



The P300 Auditory Evoked Potential in Cochlear Implant Users: A Scoping Review

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Abstract

Introduction The P300 auditory evoked potential is a long-latency cortical potential evoked with auditory stimulation, which provides information on neural mechanisms underlying the central auditory processing.

Objectives To identify and gather scientific evidence regarding the P300 in adult cochlear implant (CI) users.

Data Synthesis A total of 87 articles, 20 of which were selected for this study, were identified and exported to the Rayyan search software. Those 20 articles did not propose a homogeneous methodology, which made comparison more difficult. Most articles (60%) in this review compare CI users with typical hearing people, showing prolonged P300 latency in CI users. Among the studies, 35% show that CI users present a smaller P300 amplitude. Another variable is the influence of the kind of stimulus used to elicit P300, which was prolonged in 30% of the studies that used pure tone stimuli, 10% of the studies that used pure tone and speech stimuli, and 60% of the studies that used speech stimuli.

Conclusion This review has contributed with evidence that shows the importance of applying a controlled P300 protocol to diagnose and monitor CI users. Regardless of the stimuli used to elicit P300, we noticed a pattern in the increase in latency and decrease in amplitude in CI users. The user's experience with the CI speech processor over time and the speech test results seem to be related to the P300 latency and amplitude measurements.

Keywords

- ▶ auditory evoked potential
- ▶ cochlear implant
- ▶ electrophysiology
- ▶ neuronal plasticity
- ▶ audiology

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Introduction

The P300 auditory evoked potential is a long-latency cortical potential evoked with auditory stimulation. It is obtained by recording and mediating stimulus responses picked up with electrodes placed on the skull surface next to where the responses are generated. It distinguishes the rare auditory stimuli from the frequent ones, known as the oddball paradigm.^{1,2} In normal-hearing adults, this potential appears approximately 300 milliseconds after the stimulus is presented, with positive voltage and amplitude between 5 and 20 μ volts.³⁻⁶

Event-related potentials, evoked with auditory stimuli, provide information on neural mechanisms underlying auditory processing. This results from the person's response to the task of distinguishing the target stimuli from the pattern ones.⁷ The P300 is an objective and non-invasive technique to further study the auditory nervous system.⁸⁻¹⁰

The P300 is recorded in a sequence of peaks with negative-positive-negative-positive polarity (N1-P2-N2-P3). The literature also describes the existence of P300 recorded with two peaks, subcomponents P3a and P3b. The P3a occurs earlier, at approximately 240 milliseconds, related to the awareness process, getting automatic and involuntary attention.¹¹ It probably occurs automatically in response to the great differences in stimuli and does not vary with the task required. Recent studies have demonstrated, with a continuous performance task, the decision-making neural determinants in the intertarget interval. They also showed that the lowest pretarget levels were associated with faster reactions.¹² Meanwhile, the P3b occurs later, at approximately 350 milliseconds, and only when the person is actively distinguishing the stimuli.^{13,14}

The task proposed by the evaluator may affect the P300 recording due to the complexity of the activity requested; for example, counting mentally, lifting a finger, or pressing a button when the rare stimulus is identified.^{14,15}

The P300 can be measured in subjects with hearing loss as long as they can detect rare stimuli among the frequent ones. It can be used to monitor individuals with hearing loss who are undergoing rehabilitation, since studies have shown decreased P300 latency after rehabilitation therapy, highlighting those subjects' cognitive improvement.^{16,17} Studies show a direct association between hearing loss and impaired cognitive capacity, which may be related to the degree of hearing loss, resulting in longer N1, N2, and P300 latencies.¹⁸

The changes in the auditory function recorded with an electrophysiological assessment of the auditory system have been addressed in the literature. Subjects with auditory deprivation, even after a long period of time, can have their auditory capacities restored with electrical stimulation via the cochlear implant (CI).

It is important to highlight the consensus in the literature regarding the relationship between auditory deprivation and cognitive function loss. This is particularly due to the deficit in the afferent auditory system, related to the auditory capacities, attention, memory, and decision-making, all of which are identified in the recordings of the long-latency

auditory potentials, with longer latencies registered when the P300 results are compared between subjects with and without hearing loss.¹⁹⁻²¹

The use of CI in people with hearing loss has been quite often employed as a resource in the rehabilitation process because it restores auditory input, giving access to speech sounds. Some authors have shown that it is possible to achieve P300 potential in CI users,²² while others have presented studies in CI users with different oddball paradigms: tone-burst at different frequencies,²³⁻³⁴ speech stimuli with various contrasting sounds,³⁵⁻³⁹ even music to assess the subjects' cortical function,⁴⁰ and both pure tone and speech stimuli.^{41,42}

This review study is relevant because it aims to understand the relationships between these measures and the possibilities of monitoring the cortical responses with the new auditory input. Hence, it can aid in decision-making, intervention planning, and in the guidance and instruction of patients and family members.

Review of the Literature

Material and Methods

Considering the potential clinical applicability of P300 as a tool to monitor neuronal plasticity in CI hearing rehabilitation, our study raised the question of how the P300 is used to track CI rehabilitation, based on the scoping review PCC (Population, Concept, and Context) acronym.⁴³ We previously defined the acronym as P: adult subjects with postlingual hearing loss, C: CI surgery, and C: the P300 examination. To answer the question, our objective was to analyze the P300 latency and amplitude values in CI users who were adults with postlingual hearing loss.

Methodological Framework

The methodological approach of this study was based on the Joanna Brigs Institute (JBI) for Scoping Reviews.⁴³

Type of Study

This is a scoping review, a specific type of systematic review which aims to map relevant scientific production in a certain field – in this case, the medical field. The research question approached the current evidence in the literature regarding P300 amplitude and latency with speech and pure tone (tone-burst) stimuli, and its clinical applicability to CI users. Thus, we searched for controlled and non-controlled terms identified in the Medical Subject Headings (MeSH), the National Library of Medicine (NLM), and the Health Science Descriptors (DeCS).

We developed the search strategy with the PCC (Population – postlingual adults; Concept – CI surgery; Context – P300 result comparison) structure⁴⁴ and searched for original articles in the following databases: PubMed/Medline, EMBASE, LILACS, and Web of Science, according to their criteria and manuals. The words used as descriptors in the search are shown in **Table 1**.

The research strategy was standardized for all databases, making adjustments when necessary. The files were

Table 1 Cross-check data from PubMed/Medline, EMBASE, LILACS, Web of Science.

Database		Strategy	Population	Concept	Context
PubMed, Web of Science, EMBASE		Adult [Mesh] OR Adults OR post-linguals OR post-lingual	Adult [Mesh] OR Adults OR post-linguals OR Cochlear Implants [Mesh] OR Implants, Cochlear OR Cochlear Implant OR Implant, Cochlear OR Cochlear Prosthesis OR Cochlear Prosthesis OR Prosthesis, Cochlear OR Prosthesis, Cochlear OR Auditory Prosthesis OR Auditory Prosthesis OR Cochlear OR Auditory Prosthesis OR Auditory Prosthesis, Auditory OR Prosthesis, Auditory	Cochlear Implants [Mesh] OR Implants, Cochlear OR Cochlear Implant OR Implant, Cochlear OR Cochlear Prosthesis OR Cochlear Prosthesis OR Prosthesis, Cochlear OR Prosthesis, Cochlear OR Auditory Prosthesis OR Auditory Prosthesis, Auditory	Event-Related Potentials, P300 [Mesh] OR Event-Related Potentials, P300 OR Event-Related Potential, P300 OR P300 Event-Related Potential OR P300 Component OR P300 Components OR Event-Related Potentials, P3 OR Event Related Potentials, P3 OR P3 Event-Related Potentials OR Event-Related Potential, P3 OR P3 Event Related Potentials OR P3 Event-Related Potential OR Evoked Potentials, P300 Component OR P300 Event-Related Potentials OR P3b Event-Related Potentials OR P3b Event-Related Potentials OR Event-Related Potentials, P3b OR P3b Event-Related Potentials, P3b OR P3b Event-Related Potentials OR P3b Event-Related Potential OR P3a Event-Related Potentials OR Event-Related Potential, P3a OR Event-Related Potentials, P3a OR P3a Event Related Potentials OR P3a Event-Related Potential
LILACS		Cochlear Implantation OR Implantación Cochlear OR Implants Cochlear OR Implants Cochlear OR Implants Cochlear OR Implants Cochlear OR Implants Cochlear	Cochlear Implantation OR Implantación Cochlear OR Implants Cochlear OR Implants Cochlear OR Implants Cochlear	Cochlear Implantation OR Implantación Cochlear OR Implants Cochlear OR Implants Cochlear OR Implants Cochlear	Event-Related Potentials, P300 OR Potenciales Relacionados con Evento P300 OR Potencial Evocado P300 OR Componente P300 de Potencial Evocado

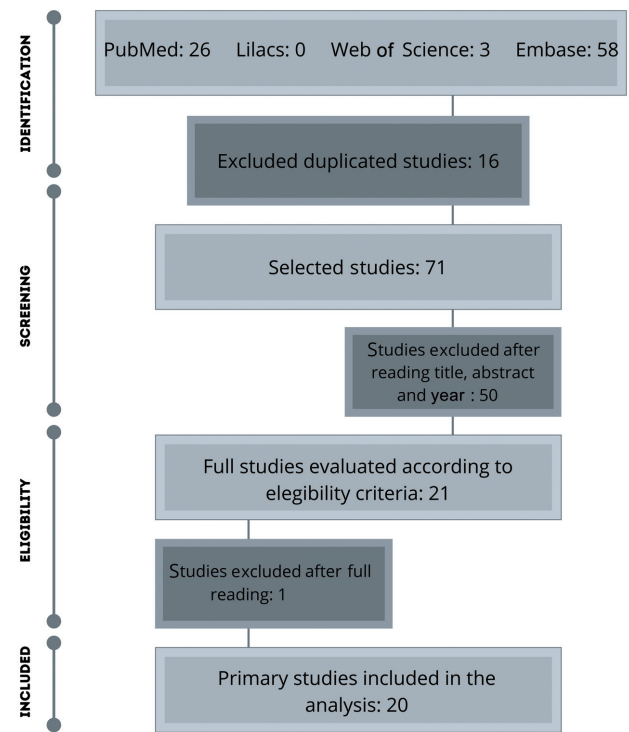


Fig. 1 Flowchart of study identification, selection, and inclusion in the scoping review.

exported to the EndNote (Clarivate Analytics, Philadelphia, PA, USA) reference manager, version X5, to remove the duplicates. Then, a new file was created and exported to Rayyan (Rayyan Systems Inc. Cambridge, MA, USA) software, a specific tool to select studies in review methods.⁴⁵

The selection criteria were as follows: studies in Portuguese, Spanish, and English; published between January 1991 and May 2018; approaching adult subjects with postlingual hearing loss, who had been submitted to CI surgery and were tested with P300. The following were excluded: case reports, reviews, articles in press, letters to the editor, and studies in languages in which the researchers are not fluent.

The flowchart (► **Fig. 1**) shows the process of identifying, selecting, and including primary studies, retrieved from the databases regardless of the level of evidence.

Two reviewers selected the studies independently, following the previously established inclusion and exclusion criteria. In the first phase, they read the titles and abstracts and excluded the articles that did not meet the criteria. The reviewers met to solve divergencies by consensus. In the second phase, texts were fully read, excluding those that did not meet the criteria. The interrater reliability was set at 90%. In case of disagreement, a third reviewer was invited.

A standardized sheet was used to extract data that characterized each study (author, year, methodological aspects, and main results), the type of stimulus they used, and the P300 measurements. Descriptive data analysis was used to present the results. They were organized in tables with the synthesis of the studies, searching for answers in each

article's latency and amplitude measurements, variables, and parameters. The data were reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).⁴⁶

Results

A total of 87 articles were selected in the Rayyan software: 58 from EMBASE, 26 from PubMed, and three from the Web of Science; none was retrieved from LILACS. Of those 87 articles, 16 were excluded for being duplicates. Another 50 were excluded from the remaining 71 articles after reading their title, authors, year, and abstract. Finally, one article was excluded for not including P300 testing. Hence, the final sample comprised 20 articles.

Among the 20 selected articles, 3 were published in 2004, and one each in 2018, 2016, 2015, 2012, 2007, 1999, 1998, 1997, 1996 (E1–E20, ►Table 2).^{23–42} All the studies were published in English: 19 in international journals and only one in a Brazilian journal, which highlights the lack of national articles on this topic.^{23–42}

The parameters used to elicit P300, including details about stimulus presentation, are described in ►Table 2. Twelve articles used pure tone stimuli (E1–E12),^{23–32} five articles used speech stimuli (E13–E17),^{35–39} one study used music stimuli (E20),⁴⁰ and two articles used both speech and pure tone stimuli (E18 and E19).^{41,42}

The sample size and type of stimuli can influence P300 recordings, specifically the latency and amplitude measures. Hence, we aimed to demonstrate results regarding these variables (►Table 3).

Discussion

Variability Among Studies

We verified that the methodologies of the selected articles were not homogeneous. Their protocols were associated with different criteria and P300 parameters, according to the objective of each study, as the test parameters are related to what is being investigated. Such heterogeneity makes it difficult to compare the studies and establish a protocol to assess and monitor CI users.

Most articles (60%) used pure tone stimuli for P300, while another five (25%) used speech, two (10%) used both speech and pure tone, and one used music stimuli (►Table 2).^{23–42} These varied P300 recording parameters⁷ have been broadly discussed in the literature and were observed in this review. It seems coherent to use speech stimuli to study cortical auditory potentials in patients who use electronic hearing systems, including CI users. In this type of intervention, the objective is to provide auditory input and give the patient access to speech sounds.

P300 Latency

Among the studies that used pure tone, 6 (E2, E3, E4, E5, E10, E17)^{24–28,39} found prolonged absolute P300 latency in the cortical potential examination. Nevertheless, absolute latency may be associated with the time of CI experience, as

observed in some studies that used pure tone and showed that absolute latency intervals decrease over time (E1, E7, and E9).^{23,29,31}

The type of stimulus may also influence the latency measures, which were found to be prolonged in a study using both pure tone and speech stimuli (E18).⁴⁰ Speech is a more complex stimulus, and it stimulates a different cortical region from the pure tone stimulus. Authors such as Linden (2005)⁴⁷ and Polich (2007)¹³ point out that P300 latency is related to task complexity and increases with more difficult discrimination stimuli.

Age has also been pointed out as a possible reason for increased absolute latency (Henkin, Y. et al., 2014),³⁸ as well as the etiology of hearing loss, as identified in E12, which focuses on meningitis patients. Moreover, higher P300 latencies are found when there are poor speech perception results.

Despite the heterogeneity, 60% of the studies in this review (►Table 3) compare CI users with normal-hearing people, and their data show increased P300 latencies in CI users (E1, E2, E3, E4, E5, E10, E11, E13, E16, E17, E18, and E20).^{23–27,32,33,35,38–41} On the other hand, some of them found similar P300 latency results between CI users and normal-hearing individuals, even after a long period of auditory deprivation (E12, E14, and E15).^{34,36,37}

Authors obtained increased P300 latencies in CI users, suggesting that such patients make a greater effort to process auditory information, considering the hearing loss impairments. Furthermore, increased latencies may be due to the P300 being recorded after the electrode beam is inserted. Hence, it picks up the sound transmitted to the retrocochlear hearing system, to the spiral ganglion neurons. Future studies must consider this, along with the influence of acoustic stimulus processing within CI systems.²⁵

P300 Amplitude

Amplitude was also a parameter of interest in this review. There were no P300 amplitude differences between monaural and binaural conditions (E5). However, it was one of the parameters that resulted in a correlation between pure tone and speech stimuli, and speech perception test results (E18 and E19).^{41,42}

Although only one study in this review used this method (E20),⁴⁰ the effect of music stimuli stood out among the other ones used to elicit P300, with decreased amplitude and increased latency. Authors point out that music-related effects in CI users show that they still have a representation of system regularities even after a long period of auditory deprivation, despite the auditory input provided by CI.

In 35% of the studies (E6, E8, E10, E11, E13, E16, and E20)^{28,30,32,33,35,38,40} the P300 amplitude values decreased in CI users. These findings may hypothetically show the influence of the CI external component, speech processor, and programming options on latency increase. The second hypothesis, which does not exclude the first one, is based on each patient's intrinsic aspects, which may interfere with these results – for instance, the listening effort of people with

Table 2 Synthesis of the primary studies, presented in order of year of publication, author, title, objective, and stimulus used.

Study	Year	Authors	Title	Objective	Type of Stimulus
E1	1996	Groenen PAP. et al. ²³	The relation between electric auditory brain stem and cognitive responses and speech perception in cochlear implant users.	To correlate results for short- and long latency potentials with speech perception tests in CI users.	Pure tone 500 and 1000Hz
E2	1997	Jordan K. et al. ²⁴	Auditory event-related potentials in post- and prelingually deaf cochlear implant recipients	To observe P300 behavior in CI users 6 months after activation.	Pure tone 400 and 1450 Hz
E3	1999	Okusa M. et al. ²⁵	Effects of discrimination difficulty on cognitive event-related brain potentials in patients with cochlear implants	To investigate the effects of discrimination difficulty with 4 stimuli conditions in CI users.	Pure tone 1000 and 2000 Hz
E4	2001	Kubo T. et al. ²⁶	Significance of auditory evoked responses (EABR and P300) in cochlear implant subjects.	To examine the significance of remaining ganglionic neurons, with auditory evoked potentials and correlate that with speech perception tests in CI users.	Pure tone 1000 and 2000 Hz
E5	2004	Iwaki T. et al. ²⁷	Comparison of speech perception between monaural and binaural hearing in cochlear implant patients	To evaluate the advantages of binaural hearing for unilateral and bilateral CI users, through tests such as P300.	Pure tone 1000 and 2000 Hz
E6	2004	Muhler R. et al. ²⁸	Visualization of stimulation patterns in cochlear implants: application to event-related potentials (P300) in cochlear implant users.	To demonstrate the effect of stimulation pattern variation in P300 in CI users.	Pure tone 200 and 8500 Hz
E7	2005	Kelly AS. et al. ²⁹	Electrophysiological and speech perception measures of auditory processing in experienced adult cochlear implant users	To determine the relationship between evoked potentials and speech perception tests in CI users.	Pure tone 1000, 1250 and 1500 Hz
E8	2007	Nager W. et al. ³⁰	Automatic and attentive processing of sounds in cochlear implant patients – electrophysiological evidence.	To evaluate whether CI users' difficulties to rare stimuli is due to attention deficit.	Pure tone 1000, 700 to 2900 Hz
E9	2009	Sasaki T. et al. ³¹	Assessing binaural/bimodal advantages using auditory event-related potentials in subjects with cochlear implants	To evaluate the advantage of binaural and bimodal hearing for CI users through evoked potentials and speech perception tests.	Pure tone 1000 and 2000 Hz
E10	2012	Obuchi C. et al. ³²	Auditory Evoked Potentials under Active and Passive Hearing Conditions in Adult Cochlear Implant Users.	To investigate the relationship between P300 and MMN using active and passive hearing paradigms with CI users.	Pure tone 1000, 1500, 2000 and 4000 Hz
E11	2015	Finke M. et al. ³³	Auditory distraction transmitted by a cochlear implant alters allocation of attentional resources	To analyze cortical responses in different stages and correlate them with visual and auditory distractors in CI users.	Pure tone 600 and 756 Hz
E12	2018	Grasel S. et al. ³⁴	P300 Cognitive Potential in Cochlear Implant Users	To assess changes in P300 latency and amplitude in CI users.	Pure tone 1000 and 2000 Hz

Table 2 (Continued)

Study	Year	Authors	Title	Objective	Type of Stimulus	Vowel and consonant
E13	2005	Beynon AJ. et al. ³⁵	Discrimination of Speech Sound Contrasts Determined with Behavioral Tests and Event-Related Potentials in Cochlear Implant Recipients	To study P300 variation in CI users with different contrasting sounds as stimulus.	Speech	/i/-/a/, /ba/-/da/
E14	2009	Henkin Y. et al. ³⁶	Cortical Neural Activity Underlying Speech Perception in Postlingual Adult Cochlear Implant Recipients	To examine the relationship between P300 and behavior measurements.	Speech	/ki/, /ku/-/ki/ /ke/, /kaga/, /kata/
E15	2014	Soshi T. et al. ³⁷	Event-related potentials for better speech perception in noise by cochlear implant users	To investigate neurophysiological and behavioral aspects for speech perception in noise by CI users.	Speech	25 Japanese words
E16	2014	Henkin Y. et al. ³⁸	Neural correlates of auditory-cognitive processing in older adult cochlear implant recipients.	To compare P300 in elderly CI users and normal-hearing older adults.	Speech	Vowel, consonant, vowel: /aba/, /ima/
E17	2016	Finke M. et al. ³⁹	On the relationship between auditory cognition and speech intelligibility in cochlear implant users: An ERP study	To investigate auditory and cognitive processing for words presented in different conditions and related to cognitive and speech intelligibility abilities in CI users.	Speech	German names
E18	1998	Makhdoum MJA. et al. ⁴⁰	Can event-related potentials be evoked by extra-cochlear stimulation and used for selection purposes in cochlear implantation?	To investigate whether P300 responses can be elicited by extra-cochlear stimulation using tone and speech stimuli.	Pure tone and Speech	125 and 250 Hz, /a/, /i/
E19	2001	Groenen PAP. et al. ⁴¹	Speech-evoked cortical potentials and speech recognition in cochlear implant users	To correlate P300 results with behavior test results and speech perception.	Pure tone and Speech	500 and 1000 Hz, /ba/ and /da/, /ba/ and /pa/, /i/ and /a/
E20	2004	Koelsch S. et al. ⁴²	Music perception in cochlear implant users: an event-related potential study.	To compare music irregularities and physical oddballs between CI users and normal-hearing individuals.	Music	Chord sequences

Abbreviations: EABR, electrical auditory brainstem response; CI, cochlear implant; MMN, mismatch negativity.

Table 3 Synthesis of article abstracts, specified by case-by-case subject analysis and obtained results.

Study	Subjects	Results
E1	7 CI users and 11 normal-hearing	The P300 latency levels were decreased in good CI users, compared with average ones. Average CI users showed increased latency when compared with normal-hearing individuals.
E2	13 CI users	Latency increased and amplitude decreased as the task's difficulty increased.
E3	8 CI users	Latency increased and amplitude decreased as the rare stimulus approaches the frequent ones.
E4	25 CI users and 25 normal-hearing	Higher P300 latency in subjects with lower speech perception scores.
E5	6 CI users	Higher P300 latency in subjects with lower speech perception scores.
E6	2 CI users	Amplitude was reduced when the task's difficulty increased.
E7	12 CI users and 12 normal-hearing	Amplitude was higher and latency lower as time of experience with CI increased.
E8	7 CI users and 7 normal-hearing	In the passive condition, P300 amplitude was lower than in active condition; CI users showed reduced amplitude when compared with the control group.
E9	15 CI users, 4 bilateral and 11 bimodal	Latency was lower in binaural subjects compared with monaural subjects.
E10	3 CI users and 3 normal-hearing	Amplitude levels were lower and latency levels were higher in CI users.
E11	12 CI users and 12 normal-hearing	P300 latency was higher, and amplitude was reduced in the presence of visual and sound distractors.
E12	26 CI users and 26 normal-hearing	P300 latency was similar to the control group in CI users with a good speech perception performance.
E13	10 CI users and 10 normal-hearing	P300 amplitude levels were reduced, and latency levels were increased for vowel and consonant contrast compared with the control group.
E14	15 CI users and 12 normal-hearing	P300 latency was similar to the control group in CI users with better speech perception test performance.
E15	17 CI users and 12 normal-hearing	Higher amplitude levels were correlated to higher speech perception test performance.
E16	9 CI users and 10 normal-hearing	P300 prolonged and decreased in CI users with age above 60.
E17	13 CI users and 13 normal-hearing	P300 prolonged in CI users exposed to noise.
E18	5 extracochlear and 9 intracochlear CI	Latency levels were prolonged in extra- and intracochlear CI users, in comparison to normal-hearing individuals. Results with pure tone were similar and there was correlation between amplitude and speech perception.
E19	9 CI users and 10 normal-hearing	A correlation was found between P300 amplitude for 500 and 1000Hz, /a/, /i/, and speech perception tests.
E20	12 CI users and 12 normal-hearing	P300 present with music stimulation, with reduced amplitude and increased latency.

Abbreviation: CI, cochlear implant.

hearing loss and cognitive aspects inherent to hearing abilities, especially related to attention and memory.

However, studies whose CI users had good results in speech perception tests found similar amplitude measurements between the CI users and normal-hearing subjects (E18 and E19),^{41,42} suggesting these results are related to better results in speech tests. These data lead us to think that the auditory pathways in adults with postlingual hearing loss can remain functional over a long time, and their central auditory system can be preserved even when conventional hearing aids do not provide optimal auditory stimulation.

The wide range of normal amplitude and latency thresholds in the literature may influence the results found. Hence, intra- and intersubject studies must be performed to establish more specific parameters for the clinical application of these results.

Relationship Between P300 Results and Cognitive Skills

Studies in the literature reinforce the association between hearing loss, cognitive ability, changes monitored with objective tests, impact of disability, improvement with hearing aids, and/or rehabilitation with auditory skill training.^{11–15,48}

Fjell and Walhovd (2003)⁴⁸ identified that P300 latency can be associated with the subject's level of cognition. The reason for this is that P300 latency is directly related to the speed of the auditory stimuli through the ascending auditory pathway in the brainstem, and its amplitude is related to the synchronous firing of many neurons. Those measures may reflect the cognitive performance, as this potential can be generated in the hippocampus and frontal lobe areas, as well as specific and non-specific auditory cortical areas that are important for cognitive skills.

Hence, the P300 recording indicates the conscious recognition of the rare sound stimuli,^{11–15} and its latency (which is generated independently of the time of conscious reaction to the stimuli) is related to cognitive efficiency.^{14,15} Nevertheless, the late occurrence of the latency suggests that it is a brain process related to the postdecisional evaluation of the rare stimulus in relation to the series of standard stimuli. In other words, the subject is aware of the task to be completed and decides for a specific stimulus, which in turn can be influenced by the listening effort.

Different Factors that Affect the P300 Parameters in CI Users

In the 20 studies we analyzed, the P300 was recorded with the patient's device. Some studies reported the need to control CI interference during the electrophysiological evaluation.^{33,35}

We did not consider CI fitting in the search strategy. Thus, there were 90% unilateral and 10% bilateral CI (E5 and E9).^{27,31} One study compared bimodal with bilateral fittings (E9).³¹ The type of fitting may be an important factor in result analysis, and future studies should consider this variable.

There seems to be a correlation between the time of CI use and P300 latency measures. In E7,²⁹ a longer CI hearing

experience was associated with lower P300 latency. These cumulative results suggest that it is possible to achieve central auditory pathway maturation with increased hearing experience, reaching a maximum level of maturation before a second CI. This leads us to reflect on the moment of surgery, which can influence its outcomes on hearing and speech skills with the second CI – especially in children with sequential bilateral CI.⁴⁹

The literature agrees that P300 results furnish strong evidence of complex interactions between speech intelligibility,^{37–39} neural processing,^{36,38} verbal working memory, and subjective classifications of hearing effort in CI users.^{25,30}

Another important factor to consider regarding the use of P300 testing is the advantage in associating objective tests (such as electrophysiological ones) with behavioral tests (such as speech perception ones). It is a novel resource that helps understand the auditory system and the limitations of neuronal plasticity and its consequences to speech perception performance. Over the last decade, studies have been giving greater importance to the need for standardizing parameters—in this case, the speech stimuli—for auditory evoked potentials, to draw nearer the real hearing activities, as demonstrated in studies E13 to E17 (►Table 2, E13–E17).^{35–39}

P300 Clinical Applications

It has been observed that the P300 latency and amplitude measures are adjusted during the first year of CI use^{50,51} with registered measures being close to those of normal-hearing people. As the multiprofessional team monitors the patients and considers the intrasubject results, they can watch for red flags and make more effective decisions when they identify that the auditory performance does not correspond to the sound accessibility made possible by the device.

Other factors have helped the professional team understand the results and make decisions regarding the device programming, including the stimulus and task used to elicit the P300. Verbal stimuli help understand the biological processes involved in speech processing (whether for cognitive, auditory, and/or linguistic reasons), as well as plan and monitor the post-CI surgery process.

The type of task used in tests may represent a significant bias. Attention and memory are important for reliable P300 recordings. Attention is registered when the patient notices the rare stimulus, while memory seems to be related to the test task (e.g., counting mentally). Most publications in this review did not specify the type of task—only four (20%) out of the 20 studies instructed the subjects to mentally count the rare stimulus (E1, E12, E19, and E20).^{23,34,40,42} This is a more complex task than lifting the finger or pushing a button.

Future Research on the P300 in CI Patients

According to the results shown here, P300 testing has proved to be a promising tool to assess and monitor auditory system functioning. It helps reach a prognosis of the intervention and, especially, assess the rehabilitation process, supporting the medical team's decision-making in terms of planning and

fine programming adjustments based on results and comparisons in the first-year of CI usage in postlingual adults.

When approaching this population to perform the P300, it is important to consider the CI characteristics, fitting (unilateral, bimodal, or bilateral), and test parameters, such as the speech stimuli, task type, stimulus intensity, and test duration.

As for clinical applicability, studies that help standardize protocols and present less variable latency and amplitude measurements contribute to both assessing and, especially, following up the intervention. This would be preferably associated with neuropsychological assessments, to ground CI indication and avoid a poor prognosis in the patient's auditory perception results.

Final Comments

This review has contributed with evidence that shows the importance of applying a controlled P300 protocol to diagnose and monitor CI users.

Regardless of the stimuli used to elicit P300, we noticed a pattern in increase of latency levels and decrease of amplitude levels in CI users.

The experience with the CI speech processor over time and the speech test results seem to be related to P300 latency and amplitude measurements.

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Conflict of Interests

The authors have no conflict of interests to declare.

References

- Duarte JL, Alvarenga KF, Costa OA. Potencial cognitivo P300 realizado em campo livre: aplicabilidade do teste. *Rev Bras Otorrinolaringol* 2004;70(06):780-785
- Massa CG, Rabelo CM, Matas CG, Schochat E, Samelli AG. P300 with verbal and nonverbal stimuli in normal hearing adults. *Rev Bras Otorrinolaringol (Engl Ed)* 2011;77(06):686-690
- Franco GM. O potencial evocado cognitivo em adultos normais. *Arq Neuropsiquiatr* 2001;59(2-A):198-200
- Hall J. *Handbook of auditory evoked responses*. Boston: Allyn & Bacon; 2006.
- Kraus N, Mcgee T. Potenciais auditivos de longa latência. In: Katz, J.; Ivey RG. (eds). *Tratado de audiologia clínica*. São Paulo: Manole; 1999;4;
- McPherson DL. *Late potentials of the auditory system*. San Diego: Singular Publishing Group; 1996.
- Picton TW, Alain C, Woods DL, et al. Intracerebral sources of human auditory-evoked potentials. *Audiol Neurotol* 1999;4(02):64-79
- Didoné DD, Oppitz SJ, Folgearnini J, Biaggio EP, Garcia MV. Auditory Evoked Potentials with Different Speech Stimuli: a Comparison and Standardization of Values. *Int Arch Otorhinolaryngol* 2016;20(02):99-104
- Martin BA, Tremblay KL, Korczak P. Speech evoked potentials: from the laboratory to the clinic. *Ear Hear* 2008;29(03):285-313Review.
- Stapells DR. Cortical event-related potentials to auditory stimuli. In: KATZ J, *Handbook of Clinical Audiology*. 5. Maryland: Lippincott Williams & Wilkins; 2002:308-406
- Huettel SA, McCarthy G. What is odd in the oddball task? Prefrontal cortex is activated by dynamic changes in response strategy. *Neuropsychologia* 2004;42(03):379-386
- O'Connell RG, Dockree PM, Kelly SP. A supramodal accumulation-to-bound signal that determines perceptual decisions in humans. *Nat Neurosci* 2012;15(12):1729-1735
- Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol* 2007;118(10):2128-2148
- Verleger R. Effects of relevance and response frequency on P3b amplitudes: Review of findings and comparison of hypotheses about the process reflected by P3b. *Psychophysiology* 2020;57(07):e13542
- Martin DA, Tremblay KL, Stapells DR. Principles and applications of cortical auditory Evoked Potentials. In Burkard RF, Don M, Eggermont, JJ. *Auditory Evoked Potentials: basic principles and clinical application*. Baltimore: Lippincott Williams & Wilkins; 2007:482-507
- Kozłowski L, Wiemes GMR, Magni C, Silva ALG. A efetividade do treinamento auditivo na desordem do processamento auditivo central: estudo de caso. *Rev Bras Otorrinolaringol* 2004;68(04):427-432
- Reis ACM, Iório MC. [P300 in subjects with hearing loss]. *Pro Fono* 2007;19(01):113-122
- Polen SB. Auditory event-related potentials. *Semin Hear* 1984;5(02):127-141
- Oates PA, Kurtzberg D, Stapells DR. Effects of sensorineural hearing loss on cortical event-related potential and behavioral measures of speech-sound processing. *Ear Hear* 2002;23(05):399-415
- Wall LG, Martin JW. The effect of hearing loss on the latency of the P300 evoked potential: A pilot study. *NSSLHA J*. 1991;18:121-125
- Torkildsen JVK, Arciuli J, Haukedal CL, Wie OB. Does a lack of auditory experience affect sequential learning? *Cognition* 2018;170:123-129
- Kaga K, Kodera K, Hirota E, Tsuzuku T. P300 response to tones and speech sounds after cochlear implant: a case report. *Laryngoscope* 1991;101(08):905-907
- Groenen P, Snik A, van den Broek P. On the clinical relevance of mismatch negativity: results from subjects with normal hearing and cochlear implant users. *Audiol Neurotol* 1996;1(02):112-124
- Jordan K, Schmidt A, Plotz K, et al. Auditory event-related potentials in post- and prelingually deaf cochlear implant recipients. *Am J Otol* 1997;18(6, Suppl):S116-S117
- Okusa M, Shiraishi T, Kubo T, Nageishi Y. Effects of discrimination difficulty on cognitive event-related brain potentials in patients with cochlear implants. *Otolaryngol Head Neck Surg* 1999;121(05):610-615
- Kubo T, Yamamoto K, Iwaki T, Matsukawa M, Doi K, Tamura M. Significance of auditory evoked responses (EABR and P300) in cochlear implant subjects. *Acta Otolaryngol* 2001;121(02):257-261
- Iwaki T, Matsushiro N, Mah SR, et al. Comparison of speech perception between monaural and binaural hearing in cochlear implant patients. *Acta Otolaryngol* 2004;124(04):358-362
- Mühler R, Ziese M, Kevanishvili Z, Schmidt M, von Specht H. Visualization of stimulation patterns in cochlear implants: application to event-related potentials (P300) in cochlear implant users. *Ear Hear* 2004;25(02):186-190
- Kelly AS, Purdy SC, Thorne PR. Electrophysiological and speech perception measures of auditory processing in experienced adult cochlear implant users. *Clin Neurophysiol* 2005;116(06):1235-1246
- Nager W, Münte TF, Bohrer I, et al. Automatic and attentive processing of sounds in cochlear implant patients - electrophysiological evidence. *Restor Neurol Neurosci* 2007;25(3-4):391-396

- 31 Sasaki T, Yamamoto K, Iwaki T, Kubo T. Assessing binaural/bimodal advantages using auditory event-related potentials in subjects with cochlear implants. *Auris Nasus Larynx* 2009; 36(05):541–546
- 32 Obuchi C, Harashima T, Shiroma M. Auditory Evoked Potentials under Active and Passive Hearing Conditions in Adult Cochlear Implant Users. *Clin Exp Otorhinolaryngol* 2012;5(Suppl 1):S6–S9
- 33 Finke M, Sandmann P, Kopp B, Lenarz T, Büchner A. Auditory distraction transmitted by a cochlear implant alters allocation of attentional resources. *Front Neurosci* 2015;9:68
- 34 Grasel S, Greters M, Goffi-Gomez MVS, et al. P3 Cognitive Potential in Cochlear Implant Users. *Int Arch Otorhinolaryngol* 2018;22(04):408–414
- 35 Beynon AJ, Snik AF, Stegeman DF, van den Broek P. Discrimination of speech sound contrasts determined with behavioral tests and event-related potentials in cochlear implant recipients. *J Am Acad Audiol* 2005;16(01):42–53
- 36 Henkin Y, Tetin-Schneider S, Hildesheimer M, Kishon-Rabin L. Cortical neural activity underlying speech perception in postlingual adult cochlear implant recipients. *Audiol Neurotol* 2009;14(01):39–53
- 37 Soshi T, Hisanaga S, Kodama N, et al. Event-related potentials for better speech perception in noise by cochlear implant users. *Hear Res* 2014;316:110–121
- 38 Henkin Y, Yaar-Soffer Y, Steinberg M, Muchnik C. Neural correlates of auditory-cognitive processing in older adult cochlear implant recipients. *Audiol Neurotol* 2014;19(Suppl 1):21–26
- 39 Finke M, Büchner A, Ruigendijk E, Meyer M, Sandmann P. On the relationship between auditory cognition and speech intelligibility in cochlear implant users: An ERP study. *Neuropsychologia* 2016; 87:169–181
- 40 Koelsch S, Wittfoth M, Wolf A, Müller J, Hahne A. Music perception in cochlear implant users: an event-related potential study. *Clin Neurophysiol* 2004;115(04):966–972
- 41 Makhdoum MJ, Hinderink JB, Snik AF, Groenen P, van den Broek P. Can event-related potentials be evoked by extra-cochlear stimulation and used for selection purposes in cochlear implantation? *Clin Otolaryngol Allied Sci* 1998;23(05):432–438
- 42 Groenen PA, Beynon AJ, Snik AF, van den Broek P. Speech-evoked cortical potentials and speech recognition in cochlear implant users. *Scand Audiol* 2001;30(01):31–40
- 43 Peters M, Godfrey C, McInerney P, Soares C, Khalil H, Parker D. The Joanna Briggs Institute reviewers' manual 2015: methodology for JBI scoping reviews [Internet]. 2015[cited 2018 May 01]. Available from: http://joannabriggs.org/assets/docs/sumari/Reviewers-Manual_Methodology-for-JBI-Scoping-Reviews_2015_v2.pdf
- 44 Systematic Reviews, Centre for Research and Dissemination, University of York., 2008https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf
- 45 Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5(01): 210
- 46 Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(07):e1000097<http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000097> Accessed May012018 [Internet]
- 47 Linden DE. The p300: where in the brain is it produced and what does it tell us? *Neuroscientist* 2005;11(06):563–576
- 48 Fjell AM, Walhovd KB. Effects of auditory stimulus intensity and hearing threshold on the relationship among P300, age, and cognitive function. *Clin Neurophysiol* 2003;114(05):799–807
- 49 Chang YS, Hong SH, Kim EY, et al. Benefit and predictive factors for speech perception outcomes in pediatric bilateral cochlear implant recipients. *Rev Bras Otorrinolaringol (Engl Ed)* 2019;85(05): 571–577
- 50 Finke M, Billinger M, Büchner A. Toward Automated Cochlear Implant Fitting Procedures Based on Event-Related Potentials. *Ear Hear* 2017;38(02):e118–e127
- 51 Amaral MSA. Comportamento do P300 em pacientes usuários de implante coclear com eletroestimulação unilateral [tesis]. Ribeirão Preto. Faculdade de Medicina de Ribeirão Preto – Universidade de São Paulo; 2019:105
- 51 Amaral MSA, Zamberlan-Amorim NE, Mendes KDS, et al. Auditory evoked potential (P300) in cochlear implant users: a scoping review. *bioRxiv* 2020; in press.