Clinically recorded cortical auditory evoked potentials from paediatric cochlear implant users fitted with electrically elicited stapedius reflex thresholds

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ABSTRACT

Objectives: This study aimed to objectively evaluate access to soft sounds (55 dB SPL) in paediatric CI users, all wearing MED-EL (Innsbruck, Austria) devices who were fitted with the objective electrically elicited stapedius reflex threshold (eSRT) fitting method, to track their cortical auditory evoked potential (CAEP) presence and latency, and to compare their CAEPs to those of normal-hearing peers.

Methods: Forty-five unilaterally implanted, pre-lingually deafened MED-EL CI users, aged 12-48 months, underwent CAEP testing in the clinic at regular monthly intervals post switch-on. CAEPs were recorded in response to short speech tokens /m/, /g/ and /t/ presented in the free field at 55 dB SPL. Twenty children with normal hearing (NH), similarly aged, underwent CAEP testing once.

Results: The proportion of present CAEPs increased and CAEP P1 latencies reduced significantly with post-implantation duration. CAEPs were scored based on their presence and age-appropriate P1 latency. These CAEP scores increased significantly with post-implantation duration. CAEP scores were significantly worse for the /m/ speech token compared to the other two tokens. Compared to the NH group, CAEP scores were significantly smaller for all post-implantation test intervals.

Conclusions: This study provides clinicians with a first step towards typical ranges of CAEP presence, latency, and derived CAEP score over the first months of MED-EL CI use. CAEPs within these typical ranges could validate intervention whereas less than optimum CAEPs could prompt clinicians to seek solutions in a timely manner. CAEPs could clinically validate whether a CI provides adequate access to soft sounds. This approach could form an alternative to behavioural soft sound access verification.

Key words: stapedius reflex; paediatric; CI; cortical; clinic

Abbreviations: aided cortical assessment (ACA), audio processor (AP), auditory neuropathy spectrum disorder (ANSD), auropalpebral reflex (APR), behavioural observation audiometry (BOA), charge level (qu), cochlear implant (CI), cortical auditory evoked potential (CAEP), electrically elicited stapedius reflex threshold (eSRT), electroencephalogram (EEG), hard-of-hearing (HOH), high definition continuous interleaved sampling (HDCIS), Listening Progress Profile" (LiP), maximum comfortable level (MCL), normal hearing (NH), Parents' Evaluation of Aural/Oral Performance of CHildren (PEACH), post switch-on (PSO), standard deviation (SD).

1. INTRODUCTION

Extensive worldwide implementation of new-born hearing screening, diagnostic technologies (i.e., (un)aided brainstem and cortical hearing status evaluation) and the proven advantages of early intervention are leading to infants being fitted with hearing aids at a younger age [1]. Similarly, improved imaging and surgical techniques are resulting in the age of cochlear implantation being decreased to below 12 months. Early cochlear implantation is important as earlier age of cochlear implant (CI) switch-on has been associated with better outcomes [1].

If children with a hearing loss wearing hearing devices are to develop spoken language, they need to be able to 'overhear' speech, i.e., benefit from incidental listening like hearing children do [2]. The amount of language input a child experiences is a very important factor affecting their spoken language development [3]. Hence to reap the benefits of early provision of devices, fitting programs need to be optimised as early as possible so that devices provide access to all speech sounds. In the case of hearing aids, there are well-established procedures for clinicians to assess hearing thresholds and to verify hearing aid prescriptions incorporating real-ear-to-coupler differences [4]. Unfortunately, these methods are not applicable to CI users. An infant's reaction to specific sounds while wearing hearing devices can be observed during behavioural observation audiometry (BOA). This technique is relatively unreliable. Sound field thresholds can be obtained using visual reinforcement or play audiometry techniques. These procedures require the child to reach certain developmental stages. In addition, feedback can be gathered from caregivers using questionnaires e.g. the LittlEARS Auditory questionnaire [5], the "Meaningful Auditory Integration Scale" [6], Parents' Evaluation of Aural/Oral Performance of CHildren (PEACH) [7], and the "Listening Progress Profile" (LiP) [8]. However, caregivers may not be able to report accurately [9]. Conversely, objective device

fitting and verification of device benefit is a welcome complementary technique in addition to behavioural testing [4,10–14].

One objective way to fit CI users is with the electrically elicited stapedius reflex threshold (eSRT) fitting method, which looks for a stapedius reflex in response to an electrical stimulus. In MED-EL (Innsbruck, Austria) CI devices, the maximum comfort level (MCL) can be set at the minimum charge level (qu) where a clear, repeatable eSRT is observed. A high correlation exists between eSRT-set and behaviourally-set MCLs in paediatric CI users [15–17]. For this reason clinicians can set MCLs of paediatric users confidently at eSRT level. For clinical CI fitting evaluation in the free field however, which evaluates whether children with CIs can hear soft speech sounds, no objective techniques are available as of yet.

The cortical auditory evoked potential (CAEP) has been reported as a relatively reliable objective measure to evaluate free field device fitting of infants and young children [10,13,14,18–21]. More specifically, short consonants /m/, /g/, and /t/ have been used to elicit CAEPs to evaluate (un)aided performance [10,13,14,20,22–30]. Depending on the presence and morphology of the CAEP, inferences can be made about the child's audibility and speech perception. Gordon and colleagues have associated unusual morphology with poor speech perception in CI users [31]. Golding and colleagues have linked CAEP presence with function measures in infants [11]. CAEP testing using /m/, /g/, and /t/ stimuli can be likened to a cortical Ling sound test: a child who can detect conversational level speech sounds that span the speech frequency range is likely to have the capacity to develop auditory oral communication skills [32,33]. Using CAEPs for device fitting evaluation has several benefits. First, CAEPs evaluate the auditory path up to the auditory cortex, including any device processing particular to these types of short sounds. Second, the presence of cortical responses correlates with functional measures in infants [11] and with speech perception in children [34], including those with

auditory neuropathy spectrum disorder (ANSD) [35,36]. Third, CAEP testing can be conducted while the client is awake. Although it is acknowledged testing an awake paediatric population is not straightforward, being able to test clients awake does away with the need for sedation, which is beneficial for evaluating all except the youngest of infants as it is difficult to find a time when they are awake [37]. Finally, the latency of the CAEP P1 component, which is the first positive deflection, can be used as a biomarker to infer the maturational status of auditory pathways in infants and children [38,39]. In normal-hearing (NH) new-borns the mean P1 latency is approximately 300 ms. Over the first 2–3 years of life there is a rapid decrease in latency to approximately 125 ms at age 3 and then a more gradual decrease during the teenage years. The mean P1 latency in NH adults (ages 22–25 years) is approximately 60 ms. This decrease in latency is a result of the maturation of the central auditory pathways as the system develops [38–41]. CAEP testing has some drawbacks as well. First, as mentioned before, CAEPs are preferably recorded while awake, which can be an issue in a very young infant population [37]. Second, due to their variable morphology, subjective interpretation of CAEP presence requires training and experience. This might increase the need for objective detection [42]. Finally, CAEP detection sensitivities using short speech tokens at suprathreshold levels (>20 dB SL) range between 68 and 77% in HOH infants and young children when false positive rates are kept at 5% [20,28]. Although response rate in this population is not necessarily higher using behavioural techniques, one needs to be cautious when interpreting the significance of absent CAEPs to audible stimuli [28].

Like with hearing aid fitting evaluation, it is hypothesised that the adequacy of (eSRT-based) CI fittings can be objectively verified by evaluating CAEP presence to soft sounds. Although an absence of a CAEP does not guarantee inaudibility, the appropriateness of the newly acquired, stable access to sound when a CAEP has been detected can be evaluated by keeping

track of (an expected decrease of) P1 latency over time. Therefore, the objectives of this study were to:

1) Provide evidence that CAEPs can be used clinically to objectively evaluate access to soft sounds in paediatric CI users, specifically in those who were fitted with the objective electrically elicited stapedius reflex threshold (eSRT) fitting method;
2) Record and track the presence and latency of CAEPs in response to 55 dB SPL speech tokens over the first months of CI use; and
3) Compare their CAEPs with those of hearing peers.

This study is different from other published studies given it reports on changes in clinically-recorded CAEPs (both presence and P1 latency) over a period of at least 6 months, including if and when a normal P1 latency was achieved.

2. MATERIAL AND METHODS

2.1 Participants

Two groups of children were included in this longitudinal study: a group of 45 children who were implanted with a CI, and a control group of 20 NH children. The CI group comprised 45 (18 female) unilaterally implanted MED-EL SONATATI^{100} CI and OPUS 2 Audio Processor (AP) users. None of the children were bilateral CI users. All used FineHearing^{TM} FS4p coding strategy. This strategy creates an enhanced perception of tone and pitch in all frequencies by improving low frequency coding using the timing of stimulation to code the temporal structure of the sound signal. An envelope based coding strategy is used for mid and high frequency sounds [43]. The mean age and standard deviation (SD) of first CI fit were 24.1 (SD 8.7) months (range 13-46 months). All implanted children except one (deafened at 18 months of age) had congenital bilateral severe to profound sensory-neural hearing loss. A review of all

45 implanted children's files revealed the following aetiologies: unknown (31, this includes 6 families where mother and father are related – consanguineous marriage), hereditary (9 – other family members deaf), infection or illness (4), and hyperbilirubinemia (1). Mean age of hearing aid provision and habilitation services were 9 (SD 7) months (range 1-24 months). All had varied lengths of experience with bilateral hearing aids prior to CI use. Thirty-seven used a standard length electrode (contact extent 26.4 mm), 5 used a medium length electrode (contact extent 20.9 mm), and 3 used a variety of electrodes designed for use with cochlear malformation.

Thirty-four CI users were implanted at Istanbul, Training and Research Hospital, Fatih, Istanbul, Turkey. The other 11 CI users were implanted at a variety of hospitals across Turkey. CI AP fitting was done at Istanbul Research and Training Hospital and MEDers Speech and Hearing Clinic, Kadikoy, Istanbul, Turkey. Both centres used identical procedures. Fitting was performed between 29 January 2011 and 14 April 2015, which involves small modifications to MCL and threshold levels according to auropalpebral reflex (APR) levels, or reactions of the patient. It may, rarely, involve a change in number of activated electrodes. The standard CI fitting schedule followed the schedule of a 2nd fit at 1 month, the 3rd fit at 3 months, and the 4th fit at 6 months post switch-on (PSO). Forty-two children were fitted using the objective eSRT fitting method, and 3 of the CI users' MCLs were set 12-15% below the charge level that elicited an APR. During eSRT fitting, the child needs to comply with having a tympanometry probe placed in one ear, wearing their AP and sitting quietly for approximately 10 minutes. The 3 CI users who had MCL set through observation of an APR were not compliant, initially. Typically, children can be quietly amused by parents or an assistant and remain compliant for the duration of eSRT testing. Electrical hearing thresholds on high definition, continuous interleaved sampling (HDCIS) channels (electrodes 5 to 12) were set at 10% of MCL. This is the level recommended by MED-EL to be used in CI users who cannot

provide reliable behavioural feedback. Thresholds on fine structure channels (electrodes 1 to 4) were set at 0 charge levels (qu; product of wave amplitude and pulse width; measured in nanocoulombs). Behavioural threshold testing of adult CI users showed thresholds on these channels to be significantly lower than thresholds on HDCIS channels. Frequency range was set at 70 – 8,500 Hz. Both maplaw and automatic sound management were set at default levels. The maplaw is a compression parameter that is applied equally to all channels and determines how acoustic sounds are mapped into the user's individually-measured electrical dynamic range. Automatic sound management involves a dual stage automatic gain control and automatic volume control.

A NH control group was added to identify if and how the CI group would be different when tested under the same conditions and evaluated with the same measures in the clinic. The control group comprised 20 children (11 male), aged 12 to 48 months (mean: 34.3 months, SD: 9.1 months). Normal hearing was defined between 0-15 dB HL, using distortion product otoacoustic emission testing and play audiometry at 5 octave frequencies (0.25 – 4 kHz), on one ear. No significant differences were found between age and gender proportion of the NH and CI children. This is important as CAEP waveforms (and P1 latencies) change with age [44]. Permission to carry out this study was obtained from the clinical research ethic committee of the Istanbul Education and Research Hospital. Each parent read and signed a form permitting CAEP recording to be performed repeatedly. Only families within easy travelling distance of the test centre were included in this study.

2.2 Aided cortical assessment (ACA)

Aided cortical assessment (ACA) was carried out in the MEDers Speech and Hearing Clinic (Istanbul, Turkey) using the HEARLab™ system (Frye Electronics, Tigard, OR, USA) as

follows. CAEPs were elicited using speech tokens /m/ (30 ms, dominant frequency at 250 Hz), /g/ (21 ms, 1250 Hz) and /t/ (30 ms, 3250 Hz) in a single, quiet but not sound-treated room [13,27]. Stimuli were presented at 55 dB SPL in a calibrated sound field via a free field loudspeaker at 1-meter distance and at 0° azimuth. Children generally sat on a caregiver's lap and were entertained with quiet, soft toys. The total testing time was approximately 15 minutes. No hearing aids were worn on the opposite ear. Three disposable Ambu N electrodes (Ambu, Copenhagen, Denmark) were placed on the child's scalp after lightly scrubbing the scalp. The active electrode was attached at Cz (vertex), the reference electrode at the mastoid contralateral to the CI, and the common (ground) electrode at the forehead. Electrode impedances were kept below 5 kOhms. CAEP presence was objectively evaluated using a Hotelling's T^2 statistical test [42]. Artefact rejection was set at +/- 150 microvolt, and the amplification of the system was 1210. Testing for each speech token was continued until the predetermined value of 200 accepted epochs was reached, or stopped manually when the p-value was observed to be ≤ 0.05 and the residual noise as displayed by the system (using a green traffic light) was ≤ 3.2 μV [28]. Because HEARLab™ presents speech tokens in blocks of 25 epochs, testing is often terminated after more than 200 epochs have been accepted.

Children in the NH group underwent a single CAEP assessment on one occasion after verification of NH thresholds. The CI group underwent ACA at 8 possible test intervals: 1 week, 1, 2, 3, 4, 5 and 6 month(s), and >6 months PSO (mean 10.3; SD 3.2; range 7-17 months). Table 1 shows the number of children that underwent ACA at each test interval. Not all CI users underwent an ACA at each test interval as not all children could attend the clinic for every appointment. The mean number of ACAs conducted on each CI child was 5.62 (range 3 – 8 ACAs). On top of ACA, CI fitting occurred as well at 2nd, 4th and 7th test intervals. On these test intervals, first CI fitting and then ACA was carried out. CI users would only undergo a second fitting on the same test interval when CAEPs were absent. This re-fit

occurred at the same day by measuring the eSRT on all active electrodes. If there was an improvement in CAEP presence to a specific speech token after a re-fit, the recorded CAEPs replaced any prior recordings in the same test interval.

Each CAEP was scored by evaluating the statistical presence and the latency of its first positive deflection (P1). This measure was named the 'ACA score'. This approach is similar to Golding and colleagues who employed CAEPs to assess hearing aid benefit [11]. In the Golding et al. study, one point was scored for each significantly present CAEP. In the present study, the scoring system was extended. Figure 1 shows three examples of how the ACA score was determined. A score of 0 was assigned when no CAEP was elicited (a p-value greater than 0.05). A score of 1 was allocated when a CAEP was significantly present ($p \leq 0.05$), with a P1 latency that was out of the age-dependent normative latency range (determined in NH children) as indicated by the shaded blue area in the HEARLab™ software. According to the HEARLab™ manual, this normative latency range is based on latencies of CAEPs obtained in two studies. The first study reported on P1 latencies of CAEPs obtained at the National Acoustic Laboratories (NAL) in 54 NH infants, aged 0.2 to 0.75 years and adult P1 latency values [45]. The second study described the P1 latencies of CAEPs in 136 normal-hearers ranging 0.1 to 20 years [46]. Based on these data, the latency range was delimited by a mean P1 latency and 2 SDs on each side. Mean P1 latency followed the equation $6.94x^3 - 7.8x^2 - 106.14x + 271$ (in ms), and its SD = -5.5x+26.1 (in ms), with x the decimal logarithm of the child's age in months. A score of 2 was allotted if P1 was considered present and its latency was within the age-dependent normative (NH) latency range. As at each test interval three speech tokens were tested, the maximum possible score was 6. The combined measure for three speech tokens was dubbed the 'combined ACA score'.

=== Figure 1 about here ===

2.3 Objective detection of CAEP presence and determination of P1 latency

CAEP presence and P1 latency were determined by reprocessing the HEARLab^{TM} data in MATLAB R2017a (Mathworks, Natick, MA, USA) to ensure a consistent determination of P1 latencies according to the same (automatic) rules. For CAEP presence, each recorded epoch was reduced to 9 averaged voltage levels, with each average having been taken within a 'bin' covering a particular latency range. The 9 equidistant bins covered the range from 101 to 550 ms, for children younger than 2 years old, and 76 to 450 ms for those older than 2. The bin width and number of bins were chosen based on earlier data [47]. Response detection was based on the p-value obtained from a one-sample Hotelling's T^2 test on the bin-averaged data. Each 'data point' was a 9-dimensional binned epoch, and the null hypothesis being tested was that the averaged cortical response in every bin was zero. Under assumptions analogous to those of a t-test (that the epochs are independent observations from the same multivariate normal distribution), it can be shown that a detection criterion of $p \leq 0.05$ results in a false detection rate of 5%. For P1 latency, P1 was determined as the first positive wave starting 50 ms after stimulus onset, unless a significantly larger positive wave followed. This was achieved by filtering the CAEP data first with a 10^{th} order Butterworth lowpass filter at 10 Hz, determine the first major peak after stimulus onset using the MATLAB command 'findpeaks' (with the parameter 'MinPeakProminence' set to 1, which allows to ignore minor positive peaks), and use this obtained maximum to find the most closely neighbouring maximum in the original CAEP waveform (which has been lowpass filtered by the HEARLab^{TM} system at 30 Hz).

2.4 Statistical methods

All models employed in this study were mixed effects models. The mixed effects were effects of stimulus, test interval (treated as categorical), and their interaction. The random effect was a subject-specific intercept. P-values and confidence intervals were adjusted for multiple comparisons.

2.4.1 Proportion of present CAEPs

For comparisons within the CI group, a mixed-effects logistic regression model was fitted, which models the probability that a CAEP is present. Effect sizes in logistic regression are expressed in terms of odds ratios. Any estimates and confidence intervals (CIs) comparing each pair of stimuli or each pair of test intervals are odds ratios. The p-values presented here are for the null-hypothesis that the true odds ratio is 1. That is, the odds (and therefore also the probability) of a response for the two stimuli at the same test interval (or test intervals for the same stimulus) are equal. For comparisons between CI and NH groups, the Barnard's unconditional exact test was used.

2.4.2 P1 latencies

For comparisons within the CI group, a linear mixed-effects model was fitted on the log(latency) dependent variable. Any estimates and confidence intervals (CIs) comparing each pair of stimuli or each pair of test intervals are ratios of latencies, obtained by exponentiating differences in log(latency). For comparisons between CI and NH groups, the Mann-Whitney test was used.

2.4.3 (Combined) ACA scores

A linear mixed-effects model was fitted with (combined) ACA score as the dependent variable. Estimates are absolute differences in (combined) ACA score. For comparisons between CI and NH groups, the Mann-Whitney test was used.

3. RESULTS

Sixty CAEP measures (20 NH children x 3 speech tokens) and 759 CAEP measures (253 test intervals recording 3 speech tokens each) were obtained from the NH group and the CI group, respectively. In 3 CI children, 8 CAEP measures contained large electrical artefacts originating from the CI, making it impossible to identify CAEPs. These 8 CAEP measures were removed together with an additional 7 CAEP measures associated with these 8 measures to retain an equal number of speech tokens for analysis. Ultimately, 744 CAEP measures (45 CI children x 3 speech tokens x 5.51 test intervals per child on average across 8 test intervals) were available from the CI group. Figures 2 to 4 show the grand averages of the three speech tokens for each test interval for the CI group. It can be noticed visually that CAEP morphologies differ between stimuli, especially when comparing /m/ versus /g/ and /t/ speech tokens. Morphologies change with test interval, with P1 latencies becoming shorter with increasing test interval. Figure 5 shows the same information for the NH group, but for a single test interval, with only small differences in morphology between the three speech tokens. Supporting materials have been provided which present all recorded CAEP waveforms for each child, including statistical waveform analysis, residual electroencephalogram (EEG) noise levels, P1 latencies and combined ACA scores.

=== Figures 2, 3, 4 and 5 about here ===

3.1 Proportions of present CAEPs

Figure 6 shows the proportion of present CAEPs for the three speech tokens and 8 test intervals for the CI group, and for the NH group who only attended one test interval. On average 54.4%, 87.4 and 91.0% of CAEPs were detected to speech tokens /m/, /g/ and /t/, respectively, when presented at 55 dB SPL in pre-lingually deafened CI children during the first 6 months of device use. CAEP presence in NH children was 100%.

The proportion of present CAEPs increased significantly with test interval ($\chi^2 = 27.7$, df = 7, $p < 0.001$). Table 2 shows the p-values of individual comparisons between test interval pairs, with values corrected for multiple comparisons. CAEP presence at test interval 1 (1 week PSO) was not significantly different from CAEP presence at test intervals 2, 3 and 7 (1, 2 and 6 months PSO). CAEP presence at test interval 2 (1 month PSO) was not significantly different from CAEP presence at test intervals 3, 4 and 7 (2, 3 and 6 months PSO). CAEP presence at test interval 3 (2 months PSO) was not significantly different from later test intervals up to 6 months PSO. Test intervals ≥4 (three or more months PSO) were not significantly different from each other concerning CAEP presence.

The main effect of stimulus was significant ($\chi^2 = 54.6$, df = 2, $p < 0.001$). Compared to /m/, both speech token /t/ (estimate odds ratio /t/-/m/: 20.31; 95% confidence interval: 9.18 – 44.92; $p < 0.001$) and speech token /g/ (estimate odds ratio /g/-/m/: 12.13; 95% confidence interval: 5.96 – 24.69; $p < 0.001$) had significantly higher odds ratios. No significant difference was found between speech tokens /g/ and /t/ (estimate odds ratio /g/-/t/: 0.60; 95% confidence interval: 0.27 – 1.33; $p = 0.29$).

No significant interaction was found between stimulus and test interval ($\chi^2 = 5.34$, df = 13, p = 0.97).

Compared to the NH group, the probability of a CAEP to speech token /m/ was significantly lower for the first 7 test intervals, or up to 6 months PSO ($p < 0.001$ to $p = 0.02$). For test interval 8 (>6 months PSO), this difference was not significant ($p = 0.07$). The probability of a CAEP to speech token /g/ was significantly lower compared to the NH group for test intervals 1 and 2, or up to 1 month PSO ($p = 0.009$ to $p = 0.04$). No significant differences were found for speech token /t/ at all 8 test intervals.

=== Figure 6 and Table 2 about here ===

3.2 P1 latencies across groups, speech tokens, and test intervals

For the analysis of CAEP P1 latencies, 584 significantly present CAEP waveforms (out of 744 CAEP measures) were used. Figure 7 shows the P1 latencies of these CAEPs evoked by the three speech tokens and 8 test intervals for the CI group, and for the NH group who only attended one test interval.

CAEP latencies reduced significantly with test interval ($F(7,516) = 46.03$, $p < 0.001$). Table 2 shows the p-values of individual comparisons between test interval pairs, with values corrected for multiple comparisons. CAEP latencies at test interval 1 (1 week PSO) were significantly longer than the CAEP latencies at all other test intervals (1 or more months PSO). CAEP latencies at test interval 2 (1 month PSO) were significantly longer than those obtained at 5 or

more months PSO. All CAEP latencies obtained up to 3 months PSO were significantly longer than those obtained ≥6 months PSO.

The main effect of stimulus was significant ($F(2, 516) = 24.76$, $p < 0.001$). Compared to /m/, P1 latencies of the CAEPs to speech token /t/ were on average 13% shorter (ratio estimate /t/-/m/: 0.87; 95% confidence interval: 0.81 – 0.92; $p < 0.001$) while those to speech token /g/ were 17% shorter (ratio estimate /g/-/m/: 0.83; 95% confidence interval: 0.78 – 0.89; $p < 0.001$). No significant difference was found between P1 latencies of the CAEPs to speech tokens /g/ and /t/ (ratio estimate /g/-/t/: 0.96; 95% confidence interval: 0.91 – 1.01; $p = 0.17$).

No significant interaction was found between stimulus and test interval ($F(14, 516) = 1.54$, $p = 0.09$).

Compared to the NH group, P1 latencies of CAEPs to speech token /m/ were significantly longer for the first 5 test intervals, and test interval 7 ($p = 0.004$ to $p = 0.04$). P1 latencies of CAEPs to speech token /g/ were significantly longer compared to the NH group for the first 3 test intervals, or up to 2 months PSO ($p < 0.001$ to $p = 0.002$). For speech token /t/, P1 latencies were significantly longer for the first 5 test intervals, or up to 4 months PSO ($p < 0.001$ to $p = 0.03$).

=== Figure 7 about here ===

3.3 ACA scores per stimulus

Figure 8 shows the ACA scores for each of the three speech tokens and 8 test intervals for the CI group, and for the NH group who only attended one test interval.

ACA scores increased significantly with test interval ($F(7,676) = 116.63$, $p < 0.001$). Table 2 shows the p-values of individual comparisons between test interval pairs, with values corrected for multiple comparisons. ACA scores at test intervals 1 and 2 (1 week and 1 month PSO) were significantly smaller than the ACA scores at all later test intervals. ACA scores at test interval 3 (2 months PSO) were significantly smaller than those obtained at test interval 8 (>6 months PSO).

The main effect of stimulus was significant ($F(2, 676) = 116.63$, $p < 0.001$). Compared to /m/, ACA scores of speech token /t/ were on average 0.77 higher (95% confidence interval: 0.64 – 0.90; $p < 0.001$) while those of speech token /g/ were 0.72 higher (95% confidence interval: 0.59 – 0.85; $p < 0.001$). No significant difference was found between the ACA scores of speech tokens /g/ and /t/ (difference estimate /g/-/t/: -0.05; 95% confidence interval: -0.18 – 0.08; $p = 0.65$).

No significant interaction was found between stimulus and test interval ($F(14, 676) = 0.62$, $p = 0.85$).

Compared to the NH group, ACA scores of speech token /m/ were significantly smaller for all 8 test intervals ($p < 0.001$ to $p = 0.006$). ACA scores to speech token /g/ were significantly smaller compared to the NH group for the first 3 test intervals, or up to 2 months PSO ($p < 0.001$ to $p = 0.05$). For speech token /t/, ACA scores were significantly smaller for the first 2 test intervals, or up to 1 month PSO ($p < 0.001$ and $p = 0.01$).

=== Figure 8 about here ===

3.4 Combined ACA scores

Figure 9 shows the ACA scores with all three speech tokens combined for each of the 8 test intervals for the CI group, and for the NH group who only attended one test interval.

Combined ACA scores increased significantly with test interval ($F(7,196) = 20.55$, $p < 0.001$). Table 2 shows the p-values of individual comparisons between test interval pairs, with values corrected for multiple comparisons. Combined ACA scores at test interval 1 (1 week PSO) were significantly smaller than the combined ACA scores at all later test intervals. Combined ACA scores at test interval 2 (1 month PSO) were significantly smaller than the combined ACA scores at test intervals 4 and later (3 months or more PSO). Compared to the NH group, combined ACA scores were significantly smaller for all test intervals ($p < 0.001$ to $p = 0.004$).

Thirty-four (76%) of 45 CI children achieved a combined ACA score of 6 within 6 months of CI use and 39 (87%) a combined ACA score of 5 or 6 within 6 months of CI use. To demonstrate the variety of performance within the CI group, participants were (rather arbitrary) divided into good and poor performers. Good performers were CI users obtained a combined ACA score of 5 or 6 earlier than or at 3 months (i.e., the 4^{th} test interval), while poor performers attained a combined ACA score of 3 or less at any of the test intervals between 4 and 6 months post switch on (i.e., 5^{th}, 6^{th} or 7^{th} test interval). Thirty (67%) of 45 CI users were classified as good performers. Three (8%) of 40 CI users were identified as poor performers.

Figures 2 to 4 show changes in CAEPs overtime. This exemplifies expected changes in P1 latency, amplitude and morphology overtime, once an implanted child has adequate access to sound.

=== Figure 9 about here ===

4. DISCUSSION

The objectives of this study were to record and track CAEPs (in terms of presence, latency and ACA scores) from paediatric CI users who were fitted with the objective eSRT fitting method over the first months PSO, and compare their CAEPs with those of hearing peers. As expected, CAEP presence, latencies and ACA scores significantly increased, decreased and increased over time, respectively. CAEPs to /m/ speech tokens were significantly less present, significantly longer, and returned smaller ACA scores compared to the same features of the CAEPs of speech tokens /g/ and /t/. Combined ACA scores increased significantly with test interval, with about three-quarters of CI children reaching a combined ACA score of 6 within 6 months of CI use. Compared to the NH group, combined ACA scores were significantly smaller for all intervals. The study was successful in recording CAEPs from a paediatric CI population in a clinical setting at regular intervals, underlining its clinical feasibility.

4.1 Proportion of present CAEPs

Using the average CAEP presence of 77.6% across the first 6 months PSO and stimuli, it is possible to compare with other young groups. In NH children who were generally younger than the population used in this study, several studies reported on CAEP presence. Cone & Whitacker showed that CAEPs were present 85 and 100% of the time at 30 and 60 dB SPL, respectively, to tone-bursts and speech stimuli in 4-12 month old NH infants [48]. Using the same stimuli as in the current study, Carter and colleagues found detection rates of 27, 55 and 77% at sensation levels of 10, 20 and 30 dB SL, respectively, in 12 (SD 3) month old normal-hearers [42]. Small and colleagues reported a 90 and 100% presence to /m/ and /t/ speech tokens, respectively, at 75 dB SPL in 16-44 week old NH children [49]. In hard-of-hearing (HOH) children, proportions of detected CAEPs were 64, 72 and 77% to the same stimuli at 1-

10, 11-20 and >20 dB SL, respectively, in 8-30 month olds [28]. Gardner-Berry and colleagues found similar rates (68%) at >20 dB SL in 6.6 (SD 2.9) month old HOH infants [25]. Finally, Rance and colleagues detected 83% of CAEPs for a /dæd/ stimulus at comfortable listening levels (20 to 40 dB SL) in 40-108 month old HOH children [35]. In 9 (SD 5) month old infants with ANSD, detection rates were 36, 44 and 38% at 1-10, 11-20 and >20 dB SL, respectively for the same stimuli as in the current study [50]. Gardner-Berry and colleagues found 83% CAEP presence for stimuli presented at >20 dB SL in 11.2 (SD 8.5) month old ANSD children [25]. Finally, Rance and colleagues detected 61% CAEPs in response to /dæd/ at a comfortable level (20 to 40 dB SL) in 6-92 month old ANSD children [35]. Given stimulus parameters vary significantly between these studies and the proportion of detected CAEPs is quite variable in all groups (NH, HOH and ANSD children), there is no evidence to treat CAEP presence in CI children differently from these groups. This arguably demonstrates the feasibility of using CAEPs to evaluate whether an objectively programmed CI provides access to soft, conversational, sounds.

The proportion of present CAEPs in response to /m/ remained significantly lower than those in response to /g/ and /t/ for the CI group, and those in response to /m/ for the NH group. This finding suggests that CI users had less access to low frequency than to mid- and high- frequency sound, unless for some unknown reason CAEPs to low-frequency stimuli in CI users are less prevalent than to stimuli with higher frequency content. Additional data collected post-study showed that by setting electrical hearing thresholds on fine structure channels (electrodes 1 to 4) at 10% of eSRT-set MCL instead of 0 qu, a previously absent CAEP to /m/ could be elicited in the majority of cases. Hence, poorer CAEPs to /m/ found in this study were possibly the result of setting thresholds on fine structure channels to 0 qu. This observation needs to be evaluated in more detail.

4.2 P1 latencies

In 20 NH children tested, CAEPs could be evoked to all three speech tokens, with all but two P1 latencies within the age-typical latency band of the HEARLab™ system. For CI children, the longer P1 latencies recorded immediately after implantation, and the sometimes unusual morphologies, reflect the sound deprivation experienced by CI candidates prior to implantation (confirming the need for CI intervention).

A significant reduction of P1 latency with increasing test interval was observed. The significant reduction of P1 latencies over time is in line with reported findings that children who receive stimulation via a CI early in childhood (<3.5 years of age) show rapidly reducing P1 latencies, and have normal P1 latencies within 6 months of implant use [40,51]. The CI users in the current study had a mean age at implant of 24.7 months, meaning implantation occurred within the sensitive period allowing for normal auditory cortical maturation [40,52–54]. The rapid decrease of P1 latency after implantation, at least for significantly present CAEPs, suggests an adequately programmed CI providing the user with access to sound. As expected, P1 latency decrease is most pronounced from 1 week to 1 month PSO. The rate of decrease is large: median P1 latencies of the CAEP to the /m/ sound drop close to 100 ms in a one-month period. Sharma and colleagues showed similar reductions in P1 latency after implantation in 3-year olds, including the statement that children obtained age appropriate latencies 8 months after switch-on [40]. The current study saw latencies to be age appropriate considerably earlier, with variation among speech tokens (3 months PSO for /g/, 5 months PSO for /t/, and >6 months PSO for /m/). This shows that these CI users' access to sound was sufficient to allow for auditory maturation. This fulfils the requirement that children fitted appropriately with electrical stimulation ought to show normal development of the central auditory pathway [52].

Unusual morphologies could be observed in some of the children 1 week PSO, which vanished generally after one or two months PSO. One type of unusual morphology is the 'deprivation negativity' (e.g., subjects 1, 5 and 7 in the first test interval). In these particular subjects, an initially large negativity dominated the CAEP with a wide negative peak around 150 to 200 ms, which was followed by wide positive peak with a maximum ranging between 250 and 500 ms. This negativity is seen in children who have a profound-to-severe hearing loss, and have an unstimulated, or little stimulated, yet plastic auditory cortex [31,54]. In other children (e.g., subjects 2, 8 and 31 in the first test interval), some evidence of a 'polyphasic waveform' could be seen. In these particular subjects, a waveform could be identified characterised by two positive deflections at 150 and 350 ms, each followed by a negative deflection at 250 and 450 ms. Polyphasic waveforms are generally seen in older children with abnormal or reorganised central auditory pathways due to sound deprivation [31,54]. Hence, it was not completely clear whether the polyphasic waveforms were genuine or the result of recording noise for two reasons: (1) the observed polyphasic waveforms in the current study seemed to be quite stimulus specific, and (2) the current population was much younger than the children in the cited studies. Notwithstanding, the observations in the current study confirm the differences seen in adolescents between NH and CI children [55].

4.3 ACA scores

Eighteen NH children recorded a combined ACA score of 6. The other two recorded a combined ACA score of 5 (i.e., all CAEPs present but one CAEP outside the expected latency range). Because of consistently poorer CAEPs to speech token /m/, average combined ACA scores of CI users stayed around 5 instead of 6, even at >6 months PSO. Although individual combined ACA scores varied, 87% of CI users attained combined ACA scores of 5 or 6 within 6 months

of CI use. This shows that CAEPs to all 3 speech tokens could be recorded in the majority of CI users. However, P1 latencies of the CAEPs in response to /m/ speech tokens generally remained out of the reference latency range. As not all CI users did undergo an ACA at each test interval, some may have reached a level of auditory maturation earlier than was actually recorded.

Three CI users had markedly poor ACA scores. The first child (subject 43) achieved a combined ACA score of only 2 after 11 months of CI use. Chronic middle ear problems prohibited the use of the eSRT fitting method. However, MCLs were set reliably by clear APRs. The child showed no signs of discomfort when using his AP but his mother reported that the child refused to wear his AP for 2-3 hours each day. To date this CI user has made slower than expected development in audition and spoken language learning which would appear not to be related to his AP program and sound access. Golding and colleagues found a significant correlation between CAEPs and Parent's Evaluation of Aural/Oral Performance in Children (PEACH) scores, which is a questionnaire examining everyday auditory functioning [11]. This child's poor language performance and poor combined ACA score support these findings. The second poor scorer on ACA (subject 33) had chronic bronchitis and middle ear infections, was restless and often crying at fitting sessions. The third child (subject 45) initially had eye blinks at eSRT level and so MCLs had to be slightly reduced. Both children are making expected progress in spoken language development. They now have combined ACA scores of 5 (subject 45 at 10 months PSO) and 6 (subject 33 at 16 months PSO).

4.4 Clinical implications

This study provides a first step towards the creation of a 'typical' range of CAEP presence, latency, and (combined) ACA score over the first months of MED-EL CI use. Recording of CAEPs in line with typically 'expected' responses could provide caregivers, teachers and

clinicians with objective evidence that a CI users' development is happening according to plan. This could boost confidence in treatment. Equally, non-typical CAEPs could prompt clinicians to seek solutions within a reasonable time frame. Typical data in terms of (combined) ACA score, as shown in Figures 8 and 9, could be used as a guideline to evaluate an individual CI user's cortical performance. Guidelines based on objective CAEPs could be especially useful when assessing CI users whose AP programs cannot be based on objective measures, e.g., CI users with no eSRTs or APRs.

According to the study's protocol, the CI user was re-fitted using the eSRT fitting method when CAEPs were less than optimum, and then underwent ACA again. Program modifications as such were not made with the goal to improve CAEP presence. Instead, CAEP absence was an indication that the user needed to be re-fitted using eSRT. However, the authors regularly use CAEP information to modify AP programs of non-study CI users. After modification, if CAEPs are still not present, the clinician should inquire into AP wearing habits, maintenance and troubleshooting of the device, and the quality and quantity of meaningful spoken languge the CI user has access to. Insufficient access to sound and speech caused by an inappropriate AP program, limited use and/or problems with the external device and inadequate input of spoken language (e.g., in the case of an infant with two deaf, signing, parents) will prevent or slow down auditory maturation. The problem causing poor CAEPs may be less resolvable, e.g., inadequate access to sound for CI users with cochlear malformation and or cochlear nerve deficiency.

4.5 Future studies

The amount of electrical charge used in the fitting map typically increases within the first 3 months after initial stimulation due to physiological changes in the cochlea and increase in

tolerance to sound. Peak P1 latency of the CAEP decreases as the amount of electrical charge increases. Therefore, if auditory cortical maturation were to be investigated, the effects of increase in stimulation level need to be evaluated and accounted for as well.

The length of auditory experience prior to implantation varies across the study population, which potentially could affect the results. Children with more auditory experience might have a higher combined ACA score in the initial ACA sessions. Keeping track of the amount of residual hearing that is left and the appropriateness of the hearing aid fitting could reduce the variability observed in the current study's results.

Future studies could compare CAEPs of children programmed using easier-to-apply fitting methods, such as measuring of evoked compound action potentials in the form of automated neural response telemetry, neural response imaging or auditory response telemetry, with CAEPs of children fitted using the eSRT fitting method to determine best practice in terms of CAEPs. It could be investigated whether evaluating CI fittings using CAEPs actually results in faster and more efficient fitting of CI clients.

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LEGENDS

Figure 1: Scoring system for aided cortical assessment (ACA) to determine the ACA score per stimulus. No CAEP detected: score 0 (left pane). CAEP detected, but abnormal P1 latency outside the normative latency range based on NH children: score 1 (middle pane). CAEP detected with normal P1 latency: score 2 (right pane). Blue highlighted areas indicate normative (NH) latency range.

Figure 2: Grand average time-domain waveforms (black solid line) and 95% confidence intervals (grey zone) of CAEPs evoked by /m/ speech token for the 8 test intervals. The number of recorded subjects (N) is displayed in the top left corner of each interval pane.

Figure 3: Identical representation as in Figure 2, for CAEPs evoked by the /g/ speech token.

Figure 4: Identical representation as in Figure 2, for CAEPs evoked by the /t/ speech token.

Figure 5: Grand average time-domain waveforms (black solid line) and 95% confidence intervals (grey zone) of CAEPs evoked by /m/, /g/ and /t/ speech tokens. The number of recorded subjects (N) is displayed in the top left corner of each interval pane.

Figure 6: Percentage of present CAEPs for each speech token across 8 test intervals for the CI group, and for the NH group. The numbers at the bottom of each bar indicate the number of participants included.

Figure 7: Boxplots of P1 latencies for each speech token across 8 test intervals for the CI group, and for the NH group. Whiskers encompass 95% of the data. Crosses are outliers. The numbers at the bottom of each bar indicate the number of participants included.

Figure 8: Mean aided cortical assessment (ACA) scores (and standard errors) for each speech token across 8 test intervals for the CI group, and for the NH group. The numbers at the bottom

of each bar indicate the number of participants included, distributed across those with an ACA score equal to 2 (top), 1 (middle) and 0 (bottom).

Figure 9: Mean combined aided cortical assessment (ACA) scores (and standard deviations) across 8 test intervals for the CI group, and for the NH group. The filled circles represent a histogram, with larger circles including more subjects for a specific combined ACA score. The numbers at the bottom of each bar indicate the number of participants included.

Figures

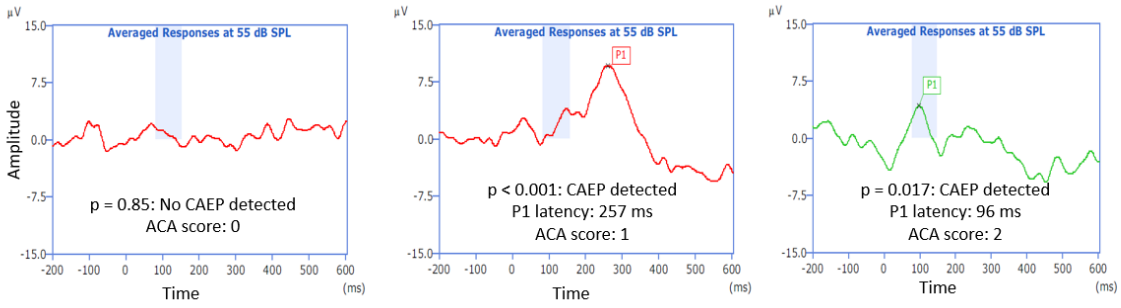

Figure 1

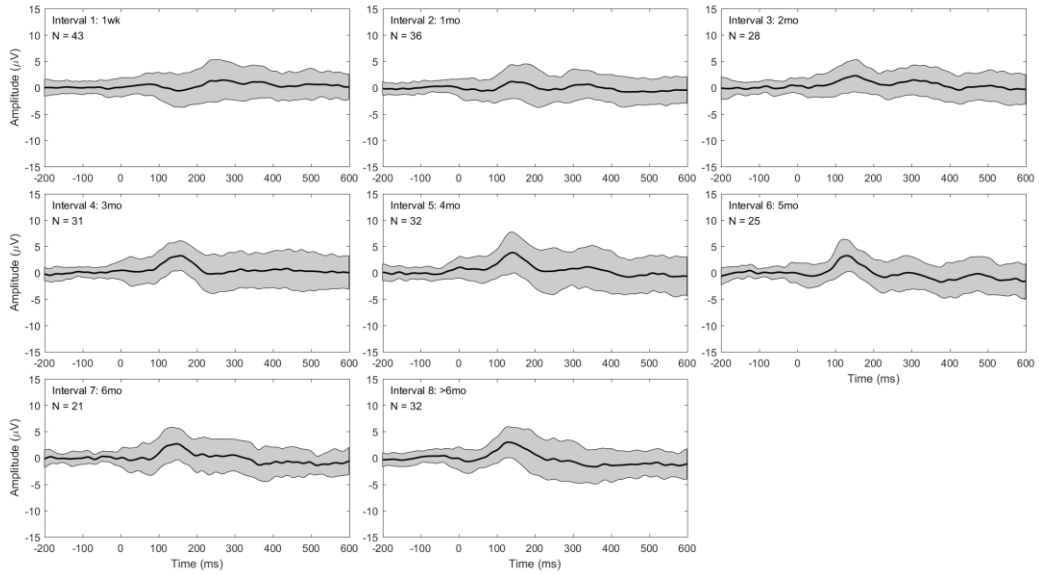

Figure 2

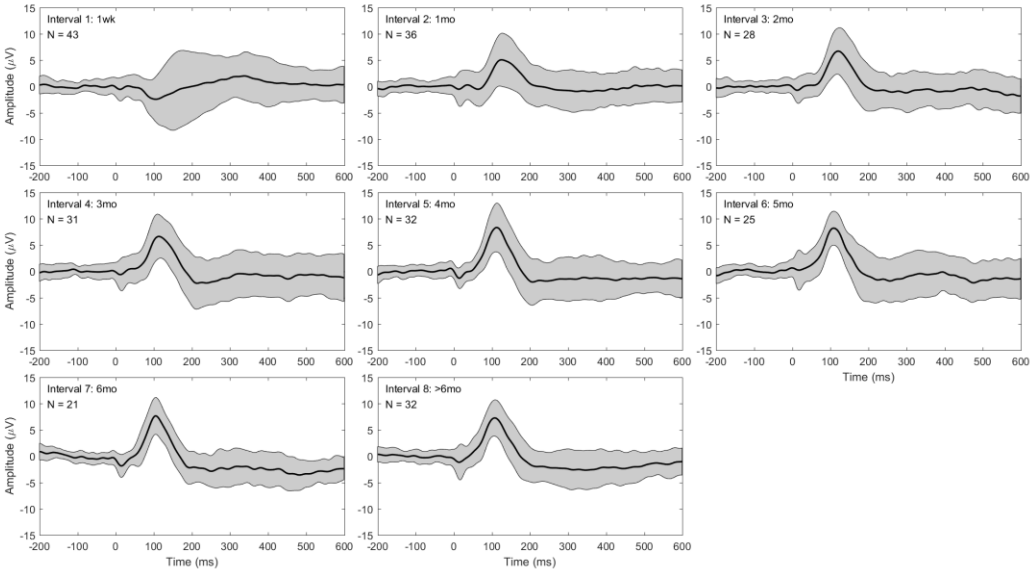

Figure 3

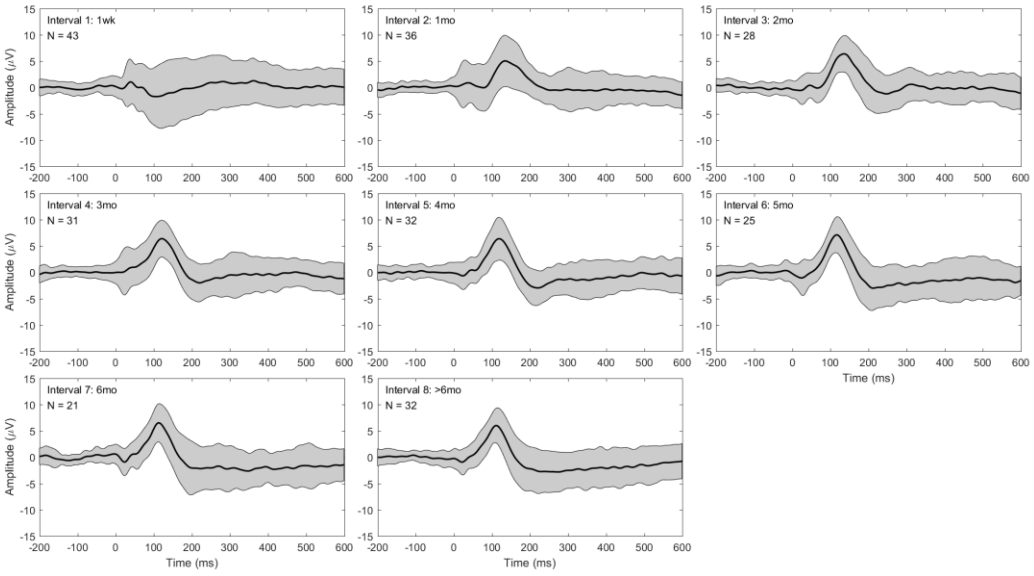

Figure 4

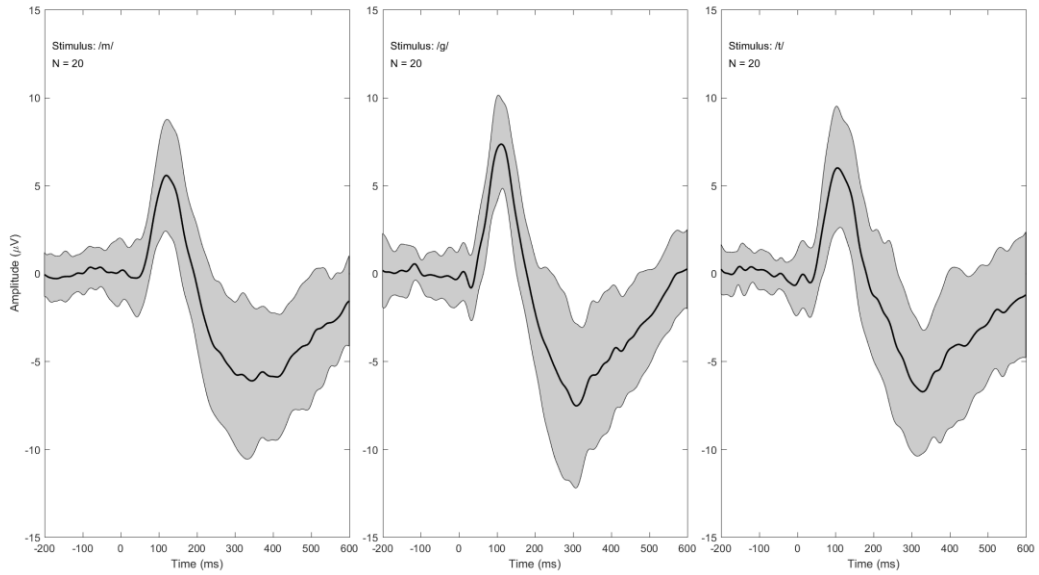

Figure 5

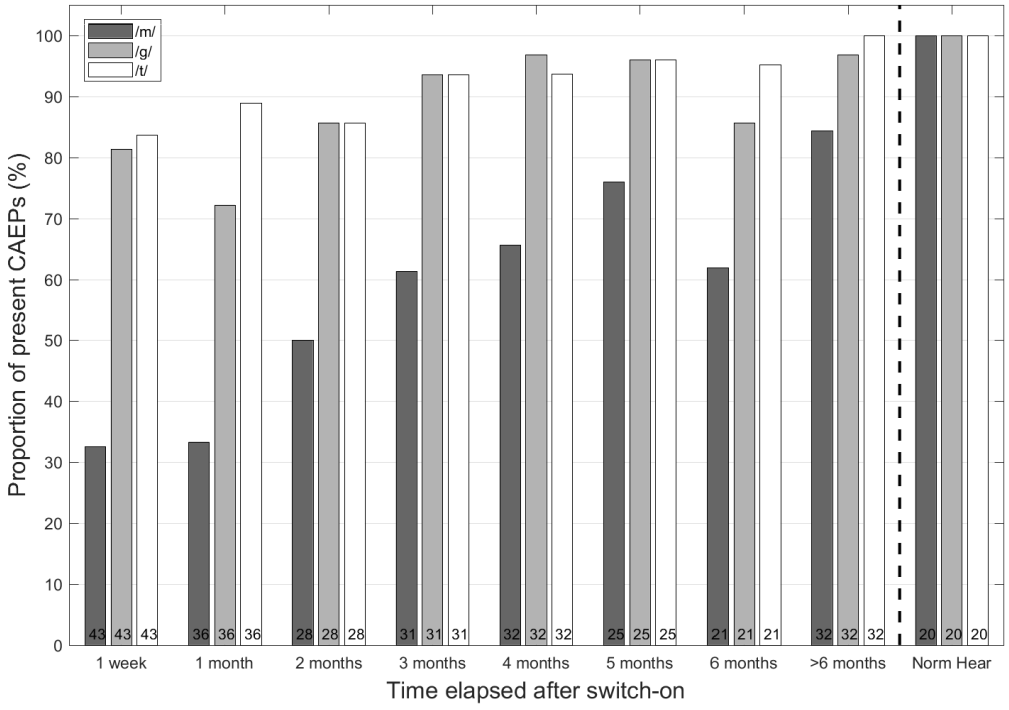

Figure 6

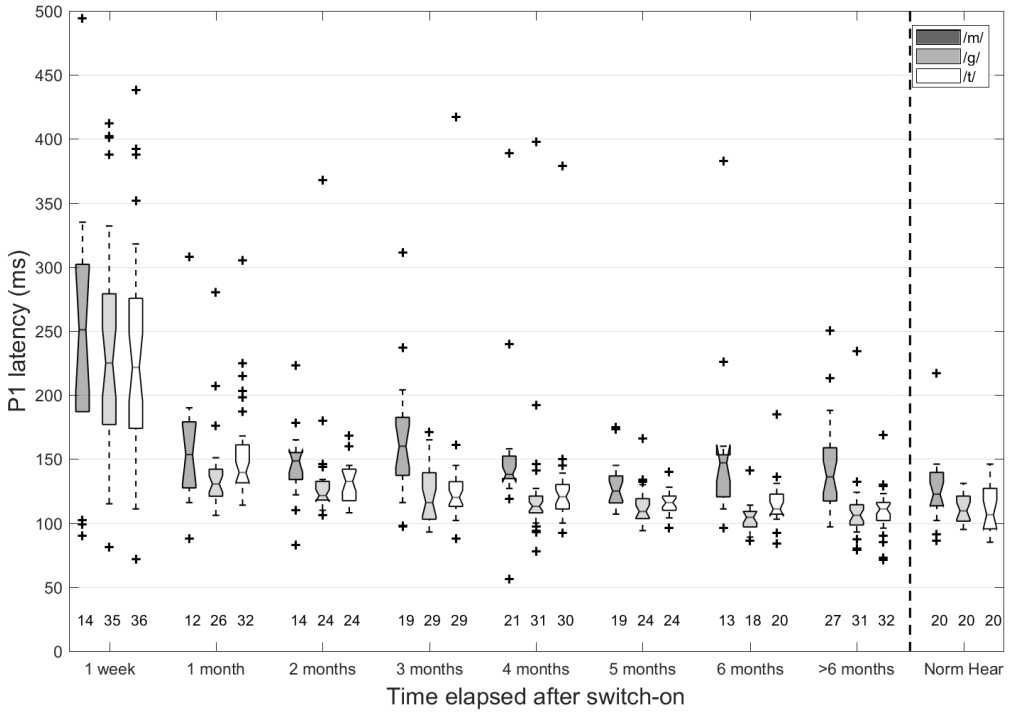
/m/
/g/
/t/
P1 latency (ms)
500
450
400
350
300
250
200
150
100
50
0
14 35 36
12 26 32
14 24 24
19 29 29
21 31 30
19 24 24
13 18 20
27 31 32
20 20 20
1 week
1 month
2 months
3 months
4 months
5 months
6 months
>6 months
Norm Hear
Time elapsed after switch-on

Figure 7

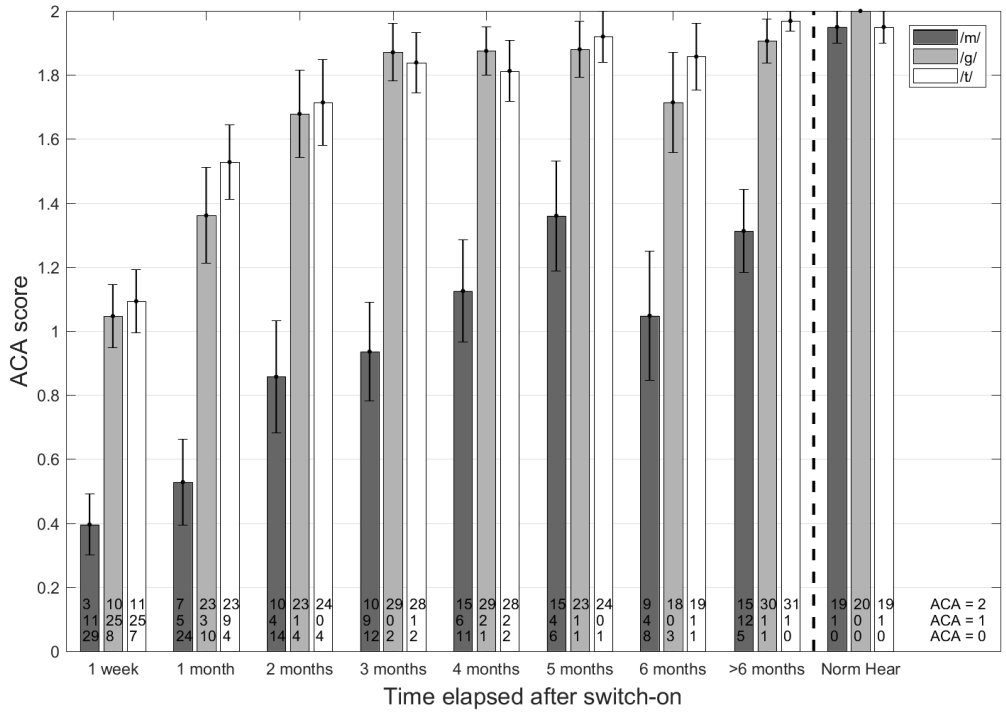
ACA score
Time elapsed after switch-on
/m/
/g/
/t/
ACA = 2
ACA = 1
ACA = 0
1 week
1 month
2 months
3 months
4 months
5 months
6 months
>6 months
Norm Hear

Figure 8

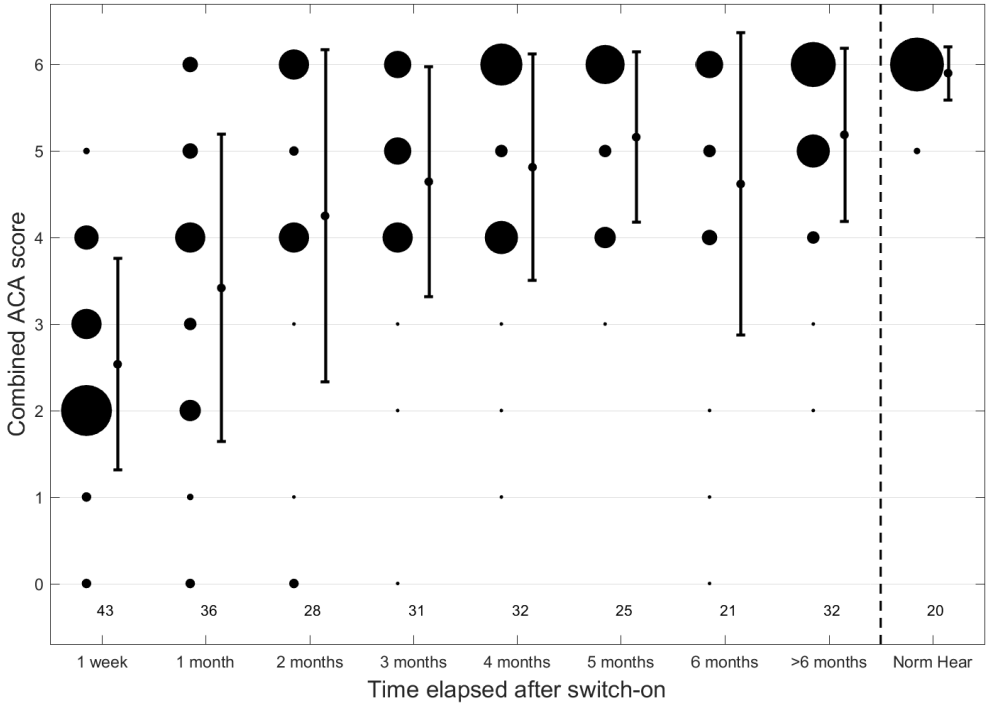
Combined ACA score
0
1
2
3
4
5
6
43
36
28
31
32
25
21
32
20
1 week
1 month
2 months
3 months
4 months
5 months
6 months
>6 months
Norm Hear
Time elapsed after switch-on

Figure 9

Table 1: Number of children at each test interval (including time after switch-on in weeks or months).

Test interval	1	2	3	4	5	6	7	8
Time after switch-on	1 week	1 month	2 months	3 months	4 months	5 months	6 months	>6 months
# children	43	36	28	31	32	25	21	32

Table 2: P-values for pairwise comparisons between test intervals. Significant differences are displayed in bold. P-values were corrected for multiple comparisons.

Presence								**Latency**							
	2	**3**	**4**	**5**	**6**	**7**	**8**		**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	1.00	0.49	**0.02**	**0.001**	**0.003**	0.11	**<0.001**	**1**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
2	-	0.48	0.03	**0.002**	**0.004**	0.11	**<0.001**	**2**	-	0.74	0.70	0.08	**<0.001**	**0.01**	**<0.001**
3	-	-	0.91	0.47	0.41	0.98	**0.003**	**3**	-	-	1.00	0.95	0.11	0.48	**0.01**
4	-	-	-	1.00	0.97	1.00	0.10	**4**	-	-	-	0.92	0.07	0.38	**0.004**
5	-	-	-	-	1.00	0.99	0.38	**5**	-	-	-	-	0.62	0.96	0.19
6	-	-	-	-	-	0.96	0.69	**6**	-	-	-	-	-	1.00	1.00
7	-	-	-	-	-	-	0.11	**7**	-	-	-	-	-	-	0.96
ACA score per stimulus								**Combined ACA score**							
	2	**3**	**4**	**5**	**6**	**7**	**8**		**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	**0.007**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**1**	**0.02**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
2	-	**0.02**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**2**	-	0.06	**0.001**	**<0.001**	**<0.001**	**0.007**	**<0.001**

3	-	-	0.97	0.70	0.33	0.98	**0.05**	**3**	-	-	0.98	0.79	0.45	0.99	0.10
4	-	-	-	1.00	0.89	1.00	0.41	**4**	-	-	-	1.00	0.93	1.00	0.55
5	-	-	-	-	1.00	1.00	0.84	**5**	-	-	-	-	1.00	1.00	0.91
6	-	-	-	-	-	0.95	1.00	**6**	-	-	-	-	-	0.96	1.00
7	-	-	-	-	-	-	0.61	**7**	-	-	-	-	-	-	0.72