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Auditory Evoked Potential Mismatch Negativity in Normal-Hearing Adults

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Abstract

Introduction   Mismatch Negativity (MMN) corresponds to a response of the central auditory nervous system.

Objective   The objective of this study is to analyze MMN latencies and amplitudes in normal-hearing adults and compare the results between ears, gender and hand dominance.

Methods   This is a cross-sectional study. Forty subjects participated, 20 women and 20 men, aged 18 to 29 years and having normal auditory thresholds. A frequency of 1000Hz (standard stimuli) and 2000Hz (deviant stimuli) was used to evoked the MMN.

Results   Mean latencies in the right ear were 169.4ms and 175.3ms in the left ear, with mean amplitudes of 4.6μV in the right ear and 4.2μV in the left ear. There was no statistically significant difference between ears. The comparison of latencies between genders showed a statistically significant difference for the right ear, being higher in the men than in women. There was no significant statistical difference between ears for both right-handed and left-handed group. However, the results indicated that the latency of the right ear was significantly higher for the left handers than the right handers. We also found a significant result for the latency of the left ear, which was higher for the right handers.

Conclusion   It was possible to obtain references of values for the MMN. There are no differences in the MMN latencies and amplitudes between the ears. Regarding gender, the male group presented higher latencies in relation to the female group in the right ear. Some results indicate that there is a significant statistical difference of the MMN between right- and left-handed individuals.

Keywords
► evoked auditory potentials
► electrophysiology
► event-related potential
► evoked potentials
► auditory
► evoked potentials

Introduction

The auditory assessment comprises an investigation of the peripheral and central auditory nervous system. Alterations in the peripheral auditory system correspond to hearing loss, while those in the central auditory nervous system reflect the central auditory processing disorder which is related to detection, discrimination and interpretation of sound stimuli.[1,2] This central auditory processing disorder can be investigated through Auditory Evoked Potentials (AEPs). This assessment is recommended by ASHA,[3] which emphasizes the use of the Long Latency Auditory Evoked Potentials (LLAEP). The LLAEP represent the brain activity and correspond to the cognitive and the central auditory process.[4,5]

The Mismatch Negativity (MMN) is one of the LLAEP and reflects an electrical cerebral response of the processing,

discrimination, and auditory memory abilities.[6,7] The main generator of the MMN is the auditory cortex, but the frontal cortex, thalamus, and the hippocampus also contribute to the response.[8] The MMN is elicited by the detection of changes in a series of standard stimuli. This detection indicates a disagreement (mismatch) between the new auditory sensorial input in relation to a standard stimulus stored in the short-term auditory sensorial memory. The MMN is a note with negative polarity (negativity) present in the record of such potential.[1,7,9]

The most important feature is that the MMN can be recorded without influence of the subject's attention and with no task requirements, which make it particularly appropriate for a clinical study in different populations, especially in the evaluation of infants, toddlers, children with difficulties of attention, and for central auditory processing disorders.[5,10,11] In addition, the MMN can provide an objective measure of overall brain degeneration and the functional state of the brain, contributing to informing of the patient's clinical conditions in other medical areas, such as psychiatry (regarding patients suffering from schizophrenia, epilepsy and those under the effect of drugs),[12–14] and in neurology (individuals with multiple sclerosis, the elderly, and comatose patients).[15–18]

The MMN is a negative deflection that occurs after the P2 response – a positive peak of the LLAEP which occurs around 160ms.[7] According to the literature,[6,8] the MMN is identified as the maximum negative deflection range from 100 to 250ms. This potential is obtained by subtracting the responses for the standard stimuli from the deviant stimuli. The latency and the amplitude are the most important parameters to identify the possible auditory processing disorders.[7,8]

The MMN can be obtained using several stimuli such as pure tone, including its variations (frequency, duration, and intensity), and by complex stimuli, including speech (phonemic differences, spatial location, and partial omission).[7,11,19] The MMN response can be determined by the attention to the stimulus rather than its frequency and intensity. For this reason, the best results can be achieved when the subject ignores the auditory stimuli presented, directing her attention to more interesting stimuli, that is, watching a video, viewing a book, playing a game in the computer or tablet, among others.[1,5,20]

The MMN is a promising tool for the assessment of the auditory function, including diagnosis, monitoring, and prognosis of the auditory rehabilitation process. Nevertheless, the investigation of the MMN in normal-hearing and without disorders of the central auditory processing is necessary to understand the normal auditory process in the brain.[1,17,20]

There is a gap in the literature of studies on the values of latency and amplitude of the MMN for normal subjects. Some researchers conclude that further studies on the MMN are necessary to standardize the values of latency and amplitude to make the MMN effectively performed in clinical practice.[1,5,17] A study with normal-hearing adults of both sexes found reference values for the MMN latency in the range of 150.70ms and 184.0ms, and amplitude between 1.435μV and 3.548μV.[1] Another research with older adults found MMN latency values in the range of 148.67ms to 171.0ms and amplitude between 1.847μV and 2.753μV,[17] while other surveys with the MMN in children reported latency ranges between 150ms to 250ms.[11,21]

Thus, given the great importance and applicability in audiological practice and to contribute to the few national and international studies on the MMN findings in normal-hearing subjects, the purpose of this study was to analyze the responses of MMN amplitudes and latencies in normal-hearing individuals aged between 18 and 29 years of both sexes, and also to compare the MMN findings between ears, gender, and hand dominance with the results found in the scientific literature.

Methods

This research is characterized as an observational, cross-sectional, contemporary, and individual study. The convenience sample consisted of individuals of both genders, with normal-hearing, aged between 18 and 29 years. The Scientific Committee and Research Ethics Committee evaluated and approved the project (protocol n°.44969115.8.1001.5334).

Still emphasizing the completeness of Resolution 466/12 which deals with human research, only the individuals who have signed the Informed Consent participated of this study. All subjects were informed about the methodology, risks, discomfort and the confidentiality of data.

The sample size was calculated, considering a significance level of 0.05, a statistical power of 90%, and an effect size of 0.7 (moderate) (EpiInfo – Statcal, CDC, Atlanta, U.S.A.). The software estimated a sample size of 38 individuals.

We conducted the study in an electrophysiology clinic of a university in Rio Grande do Sul and included individuals with normal hearing thresholds, aged between 18 and 29 years, with high school graduation, and without history of diagnosis of auditory system dysfunction, that is, auditory diseases. We excluded from study individuals with genetic abnormalities, history of neurological diseases, intellectual disability or other cognitive changes, and who did not understand the procedures.

The information about age, gender, level of education, illness, hand dominance, among others, were obtained through anamnesis. After this, all subjects were evaluated by the Pure Tone Audiometry, Speech Recognition Index (SRI), Speech Recognition Threshold (SRT), Acoustic Emittance Measurements and the Mismatch Negativity (MMN). Furthermore, we also examined the external auditory canal.

We performed the Pure Tone Audiometry through a previously calibrated model Harp Inventis audiometer (Inventis, Padova, Italy). The test took place in a soundproof booth by air conduction in the frequencies of 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000Hz, and bone conduction in the frequencies of 500, 1000, 2000, 3000, and 4000Hz. The classification of hearing level was made with the Davis and Silverman classification (1970).[22]

The SRI and the SRT took place within the same situation and using the same equipment, but just by air conduction in

both ears. We performed SRI with 25 monosyllabic words, which were presented in a comfortable intensity (40dBNA -decibel hearing level- above the tri-tone average for air conduction in the frequencies of 500, 1000, and 2000Hz) in each ear. The individuals were asked to repeat the words. The initial intensity to perform the SRT was also 40dBNA above the tri-tone average for air conduction. The intensity was reduced until reaching the intensity level at which the patient could understand and repeat 50% of the tri-syllabic words presented.

We conducted the Acoustic Emittance Measurements with the Impedance Audiometer AT235h (Interacoustics A/S, Middelfart, Denmark). We obtained the Tympanometry curves through a probe of 226Hz, inserted into the entrance of the individual's external ear canal. We investigated the Static and dynamic complacencies, and classified the curve according to Jerger (1970).[23] We obtained the acoustic reflexes with the same equipment for the frequencies of 500, 1000, 2000, and 4000Hz. We performed the assessment from ipsilateral and contralateral in both ears.

The MMN was performed in an acoustically and electrically treated room with the equipment MASBE ATC Plus (Contronic, Pelotas, Brasil). The individual was positioned in a comfortable chair with headrest. The skin was cleaned with a Nuprep exfoliating cleanser and gauze. The electrodes were fixed with electrolytic paste (Ten20 conductive) and adhesive tape. The ground electrode was placed on the forehead (Fz); the active electrode was placed close to the scalp (Fpz); and the references electrodes were placed in the right and left mastoid (M2, M1). The earphones (Earphone TONE™GOLD) were inserted in both ears. The impedance was lower than 5Ω in each derivation, and the difference between the electrodes did not exceed 2Ω. We performed an electroencephalogram scan (EEG) to detect spontaneous electrical activity in the brain, to verify artifacts that could interfere in the test. The examiner was instructed to maintain the participants relaxed and not cross legs and arms.

The type of auditory stimulus used was the tone burst. The stimuli were presented in monaural mode, but both ears were assessed. We used a frequency of 1000Hz (standard stimuli) and 2000Hz (deviant stimuli) to evoke the MMN. The stimuli were presented with 50 cycles, speed of 1.8 stimuli per second, polarity alternate, intensity of 70 to 90dBNA, high-pass filter of 1Hz, low-pass filter of 20Hz, Notch – Yes, acquisition full scale of 200μV, 95% of noise limit. The window of analyses was of 500ms and amplitude of 7.5μV. We presented the stimuli in an oddball paradigm, using 90% of standard stimuli and 10% of deviant stimuli. The equipment allowed 2000 promediations, but we stopped the assessment at least at 150 for each individual.

We gave individuals information about the test and, to deviate attention from the auditory stimuli, they received instructions to watch a quiet movie on the tablet. Two evaluators/audiologists analyzed all results at different times.

The database was made on an Excel program and analyzed by SPSS (Statistical Package for Social Sciences), version 20.0. The level of statistical significance was 5% (p ≤ 0.05). Continuous variables were described as mean, standard deviation, minimum and maximum, and the categorical variables were presented by absolute and relative frequencies. We used the Kolmogorov-Smirnov test for data distribution. We used the Student t-test to compare the variable ears when the data presented as a symmetric distribution, and the Wilcoxon test when the distribution was asymmetric. The comparison for the continuous variables between right- and left-handed individuals were made with Student t-test for the independent groups (symmetric data distribution) or the Mann Whitney U-test (asymmetric data distribution). Considering the casuistic, we compared all results based on the mean of the variables.

Results

Forty-four individuals participated in the study. Were excluded four of them, who did not meet the eligibility criteria or did not complete the proposed procedures. Thus, the results refer to a sample of 40 participants. Descriptive data are described in ►Table 1.

The information relating to the latencies and amplitudes of the MMN in the ears are shown in ►Table 2 and ►Fig. 1. There was no statistically significant difference between the ears.

The comparison of latencies of the MMN between genders showed a statistically significant difference for the right ear, being higher in male than in female. This difference did not occur for the left ear and for the comparison between amplitudes in both groups (►Table 3 and ►Fig. 2).

The latencies and amplitudes for right and left ear were compared with the individuals' hand dominance (►Table 4). There was no significant statistical difference between ears for both the right-handed and left-handed group.

For the comparison between the right and left handers for each ear, the results indicated that the latency of the right ear was significantly higher for the left handers than the right handers. the latency of the left ear also presented a significant result, which was higher for the right handers. These differences were not found for the amplitude.

Table 1 Descriptive measures for gender, age and hand dominance

Variables	Total sample (n = 40)	
	N	%
Gender		
Female	20	50.0
Male	20	50.0
Age (years)		
Mean value ± standard deviation (Minimum/Maximum)	22.3 ± 2.9 (18–29)	
Hand dominance		
Right-handed	36	90.0
Left-handed	4	10.0

Table 2 Comparison for latency and amplitude of MMN between ears

Variables	Descriptive measures ($n = 40$)				
	Mean value	Standard deviation	Minimum	Maximum	p
Latency (ms)					
RE	169.4	51.6	92.5	308.2	0.278£
LE	175.3	54.0	107.6	351.1	
Amplitude (µV)					
RE	4.6	4.5	1.0	23.3	0.562§
LE	4.2	3.8	1.0	19.7	

Abbreviations: µV, microvolt; LE, left ear; ms, milliseconds; RE, right ear.
£: Test t-Student for paired data; §: Test Wilcoxon. Level of statistical significance: $p < 0.05$.

Discussion

In our research, we investigated the MMN in normal hearing adults over 18 years old due to the maturity of the central auditory nervous system. The age group is important considering that the MMN achieves the optimum value of latency and amplitude during school age.[24,25] Also, it is known that the presbycusis may start in the age of 30,[26] so this sample consisted of individuals aged up 29. Besides the care with the aged, the number of the sample in this study was higher than others in the scientific literature, regarding the standardization of MMN.[1,17]

The MMN is automatically generated in the auditory and frontal cortex from a change in discriminating of the auditory stimulus.[8] In this study the 1000Hz was used as being the standard stimuli and the 2000Hz the deviant stimuli. Other studies consider that deviations of up to 10% are effective in producing the MMN. The big differences in the stimuli are not recommended due to the possibility of overcoming the P3, which can compromise the MMN record.[16] In this study and in other scientific researches,[1,27,28] the MMN was found in all participants even with a difference of over 10% among the stimuli presented.

In the present study, the mean latency of the MMN in normal-hearing subjects was of 169.4ms in the right ear (RE) and 175.3ms in the left year (LE). The mean amplitudes were of 4.6µV in the RE and 4.2µV in the LE (►**Table 2** and ►**Fig. 1**). These results are similar to those preconized by the scientific literature as normal MMN, with latencies ranging from 100ms to 250ms and amplitudes around 3µV.[1,7,17,20,29] The standardization of these values of MMN are important because the abnormal responses can suggest functional or anatomical changes in the auditory and frontal cortex, which are related with cognitive abilities.[30] Furthermore, the results from this research did not show differences of latencies and amplitudes between the ears, agreeing with others studies.[17,31]

In this study, the results of the latencies and amplitude of the MMN between genders showed a significant difference in the RE. The mean latencies were 187.6ms for the men and 151.1ms for the women (►**Table 3** and ►**Fig. 2**). These differences between groups were not found for the LE (188.1ms for men and 162.6ms for women). These results corroborate with other studies about the MMN standardization in adults,[1] which also found a significant statistical difference between gender, but in both ears: the cited authors found mean latency values of the MMN of 153.2ms in the RE in the women and 150.7ms in the LE; in the men, 184.0ms in the RE and 170.4ms in the LE.
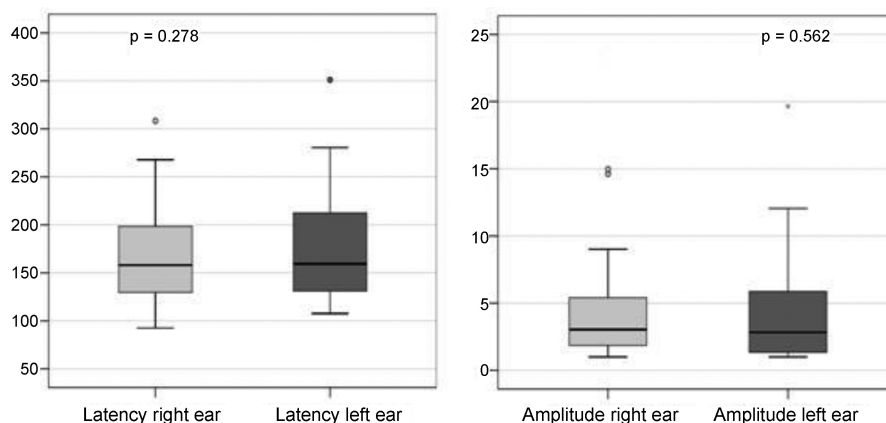
Fig. 1 Box-Plot. Distribution of amplitude and latency values in both ears.

Table 3 Comparison for latency and amplitude of MMN according to ears and gender

Variables and sex		Descriptive measures ($n = 40$)				
		Mean value	Standard deviation	Minimum	Maximum	p
Latency (ms)						
RE	Female	151.1	41.1	92.5	242.6	0.024¥
	Male	187.6	55.4	112.7	308.2	
LE	Female	162.6	41.0	107.6	261.5	0.140¥
	Male	188.1	62.9	116.5	351.1	
Amplitude (µV)						
RE	Female	4.1	3.2	1.0	15.0	0.862¥
	Male	5.1	5.5	1.0	23.3	
LE	Female	4.4	4.4	1.0	19.7	0.883¥
	Male	3.9	3.2	1.0	12.1	

Abbreviations: µV, microvolt; LE, left ear; ms, milliseconds; RE, right ear.
¥: T-Student Test for independent groups; ¥: Mann Whitney U Test. Level of statistical significance: $p < 0.05$.

This research showed no statistical significance of the amplitude values of the MMN between gender (►**Table 3** and ►**Fig. 2**). The mean amplitude in the female group was 4.1µV in the RE and 4.4µV in the LE, and for in male group it was 5.1µV in the RE and 3.9µV in the LE. These results corroborate with a previous research[1] that also did not find significant statistical differences between the gender for the amplitude and obtained similar results to this study. The mean amplitude was 3.548µV in the RE and 2.757µV in the LE for the female group and 1.867µV in the RE and 1.435µV in the LE for the male group.

Some studies[27,32,33] demonstrated neurophysiological differences between gender, particularly for verbal abilities in favor of women. Research[27,32,33] indicates that, in general, the amplitude of MMN is greater in women than in men, whereas the latency is greater in men. Nevertheless, these differences occur only for stimuli with phonemics contrasts. The women have more sensitivity to detect the differences in the temporal spectrum of sound, which are related to auditory discrimination of phonemic contrasts.[1,27]

Although in this study the stimulus used for the MMN was a tonal stimulus with frequency contrast, the difference between gender is visible for the RE. In addition, in another study[1] similar to this, the mean latency in male individuals also showed to be increased in relation to female for tonal stimuli, in both ears (►**Table 2**). Based on the present study, we can infer that women may be more favored in relation to auditory discrimination and processing of non-verbal sounds in the right ear. Thus, gender may be a factor that influences the development of normative data in studies with cognitive electrophysiological tests, such as the MMN.

Despite some controversy, there are studies that consider the left-brain hemisphere responsible for the analysis of linguistic sounds, while the right brain hemisphere is considered responsible for decoding non-linguistic sounds, such as musical and rhythmic sounds.[20,34] As a consequence of the left hemispheric dominance for language processing, a great part of the individuals are better in the attention to the stimuli heard by the right ear, due to the
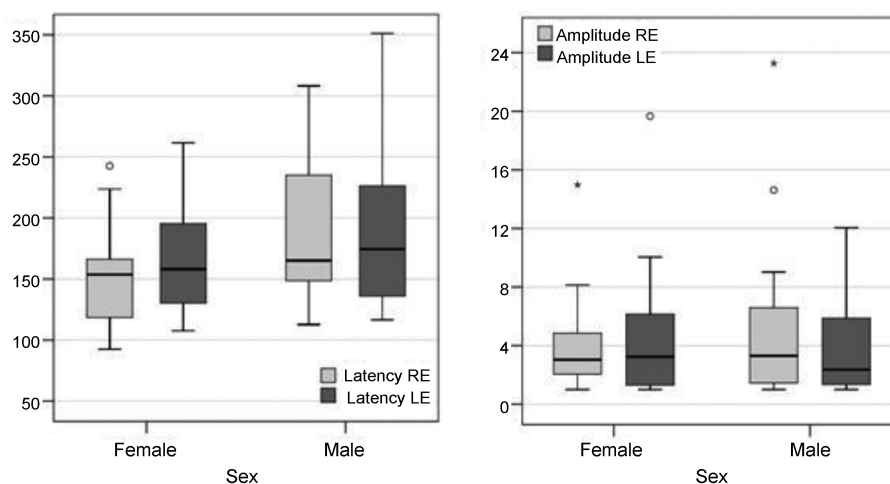
Fig. 2 Box-Plot. Distribution of amplitude and latency values in both ears according to gender. Abbreviations: LE, left ear; RE, right ear.

Table 4 Comparison for latency and amplitude of MMN according to hand dominance and ear

Hand dominance variables		Descriptive measures ($n = 40$)				
		Mean value	Standard deviation	Minimum	Maximum	p
Latency (ms)						
Right-handed	Lat RE	164.7	51.3	92.5	308.2	0.213£
	Lat LE	172.0	53.4	107.6	351.1	
Left-handed	Lat RE	211.1	36.0	159.4	242.6	0.781§
	Lat LE	205.4	57.3	127.8	261.5	
Lat RE	Right-handed	164.7	51.3	92.5	308.2	0.021¥
	Left-handed	211.1	36.0	159.4	242.6	
Lat LE	Right-handed	172.0	53.4	107.6	351.1	0.035¥
	Left-handed	205.4	57.3	127.8	261.5	
Amplitude (µV)						
Right-handed	Amp RE	4.5	4.7	1.0	23.3	0.213£
	Amp LE	4.0	4.0	1.0	19.7	
Left-handed	Amp RE	5.2	1.6	4.3	7.6	0.587§
	Amp LE	6.0	1.1	4.6	6.9	
Amp RE	Right-handed	4.5	4.7	1.0	23.3	0.755¥
	Left-handed	5.2	1.6	4.3	7.6	
Amp LE	Right-handed	4.0	4.0	1.0	19.7	0.361¥
	Left-handed	6.0	1.1	4.6	6.9	

Abbreviations: µV, microvolt; Amp, amplitude; Lat, latency; LE, left ear; ms, milliseconds; RE, right ear.
¥: Test t-Student for independent groups; ¥: Mann Whitney U Test; £: T-Student Test for paired data; §: Wilcoxon Test. Level of statistical significance: $p < 0.05$.

contralateral pathway directing to the left brain hemisphere.[35,36]

In this study, hand dominance was considered a reference for the brain hemisphere dominance in each individual and, therefore, one of the objectives was to investigate if there was any difference in the MMN latencies and amplitudes in the ears of right- and left-handed individuals (►Table 4).

The primary hypothesis of this study was that non-verbal sounds, like the tone stimuli used in this survey, heard by the left ear of right-handed individuals, could present lower latencies in relation to the right ear. Thus, the stimulus heard by the left ear would be directed to and processed more quickly by the right brain hemisphere, which seems to be more specialized in decoding non-linguistic sounds. Other studies have already demonstrated that, for tone stimuli, the left ear has shorter latencies than the right ear.[27] However, given the results (►Table 4), this assumption could not be confirmed because, although there was no statistical difference between the ears, the LE had longer latencies compared with the RE in right-handed individuals.

On the other hand, researchers have already mentioned that, for left-handed subjects, the right brain hemisphere indicates greater activation for linguistic sound processing, differently from what has been observed in right-handed individuals.[37] Thus, the authors of the present study hypothesize that the left-handed individuals could process the tone stimulus heard by the RE with a shorter latency compared with the LE, because it would reach the left hemisphere more

quickly, which could demonstrate more ability for non-linguistic sounds for the left-handers. Given the results (►Table 4), these hypotheses were not observed in this research for both latency and amplitude. However, the results showed that latency in the LE was higher for the left-handers than the right-handers. These results allow one to infer that the right-handers are quicker in decoding and processing non-verbal sounds heard by the LE compared with the left-handers, due to the lateral activation of the right brain hemisphere. The present authors consider that there should be more research papers addressing the MMN in left- and right-handers, to verify possible differences between these individuals.

Furthermore, the results from this study are important to consider that the MMN could be a useful tool for the detection of central auditory disorders. The normative values found in this research contributes to the literature and allows the clinician to have references of values of MMN.

Conclusion

It was possible to obtain references of values for the MMN. There are no differences in the MMN latencies and amplitudes between ears. The male individuals showed increased latencies compared with female individuals in the right ear. Moreover, the results indicated that there was difference in the MMN latencies for the right and left-handed individuals when comparing between ears.

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