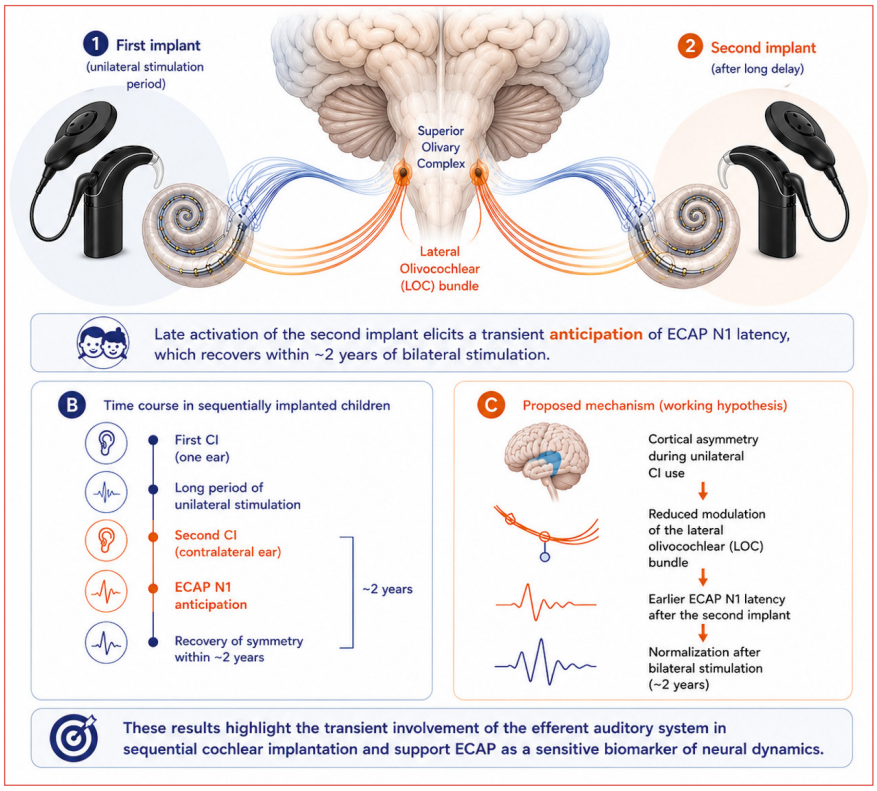
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Exploring asymmetry of electrical compound action potential latencies in sequential cochlear implants as a possible effect of the lateral olivocochlear bundle

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Cover figure. Transient anticipation of electrical compound action potential (ECAP) N1 latency following sequential cochlear implantation (CI) in congenitally deaf children. **A,B)** Activation of the second CI after a prolonged period of unilateral stimulation is associated with a transient shortening of ECAP N1 latency, which returns toward symmetry within approximately 2 years of bilateral stimulation; **C)** Proposed mechanism: cortical asymmetry related to unilateral CI use may alter lateral olivocochlear efferent modulation, leading to earlier ECAP N1 responses after activation of the second implant.

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Summary

Objective. Electrophysiological evaluations of the second cochlear implant (CI) in sequentially implanted patients usually consider the brainstem with electrically evoked auditory brainstem responses and the auditory cortex with slow responses. To further understand auditory electrophysiological behaviour after the second implantation, the present study investigated auditory nerve activity using electrical compound action potential (ECAP).

Methods. Of 167 bilaterally implanted patients, 73 were evaluated and divided into 2 groups: patients with simultaneous (33 children and 8 adults) and sequential (21 children and 11 adults) surgeries. The sequential surgeries were further grouped into "short delay" (< 4 years) and "long

delay" (> 4 years), considering the time spent between procedures. Every patient was assessed by evaluating the N1 wave of ECAP, focusing on the latencies in both ears.
Results. The ECAP's interaural latencies were not statistically different in simultaneous patients and sequential progressive/acquired deaf adults. In contrast, in sequential congenital deaf children, the latencies of the second implant were temporally earlier than those of the first implant, but symmetry recovered within 2 years after surgery.
Conclusions. The results revealed that late-sequential CI stimulation generates asymmetric interaural activity at the first neuron in congenitally deaf children. Such an asymmetry is due to the anticipation of the sequential N1 wave ECAP, rather than the expected delay. The hypothesis attributes it to a temporary lack of efferent system tuning, particularly the lateral olivocochlear bundle, which should still be active in implantees. These findings could enhance the benefits of sequential CI mapping by implementing a stimulation delay with a temporal duration similar to N1 anticipation until binaural processing normalises.

Keywords: cochlear implant, hearing loss, electric compound action potential, Neural Response Telemetry, lateral olivocochlear bundle

Introduction

Bilateral cochlear implantation (CI) has become a frequent rehabilitative choice for patients with severe to profound hearing loss. Both ears can be operated on either in the same operating session (simultaneous surgery) or at 2 different times (sequential surgery), prolonging the sensory deprivation of the second operated ear [1]. However, clinical practice and the literature show that the outcomes of sequential CI patients with a long interval between the 2 surgeries [2] are not as satisfactory as those of patients who have undergone bilateral simultaneous cochlear implantation [3]. Even the age of the first implant plays a role in the outcome [1,4] as does the patient's age at the second surgery [5].
It seems logical to consider the long period of hearing deprivation in the second implanted ear as the cause of the poor results, leading to the so-called "aural preference syndrome" [3]. Nevertheless, deprivation may not be the only explanation. A study by Burdo et al. [6] compared the results of sequentially late-implanted ears in 2 homogeneous groups: one using 2 implants and the second using only the sequential, because the first was explanted (unilateral stimulation). The unexpected results showed that the ear sequentially implanted performed worse in the bilateral group when both implants were kept active. The authors noted that this surprising difference was due to the inhibitory effect of the first-implanted ear on the second-implanted ear, since the 2 groups undergoing sequential surgeries had a similar period of hearing deprivation. In other words, since the unilateral sequential ear performed better than the bilateral patients, it is evident that the first-implanted ear would exert an inhibitory effect on the second, aggravating its poor performance due to hearing deprivation [3,6,7].
Many authors have been interested in the neurophysiological aspects of the aural preference syndrome. The initial studies compared differences in electrically evoked brainstem responses (eABR) [8], showing an increased V-wave latency in sequential patients in the second implant compared to the first [2].
Focusing on cortical activity, several studies showed that a longer P1 latency was observed up to 1 to 3 years after the latest surgery in paediatric patients with long inter-surgical interval [9], and abnormal responses with considerable variability in paediatric patients with more than 2 years between surgeries [2].
Unfortunately, no studies have investigated neural conduction in the eighth cranial nerve in sequentially implanted patients. This is because the neural activity of the auditory nerve is most frequently investigated using eABR, and the implant's electrical artifact prevents identification of the I-wave (which reflects cochlear nerve activation).
These issues can be managed using a near-field procedure, the electrically compounded action potential (ECAP), which records the synchronous activation of auditory nerve fibres triggered by electrical stimuli delivered via a CI [11].
ECAP is a routine evaluation, especially for identifying the objective thresholds for mapping the patient. However, in bilateral implantation, differences in eighth nerve responses between simultaneous and sequential CIs have not yet been evaluated. This study aims to identify the interaural differences in the N1 peak's ECAP latency, assuming latency is the main index of neural function.

Materials and methods

Patient cohort

Following approval by the Institutional Review Board of the University of Padua (protocol 34357 I.17), a retrospective review of electronic medical records and fitting parameter databases was conducted for 167 Cochlear™ Nucleus® cochlear implant (CI) recipients who were consecutively evaluated at our institution.
For the purposes of the present study, inclusion required the availability of comparable ECAP measurements, specifically the ability to reliably compare N1 amplitude values recorded at electrodes 22 and 10. Based on this predefined

electrophysiological criterion, 73 patients were ultimately selected for analysis (39 females, 34 males).
The cohort included both paediatric and adult CI recipients and comprised patients who had undergone bilateral implantation either simultaneously or sequentially, as detailed in Table I.
Of the 73 patients included, 54 were children and 19 were adults at the time of implantation. Among children, all cases were congenital deafness.
Among adults, 4 patients (21%) had congenital deafness, while 10 presented with progressive hearing loss and 5 with acquired post-lingual deafness.
Regarding the severity of hearing loss, 17 patients (23%) were classified as having severe hearing loss, while 56 patients (77%) had profound hearing loss.
All sequential CIs were hearing-aid users in a bimodal stimulation, before the second surgery.
In the paediatric group, bilateral implantation was performed: simultaneously in a subset of children, with the first surgery occurring at a mean age of 2.9 years (range: infancy to 15 years); sequentially in the remaining cases, with the first implant placed at a mean age of 3.5 years (range: 1-8 years) and the second implant at a mean age of 11.1 years (range: 4-17 years). For sequential paediatric cases, the inter-implant interval exceeded 4 years in the majority of patients.
In the adult group, bilateral implantation was carried out, which was simultaneous in patients with a mean age at surgery of 40.7 years (range: 21-52 years); sequential in patients with a mean age at first implantation of 33.1 years and at second implantation of 39.3 years. In adults undergoing sequential surgery, the inter-implant interval was shorter than 4 years in most cases, with only a minority exceeding this interval (Tab. I).
The implant models used were CI24RE (CA) (91 ears), CI512 (28 ears), CI24M (12 ears), CI24R (CS) (11 ears), CI24R (CA) (5 ears), and CI24R (1 ear). In all cases, full electrode array insertion was achieved, with no morphological or electrical abnormalities, as confirmed by postoperative cochlear view X-ray imaging and impedance telemetry data. All ECAP recordings and electrophysiological evaluations were performed by the same author (LD) to ensure methodological consistency.

Table I. Demographic characteristics of the study cohort.

	54 children		19 adults	
	Simultaneous	Sequential	Simultaneous	Sequential
Sex	16 ♀ 17 ♂	12 ♀ 9 ♂	4 ♀ 4 ♂	7 ♀ 2 ♂
Age 1st surgery	0 -> 15 years old (mean 2.9)	1 -> 8 years old (mean 3.5)	21 -> 52 years old (mean 40.7)	10 -> 50 years old (mean 33.1)
Age 2nd surgery		4 -> 17 years old (mean 11.1)		20 -> 50 years old (mean 39.3)
Interval between surgeries		> 4 years 19 pts. < 4 years 2 pts.		> 4 years 3 pts. < 4 years 8 pts.

ECAP measurements

Since all CIs were Cochlear™ Nucleus®, ECAP measurements (NRT, Neural Response Telemetry) were conducted using the dedicated Custom Sound EP 4.0, with forward masking subtraction [11].
The parameters used were a rate of 80 Hz with 50 sweeps, a gain of 50, and 120 microseconds as a delay. The AutoNRT procedure was used as protocol except when manual registration was necessary [12].
To compare the NRT latencies between ears, we chose waveforms with similar interaural N1-P1 amplitudes (+/- 15μV) to guarantee "loudness" symmetry [13]. The evaluations were performed at time 0 (the first postoperative evaluation) and 2 years after the second surgery in sequential patients, corresponding to the second year post-implantation in simultaneous ones. We considered the waves N1 temporally asymmetric when the interaural latency difference exceeded 30 microseconds.
Electrode 22 was the first choice, but if the recording was unavailable or not helpful for amplitudes, we moved on to evaluate the electrode [8], maintaining the criterion of amplitude analogy. If similar amplitudes were not found on the available electrodes in at least one reference period, the patient was excluded.
The amplitude criterion was essential to obtain homogeneous recordings, even when recording was manual in one ear and automatic in the other. After comparing the latencies of the N1, we divided the patients into age and interaural timing (delay, early, symmetric) categories for sequential implants and into right-left categories for simultaneous implants.

Statistical analysis

The results are presented as averages and standard deviations for statistical analysis. Nonparametric statistical techniques were used for the inferential analysis. In particular, the student's T test (for independent branches) was used to compare groups (group 1 vs group 2). The differences were considered to be significant if $p < 0.05$ (significance 95%) and as strongly significant if $p < 0.001$ (significance 99%). The Pearson correlation coefficients were then used to analyse

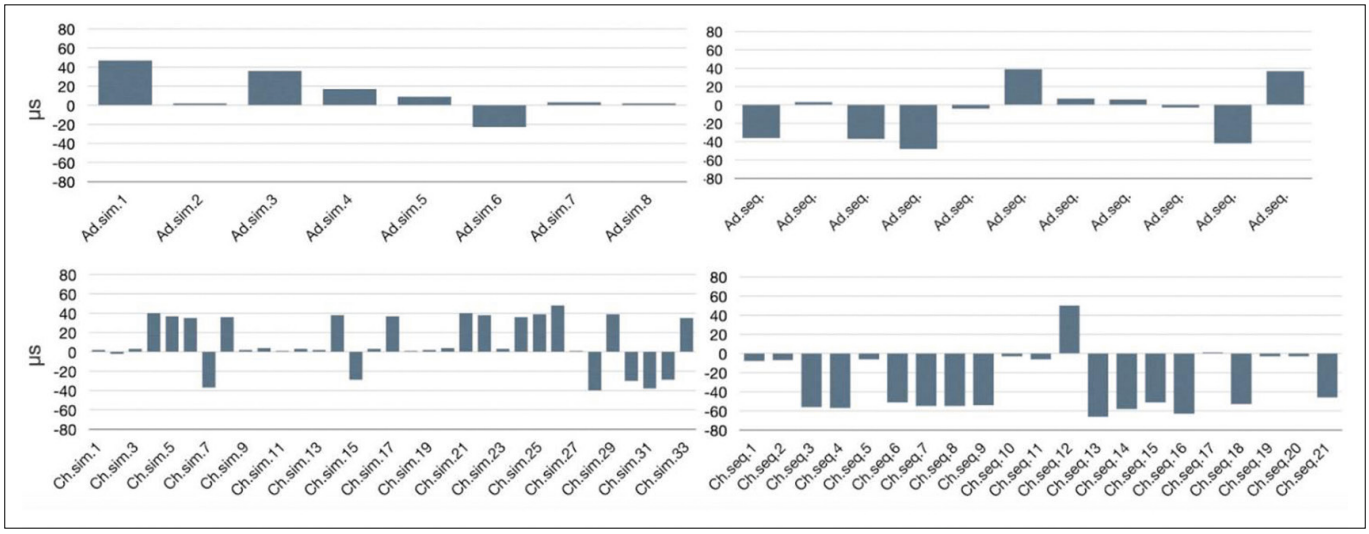


Figure 1. N1 interaural latency differences for each patient of the 4 groups (adults simultaneous, adults sequential, children simultaneous, andchildren sequential). Negative numbers indicate the anticipation entity in μs of the sequential ECAP, and the positive one indicates a delay. In the case of simultaneous patients, the differences were calculated from left minus right ear response.

the significant statistical data in the samples. Only values of roXY between 0 and 0.3 (indicating weak correlation), roXY between 0.3 and 0.7 (indicating moderate correlation), and roXY > 0.7 (indicating strong correlation) were considered.

Results

In the cohort of adult patients, the comparison between sequential and simultaneous showed no significant difference in N1 latency at the first follow-up (p = 0.3901) or at the second follow-up (p = 0.7568). The comparison between groups of the same sex did not show significant differences at either the first (males p = 0.1239; females p = 0.9014) or the second follow-up (males p = 0.9472; females p = 0.6146) (Fig. 1).

Considering the subdivision of sequential implants based on the inter-surgical interval, in adult patients, no statistically significant results were observed in the "short delay" group (first control p = 0.7514; second control p = 0.6853) compared with the "long delay" group (first control p = 0.2532; second control p = 0.4469).

In children, the N1 interaural latency difference between the groups sequentially and simultaneously implanted reported highly significant differences (p = 0.0002) at the first evaluation because the latency responses of sequential ears were earlier than the simultaneous ones, with a mean of -43 msec versus a slight and not significative delay of 15 msec in simultaneous. Ninety per cent of the sequentially implanted highlighted the N1 anticipation versus 19% of the simultaneously implanted. Conversely, at the second check, no difference between sequential and simultaneous was detected (p = 0.0945).

The sex-based subdivision remained statistically significant in paediatric patients. At the first follow-up, significance was maintained in both males (p = 0.0051) and females (p = 0.0131), but no significant difference was observed at the subsequent measurement (males p = 0.1966; females p = 0.2868).

Regarding the inter-surgical interval, the N1 latency anticipation was statistically significant and did not differ between "short" (p = 0.0007) and "long" (p = 0.0166) delay sequentially implanted children.

In the sequential children group, Pearson correlation coefficients were also performed between the N1 interaural asymmetry and the variables of sex, age at first implant, age at second, and inter-surgical interval.

While there was no correlation between sex (rxy = close to 0), there was a weak positive linear correlation with the inter-surgical interval (rxy = 0.041) and age at second implantation (rxy = 0.265), and a moderate correlation with age at first implantation (rxy = 0.315) (Fig. 2).

Discussion

The present study showed a significant interaural latency asymmetry in auditory nerve activity in children with congenital deafness who received sequential implants, due to the anticipation of the ECAP N1 wave.

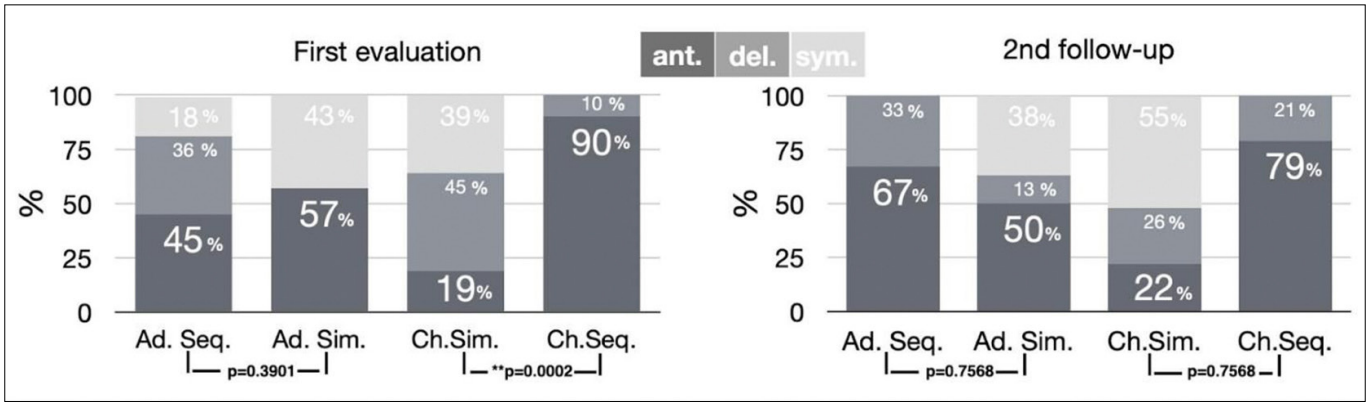


Figure 2. Proportion of the cohort with anticipated, delayed, or symmetrical latency (second minus first in sequential implants, right minus left in simultaneous) at first and second check-ups. Statistical significance is present only in the children's sequential group at the first ECAP control (N1 anticipation strong grey, delayed medium grey, symmetric light grey).

The age at the first implant is relative to the variables [4], while the absolute age and the inter-surgical interval play a less critical role. Such a child's asymmetry recovered within 2 years.

Conversely, the adult group showed no significant latency differences, but to interpret the results, we must consider that all the children were congenitally deaf, and 80% of adults had progressive or acquired auditory memory.

From a speculative point of view, there are 2 causes that may account for this surprising finding: the first technical, the second biological.

The technical one concerns an asymmetric interaural stimulus that evokes the ECAP. However, this cannot be because the study design was rigorous enough to avoid this possibility, thanks to the amplitude criterion.

The biological causes should consider 2 distinct origins: the nerve itself or a lack of modulation by the lateral olivocochlear (LOC) bundle fibers.

We exclude the nerve itself because deprivation provokes an involution of the nerve fibres regarding integrity and numbers, consequently causing a delay and not an ECAP anticipation. Therefore, for exclusion, the LOC efferent activity could cause the phenomenon, as it is the only system interfering with the eighth nerve.

The olivocochlear efferent system is under cortical control. It is a complex of descending fibres that originates at the pre-olivary region of the superior olivary complex (SOC) and divides into the medial olivocochlear (MOC) and the LOC bundle. Although the MOC bundle forms synapses with contralateral outer hair cells and therefore does not affect patients implanted, the LOC bundle forms direct synapses, predominantly ipsilaterally, with type I afferent auditory fibres, as evaluated by ECAP [14]. Another component of the efferent system, originating at the cortical level, articulates with the LOC: the rostral efferent system (RES), which modulates the action of the olivocochlear bundle too [15].

A few characteristics of the LOC's function are known. Its activity seems predominantly inhibitory, delaying and not anticipating the nerve potential, as the present study showed instead.

We can explain the contradiction in 2 ways. The first considers that LOC can also play excitatory functions mediated by acetylcholine [16]. The second could explain the transitory ECAP anticipation as the effect of an immature and inconsistent inhibitory activity at the beginning of the sequential stimulation.

Inferring the role of LOC modulation to explain the ECAP transitory latency anticipation in sequential CIs is logical because no other structures can modify nerve conductibility evaluated near-field with ECAP.

Previous animal studies highlighted the role of the cortical mechanism driving LOC activity on the acoustic nerves and its dysfunctional effects. Consistent with studies by Vale et al. [17,18] and Anderson et al. [19], the early N1 activation could be due to a pathological mechanism of disinhibition, mediated by the cortex, of the LOC system on the fibres of the newly implanted ear. Similar results to the present study were observed after a cortical lesion in rats, namely the anticipation of the I wave in the acoustic ABR, representing the far-field equivalent of ECAP [20].

Comparing the physical cortex lesion with the functional dysfunction provoked by deprivation in unilateral cochlear implantation [21], we can confirm the hypothesis of the LOC's

involvement in anticipating the neural response in the sequentially implanted ears, because it is temporarily out of control due to the auditory cortex being temporarily impaired.
The activation of binaural processing over time should have recovered the pathological mechanism underlying the return to regular N1 responses, which was no longer statistically significant in paediatric patients at 2-year follow-up. The adult patients in this study would not show such latency anticipation, since they were post-lingual and already had a well-established auditory system.
Some limitations of the present study should be mentioned. First, the study is purely electrophysiological in nature and no behavioural or functional auditory outcome measures (e.g., speech perception in noise, localisation tasks, or binaural integration tests) were available for correlation with ECAP latency asymmetries. Second, the interpretation involving the LOC system remains inferential. Third, ECAP recordings were limited to selected electrodes and required amplitude-matching criteria. Fourth, the follow-up interval was limited to 2 years. Fifth, no information was available about the use of hearing aids in the time between surgeries, another possible influencing factor on the results. Finally, no direct comparison between ECAP and eABR was performed within the same cohort.
From a scientific point of view, the comparison between ECAP and eABR data may help in better understanding this interpatient electrophysiological influence on hearing function. Also, monitoring ECAP latencies variations in shorter follow-ups may help in better clarifying this change over time.

Conclusions

The electrophysiological evaluations of sequential CIs focused on the brainstem and cortical responses, identifying a delay (V peak) starting rostrally after the olivary nuclei because the III peak latency of eABR is symmetric between ears [8].
The present study investigated the response of the eighth nerve at the beginning of the auditory pathways, completing the literature on the topic.
We identified a temporally earlier latency of the ECAP response in the second ear of sequential congenitally deaf children, potentially related to the modulation effect of the efferent system on nerve fibres, particularly the activity of LOC bundle fibers, probably wrongly driven by cortical areas stimulated asymmetrically during the CI unilateral use. The interaural latency asymmetry disappears within 2 years after surgery.
The practical effects of the present study could be to speed up the achievement of interaural latency symmetry in sequentially implanted CI patients by delaying stimulation by the same amount as the nerve latency anticipation. This suggestion, along with the recommendation of Lopez et al. [22] to simulate the medial olivocochlear bundle, could complete the preprocessing of CIs.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

All authors contributed to the interpretation of the data, critically revised the manuscript and approved the final version of it.

Ethical consideration

This research was funded by the Italian Ministry of Health with the PNRR-MAD-2022–12376739 Grant ("SYNPHONIA") awarded to Patrizia Trevisi.
The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.
Written informed consent was obtained from each participant/patient for study participation and data publication.
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