” range was noted down and used as the starting value in an adaptive procedure. More precise T levels were obtained using adaptive 3 interval forced choice one-up one-down procedures, using the same stimuli. Two adaptive procedures were used per stimulation frequency, resulting in six adaptive procedures. The adaptive procedure used 5 dBpeFS steps, and was stopped after eight reversals. The mean of the last four reversals was determined, and averaged for the two adaptive procedures. The obtained value was defined to be the behavioral T level.

2.2.4. Intra- and postoperative electrophysiological measurements

Monophasic alternating 200 μ s clicks were used with repetition rates of 33, 80 and 95 Hz. Stimulation levels were between -55 and -25 dBpeFS, in steps of 5 dBpeFS.

Two Stanford Research Systems SR560 medical pre-amplifiers were used for the EEG measurements. The amplifier gain of 20.000 or 50.000 was used and the internal linear band pass filter (6 dB/octave attenuation outside the pass band) was set to 0.3 to 30 kHz at the pre-amplifier stage. A sampling rate of 32 kHz was used for recording the amplified signals using an RME Hammerfall DSP Multiface II sound card, that supports a limited set of sampling rates. The sound card was connected to a measurement laptop where the signals were saved.

The reference (inverting) electrodes were placed on the contralateral mastoid and theinion, as shown in Figure 2. The active (non-inverting) elec-

trodes from both pre-amplifiers were placed on the forehead (Fp_z). The ground electrodes from both pre-amplifiers were placed on the contralateral clavicle. Commercially available monopolar needle electromyographic penetrating electrodes were placed subdermally for the intra-operative measurements, while for the post-operative measurements, passive electrodes were placed on the head using conductive paste to keep the electrodes in place and to minimize the impedances. Inter-electrodes impedances were checked to be below $5\text{ k}\Omega$ at 30 Hz at the start of each measurement session. Trigger pulses were used for synchronization. The transient signals were observed online in *RBA*. Analysis of the steady-state responses was done offline in *MATLAB v2013a* (The MathWorks Inc., Natick, MA, USA).

- Intra-operative measurements

First, ABRs were measured during 4 min in response to 33 Hz clicks at -45 dBpeFS and the stimulation level was increased with approximately 5 dBpeFS if no clear ABR could be observed. If a clear ABR was present, the stimulation level was decreased by approximately 5 dBpeFS , in order to find the electrophysiological threshold. In subject S3, ABR peaks and significant ASSRs could not immediately be detected. Recording durations were therefore slightly extended to 5 min in some cases.

Second, 80 and 95 Hz clicks were stimulated during 3 min at a selection of levels based on the 33 Hz ABR analysis. In subject S3, at the highest stimulation level, the recording duration was prolonged to 4 min in the hope of finding ABR peaks. Recordings with 95 Hz stimulation were not acquired in S3, since no intra-operative responses had been detected

in the other conditions and due to time constraints.

- Postoperative measurements

During the second part of the postoperative testing, electrophysiological thresholds were determined for the three stimuli described above. First, ABRs were measured during 5 min in response to 33 Hz clicks presented at various supra- and subthreshold stimulation levels. In subject S3, recording durations were 6 min, because of the extensive hearing loss and because no ABRs and ASSRs could be found intra-operatively. Second, 80 and 95 Hz clicks were stimulated during 5 min at a selection of levels based on the 33 Hz ABR analysis. Recording durations were again longer (6 min) for S3. Recording times were longer postoperatively compared to the intra-operative recordings, because larger brain background noise levels were expected in awake subjects.

2.2.5. Signal processing

Similar to [10] LI, from 400 μs before each RF pulse to 1400 μs after each RF pulse, was applied to the recorded EEG signals to remove RF artifacts. As only click stimuli were used, and as the RF artifact duration is limited for click stimuli, the LI effectively removed the RF artifact.

For ABR analysis, the resulting signals were band-pass filtered between 100 and 3000 Hz with two second order Butterworth filters using the *MATLAB* command *filtfilt* to avoid phase distortions. The filtered signal was then split in epochs, based on the trigger pulses. 5% of epochs were rejected based on their peak-to-peak amplitude to remove ocular, muscle or other artifacts. The remaining epochs were averaged for each recording channel, and

the average epoch is shown in the figures below. Due to elevated recording electrode-skin impedances and elevated noise levels, clean EEG signals could not always be obtained in the inion channel. Averaged epochs are not shown in those cases.

For ASSR analysis, the interpolated signals were high-pass filtered with second order Butterworth filter with a 2 Hz cut-off frequency (using the *MATLAB* command *filtfilt*). The filtered signals were again split in epochs, based on the trigger pulses. 5% of epochs were rejected based on the 5% highest peak-to-peak amplitudes to remove ocular, muscle or other artifacts. The remaining epochs were transformed to the frequency domain with a discrete Fourier transform (DFT). The average component over epochs at the repetition frequency f_r was determined. Its amplitude value corresponds to the ASSR amplitude, and its phase corresponds to the ASSR phase. Using a Hotelling T^2 test [25, 17], the mean component at f_r was compared to the noise level, that was determined as the standard deviation of the f_r component over epochs, to decide whether a significant ASSR at f_r was present.

3. Results and discussion

3.1. Study I: Characterization of DACI artifacts

3.1.1. RQ1: Electrical artifacts vary slightly with recording electrode position and over time

The first research question investigates whether DACI artifact morphology and amplitude vary with recording electrode position and with time. The same click stimulus ($200\ \mu s$ -50 dBpeFS with a repetition rate of 102 Hz)

was used with complete implant (R+I+A) stimulation for three recordings of 4.5 min spread in time over 30 minutes. The averaged epochs after notch filtering are shown in Figure 3. Electrical artifacts, possibly consisting of RF artifacts, actuator artifacts and trigger artifacts, are limited in duration for all recording electrode positions, and are slightly smaller for electrodes located further away from the RF coil and the implant. Electrical artifacts are not completely stable over time: electrical artifact amplitudes change from 6 to 2 μV between the first two measurements. This implies that if a RF artifact template can be made, optimal scaling parameters to account for variations with recording position and with time need to be determined for each recording and for each recording channel. Between the first two measurements the pre-amplifier inputs were manipulated, such that impedances changes could cause time variance of the measured artifacts. Impedances were only measured at the start of the recording session, such that this claim cannot be verified with the collected data.

[Please insert Figure 3 here.]

3.1.2. RQ2: Actuator and trigger may cause electrical artifacts

The second research question investigates which parts of the DACI stimulation (RF communication link, actuator, trigger pulses) contribute to the electrical artifacts seen in EEG measurements. As described above in Section 2.1.2, stimulation conditions were varied to exclude selected possible electrical artifact sources. First, toneburst stimuli with various stimulation levels were presented in the actuator alone (A) stimulation condition. In Figure 4, the average epochs after filtering are shown, and it is clear that the actuator may result in electrical artifacts at high stimulation levels. For regularly

used stimulation levels below -20 dBpeFS, actuator artifact amplitudes are so small that these are buried in the background noise. In alive subjects, background noise levels consist of background EEG activity and electrical noise, and although the background noise level decreases with averaging, these levels will be larger than the electrical noise measured in this cadaveric head. It is thus expected that actuator artifacts will be less dominant in alive DACI subjects than the ones observed here in a cadaveric head, because of both the elevated noise levels and the lower stimulation levels.

The maximum actuator artifacts amplitude measured is about $0.2 \mu V$. RF artifact amplitudes are one order of magnitude larger, i.e. in the μV range as can be seen in Figure 3. Actuator artifacts are thus only present for high stimulation levels (> -20 dBpeFS) that are not often used clinically and are an order of magnitude smaller than the RF artifacts measured. In other words, electrical artifacts are expected to be dominated by RF artifacts, for clinically used stimulation levels.

[Please insert Figure 4 here.]

A trigger artifact before the toneburst stimulus is also apparent. Note that the actuator artifact is largest in the channel closest to the implant (placed on theinion), while the trigger artifact is largest in the contralateral mastoid. This implies that the trigger artifact may be caused by the relative positioning of the recording and stimulation leads, rather than by propagation of trigger stimuli through the cadaveric head.

The trigger artifact was further investigated in three subsequent 30 s recordings. In the first recording, stimulation parameters were changed: $2 ms$ -20 dBpeFS clicks were continuously presented with the RF coil and implant

in place (condition (R+I)) at 124 Hz, with triggers associated with the first click of every click pair. The implant was then removed from the cadaveric head (condition (T)), and the same stimulation was used for the second recording. No RF artifact should thus be observed: as the RF coil is not attached to the cadaveric head during these recordings, RF artifacts cannot propagate to the recording electrodes. The trigger artifact is most likely caused by capacitive coupling between stimulation and recording leads. It is therefore expected that the trigger artifact will still be visible, as the cables are not repositioned. For the third recording, recording and stimulation leads were repositioned, with the implant still removed from the cadaveric head (condition (T)).

For the three recording, two averaged epochs, after notch filtering, are shown in Figure 5. Trigger and RF stimulation artifacts are apparent in the first recording. As expected, only trigger artifacts are visible in the second recording. After repositioning of the stimulation and recording leads, trigger artifacts disappeared. These results imply that trigger artifacts may be minimized through careful cable positioning. High-frequency interference, that could not be removed using low pass or notch filters, was present in the third recording, leading to increased noise levels in this recording, although the same number of epochs was averaged in all recordings.

[Please insert Figure 5 here.]

3.1.3. *RQ3: RF artifacts can be modeled, based on the (theoretical) RF signal*

The third research question asked whether it is possible to model the electrical artifacts observed with DACI stimulation. The electrical signals caused by the RF transmission were measured at various stages of the mea-

surement set-up, as explained and discussed in the supplementary materials included in Section 5.

−50 dBpeFS 30 Hz toneburst stimulation with the complete implant during 5 min was used to obtain the average epoch signal shown in blue in Figure 6. For regularly used stimulation levels in alive DACI subjects, that range approximately between -70 dBpeFS and -20 dBpeFS [10], electrical artifacts are mainly dominated by RF, as discussed in Section 3.1.2. Trigger artifacts can be minimized by carefully positioning of recording and stimulation leads, and actuator artifacts are only dominant at higher stimulation levels. As suggested in [10], RF artifacts could possibly be modeled based on the energy in the RF frames. Next to the RF artifact that is related to the stimulation, a decaying artifact is also apparent in Figure 6. This artifact could possibly be modeled with a decaying exponential.

[Please insert Figure 6 here.]

First, the modeling of the RF artifact is described. For the CodacsTM implant, a 5 MHz RF carrier is amplitude modulated to transmit the stimulation parameters from the implant’s external to the internal part. Cochlear Ltd provided the RF encoding protocol to our research group. Based on this protocol, the theoretical RF AM signal for the used stimulation sequences could be determined. The RF AM signal was constructed with a sample rate of 100 MHz, and is denoted as $r[k']$ with k' the time sample. This ideal RF signal has no components in the baseband: all energy is located around the 5 MHz carrier. However, demodulations, that can be observed at recording electrodes placed in a physiological saline solution, in a cadaveric head and in alive DACI subjects, result in contributions in the baseband, at the click

or toneburst repetition frequency f_r . In our model, a nonlinearity (i.e., an absolute value operation) was applied to $r[k']$, resulting in the signal $r_{nl}[k']$ with a component at f_r . High-pass and low-pass filters with the same cut-off frequency and roll-off as those used for recording were applied to $r_{nl}[k']$. The resulting signal was then down sampled to 32 kHz, the sampling rate used for signal acquisition. The resulting signal is the RF artifact template $t[k]$, with k the new time sample. A least squares estimation was used to determine the optimal scaling factor a , relating $t[k]$ to the observed signal.

Second, the exponential decay $e[k]$ was determined by fitting an exponential to the averaged epoch. The complete electrical artifact template $T[k]$ was then determined as the sum of both templates, and is shown in black in Figure 6:

$$T[k] = at[k] + e[k] \quad (1)$$

This template was then subtracted from the observed signal, thereby attenuating the electrical artifacts.

The resulting signal is shown in red in Figure 6. In the future, this template modeling and subtraction method could possibly be used to measure ABRs to toneburst stimuli in alive DACI subjects. As RF artifacts last at least as long as the stimulus, ABR peaks are completely distorted by RF artifacts for toneburst stimuli without RF artifact attenuation. The template modeling and subtraction method has also been applied to the recordings obtained using click stimulation, where the model resembled the measured DACI artifacts closely. However, at the edges the timing of the high-frequency jump was not exactly the same, resulting in peaks when the

model is subtracted from the measured signals.

3.2. Study II: Intra-operative and postoperative electrophysiological responses

3.2.1. Results: RQ4 and RQ5: 33 Hz ASSR

33 Hz ASSRs are shown in Figure 7.

[Please insert Figure 7 here.]

In subject S1, significant ASSRs were detected intra- and postoperatively. No significant synchronous activity was detected at subthreshold stimulation levels, which indicates that no residual RF artifact was present. Furthermore, ASSR amplitudes are larger postoperatively compared to the responses measured intra-operatively. Electrophysiological thresholds are -45 and -50 dBpeFS, measured intra- and postoperatively, respectively, and are close to the behavioral threshold of -50 dBpeFS determined postoperatively.

In subject S2, a significant ASSR was only detected at the highest stimulation level tested intra-operatively. Postoperatively, significant ASSRs are obtained in both recording channels, at most suprathreshold stimulation levels. No significant synchronous activity is detected at subthreshold stimulation levels, which indicates that RF artifacts are again sufficiently attenuated by the LI. At -35 dBpeFS, the intra-operative ASSR amplitude (34 nV) was remarkably smaller than the postoperative ASSR amplitude (918 nV). Despite their low amplitudes, intra-operative ASSRs are still significantly larger than the intra-operative EEG background noise, that is also reduced due to lower spontaneous brain activity during general anesthesia.

In subject S3, significant ASSRs were not detected in most conditions tested intra-operatively. Only one significant ASSR was present at -29 dBpeFS in the inion channel. This is probably a false detection due to residual RF

artifact or due to chance. Postoperatively, significant ASSRs were detected at all suprathreshold stimulation levels. In the inion channel, significant synchronous activity was also detected at -39dBpeFS , while the behavioral threshold was -38 dBpeFS . Because the tested stimulation level is so close to the behavioral threshold, it is not unlikely that a genuine neural response is present. However, the significant synchronous activity may also be caused by residual RF artifact.

3.2.2. Results: RQ4 and RQ5: 33 Hz ABR

The 33 Hz recordings were also analyzed in the time domain, after filtering, by visually detecting ABR peaks. The results are included in Figure 8, with the peak V indicated.

[Please insert Figure 8 here.]

The same conclusions can be drawn as in Section 3.2.1: (1) intra-operative responses are generally smaller than postoperative responses, and (2) no ABRs can be detected intra-operatively in subject S3 for the tested stimulation levels.

3.2.3. Results: RQ4 and RQ5: 80 and 95 Hz ABR

The 80 and 95 Hz recordings were analyzed in the time domain, after filtering, by visually detecting ABR peaks. The results are included in Figure 9, with the peak V indicated.

[Please insert Figure 9 here.]

Again, the same conclusions can be drawn as in Sections 3.2.1 and 3.2.2: (1) intra-operative responses are generally smaller than postoperative responses, and (2) no ABRs can be detected intra-operatively in subject S3 for

the tested stimulation levels.

Due to time constraints only a limited number of 90 Hz range ASSRs were acquired in each subject and condition. Unfortunately, 90 Hz range ASSRs could not consistently be detected, either intra-operatively or post-operatively in all three subjects. The results are therefore not shown here. Possibly no consistent 90 Hz range ASSRs are detected due to the chosen stimulation frequencies, which deviate slightly from those used in [10].

3.2.4. Discussion

Two research questions were investigated in this second study.

- RQ4: Detection of intra-operative responses

First, we examined whether ABRs and ASSRs could be detected intra-operatively in subjects that just received a DACI. In subjects S1 and S2, significant ASSRs and ABR peaks could be detected intra-operatively. No significant ABR and ASSRs could be found in subject S3, for the stimulation levels tested. Possible reasons for the absence of ABRs and ASSRs are discussed below. As indicated in [10], the difference between behavioral threshold levels and electrophysiological threshold levels determined based on the 40 Hz ASSR ranges from 3 dBpeFS to 22 dBpeFS. For 90 Hz ASSRs and ABRs, the differences may be even larger, ranging from 3 to 42 dBpeFS and from 6 to 52 dBpeFS, respectively.

For subjects S1 and S2, the difference between behavioral threshold levels and electrophysiological threshold levels determined intra- and postoperatively, is indicated in Figure 10. While the differences are

small (0 dBpeFS and 5 dBpeFS for post- and intra-operative responses, respectively) for S1, differences are larger (up to 14 dBpeFS for intra-operative responses) in S2.

[Please insert Figure 10 here.]

The behavioral threshold determined postoperatively in S3 is rather high: -37 dBpeFS for 33 Hz clicks and -38 dBpeFS for 80 and 95 Hz clicks. It is known that the subject had an extensive hearing loss prior to DACI surgery, which could explain the high stimulation levels needed for auditory perception. Stimulation levels intra-operatively were limited however for safety reasons. The highest stimulation level tested intra-operatively in S3 was -24 dBpeFS. The surgery, with subsequent steps of drilling with levels often exceeding 100 dB HL [26, 27, 28, 29, 30], laser and prosthesis coupling, may have caused a temporary threshold shift, which may explain the absence of electrophysiological responses [27, 31, 32, 33, 34]. Because (1) threshold levels are high in the tested subject, (2) intra-operative responses are usually smaller than postoperative responses at the same stimulation levels, (3) electrophysiological threshold levels are usually elevated compared to behavioral thresholds, and (4) the subject may have suffered from a temporary threshold shift due to the DACI implantation, it is possible that no intra-operative responses could be recorded from subject S3 at the stimulation levels used.

- RQ5: Comparison of intra-operative and postoperative responses

Second, we compared intra-operative and postoperative responses, to

determine whether ABRs and ASSRs are attenuated due to general anesthesia. Postoperative ABRs and 33 Hz ASSRs were indeed larger than intra-operative responses. This is in line with previous studies [11, 12, 13, 14, 20, 21], that found attenuated but detectable 40 Hz range ASSRs intra-operatively. 90 Hz range ASSRs could not always be reliably obtained and are therefore not shown or discussed here. Due to the limited sample size, we did not verify statistically that the difference between intra-operative and postoperative ABR and 33 Hz ASSR amplitudes differs from zero. It cannot be ruled out that larger postoperative response amplitudes are partly caused by auditory plasticity after DACI activation and during rehabilitation. However, it is likely that the decreased intra-operative response amplitudes are partly caused by the general anesthesia.

LI was used to suppress RF artifacts. Alternatively, the RF artifact modelling described in Section 3.1.3 could be used. Since LI is a computationally simple method that can easily be applied to short DACI artifacts, such as the ones resulting from click stimulation, LI is the preferred method to analyze responses to click stimulation. In order to apply the template subtraction method to click stimuli, a small LI would still be required to remove peaks due to inadequate edge modelling.

The main limitation of the current study is the limited number of subjects because of reimbursement issues, due to a less frequent pathology.

4. Conclusion

The aim of this study was twofold. First, we characterized electrical artifacts present during DACI stimulation, and investigated whether these electrical artifacts could be modeled based on prior knowledge about the stimulation sequence. For moderate stimulation levels, actuator artifacts are negligible. Trigger artifacts can be minimized by careful positioning of stimulation and recording electrode leads. RF artifacts can be modeled based on the theoretical RF sequence, encoding the stimulation parameters. In the future, the RF artifact model could be used to attenuate RF artifacts in recordings with long stimuli, such as tonebursts.

Second, intra- and postoperative responses were recorded in three DACI subjects. In two of the three subjects intra-operative ABRs and ASSRs could be measured. The absence of intra-operative responses in the third subject is probably caused by (a combination of) the large hearing loss, attenuation of intra-operative responses, the difference between electrophysiological and behavioral threshold, and a temporary threshold shift due to the DACI surgery. Detection of ABRs and ASSRs intra-operatively indicates that the DACI has effectively been coupled to the inner ear, and that there is sufficient cochlear reserve to overcome the sensorineural hearing loss. The case of subject S3 demonstrates that absence of ABRs and ASSRs is not necessarily associated with inadequate DACI coupling. The subject's hearing loss should also be considered together with the stimulation levels used to elicit the ABRs and ASSRs. Furthermore, postoperative responses are generally larger than intra-operative responses.

5. Supplementary materials

In pilot experiments, we measured the electrical signals caused by the RF transmission at various stages of the measurement set-up, as shown in Supplementary Figure 1. As in [1], stimulus artifacts caused by RF transmission were measured with electrodes in a 1 l plastic boil containing saline solution (NaCl 0.9%), mimicking the electrophysiological human head. Stimulation consisted of clicks of about $200 \mu s$, followed by $200 \mu s$ silence, resulting in a stimulation frequency of about 2500 Hz for an RF frame rate of 19607 Hz.

Using a Lecroy WaveRunner HRO 647i, the (processed) RF signal was measured at the RF coil (signal 1 in Supplementary Figure 1), with an inductive loop, as well as at the input (signal 2) and the output (signal 3) of the SR560 amplifier. In addition, the signal at the output of the SR560 amplifier was measured in RBA, with recording settings similar to the ones used in the cadaveric head study (sample rate $f_s=32$ kHz, low-pass filter cut-off $f_{LPF}=30$ kHz).

The recorded signals and the RF artifact models at various stages of the measurement set-up are shown in Supplementary Figure 2. The RF artifact measured at the RF coil and in water are shown in the top-left panel. The RF artifact is transmitted well by the water, as both signals are almost equal. In the top-right panel, the signal measured at the amplifier input, i.e. the RF signal measured in water, is compared to the model constructed based on the theoretical RF signal. Again very similar signals are observed, although the measured signal is not completely symmetric around zero, resulting in a DC artifact component, contrary to the model that is perfectly symmetric around zero, that has no DC component. The DC component is introduced

into the model by taking the absolute value of the modeled RF signal. Next, the influence of the filters is modeled. The modeled squared RF signal is low pass filtered with a first order Butterworth filter with cut-off 30 kHz. The resulting signal is compared to the measured amplifier output in the bottom-left panel. Again, both signals are very similar. The signal then travels through the sound card, with anti-aliasing filter and sampling at 32 kHz, and is registered in RBA. Again, a low-pass filter at 16 kHz and decimation at 32 kHz were simulated, and the resulting signal is compared to the signal obtained in RBA, as shown in the bottom-right panel. Again, both signals are very similar.

Acknowledgments

The authors would like to thank all DACI subjects who participated in this study. Research was funded by the Research Foundation Flanders (G.0662.13), by the Agency for innovation by Science and Technology (IWT 141243; and IWT 150432) and by Cochlear Ltd.

Author contributions

HD, RG, MH, JW and NV designed and executed the experiments. MH and HD designed and wrote the software for stimulation and recording. HD did the analysis and wrote the manuscript. NV performed the DACI surgeries in the cadaveric head and the patients. RG, JW and NV critically reviewed the manuscript.

- [1] N. Verhaert, C. Desloovere, J. Wouters, Acoustic Hearing Implants for

- Mixed Hearing Loss : A Systematic Review, *Otology & Neurotology* 34 (2013) 1201–1209. doi:10.1097/MAO.0b013e31829ce7d2.
- [2] J. W. Zwartenkot, A. F. M. Snik, E. A. M. Mylanus, J. J. S. Mulder, Amplification Options for Patients With Mixed Hearing Loss, *Otology & Neurotology* 35 (2) (2014) 221–226. doi:10.1097/MAO.0000000000000258.
- [3] R. Häusler, C. Stieger, H. Bernhard, M. Kompis, A novel implantable hearing system with direct acoustic cochlear stimulation, *Audiology and Neurotology* 13 (4) (2008) 247–256. doi:10.1159/000115434.
- [4] H. Bernhard, C. Stieger, Y. Perriard, Design of a semi-implantable hearing device for direct acoustic cochlear stimulation, *IEEE Transactions on Biomedical Engineering* 58 (2) (2011) 420–428. doi:10.1109/TBME.2010.2087756.
- [5] E. Kludt, A. Buchner, B. Schwab, T. Lenarz, H. Maier, Indication of direct acoustical cochlea stimulation in comparison to cochlear implants, *Hearing Research* 340 (2016) 185–190. doi:10.1016/j.heares.2016.01.016.
- [6] S. Busch, S. Kruck, D. Spickers, R. Leuwer, S. Hoth, M. Praetorius, P. K. Plinkert, H. Mojallal, B. Schwab, H. Maier, T. Lenarz, First Clinical Experiences With a Direct Acoustic Cochlear Stimulator in Comparison to Preoperative Fitted Conventional Hearing Aids, *Otology & Neurotology* 34 (9) (2013) 1711–1718. doi:10.1097/MAO.0000000000000225.
- [7] T. Lenarz, N. Verhaert, C. Desloovere, J. Desmet, C. D’hondt, J. C. F. González, E. Kludt, A. R. Macías, H. Skarzynski, P. Van de Heyning,

- C. Vyncke, A. Wasowski, A Comparative Study on Speech in Noise Understanding with a Direct Acoustic Cochlear Implant in Subjects with Severe to Profound Mixed Hearing Loss, *Audiology and Neurotology* 19 (3) (2014) 164–174. doi:10.1159/000358004.
- [8] T. Lenarz, J. W. Zwartenkot, C. Stieger, B. Schwab, E. a. M. Mylanus, M. Caversaccio, M. Kompis, A. F. M. Snik, C. D’hondt, H. Mojallal, C. D’hondt, H. Mojallal, Multicenter study with a direct acoustic cochlear implant, *Otology & Neurotology* 34 (7) (2013) 1215–1225. doi:10.1097/MAO.0b013e318298aa76.
- [9] E. Kludt, C. D’hondt, T. Lenarz, H. Maier, Clinical Validation of a Sound Processor Upgrade in Direct Acoustic Cochlear Implant Subjects, *Otology & Neurotology* (October 2012) (2017) 1. doi:10.1097/MAO.0000000000001404.
- [10] N. Verhaert, M. Hofmann, J. Wouters, Transient and Steady State Auditory Responses With Direct Acoustic Cochlear Stimulation, *Ear and Hearing* 36 (3) (2015) 320–329. doi:10.1097/AUD.000000000000117.
- [11] G. Plourde, T. W. Picton, Human auditory steady-state response during general anesthesia, *Anesth Analg* 71 (5) (1990) 460–468.
- [12] G. Plourde, The effects of propofol on the 40-Hz auditory steady-state response and on the electroencephalogram in humans., *Anesthesia and analgesia* 82 (5) (1996) 1015–1022. doi:10.1213/00000539-199605000-00023.

- [13] G. Plourde, C. Villemure, Comparison of the Effects of Enflurane/N₂O on the 40-Hz Auditory Steady-State Response Versus the Auditory Middle-Latency Response, *Anesthesia and analgesia* 82 (1).
- [14] G. Plourde, C. Villemure, P. Fiset, V. Bonhomme, S. B. Backman, Effect of isoflurane on the auditory steady-state response and on consciousness in human volunteers, *Anesthesiology* 89:844 (51).
- [15] G. Bernardi, T. Van Waterschoot, M. Moonen, J. Wouters, M. Hillbratt, N. Verhaert, Measurement and Analysis of Feedback and Nonlinearities for the Codacs Direct Acoustic Cochlear Implant, *IEEE Access* 5 (2017) 8702–8713. doi:10.1109/ACCESS.2017.2703635.
- [16] ASTM, International F2504-05 Standard Practice for Describing System Output of Implantable Middle Ear Hearing Devices. (2005).
- [17] M. Hofmann, J. Wouters, Improved electrically evoked auditory steady-state response thresholds in humans, *Journal of the Association for Research in Otolaryngology* 13 (4) (2012) 573–589. doi:10.1007/s10162-012-0321-8.
- [18] M. A. Bornovalova, R. Levy, A new software tool to optimize frequency table selection for cochlear implants, *Otology and Neurotology* 31 (8) (2010) 1242–1247. arXiv:NIHMS150003, doi:10.1037/a0018493.Understanding.
- [19] R. Y. Litovsky, M. J. Goupell, A. Kan, D. M. Landsberger, Use of Research Interfaces for Psychophysical Studies With Cochlear-Implant Users, *Trends in Hearing* 21 (2017) 233121651773646.

doi:10.1177/2331216517736464.

URL <http://journals.sagepub.com/doi/10.1177/2331216517736464>

- [20] R. R. McNeer, J. Bohórquez, Ö. Özdamar, Influence of Auditory Stimulation Rates on Evoked Potentials during General Anesthesia, *Anesthesiology* 110 (5) (2009) 1026–1035. doi:10.1097/ALN.0b013e31819dad6f.
- [21] R. Mühler, T. Rahne, K. Mentzel, J. L. Verhey, 40-Hz multiple auditory steady-state responses to narrow-band chirps in sedated and anaesthetized infants., *International journal of pediatric otorhinolaryngology* 78 (5) (2014) 762–8. doi:10.1016/j.ijporl.2014.02.005.
- [22] V. J. O. Verhaegen, J. J. S. Mulder, J. F. P. Noten, B. M. a. Luijten, C. W. R. J. Cremers, A. F. M. Snik, Intraoperative auditory steady state response measurements during Vibrant Soundbridge middle ear implantation in patients with mixed hearing loss: preliminary results., *Otology & neurotology* 31 (9) (2010) 1365–1368. doi:10.1097/MAO.0b013e3181f0c612.
- [23] A. T. Herdman, O. Lins, P. Van Roon, D. R. Stapells, M. Scherg, T. W. Picton, Intracerebral sources of human auditory steady-state responses, *Brain Topography* 15 (2) (2002) 69–86. doi:10.1023/A:1021470822922.
- [24] S. Rampp, L. Rensch, S. Simmermacher, T. Rahne, C. Strauss, J. Prell, Towards an optimal paradigm for intraoperative auditory nerve monitoring with auditory steady state responses, *Journal of Clinical Monitoring and Computing* 31 (1) (2017) 123–134. doi:10.1007/s10877-016-9837-5.

- [25] H. Hotelling, The Generalization of Student's Ratio, The Annals of Mathematical Statistics 2 (3) (1931) 360–378. doi:10.1214/aoms/1177732979.
- [26] P. Kylén, S. Arlinger, Drill-generated noise levels in ear surgery, Acta Oto-Laryngologica 82 (1-6) (1976) 402–409. doi:10.3109/00016487609120925.
- [27] P. Kylén, S. D. Arlinger, L. M. Bergholtz, Peroperative temporary threshold shift in ear surgery an electrocochleographic study, Acta Oto-Laryngologica 84 (1-6) (1977) 393–401. doi:10.3109/00016487709123982.
- [28] J. Holmquist, R. Oleander, O. Hallén, Peroperative drill-generated noise levels in ear surgery, Acta Oto-Laryngologica 87 (3-6) (1979) 458–460. doi:10.3109/00016487909126451.
- [29] M. G. Spencer, A. Reid, Drill-generated noise levels in mastoid surgery, The Journal of Laryngology & Otology 99 (10) (1985) 967–972. doi:10.1017/S0022215100098017.
- [30] A. F. Fitzgerald O'Connor, S. A. Hickey, Measurement of drill-generated noise levels during ear surgery, The Journal of Laryngology & Otology 105 (9) (1991) 732–735. doi:10.1017/S0022215100117153.
- [31] M. Hegewald, R. Heitman, M. L. Wiederhold, J. C. Cooper, G. A. Gates, High-frequency electrostimulation hearing after mastoidectomy, OtolaryngologyHead and Neck Surgery 100 (1) (1989) 49–56. doi:10.1177/019459988910000108.

- [32] A. A. Desai, R. G. Aiyer, V. K. Pandya, U. Nair, Post operative sensorineural hearing loss after middle ear surgery., *Indian journal of otolaryngology and head and neck surgery : official publication of the Association of Otolaryngologists of India* 56 (3) (2004) 240–242. doi:10.1007/BF02974364.
- [33] E. Karatas, M. C. Miman, O. Ozturan, T. Erdem, M. T. Kalcioğlu, Contralateral normal ear after mastoid surgery: Evaluation by otoacoustic emissions (mastoid drilling and hearing loss), *ORL* 69 (1) (2007) 18–24. doi:10.1159/000096712.
- [34] C. Arnoldner, B. Schwab, T. Lenarz, Clinical results after stapedotomy: A comparison between the erbium: Yttrium-aluminum-garnet laser and the conventional technique, *Otology and Neurotology* 27 (4) (2006) 458–465. doi:10.1097/00129492-200606000-00005.

List of Tables

- Table 1: Subject details: identifier; age in years; pure tone average (PTA) - average of thresholds at 0.5, 1, 2 and 3 kHz - air conduction (AC) / bone conduction (BC) in dB HL; side of implantation; and etiology.

Table 1: Subject details: identifier; age in years; pure tone average (PTA) - average of thresholds at 0.5, 1, 2 and 3 kHz - air conduction (AC) / bone conduction (BC) in dB HL; side of implantation; and etiology.

Subject	Age	PTA AC/BC	Side	Etiology
S1	58	120 / 65	Left	Advanced Otosclerosis
S2	76	110 / 59	Left	Advanced otosclerosis
S3	48	89 / 74	Left	Advanced Otosclerosis

List of Figures

- Figure 1: Overview of stimulation conditions tested for DACI artifact characterization.
- Figure 2: Recording channels used for characterization of DACI artifacts and intra- and postoperative ASSR and ABR recordings. Green: reference. Blue: channel 2. Red: channel 3. For intra- and postoperative ASSR and ABR recordings, only the inion Iz was used for channel 3.
- Figure 3: DACI artifact characterization RQ1: The same click stimulus ($200\ \mu s$ 50 dBpeFS repetition rate 102 Hz) was used for three recordings; the time of the recording is indicated on top. Electrical artifacts vary slightly with recording electrode position and over time - click stimulation - condition (R+I+A).
- Figure 4: DACI artifact characterization RQ2: the actuator may cause electrical artifacts at high stimulation levels - TB stimulation - condition (A).
- Figure 5: DACI artifact characterization RQ2: the trigger may cause electrical artifacts depending on the positioning of the leads from stimulation and recording equipment - click stimulation - condition (R+I) and (T). Trigger artifacts (T) are indicated with black arrows, while RF artifacts are indicated with red boxes. The start and end of every stimulation click has been indicated with vertical dash-dotted and dashed lines, respectively.

- Figure 6: DACI artifact characterization RQ3: RF artifacts can be modeled, based on the (theoretical) RF signal - TB stimulation - condition (R+I+A).
- Figure 7: 33 Hz ASSR intra- and postoperative. Significant responses are indicated with filled diamond symbols. Behavioral thresholds, determined postoperatively, are indicated with vertical dotted lines.
- Figure 8: 33 Hz ABR intra- and postoperative for S1, S2 and S3. Behavioral thresholds, determined postoperative, are indicated with gray bars.
- Figure 9: 80 and 95 Hz ABR intra- and postoperative for S1, S2 and S3. Behavioral thresholds, determined postoperative, are indicated with gray bars.
- Figure 10: Comparison of behavioral and electrophysiological threshold levels measured intra-operatively and post-operatively in subject S1 (left) and S2 (right). Intra- and postoperative thresholds correspond to the smallest threshold found for ABR and ASSR analysis. For the 90 Hz conditions, the minimum threshold for the 80 Hz and 95 Hz stimulation was taken.

Figure 1: Overview of stimulation conditions tested for DACI artifact characterization.

Figure 2: Recording channels used for characterization of DACI artifacts and intra- and postoperative ASSR and ABR recordings. Green: reference. Blue: channel 2. Red: channel 3. For intra- and postoperative ASSR and ABR recordings, only the inion Iz was used for channel 3.

Figure 3: DASI artifact characterization RQ1: The same click stimulus ($200 \mu s$ 50 dBpeFS repetition rate 102 Hz) was used for three recordings; the time of the recording is indicated on top. Electrical artifacts vary slightly with recording electrode position and over time - click stimulation - condition (R+I+A).

Figure 4: DACI artifact characterization RQ2: the actuator may cause electrical artifacts at high stimulation levels - TB stimulation - condition (A).

Figure 5: DASI artifact characterization RQ2: the trigger may cause electrical artifacts depending on the positioning of the leads from stimulation and recording equipment - click stimulation - condition (R+I) and (T). Trigger artifacts (T) are indicated with black arrows, while RF artifacts are indicated with red boxes. The start and end of every stimulation click has been indicated with vertical dash-dotted and dashed lines, respectively.

Figure 6: DACT artifact characterization RQ3: RF artifacts can be modeled, based on the (theoretical) RF signal - TB stimulation - condition (R+I+A).

Figure 7: 33 Hz ASSR intra- and postoperative. Significant responses are indicated with filled diamond symbols. Behavioral thresholds, determined postoperatively, are indicated with vertical dotted lines.

Figure 8: 33 Hz ABR intra- and postoperative for S1, S2 and S3. Behavioral thresholds, determined postoperative, are indicated with gray bars.

Figure 9: 80 and 95 Hz ABR intra- and postoperative for S1, S2 and S3. Behavioral thresholds, determined postoperative, are indicated with gray bars if they are within the displayed range.

Figure 10: Comparison of behavioral and electrophysiological threshold levels measured intra-operatively and post-operatively in subject S1 (left) and S2 (right). Intra- and postoperative thresholds correspond to the smallest threshold found for ABR and ASSR analysis. For the 90 Hz conditions, the minimum threshold for the 80 Hz and 95 Hz stimulation was taken.

6. List of supplementary figures

- Supplementary Figure 1: RF artifact signals at various stages of the measurement set-up.
- Supplementary Figure 2: Illustration of RF artifacts at each stage of the measurement set-up.

Figure 1: Supplementary figure: RF artifact signals at various stages of the measurement set-up.

Figure 2: Supplementary figure: Illustration of RF artifacts at each stage of the measurement set-up.