LATE LATENCY AUDITORY EVOKED POTENTIALS AS PERFORMANCE INDICATORS IN COCHLEAR IMPLANTEES: A SYSTEMATIC REVIEW

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CERTIFICATE

This is to certify that this dissertation entitled "**Late latency auditory evoked potentials as performance indicators in cochlear implantees: A systematic review**" is a bonafide work submitted as a part for the fulfillment for the degree of Master of Science (Audiology) of the student with Registration Number: 19AUD011 This has been carried out under the guidance of the faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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CERTIFICATE

This is to certify that this dissertation entitled "**Late latency auditory evoked potentials as performance indicators in cochlear implantees: A systematic review"** has been prepared under my supervision and guidance. It is also being certified that this dissertation has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled "**Late latency auditory evoked potentials as performance indicators in cochlear implantees: A systematic review.**" is the result of my own study under the guidance of Dr. Geetha. C, Reader in Audiology in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysuru and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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Dedicated to Maa and Paa

Gratitude is not just a word but a feeling which makes you feel an abundance of God's blessings.

One such blessing is me reaching this stage in life. *Hence,* I take this opportunity to thank a handful of people who have made my life and my world extraordinary and ,of course, have been a significant part of this dissertation directly or indirectly. Thus, at first, I am thanking The Almighty for giving these beautiful people in my life and such opportunities because of which I am here at this moment writing this chapter of my life.

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Abstract

Aim and objective: *The purpose of the current study was to summarize existing literature on the long-latency auditory evoked potentials as the outcome measure in children with the cochlear implant.* ***Method:*** *The search for the articles began with finalizing appropriate keywords, putting those through various search engines. Later the articles found were screened at various stages. At the end of all the screening stages, studies were collected, and those relevant to our research questions were taken up. Four studies were finalized at the end of the search process.* ***Results:*** *The review gave an insight into the changes in the late latency potential and behavioral measures post-implantation in children. In all the studies, the results showed an improvement in both P1 component of late latency potential and behavioral measures after cochlear implantation. The results also showed a positive correlation between electrophysiological and behavioral measures.* ***Conclusion:*** *Late latency response can be used as an objective outcome measure by the audiologist to track changes in the auditory pathway in young children with a cochlear implant.*

CHAPTER 1

INTRODUCTION

Outcome measures play an essential role in the rehabilitation of children with hearing impairment. A cochlear implant is one of the intervention options for children with severe to profound hearing loss. The primary goal of pediatric cochlear implantation is to provide hearing that will allow children to develop speech and language in the same way that their normal-hearing peers do, allowing them to participate in society fully (Musiek, 1999; Waltzman et al., 2005; Guo et al., 2016).

Understanding speech depends on the complex processing of the ascending neural signal within the central auditory pathways (Kaga et al., 1991; Eggermont et al., 1997; Jordan et al., 1997; Kraus et al., 1995, 1998a, b, 1999; Menning et al., 2000; Ponton et al., 1996a, b, 1999, 2000a, b; Tremblay et al., 2014). There are various subjective and electrophysiological outcome measures to measure the changes in the auditory pathways.

1.1 Subjective and behavioral outcome measures

Traditionally, auditory signal processing is measured using behavioral tests of speech perception (Musiek, 1999). For assessing speech perception, various speech perception tests are available to evaluate the effect of the cochlear implant. The early speech perception (ESP) exam, the Pediatric Speech Intelligibility (PSI) test, the Lexical Neighbor Test (LNT), and the pediatric Hearing In Noise Test (HINT) are some of the speech perception test materials available for children (Moog & Geers, 1990; Soli & Sullivan 1994; Eisenberg, & Dirks 1995, Yang, Wu, Lin, & Sher 2004)

The main advantage of the speech perception test is that it is a functional test with direct interpretation. It also involves the use of natural speech as a stimulus and a subjective response from the participant, which directly assists the audiologist in gaining an understanding of the child's perception abilities (Tye-Murray et al., 1995).

On the other hand, subjective measures assess the caregiver's/clinician's observations of the child's responses. Measures such as auditory awareness, sound discrimination, the child's cognitive and socio-emotional development can be evaluated to verify the benefits of hearing devices (Snik et al., 2001).

The developmental scale is one such subjective measure. Developmental scales are based on the caregiver's observations of the child's reactions to various sounds in real-life scenarios. The communicative abilities of children fitted with hearing devices in the age range of 2 to 9 years are assessed using these scales (Snik et al., 2001). Questionnaires, diaries, and structured interviews are other examples of subjective methods of evaluating a child's auditory behavior in real-life situations (Bagatto et al., 2011; Moog & Geers, 1975).

Despite many advantages, the behavioral and subjective outcome measures fall short in giving a holistic picture of the child's auditory behavior for the following reasons: When infants or young children have hearing loss, they cannot respond to behavioral threshold assessments, making aided outcome hearing threshold estimations difficult. Further, thresholds are insufficient to examine the role of amplification in the development of the central auditory system (Martin et al., 2005). Another issue with speech testing is that young children, particularly those who have just obtained hearing aids, mostly have limited linguistic abilities. Hence, speech tests lose their value in these cases (Snik et al., 2001).

When it comes to caregiver reports, there may be some administrative challenges. Questionnaires, for example, are better conducted in the family's original language, and caregivers with literacy difficulties may face difficulties reporting the outcomes (Johnson & Danhauer, 2002). The importance of parental and family motivation and expectations in cochlear implantation outcomes also affects the accurate reporting of the outcome measure through scales (Cosetti & Waltzman, 2012). Due to all the above factors, objective assessment becomes imperative in many young children.

1.2 Electrophysiological outcome measures

Late latency auditory evoked potentials (LLAEP) are objective measures commonly used to assess outcomes in children with cochlear implants (Mcneill et al., 2009). Early objective evidence of the aided ability to access speech can be acquired through recording LLAEP to speech stimuli. There are reports on the essential link between LLAEP and functional outcomes such as behavioral and psychological development in aided infants. The use of LLAEPs is equally appropriate for monitoring auditory responses to document different behaviors and growth. When auditory brainstem response (ABR)/ Electrocochleography (ECochG) data were compared to functional performance in a similar way, there was no evidence of this association (Golding et al., 2007). However, recording

LLAEPs can show that speech is detected at the brain level of the auditory system. In awake babies with normal hearing, robust LLAEPs can be recorded in response to conversational speech events (Kurtzberg, 1989; Steinschneider et al., 1992; Cone-Wesson and Wunderlich, 2003). The auditory system's detection of the stimuli is reflected in cortical auditory evoked potentials. This process, which is dependent on the maturation of auditory pathways (Alvarenga et al., 2013) and occurs before children acquire more complex auditory and cognitive skills, is critical for speech and language development (Maitre et al., 2013).

One way of examining the time limits for plasticity in the human central auditory system is using LLAEPs. The peaks P1 (latency = 50 to 70 msec), N1 (latency = 80 to 120 msec), and P2 (latency = 150 to 200 msec) are the components elicited by the recurrent presentation of a single stimulus. The P1 response was examined in deaf children who got cochlear implants at various ages To investigate the limits of plasticity in the central auditory system (Sharma & Campbell, 2011). Whereas N1 denotes conscious perception or detection of an acoustic signal (Naafanen, 1990).

The P1 peak is thought to originate in the primary auditory cortex, but it may also have contributions from the hippocampus, planum temporale, lateral temporal cortex, and neocortical areas (Musolino et al., 1994; Howard et al., 2000). P1 has a latency of around 250 milliseconds in very young infants, reducing to about 50 milliseconds with full maturity. Peaks P1 and N2 are less prominent in adults.

Plenty of research is done on LLAEP as an outcome measure in children with cochlear implants (Wilkinson & Lee, 1972; Gordon et al., 2008; Guo et al., 2016). The age at implantation is the most critical factor influencing the outcome (Geers, 2006). In early-implanted children, the latency and amplitude of this response changes over time—the latency becomes shorter and the amplitude smaller. On the other hand, this initial negativity persists for a longer period in late-implanted children, perhaps contributing to the abnormally long P1 latencies in late-implanted children. This negativity may provide another marker for assessing the plasticity of the auditory pathway (Sharma et al., 2002).

1.3 Need of the study

A systematic review enables the interpretation of old literature in the light of new developments in the field. The review also helps to establish the consistency in knowledge and relevancy of older materials and identify gaps in the knowledge of the area. This gap is further explored during the research to establish new facts or theories that add value to the field (Tolley et al., 2016).

The purpose of the current study is to summarize existing literature on the long-latency auditory evoked potentials (LLAEP) as the outcome measure in children with the cochlear implant through a systematic review. In young children, measuring improvement using behavioral tests becomes difficult (Kasari, 2002). Because infants and young children using cochlear implants may not provide accurate behavioral responses and could not comply with speech-language testing, audiologists need to rely on electrophysiological testing. LLAEP is one such objective assessment tool for evaluating cochlear implant outcomes (Guo et al., 2016). Suppose the evidence shows that the LLAEPs are significantly correlated to behavioral outcome measures in children with cochlear implants. In that case, LLAEPs can serve as a routine outcome measure in young babies without having to spend several hours on behavioral assessment in uncooperative children. This lead to the following research question: *Is there any correlation between long latency responses and outcomes measured by behavioral measures in children with a cochlear implant?*

The search for an answer to the above question revealed several studies using LLAEPs in children with a cochlear implant for documenting plasticity and outcome after listening training. A systematic review of the studies in the area would provide evidence to see any correlation between long latency responses and results measured by behavioral measures in children with a cochlear implant. LLAEP being an objective measure, can be recommended if the review provides strong evidence for the same. Hence, there is a need for a systematic review of studies on LLAEP in cochlear implants to ensure and get in-depth knowledge about its use as an objective measure and its correlation with the child's auditory performances with the implant.

1.4 Aim of the study

The present study aimed to undertake a systematic review of available evidence on the effectiveness of late latency auditory evoked potential as an objective outcome measure to assess auditory performance in pediatric cochlear implanted cases.

1.5 Objectives of the study

The objectives of the study were to-

- select studies on late latency auditory evoked potential as a performance indicator in children with a cochlear implant using Preferred Reporting Items for Systematic Reviews and Meta-analyses statement's standards (PRISMA)
- summarize studies on late latency auditory evoked potential as a performance indicator in children with cochlear implant through the systematic review using PECO format and PRISMA chart
- explore if the studies show a relationship between the long-latency auditory evoked potentials and behavioral outcome measures in children with cochlear implants

CHAPTER 2

METHOD

The systematic review was done using the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement's standards (PRISMA) (Ravi et al., 2016). PRISMA focuses on how researchers may ensure that systematic reviews and meta-analyses are reported clearly and thoroughly (Liberati et al., 2009). Thus, the PRISMA flowchart is used to identify the relevant studies to answer the proposed research question.

Various stages were followed for selecting the studies for the systematic review. The various stages of reporting followed were according to PRISMA (Page et al., 2010). The stages are as follows:

2.1. Stage 1: Identification of the articles
2.2. Stage 2: Screening of the articles
2.3 Stage 3: Finalization of studies

2.1: Stage 1: Identification of the articles.

Identification of the articles is the first stage of PRISMA. There were two main steps involved in this stage. As a first step, eligibility criteria were set for the selection of articles. According to the eligibility criteria given below in PECO format, the potential articles were identified.

2.1.1 Eligibility criteria:

The PECO given by Liberati et al. in 2009 format was also used as an inclusion criterion for selecting studies. PECO stands for patient population or disease being addressed (P), interventions or evaluation (I)/(E), control group (C), and outcome or endpoint (O) (Liberati et al., 2009). The criteria designed based on the PECO format helped in screening and analyzing the relevant articles. It also helps formulate the search strategy by identifying the key concepts that need to be in the article to answer the research question. The following are the details of the PECO format followed in the current study:

- **Population**: Pediatric cochlear implanted participants till 15 years of age.

- **Evaluation**: Late latency auditory evoked potential (LLAEP) as an objective measure to study the auditory cortex's development post-implantation and its impact on auditory performance.

- **Control group**: Studies with normal-hearing individuals as a control group or within-subjects comparisons were selected.

- **Outcomes:** LLAEP as an objective tool to measure outcomes in cochlear implanted children and the relationship of LLAEP with the behavioral measures.

2.1.2 Search strategy:

In this step, two different sets of keywords were decided by two investigators to get relevant articles. Keywords used were as follows:

1. "Speech perception"[Mesh] AND ¨Late Latency Auditory evoked Potential "[Mesh] AND Cochlear Implant " [MeSH] OR " Cortical auditory evoked potential "

2. "Word recognition scores " [Mesh] AND ¨ Cochlear Implant" "[Mesh] AND auditory evoked potential" [MeSH] OR " P 1 – N1 – P 2 complex ".

The keywords were fed in the following search engines: PubMed, Sci-Direct, J- gate, Shodhganga, and Google scholar. The strategy of the advance search was used with the following keywords extracted from the Medical Subject Headings. The articles were obtained from PubMed, Sci-Direct, and Google scholar, and no articles were found in Shodhganga and J-gate.

2.2 Stage 2: Selection of studies:

Two investigators searched separately across all electronic databases. The collected studies were assembled using a reference management system, and duplicates were removed. The authors individually screened the titles after eliminating duplicates. Both the investigators evaluated the abstracts once the titles had been screened. Any differences in judgments were resolved through verbal dialogue at all levels. For the data extraction technique, the full text of the shortlisted abstracts was retrieved. Post-screening the studies, few studies that met the inclusion criteria mentioned earlier in PECO format underwent the data extraction process.

2.3 Data Extraction:

The full-length articles of selected studies were read. All relevant information pertaining to the objective of the study were extracted. Further, a quality analysis of the selected articles was carried out.

2.4 Quality assessment:

All the studies included in the review underwent a quality assessment to know whether the studies are up to the mark and included in the review. The Critical Appraisal Skill Programme (CASP) checklist, given by Ruth Brice in 2018, was used to appraise each article critically. The cohort study version of the CASP checklist was employed because the systematic review primarily included cohort studies. CASP has 12 questions divided into three sections. The questions were rated using three categories: yes, cannot tell, and no. The questions covered the study's purpose, cohort recruitment, measurement bias, and identification and analysis of confounding factors. The checklist was also used to score the consistency of follow-up, the generalizability of the results, and their implications.

CHAPTER 3

RESULT

The present study aimed to conduct a systematic review of the studies focusing on LLAEP as an objective outcome measure and its relationship with behavioral outcome measures. Several steps lead to narrow the search of the articles for review. Following are the results of the same.

3.1. Results of the systematic search process

Many databases were used to collect articles. After integrating articles from all of the datasets, 15,928 hits were retrieved. However, there were 2290 duplicates, and hence, the 2290 articles were removed. The titles of the remaining 13,598 articles were examined, and 13,558 were eliminated because they were unrelated to the study's objective. The remaining 40 abstracts were analyzed, and 11 articles were selected for further consideration. For each of the 11 short-listed abstracts, full-text articles were found. Seven publications were excluded based on the entire text because the articles did not meet the PECO criteria. That is, the studies did not include one or more of the following: 1) late latency response measurement, 2) bilateral hearing loss, or 3) behavioral measure in conjunction with the electrophysiological test. Out of the final four articles, the study done by Pantelemon et al. (2020) had used a developmental quotient as the subjective measure. This article was still included in the review as the study assessed the hearing and understanding of the language through auditory mode as a part of the developmental quotient. The above details are given as a PRISMA flow chart in Figure 3.1.

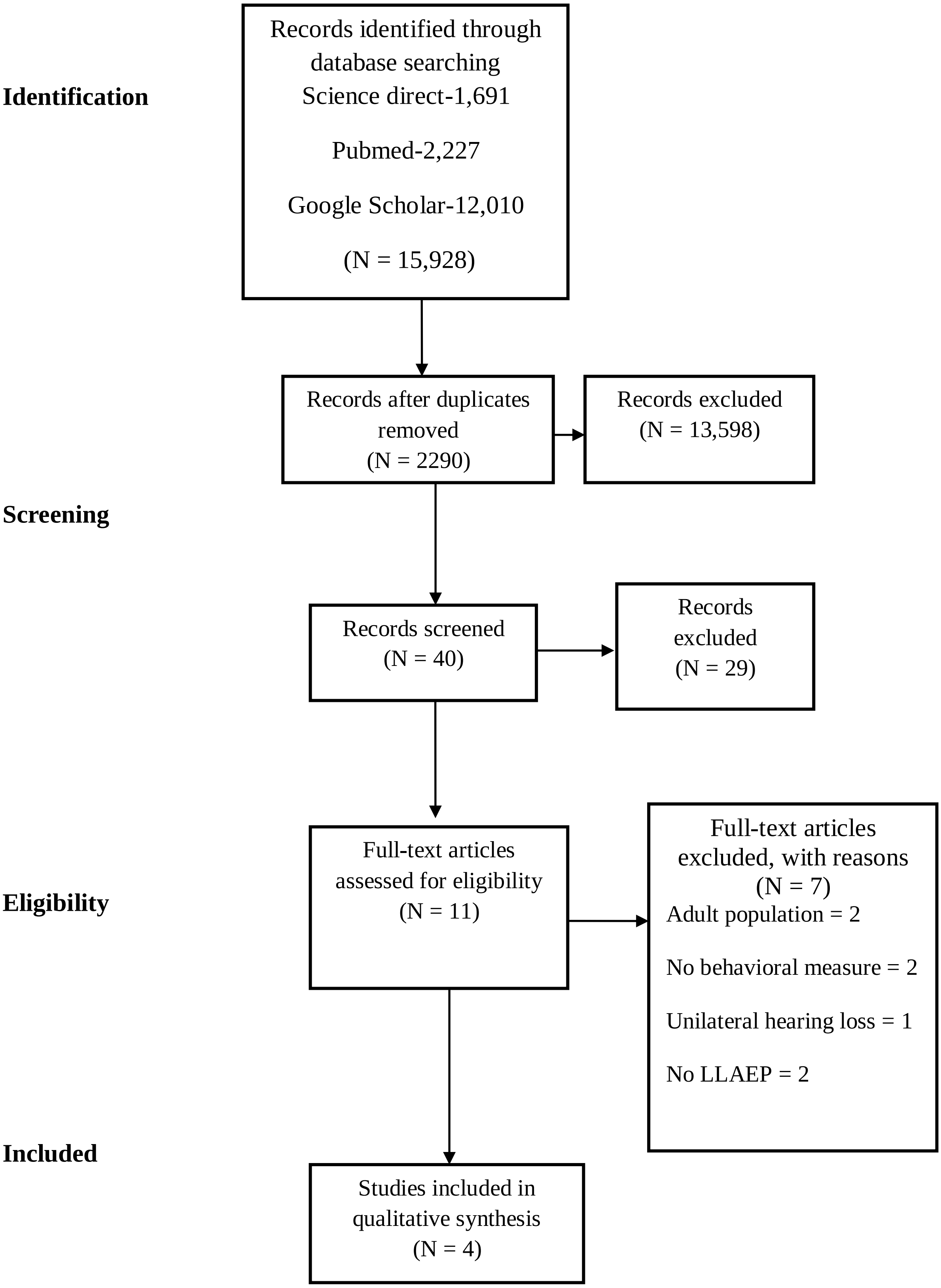

Figure 3.1

Schematic representation of the systematic search process using PRISMA

3.2. Results of qualitative analysis

The final short-listed articles underwent qualitative analysis using the CASP questionnaire. It is vital to separate research of relative higher and lower quality to organize the contribution of studies based on their quality. Typically, researchers quantify evaluation outcomes to generate an overall study quality score. A determining criterion is applied to establish comparable study quality. Review teams decide the 'tipping point' criteria based on what they believe is relevant for the aim of their review (Long et al., 2020). The inclusion criteria decided for the current study was a score of 5 or more for close-ended questions. Whereas for open-ended questions, both the reviewers came to a common conclusion for judging the quality of evidence. The result of the same is given below in Table 3.1.

Table 3.1

Results of qualitative assessment of the included studies

Sl. No.	CASP	Gordon et al. (2008)	(Silva, Couto, et al., 2017)	(Guo et al., 2016)	(Pantelemon et al., 2020)
1	Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes
2	Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes
3	Was the exposure accurately measured to minimize bias?	Yes	Yes	Yes	Yes
4	Was the outcome accurately measured to minimize bias?	Cannot tell	Cannot tell	Cannot tell	Cannot tell
5	Have the authors identified all-important confounding factors?	Yes	Yes	Yes	Yes
5	(b) Have they taken account of all the confounding factors in the design and/or analysis?	No	No	No	No

6	(a)Was the follow up of subjects complete enough?	Yes	Yes	Yes	Yes
6	(b) Was the follow-up of subjects long enough?	Yes	Yes	Yes	Yes
7	What are the results of this study?	The study found a dominant positive wave in all implant users and a larger than normal negative amplitude peak in users with fair speech perception scores which had similar scalp topography to N1	The results showed improvements in auditory and speech skills as measured by IT-MAIS and MUSS. Similarly, the long-latency auditory evoked potential evaluation revealed a decrease in P1 component latency; however, the latency remained significantly longer than that of the hearing children, even after nine months of cochlear implant use.	All the participants demonstrated improvements in the detection of speech sounds with CI. The percentages of participants who could detect all three stimuli were 26% at the first year to 100% at the fourth-year post-implantation.	The results showed progress in both general and language development through auditory tasks. Similarly, LLAEP measurements revealed a decrease in P1 latency after cochlear implantation.
8	How precise are the results?	Very precise	Very precise	Very precise	Very precise
9	Do you believe the results?	Yes	Yes	Yes	Yes
10	Can the results be applied to the local population?	Yes	Yes	Yes	Yes

11	Do the results of this study fit with other available evidence?	Yes	Yes	Yes	Yes
12	What are the implications of this study for practice?	Use of LLAEP as an objective measure along with behavioral measures	Cortical outcomes significantly positively correlated with MESP, which helps predict early speech perception in CI recipients.	Using the P1 component as a biomarker and behavioral outcome measure provides factual information about child speech and language development during the rehabilitation process.	LLAEP correlates with the behavioral measures and, hence, can be considered in a clinical setup to efficiently track children's progress with cochlear implants.
Scores		9	9	9	9

All the articles met the criteria of the quality assessment. It can also be seen in Table 3.1 that all the above four articles prove to be high-quality articles, and hence were included in the review.

3.3. Characteristics of the studies included in the review.

The study characteristics and participant characteristics of each of the four studies are given in Table 3.2. The table represents the summary of all those articles which met the inclusion criteria mentioned in the method section in the PECO format and quality assessment. The name of the behavioral tests used to assess the auditory performance of children with cochlear implants and peaks assessed in LLAEP across different studies are also given in Table 3.2.

Table 3.2

The study characteristics and participant characteristics in PECO format

Sl.no	Study	Study design	Population	Evaluation	Control	Outcome
1.	(Silva, Couto, et al., 2017)	Cohort study	30 children of both genders from the age of 5 to 11 years; 15 children in each group. First group: children with normal-hearing sensitivity Second group: cochlear	The presence and the latency of P1 were considered. The behavioral measures used were: 1. The Infant-Toddler Meaningful Auditory Integration Scale (IT	15 normal-hearing children (between-group comparison) In addition, the first evaluation was compared with the second	When the IT-MAIS /MAIS scores improved, P1 latency decreased. There was no significant association between MUSS and LLAEP. P1 latencies, MUSS and IT-MAIS/MAIS scores were converged during the second

			implant children	MAIS) 2. Meaningful Use of Speech Scales (MUSS). 3. Glendonald Auditory Screening procedure (GASP)	evaluation (within-group comparison)	evaluation.
2	(Gordon et al., 2008)	Cohort study	16 typically developed children between 11 and 18 years of age with a minimum experience of 2 years with their implants.	Late latency response components, i.e., N1, P1 N2, P2, and Phonetically Balanced Kindergarten (PBK) open-set speech	The groups were made based on good score (≥ 50 %) and fair <50%) PBK scores, and the LLAEPs were	Cochlear implant users with good PBK scores had a distinct waveform dominated by a prominent positive peak. A substantial negative peak preceded the positive peak in

				perception test were used	compared between the two groups.	implant users with fair PBK scores.
3	(Guo et al., 2016)	Cohort study	23 unilateral CI recipients. Their age of implantation ranged from 13 to 68 months.	The latency of P1 was considered and was recorded using the test stimuli /m/, /g/, /t/. Mandarin Early Speech Perception test (MESP) was administered. It is a closed set test that assesses early speech perception in	The within-group comparison was made at different time intervals.	P1 latency did not differ significantly between children who were fitted with CI before 3.5 years and those who were fitted after 3.5 years but before 7. The categories of MESP and LLAEPs were shown to have a substantial positive correlation.

				children.		
4	(Pantelemon et al., 2020)	Cohort study	There were 17 children up to the age of 6 years were taken for this study.	Latency of P1 was used along with and DDST II (Denver Developmental Screening Test).	A within-group comparison was made at different time intervals.	The LLAEP and developmental quotient (DQ) and the language DQ revealed a strong association.

3.4 Results of LLAEP as an objective outcome measure

Gordon et al. (2008) aimed to study the changes in latency and amplitude of LLAEPs in children with cochlear implants and compared that with normal-hearing children. The study included children between 11 to 15 years of age with a minimum of 2 years of experience. The children with cochlear implants were divided into two groups depending on their Phonetically Balanced Kindergarten (PBK) open-set speech perception test scores: good PBK scores (≥ 50%) and fair PBK scores (< 50%). The results showed a large negative peak in implant users with fair scores and had a slightly lower delay than the N1 in the normal group.

Further, the large positive peak in both implant groups occurred clearly and significantly later than the P1 and had a similar latency to the P2 in the normal group. The subsequent negative wave (N2) was significantly longer in latency in the fair scoring group when compared to that of normals.

Similarly, the amplitude of P1 was slightly higher in children with good scores than in children with fair scores or P2 of normal-hearing children, although there was no statistical significance. Whereas the amplitude of N2 in normal-hearing children did not differ significantly from that of the N2 in either implant group.

Guo et al. (2016) conducted the study to see a link between the presence or absence of the P1 component of LLAEPs in response to speech stimuli and speech perception performance in Chinese pediatric cochlear implant recipients (Age range = 13 to 68 months). The study also aimed to see if LLAEPs could be used as a predictor of early speech perception and if there is objective evidence of clinical LLAEP uses. The results showed no significant difference in P1 delay between children who received cochlear implants before the age of 3.5 years and those who received them after the age of 3.5 years but before the age of 7.

Silva et al. (2017) monitored the cortical maturation of children with the cochlear implant by means of electrophysiological (P1 component) and behavioral measurements for 30 children from 5 to 11 years of age (15 children with normal hearing sensitivity and 15 cochlear implanted children). Results revealed that, in both groups, the LLAEP trace analysis indicated the presence of the P1 component in 100% of the children. After nine months of auditory experience with CI use, the trace in the children with CI became more distinct.

The results also revealed that P1 latency decreased over time in both groups. In the first evaluation, the P1 component delay in children with CI was 230.3 ms, whereas, in the second evaluation, it was 157.9 ms. The mean values of the P1 component latency for hearing children were 121.9 ms in the first evaluation and 118.9 ms in the second evaluation. The reduction in latency between evaluations was more noticeable in the children with CI, implying a considerable change in P1 latency after nine months of auditory exposure.

Recently, Pantelemon et al. (2020) conducted a study to find a set of outcome measures that will allow us to monitor children with cochlear implants and, eventually, admit them into a tailored rehabilitation program. The study included the P1 component of LLAEPs. The participants taken up for this study were children up to six years of age. After cochlear implantation, LLAEP measurements demonstrated a decrease in P1 latency.

3.5 Results of behavioral/subjective measures

Gordon et al. (2008) used PBK scores to divide children into two groups and assess their speech perception ability. At the same time, Guo et al. (2016) used the Mandarin Early Speech Perception test (MESP) to evaluate the speech perception of cochlear implant children. It is a closed set test that assesses early speech perception in children. The percentages of participants who could pass the first category of MESP increased from 26% at the first year to 100% at the fourth year post-implantation. The participants demonstrated improvements throughout two years of observation post-implantation. In the fourth year of post-implantation, all children obtained the highest score in the last three categories. The percentages of participants who passed the most challenging category, i.e., Category 6, increased from 9% in the first year to 91% in the fourth year post-implantation.

Silva et al. (2017) used the adapted version of the Glendonald Auditory Screening procedure (GASP) in Brazilian Portuguese to test the hearing abilities ranging from detection to speech comprehension. The study also assesses the parent's child’s development through developmental scales such as IT-MAIS and MUSS. IT-MAIS is made up of a structured interview given to parents of children with CI. It consists of ten questions that evaluate three components of speech perception: vocalization, sound attentiveness, and sound identification. MUSS consists of a ten-question structured interview that assesses speech production from the perspective of parents of children who use CI.

The results of the behavioral data showed that the most common auditory skills gained after nine months of CI use were detection (53.5%) and discrimination (40%). Comprehension skills were only reported in one case (6.7 percent). The results of auditory and speech skills from the perspective of the parents (IT-MAIS/MAIS and MUSS questionnaires) revealed progress in the course of auditory stimulation by CI in all assessed cases. In addition, there was a positive association between the IT-MAIS/MAIS and MUSS protocols, indicating that increases in the IT-MAIS/MAIS scores were linked to increases in the MUSS scores.

Pantelemon et al. (2020) used DDST-II, which is regarded as the gold standard for evaluating the development of children aged one month to 6 years. It assesses four areas of development: personal-social, language, fine motor/adaptive, and gross motor as a behavioral measure. The language DQ showed statistically significant differences between the three evaluations at different time intervals.

3.6 Correlation between LLAEP and behavioral/subjective measures

As mentioned in section 3.4, Gordon et al. (2008) reported that children with good scores on the behavioral test showed a slightly lower delay in N1, and there was a large negative peak in implant users with poorer scores and had more delay in N1 when compared to the normal group. The same trend was obtained in P1 and N2. Similarly, the amplitude of P1 was somewhat higher in children with good scores than in children with fair or poorer scores. In contrast, the amplitude of N2 in normal-hearing children did not differ significantly from that of the N2 in either implant group.

Guo et al. (2016) also aimed to see if LLAEPs could be used to predict early speech perception. The study reported that precise relationships between the MESP categories and the LLAEP scores were seen for the first, second, and third years after implantation. The LLAEP scores exhibited a ceiling effect in the fourth year after implantation, indicating no connection between LLAEP and MESP beyond this point.

There was no significant link between LLAEPs one year after surgery and MESP categories four years later.

Silva et al. (2017) also reported that latency of the P1 component was correlated with auditory and speaking skills in children with cochlear implants soon after surgery and nine months post-implantation. The association was negative in both cases, indicating that as the IT-MAIS/MAIS scores increased, the P1 latency decreased. There was no significant association between the MUSS questionnaire and the electrophysiological examination at all the time points. However, it was decided to separate the children with CI into subgroups based on their auditory skills (detection or discrimination). The subgroup with better auditory skill (discrimination) had a lower P1 latency value and higher IT-MAIS/MAIS and MUSS scores.

Pantelemon et al. (2020) revealed a statistically significant difference between the overall DQ (developmental quotient) and language DQ before and after cochlear implantation, respectively, three and six months later. The results showed a positive correlation with LLAEP measurements which was demonstrated by a decrease in P1 latency with the increase in DQ.

CHAPTER 4

DISCUSSION

The present study aimed to review articles on LLAEP as an objective outcome measure in children with the cochlear implant in a systematic way. The results of the systematic review are discussed under the following sections:

4.1 LLAEP as an objective outcome measure in children with the cochlear implant.

4.2 Correlation between the electrophysiological and behavioral measures in children with the cochlear implant.

4.3 Factors affecting the outcomes in children with the cochlear implant.

4.4 Limitations of the reviewed studies

4.1 LLAEP as an objective outcome measure in children with the cochlear implant.

As time passes, there was improvement seen in the electrophysiological measures with the usage of the cochlear implant in the pediatric population in all the studies reviewed in the present study (Gordon et al., 2008; Guo et al., 2016; Pantelemon et al., 2020; Silva et al., 2017). All four studies recorded the LLAEP at the Cz position and for speech stimuli, except Gordon et al. Gordon et al. (2008) recorded the late latency response for the tone burst stimuli at 0.5Hz, 2KHz, and 6 kHz. All the studies included in the review indicate that neurophysiological changes are happening in the auditory pathways post-implantation. Cochlear Implantation impacts both the latency and amplitude of the late latency responses and changes in the behavioral measure (Gordon et al., 2007; Gordon et al., 2003; Korczak et al., 2005; Russo et al., 2005; Thai-Van et al., 2007). Access to speech sounds given by the cochlear implant and auditory training allows new neural connections in the central auditory nervous system. As a result of strengthening these linkages, hearing skills are gradually developed (Ouellet and Cohen 1999).

All the included studies supported the idea of neurophysiological changes post-implantation, which are either reflected in the presence or absence of P1 peak (Gordon et al., 2008; Guo, Li, Fu, Liu, Chen, Meng, et al., 2016; Pantelemon et al., 2020; Silva, Couto, et al., 2017). A single positive wave (P1) dominated the responses of cochlear implant children in most studies. Only Gordon et al. (2008) measured all the components of LLAEP as the study included much older children. The positive peak in children with cochlear implants is likely the result of synaptic efficacy and perhaps myelination (Eggermont, 1988; Ponton et al., 1996). The other reasons could be the morphological and functional changes associated with auditory sensory stimulation, such as increased neurons that respond to sound stimuli, extended dendritic branching, and synchronization. This is reflected as changes in the latency and shape of LLAEP traces due to these anatomical and physiological changes (Gordon et al., 2005; Kral & Sharma, 2012; Tae et al., 2020).

In addition, P1 response has been proved as a bio-marker of auditory plasticity and is prominent in young children (Sharma & Campbell, 2011). The presence of the P1 component suggests that the presence of LLAEPs to speech stimuli could provide early objective indications of the aided child's ability to access speech by audition (Golding et al., 2007). On the other hand, the absence of cortical responses suggested that the speech sounds may not have been detected, or that the absence of cortical responses could be related to insufficient sensation level of the amplified sounds

(Zhang et al., 2014), or the immaturity of the central auditory system. This could be a valuable objective method for ensuring the effectiveness of sound detection amplification and guiding CI mapping and rehabilitation training in the future (Chang et al., 2012).

Alternatively, in children with cochlear implants, the dominant positive wave of cortical responses could be similar to wave P2 in normal responses. It was discovered that if children were exposed to auditory deprivation for less than 3.5 years, P1 latency returned to normal after 3 to 6 months of stimulation; however, if the deprivation lasted longer than seven years, P1 waveform did not recover into normal latency (Sharma et al., 2007).

In the reviewed studies, the age of implantation ranged from 12 months to 14 years. Despite this wide range in the age of implantation, a consensus was discovered on the use of CI to provide alterations in central auditory pathways, as evidenced by the rapid decrease in P1 latency values (K. A. Gordon et al., 2008; Guo et al., 2016; Pantelemon et al., 2020; Silva, Couto, et al., 2017). The above results are applicable primarily when the CI activation occurred before the age of 3 years and six months. The decreasing P1 latency in response to the period of usage and age of CI activation are two crucial factors (Aparecida et al., 2013). In terms of CI experience, there was a trend seen in the development of the P1 with respect to the early or late implantation. The development of P1 occurs 3 to 8 months post-implantation if in children are implanted early, and the changes in P1 is slower in children who were implanted later (Alvarenga et al., 2013; Aparecida et al., 2013; Brown et al., 2015; Sharma et al., 2004)

Amplitude is another parameter used in LLAEPs (though only Gordon et al., (2008) had measured the amplitude of LLAEP). The amplitude was higher in implant users with good PBK scores than in normal-hearing children; this could be due to an immature auditory cortex. Both P1 and P2 amplitudes are big in younger normal-hearing children and decline with maturity (Ponton and Eggermont, 2001). The same trend has been reported even in children with cochlear implantation with training.

In general, it can be concluded that reduced P1 latency in children who wear the cochlear implant are directly related to the rate of cortical remodeling. According to the findings, the maturation of auditory pathways results in faster development of auditory and linguistic skills (Aparecida et al., 2013), which brings us to the following section where the electrophysiological and behavioral measures are correlated in children with the cochlear implant.

4.2 Correlation between the electrophysiological and behavioral measures in children with the cochlear implant

The P1 component of the LLAEPs is a response triggered by bioelectric activity in the primary auditory cortex (Kelly et al., 2005). A reduction in P1 latency has been linked to improvements in communicative behaviors (Sharma et al., 2004) and auditory and language processing (Alvarenga et al., 2012.; Sharma et al., 2005, 2009). Evidence of improvement in LLAEPs in the first months of CI use indicated plasticity in the auditory system, which may precede an improvement in communication skills. Children who showed progress in electrophysiological responses had better speech comprehension and, thus, tremendous success in auditory rehabilitation (Dinces et al., 2009b).

All the study included in the review found a positive correlation between the late latency response and the behavioral measures. That is, children who mastered higher auditory skills showed better P1 component. Whereas in Guo et al. (2017), there was a strong association between the first, second, and third years after implantation between the first, second, and third years after implantation MESP and LLAEP scores. However, the link between these two variables was not presented in the fourth year following surgery, implying other factors influencing MESP test results. This indicates the saturation of the LLAEP, i.e., though the scores of the behavioral measure increase, the enhancement of LLAEP response is not like that of behavioral measure (Kelly et al., 2005). Individual differences, ages at implantation, duration of deafness, family wellbeing, the language used in daily life, and parental education could all have a role (Li et al., 2015; Swami et al., 2013).

Another essential point to notice is that the behavioral measure used differs between all the four studies as the age group is quite different. Further, some have used speech perception tests, and some have used developmental scales. Irrespective of the auditory skill assessed, the studies have shown a correlation between LLAEP and auditory behavior.

In conclusion, there was a correlation between the late latency response and behavioral outcomes (Gordon et al., 2008; Guo, Li, Fu, Liu, Chen, Meng, et al., 2016; Pantelemon et al., 2020; Silva, Couto, et al., 2017) despite the differences in the method in terms of the age range, behavioral tools, the number and duration for which the cases were followed up, etc. Hence, late latency response as an objective measure could be a boon to measuring appropriate outcomes and planning the rehabilitation of a child with a cochlear implant to ensure proper auditory development.

4.3 Factors affecting the outcomes in children with the cochlear implant:

Some factors addressed in the reviewed articles are discussed in the following subsection. Beginning with the *duration of deafness*, many studies and clinicians have identified the duration of profound deafness before implantation as a crucial component in children's prognosis. The review also shows that implantation at a younger age improves speech perception in children who are deaf from birth or who are deaf at a young age (Graham et al., 2009; Leigh et al., 2016; S.. Oh et al., 2003; Svirsky et al., 2004; Tajudeen et al., 2010). Hence, *the age of intervention* is crucial. Spoken language development is aided by earlier diagnosis and improved early intervention (Geers, 2006; Yoshinaga-Itano et al., 1998)

The second factor reported was a *rehabilitation* that influenced P1 latency (Thabet & Said, 2012). The quality of rehabilitation affects the development of the auditory skills and is also a significant factor while analyzing the child's auditory performance (Geers, 2006; Klop et al., 2007). Another factor to consider is the *duration of effective hearing aid use before implantation* (Cowan et al., 1997; Dowell et al., 1995). *Auditory deprivation* seems to be responsible for modifying the topographical representation of the auditory pathway corresponding to the auditory cortex (Wieselberg & Iório, 2012), which is reflected in late latency response and behavioral measures.

The *communication method* has a substantial relationship with speech perception outcomes (Dowell et al., 2002). Children who communicated only through speech had much better speech and language outcomes than children who communicated through both speech and sign language (Geers, 2006). The underlying reason for this is cross-modal plasticity, and it is known to occur in the auditory cortex during deafness (Finney et al., 2001; Vergara-Jimenez et al., 2015), and the degree to which this occurs correlates with cochlear implant outcomes (Lee et al., 2001).

Another significant predictor of language development in children with cochlear implants is the *mother-child contact and the family's involvement* in the auditor-verbal rehabilitation process. Children from families that participate in the verbal rehabilitation procedure have significantly increased language ability (Moeller, 2000; Niparko et al., 2010). Furthermore, increased *family income* has improved language abilities in children with cochlear implants (Kushalnagar et al., 2010; Ruffin et al., 2013).

4.4 Limitations of the reviewed studies

The studies on LLAEP n children with cochlear implants have included only a small number of individuals. This could be due to procedural constraints and difficulty capturing LLAEPs at a young age (Pantelemon et al., 2020; Silva, Couto, et al., 2017). In addition, in the Guo et al.'s study, factors that influence the outcome of (re)habilitation in children with a cochlear implant such as duration of sensory deprivation, age at implantation, amount of listening training (Ouellet & Cohen, 1999; Chen et al., 2010; Geers et al., 2009; Melo & Lara, 2012; Ouellet et al., 2010) were not considered. The limitation of the study done by Gordon et al. (2008) was that the study did not measure LLAEP before implantation (baseline) to compare the outcome post-implantation. All these limitations stated above should be kept in mind while constructing a study that aims to observe the changes in the objective and subjective outcome measures in children with the cochlear implant.

CHAPTER 5

SUMMARY AND CONCLUSION

The systematic review was undertaken to establish the understanding of late latency response as an objective outcome measure that would help assess the auditory performance in children with the cochlear implant. The search for the articles began with finalizing appropriate keywords, putting those through various search engines. Later the articles found were screened at various stages. At the end of all the screening stages, studies were collected, and those relevant to our research questions were taken up. The entire procedure of searching and identifying articles was done using PRISMA. Four studies were short-listed at the end of this process.

The full-length articles of the four studies were read through, and the results of the articles were analyzed. A general trend across all the studies was an improvement in both the electrophysiological measure (LLAEP) and behavioral measure/s after cochlear implantation. The results gave an insight into the child's growth in all areas of development and from both clinician and parents' perspectives.

The review gave an understanding of the changes in the LLAEP and behavioral measure post-implantation in children. There was a correlation between the two measures. Hence, the answer to the research question is that LLAEP can be used as an auditory performance indicator in young children. P1 is the biomarker of early cortical changes and hence, can be used to assess the improvement in auditory performance in young children after cochlear implantation. However, the interpretation of the outcome should be made keeping in mind the factors affecting the same. To conclude, late latency response as an objective outcome measure in day-to-day life helps the audiologist track changes in the auditory pathway following cochlear implantation.

5.1 Clinical implication of the current review

The current systematic review gives an idea about changes in the central auditory pathways, measured with the help of LLAEP and behavioral measures. LLAEP can be used as an objective outcome in the clinical population as the present review strongly advocates for the same.

5.2 Future directions

It was observed that there are very few studies done in the area of LLAEP in children with cochlear implantation for predicting behavioral outcomes. In the pediatric population, it is crucial to understand the physiological changes and behavioral changes post-implantation. More studies are required to reach a concrete conclusion to understand the influence of many variables that affect the outcome.

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