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Systematic Review
Revisão Sistemática

Cortical auditory evoked potentials in autism spectrum disorder: a systematic review

Potenciais evocados auditivos corticais no transtorno do espectro do autismo: revisão sistemática

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Keywords

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ABSTRACT

Purpose: To identify and analyze what are the characteristic findings of Cortical Auditory Evoked Potentials (CAEP) in children and / or adolescents with Autism Spectrum Disorder (ASD) compared to typical development, through a systematic literature review. **Research strategies:** Based on the formulation of a research question, a bibliographic survey was carried out in seven databases (Web of Science, Pubmed, Cochrane Library, Lilacs, Scielo, Science Direct, and Google Sholar), with the following descriptors: *autism spectrum disorder* (transtorno do espectro autista), *autistic disorder* (transtorno autístico), evoked potentials, auditory (potenciais evocados auditivos), event related potentials, P300 (potencial evocado P300) e child (criança). This review was registered in Prospero, under number 118751. **Selection criteria:** Were selected articles published, without language limitation, between 2007 and 2019. **Data analysis:** The characteristics of the latency and amplitude aspects of the P1, N1, P2, N2 and P3 components present in the CAEP. **Results:** 193 studies were located; however, 15 original articles were included the inclusion criteria for this study. Although it has not been possible to identify any pattern of response for the P1, N1, P2 and N2 components, the results of the selected studies have demonstrated that individuals with ASD may present a decrease in amplitude and increase in latency of the P3 component. **Conclusion:** Individuals with ASD may present different responses to the components of the CAEP, and the decrease of the amplitude and increase of the latency of the P3 component were the most common characteristics.

RESUMO

Objetivo: Identificar e analisar quais são os achados característicos dos Potenciais Evocados Auditivos Corticais (PEAC) em crianças e/ou adolescentes com Transtorno do Espectro do Autismo (TEA) em comparação do desenvolvimento típico, por meio de uma revisão sistemática da literatura. **Estratégia de pesquisa:** Após formulação da pergunta de pesquisa, foi realizada uma revisão da literatura em sete bases de dados (Web of Science, Pubmed, Cochrane Library, Lilacs, Scielo, Science Direct, e Google acadêmico), com os seguintes descritores: transtorno do espectro autista *(autism spectrum disorder*), transtorno autístico (*autistic disorder*), potenciais evocados auditivos (evoked potentials, auditory), potencial evocado P300 (event related potentials, P300) e criança (child). A presente revisão foi cadastrada no Próspero, sob número 118751. **Critérios de seleção:** Foram selecionados estudos publicados na integra, sem limitação de idioma, entre 2007 e 2019. **Análise dos dados:** Foram analisadas as características de latência e amplitude dos componentes P1, N1, P2, N2 e P3 presentes nos PEAC. **Resultados:** Foram localizados 193 estudos; contudo 15 estudos contemplaram os critérios de inclusão. Embora não tenha sido possível identificar um padrão de resposta para os componentes P1, N1, P2, N2 e P3, os resultados da maioria dos estudos demonstraram que indivíduos com TEA podem apresentar diminuição de amplitude e aumento de latência do componente P3. **Conclusão:** Indivíduos com TEA podem apresentar respostas diversas para os componentes dos PEAC, sendo que a diminuição de amplitude e aumento de latência do componente P3 foram as características mais comuns.

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INTRODUCTION

Autism is a developmental disorder characterized by impairments in communication and social interaction. Children and adults with Autism Spectrum Disorder (ASD) present standardized behaviors, stereotyped speech and motor movements, repetitive routines with restricted interests, and perceptual changes in attention and memory[1,2].

Considering the importance of hearing for the effective establishment of oral communication, and that individuals with ASD can be confused with hearing-impaired individuals, a complete hearing assessment, both of the peripheral and central systems, becomes important for evaluating the integrity of all structures of the auditory system - from the outer ear to the auditory cortex – in this population[3,4].

Several studies have observed, through behavioral methods, normal hearing thresholds in individuals with ASD[5-7]. Despite this, it has been described in the literature that children with ASD can present both discomfort with sounds of medium intensity and indifferent behaviors to sounds of strong intensity or noises, as they may be hyper- or hyposensitive to sensory stimuli[8].

One way to objectively verify auditory integrity and functionality is through the assessment of Auditory Evoked Potentials (AEP), which are traces generated by bioelectric activity from the thalamocortical auditory pathways after acoustic stimulation[9-11]. Because this is an objective method, it has the great advantage of enabling a complementary behavioral assessment in individuals who are difficult to be evaluated, such as children with ASD[12].

Assessment using the Cortical Auditory Evoked Potentials (CAEP) is able to reflect the functionality of central auditory processing to verbal or non-verbal sounds through the analysis of positive and negative peaks called P1, N1, P2, N2 and P3[9-11,13].

The P1, N1, P2 and N2 components are considered exogenous potentials, that is, they do not depend on the individual's active response, and can provide information about the integrity of the auditory pathway, neural coding, and perception and detection of the acoustic stimulus[9,14]. On the other hand, the P3 component is considered an endogenous potential, as it requires an active response from the individual to perform certain tasks, and reflects more central auditory processes such as auditory discrimination and temporal processing[9,15].

Several studies have demonstrated changes in Brainstem Auditory Evoked Potentials (BAEP) in individuals with ASD; in addition, a literature review described that abnormalities in the processing of sound information can be observed in individuals with ASD, with increased wave V latency and, consequently, increased I-IV or III-V inter-peaks as the most commonly observed change[16].

Regarding the cortical evaluation, little is known about the possible results of CAEP in individuals with ASD. These potentials are capable of verifying the functionality of auditory processing objectively, thus they are a clinical resource to be considered in the evaluation of these patients, given the difficulty to apply behavioral tests in this population. In addition, this assessment has been highlighted as effective in monitoring changes in the Central Auditory Nervous System (CANS) after therapeutic intervention[17-20].

Therefore, a survey of the results described in the literature with regard to the findings of CAEP in children and/or adolescents with ASD, highlighting the differences in comparison with their typically developing peers, is of great interest to verify whether there are specific characteristics in the responses obtained in this population.

OBJECTIVE

The present study aimed to identify and analyze the findings characteristic of CAEP in children and/or adolescents with ASD and compare them with those of their typically developing peers through a systematic review of the literature.

RESEARCH STRATEGY

This review was based on the following research question: What are the differences in the results of CAEP in children with ASD compared with those of typically developing children?

This systematic review was registered in the PROSPERO system under protocol no. 118751 and the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[21] were followed. The following evidence-based items were established according to the Population, Intervention, Comparison/control, Outcome (PICO) framework[17,21]:

- **Patient (P):** children or adolescents with ASD;
- **Intervention (I):** individuals with ASD who underwent CAEP assessment;
- **Comparison (C)**: articles including a control group composed of individuals with typical development were considered;
- **Outcomes (O)**: whether or not there is change in the CAEP components.

In order to answer the study question, a search was conducted in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) systems to define the descriptors to be used in the bibliographic survey; such descriptors were crossed using the Boolean operator "AND". Subsequently, the following descriptors in English and (*Portuguese*) were selected: autism spectrum disorder (*transtorno do espectro autista*); autistic disorder *(transtorno autístico*); evoked potentials, auditory (*potenciais evocados auditivos*); event-related potentials, P300 (*potencial evocado P300*); child (*criança*).

Between April and May 2019, a bibliographic search was carried out in seven databases: Web of Science, PubMed, Cochrane Library, LILACS, SciELo, ScienceDirect, and Google Scholar. The references used in the selected articles were also analyzed to identify a larger number of potentially relevant studies.

Selection criteria

The following inclusion criteria were used in the present systematic literature review: full original peer-reviewed scientific articles and dissertations and theses that contemplated the analysis of the CAEP in children and adolescents with ASD with inclusion of a control group for comparison. In the case of dissertations and theses, a search was carried out to find the full article originating from them, and when the latter were found, they were used in substitution for the former.

Thus, we selected studies published between 2007 and 2019, without language limitation, that answered the research question and evaluated the presence and absence, as well as the latency and/or amplitude values, of the P1, N1, P2, N2 and P3 CAEP components in children and adolescents with ASD and compared them with those of their typically developing peers.

Articles that assessed potentials other than the CAEP, did not use auditory stimulus, did not have a clear methodology or used a control group for comparison, or did not present the outcome of interest of the present study were excluded.

Data analysis

After completing the search, articles with repeated titles were excluded and the results were blindly analyzed by two reviewers who read the titles and abstracts of the articles and verified whether they met the inclusion criteria. If the study was considered for reading the title by at least one of the reviewers, it was maintained in the study and read in full.

After that, the selected papers were read in full by two independent reviewers; disagreements were resolved through discussion and, when necessary, a third reviewer was consulted.

The articles were analyzed for the purpose of the systematic review, methodology used (type of study, case series, procedures, data analysis), results obtained (latency and amplitude values of the P1, N1, P2, N2 and P3 components of the CAEP), and conclusion.

The quality of the studies included in the review was analyzed according to the Methodological Index for Non-randomized Studies (MINORS), which is a protocol composed of eight items (1 to 8) to evaluate non-comparative studies and 12 items (1 to 12) to assess comparative studies, with each item receiving a score between zero and two (0 = not reported; 1 = reported but inadequately; 2 = reported adequately)[22]. The divergences found in the analysis of the studies were resolved through discussion among the reviewers.

RESULTS

Results of the electronic databases

The search conducted in the aforementioned electronic databases found 189 studies, and PubMed yielded the largest number of results. In addition to these, four studies were identified in the bibliographic reference lists of other articles. Only 15 studies met the inclusion criteria and were considered in the present review. Figure 1 shows the article selection procedure in detail.

Analysis of selected studies

After reading each study in full, an individual detailed analysis was carried out considering the main objectives, methodological aspects, and main results (Chart 1).

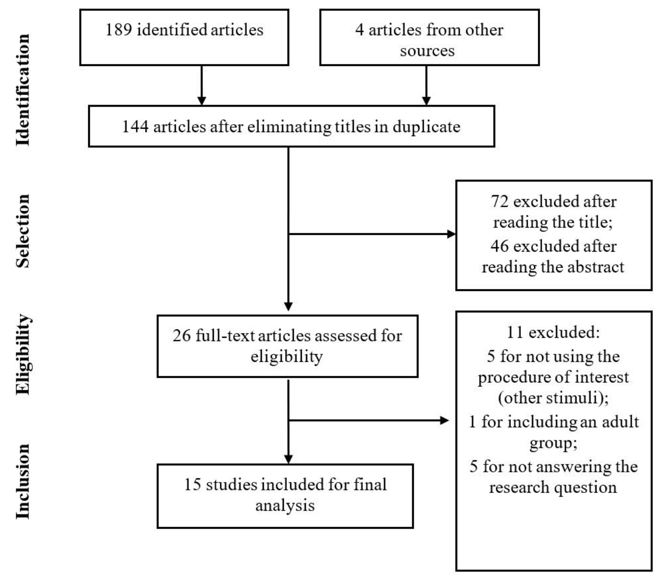

Figure 1. Flowchart of the selection of articles for analysis

Regarding the risks of bias (Table 1), all included studies had similar scores (14-18 points out of 24, considering that all studies were comparative) and showed similar profiles with respect to quality criteria.

As for the methodological aspects, study sample size varied between 10[29,36] and 30[36] individuals with ASD with ages ranging from 4[25,31,34] to 20[4] years; thus, it can be observed that some studies evaluated a wide age group (children and adolescents). As for the profile of the population that comprised the groups of individuals with ASD found in the studies, most of the participants in all studies were male.

It is known that maturation of the CANS and, consequently, of CAEP occurs throughout childhood until adolescence[37]. Thus, age is a variable that can significantly interfere with the findings of CAEP and may cause a bias in the analysis between studies. However, all studies analyzed here included a control group with individuals with Typical Development (TD) in order to obtain an equivalent comparison with respect to age. Thus, it is believed that age was not a variable that may have influenced the results of the studies selected for this review.

Concerning the distribution by gender, a larger number of male individuals were observed in the selected articles; this finding may be due to the fact that ASD is four times more prevalent in males than in females[2].

Still regarding the methodological aspects, it was observed that most studies were carried out with non-verbal stimulus[4,24,25,27-33]. One study used only verbal stimulus[34], three studies used both verbal and non-verbal stimuli[23,34,35], and one used biological sound stimuli (finger snap and mouth sucking)[36] (Chart 2).

Variability in the stimuli used to collect the CAEP can generating different cortical responses. It is known that the verbal stimulus is more complex than the non-verbal stimulus, as it is captured if there is sensitive perception of signals that present rapid changes in their spectrum and rapid rates of stimulation[6]. In addition, the verbal stimulus has a longer duration compared with that of the non-verbal stimulus and presents greater acoustic

Chart 1. Summary of the main findings of the selected articles

Author	Methodology					Main results	Limitations
	Type of study	Sample SG	Sample CG	Diagnostic criterion for ASD	CAEP stimulus		
Whitehouse and Bishop[23]	Prospective cross-sectional	15 boys aged 7 to 14 years	15 (11 boys) aged 7 to 14 years	DSM-IV	Verbal and non-verbal. Oddball Paradigm.	For the non-verbal stimulus, there was no difference between the groups, but there was a difference for the verbal stimulus, and the SG presented reduced amplitude for the P1, N2 and P3 components.	Analysis of amplitude only; it only presents the numerical values of the verbal stimulus; it only analyzes the P1, N2 and P3 components.
Matas et al.[24]	Prospective cross-sectional	10 (9 boys) aged 8 to 19 years	20 (3 boys) aged 8 to 19 years	DSM-IV	Non-verbal (tone burst). Oddball Paradigm.	P3 responses were altered by 15% in the CG (latency delay) and 40% in the SG (50% showed delayed latency and 50% showed no response).	It does not present the results numerically; small sample size for the SG; evaluated only the P3 component; analyzed only the latency variable.
Orekhova et al.[25]	Prospective cross-sectional	21 (17 boys) aged 4 to 8 years	21 (18 boys) aged 4 to 8 years	DSM-IV-TR and ICD-10 confirmed by DISCO-10	Non-verbal sounds presented at different intervals. Oddball Paradigm.	The SG demonstrated reduced amplitude of N1 and N2 components.	It does not present the results numerically; evaluated only the N1 and N2 components; evaluated only the amplitude variable.
Russo et al.[26]	Prospective cross-sectional	16 (14 boys) aged 7 to 13 years	11 (7 boys) aged 7 to 13 years	ADOS and ADI-R	Verbal with and without noise. Without using the Oddball paradigm.	The SG showed increased latencies and decreased amplitudes of the P1 and N1 components.	Evaluated only P1 and N1 components; small sample size for the CG.
Magliaro et al.[4]	Prospective cross-sectional	16 (15 boys) aged 11.94 years on average	25 (9 boys) aged 12.16 years on average	DSM-IV	Non-verbal (tone burst). Oddball Paradigm.	Absence of response (60% of cases) was the predominant type of change in the SG compared with the CG (0% absence).	It does not present the results for latency and amplitude; evaluated only the P3 component.
Gomot et al.[27]	Prospective cross-sectional	27 (21 boys) aged 5 to 11 years	27 (21 boys) aged 5 to 11 years	DSM-IV-R	Non-verbal (tone burst). Oddball paradigm, non-attentional.	The SG showed decreased latency and increased amplitude values for the P3 component.	Evaluated only the P3 component.
Andersson et al.[28]	Prospective cross-sectional	11 boys aged 16 years on average	12 boys aged 15.3 years on average	DISCO	Non-verbal (tone burst). Oddball Paradigm.	There were no differences between groups for the components analyzed (N1, P2, P3a, and P3b).	Small sample size.

Caption: SG: Study Group; CG: Control Group; CAEP: Cortical Auditory Evoked Potentials; RH: Right Hemisphere; LH: Left Hemisphere; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DISCO: Diagnostic Interview for Social and Communication Disorders; ADOS: Autism Diagnostic Observation Schedule; ADI-R: Autism Diagnostic Interview-Revised; ADOS-2: Autism Diagnostic Observation Schedules-2; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; ADOS-G: Autism Diagnostic Observation Schedule - Generic

Chart 1. Continued...

Author	Methodology					Main results	Limitations
	Type of study	Sample SG	Sample CG	Diagnostic criterion for ASD	CAEP stimulus		
Stroganova et al.[29]	Prospective cross-sectional	10 boys aged 75.3 months on average	19 boys aged 76.8 months on average	DSM-IV-TR and ICD-10	Non-verbal Without using the Oddball paradigm	Change in the CAEP at the level of temporal processing in the SG. There was an asymmetry in the responses of the cortical hemispheres, with those of the RH attenuated compared with those of the LH. The SG showed lower amplitude value for the P1 component when compared with that of the CG.	It does not present the results numerically; small sample size for the SG, with a significant difference in sample size between the groups; evaluated only the P1 component.
Azouz et al.[30]	Prospective cross-sectional	30 (23 boys) aged 5.5 years on average	15 (unspecified gender) aged 5.5 years on average	DSM-IV-TR and ADI-R	Not specified. Unspecified paradigm.	Greater latency and smaller amplitude of the N1 component in both ears in the SG compared with the CG, with components amplitude observed for the left ear.	It does not present the results numerically; significant difference in sample size between groups; evaluated only the N1 component; did not describe the protocol for collecting and analyzing the CAEP.
Donkers et al.[31]	Prospective cross-sectional	28 (22 boys) aged 4 to 12 years	39 (31 boys) aged 4 to 12 years	ADI-R and ADOS-2	Non-verbal. Oddball Paradigm.	The SG presented reduced amplitude of the P3a component. Lower latency values for the P1 and N2 components in the SG. The other components showed no statistically significant difference.	Evaluated only the P1, N2 and P3 components.
Gonzalez-Gadea et al.[32]	Prospective cross-sectional	24 (23 boys) aged 8 to 15 years	19 (15 boys) aged 8 to 15 years	DSM-5	Non-verbal performed in three different presentations: frequent, rare-expected and rare-unexpected.	P3 rare-expected for the SG: activation on the left side was greater. Rare-unexpected P3: decrease in P3 amplitude with greater activation on the right side. When comparing these results with the findings of the frequent stimulus, the only group that did not present better responses was the SG.	It does not present the results numerically; evaluated only the P3 component.

Caption: SG: Study Group; CG: Control Group; CAEP: Cortical Auditory Evoked Potentials; RH: Right Hemisphere; LH: Left Hemisphere; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DISCO: Diagnostic Interview for Social and Communication Disorders; ADOS: Autism Diagnostic Observation Schedule; ADI-R: Autism Diagnostic Interview-Revised; ADOS-2: Autism Diagnostic Observation Schedules-2; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; ADOS-G: Autism Diagnostic Observation Schedule - Generic

Chart 1. Continued...

Author	Methodology					Main results	Limitations
	Type of study	Sample SG	Sample CG	Diagnostic criterion for ASD	CAEP stimulus		
Sokhadze et al. [33]	Prospective Longitudinal	18 (15 boys) aged 11 years on average	16 (12 boys) aged 12 years on average	DSM-IV-TR and ADI-R	Non-verbal. Oddball Paradigm.	Pre-training: increased latency values of the N1, P3a and P3b components in the SG. Post-Training: latency decreased in the SG, but was still increased compared with the CG. The amplitude of P3a decreased in the SG, and difference compared with the CG was no longer observed.	It does not present the results numerically; evaluated only the N1, P3a and P3b components.
Galilee et al.[34]	Prospective cross-sectional	14 (12 boys) aged 4 to 6 years	14 (12 boys) aged 4 to 6 years	ADOS-G	Verbal and non-verbal, with a new paradigm of repetition pairs. Oddball Paradigm.	The SG detected and discriminated verbal and non-verbal stimuli similarly to the CG (N330 and P350); however, the SG used only the LH for this processing, unlike the CG, which used both hemispheres.	It does not present the results numerically; small sample size; evaluated only the N330 and P350 components.
Kamita[35]	Prospective cross-sectional	15 (13 boys) aged 7 to 12 years	15 (13 boys) aged 7 to 12 years	Not specified	Verbal and non-verbal. Oddball Paradigm	No statistically significant difference was found between the groups.	There is no diagnostic criterion for ASD.
Lortie et al.[36]	Prospective cross-sectional	10 (9 boys) aged 6 years on average	12 (8 boys) aged 6 years on average	DSM-IV-TR	Biological sounds and control stimuli with P3 component analysis with involuntary attentional guidance. Oddball Paradigm.	The SG presented higher latency for biological sounds than the CG; however, the SG presented lower latency for the control stimuli compared with the CG.	It does not present the results numerically; small sample size; evaluated only the P3 component; evaluated only the latency.

Caption: SG: Study Group; CG: Control Group; CAEP: Cortical Auditory Evoked Potentials; RH: Right Hemisphere; LH: Left Hemisphere; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DISCO: Diagnostic Interview for Social and Communication Disorders; ADOS: Autism Diagnostic Observation Schedule; ADI-R: Autism Diagnostic Interview-Revised; ADOS-2: Autism Diagnostic Observation Schedules-2; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; ADOS-G: Autism Diagnostic Observation Schedule - Generic

Chart 2. Summary of the CAEP collection protocols

Author, year	CAEP stimulus	Characteristics of the stimulus and electrodes used	Instruction
Whitehouse and Bishop[23]	Verbal and non-verbal. Oddball Paradigm.	For the verbal stimulus, the standard and deviant stimuli were the vowel sounds (standard: /a/; deviant: /i/), and the novel sound was a tone (800 Hz complex tone). For the non-verbal stimulus, the standard and deviant stimuli were complex tones (standard: 500 Hz complex tone; deviant: 800 Hz complex tone) and the novel sound was a vowel (/i/). Each block contained 750 stimuli (standard=600=80%; deviant=75=10%; novel=75=10%). The stimuli were presented binaurally through headphones at 55 dB. Eleven electrode channels were used; however, the responses of the Cz electrode were used for comparison purposes.	In the active condition, children were instructed to click on the computer mouse whenever they heard the rare stimulus. In the passive condition, the children watched a silent video of their choice in an acoustically treated booth.

Chart 1. Continued...

Author, year	CAEP stimulus	Characteristics of the stimulus and electrodes used	Instruction
Matas et al.[24]	Non-verbal (tone burst). Oddball Paradigm.	A total of 300 tone burst stimuli were used at 75 dB nHL at frequencies of 1000 Hz (frequent stimulus – 80-85%) and 1500 Hz (rare stimulus – 15-20%), presented randomly with a 512 ms analysis window, 30.00 Hz high pass and 1.00 Hz low pass filters, and gain of 15000. The reference electrode was Cz.	Each individual was instructed to identify the rare stimuli by mentally counting them or raising their hand whenever they heard them.
Orekhova et al.[25]	Non-verbal sounds presented at different intervals. Oddball Paradigm.	100 pairs of clicks (white noise; 90 dB SPL; 4 ms in duration) were presented binaurally through wireless headphones with the help of Presentation software. The inter-pair intervals (S2-S1) randomly ranged from 7 to 9 s, while the intra-pair interval (S1-S2) was fixed at 500 ms. The stimuli were roughly organized into two equal sessions with a 40s interval.	During the experimental session, the child was watching silent cartoons on a computer. The behavior was recorded on video and the video data were stored synchronized with the electrophysiological records. Video records were analyzed to reveal differences between groups.
Russo et al.[26]	Verbal with and without noise. Without using the Oddball paradigm.	It was performed with the syllable /da/ presented with alternating polarity. The evoked responses were collected in two different conditions: at speech level in silence (80 dB SPL) and with background noise (75 dB SPL), with an interstimulus interval of 631 ms and a 0.5–100 Hz filter (12 dB/octave), using a 60 Hz notch filter, to isolate the frequencies that are more robustly encoded at the cortex level.	The children watched a movie of their choice.
Magliaro et al.[4]	Non-verbal (tone burst). Oddball Paradigm.	The tone-burst stimulus presented monaurally at 75 dB nHL at a presentation rate of 1.1 stimuli per second (total of 300 stimuli) was used for the P300 component. The frequent (80%) and rare (20%) stimuli were presented at 1000 and 1500 Hz, respectively.	The participant was instructed to identify the rare stimuli that appeared randomly in a series of stimuli, and was asked to count the rare stimuli aloud. A brief training was carried out before the exam to ensure understanding of the test procedures. Instructions regarding audiological tests were provided and reinforced to all participants during the procedures.
Gomot et al.[27]	Non-verbal (tone burst). Oddball paradigm, non-attentional.	The auditory stimulus sequences consisted of 1,000 Hz standard tones and 1,100 Hz deviating tones (probability of occurrence: p=0.15) presented randomly at 70 dB SPL intensity and 50 ms duration. The stimuli were presented monaurally through headphones with an inter-stimulus interval of 700 ms. Seven electrode channels were used; however, the responses of the Cz electrode were used for comparison purposes.	Participants watched a silent film on the TV screen during the 25-min recording session.
Andersson et al.[28]	Non-verbal (tone burst). Oddball Paradigm.	Three-stimuli oddball paradigm consisting of 360 stimuli (72% frequent, 14% rare, and 14% rare distracting). The rare stimuli differed from the standard in terms of frequency (1500 Hz). The third type of stimulus, the distracting sound, was a spectrally filtered noise of 95 dB with duration of 100 ms. 14 electrode channels were used; however, the Cz electrode responses were used for comparison purposes.	The individuals were instructed to respond to the rare tones by pressing an answer key.
Stroganova et al.[29]	Non-verbal. Without using the Oddball paradigm.	Pairs of clicks (white noise; 90 dB SPL, 4 msec in duration) were presented monaurally through headphones, with inter-stimulus intervals ranging randomly from 7 to 9 s the inter-pair interval fixed at 1000 ms. A 1 Hz high-pass filter was used. 32 electrode channels were used; however, the Cz electrode responses were used for comparison purposes.	The child remained seated in an armchair watching silent cartoons.
Azouz et al.[30]	Not specified. Unspecified paradigm.	Not specified	Not specified.

Chart 2. Continued...

Author, year	CAEP stimulus	Characteristics of the stimulus and electrodes used	Instruction
Donkers et al.[31]	Non-verbal. Oddball Paradigm	The stimuli included standard tones (200 ms in duration, 1000 Hz, 88%), deviating tones (200 ms in duration, 1100 Hz, 4%), deviating tones in duration (190 ms in duration, 1000 Hz, 4%), and novel sounds (200 ms, unique environmental sounds, such as dog barks, 4%). 12 electrode channels were used; however the responses of the Cz electrode were used, for comparison purposes.	The children sat on their parents' laps in a dimly lit acoustic booth and were instructed to watch a video in low volume (<60 dB) and remain as still as possible.
Gonzalez-Gadea et al.[32]	Non-verbal performed in three different presentations: frequent, rare-expected, and rare-unexpected.	The stimuli consisted of sequences of five complex sounds lasting 50 ms with an inter-stimulus interval of 150 ms. Each complex sound was composed of three sinusoidal tones, type A (500, 1,000 and 2,000 Hz) or type B (350, 700 and 1,400 Hz). Several electrodes were used to capture the response, but in order to compare the results with the findings of other studies, the responses obtained with the Cz electrode were used as a reference.	Participants were asked to count the rare stimulus sequences presented in the same ear as the frequent stimulus sequences. At the end of each block, the individuals were asked to report their final count.
Sokhadze et al.[33]	Non-verbal; Oddball Paradigm.	Two types of stimuli were presented: the frequent stimuli were 1000 Hz sinusoidal tones of 100 ms duration and represented 80% of the stimuli in each sequence; the rare stimuli were 1300 Hz sinusoidal tones lasting 100 ms and represented 20% of the stimuli in each sequence, and were presented randomly between the standard stimuli. Several electrodes were used to capture the response, but in order to compare the results with the findings of other studies, the responses obtained with the Cz electrode were used as a reference.	During the recording sessions, the individual's attention was directed to a computer screen showing instructions for standing still.
Galilee et al.[34]	Verbal and non-verbal, with a new paradigm of repetition pairs. Oddball Paradigm.	Three consonant-vowel syllables were used: /ba/, /da/, and /ga/. For the non-verbal stimuli, five sinusoidal tones were created. Several electrodes were used to capture the response, but in order to compare the results with the findings of other studies, the responses obtained with the Cz electrode were used as a reference.	The children watched a silent video during the examination.
Kamita[35]	Verbal and non-verbal. Oddball Paradigm.	The LLAEP with tone burst stimulus was performed at 75dBnNA monaurally, and the stimuli were presented at a speed of 1.1 stimuli per second, totaling 300 stimuli. The frequent stimulus was presented at 1000 Hz and the rare stimulus at 2000 Hz. The LLAEP with speech stimulus was performed with the syllables /ba/ (frequent) and /da/ (rare), presented monaurally at 75 dBnNA at a presentation speed of 1.1 stimuli per second, totaling 300 stimuli. The Cz electrode was used as a reference.	The patients were asked to raise their hand whenever they heard a rare stimulus.
Lortie et al.[36]	Biological sounds and control stimuli with P3 component analysis with involuntary attentional guidance. Oddball Paradigm.	The stimuli consisted of two biological sounds, representing a finger snap (1981Hz) and a mouth suction (5857Hz), and two corresponding control sounds. Corresponding control stimuli faithfully replicating the properties of natural sounds in duration, peak frequency, envelope, onset latencies, and peaks were also created. In addition to these four sounds, two stimuli with intermediate acoustic properties and a different envelope were created: one was used as the standard stimulus while the other was used as the deviant stimulus, similarly to the original protocol. Several electrodes were used to capture the responses, but in order to compare the results with the findings of other studies, the responses obtained with the Cz electrode were used as a reference.	Participants were instructed to ignore the auditory stimuli while they watched a silent movie.

Table 1. Analysis of the quality of original articles selected according to MINORS

	Whitehouse and Bishop[23]	Matas et al.[24]	Orekhova et al.[25]	Russo et al.[26]	Magliaro et al.[4]	Gomot et al.[27]	Andersson et al.[28]	Stroganova et al.[29]	Azouz et al.[30]	Donkers et al.[31]	Gonzalez-Gadea et al.[32]	Sokhadze et al.[33]	Gaillee et al.[34]	Kamita[35]	Lortie et al.[36]
1. Clearly stated aim	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2
3. Prospective collection of data	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
7. Loss of follow up less than 5%	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9. An adequate control group	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
11. Baseline equivalence of groups	2	2	2	2	2	2	2	1	1	2	2	2	2	2	2
12. Adequate statistical analyses	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	16	16	16	15	16	16	16	15	14	16	16	18	16	16	16

Caption: 0 = Not reported; 1 = Reported but inadequately; 2 = reported adequately

complexity; thus, it takes longer to be coded and processed in the auditory cortex(12).

Although this aspect hindered comparison between the studies, the same stimulus was used to evaluate both groups (with ASD and with TD) in all of them and in none of them was a different response pattern reported for a given type of stimulus (verbal or non-verbal) in individuals with ASD.

The analyzed studies presented the results in different ways: some of them described the results quantitatively, using latency and amplitude values, while others described them qualitatively, analyzing the presence/absence or normal/altered results of the components. The articles were also diversified as to the choice of the components analyzed, with the majority putting greater emphasis on the analysis of the P3 component(4,23,24,27,32).

Among the 11 studies that considered the analysis of the P3 component, five studies registered the CAEP in the passive condition(27,31,33,34,36), and in all of them the participants watched a video during the procedure; another five studies performed the exam in the active condition(4,24,28,32,35), that is, the participants were instructed to pay attention to the auditory stimulus and perform some predetermined tasks, such as counting the rare stimuli(4,24,32), pressing a button(28), or raising their hands when identifying a rare stimulus(35). In addition, a study performed collection of the CAEP in both conditions (active and passive)(23).

Regarding the exogenous components in relation to the characteristics of the latency values, higher latency values were observed among individuals with ASD for the P1(26) and N1(26,30) components. On the other hand, in other studies, the latency values for the P1(31), N1(28), P2(28) and N2(31) components were lower or equal between individuals with ASD and with TD.

Likewise, different results have also observed for amplitude, with some studies observing lower P1-N1 amplitude values for children with ASD(26,30) and others reporting differences for the P1, N1, P2 and N2 amplitude values between the ASD and TD groups(28,31).

Increased latency suggests a decrease in the transmission speed of auditory information in the neural pathways or in synaptic connections in the secondary auditory cortex in children with ASD(30). Regarding amplitude, lower values were observed in children with ASD(26,30), demonstrating hyporeactivity to auditory stimuli(30).

However, it is worth noting that these were occasional results of some studies. Thus, these findings should not yet be generalized, and further studies are needed to confirm them and strengthen these hypotheses.

As for the non-attentional P3 component, obtained in the passive condition, a study observed no difference between latency values, but found decreased amplitude values in individuals with ASD compared with those of individuals with TD(31); a study reported lower latency and increased amplitude values in individuals with ASD(27); two studies observed a delay in the P3 component latency in the population with ASD compared with that in the population with TD(34,36).

Regarding the attentional P3 component, that is, obtained in the active condition, one study found no difference between the latency values, but observed decreased amplitude values in the group with ASD compared with those of the TD group(28); two studies reported a delay in the P3 component latency in the population with ASD compared with that of the population with TD(4,24); two studies observed decreased amplitude in the group with ASD(23,32); one study found absence of response(24).

Greater agreement was observed between the latency and amplitude values for both the attentional and non-attentional P3 components since they were analyzed in a larger number of studies and thus presented greater power of comparison. Although studies have found no difference between the latency values between groups with ASD[28,31], one study observed lower latency values in individuals with ASD compared with those in the group with TD; the authors attributed this finding to the fact that children with ASD tend to pay more attention to new stimuli[27].

In contrast, most studies have observed a delay in the P3 component latency[4,24,34,36] or even lack of response[24]. These results suggested impairment or immaturity of the auditory pathway in cortical regions and deficits in the processing of attention and auditory discrimination or in memory[4]. In addition, these findings may be associated with perception and verbal processing, and the efferent pathway seems to be more impaired in relation to the afferent pathway, as well as to the processes related to attention[23].

Likewise, with regard to the results of the P3 component amplitude, although one study found higher values in the group with ASD[27], most studies have reported a tendency to decreased amplitude[23,28,31,32]. These findings, again, demonstrated changes in the sensory processing of hearing at the cortical level[31], as well as hyporeactivity, and may be related to the stereotype of interests restricted to new stimuli commonly observed in individuals with ASD[32]. Also, some authors believe that the decreased attention can influence this process[23].

Moreover, some studies have correlated the electrophysiological assessment of CAEP with behavioral assessment, and all of them have found a correlation between these measures[25,27,29-31]. In addition, a study evaluated the CAEP before and after auditory training in individuals with ASD, and found evolution in the results of the CAEP after intervention[33]. These results demonstrated that the CAEP can be useful to predict or complement the results of behavioral assessments in the population with ASD, or even to monitor the plasticity of the central auditory pathways and the changes in the auditory processing of the information after therapeutic intervention.

Furthermore, four studies analyzed hemispheric activity for the processing of verbal and non-verbal sounds and presented unanimity in their findings, with predominance of the left hemisphere for the processing of acoustic information in individuals with ASD[25,29,34]. On the other hand, a study reported an opposite result, with predominance of acoustic processing for the responses of the right hemisphere (left ear)[30].

It should be noted that few articles presented the findings of latency and amplitude using numerical values, since most of them described the results qualitatively or in the form of graphs, which, despite facilitating visualization, prevents the presentation of accurate latency and amplitude values.

This profile ended up limiting greater comparisons between the studies and made it impossible to carry out a meta-analysis, as well as to present the magnitude of the observed effects in a more solid way. Thus, the data of the present study were analyzed only qualitatively. This aspect hindered determination of the expected standards with respect to the latency and amplitude values of each component of the CAEP.

A limitation to the present study was the restricted time of publication of the articles; however, the proposal was to present a more current approach regarding the results of the CAEP in the population with ASD.

Therefore, further studies in this area, conducted with larger sample sizes and evaluating the latency and amplitude values of all components, are needed to investigate whether there is a response pattern for the P1, N1, P2, N2 and P3 components present in the CAEP, and thus allow a better understanding of how sound processing occurs in the population with ASD.

CONCLUSION

Results of the selected studies demonstrated that the population with ASD may present different responses to the CAEP components compared with those of their typically developing peers, and that decreased amplitude and increased latency values of the P3 component are the characteristics most commonly found in the studied literature.

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Author contributions

MKK: collection, tabulation and analysis of the data and writing of the manuscript; LAFS: analysis of the data and writing of the manuscript; CGM: study design, general guidance on the study stages, and writing of the manuscript.