Long-term auditory processing outcomes in early implanted young adults with cochlear implants: the MMN vs. P300 response

Rosanne Abrahamse[1], Andy Beynon[2,3], Vitoria Piai[1,3]

[1]Radboud University, Donders Centre for Cognition, Montessorilaan 3, 6525 HR Nijmegen, Netherlands
[2]Radboud University Medical Center, Department of Otorhinolaryngology, Philips van Leijdenlaan 15, 6525 EX Nijmegen, Netherlands
[3]Radboud University Medical Center, Donders Centre for Medical Neuroscience, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, Netherlands

Corresponding author: Rosanne Abrahamse
Department of Linguistics, Macquarie University, NSW 2109, Australia
Email: rosanne.abrahamse@hdr.mq.edu.au

Abstract

Objective: Long-term outcomes of early implanted, young adult cochlear implant (CI) users remain variable. We measured auditory discrimination by means of event-related potentials in this population to examine whether variability at the level of cortical auditory processing helps to explain speech abilities.
Methods: Using an auditory oddball paradigm, the P300 and Mismatch Negativity (MMN) were measured in 8 young adult CI users and 14 normal-hearing peers. We related P300 amplitude and latency to clinical speech perception scores in quiet and to duration of deafness.
Results: All individuals showed P300 responses. The MMN response was less robust in both groups. There was no evidence for differences in P300 responses between CI users and controls. P300 amplitude was associated with speech perception scores ($r = .70$, $p = .05$) and duration of deafness ($r = -.83$, $p = .009$).
Conclusions: Early CI implantation yields good auditory processing outcomes at young adult age and, in contrast to MMN, the P300 provides a robust measure for auditory processing on an individual level.
Significance: At the cortical level, early implanted, long-term CI users have good auditory discrimination, leaving variability in implantation outcomes unexplained. This group shows unique insight into the long-term neurophysiological underpinnings of early implantation.

Keywords: *Cochlear implants; Auditory Cortical Response; Auditory Discrimination; P300; Mismatch Negativity (MMN); Speech perception*

1. Introduction

It is known that the plasticity of the central auditory system declines as a function of the duration of auditory deprivation, with cochlear implant (CI) implantation within 3.5 years after onset of deafness noted as the most beneficial for the later development of good speech perception (Sharma et al. 2002; Eggermont and Ponton 2003; Sharma and Dorman 2006). While speech perception outcomes of pre-lingually deaf CI users have improved with early implantation, they remain varied and below those of their normal hearing peers (e.g. Cupples et al., 2018; Pisoni, Cleary, Geers, & Tobey, 1999). This can have an impact on developing peer-like language, speech, and socio-emotional skills during childhood, as well as broader academic skills and everyday functioning later in life (Tambs 2004; Punch and Hyde 2011; de Hoog et al. 2016; Haukedal et al. 2018). Although factors such as communication mode or IQ have been reported to contribute (Geers 2002; Ruffin et al. 2013), a considerable proportion of variability remains unexplained.

The observed limited and variable speech perception outcomes on a behavioural

level have motivated researchers in the past to investigate auditory processing abilities at the neural level, using objective methods such as electroencephalography (EEG). A well-suited approach is to measure late auditory event-related potentials (ERPs), such as the Mismatch Negativity component (MMN) (Näätänen, Paavilainen, Rinne, & Alho, 2007), and the P300 (or P3b) component (Polich 1987). Both these components appear when the brain performs auditory discrimination of two stimuli, and are elicited using an auditory oddball paradigm. However, they differ with respect to the cognitive processes underlying discrimination. The MMN response is thought to reflect how accurately the auditory memory system can perform lower-level discrimination, based on the perceptual characteristics of the stimuli (Näätänen, 2001). It requires no attention from the listener. The P300 is thought to reflect a more conscious, higher-level cognitive process. Each stimulus is evaluated against a model of the earlier stimulus held in working memory. If a change in stimulus is detected, the model is updated. Besides perceptual discrimination, attention to the stimuli is required for updating this model (Polich 2012). These components furthermore differ in where in the brain they are generated, and at what time after stimulus presentation they appear. The MMN appears as a negative deflection around 150-250 ms after stimulus presentation, and is often observed over fronto-central regions of the brain (e.g. Paavilainen et al., 2003). The P300 appears as a positive deflection around 300 ms after stimulus presentation and is observed over fronto- and parietal regions of the brain (e.g. Kam et al., 2018). Studies on normal-hearing subjects have shown that more complex input contrasts (such as speech vs. non-speech) can yield longer latencies and decreased amplitudes (P300: Polich, 1987; MMN: Näätänen et al., 2007 for a review).

Early studies have shown that both ERPs are able to measure the central auditory processing function of CI users who became deaf either pre- or postlingually. These studies have shown that the components can be present or absent in individual CI users (MMN: Kileny, Boerst, & Zwolan, 1997; Kraus et al., 1993; Obuchi, Harashima, & Shiroma, 2012; P300: Groenen, Beynon, Snik, & Van den Broek, 2001; Obuchi et al., 2012). Furthermore, these studies have shown that the morphology of the ERP can differ when CI users are compared to normal-hearing controls, with CI users' ERPs showing altered amplitudes and prolonged latencies (MMN: Turgeon, Lazzouni, Lepore, & Ellemberg, 2014 2014; P300: Beynon, Snik, Stegeman, & Van Den Broek, 2005). In addition, correlations between the amplitude and duration of the ERPs and behavioural measures of speech perception have been found (MMN: Kelly, Purdy, & Thorne, 2005; Turgeon et al., 2014; P300: Beynon et al., 2005; Jacquemin, Mertens, Schlee, Van de Heyning, & Gilles, 2019), indicating that a low-level discrimination task (e.g., discriminating between two tones or syllables) can be related to more realistic speech perception tasks such as word intelligibility. Notably, most previous studies focused on either postlingually deaf CI users, whose auditory cortex has already had time to develop before onset of deafness, or prelingually deaf CI users with relatively late ages of implantation (AoI).

The current study focuses specifically on measuring auditory processing abilities in prelingually deaf, early implanted young adults (age range 16-25 years old), as operationalised by the MMN and P300 components. These young adults were among the first for whom early implantation with a CI device became regular practice. This means that they have long-term experience with a CI, as well as a good prognosis for developing peer-like auditory processing skills. This group provides a unique opportunity to gain insight into long-term implantation outcomes, as well as the impact of long-term implant use on the brain. Research in this group is scarce, primarily due to the fact that data on this group are only now becoming available. Interestingly, one study investigating speech perception and language outcomes, rather than auditory processing, of this group (15 years of CI experience) reported lower outcomes than a group of CI users with less long-term use (Ruffin et al. 2013). This is in line with subjective reports of clinicians emphasizing large individual differences in the speech perception and language outcomes of the prelingually deaf, early implanted young adults. Although certain risk factors (i.e., aetiology, mode of communication, age of

implantation) seemed to have accounted in part for the results of Ruffin et al. (2013), the role of auditory processing ability was not assessed, and has, to our knowledge, not yet been assessed as such in other studies. It is necessary to establish whether large variations in auditory processing are still present for these young adults. This variability may partially underlie the lower and variable speech perception and language outcomes mentioned above. Alternatively, there may be a discrepancy between auditory processing on the one hand, and speech perception and language abilities, on the other.

To our knowledge, there are no studies reporting on the P300 and MMN response in prelingually deaf, early implanted young adults, i.e. before the age of 6 years. A few studies report on prelingually deaf, early implanted subjects in their childhood or adolescence. Notably, many of those subjects would now belong to the age group of young adults as described in this study. As for the P300, studies on children and adolescents in the age range of 4-16 years old have shown that a P300 in response to speech contrasts (ba/da or hee'd/who'd) can be identified (Kileny et al. 1997; Beynon et al. 2002). It should be noted, however, that in the study of Kileny et al. (1997), a passive instead of an active listening paradigm was used to elicit the P300. They have also shown that relations with behavioural speech perception scores are present, where higher behavioural scores were correlated with a more robust P300 (Kileny et al. 1997; Beynon et al. 2002). Interestingly, when divided into two groups (poor vs. well performing) on the basis of behavioural speech perception scores (% correctly repeated mono-syllabic phonemes), the P300 response was either delayed or absent in poor performing children. In contrast, well performing children showed P300 responses similar to normal-hearing controls (Beynon et al. 2002). This suggests variance amongst implanted children in terms of their auditory processing skills.

The discrepancy between poor performers and good performers was replicated for the MMN component in prelingually deaf children and adolescents (7-17 years old). An MMN in response to speech contrasts (ba/da) was detected in 80-85% of well performing children, compared to only 16-20% of the poor performers (Singh et al. 2004). A more recent study reported that variability in MMN responses was related to language performance, and not to speech perception scores (Ortmann et al. 2013). Children (7-19 years old) with good language performance showed a peer-like MMN response, while children with low language performance showed a smaller MMN amplitude. One study found no difference between the amplitude of the MMN in children with CIs as opposed to normal-hearing controls (7-14 years old) (Watson et al. 2007). Studies on cortical maturation in this population suggest that the MMN is a robust component, regardless of age of implantation or longer experience. Liang et al. (2013) found a greater incidence of MMN responses as well as shorter latencies for children (1-6 years old) as early as six months, compared to the same children at three months after implantation. An MMN was also found in all participants (6-18 years old) in a study of Ponton et al. (2000). However, many of these children were noted to have become deaf at an age when the brainstem was likely to have matured.

The brief review above indicates that it is unclear whether variance still exists among the auditory processing abilities of prelingually deaf, early implanted young adults. Notably, with the exception of Ponton et al. (2000), these studies lack an objective assessment of whether ERPs are present or not. Furthermore, data on an individual level is not always reported in detail, and not all studies report a normal-hearing control group. These three aspects are important when answering any questions on variability in auditory processing. The children discussed in these studies are of a similar implantation generation as the young adults investigated in the current study. Importantly, however, the duration of CI use since implantation, and thus, experience with a CI, is significantly increased in our group, ranging from 13-21 years (median = 17.5 yrs). This contrasts with the durations of CI use reported in the above-mentioned studies, which range from 3 months to 15 years (Kileny et al. 1997; Beynon et al. 2002; Singh et al. 2004; Watson et al. 2007; Liang et al. 2013; Ortmann et al. 2013). If auditory function indeed develops with implant experience, we would expect our young adults to show less variability in auditory processing as measured by the P300

and/or MMN component in response to a basic discriminative contrast.

Not many studies have compared outcomes of the P300 and MMN in the same participants (Obuchi et al. 2012). The comparison serves a clinical goal. In the past, studies have discussed the clinical potential of either component to mark auditory function development of individuals with cochlear implants (Kileny et al. 1997; Johnson 2009; Turgeon et al. 2014). The MMN is significantly advantageous because it can be measured inattentively, and thus used with younger cochlear implant users. The task-requirements of the P300 restrict measurements in CI users to children from ages 3-4 onwards (Johnson 2009). However, robust results have been found for the P300 with measurements much shorter (12 minutes, Oviatt and Kileny 1991; Groenen et al. 2001; Beynon et al. 2002, 2005) than for the MMN (25-40 minutes, Kraus et al. 1993; Singh et al. 2004; Turgeon et al. 2014). To evaluate the clinical potential of both components to measure auditory processing in individuals, we kept the number of stimuli, and thus the duration of each experiment, equally short.

The primary goal of the current study is to examine how prelingually deaf, early implanted young adults (16-25 years old) process sound using basic input contrasts. This basic knowledge is necessary before exploring the limits of their processing abilities using more complicated, real-life inputs. We measured the P300 as well as the MMN component using two input contrasts, a ba/da syllable contrast and a 500/1000Hz tone contrast. Duration of the measurements for both components was kept to approximately 10 minutes each. Presence of the ERP effects, as well as their amplitudes and latencies, were assessed statistically on an individual and group level. We, furthermore, measured the components in a group of age-matched normal-hearing controls. As a secondary goal, for CI users, behavioural speech perception scores as obtained in the clinic, as well as duration of deafness, were related to the amplitude of the component that provided robust results, to explore relations between neurophysiological and behavioural outcomes. As such, our study has implications for understanding the long-term implant outcome of prelingually deaf, early implanted CI users, as well as how experience with a CI affects the development of the central auditory function. In addition, it provides insight into the neurophysiological correlates underlying variability among this population. Lastly, we hope to draw conclusions about the clinical usefulness of the P300 and MMN component to measure auditory processing skills.

2. Methods

2. 1 Participants

Eight Dutch prelingually deaf young adults with a CI (mean age 19.9 years old) were recruited through the otolaryngology department. Table 1 describes their characteristics. All of the adolescents had profound bilateral hearing loss. Exclusion criteria consisted of having an IQ < 85, a developmental or neurological disorder, or any serious head-trauma in the past. All participants underwent a complete insertion of cochlear implant array, used the same implant processor (Cochlear Corp, Australia), and none of them used additional conventional hearing aids. All used speech as the main mode of communication, except for participant 6 (half-half). For the participants with bilateral implants, EEG was recorded with only one implant on (their preferred one). Two standardized language scores are reported in Table 1, the PPVT-III-NL (Dunn and Dunn 2005), a test of receptive word knowledge, and the CELF-4-NL Recalling Sentences sub-score (Kort et al. 2008), a test of semantic, morphological and syntactic competence. For completeness, in Table 1 we report not only the speech perception scores in quiet but also in noise.

Table 1. *Participant characteristics.*

ID	Sex	Age (yrs)	Educ. Level	Etiology	AoI (yrs)	DD (yrs)	Bi/ Uni	CI use per day (hrs)	Dur. of CI use (yrs)	Perc. in quiet (%)	Perc. in noise (%)	PPVT-III	CELF-4 (recalling sentences)
1	M	24.9	5	Meningitis	3	2.08	Uni	14	21.9	88	32	71	9
2	M	25.6	6	Meningitis	3.6	2.17	Uni	16	23	75	25	88	4
3	M	23.2	5	Congenital	2.7	2.7	Uni	14	20.5	87	38	83	6
4	M	18.6	4	Meningitis	1.6 and 1.6	0.08	Bi	15	17	100	70	85	3
5	M	16.4	4	Prematurity	2.1 and 5	2.08	Bi	12	14.3	100	75	103	4
6	F	16.5	4	Unknown	3	3	Uni	16	13.5	87	55	<55	1
7	F	18.3	6	Meningitis	1	0.5	Uni	16	17.3	96	51	99	12
8	M	19.6	6	Congenital	5.8 and 19	5.8	Bi	14	13.7	95	78	102	6

Note. For the CELF-4 recalling sentences test, 19-year old norm-scores were used for participants aged >19 as the CELF norm scores do not go higher than 19. The PPVT could not be administered for one participant, but was estimated by the speech-language therapist at <55. For PPVT-III, the standard score is reported. For CELF-4, the recalling sentences standard score is reported. Perception in noise was measured with and S/N ratio of +10dB. Yrs = years; Educ. = Education; AoI = age of implantation; DD = duration of deafness; Bi/Uni = bilateral or unilateral implantation; CI = cochlear implant; Hrs = hours; Dur. = duration; Perc. = perception; PPVT = Peabody Picture Vocabulary Test; CELF = Clinical Evaluation of Language Fundamentals.

A group of 14 Dutch normal-hearing participants was tested as a control group (mean age 21.4 years old, ranging from 18-25; 6 males). Similar exclusion criteria applied to this group. In order to better match the groups we restricted the education levels of the normal-hearing participants to level 6 (out of 7), according to the Dutch neuropsychological education level coding (Hendriks et al. 2014). Age did not differ significantly between groups, as tested using a Wilcoxon rank-sum test (W = 73.5, p = .24). All participants received monetary compensation for their participation. This research was approved by the ethical review board of the Radboudumc.

2.2 Materials

Two attention states, an inattentive and an attentive state, were designed to elicit the MMN component and the P300 component respectively. In both states, the auditory oddball paradigm was used. Two stimuli types were used: a frequency contrast (a 500 vs. 1000 Hz tone) and a consonant contrast (syllables /ba/ vs. /da/). For the frequency contrast, a 500 Hz and a 1000 Hz pure tone burst of 120 ms each were generated with Praat (Boersma & Weenink, 2020; settings: stereo channels, 20 ms linear rise and fall time, 80 ms plateau time, sampling frequency of 44.1 kHz). The 500 Hz tone was used as the standard stimulus, the 1000 Hz tone was used as the deviant stimulus. For the consonant contrast we used the /ba/ syllable as the standard and the /da/ syllable as the deviant stimulus, each 170 ms in duration. These were synthesized stimuli as used in Beynon et al. (2005), adapted from Groenen et al. (2001). We refer to these articles for a more detailed description.

2.3 Procedure

Before each set of ERP measurements, participants performed two short reaction-time (RT) tasks to assess subjective discrimination (see Figure 1). The same stimuli as in the ERP measurements were randomly presented 20 times (50% standard, 50% deviant). After a short practice, participants had to press the left button when they heard the standard stimulus, and the right button when they heard the

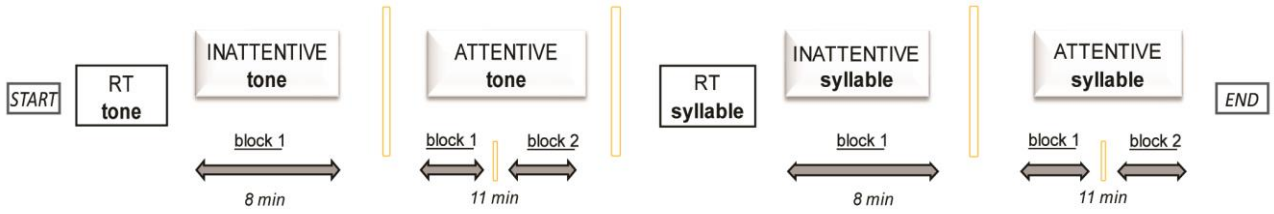

Fig 1. Outline of experimental procedure. Yellow lines indicate breaks. The figure presents an outline for one version (version A). In version B, tones and syllables are reversed. RT = reaction time.

deviant stimulus. Reaction times were analysed. After this task, participants were asked to judge the loudness of the stimuli on a 5-point scale with 1=too soft and 5=too loud. Subsequently, CI participants were given the opportunity to adjust their speech processor in case of any discomfort listening to the stimuli. None of the CI users adjusted their processors. Loudness was rated as 2 ('a bit soft', 1 participant) or 3 ('good', 7 participants).

The entire session had six parts. It began with one of the contrasts (i.e., either tone or syllable) in the following order: subjective discrimination, ERP inattentive state, ERP attentive state, followed by the same order for the other contrast. Figure 1 shows how these parts were administered in version A of the task (given to half of the participants), as well as their duration. In version B, the order of appearance of the consonant and frequency type contrast was swapped.

ERP measurements were performed in a sound-proof EEG lab. Subjects were seated in a comfortable chair. Sound was presented via speakers that were approximately 2.5 m away from the participant. The sound presentation at ear-level was kept at 65 dB at all times, as measured by a measuring amplifier (Bruel & Kjaer Type 2610) and a microphone (Bruel & Kjaer Type 4192). Stimuli were presented with Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com). For both the inattentive and the attentive measurements, the standard stimuli occurred at a probability rate of 85%. In each of the four ERP measurements, there were two blocks of 220 stimuli, resulting in a total of 440 stimuli per measurement. Per block, 20 standard stimuli were presented first, followed by 30 deviant stimuli that were randomly embedded in 170 standard stimuli. It was made sure that between every two deviant stimuli, at least three standard stimuli were presented. We controlled for list-specific effects by generating 3 stimuli lists per ERP measurement (12 in total) and assigning these at random to the participants. The lists were generated with Mix (Van Casteren and Davis 2006), and adjusted by hand to remove repetitive patterns that arose even after randomization.

During the inattentive measurements, participants watched two different snippets of a silent film with emotionally neutral content. They were instructed not to pay attention to the sounds presented. Stimuli were presented with an inter-stimulus interval (ISI) of 1000 ms with 10% jitter. During the attentive measurements, participants were instructed to count in their heads the number of deviant stimuli that occurred. At the end of each block, they were asked to type in how many deviant stimuli they had heard (30 per block). Stimuli were presented with an ISI of 1500 ms with 10% jitter. We chose a longer ISI here because the P300 is a component that spreads out over a longer time window, and we did not want to risk overlap in the neurophysiological responses to the stimuli. The participants were allowed to close their eyes during the attentive measurements, but they were told to be careful not to fall asleep.

2.4 EEG-recordings

Continuous EEG was recorded using 24 active electrodes (10-20 arrangement), referenced online to Cz. The ground electrode was placed at AFz. Electrode places around the cochlear implant(s) and its contralateral side (CP6; T8; P8; TP10; TP9; T7; CP5; P7) were not filled. This configuration was kept for both normal-hearing participants and CI users for consistency. EOG was recorded from two

horizontal electrodes, placed at the left and right temples, and two vertical electrodes, placed above and below the left eye. Electrode impedance was kept below 20 kΩ. EEG and EOG signals were sampled at 500 Hz, filtered online between 0.016 Hz and 125 Hz.

2.5 Data Analysis

2.5.1 EEG pre-processing

We analysed the EEG data using the toolbox Fieldtrip (Oostenveld et al. 2011). The EEG signal was re-referenced offline using the common average method. Data were cut into segments of -0.3 to 0.7 seconds (inattentive measurements) and -0.3 to 1 seconds (attentive measurements) relative to stimulus onset. Vertical and horizontal EOG were re-referenced following a bipolar montage. The data were de-trended. Data were filtered with a low-pass filter of 80 Hz. For removal of eye-artefacts, as well as CI-artefacts, we performed an independent component analysis (ICA) (Jung et al. 2000) over all four ERP measurements together. We visually inspected component topographies, time courses and corresponding EEG segments to remove eye-movement components. ICA components reflecting eye movements were discarded. Data of the inattentive frequency condition of one control participant (pp9) were missing due to an experimenter error.

We developed a procedure for the removal of possible CI-artefacts. The implant artefact on the EEG is independent of brain processes or task design, as it is a reaction of the implant electrode array to the presentation of a sound. The artefacts are described in the literature as a systematically occurring increased or decreased amplitude peak (Gilley et al. 2006; Viola et al. 2012; Turgeon et al. 2014). The artefacts did not occur in each CI user, but only in some of them. To attenuate these CI artefacts, we averaged the time-locked ICA components over all trials (see Han et al., 2016 for a similar procedure). Given that the CI artefact has a systematic timing and spatial distribution over all trials, a few ICA components will specifically reflect this artefact. These components can be identified and removed. We performed this artefact inspection for all participants with a CI. We checked whether the spatial topographies and waveform morphologies of the ICA components resembled those of earlier papers (Gilley et al. 2006; Viola et al. 2012). ICA components were only removed if they occurred within 0-150 ms after stimulus presentation. Following this procedure, we removed 1 or 2 ICA components for 4 out of 8 CI users. It is unlikely that we removed biological activity related to the P300 or MMN, because the neural processes underlying these components are known to occur later than at stimulus presentation. Besides the artefact, auditory presentation is the only factor that also occurs at the same time point in all conditions. It is, therefore, possible that biological processes related to this auditory presentation (such as the N1 or P2) are filtered out by the CI-artefact rejection procedure. However, these are not the processes we focus on in this study.

After ICA, the data (per participant) were split into the four individual parts of the experiment. We performed a semi-automatic artefact rejection procedure on each part separately to remove any remaining artefacts not removed by ICA. For each participant per part, on average 17 (CI users) and 18 (controls) out of 440 trials were discarded. Channels that were noisy were noted down for each participant. Later on, this information was taken into consideration when selecting the channels to perform statistics on.

2.5.2 ERP Statistics

The artefact-free data were used to compute individual-subject and group ERPs. The ERPs were computed by averaging waveforms across trials per stimulus condition (standard vs. deviant), per task by contrast condition (attentive-frequency, attentive-consonant, inattentive-frequency, inattentive-consonant) for each individual. Group averaged ERPs were calculated for each group separately (normal-hearing and CI user). The data were filtered with a low-pass filter of 50 Hz and down-sampled to 512 Hz. We used cluster-based permutation tests (Maris and Oostenveld 2007) to statistically evaluate the presence of the ERPs in all four conditions per group. This was done using a within-subjects design in which the grand average response to the standard trials was compared to the grand average response to the deviant trials. Statistics were performed as follows: first a dependent samples t-test was calculated for every electrode by

time-point. The comparison was based on all time-points from 150 ms to 800 ms post-stimulus onset for the attentive task-condition and 50 ms to 350 ms for the inattentive task condition. Statistical tests were based on channels 'CP1', 'CP2', 'P3', 'P4', 'Pz', 'C3', 'C4' for the attentive task-conditions and 'Fz', FCz', 'F3', 'F4', 'FC1' and 'FC2' for the inattentive task conditions. Decisions for these time-points and channels were based on previous literature describing the location and time course of these effects (e.g. Näätänen et al., 2007; Polich, 2007), and on the exclusion of channels that were deemed excessively noisy during data acquisition. The electrodes/time points were clustered based on spatial and temporal adjacency at an alpha level of 0.05. Channels had on average 3.3 neighbours. Cluster-level statistics were calculated by taking the sum of the t-values within every cluster. The largest cluster-level statistic was taken for evaluation under a permutation distribution. This distribution under the null hypothesis of exchangeability between conditions was constructed by randomly re-assigning the standard trial and the deviant trial labels to the original individual ERP waveforms, followed by the construction of spatiotemporal clusters, in the same way as for the observed data. 1000 permutations were used to make the permutation distribution. The p-value was determined as the proportion of random permutations that yielded a more extreme cluster statistic than the cluster in the original data (Monte Carlo p). The alpha-level was set to 0.05 (two-sided test). If the p-value was smaller than alpha, the difference between the standard and the deviant trials was deemed significant.

We also performed individual-participant ERP analyses per stimulus-condition (standard vs. deviant) per task by contrast condition (attentive-frequency, attentive-consonant, inattentive-frequency and inattentive-consonant). To test for ERP presence, we used the same cluster-based permutation procedure as described above for the group analysis (independent samples t-tests were used over trials). That is, we tested the difference between the standard and the deviant waveforms per individual at the single-trial level.

2.5.3 Amplitude and latency analyses

Pre-empting the results, the attentive task-condition yielded robust results for all participants for both contrast conditions, while the inattentive task condition did not (see Results in section 3.2.1 below). Therefore, we performed the amplitude and latency analyses only on the attentive task-condition data. To avoid the different sample sizes of the two groups, we took a sub-sample of normal-hearing participants (n = 8) to match the sample of CI user participants (n = 8). This sub-sample firstly was matched to the CI user group on the order in which the contrast conditions appeared during data collection. Then, each CI user was matched to a control on at least one of the following three criteria: education level, age, or sex. In the end, the sub-sample consisted of normal-hearing controls 1, 3, 4, 5, 6, 8, 11 and 12. Their significant clusters and time-windows from the individual ERP statistics are reported in Appendix A. We performed the amplitude and latency analysis over one electrode: 'Pz'. This decision was based on earlier studies that also performed their analyses over one or two electrodes (Groenen et al. 2001; Beynon et al. 2002, 2005; Obuchi et al. 2012). In this way, we would be able to more accurately relate our findings to previous ones.

2.5.3.1 Amplitude analysis. We calculated the mean amplitude (MA) over the difference waveforms and assessed differences between groups, per contrast condition. For the frequency condition we calculated MA over 220-705 ms and for the consonant condition we calculated MA over 315-760 ms. These windows were based on the minimum and maximum time points between which the individual ERPs were significant, as present in the cluster-based statistics (see Results below). Mean differences between groups were tested using a non-parametric Wilcoxon rank-sum test and mean differences between contrast conditions were tested using a Wilcoxon signed-rank test. A Wilcoxon rank-sum test was furthermore used to explore an interaction effect between contrast condition and group. We furthermore used the Fligner-Killeen test to test for homogeneity of variances between groups.

2.5.3.2 Latency analysis. Latency was calculated for groups and contrast conditions. Measuring ERP latency differences on a single-subject level can be problematic. Firstly, the relationship between the underlying component and the local shape of a component is not obvious (Luck 2005). Secondly, the signal-to-noise level is low due to averaging over a small amount of trials. Therefore, we measured latency differences with a jackknife-based approach (Kiesel et al. 2008). In this approach, latencies are scored for each of *n* grand average waveforms in a group, with each grand average waveform computed from a subsample of *n-1* individual waveforms. Each participant in a group is omitted from the analysis once, and each latency score is calculated not from a single-subject waveform, but from a grand average. Using the peak latency of the component as a scoring method has been deemed misleading and arbitrary in the ERP literature (Luck 2005; Woodman 2010). Therefore, the scoring was done as follows (based on Kiesel et al., 2008): First, we determined a latency onset criterion from 300 ms to 700 ms. This time window was chosen because the peaks of all our participants fell in this window. The P300 ERP was determined as the first positive going peak from the set onset criterion (300 ms in our case). Then, for each subsample, ERP latency was calculated using a relative criterion technique: "the time-point at which the amplitude reaches a constant, pre-specified percentage of the peak value" (Kiesel et al., 2008, page 252), in our case 50% (see simulation results in Kiesel et al., 2008). We submitted the latency outcome values of this jackknife-based approach to a 2x2 repeated measures analysis of variance (ANOVA; group x condition). The F-value of this ANOVA was corrected according to the following formula: $Fc = \frac{F}{n-1}$ (Ulrich and Miller 2001), where Fc stands for the corrected F-value, and *n* denotes the number of observations in each cell. It was not possible to assess individual differences using the Jack-knife based approach. We therefore also calculated the latency values per single-subject waveform (with the same scoring method and settings) and used the Fligner-Killeen test to test for homogeneity of variance between-groups. Although we are aware of the pitfalls of the single-subject waveform method, we wanted to be as complete as possible in exploring differences in variability per group.

2.5.4 Correlational measures

Lastly, mean amplitude of the P300 (as explained in 2.5.3.1 Amplitude analysis) was correlated with behavioural speech perception scores and with duration of deafness (DD) using a non-parametric Spearman's rho test. In the standardized speech perception task, participants are asked to repeat (monosyllabic) wordlists (NVA lists, Bosman, Wouters, & Damman, 1995). The percentage correctly repeated phonemes is used as an outcome measure. All scores were obtained within half a year of conducting the EEG experiment, except for the scores of 2 users (5 and 1 year(s) prior). These were still included in the analysis because the perception scores were assumed to have relatively stabilized over the years. The three bilaterally CI users were tested with the same CI on as they chose to have on during the EEG experiment.

3. Results

3.1 Behavioural assessments

3.1.1 Reaction-time experiment

Results for the behavioural reaction-time task, per group per contrast condition, are displayed in milliseconds in Figure 2A. A two-way ANOVA revealed a main effect of group ($F(1,40) = 15.56$, $p < 0.001$). The normal-hearing group pressed significantly faster (M = 458, SD = 109) than the CI user group (M = 588, SD = 162) in both contrast conditions. There was also a main effect of contrast condition ($F(1,40) = 21.17$, $p < .001$). Both groups pressed significantly faster in the frequency contrast condition (M = 432, SD = 125) than in the consonant contrast condition (M = 579, SD = 124). Descriptively, the figure shows that the CI user group tends to be slower than the normal-hearing group in the consonant contrast condition. This interaction effect was, however, not significant ($F(1,40) = 2.72$, $p = .100$).

3.1.2 Counting deviants

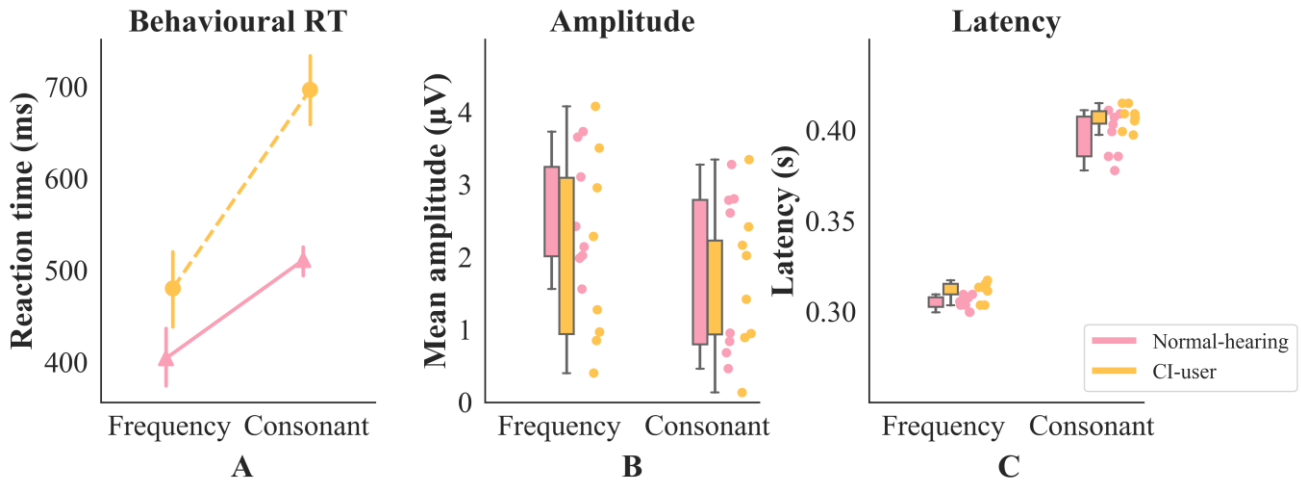

Fig. 2. Behavioural reaction time (RT) and P300 results. A. Behavioural RT task results. Mean RT and standard error in milliseconds as a function of group (Normal-hearing (n=14), CI users (n=8)) and contrast condition (frequency, consonant). B. Amplitude results per group (Normal-hearing (n=8), CI users (n=8)) per contrast condition, calculated over electrode 'Pz'. Boxplots and individual data points show the amplitude in microvolt of the difference waveforms per group per contrast condition, as measured in the attentive task condition (P300**)**. C. Latency results per group (Normal-hearing (n=8, CI users (n=8)) per contrast condition, calculated over electrode 'Pz'. Boxplots and individual datapoints show the latency outcome value in seconds, as measured in the attentive task condition (P300). Results were obtained using a Jack-knife based approach and a 50% relative criterion scoring technique with a time-window of 300-700 ms. RT = reaction time; CI = cochlear implant.

During the attentive measurements, participants were asked to count the number of deviants they heard in their head, and report this after each block. In total, 30 deviants could be counted in each block, with two blocks per contrast condition. The normal-hearing group had a mean of 29.60 (SD = 2.47) over both blocks in the frequency contrast condition, and a mean of 29.82 (SD = 1.70) over both blocks in the consonant contrast condition. The CI user group had a mean of 30.50 (SD = 1.32) over both blocks in the frequency contrast condition and a mean of 29.38 (SD = 2.00) over both blocks in the consonant contrast condition.

3.2 EEG results

3.2.1 Individual and group ERP results

Individual and group ERP results per task condition per contrast condition, averaged over the electrodes 'Fz', FCz', 'F3', 'F4', 'FC1' and 'FC2' for the inattentive task condition (MMN), and 'CP1', 'CP2', 'P3', 'P4', 'Pz', 'C3', 'C4' for the attentive task condition (P300) are displayed respectively in Figures 3 and 4. In both figures, the difference waves (average standard minus deviant trials) of all individuals (CI=8, NH=14), as well as the grand-average group difference wave (in thick line), and corresponding scalp topographies, are plotted per group (CI, NH) per contrast (frequency, consonant). The time-window(s) in which the grand-average difference waves were significant are shown in dashed lines.

In the attentive task condition, time-locked EEG-activity for the deviant trials in the normal-hearing group was significantly more positive in amplitude than activity for the standard trials, for both the frequency (Monte Carlo p = .002) and the consonant contrast (Monte Carlo p = .002). The most prominent differences for the frequency contrast were found in the 270-690 ms time-window, while for the consonant contrast they were found in the 390-690 ms time-window. The CI user group yielded similar results. A significant positive deflection was found for the frequency (p = .002) and the consonant contrast (p = .002), with most prominent differences found in the 270-600 ms time-window for the frequency, and 350-660 ms time-window for the consonant contrast. The time-windows correspond roughly to the P300 component as

Table 2. *Number of individuals per group per contrast condition (n) that showed a statistically significant P300 and/or MMN as a function of the total N (n/N). CI = cochlear implant; MMN = Mismatch Negativity.*

	Frequency condition		Consonant condition	
	MMN	P300	MMN	P300
Normal-hearing	6/13	14/14	1/14	14/14
CI-users	6/8	8/8	1/8	8/8

described in the literature (usually present from 350-500 ms).

For the inattentive task condition, time-locked EEG activity for the deviant trials was significantly more negative in amplitude than activity in the standard trials, but only for the frequency contrast. This was found for the normal-hearing group (Monte Carlo p = .020), as well as for the CI user group (Monte Carlo p = .020), with most prominent differences found in the time-windows 90-160 ms (NH) and 120-200 ms (CI). The time-windows correspond roughly to the MMN component as described in the literature (usually present from 150-250 ms). For the consonant contrast, significant negative deflections were found for neither the normal-hearing group (p = .090), nor the CI user group (p = 1.000).

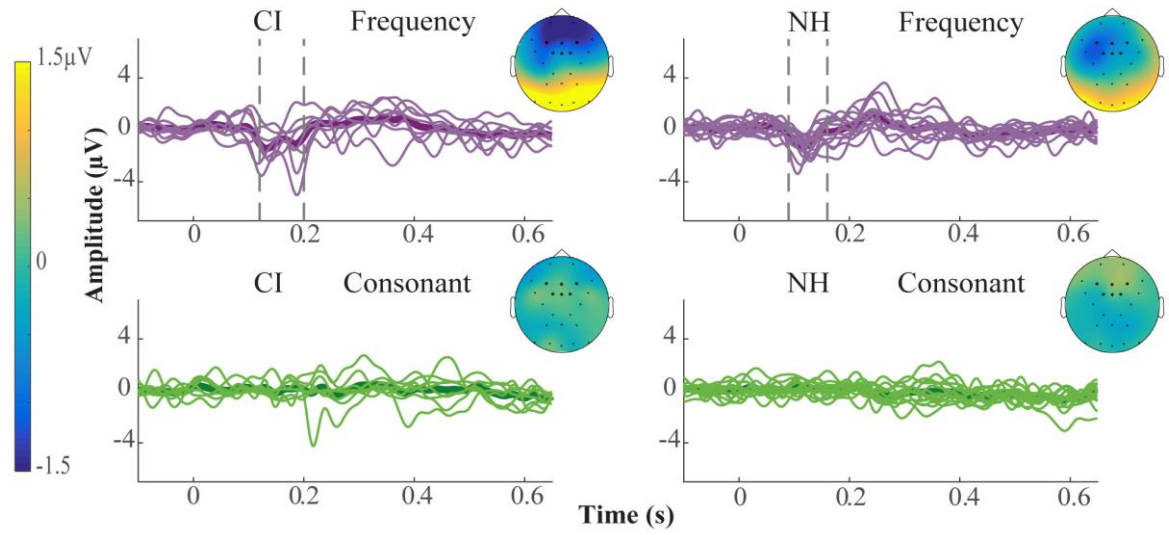

Fig. 3. ERP results of the inattentive measurements (MMN) and corresponding scalp topographies. Grand average (thick line) and individual (thin lines) difference waves are shown for both groups (CI-users, N = 8), normal-hearing (N = 13 for frequency, N = 14 for consonant) and contrast conditions (frequency, consonant). Dashed lines indicate the significant cluster window of the *grand average* waveform. For significant individual cluster timepoints please consult Appendix A. Scalp topographies are shown corresponding to the time-windows in which a significant difference between standard and deviant trials was found. Star dots denote the channels over which the cluster-based permutation tests were performed. Thin dots denote the remaining channels in the EEG cap configuration. Color bars represent amplitude in microvolt. For the consonant contrasts, we used the time-windows of the frequency contrast in both groups (90 – 200 ms). ERP = Event Related Potential; MMN = Mismatch Negativity; CI = cochlear implant; EEG = Electroencephalography.

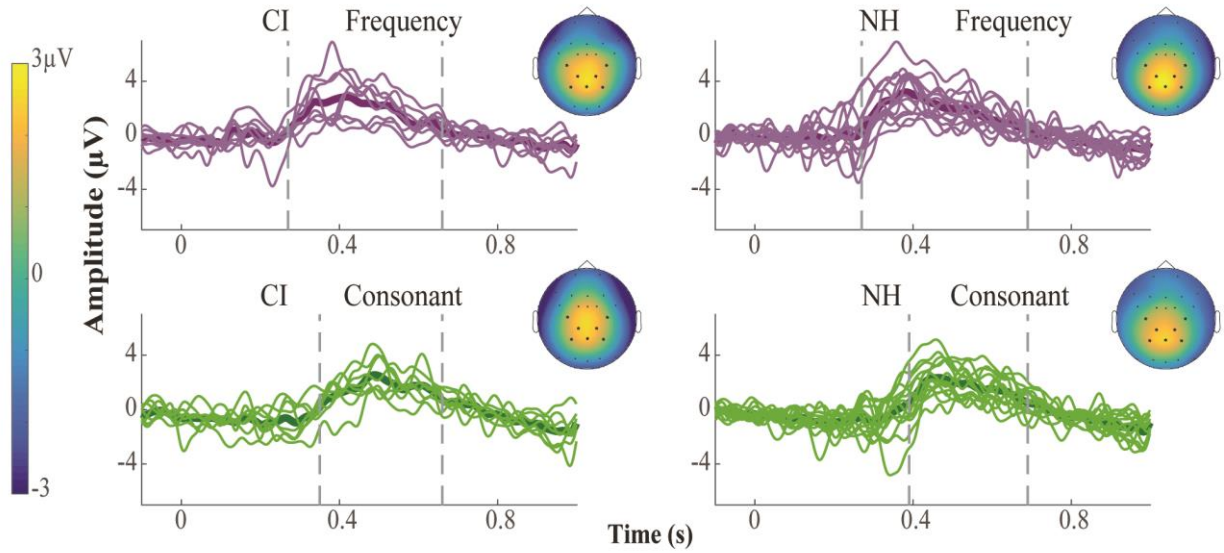

Fig. 4. ERP results of the attentive measurements (P300) and corresponding scalp topographies. Grand average (thick line) and individual (thin lines) difference waves are shown for both groups (CI-users N = 8), normal-hearing (N = 14) and contrast conditions (frequency, consonant). Dashed lines indicate the significant cluster window of the *grand average* waveform. For significant individual cluster timepoints please consult Appendix A. Scalp topographies are shown corresponding to the time-windows in which a significant difference between standard and deviant trials was found. Star dots denote the channels over which the cluster-based permutation tests were performed. Thin dots denote the remaining channels in the EEG cap configuration. Color bars represent amplitude in microvolt. ERP = Event Related Potential; CI = cochlear implant; EEG = Electroencephalography.

The number of individuals per group per contrast condition that showed a significantly present P300 or MMN effect at the single-trial level are shown in Table 2. A waveform was deemed to have a present P300 or MMN effect if there was at least one positive (for the attentive task condition) or one negative (for the inattentive task condition) significant cluster in the pre-specified time-windows. The time-window(s) in which the (individual) difference waves were significant for each individual, as well as their p-values, can be viewed in Appendix A. Due to the marginal robustness of the MMN responses in both groups, we decided to perform amplitude and latency measurements over data from the attentive-task condition only.

3.2.2 Amplitude and latency results

3.2.2.1 Amplitude results

Boxplots and individual data points of the mean amplitude as measured in the attentive measurement condition (P300) over electrode 'Pz', per group per contrast condition, are displayed in Figure 2B. The Wilcoxon rank-sum test (for group) and signed-rank test (for condition) did not show significant differences between groups and contrast conditions ($W = 107$, $p = .45$ for the group comparison, $V = 38$, $p = .12$ for the contrast condition comparison). To test for the interaction effect of group by condition we calculated the difference of the frequency minus the contrast condition for each individual. Consequently, we tested the difference as a function of group, again using the Wilcoxon rank-sum test, revealing no interaction effect ($W = 20$, $p = .23$). Furthermore, the Fligner-Killeen test showed no main effect of group or condition on the variance within groups ($\chi2\ (1) = 0.42$, $p = .51$ for group, $\chi2\ (1) = 0.02$, $p = .90$ for condition), nor was there a significant interaction between group and condition ($\chi2\ (3) = 4.55$, $p = .20$) on the variance within groups. Thus, there was no evidence indicating that the variance in P3 amplitude between groups was greater in one contrast condition as opposed to the other.

3.2.2.2 Latency results

Boxplots and individual data points of latency as measured in the attentive measurement condition over electrode 'Pz', per group per contrast condition, are displayed in Figure 2C. Results were obtained using a Jack-knife based approach with a 50% relative criterion scoring technique and a time-window of 300-700 ms. A two-way ANOVA revealed a main effect of condition ($F(1,28) = 23$, $p < .001$). The latency was significantly later in the consonant ($M = 402$, $SD = 10$) than in the frequency contrast condition ($M = 308$, $SD = 10$) across the two groups. There was no main effect of group ($F(1,28) = 0.18$, $p = .67$), nor an interaction effect of group by condition ($F(1,28) = 0.004$, $p = .95$). The Fligner-Killeen test did not indicate heterogeneity of variance between groups ($\chi2(1) = 0.55$, $p = .46$) and between contrast conditions ($\chi2\ (1) = 0.65$, $p = .41$), and there was no significant interaction effect between group x contrast condition ($\chi2\ (3) = 2.8$, $p = .41$). Thus, we found no evidence indicating that the variance in P3 latency between groups was greater in one contrast condition as opposed to the other.

3.3 Correlations between speech perception, duration of deafness, and amplitude and latency of the attentive measurements

Results of the relationship between the behavioural speech perception scores, duration of deafness, and mean amplitude of the attentive measurements (P300) per contrast condition are displayed in Figure 5. As for speech perception, no significant relation was found between mean amplitude of the P300 components and the behavioural speech perception scores in the frequency condition ($r = -.26$, $p = .53$). For the consonant condition, however, there was a strong correlation between the mean amplitude of the P300 component and the behavioural speech perception scores ($r = .70$). However, this effect did not pass the alpha-level threshold of .05 ($p = .05$). The relation is positive: the higher the behavioural speech perception score of the individual, the greater the amplitude of the P300 component. As for duration of deafness, we found no significant relation between mean amplitude of the P300 components and duration of deafness in the frequency condition ($r = -.33$, $p = .41$). There was, however, a significant and strong correlation between the

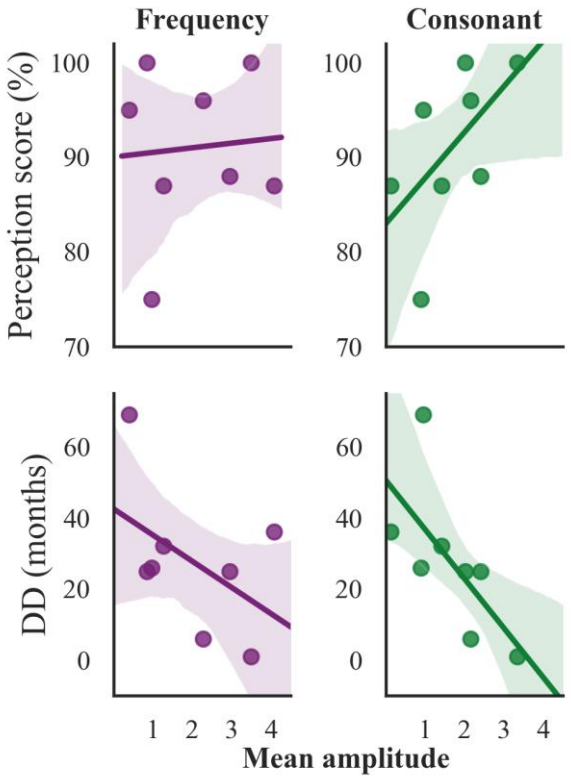

Fig. 5. Relationships between behavioural speech perception, duration of deafness, and amplitude of the attentive measurements (P300). Scatterplots showing the correlation between the behavioural speech perception score in % (top), duration of deafness (DD) in months (bottom) and the mean amplitude in microvolt for each contrast condition (left: frequency, right: consonant). Each dot indicates one individual. Lines indicate the ordinary least squares regression lines; shaded areas indicate the 95 % confidence intervals.

mean amplitude of the P300 components and duration of deafness in the consonant condition ($r= -.83$, $p = .009$). The relation is negative, i.e., the shorter a CI user has been deaf, the higher the amplitude of the P300 component. We furthermore performed non-parametric correlations on latency as measured using the single-subject waveform approach. These did not correlate with behavioural speech perception scores or duration of deafness, in either condition (duration of deafness and latency for the frequency contrast: $r = .19$, $p = .64$ and the consonant contrast: $r =.06$, $p = .88$; behavioural speech perception and latency for the frequency contrast: $r = -.15$, $p =.75$ and the consonant contrast: $r = -.41$, $p = .30$).

4. Discussion

This study evaluated the auditory discrimination of a frequency (500 vs. 1000Hz tone) and a consonant (/ba/ vs. /da/ syllable) contrast in a group of early implanted, pre-lingually deaf CI-users and a group of normal-hearing peers. Our aim was to understand whether variations in the auditory processing of these contrasts are still present for early-implanted, long-term CI users. We used an attentive and an inattentive odd-ball paradigm to elicit P300 and MMN components as measured with EEG and state-of-the-art techniques to analyse the data. Measurement durations were kept equally short (approximately 10 minutes) to be able to compare both components in their ability to measure auditory processing functioning in the clinic.

In the inattentive-task paradigm (MMN), we did not find a robust presence of the MMN component in our sample. While in the frequency contrast condition half of the CI users and normal-hearing participants showed a significant difference between the standard and deviant waveforms in the expected time window, in the consonant contrast only one participant in each group showed the effect. The similar pattern of results for both the CI-user and the normal-hearing group points towards an inability to elicit the MMN with our procedure in participants in general, as opposed to this effect being due to differences in auditory function. The explanation for this failure to elicit the component is likely to be the lack of sufficient signal-to-noise ratio, due to the short measurement duration that we chose with the purpose of clinical application (but see Obuchi et al., 2012 that used only 3-minute recordings). Because parameters of the MMN have been shown to increase or decrease with stimulus complexity, it is possible that the difference in robustness between the frequency and consonant conditions can be explained by a combination of the short measurement duration and a more complex contrast condition. In the attentive-task paradigm (P300), all individuals in the CI-user group and the normal-hearing group showed a significant difference between the standard and the deviant waveforms in response to the consonant and the frequency contrasts. This indicates that all individuals were able to perform auditory discrimination of both stimuli contrasts.

These results suggest that when measurements are kept equally short in duration to increase clinical value, the P300 response is a more sensitive and reliable component than the MMN response to capture individual auditory processing abilities. The quantifiable statistical approach to analyse the attentive measurements on an individual level, furthermore, provides a window for future research in which the P300 response can be used with different inputs (i.e. auditory discrimination in quiet and in noise), to measure variability in auditory maturation and processing ability longitudinally after implantation. One of the reasons why the MMN would be advantageous in the clinic is that it does not require attention. Our study highlights the trade-off between robustness of the measurement with a short duration and age of first possible measurement.

To complement our cluster-based analyses on the presence of the ERPs, we performed additional amplitude and latency analyses for the attentive (P300) condition, to measure altered and/or slower processing of the contrasts. We found no evidence for a difference between the P300 amplitude of the group of CI users and the normal-hearing group in either contrast condition. Furthermore, we did not find evidence for a larger difference in variance within the CI user group as opposed to within the normal-hearing group. A similar pattern of results was found for the latency of the P300 component. The finding that a P300 response was present in individual CI-users is in line with earlier research on both pre-and post-lingual CI users, although only with the ERP results of well-performing users (characterised on the basis of clinical speech perception scores, Beynon et al., 2002; Groenen et al., 2001). We therefore conclude that auditory discrimination ability as measured with the P300 response is to a certain extent aligned with (a coarsely defined) level of behavioural performance. That said, when we compare our CI users and normal-hearing controls on reaction time in a behavioural discrimination task (a more fine-grained measure), we show that at a behavioural level, the CI user group is slower than the normal-

hearing group to discriminate between the contrasts.

To seek additional evidence for the assumption that the measured P300 component relates to auditory processing, our secondary goal, we related our P300 results to clinical speech perception scores (% correctly repeated monosyllabic phonemes) and duration of deafness (i.e., onset of deafness until time of implantation). We firstly found, for the consonant contrast only, that there was a robust relation between duration of deafness and the amplitude of the P300 response. The longer a CI user has been deaf before implantation, the lower their P300 amplitude is in response to (the discrimination of) speech stimuli, implying that it is harder for this individual to discriminate between these speech stimuli. This finding is in line with the claim that the auditory cortex is flexible enough to adapt to speech input after implantation, but much more so when implantation is performed early in development (Sharma et al. 2002; Eggermont and Ponton 2003; Sharma and Dorman 2006). This notion of a sensitive period for implantation is well established in the literature on obligatory cortical auditory evoked potentials such as the N1 and P2 (Sharma et al. 2002; Eggermont and Ponton 2003; Sharma and Dorman 2006), but has not often been confirmed using the discriminative evoked potential P300. Lower speech perception scores seemed to be related to a lower amplitude of the P300 response for the consonant contrast, but the small sample size limited the statistical power of this analysis. This correlation would mean that the harder it is to perform auditory discrimination between the phonemes (/ba/ vs. /da/), the harder it is to repeat monosyllabic words. This interpretation assumes that the process underlying the P300 amplitude indeed is auditory discrimination ability. However, while discrimination is necessary, it is not sufficient for the P300 to appear. It is possible that, in addition, other processes such as working memory or attention allocation play a role in both measures (i.e., P300 amplitude, as well as repetition of monosyllabic words, cf. Polich, 2007, 2012).

The correlation of the P300 amplitude with duration of deafness is stronger than with behavioural speech perception scores. A possible explanation for this could be that the speech perception scores (% correctly repeated phonemes in a word intelligibility task) are influenced by various task-related factors that influence performance (e.g. attention, vocabulary knowledge, and articulation). Duration of deafness is not a task dependent factor. With our sample size, we could not assess the relative weight of both duration of deafness and behavioural speech perception scores to the P300 amplitude. Therefore, we do not draw conclusions about the order and magnitude in which these aspects (duration of deafness, word perception and auditory discrimination) interact.

In the frequency condition, relations between the P300 amplitude, clinical speech perception scores, and duration of deafness were less evident, although the direction of the slope of the effect is similar. Regarding speech perception scores, it may be that the correlation with P300 amplitude in response to the frequency is less evident because it entails non-speech as opposed to speech discrimination. For duration of deafness, it is less clear why the correlation is less robust in the frequency condition. One possibility is that the frequency contrast was especially easy for our well-performing users, leading to less variability in the scores.

4.1 Recommendations and Limitations

Combined, the results of this study show no evidence that the auditory processing of basic sound contrasts of early implanted, long-term CI users differs from normal-hearing peers. The robustness and reliability of the P300 component at an individual level is furthermore backed up by its significant relationship with duration of deafness (and its less robust relationship with speech perception in quiet). These correlations, although obtained with a small sample size, provide further support for the idea that early implantation is beneficial for later auditory processing. However, we urge the reader to be careful in generalizing auditory processing outcomes of this population in response to a quiet input condition, that seem peer-like, to the overall implantation outcome of this group. Several reports on speech in noise and language outcomes of early implanted CI users report low and variable standardized scores (Ruffin et al. 2013, de Hoog et al, 2016, Ortmann et al. 2013). This is

also seen descriptively in the speech in noise and language outcomes of our sample (see Table 1). While the ERP results in individuals were robust (but not the single-subject latency measurements), the sample size for drawing conclusions on the correlational analysis remains small. In future research, it is advised to investigate the relation between duration of deafness, speech perception scores and P300 amplitude with a larger pool of participants.

Lastly, we wish to emphasize that the sample in our study is a unique group, in the way that their characteristics may already start to differ from children that are implanted nowadays. Ages of implantation around the word still decrease and intervention before 12 months of age is becoming more and more common (EU: Bruijnzeel et al. 2017; US: Teagle, Park, Brown, Zdanski, & Pillsbury, 2019; AUS: Ching et al., 2017), possibly yielding different predictions for the long-term implantation outcomes of new generations.

5. Conclusions

The aim of this study was to evaluate the auditory processing function in response to two input contrasts in prelingually deaf, early implanted young adults, using a P300 as well as an MMN paradigm. Results indicate that the P300 can be reliably and robustly measured in both CI-users and normal-hearing controls. The MMN response could not be detected reliably in both groups, indicating that with a measurement that is restricted in length, the MMN is not a viable tool to measure auditory processing in our population. Furthermore, for both frequency and contrast condition, we did not find evidence for a difference between groups in amplitude and latency of the P300, and within-group variance did not differ between groups either. Lastly, we found for our CI-users that a larger amplitude of the P300 was associated with better clinical speech perception scores in quiet, and a shorter duration of deafness. These results suggest that for basic speech and tone contrasts in quiet, the auditory discrimination abilities of prelingually deaf, early implanted young adults resemble those of their normal-hearing peers. Future research should focus on measuring the auditory processing abilities of long-term, prelingually deaf, early implanted young adult CI users in response to more complicated and ecologically valid input. This may yield more insights into the neurological underpinnings of variation in implant outcome in this population.

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Author Contributions. Conception and design of the study (R.A., A.B., V.P.); data acquisition and analysis (R.A.); interpretation of data (R.A., A.B., V.P.); drafting the manuscript (R.A.); revising the manuscript critically (R.A., A.B., V.P.); final approval of the version to be published (R.A., A.B., V.P.).

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