MANUSCRIPT FOR HEARING RESEARCH

Electrically-evoked auditory steady-state responses as neural correlates of loudness growth in cochlear implant users

November 29, 2017

Maaike Van Eeckhoutte, Jan Wouters, Tom Francart
KU Leuven, Department of Neurosciences, ExpORL

Herestraat 49-721, B-3000 Leuven, Belgium
maaike.vaneeckhoutte@med.kuleuven.be
jan.wouters@med.kuleuven.be
tom.francart@med.kuleuven.be

ABSTRACT

Loudness growth functions characterize how the loudness percept changes with current level between the threshold and most comfortable loudness level in cochlear implant users. Even though loudness growth functions are highly listener-dependent, currently default settings are used in clinical devices. This study investigated whether electrically-evoked auditory steady-state response amplitude growth functions correspond to behaviorally measured loudness growth functions. Seven cochlear implant listeners participated in two behavioral loudness growth tasks and an EEG recording session. The 40-Hz sinusoidally-amplitude-modulated pulse trains were presented to CI channels stimulating at a more apical and basal region of the cochlea, and were presented at different current levels encompassing the listeners' dynamic ranges. Behaviorally, loudness growth was measured using an Absolute Magnitude Estimation and a Graphical Rating Scale with loudness categories. A good correspondence was found between the response amplitude functions and the behavioral loudness growth functions. The results are encouraging for future advances in individual, more automatic, and objective fitting of cochlear implants.

KEYWORDS

- Loudness perception
- Electrically-evoked auditory steady-state responses
- Objective fitting
- Cochlear implants

HIGHLIGHTS

- Amplitude growth functions of electrically-evoked auditory steady-state responses matched with behavioral loudness growth functions
- Both basal and apical regions of the cochlea showed this match, and the best results (smallest mean square errors) were found for apical stimulation
- These findings have potential for objective cochlear implant fitting

ABBREVIATIONS

- AME: Absolute Magnitude Estimation
- ASSR: Auditory Steady-State Response
- CAEP: Cortical Auditory Evoked Potential
- CI: Cochlear Implant
- EABR: Electrically-Evoked Auditory Brain Stem Response
- EASSR: Electrically-Evoked Auditory Steady-State Response
- ECAP: Electrically-Evoked Compound Action Potential
- EEG: Electroencephalogram
- ESRT: Electrically-Evoked Stapedius Reflex Threshold
- GRS: Graphic Rating Scale
- MCL: Most Comfortable Loudness
- MSE: Mean Square Error

- T: Threshold
- UCL: Uncomfortable Loudness

1 INTRODUCTION

For most commercial cochlear implant (CI) devices, the fitting or programming for an individual listener is done by setting the current level corresponding to the threshold of hearing (T level), and the current level corresponding to the most comfortable loudness level (MCL level, depending on the brand sometimes also referred to the C, M, or MAL level with slightly different definitions), for each CI channel.

The loudness percept changes with current level can be characterized by a loudness growth function between the T and MCL level, i.e. the dynamic range. Loudness growth functions show a large variability across subjects, channels, and stimulus properties, such as the rate of stimulation and phase duration (Chatterjee et al., 2000; Fu, 2005; Hoth, 2007; Sanpetrino and Smith, 2006; Shannon, 1985; Zeng and Shannon, 1994; Busby and Au, 2017).

As the electrical dynamic range is much smaller than the acoustical dynamic range of normal hearing listeners, compression is used to map the acoustical channel output levels to electrical current levels used for stimulation. For equal loudness growth across channels, or loudness growth corresponding to normal hearing, this mapping needs to be individualized by measuring the complete loudness growth functions and dynamic ranges for each channel. However, usually the default settings are used in clinical practice and complete loudness growth functions are not measured to save measurement time. However, CI listeners are sensitive to changes in the mapping and it affects their loudness perception (Theelen-van den Hoek et al., 2016), and the best performance on speech perception is found when normal loudness growth is restored

(Fu and Shannon, 1998).

The aim of this study was to find an objective measure of loudness growth in cochlear implant participants. Such an objective method has the potential to more automatically fit cochlear implants. As behavioral measures of loudness growth are sometimes judged as difficult and complicated, an objective measure might be more reliable. An objective method also gives the possibility to test listeners who are unable to give reliable behavioral responses, such as listeners with an intellectual disability or young children.

In a previous study we have shown that the 40-Hz auditory steady-state response (ASSR) amplitude function is a good neural correlate of the loudness growth function in case of acoustical hearing, tested in normal hearing and hearing impaired listeners (Van Eeckhoutte et al., 2016). The ASSR is a frequency-specific, stationary auditory evoked potential that can be detected in the electroencephalogram (EEG), purely objectively using a statistical test, i.e., without any subjective judgements (Picton, 2011). A modulation frequency of 40 Hz was used for two reasons. First, it yields the best signal-to-noise ratios in awake adult participants. Second, when using this modulation frequency a clear dominant source is found at the primary auditory cortex, as well as some subcortical contributions (e.g., Reyes et al., 2005; Steinmann and Gutschalk, 2011; Darestani Farahani et al., 2017), and a cortical basis of loudness has been suggested (Heinz et al., 2005; Thwaites et al., 2016).

We hypothesize that the same correspondence between loudness growth and ASSR amplitude growth functions can be found for electrically-evoked auditory steady-state responses (EASSR) in cochlear implant users. To make a direct comparison between the behavioral loudness and neural amplitude growth functions, we kept the stimuli for both measurements as similar as possible.

2 MATERIAL AND METHODS

2.1 Participants

Seven native Dutch-speaking cochlear implant users (2 women, 5 men) participated in this study. They were recruited from the Ear-Nose-Throat department of the University Hospital UZ Leuven, of which the medical ethics committee approved the project. The mean age of the participants was 43.4 ± 22.3 years. Since age does not affect the 40-Hz ASSR amplitudes of adult participants (e.g., Goossens et al., 2016; Grose et al., 2009), this broad range of ages should not confound our results. All participants provided informed consent in accordance with the declaration of Helsinki. They all had a Nucleus device of Cochlear Ltd. Table 1 provides an overview of the implant type, test side, experience with the CI and etiology of the participants. The Edinburgh Handedness Inventory was completed by all participants. One participant was left-handed and one ambidextrous. Since the same results were found for all participants, we did not exclude any left-handed participants. The participants' travel expenses were reimbursed.

[Insert Table 1 near here]

2.2 Stimuli

Electric stimulation consisted of sinusoidally-amplitude-modulated biphasic cathodic-first pulse trains presented to one CI (the implanted side or randomly chosen in case of bilateral CIs). The amplitude modulation mode of the stimulus was set in Amperes, and a modulation frequency of 40 Hz was used. The pulse rate was 900 pps and the inter-phase-gap 8 μs, to be consistent with the stimulus used in the clinical processors of the participants. A pulse width of 60 μs was chosen in combination with bipolar stimulation (BP + 2). In this way we could use linear interpolation over the duration of the CI artifact, as it is the easiest and most efficient method of removing the CI artifacts resulting from the electrical stimulation that contaminate the EEG (Hofmann and Wouters, 2012; Deprez et al., 2017). A change in loudness growth can be obtained by changing either the pulse duration or the pulse amplitude. In this study, the pulse duration was held constant, and only the pulse amplitudes were modified. CI channels 15 (stimulation to 15-12) and 6 (stimulation to 6-3) were stimulated in blocks, in order to stimulate at a more apical and basal region of the cochlea. The stimuli were presented at different current levels encompassing the participants' dynamic ranges. The stimuli were presented for 1 s during the behavioral tasks, and for 600 epochs of 1.024 s (614.4 s) for EEG recordings. The modulation frequency was rounded to 40.0391 Hz in order to have an integer number of periods and pulses for each epoch. The stimuli were created in Matlab R2013a (The MathWorks, Inc., Natick, MA) and RBA, the software platform for the Recording and analysis of Brain responses to Auditory stimulation (Hofmann and Wouters, 2012), at a stimulation sampling rate of 96 kHz. The stimuli were validated with an oscilloscope and an implant-in-a-box.

2.3 Procedures and apparatus

The participants were tested in two sessions. The more apical channel (channel 15) was stimulated in the first session and the more basal channel (channel 6) in the second session. The time between two test sessions was not longer than 28 days and usually within two weeks. Behavioral tests took place in a normal room (outside the audio booth), while EEG recordings were made in the electromagnetically shielded sound booth.

A research processor (L34) and programming device (POD), controlled by the Nucleus Implant Communicator (NIC) interface was used. All the requisites were provided by Cochlear Ltd.

Dynamic range determination For the determination of the dynamic range, the T level was defined as the level at which the participant perceived a just audible, very soft sound and the MCL level was defined as the level at which the participant perceived a loud to very loud sound that was still tolerable.

In a first step we measured the T and MCL levels for the unmodulated pulse trains during an adjustment procedure. During this procedure, the participants had to rate the loudness of the stimuli using a graphical rating scale (GRS) with categories ("Inaudible", "Very soft", "Soft", "OK/comfortable", "Loud", "Very loud", "Unbearable"), by choosing any position on the scale, with the loudness categories serving only as guidelines. The start level was set at a safe level below the T level of the participant's clinical map in monopolar mode. The experimenter increased or decreased the current levels according to the feedback of the participants, to find the unmodulated T and MCL level.

In a next step, the levels were adjusted to find the MCL level for the modulated pulse train, modulating between the unmodulated T level and a changing maximum level. The difference between the MCL level of the modulated pulse train and the T level of the unmodulated pulse train was set as the fixed amplitude modulation depth in further steps. The amplitude modulation depth was chosen in such a way to obtain an equal perceptual 100 % amplitude modulation depth across subjects.

Subsequently, the T level of the modulated pulse train was measured using a more precise adaptive procedure implemented in the software platform APEX3 (Francart et al., 2008). The adaptive procedure consisted of a three-alternative forced-choice procedure without feedback with a two-down, one-up rule, converging to 71% correct, and a step size of 10 current levels that was reduced to 5 current levels after the first reversal. The participants had to choose one out of three intervals on a computer screen that were lighted up consecutively with only one interval containing the stimulus. The task ended after 6 reversals, and the T level was calculated as the mean level of the last 6 trials. This level was used for the final estimation of the dynamic range, i.e. the difference between the MCL level of the modulated pulse train and the T level of the modulated pulse train.

Behavioral measures of loudness growth Two loudness growth tasks were administered (see Van Eeckhoutte et al. (2016) for details). In these tasks, the stimuli were presented at different current levels depending on the participant's dynamic range for the tested channel. The dynamic range was divided in equally spaced steps leading to e.g., 15-20 different current levels. To reduce context effects caused by the tendency of participant to judge the loudness of a stimulus relatively to the previous stimulus (Brand and Hohmann, 2001), the stimuli were presented in a pseudorandom order, such that the maximum difference in current levels between two successive stimuli never exceeded more than half of the participant's dynamic range. The first stimulus was presented at a current level halfway the dynamic range. For both loudness growth tasks, each current level was presented 4 times.

In the first loudness growth task, the *Absolute Magnitude Estimation (AME)*, the participants had to rate the loudness of the stimuli by typing numbers (Hellman and Meiselman, 1990; Marks and Florentine, 2011). In the second loudness growth task, the participants had to choose a position on a *Graphic Rating Scale (GRS)* with loudness categories that corresponded to the loudness of the stimuli (Allen et al., 1990; Brand and Hohmann, 2001; Svensson, 2000). In both tasks, the participants were free to choose any number or any position on the scale, i.e., also decimals or a position between two loudness categories. The loudness growth tasks were implemented in APEX3.

EEG recordings for EASSR growth functions For the EEG recordings, up to 7 current levels for each participant were chosen from the current levels used in the behavioral tasks. Current levels near the threshold that would lead to non-detectable EASSRs and current levels that would be too loud to listen to for several minutes were not chosen for stimulation. Feedback of the loudness of the stimuli was also asked while presenting the highest current level chosen for stimulation during EEG recordings.

EEG was recorded with the ActiveTwo System Software (Biosemi) using a recording sampling rate of 8192 Hz. A head cap consisting of 64+2 Ag/AgCl active scalp electrodes was mounted on the head of the participants, in accordance to the standard 10-20 electrode position system. The recording electrodes positioned on top of the CI-coil were not used. The participants could sit in a comfortable chair or lie down in a bed, and were asked to relax. A self-chosen, subtitled, and silent video was presented to the participants to prevent them from falling asleep and to keep the attentional state constant across participants and measurement conditions. The stimuli were consecutively presented with increasing current level. The participants were also given breaks depending on their needs.

The data were analyzed offline in Matlab R2013a (The MathWorks, Inc., Natick, MA). The raw data were first converted into epochs of 1.024 s each. Linear interpolation was used to eliminate CI stimulation artifacts, from 100 μs before the onset of the stimulation pulse until 1000 μs after the stimulation pulse. This means that the maximum possible interpolation duration or the interpulse interval, which is the inverse of the pulse rate, equals 1.1 ms for stimulation at 900 pps, and that one sample per pulse period, the pre-stimulus sample, is retained. (Hofmann and Wouters, 2012; Deprez et al., 2017). Thereafter the data was filtered using a second-order butterworth high-pass filter with a cut-off frequency of 2 Hz, and the 5% epochs with the highest peak-to-peak amplitude were rejected to remove other remaining recording artifacts.

The recording channels were referenced to recording electrode Cz. A Fast Fourier Transformation (FFT) was used to convert the epochs to the frequency domain. The Hotelling t^2-test determined the significance level of the response at the frequency bin corresponding to the modulation frequency. The significance level was set at $\alpha = 0.05$. Only significant EASSR amplitudes will be shown, which can be interpreted as the response at the modulation frequency being significantly different from random EEG activity.

The electrode selection we will present was based on Van Eeckhoutte et al. (2016). Of this electrode selection, only the recording electrodes on the contralateral side of the CI were used in order to avoid CI stimulation artifacts. This resulted in the following electrode selections: 'P1, P3, P5, P7, P9, PO3, PO7, O1' in case of a CI in the right ear or 'P2, P4, P6, P8, P10, PO4, PO8, O2' in case of a CI in the left ear.

2.4 Data transformation and analysis

Similar to Van Eeckhoutte et al. (2016), the data was transformed and normalized in order to directly compare the different measures. First, for the behavioral experiments, the mean response across trials with the same current level was calculated. Usually data was collected for more levels (near threshold or too loud to listen to for 5 minutes) for the behavioral measures AME and GRS than for recording EASSRs. For the transformation, the same range of current levels was used, i.e. the range between the lowest and highest level used for EASSR recording. Then, for each measure (GRS, AME, or EASSR) the logarithm of the responses was taken, and the mean logarithm across current levels was subtracted from the logarithm of each response to obtain zero-mean curves. For easier interpretation, we transformed the values back to GRS values by elevating 10 to the power of the sum of the transformed responses and the mean of the transformed GRS responses (see Van Eeckhoutte et al. (2016) for equations).

After transformation, mean square errors (MSEs) were calculated between pairs of measures (i.e., MSEs between AME and GRS curves, between AME and EASSR curves, and GRS and EASSR curves). To statistically test for differences in MSEs, a linear mixed-effects model was used that included the fixed factors "Channel" (either 6 or 15) and "MSE comparison" (AME-GRS, AME-EASSR, or GRS-EASSR), set as repeated measures, and the random factor "Participant". The contrast "Beh-EASSR" tested the behavioral MSE comparison (AME-GRS) against the MSE comparisons that also contained EASSR responses (AME-EASSR and GRS-EASSR), and the contrast "Diff-EASSR" tested the difference between both MSE comparisons that included EASSR responses (AME-EASSR and GRS-EASSR). To ensure normally distributed residuals of the model, first outliers were removed for each MSE comparison based on the median absolute deviation or MAD-median rule (Wilcox et al., 2013). In total 9 out of 42 values (7 participants x 2 CI channels x 3 MSE comparisons) were removed for statistical testing. A significance level of $\alpha = 0.05$ was chosen. The analyses were performed using R (R Core Team, version 3.3.1, 2016).

3 Results

Figure 1 shows the result of a typical CI listener. Like with acoustical stimulation, for both CI channels, the EASSR amplitudes increased with increasing current level, while the EEG background noise remained the same across current levels, with an average noise amplitude of $0.029 \pm 0.003 \mu V$ across participants. Furthermore, the EASSR amplitude growth functions had a similar shape to both behavioral loudness growth functions, for channel 15 as well as channel 6.

[Insert Figure 1 near here]

The individual transformed responses are shown in Figure 2. As can be seen in the figure, in most cases the curves of the three measures (AME, GRS and EASSR) were close to each other. Also note that both the T and MCL levels were different among all seven participants, which is different from acoustical hearing where the maximum level of the dynamic range is similar across participants.

[Insert Figure 2 near here]

The median values of the MSE comparisons AME-GRS, AME-EASSR, and GRS-EASSR were 0.003, 0.006, and 0.003 for channel 15, and 0.008, 0.009, and 0.005 for channel 6, respectively, and are shown in Figure 3. Thus, the median values were always below 0.010. The mean values were also around 0.010, except for two MSE comparisons that contained the same outlier of one participant who had MSE values of 0.38 and 0.50 for the MSE comparisons AME-GRS and AME-EASSR for channel 15. The MSE values were caused by the same AME result, i.e., an AME response that was not expected given the other data of this participant.

[Insert Figure 3 near here]

The median MSE values were slightly higher for channel 6 than for channel 15. After outlier removal, the linear mixed-effects model indicated a significant effect of the factor "Channel" (see Table 2). Both contrasts were not significant. For the contrast "Beh-EASSR" this means that the MSE values of the behavioral measures were not significantly different from the MSE values that contained EASSR values (i.e., AME-GRS vs. AME-EASSR and GRS-EASSR). For the contrast "Diff-EASSR" this means that the MSE values within MSE comparisons that contained EASSR values were not significantly different from each other (i.e., AME-EASSR vs. GRS-EASSR). In conclusion, the loudness estimations based on behavioral responses were not significantly different from the loudness estimations based on EASSR amplitudes.

[Insert Table 2 near here]

4 DISCUSSION

4.1 Main findings

Behavioral loudness growth and EASSR amplitude growth functions were measured in seven CI participants. Behavioral loudness growth functions had the same shape as the EASSR amplitude growth functions. After transformation, median MSE values between two measures were always below 0.010. Moreover, the MSE values between two behavioral loudness growth tasks were not significantly different from the MSE values between a behavioral loudness growth task and the EASSR amplitudes. Consequently, a good correspondence between loudness estimates based on behavioral responses and loudness estimates based on EASSR amplitudes was found.

We used stimuli that were similar to the stimuli used in current clinical CI processors, but we used bipolar stimulation instead of monopolar stimulation to reduce the CI stimulation artifact. We hypothesize to find similar results using monopolar stimulation in future studies, when more advanced methods to remove the CI stimulation artifact are validated (Deprez et al., 2017).

For the hearing impaired participants in our previous study with acoustical stimulation (Van Eeckhoutte et al., 2016), carrier frequencies of 500 Hz and 2000 Hz were used, which stimulated at a more apical and a basal part of the cochlea. The best results were found for the 500 Hz carrier frequency. As channel 15 also stimulates at a more apical part of the cochlea compared to channel 6, the better results (lower median MSE values) for channel 15 are likely a result of the place of stimulation in the cochlea. Longer durations of deafness or hearing impairment are generally found at more basal places of the cochlea. Note that we always stimulated at 900 pps in this study, but different places of the cochlea were stimulated by stimulating channels 15 and 6.

The MSE values found in this study were very similar to the ones found in the acoustical study. Median MSE values were between 0.005 and 0.016 for MSE comparisons including ASSRs in the acoustical study, and median MSE values were between 0.003 and 0.009 for the same comparisons in this study. To make a direct comparison to both studies, we conducted a Wilcoxon rank-sum test that yielded no significant differences between the MSE values of the hearing impaired participants of the acoustical study and the MSE values of the CI participants (W = 1261, p = 0.997).

As MSE values might be hard to interpret, we converted the values to a typical root mean square error in loudness scale units, as this may be more intuitive to interpret. Converting the MSE values 0.003 and 0.009 to a typical root mean square error on a GRS loudness scale (between 0 and 1) gives errors of 0.06 and 0.1. Converting the values to a loudness scale with loudness categories between 0 and 50, from "Inaudible" to "Too Loud" (Brand and Hohmann, 2001), gives errors of 2.7 and 4.7 categorical units, respectively. As one category on the latter scale contains 5 categorical units, this means that the median measurement errors found in this EASSR study were within one loudness category.

4.2 Objective measures of loudness growth in CIs

We found a good correspondence between the EASSR amplitude growth function and the loudness growth function measured behaviorally. Other measures have been proposed as well for cochlear implant users, with less positive results.

Although with increasing stimulus level, monotonic amplitude growth functions were described for the electrically-evoked auditory brainstem response (EABR) (e.g., Abbas and Brown, 1991), Steel et al. (2014) reported no relation of wave V amplitude growth with loudness growth in CI adolescents.

Another measure that has been used is the electrically-evoked compound action potential (ECAP), which is a measure of the synchronous, summed neural activity of auditory nerve fibers. The ECAPs can be measured easily and fast using the intracochlear electrodes of the cochlear implant. Steel et al. (2014) reported a positive correlation between the ECAP amplitude growth and loudness growth in CI users, but only for the upper part of the dynamic range (with $r = 0.75$), and not for the lower part of the dynamic range (with $r = 0.11$).

More recently, research has focused on cortical auditory evoked potentials (CAEPs). The CAEP amplitudes increase with increasing stimulus level (Firszt et al., 2002; Visram et al., 2015). Hoppe et al. (2001) reported correlations of $r = 0.82$, $r = 0.69$, and $r = 0.83$ between CAEP amplitudes and behavioral loudness judgments for basal, medial, and apical channels. However, while many studies (also described above) showed group mean data, it is also necessary to investigate the correspondence between behavioral loudness ratings and objective measures for each individual, as done in the current study.

While we prefer the analysis presented for analyzing non-linear relations, like the relation between level and loudness, we calculated Pearson correlation coefficients on our data in order to facilitate comparison with literature. On individual level, linear correlations were on average for channel 15 $r = 0.88 \pm 0.17$ and $r = 0.91 \pm 0.09$, and for channel 6 $r = 0.86 \pm 0.12$ and $r = 0.91 \pm 0.08$ for GRS and AME, respectively. On group level, using transformed responses, for channel 15 we found $r = 0.91$ and $r = 0.81$, and for channel 6 $r = 0.86$ and $r = 0.87$, for GRS and AME scales, respectively. Overall, the correlation coefficients found in this study are larger than the correlation coefficient found for the upper dynamic range using ECAPs (Steel et al., 2014), and are higher or at least in the same range of the correlation coefficients for CAEP amplitudes reported by Hoppe et al. (2001).

The lack of correspondence using EABRs and ECAPs might be explained by the cortical basis of loudness that has been suggested (Heinz et al., 2005; Thwaites et al., 2016). As for CAEPs, cortical sources have been described for the 40-Hz ASSR, as well as subcortical contributions (e.g., Reyes et al., 2005; Steinmann and Gutschalk, 2011).

The lack of correspondence is possibly also partly due to the difference in stimulation, for ECAP measurements needed to cancel out the stimulus artifact. It has been shown that the correlation between ECAP measures and loudness varies with stimulation rate (Zimmerling and Hochmair, 2002). However, the correlation between EABR and behavioral thresholds does not improve when using the same stimulus duration and rate for both measures (Davids et al., 2008a,b). In our study, a good correspondence was found using the same stimuli for behavioral and EEG measures.

4.3 Clinical applications for CI fitting

For the objective fitting of cochlear implants, an objective estimation of the MCL and T levels are needed. Below we discuss other neural correlates that have been described for objective CI fitting, with mixed results.

For the estimation of the MCL level, positive results have been found with the electrically-evoked stapedius reflex threshold (ESRT). This brainstem reflex mechanism is a contraction of the stapedius muscle and is measured using visual observation or tympanometry (Pau et al., 2011). Even though a large intersubject variability was described, the ESRTs have been shown to correlate well postoperatively with behavioral comfort levels (Hodges et al., 1997; Caner et al., 2007; Gordon et al., 2004) or MCL levels (Allum et al., 2002; Stephan and Welzl-Müller, 2000), and rarely exceed the uncomfortable loudness (UCL) levels (Battmer et al., 1990; Spivak and Chute, 1994; Stephan et al., 1990). This makes the ESRT a safe measure for clinical practice. Moreover, the ESRT tends to be more stable over time compared to the behaviorally measured MCL level (Spivak and Chute, 1994). However, in about 20 to 50% of the patients the reflex cannot be measured, mainly due to middle ear pathologies or meningitis

(Battmer et al., 1990; Bresnihan et al., 2001; Hodges et al., 1997; Spivak and Chute, 1994; van den Borne et al., 1996).

The EABR has also been intensively investigated for correspondence with either T or MCL levels. Some authors have claimed that the EABR threshold correlates with the behavioral T level (Abbas and Brown, 1991; Mason et al., 1993; Truy et al., 1998), while others described better correspondence to the behavioral MCL level (Shallop et al., 1991), or UCL level (Gallégo et al., 1999). Most studies report a large variability between patients, with the only confidence that the EABR threshold corresponds to a level that is audible for the patient, but can be anywhere between the behavioral T level and the UCL level (Brown et al., 1994).

Similar results have been described for the ECAPs. Considerable inter- and intra-subject variability and only weak to moderate correlations have been found for ECAP thresholds and T or MCL levels (Brown et al., 2000; Cafarelli Dees et al., 2005; Cohen, 2009; Eisen and Franck, 2004; Franck and Norton, 2001; Hughes et al., 2000; Smoorenburg et al., 2002; King et al., 2006; Lai and Dillier, 2007; Potts et al., 2007; Thai-Van et al., 2004; Van Den Abbeele et al., 2012), such that it should not be used as the sole method for objective CI fitting (McKay et al., 2013; Abbas and Brown, 2015).

For CAEPs, a tendency to saturate at higher stimulus levels was reported (Abbas and Brown, 2015), as well as a high correlation ($r = 0.93$) between behavioral thresholds and CAEP thresholds, with the latter obtained using extrapolation of global field power amplitude growth functions (Visram et al., 2015).

Furthermore, as thoroughly shown for acoustical thresholds (e.g., Luts et al., 2006; Picton, 2011), for cochlear implant users Hofmann and Wouters (2010, 2012) demonstrated that 40-Hz EASSR thresholds can be used to reliably predict behavioral T levels using bipolar stimulation. More advanced methods to remove the CI stimulation artifacts for monopolar stimulation are promising (Deprez et al., 2017).

In summary, for cochlear implant users it seems that the 40-Hz EASSRs and CAEP thresholds have the greatest potential to be used to objectively estimate behavioral T levels, and if it is possible to measure, the ESRTs to estimate the behavioral MCL levels. As demonstrated in this study, the 40-Hz EASSR amplitudes correspond to the loudness growth within the dynamic range. Given the current relatively long measurement times that are still needed for CAEP and EASSR measurements, in many cases a combination of behavioral and objective measures will still be desirable to ensure reliable and relatively fast clinical measurements. However, this study demonstrates the feasibility of using the 40-Hz EASSR for future objective, more automatic, and individualized CI fitting.

5 Conclusions

EASSR amplitude growth functions behave in the same way as loudness growth functions, as shown in this study for seven CI listeners who were involved in two behavioral loudness growth tasks and one EEG recording session. After transformation to directly compare the different measures, a good match was always found between two measures, with median MSE values below 0.010. As this was true for stimulation at apical (channel 15) as well as basal (channel 6) regions in the cochlea, EASSR have potential for the objective fitting of cochlear implants in clinical practice.

Acknowledgments

We thank our volunteers for participation. Maaike Van Eeckhoutte was supported by a PhD grant for Strategic Basic Research by the Agency for Innovation by Science and Technology in Flanders (IWT 131106, now FWO-SB). Cochlear Ltd provided the necessary equipment. The authors report no conflict of interest.

LIST OF TABLES

LIST OF FIGURES

REFERENCES

Abbas, P.J., Brown, C.J., 1991. Electrically evoked auditory brainstem response: growth of response with current level. Hearing Research 51, 123–137.

Abbas, P.J., Brown, C.J., 2015. Assessment of responses to cochlear implant stimulation at different levels of the auditory pathway. Hearing Research 322, 67–76.

Allen, J.B., Hall, J.L., Jeng, P.S., 1990. Loudness growth in 1/2-octave bands (LGOB): a procedure for the assessment of loudness. The Journal of the Acoustical Society of America 88, 745–753.

Allum, J.H.J., Greisiger, R., Probst, R., 2002. Relationship of intraoperative electrically evoked stapedius reflex thresholds to maximum comfortable loudness levels of children with cochlear implants. International Journal of Audiology 41, 93–99.

Battmer, R.D., Laszig, R., Lehnhardt, E., 1990. Electrically elicited stapedius reflex in cochlear implant patients. Ear and Hearing 11, 370–374.

van den Borne, B., Snik, A.F.M., Mens, L.H.M., Brokx, J.P.L., van den Broek, P., 1996. Stapedius reflex measurements during surgery for cochlear implantation in children. The American Journal of Otology 17, 554–558.

Brand, T., Hohmann, V., 2001. Effect of hearing loss, centre frequency, and bandwidth on the shape of loudness functions in categorical loudness scaling. Audiology 40, 92–103.

Bresnihan, M., Norman, G., Scott, F., Viani, L., 2001. Measurement of comfort levels by means of electrical stapedial reflex in children. Archives of Otolaryngology: Head & Neck Surgery 127, 963–966.

Brown, C.J., Abbas, P.J., Fryauf-Bertschy, H., Kelsay, D., Gantz, B.J., 1994. Intraoperative and postoperative electrically evoked auditory brain stem responses in nucleus cochlear implant users: implications for the fitting process. Ear and Hearing 15, 168–176.

Brown, C.J., Hughes, M.L., Luk, B., Abbas, P.J., Wolaver, A., Gervais, J., 2000. The relationship between EAP and EABR thresholds and levels used to program the nucleus 24 speech processor: data from adults. Ear and Hearing 21, 151–163.

Busby, P.A., Au, A., 2017. Categorical loudness scaling in cochlear implant recipients. International Journal of Audiology , 1–8.

Cafarelli Dees, D., Dillier, N., Lai, W..K., Von Wallenberg, E., van Dijk, B., Akdas, F., Aksit, M., Batman, C., Beynon, A., Burdo, S., Chanal, J..M., Collet, L., Conway, M., Coudert, C., Craddock, L., Cullington, H., Deggouj, N., Fraysse, B., Grabel, S., Kiefer, J., Kiss, J..G., Lenarz, T., Mair, A., Maune, S., Müller-Deile, J., Piron, J..P., Razza, S., Tasche, C., Thai-Van, H., Toth, F., Truy, E., Uziel, A., Smoorenburg, G..F., 2005. Normative findings of electrically evoked compound action potential measurements using the neural response telemetry of the nucleus CI24M cochlear implant system. Audiology and Neurotology 10, 105–116.

Caner, G., Olgun, L., Gültekin, G., Balaban, M., 2007. Optimizing fitting in children using objective measures such as neural response imaging and electrically evoked stapedius reflex threshold. Otology & Neurotology 28, 637–640.

Chatterjee, M., Fu, Q.J., Shannon, R.V., 2000. Effects of phase duration and electrode separation on loudness growth in cochlear implant listeners. The Journal of the Acoustical Society of America 107, 1637–44.

Cohen, L.T., 2009. Practical model description of peripheral neural excitation in cochlear implant recipients: 1. Growth of loudness and ECAP amplitude with current. Hearing Research 247, 87–99.

Darestani Farahani, E., Goossens, T., Wouters, J., van Wieringen, A., 2017. Spatiotemporal reconstruction of auditory steady-state responses to acoustic amplitude modulations: potential sources beyond the auditory pathway. NeuroImage 148, 240–253.

Davids, T., Valero, J., Papsin, B.C., Harrison, R.V., Gordon, K.A., 2008a. Effects of stimulus manipulation on electrophysiological responses in pediatric cochlear implant users. Part I: Duration effects. Hearing Research 244, 7–14.

Davids, T., Valero, J., Papsin, B.C., Harrison, R.V., Gordon, K.A., 2008b. Effects of stimulus manipulation on electrophysiological responses of pediatric cochlear implant users. Part II: rate effects. Hearing Research 244, 15–24.

Deprez, H., Gransier, R., Hofmann, M., van Wieringen, A., Wouters, J., Moonen, M., 2017. Characterization of cochlear implant artifacts in electrically evoked auditory steady-state responses. Biomedical Signal Processing and Control 31, 127–138.

Eisen, M.D., Franck, K.H., 2004. Electrically evoked compound action potential amplitude growth functions and HiResolution programming levels in pediatric CI implant subjects. Ear and Hearing 25, 528–538.

Firszt, J.B., Chambers, R.D., Kraus, N., Reeder, R.M., 2002. Neurophysiology of cochlear implant users I: Effects of stimulus current level and electrode site on the electrical ABR , MLR , and N1-P2 Response. Ear and Hearing 23, 502–515.

Francart, T., van Wieringen, A., Wouters, J., 2008. APEX 3: a multi-purpose test platform for auditory psychophysical experiments. Journal of Neuroscience Methods 172, 283–293.

Franck, K.H., Norton, S.J., 2001. Estimation of psychophysical levels using the electrically evoked compound action potential measured with the neural response telemetry capabilities of Cochlear Corporation's CI24M device. Ear and Hearing 22, 289–299.

Fu, Q.J., 2005. Loudness growth in cochlear implants: Effect of stimulation rate and electrode configuration. Hearing Research 202, 55–62.

Fu, Q..J., Shannon, R.V., 1998. Effects of amplitude nonlinearity on phoneme recognition by cochlear implant users and normal-hearing listeners. The Journal of the Acoustical Society of America 104, 2570–2577.

Gallégo, S., Garnier, S., Micheyl, C., Truy, E., Morgon, A., Collet, L., 1999. Loudness growth functions and EABR characteristics in Digisonic cochlear implantees. Acta oto-laryngologica 119, 234–8.

Goossens, T., Vercammen, C., Wouters, J., van Wieringen, A., 2016. Aging affects neural synchronization to speech-related acoustic modulations. frontiers in Aging Neuroscience Accepted, 1–23.

Gordon, K.A., Papsin, B.C., Harrison, R.V., 2004. Toward a battery of behavioral and objective measures to achieve optimal cochlear implant stimulation levels in children. Ear and Hearing 25, 447–463.

Grose, J.H., Mamo, S.K., Hall, J.W., 2009. Age effects in temporal envelope processing: speech unmasking and auditory steady state responses. Ear and Hearing 30, 568–575.

Heinz, M.G., Issa, J.B., Young, E.D., 2005. Auditory-nerve rate responses are inconsistent with common hypotheses for the neural correlates of loudness recruitment. Journal of the Association for Research in Otolaryngology 6, 91–105.

Hellman, R.P., Meiselman, C.H., 1990. Loudness relations for individuals and groups in normal and impaired hearing. The Journal of the Acoustical Society of America 88, 2596–2606.

Hodges, A.V., Balkany, T.J., Ruth, R.A., Lambert, P.R., Dolan-Ash, S., Schloffman, J.J., 1997. Electrical middle ear muscle reflex: use in cochlear implant programming. Otolaryngology: Head and Neck Surgery 117, 255–261.

Hofmann, M., Wouters, J., 2010. Electrically evoked auditory steady state responses in cochlear implant users. Journal of the Association for Research in Otolaryngology 11, 267–82.

Hofmann, M., Wouters, J., 2012. Improved electrically evoked auditory steady-state response thresholds in humans. Journal of the Association for Research in Otolaryngology 13, 573–589.

Hoppe, U., Rosanowski, F., Iro, H., Eysholdt, U., 2001. Loudness perception and late auditory evoked potentials in adult cochlear implant users. Scandinavian Audiology 30, 119–25.

Hoth, S., 2007. Indication for the need of flexible and frequency specific mapping functions in cochlear implant speech processors. European Archives of Oto-rhino-laryngology 264, 129–38.

Hughes, M.L., Brown, C.J., Abbas, P.J., Wolaver, A.A., Gervais, J.P., 2000. Comparison of EAP thresholds with MAP levels in the nucleus 24 cochlear implant: data from children. Ear and Hearing 21, 164–174.

King, J.E., Polak, M., Hodges, A.V., Payne, S., Telischi, F.F., 2006. Use of neural response telemetry measures of objectively set the comfort levels in the nucleus 24 cochlear implant. Journal of the American Academy of Audiology 17, 413–431.

Lai, W.K., Dillier, N., 2007. Comparing neural response telemetry amplitude growth functions with loudness growth functions: preliminary results. Ear and Hearing 28, 42S–45S.

Luts, H., Desloovere, C., Wouters, J., 2006. Clinical application of dichotic multiple-stimulus auditory steady-state responses in high-risk newborns and young children. Audiology and Neurotology 11, 24–37.

Marks, L.E., Florentine, M., 2011. Measurement of loudness, part I: methods, problems, and pitfalls, in: Florentine, M., Popper, A.N., Fay, R.R. (Eds.), Loudness. Springer, New York, pp. 17–56.

Mason, S.M., Sheppard, S., Garnham, C.W., Lutman, M.E., O'Donoghue, G.M., Gibbin, K.P., 1993. Application of intraoperative recordings of electrically evoked ABRs in a paediatric cochlear implant programme. Advances in oto-rhino-laryngology 48, 136–141.

McKay, C.M., Chandan, K., Akhoun, I., Siciliano, C., Kluk, K., 2013. Can ECAP measures be used for totally objective programming of cochlear implants? Journal of the Association for Research in Otolaryngology 14, 879–890.

Pau, H.W., Ehrt, K., Just, T., Sievert, U., Dahl, R., 2011. How reliable is visual assessment of the electrically elicited stapedius reflex threshold during cochlear implant surgery, compared with tympanometry? The Journal of Laryngology and Otology 125, 271–273.

Picton, T.W., 2011. Auditory steady-state and following responses: dancing to the rhythms, in: Human auditory evoked potentials.. Plural Publishing Inc., pp. 285–333.

Potts, L.G., Skinner, M.W., Gotter, B.D., Strube, M.J., Brenner, C.A., 2007. Relation between neural response telemetry thresholds, T- and C-levels, and loudness judgments in 12 adult nucleus 24 cochlear implant recipients. Ear and Hearing 28, 495–511.

Reyes, S.A., Lockwood, A.H., Salvi, R.J., Coad, M.L., Wack, D.S., Burkard, R.F., 2005. Mapping the 40-Hz auditory steady-state response using current density reconstructions. Hearing Research 204, 1–15.

Sanpetrino, N.M., Smith, R.L., 2006. The growth of loudness functions measured in cochlear implant listeners using absolute magnitude estimation and compared using Akaike's information criterion, in: Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings, pp. 1642–1644.

Shallop, J.K., Goin, D.W., Van Dyke, L., Mischke, R.E., 1991. Prediction of behavioral threshold and comfort values for nucleus 22-channel implant patients from electrical auditory brain stem response test results. The annals of otology, rhinology, and laryngology 100, 896–898.

Shannon, R.V., 1985. Threshold and loudness functions for pulsatile stimulation of cochlear implants. Hearing Research 18, 135–143.

Smoorenburg, G.F., Willeboer, C., Van Dijk, J.E., 2002. Speech perception in nucleus CI24M cochlear implant users with processor settings based on electrically evoked compound action potential thresholds. Audiology and Neuro-Otology 7, 335–347.

Spivak, L.G., Chute, P.M., 1994. The relationship between electrical acoustic reflex thresholds and behavioral comfort levels in children and adult cochlear implant patients. Ear and Hearing 15, 184–192.

Steel, M.M., Abbasalipour, P., Salloum, C.A.M., Hasek, D., Papsin, B.C., Gordon, K.A., 2014. Unilateral Cochlear Implant Use Promotes Normal-Like Loudness Perception in Adolescents With Childhood Deafness. Ear and Hearing 35, 1–11.

Steinmann, I., Gutschalk, A., 2011. Potential fMRI correlates of 40-Hz phase locking in primary auditory cortex, thalamus and midbrain. NeuroImage 54, 495–504.

Stephan, K., Welzl-Müller, K., 2000. Post-operative stapedius reflex tests with simultaneous loudness scaling in patients supplied with cochlear implants. Audiology 39, 13–18.

Stephan, K., Welzl-Müller, K., Stiglbrunner, H., 1990. Stapedius reflex growth function in cochlear implant patients. Audiology 29, 46–54.

Svensson, E., 2000. Comparison of the quality of assessments using continuous and discrete ordinal rating scales. Biometrical Journal 42, 417–434.

Thai-Van, H., Truy, E., Charasse, B., Boutitie, F., Chanal, J..M., Cochard, N., Piron, J..P., Ribas, S., Deguine, O., Fraysse, B., Mondain, M., Uziel, A., Collet, L., 2004. Modeling the relationship between psychophysical perception and electrically evoked compound action potential threshold in young cochlear implant recipients: Clinical implications for implant fitting. Clinical Neurophysiology 115, 2811–2824.

Theelen-van den Hoek, F.L., Boymans, M., van Dijk, B., Dreschler, A., 2016. Adjustments of the amplitude mapping function: Sensitivity of cochlear implant users and effects on subjective preference and speech recognition. International Journal of Audiology 55, 674–687.

Thwaites, A., Glasberg, B.R., Nimmo-Smith, I., Marslen-Wilson, W.D., Moore, Brian.C.J., 2016. Representation of Instantaneous and Short-Term Loudness in the Human Cortex. Frontiers in Neuroscience 10, 1–11.

Truy, E., Gallego, S., Chanal, J.M., Collet, L., Morgon, A., 1998. Correlation between electrical auditory brainstem response and perceptual thresholds in digisonic cochlear implant users. Laryngoscope 108, 554–559.

Van Den Abbeele, T., Noël-Petroff, N., Akin, I., Caner, G., Olgun, L., Guiraud, J., Truy, E., Attias, J., Raveh, E., Belgin, E., Sennaroglu, G., Basta, D., Ernst, A., Martini, A., Rosignoli, M., Levi, H., Elidan, J., Benghalem, A., Amstutz-Montadert, I., Lerosey, Y., De Vel, E., Dhooge, I., Hildesheimer, M., Kronenberg, J., Arnold, L., 2012. Multicentre investigation on electrically evoked compound action potential and stapedius reflex: how do these objective measures relate to implant programming parameters? Cochlear Implants International 13, 26–34.

Van Eeckhoutte, M., Wouters, J., Francart, T., 2016. Auditory steady-state responses as neural correlates of loudness growth. Hearing Research 342, 58–68.

Visram, A.S., Innes-brown, H., El-deredy, W., Mckay, C.M., 2015. Cortical auditory evoked potentials as an objective measure of behavioral thresholds in cochlear implant users. Hearing Research 327, 35–42.

Wilcox, R.R., Granger, D.A., Clark, F., 2013. Modern robust statistical methods: basics with illustrations using psychobiological data. Universal Journal of Psychology 1, 21–31.

Zeng, F..G., Shannon, R.V., 1994. Loudness-coding mechanisms inferred from electric stimulation of the human auditory system. Science 264, 564–566.

Zimmerling, M.J., Hochmair, E.S., 2002. EAP recordings in ineraid patients–correlations with psychophysical measures and possible implications for patient fitting. Ear and Hearing 23, 81–91.

Table 1: Overview of the participants' CI details.

Participant	Implant type	Test side	CI experience (years)	Etiology
S1	CI24R	Left	11	Progressive
S2	CI24RE	Right	8	Unknown
S3	CI24RE	Right	4	Unknown
S4	CI24M	Left	11	Unknown
S5	CI24M	Left	11	Progressive/Mumps
S6	CI24RE	Right	3	Progressive/Hereditary
S7	CI24M	Left	14	Unknown

Table 2: The linear mixed-effects model that included the contrasts “Beh-EASSR", which compared MSE values that contain only behavioral loudness growth (AME-GRS) and that contain EASSR data (AME-EASSR and GRS-EASSR), and the contrast “Diff-EASSR", which compared MSE values for conditions that contain EASSR data (AME-EASSR and GRS-EASSR). The factor "Channel" means the CI stimulation channel, i.e. either channel 15 or channel 6.

Factor	Coefficient	t-value	p-value	95% CI
Intercept	0.003	2.208	0.049	[0.0003;0.006]
Contrast Beh-EASSR	-0.0001	-0.189	0.853	[-0.002;0.001]
Contrast Diff-EASSR	-0.001	-0.755	0.467	[-0.004;0.002]
Channel	0.006	4.536	0.001	[0.003;0.008]
Contrast Beh-EASSR x Channel	-0.0004	-0.481	0.640	[-0.002;0.001]
Contrast Diff-EASSR x Channel	-0.0002	-0.136	0.895	[-0.003;0.003]

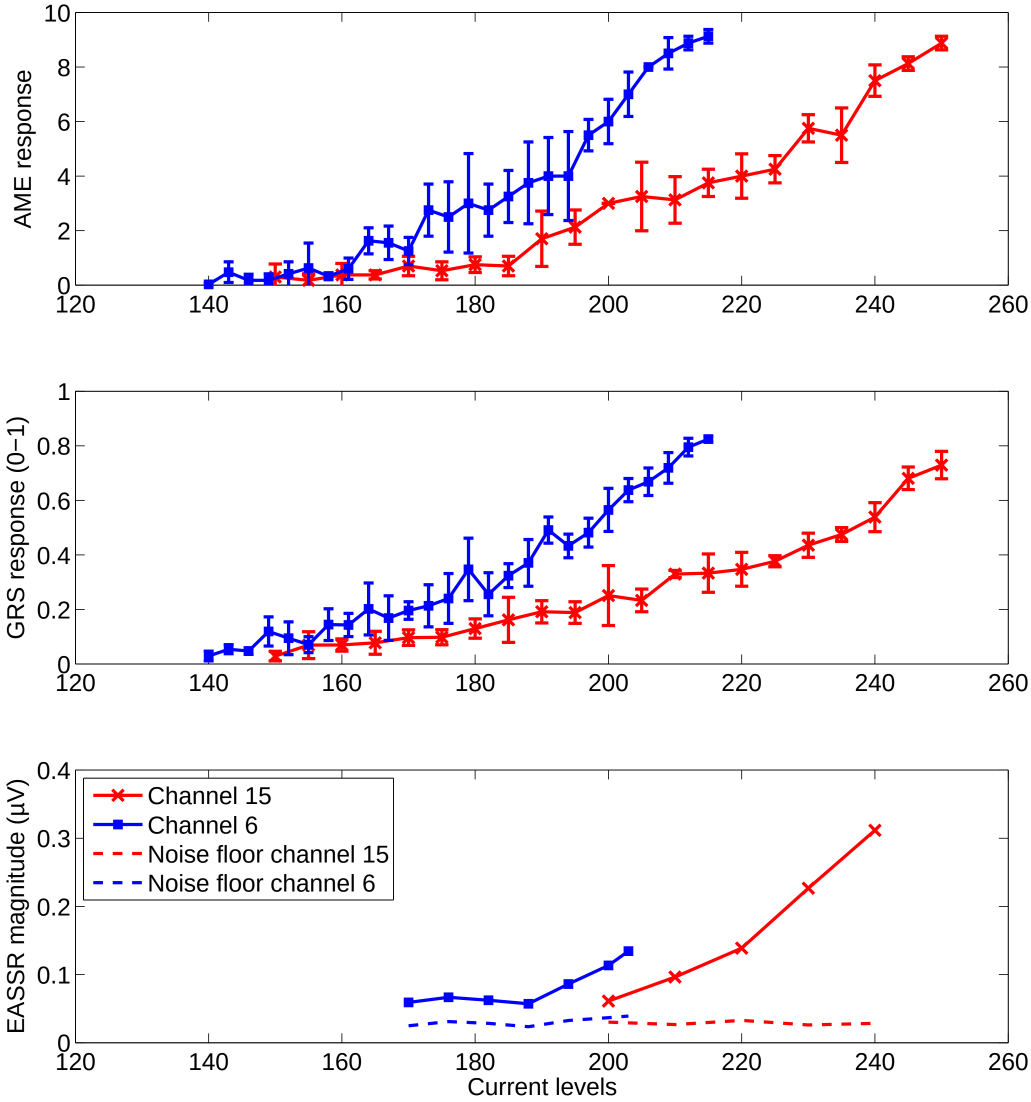

Figure 1: The raw results of a typical CI listener (CI7) for stimulation of CI channels 15 and 6. The top two panels show the results of the behavioral loudness measures, i.e. the numbers that the participants typed in the Absolute Magnitude Estimation (AME) task (on a linear scale), and the responses on the Graphic Rating Scale (GRS). The bottom panel shows the EASSR amplitudes and the recorded EEG noise (solid and dashed lines, respectively). The error bars indicate the mean ± one standard deviation of the behavioral responses for each current level.

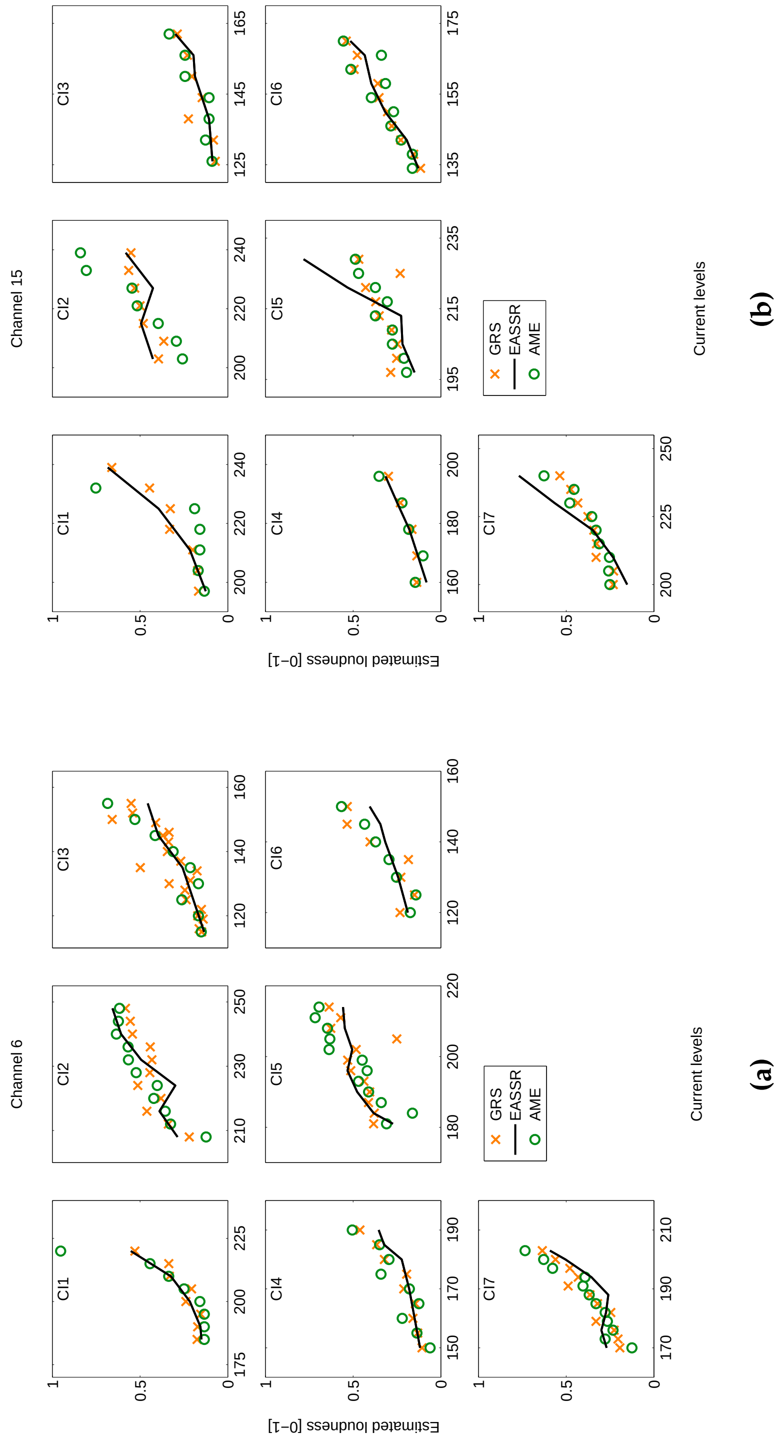

Figure 2: Individual transformed results for channels 6/3 (a) and 15/12 (b).

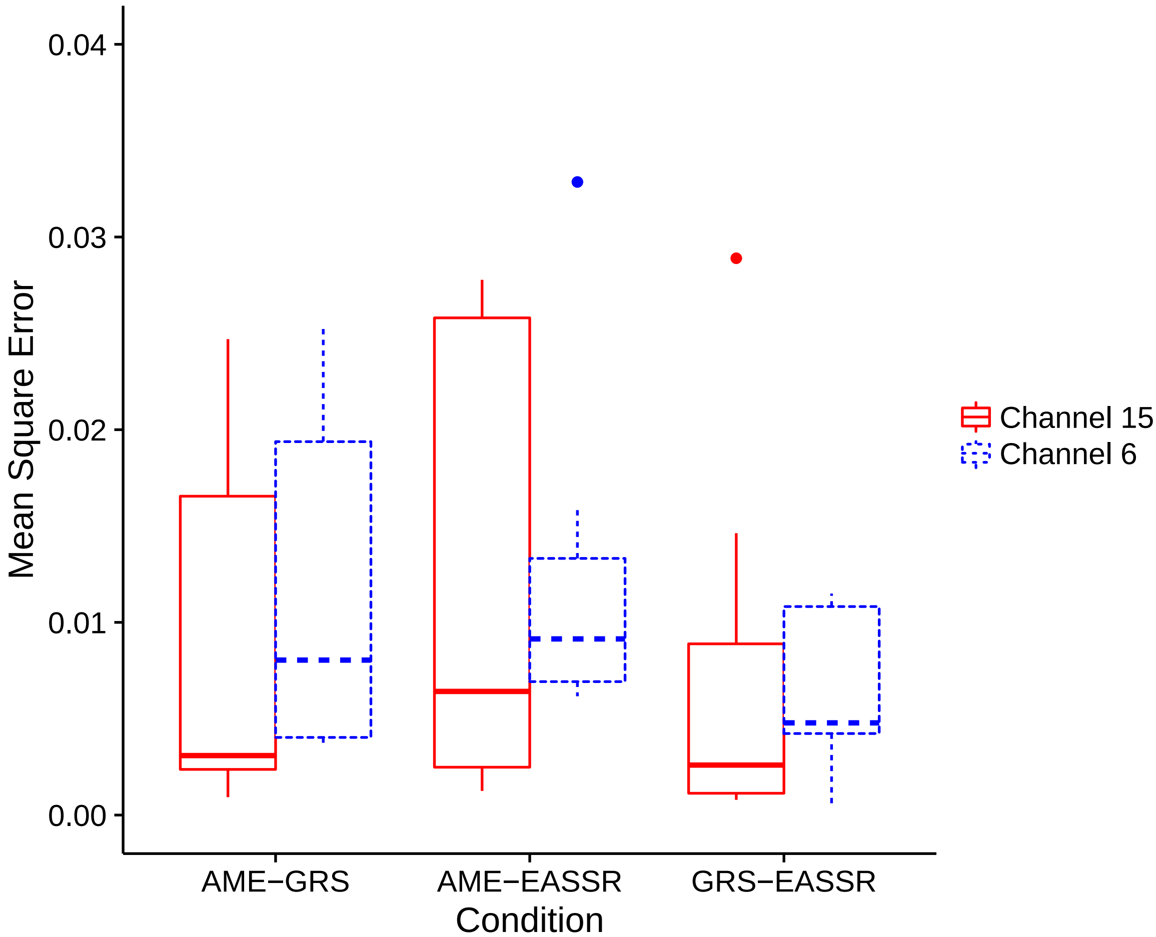

Figure 3: Mean square errors (MSEs) of the transformed data for each CI participant between 1) the AME and GRS responses, 2) the AME and EASSR responses, and 3) the GRS and EASSR responses, for stimulation of channel 15/12 and channel 6/3. Two outliers, with MSE values of 0.38 and 0.50, were not visualized to make the figure more clear. These outliers were from channel 15 and the same participant (CI1), and correspond to the MSEs of AME-GRS and AME-EASSR respectively. The boxplots show median values with first and third quartiles.