Systematic Review Revisão Sistemática

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Descritores

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Maturation of long latency auditory evoked potentials in hearing children: systematic review

Maturação dos potenciais evocados auditivos de longa latência em crianças ouvintes: revisão sistemática

ABSTRACT

Purpose: To analyze how Auditory Long Latency Evoked Potentials (LLAEP) change according to age in children population through a systematic literature review. Research strategies: After formulation of the research question, a bibliographic survey was done in five data bases with the following descriptors: Electrophysiology (Eletrofisiologia), Auditory Evoked Potentials (Potenciais Evocados Auditivos), Child (Criança), Neuronal Plasticity (Plasticidade Neuronal) and Audiology (Audiologia). Selection criteria: Level 1 evidence articles, published between 1995 and 2015 in Brazilian Portuguese or English language. Data analysis: Aspects related to emergence, morphology and latency of P1, N1, P2 and N2 components were analyzed. Results: A total of 388 studies were found; however, only 21 studies contemplated the established criteria. P1 component is characterized as the most frequent component in young children, being observed around 100-150 ms, which tends to decrease as chronological age increases. The N2 component was shown to be the second most commonly observed component in children, being observed around 200-250 ms. The other N1 and P2 components are less frequent and begin to be seen and recorded throughout the maturational process. Conclusion: The maturation of LLAEP occurs gradually, and the emergence of P1, N1, P2 and N2 components as well as their latency values are variable in childhood. P1 and N2 components are the most observed and described in pediatric population. The diversity of protocols makes the comparison between studies difficult.

RESUMO

Objetivo: Analisar como os Potenciais Evocados Auditivos de Longa Latência (PEALL) variam de acordo com a idade na população infantil, por meio de revisão sistemática da literatura. Estratégia de pesquisa: Depois da formulação da pergunta da pesquisa, o levantamento bibliográfico foi realizado em cinco bases de dados, com os seguintes descritores: Eletrofisiologia (Electrophysiology), Potenciais Evocados Auditivos (Auditory Evoked Potentials), Criança (Child), Plasticidade Neuronal (Neuronal Plasticity) e Audiologia (Audiology). Critérios de seleção: Artigos com nível de evidência 1, publicados na íntegra entre os anos de 1995 e 2015 na língua Portuguesa Brasileira ou Inglesa. Análise dos dados: Foram analisados os aspectos relacionados ao surgimento, morfologia e latência dos componentes P1, N1, P2 e N2. Resultados: Foram localizados 388 estudos; contudo apenas 21 contemplaram os critérios de inclusão para análise. O componente P1 caracteriza-se como o de maior ocorrência em crianças pequenas, sendo observado por volta de 100-150 ms, o qual tende a diminuir com o decorrer da idade cronológica. O componente N2 mostrou-se como o segundo componente mais registrado em crianças, sendo observado por volta de 200-250 ms. Os demais componentes N1 e P2 mostram-se menos frequentes e passam a ser visualizados e registrados ao longo do processo maturacional. Conclusão: A maturação dos PEALL acontece gradativamente, sendo o surgimento dos componentes P1, N1, P2 e N2 bem como seus valores de latência variáveis na infância. Os componentes P1 e N2 são os mais observados e descritos na população pediátrica. A diversidade de protocolos dificulta a comparação entre os estudos.

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INTRODUCTION

Auditory sensibility is a sense that exists since the twenty-fifth week of intrauterine life in humans. From then on, the experiences lived by each person allow the Central Auditory Nervous System (CANS) to undergo neurophysiological changes, through neuronal plasticity, enabling auditory learning. It is this phenomenon of maturation and modification of the central auditory pathways that allows people to be able not only to listen, but also to allow the auditory abilities to be developed and, this way, the audible stimuli heard can be detected, discriminated, recognized and understood⁽¹⁾.

With sensorial stimulation of hearing, there are morphological and functional modifications, such as increase of neurons that begin to respond to sound stimuli, amplification of dendritic branch, increase of neuronal myelination and improvement of connections and synaptic synchronizations⁽²⁻⁵⁾.

This neuroplasticity can be investigated through the analysis of Long-Latency Auditory Evoked Potentials (LLAEP), which has been shown to be an instrument capable of monitoring neurophysiological changes occurring in the CANS, by analyzing the components P1, N1, P2, N2, generated by bioelectrical activity of the thalamo-cortical regions, after acoustic stimulation⁽⁶⁻⁸⁾.

It is known that, with auditory stimulation, maturation of CANS allows gradual appearance of components of P1-N1-P2-N2 complex, which decrease in latency with advancement of age, being fully mature around 14 years old⁽⁹⁻¹²⁾. Despite this, a standardization in relation to the onset period of each component of the complex, as well as the expected latency values for each age group has not been defined yet.

Considering that LLAEPs have been widely used in clinical practice to monitor the maturation of CANS after therapeutic or surgical intervention, it is clear the necessity of raising reference values in hearing children with typical development for comparison purposes.

OBJECTIVE

The aim of this study was to analyze the way LLAEP components vary according to age in the child population, through a systematic literature review.

Research strategy

The first step of research consisted in elaborating the question for bibliographic review: "How do the P1, N1, P2 and N2 components of Long Latency Auditory Evoked Potentials vary according to age in child population?"

The systematic review of scientific literature was based on the search for Portuguese and English studies published in the last twenty years (between 1995 and 2015). The databases searched were: *Lilacs, Scielo, Science Direct, Pubmed and Medline*.

As descriptors of search, the following terms were used according to the DeCS system (Health Sciences Descriptors): *Eletrofisiologia, Potenciais Evocados Auditivos, Criança,*

Plasticidade Neuronal and *Audiologia* with their English correspondents (Electrophysiology, Auditory Evoked Potentials, Child, Neuronal Plasticity and Audiology).

Selection criteria

The inclusion criteria of these studies were articles that answered the question of the research and that evaluated the maturation of the auditory pathways in children up to 12 years old, without auditory impairment. Regarding the level of evidence, level 1 articles according to the *Oxford Center for Evidence-based Medicine*⁽¹³⁾ were considered, which include: Systematic review of randomized controlled clinical trials; Randomized controlled clinical trial with confidence interval; Therapeutic results of "all or nothing" type.

Data analysis

Initially, the search of studies in all the cited databases was carried out using the pre-determined keywords. The result of this search was blindly analyzed by two reviewers who read the titles and abstracts of each article and should answer the following questions:

- What is the level of evidence of the study?
- Does the study present data regarding the analysis of the LLAEP?
- Was the study conducted in child population?

After completing this phase, the selected papers were read in full, checking aspects related to the research objective, the methodology used (type of study, participants and registration methodology and type of analysis), the results obtained (appearance, morphology and latency of the components P1, N1, P2 and N2) and the conclusion of each study. The data extracted from this selection were recorded in forms, which were analyzed by a third reviewer. The differences found in the analysis of the studies were revolved through discussion among the reviewers.

RESULTS

Results in electronic databases

As result of the search, 388 studies were found distributed in databases researched. Of these, 63 studies were found in more than one database and, for this reason, were excluded. Of the 325 titles selected, three could not be recovered because they were not available for free electronic access. Thus, the titles and summaries of the 322 articles retrieved were read, but 261 were excluded because they did not meet one or more defined criteria. A total of 61 studies on LLAEP in hearing children were selected and read in their entirety, and of these, 40 were excluded because they did not answer the research question. Thus, 21 studies were analyzed in this review (Table 1).

Articles Included

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Selected studies analysis

The selected studies results showed large modifications in the LLAEP trajectories due to the auditory system development with the increase in chronological age. It is known that CANS maturational process is complex and extends until the second decade of life⁽¹⁴⁾. The components P1, N1 and P2 gradually emerge in the tracings and become similar to those of adults around the age of 14⁽¹⁵⁾, and may also change in terms of latency and amplitude up to 20 years of age⁽¹⁴⁾.

In one study, the LLAEP maturation at birth up to one year of age was evaluated, and was monitored every three months. The authors observed that all peaks present at 12 months of

age (P150, N250, P350 and N450) were already identified at birth. As age increased, peak amplitudes increased and latencies decreased⁽¹⁶⁾.

When evaluating children between ages six to seven years, other authors described that the LLAEP trajectory was dominated by a large positive peak observed at around 100 ms, and that although there was considerable variation from individual to individual, this peak decreased in latency with the course of the age; Then, the authors suggested that this peak would probably correspond to the P1 component observed in adults. In younger children, it was also observed that this positive peak was followed by a negative peak that appeared around 200 ms⁽¹⁷⁾.

In the following year, a study was published confirming these data; However, the authors added that, especially in older children, a negative peak that happened before the 200 ms was observed, which the authors named from N1a, for the first peak, and N1b, for the second negative peak. According to the authors, all children have N1b; However, N1a becomes more frequent with increasing age. Both peaks decrease in latency with advancing chronological age; however, the relation of N1a and N1b to N1 observed in adults was not clear yet⁽¹⁴⁾.

Recent studies have reported that the young children trait characteristic is formed by a large positive peak (P1) that appears around 100-150 ms, followed by a negative peak (N2) that occurs around 200-250 ms^(10,18-20). During maturation, some authors observed that the components N1 and P2 arise from a P1 bifurcation component^(10,20), and that they begin to be observed more frequently from the age of 12⁽¹⁸⁾. There are findings that, at 14 years of age, the P1-N1-P2 complex becomes similar to the adults one⁽¹⁵⁾.

The broadband stimulus study results in a group of children show that maturation occurs throughout childhood and is not complete until five years of age. From this stimulus, the authors observed that, in children, a large positive wave is dominant and a second negative peak is present, but with variable latencies. In this study, the P2 component was shown to be more frequent and the components P1 and N1 were poorly identifiable in infants and children⁽²¹⁾.

On the other hand, in another study, in which children from three months to seven years of age were evaluated, it was observed that only the P1 peak was clearly present at all ages. The authors also reported that significant differences were observed between the tracings of children less than eight months old and over 12 months of age, suggesting that this age group is an important maturation period of the sources generating the P1 component⁽²²⁾. Other researchers observed that the latency of the P1 component increased from about 180 ms at three months to approximately 140 ms at 24 months, demonstrating

a rapid maturation of the auditory pathways during the first two years of life⁽²³⁾.

Also, in regard to the evaluation of infants, it was observed in a study that, when present, the components P1-N1-P2-N2 showed latency values ranging from 150 to 190 ms, 210 to 260 ms, 250 to 331 ms and 250 to 450 ms, respectively for each component⁽²⁴⁾.

In addition, 10 other studies also described the latency values obtained in children between ages 2 to 12 years. It was generally observed that, although there is a variation between the studies, a reduction in the latency values is commonly noticed with the increase of the age group (Table 2). It has been found in the literature that the P1 component latency has a strong relation with age, decreasing about 1.6 ms per year⁽¹²⁾, which is not equal to the adult until the 15 years of age⁽⁹⁾ and, besides that, the reduction in latency values of this component can be observed until around 20 years of age⁽¹⁴⁾.

The chronological age is able to explain approximately 41% of the variance in the latency values; In the others, variations may be related to other issues, such as gender and each individual intelligence coefficient⁽²⁶⁾.

Regard the N1 component, the age expected to be visualized in the LLAEP traces⁽²⁹⁾ is not known with precision yet. Some authors have observed that the appearance of the N1 component begins around three and four years of age⁽²⁵⁾. On the other hand, other authors did not observe concrete evidence of the N1 component in four and eight-year-old children; Despite this, they described the occurrence of a negative peak, similar to N1, in some cases⁽¹⁹⁾. There is also another study in which this component was rarely found in children between six and eight years of age, and its occurrence increased from 71% in children up to nine years to 91% in children above this age. Thus, the authors stated that the analysis of the N1 component in young children may be limited due to the low occurrence of this component in this age group⁽¹⁵⁾.

Table 2. Average interval of the latency values of the P1 component (in milliseconds) obtained in each study, according to the age group

	Sharma et al. (1997) ⁽¹⁴⁾	Ponton et al. (2000)®	Albrecht et al. (2000) ⁽¹⁸⁾	Čeponiene et al. (2002) ^(≥5)	Gilley et al. (2005) ⁽¹⁰⁾	Sussman et al. (2008) ⁽²⁰	King et al. (2008) ⁽¹⁹⁾	Kabel et al. (2009) ⁽²⁶⁾	Kihara et al. (2010)≀≀≀	Mahajan e McArthur (2012)≅®
2.3 to 3.9 years	-	-	-	-	-	-	126-149	-	-	-
3 years		-	-	-	95-105	-	-	-		-
4 years	-	-	-	98-114		-	-	-	90.00	-
5 years	-	70.06	01 106	-	-	-	-	-	- 89-99 -	-
6 years	87	79-86	91-106	-	-	-	-	162	01.00	-
7 years	81	73-81	04.100	-	-	-	-	-	91-99 -	-
8 years	79	66-70	94-122	-	-	85-114	-	113		-
9 years	81	65-68	88-113	104-124	-	76-104	-	-	83-102 -	-
10 years	74	64-71		-	-	79-108	-	-		71
11 years	78	60-65	80-107		75 00	73-93	-	-	74-86	71
12 years	74	50-65		-	75-82	-	-	-		-

In the present review, only three studies were observed, among the 21 articles analyzed, which accurately described the latency values obtained in the N1 component.

There is a great variability between the results, which indicates that more studies on the N1 component analysis are still necessary in order to estimate the expected values for each age group more accurately (Table 3).

The second positive peak present in the LLAEP, the P2 component, can be identified more frequently from 10 years old^(15,30). Despite this, a study in the literature has been found, in which the authors observed the appearance of this peak between eight and 30 months of age⁽²²⁾.

It should be noted that the results were generally convergent among the studies and that this component does not seem to undergo major modifications with the passage of chronological

Table 3. Average interval of the latency values of the N1 component (in milliseconds) obtained in each study, according to the age group

Ponton et al. (2000) ⁽⁹⁾	Albrecht et al. (2000) ⁽¹⁸⁾	Mahajan e McArthur (2012) ⁽²⁸⁾
127-138	172-154	-
98-105	- 170 000 -	-
106-119	170-229	-
92-113	- 170 000 -	-
98-114	172-223	102-108
89-108	- 150 202 -	104-110
12 years 90-106		-
	(2000) ⁽⁹⁾ 127-138 98-105 106-119 92-113 98-114 89-108	(2000) ⁽⁹⁾ (2000) ⁽¹⁸⁾ 127-138 172-154 98-105 106-119 92-113 98-114 89-108 159-202

Table 4. Average interval of the latency values of the P2 component (in milliseconds) obtained in each study, according to the age group

	Ponton et al. (2000) ⁽⁹⁾	Sussmam et al. (2008) ⁽²⁰⁾	Mahajan e McArthur (2012) ⁽²⁸⁾
5 to 6 years	135-153	-	-
7 years	136-158	-	-
8 years	143-157	139	-
9 years	136-147	141-147	-
10 years	141-157	140-146	145-148
11 years	142-154	137-142	143-148
12 years	144-162		

age regarding the latency values. However, it is important to note that only one study evaluated a broad age group, which may be justified by the difficulty to observe this component in young children (Table 4).

Finally, with regard to the N2 component, six studies were found that described the changes in latency values with chronological age (Table 5). Analyzing these studies, it was not possible to observe very evident changes in relation to the decrease of latency of this component with the advancement of chronological age. Likewise, other authors also haven't observed significant differences in the latency values of the N2 component among children aged four and nine years⁽²⁵⁾.

A number of findings were observed in the present review regarding the modifications of the LLAEP. According to some authors, the maturation of the auditory system happens gradually, and as the age increases, the tracings become more defined, the latency values of the components P1, N1 and P2 tend to decrease and present lower variability. In addition, it was observed that the amplitude of the P1 component decreased, whereas the components N1 and P2 did not present modifications⁽¹²⁾.

For other authors, the main changes in the LLAEP due to maturation include the decrease in the latency and amplitude of the component P1, increase in the amplitude of the N1 component, increase in the latency and reduction of the amplitude of the P2 component and a decrease in the latency and amplitude of the component N2⁽²⁰⁾.

As far as amplitude measurements are concerned, there is a description that this variable is related to age, and, throughout development, the amplitude of the components P1 and N2 tend to decrease, whereas the amplitude of the components N1 and P2 tend to increase⁽¹¹⁾.

In another study, it was observed that the maturational changes lead to gradual modifications with respect to the latency measures, with more significant changes in relation to the amplitude values. For these authors, the P1 and N1b components latency decreased as a function of age, while the latency of the P2 component did not change significantly and the latency of the N2 component increased. In general, abrupt changes in amplitude measurements were observed around 10 years of age⁽³⁰⁾.

Table 5. Average interval of the latency values of the N2 component (in milliseconds) obtained in each study, according to the age group

		Ponton et al. (2000) ⁽⁹⁾	Ceponiene et al. (2002) ⁽²⁵⁾	Sussman et al. (2008) ⁽²⁰⁾	King et al. (2008) ⁽²⁷⁾	Kihara et al. (2010) ⁽²⁸⁾
2.3 to 3.9 years	-	-	-	238-251		-
4 years	-	295-307	-	-	004 045	_
5 years	100.010	-	-	-	231-245	-
6 years	196-218	-	-	-	000.040	_
7 years	207-214	-	-	-	228-243	-
8 years	206-221	-	224-243	-	007.040	-
9 years	208-216	285-286	232-233	-	227-246	-
10 years	218-237	-	221-232	-		240-268
11 years	218-231	-	216-226	-	220-243	241-268
12 years	222-232	-	-	-		-

Recently, it was observed in a study that infants and children records a large positive peak (P1), followed by a negative peak (N2), which decreased in latency with increasing age until around four and three years of age, respectively for both components. After approximately seven months, these authors also observed the presence of a positive peak (which they called P2), after the peak N2, which seemed to change between 18 and 24 months of age, being more stable between 24 months and 8 years old⁽²²⁾.

It is known that the maturation of the CANS of each individual is variable, so the appearance, as well as the latency values of the components, P1, N1, P2 and N2 present in the LLAEP can be influenced by the stimulation and rate of development. In addition, scientific advances in the area of hearing electrophysiology have now provided a wide range of protocols available for the collection of LLAEP. These parameters, while very useful as a study tool for a better understanding of the conduction and processing of sounds by CANS, may influence electrophysiological responses and lead to greater variability in determining the expected aspects for each age.

Due to the wide diversity of methods used to collect LLAEP, some authors compared different collection parameters, in a same group of children, by changing the time interval between the interstimulus interval(10,20,31), the electrode site(9,21,25,27,30) and the characteristics of the stimuli(11,28), and some of them observed important differences.

Regarding the speed presentation of the stimuli, it was observed that, in children between ages 3 to 12, the longer the interstimulus interval (2000 ms), the more components could be seen and with a lower latency value compared to the lower interstimulus interval evaluated (360 ms). From the age 11, all components were seen at all rates of stimulation for the majority of children; However, the longer the interstimulus interval, the more defined the tracings⁽¹⁰⁾. On the other hand, in another study, no significant differences were observed with the range of interstimulus interval (200 to 1000 ms) in children between ages six and eight; However, greater amplitude of the N1 component was observed for greater interstimulus interval⁽³¹⁾.

Other authors observed in children between ages 8 and 12 that: the lower the interstimulus intervals (200 ms), the higher the P1 component values latency; It was not possible to register the N1 component at any stimulation rate; It was not possible to identify the P2 component with the use of a lower interstimulus interval in any of the age groups, but this component was observed in the largest interstimulation interval (800 ms) at all ages; The latency value of the N2 component increased when the interstimulation interval was higher⁽²⁰⁾.

Regarding the electrode localization, some authors observed little variation over time in the latency of components P1 and N1b measured from different electrode positions located under the scalp. Up to 10 years of age, the P2 component presents greater changes, when measured in later regions (Pz), than in the earlier electrode sites (Cz and Fz). However, with increasing age, the P2 component becomes more prominent at sites of anterior than posterior electrodes. Regarding the latency of the N2 component, there was an increase as a function of age in the central electrodes (Cz, C3 and C4), but no change when recorded in the frontal electrode (Fz). For these authors, the

LLAEP latency maturation analysis depends on the location of the recording electrode and different generating sources with distinct maturation rates may be responsible for the formation of a single peak⁽⁹⁾.

In this perspective, a new analysis with these same data was made through three sources of dipoles (tangential, radial and sagittal). In the tangential analysis, the interest peaks of the present study were observed. For younger children (5 years of age), the tracing morphology consisted basically of a positivity, P1 component, with latency values similar to N1b observed in adults. Following this component, a negative peak (N2 component) was observed. The P2 component emerged at 9 years of age as a bifurcation in the P1 component⁽³⁰⁾.

In this direction, another study described that the P1 component did not change over time in relation to the recording electrode sites (Fz, Cz, Pz, C4, T4, C3, T3), suggesting that this component originates in the primary auditory cortex hearing in the Heschl spin. As for the components N1 and P2, it was observed that the activation distribution was distinct throughout childhood; Activation in children less than four years of age was mainly in the central, frontal, parietal and temporal regions; From this age, activation of these regions was still observed, however, mainly in the contralateral hemisphere. Finally, it was observed that the N2 component has a wide distribution throughout the scalp, and its activation is more evident in adulthood⁽¹¹⁾.

There are findings that the latency of the N1 component was higher in the lateral regions and lower in the mediastinal regions⁽³¹⁾. As for the components P1 and N2, they were better visualized on the electrodes around the apex of the head compared to the frontal and posterior (anteroposterior effect)⁽²⁵⁾. However, in another study, when comparing two electrodes close to the Fz (left and right), didn't observe differences between the latency values of the components P1, N2 and P2⁽²²⁾.

Also, a study was observed in which a decrease in the latency of the P1 component with increasing age was observed regardless the location of the electrode or type of stimulus (2 kHz tone - frequent stimulus - 1.5 kHz tone - stimulus Rare - and environmental sounds - rare stimulus). The N2 component was most influenced by the collection and analysis parameters, and the results were very variable: when collected with the stimulus of environmental sounds, the N2 component did not change with age, but presented changes when measured by the other stimuli⁽²⁷⁾.

Regarding stimulus, other authors compared different acoustic stimuli in children under six years of age: severe tone (400 Hz), acute tone (3000 Hz) and word. Word stimulation was effective for recording LLAEP at all ages and often generated greater responses than tonal stimulation. The N1 component was not as affected by tone frequency in children younger than 6 years of age, unlike in N2, where the stimulus frequency did not interfere with the adult response. For the P2 component, in general, the acute sound generated less amplitude responses than those recorded with severe sound⁽¹¹⁾. In a similar way, other authors observed a greater amplitude of the components P1 and P2 with the speech stimulus and lower latency value for the N2 component with tone stimulus⁽²⁸⁾.

CONCLUSION

The LLAEP maturation occurs gradually, and the appearance of the components P1, N1, P2 and N2, as well as their latency values, are variable in childhood. The components P1 and N2 are the most observed and described in the pediatric population.

The components P1 and N2 are the most observed and described in the pediatric population. The other components N1 and P2 are now visualized and recorded throughout the maturational process.

The definition of standardized methodologies for the recording and analysis of LLAEP results in the pediatric population, as well as longitudinal character studies, are still necessary to understand better the maturational process during child development.

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Author contributions

LAFS was responsible for collecting, tabulating and data analysis, as well as, drafting the manuscript; FCLM collaborated with the collection and data analysis; ACMC was responsible for the study design and general guidance of the stages of execution and preparation of the manuscript; CGM was responsible by delineating the study and general orientation of the stages of execution and preparation of the manuscript.