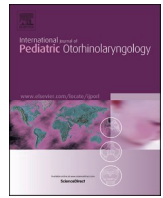




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# A longitudinal study of cortical auditory maturation and implications of the short inter-implant delay in children with bilateral sequential cochlear implants

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## ABSTRACT

**Objective:** This longitudinal study aimed to investigate the maturational development of P1 latency and the effects of a short inter-implant delay in children who received bilateral sequential cochlear implants.

**Materials and methods:** Fourteen children (first CI mean age:  $1.4 \pm 0.4$  years and Second CI mean age:  $3.3 \pm 0.5$  years) who had received sequential bilateral cochlear implants during the sensitive period for auditory maturation participated in our study. The speech-evoked cortical P1 response was recorded after the activation of the second CI at four intervals (implant activation, 3 months, 6 months, 12 months) under three listening conditions (first CI, second CI, binaural).

**Results:** Our results showed that the P1 latencies of the second CI reached normative values within 3 months, but did not reach the P1 latency of the first CI until 12 months. We found a strong negative correlation between the inter-implant delay and the P1 latencies of the second CI when the second CI was activated.

**Conclusion:** Changes in cortical auditory responses over time resulted in normal auditory maturation in children with sequential bilateral cochlear implants during the sensitive period. The results also provide evidence that the timing of auditory experience in the first ear during the sensitive period may influence the speed of compensation in children receiving sequential cochlear implants.

## 1. Introduction

Bilateral cochlear implantation (BCI) in the pediatric population is becoming increasingly common in clinical practice, due to the evidence that it provides a better ability to localize sounds, speech understanding in noise, and language outcomes than unilateral cochlear implant (CI) use [1–3]. Early cochlear implantation preserves the integrity of the central auditory system and helps the auditory pathways develop normally [4,5]. Cortical auditory maturation can be studied using the P1 response, a major component of cortical auditory evoked potentials in childhood [6]. P1 responses are an objective measure of auditory performance after cochlear implantation which can be used to evaluate postoperative outcomes and monitor central auditory maturation [7].

Several studies have shown that BCI leads to rapid cortical auditory maturation at an early age [8,9]. Because BCI is performed either simultaneously or sequentially, studies have focused on the effects of these two methods on CI users. One of the factors that may be important

for cochlear implant (CI) success in bilateral sequential cochlear implantation is the time interval between implantations. It is well-known that a long inter-implant delay between implants leads to poor speech perception and auditory performance in children with bilateral sequential cochlear implants (BSCI) [10–13]. When they listen with their second CI, weaknesses in auditory behavioral performance have been observed, as well as prolonged P1 responses [14–16]. Gordon et al. compared two groups of BSCI recipients who received a second CI with shorter and longer delays. The children with short inter-implant delays showed better speech perception performance, and shorter P1 latency than children with long inter-implant delays. Additionally, wave eV latencies between ears were similar in eABR assessment for children with short inter-implant delays [16]. Vicente et al. examined differences in speech perception and cortical auditory response between first, second, and bilateral CI stimulation at repeated time points after second CI surgery in sequential bilateral CI user children. They observed significant cortical response asymmetries between first and second CI in

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**Table- 1**  
Participant demographics.

Participants	Sex	Age CI1 (years)	Age CI2 (years)	IID (years)	CI1		CI2		Etiology
					Sound Processor	Device	Sound Processor	Device	
P1	M	1,3	3,5	2,2	Sonatati100	Opus2	Sonatati100	Opus2	Unknown
P2	F	1,0	2,8	1,7	CI422	N6-CP910	CI24RE (CA)	N6-CP910	Unknown
P3	F	1,3	3,9	2,6	Sonatati100	Opus2	Sonatati100	Opus2	Hereditary
P4	F	1,0	3,4	2,4	Sonatati100	Opus2	Sonatati100	Opus2	Unknown
P5	M	1,8	3,4	1,5	Sonatati100	Opus2	Sonatati100	Sonnet	Premature Birth
P6	F	1,4	3,9	2,5	Sonatati100	Opus2	Sonatati100	Opus2	Unknown
P7	F	1,2	3,9	2,6	Sonatati100	Opus2	Sonatati100	Sonnet	Unknown
P8	F	1,7	2,5	0,7	Sonatati100	Sonnet	Sonatati100	Sonnet	Unknown
P9	F	1,0	2,2	1,1	CI24RE(CA)	N5 CP810	CI24RE(CA)	N6-CP910	Hereditary
P10	F	1,1	3,6	2,4	Sonatati100	Sonnet	Sonatati100	Sonnet	Unknown
P11	M	1,0	3,2	2,1	CI24RE(CA)	N6-CP910	CI422	N6-CP910	Unknown
P12	M	2,3	3,4	1,1	CI24RE(CA)	N6-CP910	CI512	N6-CP910	Unknown
P13	F	1,0	2,6	1,6	CI24RE(CA)	N6-CP910	CI24RE(CA)	N6-CP910	Hereditary
P14	M	2,5	3,3	0,8	CI24RE(CA)	N6-CP910	CI24RE(CA)	N6-CP910	Hyperbilirubinemia, ANSD

CI1, first cochlear implant; CI2, second cochlear implant; M, male; F, female; IID, inter-implant delay; ANSD, auditory neuropathy spectrum disorder.

children with longer inter-implant delays. The study found that the auditory performance of the later implanted ear deteriorated with an increasing delay between implants. Moreover, bilateral cortical responses were similar to those of the first CI [17]. Sharma et al. looked at the difference in cortical development in children who received early, simultaneous, BCIs compared with those who received early, sequential, BCIs. The study found that there was no significant difference in P1 responses between the two groups over 15 months [18]. Jeong et al. highlighted the importance of using the first CI, instead of the second CI surgery time for BSCI. If the first CI surgery was performed during the sensitive period, the time intervals between the two surgeries resulted in decreased P1 latency which means inter-implant delay facilitates the early cortical auditory maturation of the second ear [19]. However, it remains unclear whether the length of the delay period is crucial for the development of the auditory cortex in BSCI patients.

Children in Turkey reach out to BCI with a government statement on health applications released in 2016 [20]. To qualify, the child must be younger than four years old with severe to profound sensorineural hearing loss. The aim of this longitudinal study was to determine whether maturational changes in P1 latency occur in children who receive bilateral sequential implants before the age of four, and the effect of inter-implant delay on the time intervals between first and second CI.

## 2. Materials and Methods

### 2.1. Subjects

The study included 14 children (nine female, five male) who had received sequential bilateral cochlear implants. They received the first CI at the mean age of  $1.4 \pm 0.4$  years and the second CI at the mean age of  $3.3 \pm 0.5$  years. The mean inter-implant delay (years) was  $1.8 \pm 0.6$ . Seven children used the Cochlear Nucleus CI system (Sydney, Australia), and 7 children used the MED-EL CI System (Innsbruck, Austria). Subjects were recruited for the study after their second CI surgery at the Marmara University Istanbul Pendik Education and Research Hospital. The study was approved by the local ethical committee of the Marmara University School of Medicine under protocol number 09.2017.440. Informed consent was obtained from the subjects before the study. The inclusion criteria were congenital or prelingual bilateral severe to profound sensorineural hearing loss and no cochlear malformations. All subjects were implanted bilaterally before 4 years of age. The participant demographics of the subjects are shown in Table 1.

### 2.2. Stimulus and presentation

A synthesized speech syllable/da/was used to elicit the P1 response.

**Table- 2**

The parameters of the stimulus/da/.

Stimulus Duration:	206.275 ms
Consonant Duration:	9 ms
Vowel Duration:	174 ms
Pitch (Start - Finish):	109.1–102.1 Hz
F1 Formant Frequency:	732 Hz.
F2 Formant Frequency:	1335 Hz.
F3 Formant Frequency:	2498 Hz.
F4 Formant Frequency:	3058 Hz.
F5 Formant Frequency:	3828 Hz.

The Intelligent Hearing System (SmartEP, Miami, USA) generated and provided the stimulus. The parameters of the stimulus are summarized in Table 2. The level of the stimulus was checked using a sound level meter on the A scale in loudspeakers (Bruel & Kjaer, type 2235, Naerum, Denmark). The stimulus was presented at 70 dB (A). Ambient background noise was below 30 dB (A). A loudspeaker was placed 1 m from the center of the subject's head at a 0-degree angle. The children were seated alone or on a parent's lap in a comfortable chair. The sound processor was set according to the participants' daily listening program. All the children were full-time CI users. During the assessment, the subjects watched a silent cartoon on a computer screen placed in front of them in the sound booth. The P1 response was recorded under the three listening conditions. Initially, the first CI sound processor was active and the second CI was off. Later, the second CI sound processor was active and the first CI was off. Finally, both sound processors were active.

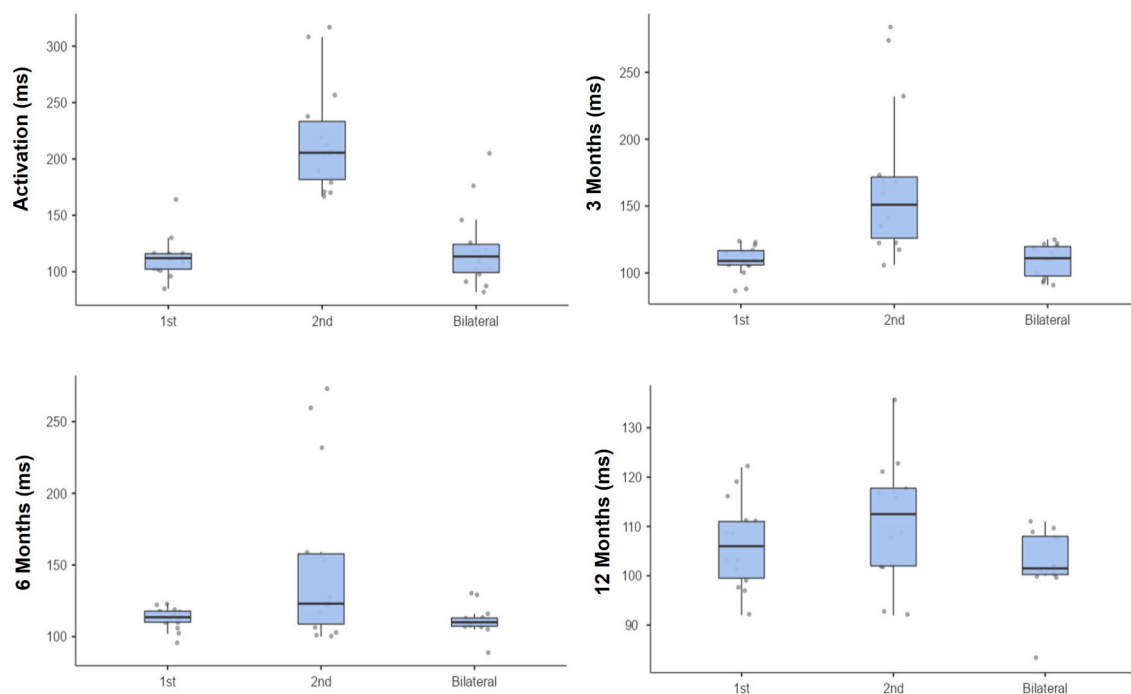
### 2.3. Electrophysiological recording

A two-channel-evoked potential system; Intelligent Hearing System (SmartEP, Miami, USA) was used for electrophysiological recording. The analysis time included a window of 600 ms and a 100 ms pre-stimulus baseline. The inter-stimulus interval was 1.1 s. Responses were filtered from 1 Hz to 40 Hz (6 dB/octave roll off). The artifact rejection level was adjusted at 100  $\mu$ V. Three gold-cup electrodes were used for one-channel recording. Vertex (Cz) was used for the non-inverting electrode. In unilateral listening conditions, the inverting electrode was placed on the contralateral earlobe. The nape of the neck was used as an inverting electrode under the binaural listening condition to reduce CI stimulus artifacts. The second channel of the EP system was used for monitoring the eyeblinks. Electrodes were placed above and below the left eye. Electrode impedances were lower than 3 k $\Omega$  and inter-electrode impedances were 1 k $\Omega$ . Two separate traces were recorded with more than 150 stimuli. The sweeps were summed, and a sweep-weighted grand average of the waveforms was created for each subject. The averaged waveforms were used for analysis. P1 latency was defined as the first

**Table- 3**  
P1 latency values (ms) of each participant based on listening conditions.

Participants	Activation			3 Months			6 Months			12 Months		
	CI1	CI2	Bilateral	CI1	CI2	Bilateral	CI1	CI2	Bilateral	CI1	CI2	Bilateral
P1	111	170	91	108	123	111	115	159	105	122	123	109
P2	108	317	126	100	284	97	119	117	129	111	102	102
P3	102	205	103	106	232	93	106	232	107	101	93	101
P4	113	179	205	123	168	110	111	100	113	92	118	110
P5	96	238	82	110	274	100	110	273	113	99	102	102
P6	85	171	87	87	142	91	102	101	110	97	92	83
P7	103	167	103	106	160	119	96	154	89	111	136	100
P8	101	219	118	117	135	122	117	103	108	98	117	100
P9	116	206	98	116	135	111	113	123	111	109	109	101
P10	116	190	118	115	106	120	110	106	107	103	108	108
P11	164	213	176	124	117	122	118	122	116	109	116	101
P12	113	257	119	121	168	115	122	260	109	119	121	108
P13	116	204	109	106	122	125	114	127	110	116	117	111
P14	130	308	146	88	173	94	123	123	130	103	102	100
Lower Bound 95% CI	103	192	102	103	137	103	109	119	106	102	105	98
Upper Bound 95% CI	122	242	138	115	197	116	117	181	116	111	118	106
Median	112	206	114	109	151	111	114	123	110	206	113	102
Mean	112	217	120	109	167	109	113	150	111	106	111	103

CI1, first cochlear implant; CI2, second cochlear implant.



**Fig. 1.** The box plot illustrates P1 latencies with jittered data at activation, 3 months, 6 months, 12 months for listening conditions (1st CI, 2nd CI, Bilateral). Error bars indicate the 95% confidence interval.

robust positivity between 80 and 300 msn. P1 responses were recorded at the second CI activation and 3, 6, and 12 months after the second CI activation.

**2.4. Statistical analyses**

Because the data were not normally distributed, nonparametric statistics were used. The Friedman analysis of variance test for related samples was used to examine the changes in P1 latency within time intervals for each listening condition. Spearman’s rank-order correlations were calculated to evaluate the relationship between P1 latency and delay between implants, the age of CI implantation in the first year, and the age of CI implantation in the second year.

**3. Results**

In this study, we investigated whether there was any significant difference in P1 response latencies during the one year of BCI experience in children who received BSCI before 4 years of age. We also examined the relationship between these latency differences and the age of implantation and inter-implant delay. At the activation of the second CI, the P1 latencies recorded from the first implanted ear were within the normal range [4,21] whereas the P1 latencies of the second implanted ear were delayed compared with the first implanted ear. The latency of the P1 response of the second ear decreased after 1 month of CI use and reached the normal levels after 3–6 months, depending on the age of implantation. The P1 latency values for each participant, as well as the 95% upper and lower limits, the median values, and the mean values,

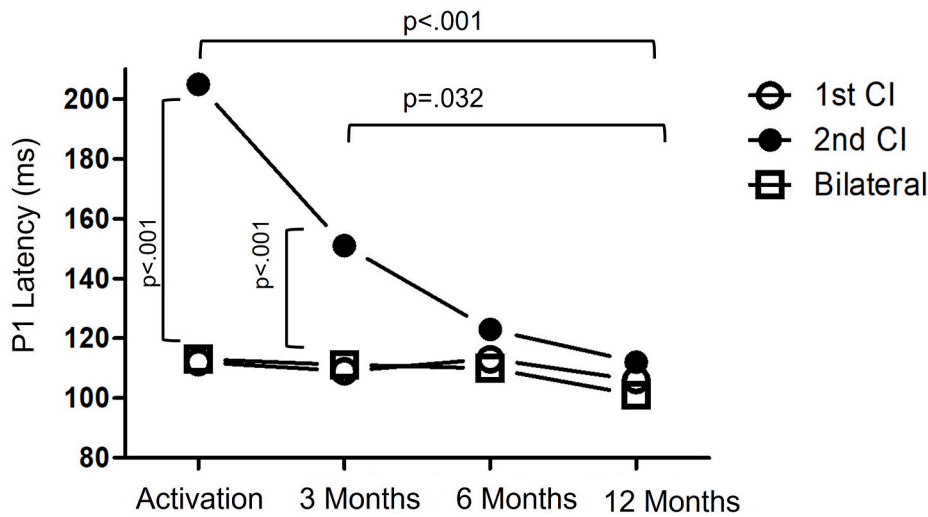


Fig. 2. The plot shows P1 latency medians (ms) with statistically significant differences at time intervals and listening conditions.

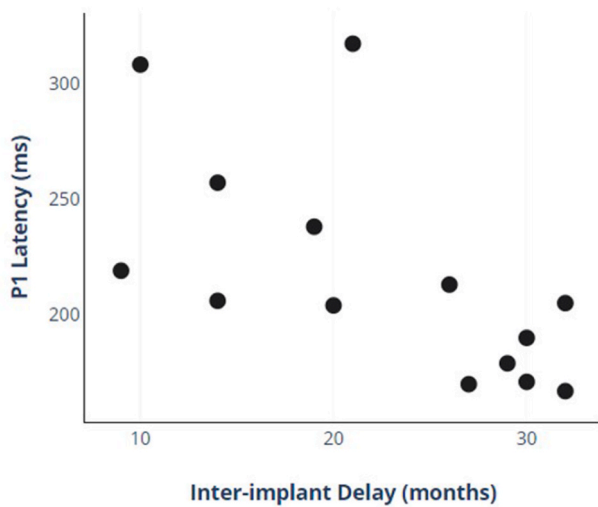


Fig. 3. The scatterplot showing the P1 latencies (ms) of the Second CI activation and Inter-Implant Delay (months).

are presented in Table 3. A box plot with jittered data illustrates the P1 latencies for the first CI, second CI, and bilateral stimulations in Fig. 1.

P1 latency from second CI was statistically significantly different ( $\chi^2(3) = 23.584, p < .001$ ) at the post-implantation intervals. Pairwise comparisons were performed with a correction for multiple comparisons using the Bonferroni correction. Post hoc analysis revealed that P1 latency from the second CI at 12 months was statistically significantly shorter than P1 latency from the second CI at implant activation ( $p < .001$ ), and at 3 months ( $p = .032$ ). There was no difference in the second CI hearing conditions at the other post-implant intervals.

We compared P1 latencies under bilateral CI, first CI only, and second CI listening conditions in the same interval. We found differences at the second CI activation and 3 months after activation between second CI listening and first CI listening ( $p < .001$ ) and between second CI listening and the bilateral listening condition. There was no difference between 6 months and 12-month intervals. The P1 latency medians for listening conditions throughout time intervals are displayed in Fig. 2.

There was a statistically significant ( $p < .05$ ), strong negative correlation between P1 latency at second CI activation and inter-implant delay, ( $r_s = -0.717, p = .004$ ) (Fig. 3), a moderate negative correlation between P1 latency at second CI activation and age of second CI ( $r_s$

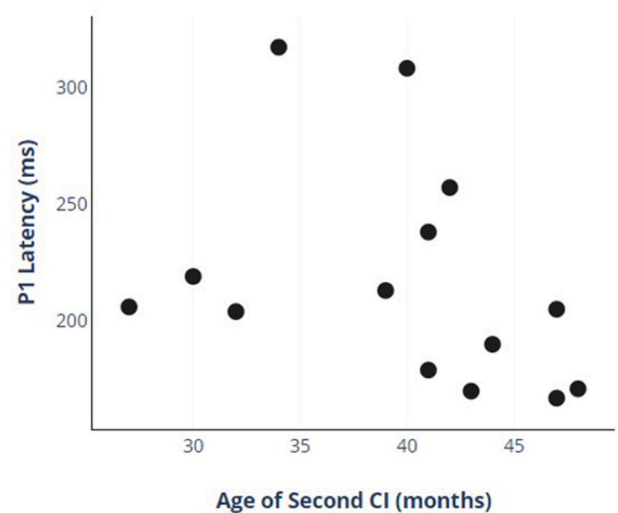


Fig. 4. The scatterplot showing the P1 latencies (ms) of the Second CI activation and age of Second CI (in years).

$= -0.551, p = .041$ ) (Fig. 4). There was no correlation between inter-implant delay and age of implantation with P1 latencies at the 3-month, 6-month, and 1-year intervals.

#### 4. Discussion

In this paper, we described the longitudinal development of the P1 response in children who received BSCIs. All children received their CIs during the sensitive period for cortical auditory maturation described by Sharma et al. [4,6]. All children had a short inter-implant delay of less than two years. Our results showed that the P1 latency of the second CI reaches normative values within 3 months in most children. However, there were differences in the P1 latencies between the unilateral and bilateral listening conditions. We found that P1 latencies were significantly longer for the second CI compared with the first CI and bilateral CI conditions up to 3 months after bilateral CI use. Although not statistically significant, the second-ear P1 latencies were prolonged compared to the first-ear P1 latencies up to 12 months. After 12 months of bilateral CI use, there were no notable differences between listening conditions. We found a strong negative correlation between the inter-implant delay and P1 latencies of the second CI at activation.

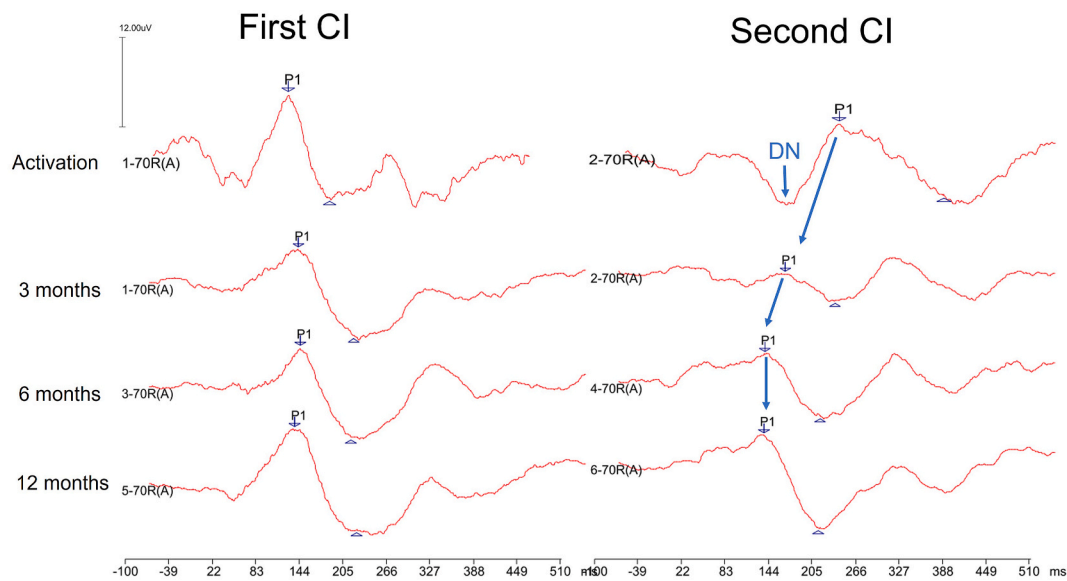


Fig. 5. The grand averaged P1 waveforms of the first and second CI (unilateral listening conditions) at the time intervals. DN: Deprivation Negativity.

Cortical auditory maturation is a process by which the brain changes and develops during childhood and adolescence. This process is characterized by deprivation negativity and abnormal P1 latency in the early stages of electrical stimulation in children with profound hearing loss. However, with increasing duration of use, the late responses shorten and eventually reach the values of normal-hearing peers when the children receive their CI during the sensitive period. Sharma et al. reported that in patients who underwent surgery during the critical period and used unilateral, simultaneous bilateral, or sequential bilateral cochlear implants, P1 latency reached normal levels by the third month [18]. We obtained a similar tendency in our research. P1 response of unilateral second CI listening condition had late latency and poor morphology at the activation time and reached the normative values after three months of bilateral cochlear implant use. This result contributes to the evidence that early implantation leads to normal auditory maturation. In their study, Sharma et al. also observed no significant difference in cortical responses between the first implanted and second implanted ears over the 15 months [18]. This differs from the findings presented here because our study did not track the maturation process of the first ears. Our study began after the start of bilateral CI use. The P1 latency values of the second implanted ear were significantly longer at 3 and 6 months but approached the values of bilateral and first CI listening conditions at 12 months. These findings suggest that although latency values reach the normative values after 3 months of CI use, cortical auditory maturation still lags behind the experienced ear until 12 months of CI use. Fig. 5 illustrates the sweep-weighted grand averaged P1 waveforms of the first and second CI (unilateral listening conditions) at the time intervals.

BSCI users' cortical response and speech understanding performance depend on which ear they use for listening [22,23]. Vicente et al. found persistent cortical response asymmetry between the first and second CI, though no difference between bilateral and first CI listening conditions. They explained their results with the development of aural preference syndrome, which means first CI predominantly contributes to bilateral listening [17]. We also found no difference in cortical responses between bilateral and first CI listening conditions at all time points. However, our results showed no remarkable asymmetry in P1 latencies between the first and second CI listening conditions after six months of bilateral use. Our findings indicate that aural preference syndrome may not take place in short inter-implant delay.

Our data revealed that there was a strong negative correlation between the latency of the P1 response at the second CI activation and the

inter-implant delay. Although there was a relatively long inter-implant delay, the hearing experience with the first CI was greater, so it concluded with shorter p1 latency at the second CI. This result supports the idea of Jeong et al. [19] that the time of the auditory experience with a cochlear implant in the first ear might allow for a faster compensation process in the contralateral ear, as these individuals experience less auditory deprivation. Sharma et al. reported cortical responses of a subject with unilateral hearing loss who used CI in the deaf ear. Cortical responses were similarly compensated rapidly, reduced listening effort, and reversed somatosensory plasticity [24]. These reports suggest that exposing auditory stimuli during the sensitive period is crucial for cortical auditory maturation.

We found no relationship between inter-implant delay, and second CI P1 latencies at 3 months, 6 months, and one-year post-implantation intervals. This is evidence that P1 latencies from first CI and Second CI stimulation are closing each other after the 3 months of bilateral cochlear implant usage.

There are several limitations to this study that should be noted. First, our research is not covering to sequential CI users with a long inter-implant delay of more than four years. Further research should be undertaken to investigate this consideration and compare the difference between long and short inter-implant delay. Second, we do not have normative P1 latency standards, thus we commented on our results according to the literature. Third, although we used the artifact elimination techniques such as eye-blink monitorization and electrode montage modifications, the one-channel recording had limited potential for pure elimination of the electrical artifacts. This restriction may negatively affect the results, especially for the binaural recording. Finally, due to the limited sample size, these results should be interpreted cautiously.

## 5. Conclusion

Our results indicate that longitudinal changes in cortical auditory evoked responses lead to normal auditory maturation and support the idea that the time of the auditory experience in the first ear might allow for a faster compensation process for sequentially implanted children with short inter-implant delay. We believe we should better understand the cortical auditory maturation process in the early period of sequential bilateral cochlear implantation. This is because the BSCI could be a necessity instead of an option, especially if there are indications of vestibular concerns [25,26]. Our results will help and enlighten future studies in this perspective.

## Declaration of competing interest

The authors declare no conflicts of interest.

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