

Mismatch Negativity in Children: Reference Values

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Int Arch Otorhinolaryngol 2019;23:142–146.

Abstract

Introduction The Mismatch Negativity (MMN) auditory evoked potential evaluation is a promising procedure to assess objectively the ability of auditory discrimination.

Objective To characterize the latency and amplitude values of MMN in children with normal auditory thresholds and without auditory complaints.

Methods Children between 5 and 11 years old participated in the present study. All participants underwent acoustic immittance measurements and tonal and vocal audiometry. The MMN was recorded with the MASBE ATC Plus system (Contronic, Pelotas, RS, Brazil). The electrodes were fixed in Fz (active electrode), Fpz (ground electrode) and in M2 and M1 (references electrodes). The intensity used was 80 dBHL, the frequent stimulus was 1,000 Hz and the rare stimulus was 2,000 Hz. The stimuli were presented in both ears separately.

Results For the female group, the mean latencies and amplitude of MMN were 177.3 ms and 5.01 μ V in the right ear (RE) and 182.4 ms and 5.39 μ V in the left ear (LE). In the male group, the mean latencies were 194.4 ms in the RE and 183.6 ms in the LE, with an amplitude of 5.11 μ V in the RE and 5.83 μ V in the LE. There was no statistically significant difference between ears ($p = 0.867$ - latency and $p = 0.178$ - amplitude), age ($p > 0.20$) and the gender of the participants ($p > 0.05$).

Conclusion Using the described protocol, the mean latency value of MMN was 184.0 ms for RE and 182.9 ms for LE, and the amplitude was 5.05 μ V and 5.56 μ V for the left and right ears, respective.

Keywords

- ▶ auditory evoked potential
- ▶ electrophysiology
- ▶ children

Introduction

In audiological practice, long-latency auditory evoked potentials (AEPs) can be used as an objective measurement of cognitive processes.^{1,2} The great advantage of AEPs when compared with other neurocognitive methods, is the possibility of recording the neuronal activation associated with brain processing, making it possible to assess the brain areas activated during cognitive processing tasks.³

The mismatch negativity (MMN) AEP allows the understanding of the central processes of auditory perception, of different forms of memory and attention.⁴ The origin process of AEPs is preattentive,³ and its main generator is the

auditory cortex, with contributions from the frontal cortex, the thalamus and the hippocampus.⁵

Mismatch negativity is elicited by the presentation of low probability (rare) auditory stimuli that constitute a physical change from repetitive standard stimulation (frequent stimuli). This is generated automatically, regardless of the attention of the subject,^{3,6–11} whenever an afferent stimulus does not coincide with the sensorial representation of the repetitive stimulation presented.^{3,12} The MMN reflects the ability of the brain to discriminate sounds,¹³ auditory memory and involuntary attention.¹¹ The MMN assessment has the benefit of having a good correlation with other assessments of auditory discrimination.^{8,13}

received
August 7, 2017
accepted
June 2, 2018
published online
October 24, 2018

DOI <https://doi.org/10.1055/s-0038-1667313>.
ISSN 1809-9777.

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The MMN can be generated in infants,¹⁴ in children with typical development, with language and auditory processing disorders,¹⁵⁻¹⁷ with reading and writing disorders and dyslexia,¹⁷⁻²⁴ with stuttering,²⁵ with aphasia,²⁶ among others. Nevertheless, despite the possibility of clinical application in the children population, it is still necessary to standardize the values of latencies and amplitudes of the MMN due to the variability in its measurements and the protocols used.¹⁰

It is believed, therefore, that normative procedures should be treated and are of great value for wider application in specific groups of children in the health field, increasing the knowledge in their accomplishment and in the interpretation of the results. Thus, in view of the possibility of applicability in the audiological practice for differential diagnosis and to contribute with the scientific literature on the findings of the MMN in children with normal hearing, the purpose of the present study was to characterize the values of the latencies and amplitudes of MMN in children with normal auditory thresholds and without otological complaints and to relate the values to the ears, gender and age of the participants.

Methods

Thirty-six Brazilian school children (22 females and 14 males) in the age group between 5 and 11 years were recruited for convenience. All the participants presented normal auditory thresholds (< 15 dBHL) according to the classification proposed by Northern et al²⁷ with an air-to-bone gap > 10 dBHL. In addition, they had acoustic reflexes and type A tympanometric curves, according to the classification proposed by Jerger²⁸. Information about schooling, learning difficulties, language, speech and hearing, as well as otological history, family history of hearing problems and/or language and manual preferences of the participants were collected. Subjects with cognitive dysfunctions, self-reported learning difficulties, and genetic or craniofacial abnormalities were excluded.

The ethical and methodological issues of the present research were approved by the Research Ethics Committee of the Research Ethics Committee of the UFRGS Institute of Psychology (process number 55977316.8.0000.5334). All the procedures of the present study were performed at the Nucleus of Studies in Electrophysiology of the Audit of the Audiology Clinic of UFRGS, after the person responsible for the child signed the informed consent form. Previous instructions were given to each child regarding each procedure that would be performed.

Initially, the external acoustic meatus was inspected with the otoscope, (Welch Allyn Inc., Skaneateles Falls, NY, USA) and, if no cerumen was present, the participant was sent to perform the exams. Acoustic immittance measurements (AIM) were searched with Impedance Audiometer AT235h (Interacoustics, Middelfart, Denmark). Static and dynamic complacencies were verified, and the curve was plotted and classified according to the Jerger classification.²⁸ In the investigation of the ipsilateral and contralateral acoustic reflexes, the thresholds in the frequencies of 500, 1,000,

2,000 and 4,000 Hz in both ears were investigated. The pure tone audiometry (ATL) was performed in an acoustically treated booth with the previously calibrated *HerplInventis* audiometer (Inventis, Padova, Italy). The thresholds were performed by air conduction at the frequencies of 250, 500, 1,000, 2,000, 3,000, 4,000, 6,000 and 8,000 Hz, and by bone conduction at the frequencies of 500, 1,000, 2,000, 3,000 and 4,000 Hz in both ears.

After that, a speech audiometry was performed, with the percentage of speech recognition index (SRI) and speech recognition threshold (SRT). For the SRI, 25 monosyllabic words were presented at an intensity of 40 dBHL above the tritonal average in the air conduct of 500, 1,000 and 2,000 Hz in each ear. The children were asked to repeat the words. For the SRT, the initial intensity used was also 40 dBHL above the tritonal average, which was reduced until reaching the level of intensity in which the child could understand and repeat correctly 50% of the presented trisyllabic words.

After the peripheral auditory assessment, the children were referred to an acoustic and electrically treated room to perform the MMN assessment. The examiner cleaned the skin with a Nuprep - skin prep gel - exfoliant (Weaver and Company, Aurora, CO, USA) and with gauze. Subsequently, silver electrodes were placed with Ten20 conductive electrolytic paste (Weaver and Company, Aurora, CO, USA) and Micropore surgical tape (3M, St. Paul, MN, USA). The ground electrode was placed on the front (Fpz) and the active electrode at Fpz, close to the scalp. The reference electrode was positioned on the right (M2) and on the left (M1) mastoids. The earphones EarTone 3A/5A (Contronic, Pelotas, RS, Brazil) were placed on both ears. For the test, the MASBE ATC Plus system (Contronic, Pelotas, RS, Brazil) was used. The electrical impedance was maintained below 5Ω in each lead and the difference between the 3 electrodes did not exceed 2Ω .

After the impedance check, an electroencephalogram (EEG) scan was performed to verify the spontaneous brain electrical activity and to verify artifacts that might interfere in the MMN. The children were instructed to not hold their limbs and to not cross their legs and arms during the procedure.

For the MMN recording, standard stimuli were presented with short interstimulus interval and were being intercalated by stimuli that differ in frequency (rare/deviant stimulus).

In relation to the parameters used to register the MMN, the auditory stimuli were presented in monaural mode, first in the left ear (LE) and then in the right ear (RE), with a frequency of 1,000 Hz (50 cycles) for the standard stimulus and 2,000 Hz (50 cycles) for the deviant stimulus, at an intensity of 80 dBHL for standard and deviant stimuli. The equipment allowed 2,000 premeditations and the oddball paradigm used was 90/10, with alternate polarity. In the acquisition, the full scale was $200\mu\text{V}$, with a high pass filter of 1 Hz, low pass filter of 20 Hz, Notch of 60 Hz - YES, 90% noise limit, time window of 500 ms, and amplitude of the trace up to $7.5\mu\text{V}$. It should be noted that, to guarantee a greater reliability in the analyzes, all electrophysiological records were analyzed by two different evaluators at different times and two collections were performed in each ear to allow the reproducibility of traces.

The results were organized as descriptive statistics, in which the quantitative variables were described by average, standard deviation (SD) and amplitude of variation. The qualitative variables were described by absolute and relative frequencies. To compare the ears in relation to the latency and amplitude results, the t-student test for paired samples was applied. In the comparison of averages between genders, the t-student test for independent samples was applied. The association of latency and amplitude results with age was assessed by the Pearson correlation coefficient.

The significance level adopted was 5% ($p < 0.05$) and the analyzes were performed in the SPSS software version 21.0 (IBM Corp., Armonk, NY, USA).

Results

The study consisted of 41 children. Five of them, who did not complete all the proposed procedures, were excluded. Thus, the results refer to a sample of 36 participants. Characterization data of the sample are described in **Table 1**.

All the children presented MMN, and no participant had to be excluded. There was no statistically significant difference in the comparison between the average of the latencies and amplitudes between the RE and the LE, indicating that the RE and the LE presented equivalent values of latency and amplitude. **Table 2** shows the values of the latencies and amplitudes of MMN in both ears.

No statistically significant differences were found in the comparison of the values of latencies and amplitudes of the MMN between genders (**Table 3**). In this way, in the present research, there is no evidence that the latency and amplitude values of children are influenced by their gender.

Table 1 Sample characterization

Variables	<i>n</i> = 36
Age (years) – average \pm SD [min – max]	8.00 \pm 2.11 [5–11]
Gender – <i>n</i> (%)	
Male	14 (38.9)
Female	22 (61.1)

Abbreviations: max, maximum; min, minimum; SD, standard deviation.

Table 2 Comparison between ears

Variables	Right ear	Left ear	<i>p</i> *
	Average \pm SD [min–max]	Average \pm SD [min–max]	
Latency (ms)	184.0 \pm 43.4 [116.5–317.04]	182.9 \pm 37.9 [113.95–269,45]	0.867
Amplitude (μ V)	5.05 \pm 1.76 [1.32–8.73]	5.56 \pm 2.42 [1.05–11.83]	0.178

Abbreviations: μ V, amplitude; max, maximum; min, minimum; ms, milliseconds; SD, standard deviation.

*t-student test for paired data.

Table 3 Comparison between genders

Variables	Male (<i>n</i> = 14)	Female (<i>n</i> = 22)	<i>p</i> *
	Average \pm SD	Average \pm SD	
Latency (ms)			
Right ear	194.4 \pm 53.6	177.3 \pm 35.3	0.257
Left ear	183.6 \pm 37.5	182.4 \pm 39.0	0.928
Amplitude (μ V)			
Right ear	5.11 \pm 2.01	5.01 \pm 1.62	0.868
Left ear	5.83 \pm 2.04	5.39 \pm 2.67	0.603

Abbreviations: μ V, amplitude; ms, milliseconds; SD, standard deviation. *t-student test for paired data.

Discussion

To estimate the standardized effect size of 0.9, a sample size of 36 individuals was calculated. A significance of 0.05 was accepted with 90% confidence interval (CI). The data analysis was performed with the EpiInfo (Centers for Disease Control and Prevention, Atlanta, GA, USA) and the STATCAL (Prana Ungiana Gio, Indonesia) software. It is pointed out in the literature that the responses of MMN present a high level of unsystematic variation. Therefore, it is recommended that a large number of subjects should be measured to allow significant differences between the control group and the study group.²⁹ It is observed that most of the studies with control group present a reduced number of children in their samples.^{15,16,19,20,23–26,30–33} It should be emphasized that the casuistry of the present research is larger than others found in the scientific literature, but researches with different age groups and larger groups are necessary.

The parameter used to elicit the MMN potential was the oddball paradigm with tone burst with difference between frequencies. The frequent stimulus was set at 1,000 Hz and the rare stimulus was set at 2,000 Hz. It is recommended that large differences between stimuli be avoided so that a P3 component does not overlap the response, thereby compromising the recording of the MMN.³ Although the difference in the present study is greater than 10%, all children present the MMN potential, as well as in a normative study conducted in an adult population with the same parameters.¹²

It is pointed out that, if applied to the same child in a retest situation, the tone burst stimulus is more reliable when compared with the speech stimulus when applied to the same child in a retest situation.²⁹ Likewise, the choice of stimulus and task conditions influences the replicability of the MMN,³⁴ as well as the characteristics of their appearance.¹¹ It can be seen, however, that the tone burst stimulus is highly used in national and international studies with children.^{16,18,19,25,26,30,35–41}

The mean values of the MMN latencies in children with normal hearing were 184 ms in the RE and 182.9 ms in the LE) The mean amplitude verified was 5.05 μ V in the RE and 5.56 μ V in the LE.

The latency of the AEP shows the time course of the electrophysiological activity¹⁰ and its values for the children

population are higher than those found in adults,¹² since the maturation process of the auditory pathway interferes with the values of latency and amplitude in different age groups.⁴² Regarding the values found the present this study, similar results were found in children without specific alterations, described in the national and international literature, where the MMN appears between 150 and 300 ms,^{16,17,21,26,30,31,35–37,42–44} regardless of the stimulus used and the position of the electrodes. The MMN can be obtained in children in latencies ≤ 350 ms.^{33,45} In addition, studies with children and adults did not identify differences in latencies and amplitudes between the ears tested.^{12,19,30,46}

The MMN amplitude demonstrates the extent of neural allocation involved in the cognitive processes.¹⁰ Regarding the amplitude, the literature recommends values of approximately of 0.5 to 5 μV .⁴⁷ Studies show amplitudes, in general, smaller than 5 μV .^{7,13,22,26,30–32,36,37} However, it is reported that as the degree of discrepancy between the frequent and rare stimulus increases, the amplitude of the MMN may also increase.⁴⁸ It is believed that this may be the reason why the amplitude values of the present study presented values close to the maximum amplitude described, as well as other studies reported in the literature.^{16,21,49}

Although the age group of the present sample presented variability, children aged between 5 and 11 years old, and the literature report that the values depend on the age and the maturation process of the auditory pathway,^{13,29,42} there was no association of the latency and amplitude results with the age of the subjects ($p > 0.20$). This finding is in agreement with studies in the international literature^{13,29} that investigated the MMN in neonates and children and, likewise, did not find differences regarding the age of the participants and the amplitude of this potential. However, in latency values, a significant difference was observed in the literature when comparing full-term with preterm neonates, but this discrepancy was not found when comparing full-term infants with 3-month-old infants.¹³

Similar results were found in relation to the gender of the participants. Although other studies with adults and elderly subjects demonstrate higher values of latency and amplitude in males than in females,^{6,12,50} in the present study no statistically significant differences were found between genders. These results corroborate with studies performed in neonates using long-latency potentials⁵¹ and in young adults with MMN,⁵² which similarly did not show differences between genders in the procedures performed.

Few studies describing normative values for MMN in children were found. Thus, it is believed that the present research can promote subsidies in the interpretation of MMN results, and that it can be used as reference for this potential when the same parameters are used. In addition, the present study may place researchers on future analyzes with MMN in the children population considering the variability of the range of normality, as well as bring new knowledge about the forms of application of the exam. It should be noted, however, that further scientific research with different parameters for the use of this potential in different age groups is still necessary.

Conclusion

The MMN appeared in all children who participated in the present study. No statistical differences were found for the latencies and amplitudes of the MMN in relation to the gender and age of the participants. Likewise, a similarity was verified between the ears of the the participants. Using the described protocol, the mean latency value of MMN was 184.0 ms for the RE and 182.9 ms for the LE, with minimum and maximum values of 113.95 ms and 317.04 ms, respectively. Regarding the amplitude, values of 5.05 μV and 5.56 μV were obtained for the REs and LEs, respectively.

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