Research Article

Altered Cortical Activity in Prelingually Deafened Cochlear Implant Users Following Long Periods of Auditory Deprivation

MARC J. W. LAMMERS,^{1,2} HUIB VERSNEL,^{1,2} GIJSBERT A. VAN ZANTEN,^{1,2} AND WILKO GROLMAN^{1,2}

¹*Department of Otorhinolaryngology and Head & Neck Surgery, University Medical Center Utrecht, Room G.02.531, P.O. Box 855003508 GA, Utrecht, The Netherlands*²*Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands*

Received: 4 July 2014; Accepted: 16 September 2014; Online publication: 15 October 2014

ABSTRACT

Auditory stimulation during childhood is critical for the development of the auditory cortex in humans and with that for hearing in adulthood. Age-related changes in morphology and peak latencies of the cortical auditory evoked potential (CAEP) have led to the use of this cortical response as a biomarker of auditory cortical maturation including studies of cortical development after deafness and subsequent cochlear implantation. To date, it is unknown whether prelingually deaf adults, with early onset deafness (before the age of 2 years) and who received a cochlear implant (CI) only during adulthood, would display absent or aberrant CAEP waveforms as predicted from CAEP studies in late implanted prelingually deaf children. In the current study, CAEP waveforms were recorded in response to electric stimuli in prelingually deaf adults, who received their CI after the age of 21 years. Waveform morphology and peak latencies were compared to the CAEP responses obtained in postlingually deaf adults, who became deaf after the age of 16. Unexpectedly, typical CAEP waveforms with adult-like P1-N1-P2 morphology could be recorded in the prelingually deaf adult CI users. On visual inspection, waveform morphology was comparable to the CAEP waveforms recorded in the postlingually deaf CI users. Interestingly, however, latencies of the N1 peak were significantly shorter and amplitudes were significantly larger in the prelingual group than in the postlingual

group. The presence of the CAEP together with an early and large N1 peak might represent activation of the more innate and less complex components of the auditory cortex of the prelingually deaf CI user, whereas the CAEP in postlingually deaf CI users might reflect activation of the mature neural network still present in these patients. The CAEPs may therefore be helpful in the assessment of developmental state of the auditory cortex.

Keywords: cortical auditory evoked potential, cochlear implant, plasticity, auditory cortex, prelingual deaf, hearing loss, deafness

INTRODUCTION

Cochlear implantation in adults has been found to be especially successful in those with postlingual deafness. Postoperative results in terms of speech perception tend to be much poorer in prelingually deaf adults when they received their cochlear implant after a long duration of deafness (Teoh et al. 2004; Klop et al. 2007). These poor performances might be explained by a hampered development of the auditory pathway and cross-modal changes during the period of auditory deprivation (Doucet et al. 2006; Lee et al. 2007; Kral and O'Donoghue 2010; Kral and Sharma 2012).

Absent auditory input during early childhood is thought to lead to underdevelopment of the auditory cortex including reduced axonal density in supragranular layers (Ponton and Eggermont 2001; Eggermont and Ponton 2003) and corticocortical

Correspondence to: Huib Versnel · Brain Center Rudolf Magnus · University Medical Center Utrecht · Utrecht, The Netherlands. email: h.versnel@umcutrecht.nl

decoupling between the different layers of the primary auditory cortex and between the primary and higher order auditory cortex (Kral and Sharma 2012). Corticocortical decoupling between the supragranular and the infragranular layers could affect the descending projections which are thought to be important in the top-down modulation of incoming auditory stimuli, whereas decoupling between the primary and higher order auditory cortex might result in cross-modal cortical reorganization (Kral and Sharma 2012).

Several electrophysiological studies have used cortical auditory evoked potentials (CAEP) to monitor auditory cortex development since the morphology of these responses changes during childhood, possibly reflecting auditory cortex development (Sharma et al. 1997; Ponton et al. 2000; Wunderlich and Cone-Wesson 2006). In young children, the CAEP waveform is dominated by a large and broad positive peak, labeled P1, of which the latency decreases with age. By 9–12 years of age, a negativity, known as the N1, becomes present, resulting in the emergence of the typical P1-N1-P2 complex (Ponton et al. 2000; Ponton and Eggermont 2001; Wunderlich and Cone-Wesson 2006). In adults, the N1 peak, occurring at approximately 100 ms after stimulus onset, has been found to be the most robust component and its source is hypothesized to be located in the supragranular layers (II, III) of the auditory cortex (Ponton and Eggermont 2001).

Studies in prelingually deaf children who received a cochlear implant after several years of auditory deprivation and beyond the supposed sensitive period of 3.5 years revealed that the N1 peak did not develop and only an aberrant P1 peak was present (Ponton and Eggermont 2001; Sharma et al. 2002; Dorman et al. 2007; Kral and Sharma 2012). This lack of N1 might reflect corticocortical deficits within the superficial supragranular layers caused by long-term auditory deprivation. In contrast, Gordon et al. (2008) described a large negative peak with a short latency (around 80 ms) in poorly performing, prelingually deaf children, including those who received their implant late. Although the cortical responses of these children resemble the typical P1-N1-P2 waveform morphology, the negativity that appears 20 ms earlier than the typical N1 is thought to reflect abnormal cortical functioning (Gordon et al. 2008).

Thus, after early deafness, the cortex undergoes underdevelopment, possibly followed by cross-modal plasticity and then by providing new auditory input by means of a cochlear implant the cortex may change again. We addressed this cascade of cortical developmental events by recording CAEPs in adult cochlear implant users who became deaf before the age of 2 years and received their implants during adulthood

and had therefore much longer durations of auditory deprivation than the late implanted, prelingually deaf children in the abovementioned studies. The long period of auditory deprivation will most likely prevent neural maturation processes, which may normally occur throughout adolescence, such as synaptic pruning (Huttenlocher and Dabholkar 1997), to emerge after cochlear implantation. Extrapolating the results of Gordon et al. (2008) a (near-) normal N1 would be possible in these subjects; based on the other studies their CAEPs are expected to lack a significant N1. The aim of our study was therefore to characterize cortical responses in late implanted prelingually deaf adults and compare these responses with those of adult CI users who became deaf during adulthood after normal development of the auditory cortex.

METHODS

Participants

A consecutive series of adult CI users, who visited the outpatient clinic for their routine evaluations, was asked to participate in this study. Twenty-three adults, who received their CIs after 18 years of age and who had a minimum of 6 months experience with their implants, agreed to participate and could be enrolled in this study. Prelingually deaf subjects were selected based on the following criteria: severe to profound bilateral hearing loss with its onset before the age of 2 years (based on patient information, medical histories, and diagnostic audiometry results). The diagnosis of prelingual deafness was confirmed by the evaluation of the multidisciplinary CI team prior to cochlear implant surgery. Twelve of those 23 adults met these criteria. In one prelingually deaf subject, no reliable CAEPs could be evoked due to excessive muscle artifacts and this subject was therefore excluded. Eleven adults became deaf during adolescence or adulthood (>15 years of age) and were classified as postlingually deafened. All participants were users of Nucleus multi-channel cochlear implants. Table 1 provides details of all 22 participants including their pre- and postoperative phoneme score on the consonant-vowel-consonant (CVC) word test.

Speech Perception

Pre- and postoperative speech perception scores were obtained using the Dutch Society of Audiology standard CVC word list at 65 dB SPL (Versfeld et al. 2000). In this auditory-only presented open-set test, speech perception was scored as the percentage of phonemes correct. The most recent scores for each subject, prior to the evoked potential recordings, were used (time intervals between evoked potential recordings and

TABLE 1
Subject demographics

Subject	Group	Side CI	Etiology	Age at test (years)	Age at onset deafness (years)	Age at CI (years)	Implant experience (years)	Pre-op CVC score (%)	Post-op CVC score (%)	Primary mode of communication (pre-operative)
Pre 1	Prelingual	Right	Meningitis	23	0.5	21	1.7	0	22 (3)	Lipreading
Pre 2	Prelingual	Right	Congenital	38	0	37	0.6	0	0 (1)	Lipreading and sign language
Pre 3	Prelingual	Left	Rubella	56	0.3	54	2.5	0	82 (5)	Lipreading
Pre 4	Prelingual	Left	Varicella	55	2	55	0.6	0	26 (5)	Lipreading and sign language
Pre 5	Prelingual	Left	Rubella	47	0	46	1.5	48	66 (4)	Oral and lipreading
Pre 6	Prelingual	Left	Meningitis	55	0.8	49	5.7	12	18 (0)	Lipreading and sign language
Pre 7	Prelingual	Left	Meningitis	47	0.8	41	5.7	0	28 (5)	Lipreading and sign language
Pre 8	Prelingual	Right	Congenital	43	0	40	2.9	0	0 (9)	Lipreading and sign language
Pre 9	Prelingual	Left	Unknown	31	0	27	3.2	0	15 (8)	Lipreading and sign language
Pre 10	Prelingual	Right	Rubella	42	0	41	1.4	0	0 (1)	Lipreading and sign language
Pre 11	Prelingual	Left	Unknown	36	0	27	8.9	28	77 (0)	Lipreading and sign language
Mean				43	0	40	3.2	8	30	
Post 1	Postlingual	Right	Progressive	67	59	60	6.4	39	83 (4)	Oral
Post 2	Postlingual	Right	Otitis media	80	64	75	5.3	37	89 (2)	Oral
Post 3	Postlingual	Right	Otitis media	58	27	43	14.4	-	60 (3)	Oral and lipreading
Post 4	Postlingual	Right	Unknown	73	50	59	13.8	-	72 (0)	Oral
Post 5	Postlingual	Right	Progressive	57	29	50	6.9	28	95 (7)	Oral and lipreading
Post 6	Postlingual	Left	Trauma	22	16	16	6.5	0	90 (0)	Oral
Post 7	Postlingual	Left	Otosclerosis	66	30	64	1.9	33	84 (9)	Oral
Post 8	Postlingual	Right	Progressive	59	43	45	13.3	25	85 (3)	Oral and lipreading
Post 9	Postlingual	Right	Progressive	53	40	41	11.9	11	84 (8)	Oral
Post 10	Postlingual	Right	Otosclerosis	66	30	51	14.4	-	89 (3)	Oral
Post 11	Postlingual	Left	Meningitis	33	15	25	8.2	0	97 (0)	Oral
Mean				58	37	48	9.4	22	84	

Months between CAEP recording and CVC measures are displayed between parentheses in the post-op CVC score column
- not performed

most recent postoperative speech perception scores ranged from 0 to 9 months; see Table 1).

Procedure and Stimuli

Participants were seated in a comfortable reclining chair in an electrically shielded, sound-attenuated booth and were allowed to watch a silent, captioned movie. They were carefully instructed prior to each recording to minimize movements and to fixate the center of the video screen to minimize muscle and eye movement artefacts.

Cortical auditory evoked potentials (CAEP) were evoked by a short train of electric biphasic pulses at 250 pulses per second for 36 ms. This stimulus was also used by Gordon et al. (2008) and Jiwani et al. (2013). A monopolar stimulation electrode configuration was applied, and the electrode position was varied: It was at the apical end of the array (typically electrode no. 20), at a central position (typically no. 11), or at the basal end of the array (typically no. 2). Pulse trains were generated using the Cochlear Custom Sound EP 3.1 software and presented at a rate of 0.9 Hz at the individual's maximum comfortable loudness level (C-level). These settings of stimulation rate and level are very similar to settings in the CI literature (Ponton and Eggermont 2001; Sharma et al. 2002; Gordon et al. 2008; Jiwani et al. 2013). For all participants, phase widths of the biphasic pulses were set at 25 μ s and interphase gaps at 8 μ s. In each participant, 100 responses to a pulse train were averaged and at least one repetition was done. Pilot experiments in normal-hearing subjects and CI users had indicated that 200 accepted trials was adequate to yield clear responses. More repetitions were obtained in cases with higher noise levels due to, e.g., muscle artifacts.

Evoked Potential Recording

Responses were recorded by Ag/AgCl electrodes placed according to the 10–20 system using a Medelec Synergy T-10 Evoked Potential system. The active electrode was placed at the vertex of the skull, Cz, the contralateral mastoid was used as reference electrode (A1/A2), and the ground electrode was placed on the forehead, Fpz. Electrode impedances were kept below 5 k Ω . Eye movements and blinks were monitored using electrodes on the forehead above the eye. The electrode signals were filtered from 0.01 to 100 Hz and recorded with a sampling rate of 50 kHz. Responses were acquired in a 500-ms time window, consisting of a prestimulus period of 100 ms and a poststimulus period of 400 ms. Responses containing amplitudes of >100 μ V at any electrode were rejected and not included in the averaged response.

Management of Stimulus Artifact

In order to clearly differentiate the auditory response from the stimulus artifact, we used several techniques. First, we directly stimulated the CI by presenting short pulse trains to the individual electrodes. This direct method has no disadvantage of the indirect method by acoustic signal presentations in which FM signals are transmitted by the transmitting coil to the internal device, which could contaminate the recordings. Second, by using a short pulse train of only 36 ms, we expect that the stimulus artifact including possible poststimulus ringing of the response acquisition system would end before the typical region of interest of the N1 peak (Gordon et al. 2008). Third, in an additional recording channel, we used Fz as active electrode since we have found that stimulus artifacts are usually smaller or absent when recorded more frontally. By visual inspection and comparison with the waveforms obtained at Cz and Fz, artifact and response could readily be differentiated in all cases. Fourth, after the actual recordings, we recorded 100 sweeps at a stimulus level just below the threshold. In this recording, the stimulus artifact could be identified while the CAEP was absent. Finally, in cases with a large stimulus artifact which could possibly interfere with the CAEP, an additional recording of 100 accepted sweeps at a slower repetition rate of 0.45 Hz was performed. By reducing the repetition rate, the CAEP can be easily differentiated from the artifact, since the amplitude of the CAEP increases, whereas the size of the stimulus artifact including poststimulus ringing remains identical (Friesen and Picton 2010). These recordings were only used to accurately differentiate the CI artifacts from the actual response. For our analyses, only the Cz recordings obtained at the repetition rate of 0.90 Hz were used.

Data Analyses

Averaged evoked potential data were analyzed using custom scripts in MATLAB (version 7.11.0, Mathworks, Natick, MA, USA). The two repetitions of 100 accepted responses obtained at the stimulus rate of 0.9 Hz were averaged for each subject. CAEP peak amplitude and latency analyses were performed on these individual averages recorded at Cz. N1 was defined as the most negative peak at 70 to 150 ms after stimulus onset. P2 was defined as the first pronounced positive peak occurring after N1 at 120 to 250 ms after stimulus onset. Absolute N1 amplitude was computed relative to the start of the N1 wave. Furthermore, the N1-P2 peak-to-peak amplitude was used for data analyses.

CAEPs were included for analyses when the N1-P2 amplitude was at least four times the root mean

square amplitude of the 100-ms prestimulus trace segment. The CAEP was further evaluated by the correlations between 50 and 250 ms poststimulus segments of the two recording runs.

Statistical Analyses

Statistical analyses were completed using SPSS version 20.0 software (IBM, Armonk, NY, USA). Repeated measure ANOVAs with the three different stimulation electrode locations (i.e., basal, middle, and apical) as within-subject factor and group (i.e., prelingual or postlingual) as between-subject factor were used. Significant main effects and interactions ($p < 0.05$) were followed with Bonferroni post hoc tests, and the Greenhouse-Geisser correction was applied to compensate for violations of the sphericity assumption. Group differences in peak latencies and amplitudes were calculated with unpaired two-tailed t tests or the Mann-Whitney test for independent samples. Stepwise multiple linear regression analyses were performed to evaluate the influence of other variables. A linear regression analysis was conducted on the N1 and P2 amplitudes and latencies with postoperative CVC phoneme scores as independent variables to assess the relation between CAEP characteristics and speech perception.

RESULTS

Patient Demographics and Speech Perception

Reproducible CAEP waveforms could be obtained in 22 out of 23 participants (96 %). In one prelingually deaf subject, no reliable and reproducible waveforms could be evoked on either of the three stimulation

locations due to excessive muscle artifacts, and therefore, this subject's responses were excluded from the analyses. Patient demographics of the 22 included subjects are presented in Table 1. As can be seen, the prelingual group and the postlingual group differed significantly in age at testing (mean difference, 15 years; unpaired two-tailed t test, $t_{20} = 2.4$, $P = 0.024$) and implant experience (mean difference, 6.2 years; unpaired $t_{20} = 4.1$, $P = 0.001$). Age at implantation did not differ significantly (unpaired, $t_{20} = 1.4$, $P = 0.193$). CVC phoneme scores demonstrated a large variability, varying from 0 to 82 % in the prelingual group and from 60 to 97 % in the postlingual group (Fig. 1). The difference in scores was highly significant (median difference, 63 %; Mann-Whitney $U = 116$, $P < 10^{-4}$). In both patient groups, speech perception reached a stable performance level within 1 year after implantation as illustrated in Figure 1B. The CVC phoneme scores taken prior to the CAEP recordings represent stable speech perception in all patients, including the two prelingual patients who had only 6 months CI experience (Pre 2 and Pre 4) and who continued to have similarly low speech perception scores after 2 years follow-up.

C-levels were significantly lower in the prelingual group than in the postlingual group ($F_{(1,20)} = 5.436$, $P = 0.030$). The C-levels for the prelingual group were around 165 current units (CU) and for the postlingual group were around 190 CU (mean difference basal electrode, 25 CU unpaired two-tailed t test, $t_{20} = 2.6$, $P = 0.016$; mean difference middle electrode, 24 CU, $t_{20} = 2.4$, $P = 0.029$; mean difference apical electrode 16 CU, $t_{20} = 0.7$, $P = 0.098$). Detection threshold levels (T-levels) for the prelingual group were around 129 CU and for the postlingual group

FIG. 1. A Consonant-vowel-consonant word (CVC) phoneme scores of the prelingual and postlingual group at the time of the evoked potential recordings. Each dot represents an individual subject. The horizontal lines represent the median scores (prelingual group, 22 %; postlingual group, 85 %). Subjects who had some hearing experience (Pre 1, 3, 4, 6, and 7) are marked with *yen* sign; subject Pre 5, who used both visual speech cues (as lipreading) and oral communication preoperatively, is marked with *section* sign.

B Mean CVC phoneme scores over time following cochlear implantation presented for both groups. Postoperative CVC scores were obtained after 1, 3, 12, 24, and 36 months of cochlear implant use. Four subjects in the prelingual group (Pre 1, Pre 2, Pre 8, and Pre 10) were not able to obtain speech perception at any level if only auditory cues were available; three of these subjects were non-users at the 3-year interval (Pre 1, Pre 2, and Pre 10); at these intervals, a CVC phoneme scores of 0 % was noted for these subjects.

around 140 CU for all three electrode locations. T-levels were not significantly different between the two groups ($F_{(1,20)}=1.385$, $P=0.253$).

CAEP Waveforms in the Pre- and Postlingual Groups

Figure 2 shows the individual and unfiltered CAEP waveforms evoked at a middle electrode (typically electrode number 11). All subjects in the postlingual group (right column) demonstrated CAEP waveforms comparable to the typical adult waveform morphology found in normal hearing adults in response to acoustic stimuli, with the N1 peaking around 100 ms and the P2 around 200 ms (Wunderlich and Cone-Wesson 2006; Martin et al. 2008). Although in some waveform stimulus artifacts were present, careful inspection of the waveforms revealed N1 and P2

peaks in all subjects. In some of the postlingual subjects, the N1-P2 complex was weakly present with a low N1-P2 amplitude relative to the prestimulus noise level (less than 10 times the root mean square) and/or a low correlation between the two recording runs ($r<0.7$). The waveforms in all prelingual subjects (Fig. 2, left column) demonstrated a clear N1-P2 complex. The N1, peaking around 90 ms in the prelingual group, predominates the response and is followed by the P2, with its maximum around 200 ms. All waveforms presented in Figure 2 could be reproduced on both the basal and apical stimulating electrode locations. Due to the larger stimulus artifact present in the CAEP waveforms obtained after stimulation of the basal electrodes, these responses were less clear as compared to the middle and apical electrodes. In ten subjects (eight postlingual ones), the N1-P2 complexes were weakly present.

FIG. 2. Individual CAEP waveforms evoked at a middle CI electrode (typically no. 11). The stimulus consisted of a 36-ms pulse train with a pulse rate of 250Hz. For almost all subjects, waveforms were measured at recording electrode Cz. In case of a large stimulus artifact at the recording electrode Cz, waveforms measured at electrode Fz are presented (indicated with *double dagger*). In all subjects in both groups, an N1 (indicated with *downward arrowhead*) and a P2 peak (indicated with *upward arrowhead*) could be identified. At the *right side* of the individual waveforms, the CVC

phoneme scores are presented. At the *left side*, the correlations between two successive recordings (in the response window 50–250 ms after stimulus onset) are indicated with their coefficient. The *vertical line* at 100 ms indicates the typical N1 latency found in normal hearing adults; the *vertical line* at 200 ms indicates the typical P2 latency found in normal hearing adults. Subjects who had some hearing experience (Pre 1, 3, 4, 6, and 7) are marked with *yen sign*; subject Pre 5, who used both visual speech cues and oral communication preoperatively, is marked with *section sign*.

FIG. 3. Grand average CAEP waveforms measured at Cz for all subjects in both groups. Grand mean waveforms are presented for the three electrode stimulation locations separately (i.e., basal,

middle, and apical). The blue and red traces represent the waveforms of the prelingual and postlingual groups, respectively.

Nevertheless, cortical responses could be easily differentiated from stimulus artifacts, and on visual inspection, N1 and P2 peaks could be identified. Correlations between two recording repetitions were generally high. For the response segments, 50 to 250 ms after stimulus onset correlation coefficients were on the average 0.72 for basal to 0.88 for apical electrode stimulation. All subjects had reproducible recordings with apical stimulation ($r > 0.64$). The noise levels in the recordings, assessed on 100 ms prestimulus trace segments, were on the average 0.5 μ V (root mean square), and they were similar for the pre- and postlingual group ($F_{(1,20)} = 1.74$, $P = 0.24$). Figure 3 presents grand mean waveforms recorded from Cz for all three stimulating electrode locations separately for each group. It shows two features: First, the N1-P2 complex appeared earlier and larger in the prelingual group than in the postlingual group. Second, in both groups, the responses evoked by apical electrode stimulation were larger than the basally evoked responses.

Latencies

N1 latencies were significantly shorter in the prelingual group than in the postlingual group for all three electrode locations ($F_{(1,20)} = 11.78$, $P = 0.0026$) (Fig. 4). The N1 latencies for the prelingual group were around 90 ms and for the postlingual group were around 105 ms (mean difference basal electrode, 14 ms unpaired two-tailed t test, $t_{20} = 2.3$, $P = 0.029$; mean difference middle electrode, 17 ms, $t_{12} = 3.7$, $P = 0.0013$; mean difference apical electrode, 14 ms, $t_{20} = 3.5$, $P = 0.002$). There was no interaction effect of stimulating electrode location ($F_{(2,40)} = 0.20$, $P = 0.818$), and the N1 latencies did not vary with stimulating electrode location ($F_{(2,40)} = 1.89$, $P = 0.16$).

Analysis of the P2 latencies did not reveal differences between the prelingual (average latency per electrode: basal 186 ms, middle 177 ms, apical 177 ms) and the postlingual group (average latency per electrode: basal 174 ms, middle 187 ms, apical 182 ms) ($F_{(1,20)} = 0.003$, $P = 0.96$) or the different electrode stimulation locations ($F_{(2,40)} = 0.36$, $P = 0.70$).

In order to assess whether group differences in age at implantation and age at testing and implant experience could have contributed to the group differences found in N1 latency, stepwise multiple linear regression analyses were performed. Pre- or postlingual deafness accounted for 41 % of the variability in N1 latency on the middle electrode ($r^2 = 0.41$, $F_{(1,20)} = 13.99$, $P = 0.0013$). Although implant experience and age at testing were identified as significant factors explaining the N1 latency, these variables did not provide further significant improvement to the regression model ($P = 0.080$ and $P = 0.275$).

FIG. 4. N1 latencies of the prelingual (*pre*) and postlingual (*post*) groups presented for the three stimulation electrode locations, i.e., basal, middle, and apical. At all three stimulation locations, a significant difference in N1 latency between the two groups was found. The box plots represent the lower and upper quartile with the median. Whiskers indicate the 5–95 percentiles. * $P < 0.05$; ** $P < 0.01$.

FIG. 5. N1 (A) and N1-P2 (B) amplitudes of the prelingual (*pre*) and postlingual (*post*) groups presented for the three stimulation electrode locations, i.e., basal, middle, and apical. For both N1 and N1-P2 amplitude, a gradual increase in amplitude was found with a more

apical location of stimulation. The box plots represent the lower and upper quartile with the median. Whiskers indicate the 5–95 percentiles. * $P < 0.05$.

respectively). On the basal and apical electrodes, implant experience and age at testing were not even identified as significant factors.

Amplitudes

N1 amplitudes were significantly larger in the prelingual group than in the postlingual group (mean difference 1.64 μV , $F_{(1,20)} = 5.03$, $P = 0.036$) (Fig. 5A). There was no interaction effect of stimulating electrode location ($F_{(2,40)} = 0.24$, $P = 0.64$), but the N1 amplitudes did vary with stimulating electrode location ($F_{(2,40)} = 6.60$, $P = 0.009$). Bonferroni post hoc analyses revealed that the amplitudes at the basal electrode were significantly smaller than at the middle (mean difference, 0.97 μV ; $P = 0.027$) and the apical electrode (mean difference, 1.80 μV ; $P = 0.027$).

The N1-P2 amplitude (Fig. 5B) showed similar trends as the N1 amplitude, albeit that the difference in N1-P2 amplitude between the two groups was not significant ($F_{(1,20)} = 2.31$, $P = 0.14$). The N1-P2 amplitudes varied with stimulating electrode location ($F_{(2,40)} = 6.64$, $P = 0.0032$); specifically, the amplitudes at the apical electrode were significantly larger than at the basal electrode (Bonferroni, mean difference 2.39 μV , $P = 0.016$).

Stepwise multiple linear regression analyses showed that age at implantation and age at testing or implant experience were not predictive for N1 amplitudes on either of the three stimulating electrode locations.

Figure 6 shows a joint N1-amplitude-latency scatter plot revealing remarkably clear clustering of the two groups. The prelingual CI users mainly displayed large N1 amplitudes with short latencies, whereas the postlingual group had long latencies and/or small amplitudes. This clustering was most clear on the

middle (Fig. 6) and apical (not shown) electrodes. Note that the three prelingual subjects with high speech perception scores (indicated with open circles) tended to be near the border between the two clusters.

Relationship Between CAEP and Speech Perception

As demonstrated in Figure 2, a CAEP with a typical N1-P2 waveform could be recorded irrespective of

FIG. 6. N1 amplitude as a function of N1 latency presented for the middle electrode reveals clustering of the two groups. Blue dots represent individual subjects in the prelingual group; red squares represent postlingual subjects. The three prelingual subjects with postoperative CVC scores of $\geq 66\%$ are marked as a blue open circle: subject Pre 3 (CVC score 82 %, N1 latency 90 ms, N1 amplitude 3 μV), Pre 5 (CVC score 66 %, N1 latency 92 ms, N1 amplitude 5.4 μV), Pre 11 (CVC score 77 %, N1 latency 85 ms, N1 amplitude 2.2 μV).

speech perception score and onset of deafness. Since the poorly performing prelingual group demonstrated shorter N1 latencies, N1 latency might be related to speech perception. There was only a fair correlation between speech perception and N1 latency in the prelingual group when stimulated at an apical electrode ($r^2=0.43$, $P=0.028$), independent of implant experience or age at test. On the basal and middle electrode, this correlation was not present (Fig. 7). In the prelingual group, there were no significant correlations between speech perception and P2 latency or N1, N1-P2, and P2 amplitudes on any of the three stimulating electrode locations ($r^2<0.28$, $P>0.093$). Speech perception scores in the postlingual group were not related to the latencies or amplitudes of the N1 and P2 peaks on either of the three stimulating electrode locations ($r^2<0.30$, $P>0.082$).

DISCUSSION

In this study, we assessed cortical activity in pre- and postlingually deaf adult CI users by recording CAEP waveforms in response to electric stimuli presented at basal, middle, and apical CI electrodes. Given the current literature on the development of the CAEP response, the CAEP waveforms including clear N1-P2 peaks that we obtained in prelingually deaf patients, who received their CI only in adulthood and supposedly had an abnormal development of the auditory cortex, were highly unexpected. While on first visual inspection their waveforms were comparable to those obtained in postlingually deaf CI users, who supposedly had a normal development of the auditory cortex during childhood, there seems to be a consistent

FIG. 7. CVC phoneme score as a function of N1 latency presented for the middle electrode. Each red square represents a subject in the postlingual group. Each blue dot represents a subject in the prelingual group.

difference in N1 latency and amplitude between both groups, possibly implying different underlying mechanisms.

Development of CAEPs with Age

In normal hearing children, it has been demonstrated that the CAEP waveform morphology alters with increasing age (Sharma et al. 1997; Ponton et al. 2000; Wunderlich and Cone-Wesson 2006; Wunderlich et al. 2006). Before ages 9–12, the CAEP response is predominated by a large positive peak (P1), which is characterized by a decreasing peak latency with age (Sharma et al. 1997; Ponton et al. 2000). Only after this period a negativity becomes present, which eventually develops into a robust negative peak (N1) in adulthood dominating the CAEP (Sharma et al. 1997; Ponton et al. 2000; Wunderlich and Cone-Wesson 2006). The development of the N1 peak is thought to reflect maturation of thalamo-cortical and corticocortical pathways in the superficial layers of the cortex, which are essential in the transfer of auditory input to the cortex and the communication between the two hemispheres and other cortical areas (Ponton et al. 2000; Ponton and Eggermont 2001; Eggermont and Ponton 2003). Since the emergence of the N1 peak coincides with the development of complex auditory skills in children, it is suggested that these pathways play an important role in the processing of sounds in complex conditions such as speech in noise (Ponton et al. 2000; Eggermont and Ponton 2003). In prelingually deaf children, who have been fitted with a cochlear implant early in life, the maturation of the predominant positive P1 peak follows the normal pattern as seen in normal hearing children (Sharma et al. 2002; Dorman et al. 2007). In such children, a normal N1 may develop after the long use of the CI (Jiwani et al. 2013). After long durations of deafness (>6 years), there are signs that the maturation of the more superficial layers of the auditory cortex becomes impaired, resulting in the absent development of the N1 and the predominance of the positive peak in these prelingually deaf and late implanted children (age at implantation >6.5 years) (Sharma et al. 2002; Dorman et al. 2007). Also, shorter periods of deafness (~3 years) during early childhood (3.5–6.5 years of age) may block N1 development (Ponton and Eggermont 2001). With the assumed association of N1 to normal-like cortical development, it is puzzling that of prelingually deaf children with several years of auditory deprivation and long CI experience, the ones with poor to fair speech perception show large N1 peaks (Gordon et al. 2008).

If existence of an N1 peak reflects normal-like cortical development, one would expect that subjects

with prelingual deafness who have received their CI in adulthood would exhibit abnormal CAEP waveforms, in particular missing the N1 around 100 ms. On the contrary, without exception, all prelingually deaf adults that were included in this study did display on first visual inspection the typical adult P1-N1-P2 morphology (Figs. 2 and 3). Furthermore, the responses in this prelingual group were not different from adult CI users, who have had a normal auditory development during childhood (up to age 16, postlingual group). Our data are in line with the findings of Gordon et al. (2008) in prelingually deaf children, first of all in the sense that a significant N1 can be generated in spite of abnormal cortical development. Furthermore, our study compares with Gordon et al. (2008) with respect to the N1 latency. The poor performing children in the latter study demonstrated a significantly shorter N1 latency (~80 ms) than normal hearing children (~100 ms). In our study, we found a comparable difference in N1 latency between the prelingual and the postlingual group of approximately 15 ms. To a lesser extent, there is agreement in N1 amplitude. We found significantly larger amplitudes in the prelingual than in the postlingual group while Gordon et al. reported larger than normal N1 peaks in the poor performing CI children. In contrast to the study by Gordon et al. (2008), who found a great difference in N1 amplitude between poor/fair performers and good performers, the N1 amplitude found in our study was only weakly associated with speech perception. Since the adult-like CAEP responses found in our study were not related to the duration of implant use, the maturation of the CAEP response might be more driven by age-related changes of the innate auditory pathway independent of auditory stimulation. Future longitudinal studies should address these issues by studying the development of the CAEP waveform morphology over time in prelingual CI users.

CAEP Differences Between Postlingually and Prelingually Deaf Subjects

Although the CAEP waveform morphology in the prelingual group might be similar to those in the postlingual group, the generation sites of the different peaks may differ between prelingual and postlingual CI users. The waveforms and peak latencies in the postlingual group are comparable to those found in normal hearing subjects. The average N1 latencies of around 105 ms are comparable to those reported in normal hearing subjects (90–120 ms: Näätänen and Picton 1987; Wunderlich and Cone-Wesson 2006; Martin et al. 2008). The normal-like CAEPs of the postlingually deafened adults follow from the development of the CAEPs in normal-hearing children and

probably represent activation of the previously matured auditory pathway.

The presence of the typical CAEP response in the absence of sufficient auditory stimulation, however, needs a different explanation. It may be explained by activation of the more innate auditory network in conjunction with residual plasticity which is probably still present even after long durations of deafness (Kral and Sharma 2012). The consistent early N1 latency might also be a representation of activation of these innate and less complex components of the auditory system. Due to the impaired sensory input, the normal exuberant development and axonal selection might have become impaired, leading to a disrupted selection of axonal populations within the auditory cortex (Innocenti and Price 2005). In turn, this might lead to activation of a large number of less specific axons, rather than a few specialized neurons (Innocenti and Price 2005). Since synaptic pruning is thought to be completed by around 12 years of age in the auditory cortex (Huttenlocher and Dabholkar 1997), these aberrant cortical connections might last and be stabilized due to the long-term auditory deprivation in our prelingually deaf group (Innocenti and Price 2005; Uhlhaas and Singer 2011). Kral et al. (2006) demonstrated that the naïve auditory cortex of congenitally deaf cats has a reduced sensitivity to auditory input, leading to a smeared representation of auditory stimuli with a deficient representation of auditory features including loss of tonotopy (Kral et al. 2006). Thus, a larger cortical area responds to a stimulus, leading to a larger evoked potential. Furthermore, due to long-term auditory deprivation, corticocortical de-coupling might occur in these prelingually deaf CI users resulting in less corticocortical interactions with other brain regions and less influence of top-down inhibition by higher order neurons (Kral and Eggermont 2007; Kral and Sharma 2012). The combination of these factors might result in a wide spread of evoked activity which promotes more synchronous activation of several axonal populations, giving rise to the early and large N1 peak.

Our findings that typical CAEP responses could be evoked regardless of postoperative performance (Fig. 2) suggest a limited role of the CAEP as an objective predictor of postoperative speech perception. In contrast to our study, studies in children with auditory neuropathy spectrum disorder suggested that CAEPs can be applied as objective predictor as they found that poor performing children revealed longer P1 latencies (Alvarenga et al. 2012; Cardon and Sharma 2013). Although our study population did not display consistent relations between speech perception and CAEP morphologies (Fig. 7), the results do demonstrate that the prelingual CI users mainly

display large N1 amplitudes with short latencies (Fig. 6). These responses can therefore be helpful in the assessment of developmental state of the auditory cortex.

Neither age at test nor implant experience explained the differences found in N1 latency and N1 amplitude between the two groups. In the prelingual group, we included subjects with 0.5 to almost 9 years of implant experience (Table 1). If implant experience would affect N1 latency and amplitude, then we would at least expect a certain trend to be present in this group with this broad range in implant experience. Given the absent relation in both groups, we are confident that the N1 differences can be attributed to the age of onset of deafness, rather than to implant experience. Further, it should be noted that the current levels applied to evoke the CAEPs cannot explain the larger and earlier responses in the prelingual group. In fact, because of the lower comfortable levels, the levels used for the prelingually deaf subjects were lower than for the postlingually deaf. This would contribute to smaller and later CAEPs, which indicate that the found differences would have been even larger when the same current levels were applied.

One may wonder whether the presence of the N1 peak is related to the choice of stimulus. The group of Sharma (Sharma et al. 2002; Dorman et al. 2007) who reports a lack of N1 used a different stimulus, a 90-ms speech segment acoustically delivered to the CI processor, than studies reporting an N1 (Gordon et al. 2008; Jiwani et al. 2013; current study) who used a short train of pulses presented through a single electrode or a pair of electrodes. However, Ponton and Eggermont (2001) reporting a lack of N1 also used a short pulse train. Therefore, and because various stimuli as tones, clicks, speech-like sounds, and acoustic changes yield similar CAEP waveforms including the N1 peak around 100 ms (Wunderlich and Cone-Wesson 2006; Martin et al. 2008), the type of stimulus does not seem to be an important factor for this onset response. The rate we used is somewhat slower (0.9 Hz) than the rate of Ponton and Eggermont (2001) and Sharma et al. (2002) who used 1.3–1.4 Hz, and although the N1 decreases with increase of stimulation rate, it seems unlikely that this difference in rates can explain the different results since only at high rates (>3 Hz) the N1 disappears (Wunderlich and Cone-Wesson 2006).

Patient Selection

Despite the careful selection of our prelingually deaf subjects, one could argue that possible residual hearing might have affected the maturation of the CAEP waveforms in these subjects. Although we

cannot exclude that some subjects (e.g., Pre 5; see Table 1) used little residual hearing in conjunction with acoustical amplification for sound detection, as in all other prelingual subjects, their deafness has led to serious impairment of their speech production and language skills. Other subjects explicitly stated that they were deaf during childhood and reported that even as a child, they did not use their hearing aids due to the absent value, such as subject Pre 7. Also, these subjects had typical CAEP waveforms (Fig. 2).

Another issue of debate is the assessment of onset of deafness. Determining the age at which adult individuals became deaf is often not straightforward since it is based on patient-reported data about age of first suspicion of hearing impairment, age of first diagnostic audiometry and its outcome, and age of first hearing aid use. In particular, one could wonder in this respect if the three prelingually deaf subjects with high postoperative CVC scores in the same range as the postlingually deaf individuals (Fig. 1A) were correctly judged as prelingually deaf. Although their N1 latencies were in the range of the other prelingually deaf individuals (Fig. 7), the joint N1-amplitude-latency scatter plot (Fig. 6) indicates these three cases near the border between the prelingual and postlingual clusters. Based on these N1 data, one might surmise that (some of) these three cases have been misjudged as being prelingually deaf. Nevertheless, we conclude that even if some subjects were misjudged according to strict definitions, the objective N1 measures do indicate that the prelingually labeled subjects differed in auditory development from the postlingually labeled subjects.

Methodological Considerations

Since we did not make use of multichannel recordings, several stimulus artifact reduction methods proposed in the literature, such as independent component analysis, could not be applied. In order to confidently differentiate the actual cortical response from a possible stimulus artifact, we used several techniques as described in “Methods,” including the technique of altering the inter-stimulus interval as proposed by Friesen and Picton (2010). Furthermore, we were able to replicate and reproduce all CAEP responses in all subjects on different stimulating electrodes. Although in some subjects a residual stimulus artifact can still be seen in the unfiltered waveforms, as presented in Figure 2, we are confident that we could clearly separate CAEP response from stimulus artefacts in all cases since we used the aforementioned methods to differentiate CAEP response from stimulus artifact.

Due to the limited number of recording channels used in our setup, source analysis of the N1 genera-

tors could not be performed. Although it would be of interest to assess whether the generators of the N1 would differ between postlingually deaf CI users and late implanted prelingually deaf CI users, the spatial resolution of EEG source localization might be too low to reveal small differences within the auditory cortex (Pascual-Marqui 2002).

CONCLUSION

Results from the present study demonstrate that cortical auditory evoked potentials with a typical N1-P2 waveform can be evoked in prelingually deaf and very late implanted cochlear implant users. N1 peak latencies are however significantly earlier and N1 amplitudes are larger in this group, which might be caused by the activation of more innate and less complex auditory cortical network.

ACKNOWLEDGMENTS

The authors thank all the participants for their time and support and the members of the Cochlear Implant Team of the UMC Utrecht for their contributions. This study is supported by an unrestricted research grant from Cochlear Ltd.

Conflict of Interest Wilko Grolman received an unrestricted research grant from Cochlear Ltd. for this study. Wilko Grolman received unrestricted research grants from MED-EL GmbH and Advanced Bionics. No competing interests declared by the other authors.

REFERENCES

- ALVARENGA KF, AMORIM RB, AGOSTINHO-PESSE RS, COSTA OA, NASCIMENTO LT, BEVILACQUA MC (2012) Speech perception and cortical auditory evoked potentials in cochlear implant users with auditory neuropathy spectrum disorders. *Int J Pediatr Otorhinolaryngol* 76:1332–1338
- CARDON G, SHARMA A (2013) Central auditory maturation and behavioral outcome in children with auditory neuropathy spectrum disorder who use cochlear implants. *Int J Audiol* 52:577–586
- DORMAN MF, SHARMA A, GILLEY P, MARTIN K, ROLAND P (2007) Central auditory development: evidence from CAEP measurements in children fit with cochlear implants. *J Commun Disord* 40:284–294
- DOUCET ME, BERGERON F, LASSONDE M, FERRON P, LEPORE F (2006) Cross-modal reorganization and speech perception in cochlear implant users. *Brain* 129:3376–3383
- EGGERMONT JJ, PONTON CW (2003) Auditory-evoked potential studies of cortical maturation in normal hearing and implanted children: correlations with changes in structure and speech perception. *Acta Otolaryngol* 123:249–252
- FRIESEN LM, PICTON TW (2010) A method for removing cochlear implant artifact. *Hear Res* 259:95–106
- GORDON KA, TANAKA S, WONG DDE, PAPSIN BC (2008) Characterizing responses from auditory cortex in young people with several years of cochlear implant experience. *Clin Neurophysiol* 119:2347–2362
- HUTTENLOCHER PR, DABHOLKAR AS (1997) Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol* 387:167–178
- INNOCENTI GM, PRICE DJ (2005) Exuberance in the development of cortical networks. *Nat Rev Neurosci* 6:955–965
- JIWANI S, PAPSIN BC, GORDON KA (2013) Central auditory development after long-term cochlear implant use. *Clin Neurophysiol* 124:1868–1880
- KLOP WM, BRAIRE JJ, STIGGELBOUT AM, FRIJNS JH (2007) Cochlear implant outcomes and quality of life in adults with prelingual deafness. *Laryngoscope* 117:1982–1987
- KRAL A, EGGERMONT JJ (2007) What's to lose and what's to learn: development under auditory deprivation, cochlear implants and limits of cortical plasticity. *Brain Res Rev* 56:259–269
- KRAL A, O'DONOGHUE GM (2010) Profound deafness in childhood. *N Engl J Med* 363:1438–1450
- KRAL A, SHARMA A (2012) Developmental neuroplasticity after cochlear implantation. *Trends Neurosci* 35:111–122
- KRAL A, TILLEIN J, HEID S, KLINKE R, HARTMANN R (2006) Cochlear implants: cortical plasticity in congenital deprivation. *Prog Brain Res* 157:283–313
- LEE HJ, GIRAUD AL, KANG E, OH SH, KANG H, KIM CS, LEE DS (2007) Cortical activity at rest predicts cochlear implantation outcome. *Cereb Cortex* 17:909–917
- MARTIN BA, TREMBLAY KL, KORCZAK P (2008) Speech evoked potentials: from the laboratory to the clinic. *Ear Hear* 29:285–313
- NÄÄTÄNEN R, PICTON T (1987) The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology* 24:375–425
- PASCUAL-MARQUI RD (2002) Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods Find Exp Clin Pharmacol* 24(Suppl D):5–12
- PONTON CW, EGGERMONT JJ (2001) Of kittens and kids: altered cortical maturation following profound deafness and cochlear implant use. *Audiol Neurotol* 6:363–380
- PONTON CW, EGGERMONT JJ, KWONG B, DON M (2000) Maturation of human central auditory system activity: evidence from multi-channel evoked potentials. *Clin Neurophysiol* 111:220
- SHARMA A, KRAUS N, MCGEE TJ, NICOL TG (1997) Developmental changes in P1 and N1 central auditory responses elicited by consonant-vowel syllables. *Electroencephalogr Clin Neurophysiol* 104:540–545
- SHARMA A, DORMAN MF, SPAHR AJ (2002) A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. *Ear Hear* 23:532–539
- TEOH SW, PISONI DB, MIYAMOTO RT (2004) Cochlear implantation in adults with prelingual deafness. Part I. Clinical results. *Laryngoscope* 114:1536–1540
- UHLHAAS PJ, SINGER W (2011) The development of neural synchrony and large-scale cortical networks during adolescence: relevance for the pathophysiology of schizophrenia and neurodevelopmental hypothesis. *Schizophr Bull* 37:514–523
- VERSFELD NJ, DAALDER L, FESTEN JM, HOUTGAST T (2000) Method for the selection of sentence materials for efficient measurement of the speech reception threshold. *J Acoust Soc Am* 107:1671–1684
- WUNDERLICH JL, CONE-WESSON BK (2006) Maturation of CAEP in infants and children: a review. *Hear Res* 212:212–223
- WUNDERLICH JL, CONE-WESSON BK, SHEPHERD R (2006) Maturation of the cortical auditory evoked potential in infants and young children. *Hear Res* 212:185–202