Published online: 2019-05-28

Mismatch Negativity in Children with Cochlear Implant

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Int Arch Otorhinolaryngol 2019;23:e292–e298.

Abstract

Introduction The mismatch negativity (MMN) is a negative long-latency auditory potential elicited by any discriminable change in a repetitive aspect of auditory stimulation. This evoked potential can provide cortical information about the sound processing, including in children who use cochlear implants.

Objective To identify MMN characteristics regarding latency, amplitude, and wave area in cochlear implanted children and to identify associations among language development, speech perception and family involvement.

Methods This is a descriptive, observational, cross-sectional study, which compared two groups: study group—children with cochlear implant, and control group—hearing children. The children were submitted to MMN evaluation with non-verbal tone burst stimulus, differing in frequency in sound field at 70 dBHL, with SmartEP equipment (Intelligent Hearing Systems, Miami, FL, USA). Speech perception and language development questionnaires were also applied, and the family participation in the rehabilitation process was classified.

Results The occurrence of MMN was 73.3% for the control group and 53.3% for the study group. Values of latency, amplitude and area of MMN of children using cochlear implants were similar to those of hearing children, and did not differ between groups. The occurrence of MMN was not correlated to the variables of hearing, language and family categories.

Conclusion Children with cochlear implants showed similar MMN responses to those of the children in the control group, with mean latency, amplitude and area of 208.9 ms (±12.8), -2.37 μV (±0.38) and 86.5 μVms (±23.4), respectively. There was no correlation between the presence of MMN and children's performance in the auditory and language development tests or family involvement during rehabilitation.

Keywords

- cochlear implants
- electrophysiology
- hearing loss
- language development

Introduction

The cochlear implant (CI) is an electronic prosthesis that was initially developed for cases of hearing loss (HL) in which conventional prostheses do not bring the expected benefits. It is now widely recommended for both postlingually and prelingually deaf people, in cases of unilateral or bilateral deafness.[1] It is also a treatment option for children who are born with severe or profound HL. The inner part of the implant is inserted surgically by an ear, nose and throat (ENT) surgeon experienced in the area, and the external part, known as speech processor, is programmed by the speech therapist to provide audibility to all speech sounds.[2]

In a review of literature on pediatric implantation, Vincenti et al (2014)[3] pointed that it is known that early implantation (12–18 months) provides children with better outcomes, taking advantage of sensitive periods of auditory development.

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received
February 9, 2019
accepted
April 4, 2019

DOI https://doi.org/10.1055/s-0039-1688967.
ISSN 1809-9777.

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Ideally, the implementation in children should happen at ages in which they still cannot mention auditory comfort and discomfort, or detect sounds at different speech frequencies. Therefore, evaluations measuring the responses to the sounds regardless of the baby's or child's attention are needed. One of the most common procedures in children assessment is the application of auditory evoked potentials (AEPs) testing.

There has been an increasing use of AEPs in clinical practice, as this procedure provides a thorough functional evaluation of the auditory pathway, as well as information on the maturation process of the auditory pathway, reflecting sound processing through latencies and amplitudes.[4] Especially in cases of HL, the electrophysiological assessment can provide information about the auditory pathway of the patient before and after an intervention, and it is effective to complement the behavioral assessment previously performed.

The mismatch negativity (MMN) is a long-latency auditory potential that was first reported by Nããtãnaen in 1978. Nããtãnen and Escera (2000)[5] defined MMN as a negative component of the electric brain response, elicited by any discriminable change (rare stimulus) in a repetitive aspect of auditory stimulation (frequent stimulus).

To elicit MMN, the individual does not need to perform any task, be it behavioral or attentional.[6] That enables its application in young children, as well as in children with other commitments in addition to the HL. This feature of MMN is advantageous in comparison to P300-long-latency AEP, as the latter requires the subject evaluated to pay attention to the acoustic stimuli in elicit P300, unlike MMN, in which attention to auditory stimuli is entirely discouraged.

Mismatch negativity can contribute to the investigation of auditory discrimination with passive auditory stimulation, and may correlate to the auditory responses of behavioral tasks, providing a measure of the short-term auditory memory processes and of the capacity to store and discriminate differences in the auditory sensory input.[7] In addition, authors[8] report that MMN could be used as an objective measure to assess the evolution of the auditory capacities, the progress and the efficiency of auditory training of CI users. The authors' study also supported the applicability of MMN as a tool for the objective assessment of CI functioning, and the gradual monitoring of the evolution of the auditory discrimination after activation.

As a result of the applicability of MMN in children users of CIs, this study aimed to identify the characteristics of MMN in relation to latency, amplitude, and wave area in children aged 2 to 8 years, users of CIs and undergoing language therapy. It also aimed to identify associations with the variables of language development, auditory perception, and family involvement.

Method

The sample was composed of 34 children, split into 2 groups: a study group, composed of 15 children users of CIs, aged 2 to 8 years, 11 male and 4 female; and the control group, composed of 19 normal-hearing children in the same age group, 12 male and 7 female.

It was an observational, descriptive, cross-sectional study, which drew a comparison between groups. The study was approved by the Research Ethics Committee of the institution Universidade Federal de São Paulo under number 2,067,502.

All guardians read and signed the free and informed consent form, and children above 4 years signed the agreement form, giving consent to the participation in the research, under the supervision of a guardian.

The following inclusion criteria were adopted to compose the study sample: diagnosis of severe or profound bilateral sensorineural HL, with prelingual or peri-lingual occurrence and varied etiology, currently undergoing phonoaudiological rehabilitation with aurioral approach, and effective use of a CI for at least 6 months. Patients with previously diagnosed neurological and otorhinolaryngologic comorbidities were excluded from the study. Of the 24 children recruited for the study group (SG), 15 met the inclusion criteria.

Children composing the control sample were recruited in a school and/or by indication of friends of patients. The following inclusion criteria were adopted: age between 2 and 8 years; motor and language development as expected for the age; type A tympanometric curves; hearing thresholds ≤ 15 dB HL for children up to 7 years and ≤ 25 dB HL for children from 7 to 8 years; absence of hearing or language complaints. The individuals excluded were the ones with delays in motor or language development, or indicators of neurological, otorhinolaryngologic or sensory alterations. Of the 24 children recruited for the control group (CG), 19 met the inclusion criteria.

All the children in the study group were subjected to anamnesis, electrophysiological MMN evaluation, application of the meaningful auditory integration scale (MAIS) or infant-toddler meaningful auditory integration scale (IT-MAIS) questionnaires[9,10] according to age group, meaningful use of speech scale (MUSS)[11] questionnaires, and Family Involvement Scale,[12] as well as assessment test for minimum hearing capacity (TACAM)[13] or Glendonald auditory screening procedure (GASP)[14] speech perception tests, according to chronological age.

According to the results obtained in the questionnaires and speech perception tests, the subjects were classified into one of the six hearing categories[15]: Category 0 - does not detect speech; Category 1—detects speech; Category 2—differentiates words according to suprasegmental features; Category 3—begins identification in closed-set words (identical words in length, but with multiple spectral differences); Category 4—identifies words by recognizing the vowel in a closed context; Category 5—identifies words by recognizing the consonant in closed set; and, Category 6—recognizes open-set words.

The children were classified into one of the language categories[16] according to the answers to the MUSS questionnaire, the perception of the evaluator and the reporting of the parents. Category 1—the child does not speak and may present undifferentiated vocalizations; Category 2—the child only speaks 13 isolated words; Category 3—the child builds sentences with 2 or 3 elements; Category 4—the child builds sentences with 4 or 5 words, and has begun using linking words; Category 5—the child builds sentences with more than 5 words, conjugates verbs, uses linking words, and is fluent in oral language.

The scale used[12] to classify family involvement in the therapeutic process labels families with limited and below-average involvement as "1," and ideal families in terms of involvement as "5."

The MMN was recorded using a two-channel SmartEP equipment (Intelligent Hearing Systems, Miami, FL, USA) after cleaning the patient's skin with gauze and Nuprep (Weaver and Company, Aurora, CO, USA) abrasive paste. The electrodes were fixed using MaxxiFix (Carbogel Industry, São Paulo, SP, Brazil) electrolytic paste and micropore tape, in the areas established beforehand.

The recommendations of the system were followed for the placement of electrodes 10 to 20. Thus, for the SG, the active electrode was placed in Fz, the reference electrode was placed in the earlobe contralateral to the ear with the implant. For the CG, the left lobe was chosen due to the prevalence of the right hemisphere in this type of stimulus. The negative electrode was placed in the lobe contralateral to the reference electrode, and the ground electrode was positioned on the forehead. The impedance remained lower than or equals to 3 kohms. During the evaluation, the children continued using the usual CI program, and those using contralateral hearing aid ($n = 4$), that is, 27% of the sample, were asked to remove the device during the electrophysiological evaluation.

The electrophysiological evaluation was held in an acoustically-treated room, where the individual would sit comfortably in a soft chair. During the register, we had children watch a movie that had been previously selected based on their interests, with presentation level up to 40 dB HL. Younger children (2 to 3 years) were placed on the lap of the people in charge of the assessment, so that they would not call their parents or get distracted because they were sitting alone.

The acoustic stimulation was performed in the sound field, with speakers at 90° azimuth and 40 cm from the implanted ear. Mismatch negativity was examined using a tone burst nonverbal stimulus that was different in frequency (frequent stimulus: 1,000 Hz; rare stimulus: 1,500 Hz). The stimulation was performed at a rate of 1.1 stimuli per second, and the duration of both stimuli was 100,000 µs (100 ms) with inter-stimulus interval (ISI) of 1s. A total of 750 stimuli were presented at 70 dB HL in the oddball paradigm, and the rare stimulus probability was 20%. After capturing the oddball paradigm, 150 rare stimuli were elicited (1,500 Hz) with the same parameters used in the oddball paradigm. This was considered the control situation for MMN subtraction.

The AEPs were captured and viewed on the computer to which the equipment was coupled. The tracing was filtered using a high-pass filter 1.0 Hz and a low-pass filter of 30.0 Hz. The recording window ranged from -50 to 500 ms. The protocol used for the CG was not different from the one used for the SG, except for the position of the reference electrode previously described.

The MMN wave was displayed after the subtraction of the rare stimulus wave minus the wave of the control situation.

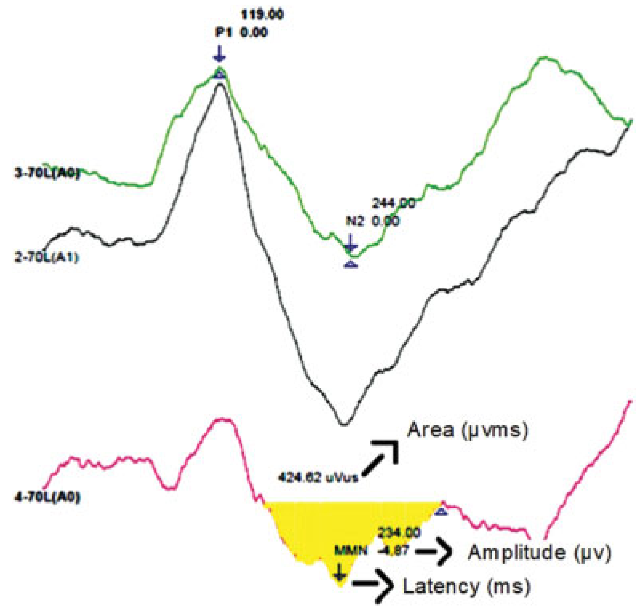

Fig. 1 Control group recording.

The presence or absence of MMN was evaluated. In case of presence, the variables studied were amplitude, latency and wave area. Latency was determined by the most negative peak viewed in the latency period of 100 to 300 ms. In case an extra negativity emerged around the P1 area, it was ignored.[17] The amplitude was measured by calculating the mean voltage from the MMN peak to the baseline, and the area was automatically calculated by the software meanwhile amplitude was measured.

In regards to the tracing analysis, two speech pathologists experienced in electrophysiology were invited to separately analyze and mark the tracings. A third speech pathologist would state her position when there was disagreement between these analyses and that of the lead researcher.

►**Fig. 1** shows an example of the tracing of a 2-year-old child of the CG, with the corresponding analyses.

The data was tabulated in Excel 2010 (Microsoft Corp., Redmond, WA, USA) spreadsheets, and the statistical analysis was performed using the version 1.7 Minitab software (Minitab, LLC., State College, PA, EUA).

The Chi-square test of independence[18] was applied to check if there was an association in the occurrence of MMN between groups, and in the presence/absence of MMN and hearing, language and family categories.

For all quantitative variables, the hypothesis of homoscedasticity between the groups was verified (p-values > 0.05). The two-independent-samples t-student test[18] was applied to compare both groups in terms of the variable latency, in cases where the normality assumption was verified. The non-parametric Mann-Whitney test[19] was used to compare the groups in relation to the variables area and amplitude.

Results

►**Table 1** shows the occurrence of the MMN in the groups studied.

Table 1 Occurrence of mismatch negativity according to group

	MMN		
Group	Absent	Present	TOTAL
CG	5 (26.3%)	14 (73.7%)	19 (100%)
SG	7 (46.7%)	8 (53.3%)	15 (100%)
p-value = 0.218	12 (35%)	22 (65%)	34 (100%)

Abbreviations: CG, control group; MMN, mismatch negativity; SG, study group.
Chi-square test of independence.

There was no evidence of difference in the occurrence of MMN between groups.

►**Table 2** presents the mean values of latency, area and amplitude of the tests with the presence of MMN ($n = 22$).

There was no statistical difference between the SG and the CG in the values of latency, amplitude and area.

►**Tables 3**, **4** and **5** show the associations between the occurrence of MMN and the hearing, language and family categories.

There was no evidence of association between the presence of MMN and the categories of hearing, language and family.

►**Table 6** summarizes the SG evaluation data.

Discussion

The MMN is an event-related potential, which can be elicited in children users of CI, although there may be differences in cortical distribution compared with normal-hearing children.[7] This potential can provide a measure of short-term memory, including the ability to save and discriminate differences in hearing, and it is useful in the evaluation of children users of CI.[7] This potential's applicability in the evaluation of children is useful and interesting, for it does not require full attention to an activity for the potential to be recorded, but only that the child stays seated in silence and watches a video. To make this task easier, the author[7] suggests that the subjects be encouraged to read or watch a previously recorded movie.

During the data collection of the study, we had all the children remain seated and watch a video that had been previously chosen. It was observed that a familiar video was not as effective as a new video of a favorite character to ensure that the child remained calm and quiet, allowing the tests to be run.

It was difficult to carry out the research with children over 4 years with good auditory development, as they would still pay attention to the auditory stimulus even after the guidelines were given several times. These children were attentive to the stimuli, performing activities such as rocking their foot in the corresponding rhythm, moving their mouths, and even

Table 3 Association between the occurrence of the mismatch negativity and the hearing category in the study group

	MMN		
Hearing Category	Absent	Present	TOTAL
0 or 1	5 (62.5%)	3 (37.5)	8 (100%)
2–6	2 (28.6%)	5 (71.4)	7 (100%)
p-value = 0.189			

Abbreviation: MMN, mismatch negativity.
Chi-square test of independence.

Table 4 Association between the occurrence of mismatch negativity and the language category in the study group

	MMN		
Language category	Absent	Present	TOTAL
1 or 2	4 (57.1%)	3 (42.9%)	7 (100%)
3–5	3 (37.5%)	5 (62.5%)	8 (100%)
p-value = 0.447			

Abbreviation: MMS, mismatch negativity.
Chi-square test of independence.

Table 5 Association between the occurrence of mismatch negativity and the family category in the study group

	MMN		
Family Category	Absent	Present	TOTAL
1–3	3 (42.9%)	4 (57.1%)	7 (100%)
4 or 5	4 (50.0%)	4 (50.0%)	8 (100%)
p-value = 0.782			

Abbreviation: MMN, mismatch negativity.
Chi-square test of independence.

Table 2 Descriptive measures of latency (ms), area (μVms) and amplitude (μV) per group

Variable	Group	Mean	Standard error	Minimum	Median	Maximum	*p*-value
Latency	CG ($n = 14$)	212.9	10.4	156.0	210.0	283.0	0.815
	SG ($n = 8$)	208.9	12.8	160.0	208.0	273.0	
Area	CG ($n = 14$)	158.4	32.4	10.2	113.2	424.6	0.140
	SG ($n = 8$)	86.5	23.4	20.0	59.1	189.6	
Amplitude	GC ($n = 14$)	-2.94	0.40	-0.52	-2.61	-5.64	0.357
	SG ($n = 8$)	-2.37	0.38	-1.25	-2.07	-4.23	

Abbreviations: CG, control group; SG, study group.
Student *t*-test.

Table 6 Questionnaires' results, categories and time of cochlear implant use

	Age	Time of CI use (years)	Age at CI surgery (years)	MAIS/ IT-MAIS (%)	MUSS (%)	Hearing Category (1 to 6)	Family Category (1 to 5)	Language category (1 to 5)	PTA (dB)	MMN (presence x absence)
1	2.6	1.1	1.4	75	50	1	5	2	48	absent
2	2.3	0.7	1.7	50	22.5	1	3	1	45	present
3	3	1.9	1.3	52.5	32.5	4	4	2	25	present
4	3.2	1.8	1.5	85	52.5	1	2	3	27	present
5	3.3	2.2	1	90	90	6	4	3	35	present
6	2.8	0.5	2.2	62.5	32.5	1	2	1	25	absent
7	3.9	2	1.8	90	50	2	2	3	25	present
8	3.4	0.9	2.5	72.5	47.5	1	4	2	35	absent
9	4.6	1.2	3.3	65	57.5	1	2	1	40	absent
10	4.8	1.4	3.3	87.5	47.5	1	3	3	55	absent
11	5.1	1.5	3.7	67.5	50	1	3	1	20	present
12	5.2	2.8	2.6	95	97.5	6	5	5	30	absent
13	5.6	2	3.5	97.5	85	4	4	3	37	present
14	7.8	2	5.7	92.5	95	6	4	3	30	present
15	8.3	4.5	4.1	97.5	97.5	6	5	5	30	absent
MEAN	4.4	1.8	2.6	79%	60.5%	2.8	3.5	2.5	34	–

Abbreviations: CI, cochlear implant; IT-MAIS, infant-toddler meaningful auditory integration scale; MAIS, meaningful auditory integration scale; MMN, mismatch negativity; MUSS, meaningful use of speech scale; PTA, pure tone audiometry.

verbally repeating sounds very similarly to the sounds listened. This enabled the emergence of the evoked potential P3a, a passive component of P300[20] in some tests, which directly influenced the appearance of the MMN. The literature points that to elicit the MMN, the individual cannot be paying attention to the acoustic stimuli, regardless of age, since there may be an influence of other evoked potentials while recording MMN.[6,7]

In this study, the occurrence of MMN was 75% in the CG, and 53% in the SG (►**Table 1**). That is different from the findings in the literature,[21] which refer that all normal-hearing children and 75% of the implanted children presented MMN for the deviant stimulus of 1,500 Hz. Another evaluation of 50 normal-hearing subjects aged 18 to 25 years found an occurrence of 66% of MMN,[17] which is a similar value to the one found in this study (75%). Such differences in results can be attributed to the differences in protocol, etiology, subject age, equipment used, and mean averaging across the studies. Additionally, a researcher[22] also points that the difficulty faced in the area of electrophysiology is precisely integrating findings of different studies, as a variety of methods is used, making it difficult to define reliable and replicable findings.

In the current study, the mean values of latency, amplitude and area were, respectively, 208.9 ms (±12.8), -2.37 µV (±0.38) and 86.5 µVms (±23.4) for the SG, and 212. 9 ms (±10.4), -2.94 µV (±0.40) and 158.4 µVms (±32.4) for the CG. No statistical difference was found between the groups (►**Table 2**).

The values of this study were similar to those found in the literature evaluating the MMN in adult users of CI by tone burst (TB) stimulus.[21,23,24]

The latency values in this study ranged from 160 to 273 ms, with mean value of 208.9 ms (±12.8), in the SG, and 156 to 283 ms, with mean value of 212.9 ms (±10.4), in the CG; no difference was found between the groups. However, Roman et al (2005)[23] found that MMN latency for the contrast of TB stimulus of 1,000/1,500 Hz 55 ms occurred later in CI users compared with normal-hearing individuals, unlike the findings of this study. Even though the stimuli used were the same in both studies, Roman et al (2005)[23] described longer duration of the stimulus, and a higher number of averaging, which may have contributed to such differences. In addition to that, factors such as time of auditory deprivation (2–9 years) and age of the CI users (40–68 years) may have influenced the results. On the other hand, no differences were found between the group of normal-hearing subjects and the group of CI users in regards to amplitude and area, which corroborates the present study.

Authors[24] evaluated the MMN in CI users, and found that latency and amplitude values were close to those of this study, despite the differences in age and equipment. Indeed, the stimuli used, the averaging, and the rare/frequent stimulation were very similar to those of the current study. When present, the MMN latency for the SG of Obuchi et al (2012)[24] was higher than for the CG, even though there was no statistical difference. Regarding amplitude values, the authors found individual differences in both groups, but did not observe consistency in these data, probably because it was a small sample ($n = 3$). The amplitude seemed smaller for the rare stimulation of 1,500 Hz in the 3 subjects studied, ranging from around -1 to -3µV. These values were similar to the ones found in the present study.

Despite having used speech stimuli, researchers[1] evaluated groups of children/adolescents who were CI users and had different speech perception results. Their brain activity was found to range from 155 to 250 ms, similarly to the values obtained in the current study (208.9 ± 12.8). The authors found no difference in the MMN topography comparing both groups, showing greater evidence of the frontal cortex in the MMN response in the group with good results of language and auditory perception. The literature[25] had already proposed that the frontal lobe contributed to capture MMN. Unfortunately, in this study it was not possible to perform the MMN topography because of the equipment used, but the use of this tool is extremely important to evaluate and learn more about the recording mechanism and the MMN response.

In a prospective study[26] of children until 3 years of age using speech stimuli, no statistical difference was found between the latencies of the SG and the CG, similar to this study. The authors concluded that the effective use of the CI provides implanted individuals with access to speech sounds and an auditory pathway development that is similar to that of normal listeners.

Considering this study's SG, the amplitude values ranged from -1.25 µV to -4.23 µV, with mean value of -2.37 µV (±0.38). As for the CG, they ranged from -0.52 µV to -5.64 µV, with mean value of -2.94 µV (±0.40) (►**Table 2**). These results corroborate those found by Singh et al (2004),[27] who found a mean amplitude value of approximately -5 µV in children and adolescent users of CI. As the authors used speech stimulus, the amplitude was higher when compared with the current study. The authors[27] justification for the increase in amplitude in the presence of speech stimuli was that there was a greater neural population responding to that stimulus in comparison to TB. The same authors found MMN latency around 300 ms using speech stimulus. This was expected, for speech stimuli requires longer processing in the auditory system due to its complexity, compared with TB.

In the evaluation of adults and senior adults by MMN, Singh et al.[28] found mean amplitude of -1.13µV for TB stimulus of 1,000 and 2,000 Hz, which demonstrates the applicability of the MMN in different age groups.

The values of MMN area ranged from 20 to 189.6 µVms in this study, with mean value of 86.5 µVms (±23.4), for the SG, and 10.2 to 424.6 µVms, with mean value of 158.4 µVms (±32.4), for the CG (►**Table 2**). In the equipment used, the area is measured automatically by the software when the evaluator measures the amplitude until the baseline. At such moment, the software calculates it, considering the MMN latency and amplitude for that individual, and then finds the area. Only two studies analyzing the area of MMN were found in the literature. Both showed discrepancies in value and did not describe the area calculation, what hinders the comparison. Vavatzanidis et al.[29] found lower mean values (1.46 µVms ± 0.77), while Kelly et al (2005)[21] obtained higher mean values (134.9 µVms ± 60). Such differences may explain why most studies did not include the analysis of the area, even though the literature[22] suggests the inclusion of the area calculation in MMN studies.

Moret e Costa[17] evaluating normal-hearing adults with the same equipment as the one used in the current study found area values of 214.73 µVms (±113.58), that is, higher than this study's results with children.

There was no association between the presence of MMN and the categories hearing, language and family (►**Tables 3**, **4** and **5**). Authors studying study the MMN by speech stimulation[27] identified the presence of the potential in only 28% of the teenagers studied. The absence of MMN was associated with poor performance on the behavioral test, being found in only one individual whose performance was considered "good." Liang et al (2014)[30] evaluated the correlation of the auditory categories and the MMN incidence at 3 and 6 months of CI use. However, it was not possible to verify any statistical correlation. No studies associating MMN to language and family were found in the literature.

In spite of the differences in protocols and procedures, the studies analyzed support the applicability of MMN research both in normal-hearing individuals and in CI users as a tool for evaluating their rehabilitation process.

One of the limitations of this study is the size of the sample for the wide age range, hindering the analysis of the results according to age. Also, the exams were not retested at a different moment to verify tracing steadiness.

In terms of future perspectives, the MMN is considered an interesting tool for objective evaluation of the benefits of CI and, possibly, hearing aid users of different age groups. In addition to that, children with other comorbidities, who collaborate for the difficulty in using conventional audiological evaluation, can also take advantage from evaluations using this procedure.

Conclusion

The MMN responses in children with CIs undergoing speech therapy were similar to those of listeners of the same age, with mean latency, amplitude and area of 208.9 ms (±12.8), -2.37 µV (±0.38) and 86.5 µVms (±23.4), respectively.

No correlation was found between the presence and the absence of the MMN considering the categories hearing, language and family.

Note

Research realized at Speech Language Pathology and Audiology Department at UNIFESP, São Paulo, SP, Brazil.

Sources of Research Assistance

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, in the Portuguese acronym).

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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