



Mismatch Negativity in Children and Adolescents with Autism Spectrum Disorder

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Abstract

Introduction Individuals with autism spectrum disorder (ASD) have abnormalities in auditory perception and sensitivity. The mismatch negativity (MMN) component of the evoked potential demonstrates a brain detection response to an auditory change due to memory, and enables the identification of changes in the auditory system.

Objective To analyze MMN responses in children and adolescents with ASD and compare them with those of a control group.

Methods Cross-sectional and comparative study. The sample was composed of 68 children and adolescents, divided into study group (SG), which contained those diagnosed with ASD, and the control group (CG), which contained those with typical development, normal hearing thresholds, and without hearing complaints. All participants were submitted to peripheral and central electrophysiological auditory evaluations. For the electrophysiological auditory evaluation and MMN recording, the electrodes were fixed in the following positions: Fz (active electrode), M1 and M2 (reference electrodes), and on the forehead (ground electrode). Auditory stimuli were presented in both ears simultaneously, with a frequency of 1,000 Hz for the frequent stimulus, and of 2,000 Hz for the rare stimulus, in an intensity of 80 dBNA.

Results Latency and amplitude values were increased in the SG, with a statistically significant difference in comparison with the CG. In the MMN analysis, there was no statistically significant difference in the comparison between right and left ears and between genders.

Conclusion Children and adolescents with ASD had higher latency and amplitude values in the MMN component than the individuals in the CG.

Keywords

- ▶ autism spectrum disorder
- ▶ auditory evoked potentials
- ▶ electrophysiology
- ▶ auditory perception
- ▶ child
- ▶ audiology

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Introduction

Autism spectrum disorder (ASD) is characterized by deficits in communication and social interaction in several contexts, especially in social reciprocity, in non-verbal communication behaviors used for social interaction, and in the ability to develop, maintain and understand relationships. Individuals with this diagnosis also have restricted and repetitive patterns of behavior, interests or activities.¹⁻³ The current prevalence of this disorder in the United States is of 1:59 cases, while in the world it is estimated to be 1:100.^{2,4} In Brazil, epidemiological studies have been conducted, which have detected prevalences of 0.3%⁵ and 1%.⁶

Since the communication and language impairments are important clinical manifestations in ASD, central disorders that may interfere in such skills must be investigated. Therefore, it is valid to study the central auditory system, as disturbances related to the processing of auditory information have been understood of the causes of language development disorders. Some studies,⁷⁻⁹ for instance, suggest that alterations in auditory processing skills can contribute to clinical manifestations of inattention and difficulty in developing and understanding language. Hence, it is recommended that objective and non-invasive assessments of the central auditory system be performed to identify potential abnormalities earlier.¹⁰ These tests can provide an accurate diagnosis and result in an effective intervention, which will contribute to improve the quality of life of these individuals, especially as regards to the level of functioning.¹⁰⁻¹³ From this vantage point, the electrophysiological assessment of hearing, which provides objective measurements of neuroelectric activity from the auditory pathway in response to an acoustic stimulus, is a viable resource.

Long-latency auditory evoked potentials (LLAEPs) are electrophysiological tests that provide measures from the cerebral cortex and have the advantage of enabling the assessment of patients in whom the performance of behavioral evaluations is difficult.¹⁴⁻¹⁶ Among the LLAEPs, mismatch negativity (MMN) is also highlighted, once it demonstrates a brain detection response to an auditory change due to memory. This detection is independent of the attention of the subject to the sounds heard in the examination: the answer is passive, and not dependent on behavioral reaction.^{17,18} The test shows a correlation between automated processes and higher-level cognitive functions in the auditory cortex, and it has paradigms that are used to identify many issues. Therefore, it enhances the understanding of the main neuropsychiatric and neurological diseases, such as the mechanism behind neurodevelopment disorders.¹⁹

Studies^{9,20-24} testing MMN in children and/or adolescents with ASD using different paradigms, methodologies, and conclusions have been conducted. However, according to the surveyed literature, there is a lack in studies in Brazil specifically on the MMN results in ASD; there are only studies with other LLAEP tests in these children.²⁵⁻²⁷ Thus, the present study is justified, as it is intended to be a complementary source to the knowledge on the central

auditory system and its abilities in individuals with ASD, and due to the importance in terms of epidemiological data of studies with local samples.

The objective of the present study was to describe MMN responses in children and adolescents diagnosed with ASD, and to analyze the values of MMN latencies and amplitudes in this population and compare these results with a control group of typically developing children without any hearing complaints.

Methods

The present is an experimental, cross-sectional, observational, and comparative study. It was approved by the institutional Ethics in Research Committee under process number 77900517.2.0000.5334. The procedures of the present study were performed at Núcleo de Estudos em Eletrofisiologia da Audição at Universidade Federal do Rio Grande do Sul (UFRGS), after the parents or legal guardians of the patients signed an informed consent form.

Population

The sample was composed of 68 individuals divided initially into 2 groups: the study group (SG) and the control group (CG). The CG was composed of 51 individuals. The SG was composed of 17 children and adolescents aged between 7 and 17 years, previously diagnosed with ASD by pediatric neurologists, who attended the Neuropediatrics and Autism Unit of a reference hospital in the city of Porto Alegre, Brazil. The diagnosis was established by applying the Autism Screening Questionnaire (ASQ),²⁸ which consists of questions directed to parents, who answer them based on their observations of their children's behavior. This questionnaire is typically used to track invasive developmental disorders, and it provides an operational diagnosis that is based on scores on the following observed behaviors items by: reciprocal social interaction; language and communication; and repetitive and stereotyped patterns of behavior.²⁸

The CG was composed of children and teenagers aged between 7 and 17 years, with normal development, normal school performance, normal hearing thresholds, MMN data considered normal according to reference values, without any hearing complaints or language disorders, matched by gender and age with the SG. The data on the CG came from the database records of Núcleo de Estudos em Eletrofisiologia da Audição, and these individuals were triply paired with the SG in relation to age and gender.

Subsequently, both groups were subdivided into children (aged between 7 and 11 years) and adolescents (aged between 12 and 17 years). Thus, there were four groups.

The inclusion criteria were:

- Hearing thresholds lower than 15 dBNA²⁹ for all frequencies evaluated;
- Tympanogram tracing type A and presence of acoustic reflexes in both ears;^{30,31} and
- Absence of history of genetic syndromes and associated neurological diseases.

Instruments

The following procedures were performed:

- a) Anamnesis: it was performed to collect general data, as well as the medical, otorhinolaryngologic and hearing history. At this moment, we asked if the child exhibited symptoms of auditory hypersensitivity. We also explained the informed consent form, and it was signed.
- b) Meatoscopy: a first inspection of the external acoustic meatus was performed with a Welch Allyn (Skaneateles Falls, NY, US) otoscope, to rule out interference factors (presence of cerumen and/or of strange bodies) for the following evaluations.
- c) Acoustic immittance measures: they were researched to verify the functioning of the middle ears using an AT235h impedance audiometer (Interacoustics, Middelfart, Denmark). The static and dynamic compliances were identified, and the tympanogram was drawn and classified according to the classification proposed by Jerger.^{30,31} Ipsilateral and contralateral acoustic reflexes were investigated in the frequencies of 500 Hz, 1,000 Hz, 2,000 Hz and 4,000 Hz in both ears.
- d) Pure-tone audiometry: it was performed to check the peripheral hearing in an acoustically-treated booth, using headphones and a Harp model audiometer (Inventis, Padiva, Italy). The hearing thresholds of the frequencies of 250 Hz, 500 Hz, 1,000 Hz, 2,000 Hz, 3,000 Hz, 4,000 Hz, 6,000 Hz, and 8,000 Hz were investigated by air-conduction, while those of the frequencies of 500 Hz, 1,000 Hz, 2,000 Hz, 3,000 Hz, and 4,000 Hz, by bone-conduction.
- e) Transient evoked otoacoustic emissions: the response of this test was automatic, to assess the estimated hearing threshold of both ears in the frequencies of 1,000 Hz, 2,000 Hz, 3,000 Hz, and 4,000 Hz. To perform this examination, click stimulus was used with the Titan equipment (Interacoustics). And as the analysis criterion, we considered the presence of response when the signal-to-noise ratio was ≥ 6 dB in at least 3 consecutive frequency bands, with mandatory presence at 4,000 Hz, and reproducibility $\geq 75\%$.
- f) Vocal audiometry: performed with the Speech Recognition Percentage Index (SRPI) and the Speech Recognition Threshold (SRT). The patient should repeat the words presented and/or point to the requested figures. To perform the SRPI, 25 monosyllabic words were presented, at an intensity of 40 dBNA above the pure-tone average value of the airway thresholds, in each ear. To perform the SRT, the initial intensity used was the same as that of the SRPI, but it was gradually reduced until reaching a level of intensity in which the patient could understand and be able to correctly repeat 50% of the trisyllabic words presented.
- g) Auditory evoked potential MMN: recording was performed in an acoustically- and electrically-treated room, with the individual awake and sitting on a comfortable chair. Children and adolescents were

told and motivated to watch a video without any sound on a tablet during the procedure. The equipment used to carry out the exam was the ATC Plus Masbe (Contronic, Pelotas, RS, Brazil). The examiner cleaned the patients' skin with a skin prep gel (Nuprep, Weaver and Company, Aurora, CO, US) and common gauze. Subsequently, silver electrodes were placed with an electroencephalogram (EEG) conductive paste (Ten20, Weaver and Company) and micropore tape. The ground electrode was placed on the forehead; the active electrode (Fz), near the scalp; electrode M1 was positioned on the right mastoid, and M2, on the left mastoid. Finally, earphones were placed in both ears. The electrical impedance was lower than 5Ω on each ear, and the difference among the three electrodes did not exceed 2Ω . After the impedance measurement, EEG scanning was performed to capture spontaneous brain electrical activity to identify artifacts that could interfere in MMN results. The survey respondents were told not to tighten the limbs or cross their legs and arms throughout the procedure.

For the MMN recording, several equal auditory stimuli (frequent stimulus) were presented in short time intervals, alternated by stimuli that differed in frequency (rare stimulus). The parameters used for the MMN recording were the binaural and simultaneous presentations of tone burst auditory stimuli, with a frequency of 1,000 Hz (for 50 cycles) for the frequent stimulus, and of 2000 Hz (for 50 cycles) for the rare stimulus, in an intensity of 80 dBNA for both. On average, 300 stimuli were presented, and the oddball paradigm in use was 90/10, with alternating polarity. During acquisition, the full scale was of 200 μ V; the high-pass filter, of 1 Hz; the low-pass filter, of 20 Hz; Notch - YES; 90% noise limit; the time window, of 500 ms; and the tracing amplitude, of 7.5 μ V;

The registration protocol used for the MMN was based on that of another study³² that used the same equipment and tested individuals with the same age as those in the SG of the present study. It should be noted that, to provide greater reliability to the analysis, the test was performed at least twice in each ear to register the results and ensure the reproducibility of the waves. After that, we analyzed the latency values, classifying them as delayed or not; the amplitude values, which were classified as reduced or increased; and the morphology of the MMN waves, which were classified as appropriate, abnormal, or very abnormal, based on the difficulty to identifying their peaks.³³ For wave marking, the subtraction of the tracing corresponding to frequent stimuli from the tracing corresponding to rare stimuli was considered. The latency marking was made in the highest negative peak observed between 100 ms and 250 ms, after the N1 component. To identify the amplitude, the baseline (point zero) was considered as the starting point until the greatest deflection, recognized as the MMN. To ensure greater reliability of the analyses, the electrophysiological records were performed at different moments by two evaluators with experience in electrophysiology, and the

results were considered valid only when there was agreement between the evaluators.

In the present study, the numerical variables were expressed as means and standard deviations, while the categorical variables, as absolute and relative frequencies. The Shapiro-Wilk test was used to evaluate normality, and the Levene test, to assess variances, with both assumptions done. To evaluate gender and other variables, due to lack of normality, the nonparametric Wilcoxon rank-sum test was used. The samples were considered, similar to a normal distribution. Thus, to calculate the difference in the averages of the studied variables using the *t*-test for two independent samples averages with the assumption of equal variances and the paired *t*-test. The significance level adopted was 5%, with 95% confidence intervals (95% CIs). The software used was the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, US), version 20.0.

Results

To form the SG, we invited 53 children and teenagers; 31 of them accepted the invitation, and attended the evaluation session during the period of data collection. A total of 14 were excluded for failing to properly complete all procedures proposed. Thus, the results refer to a sample of 17 individuals in the SG (10 children and 7 teenagers) and 51 in the CG (30 children and 21 adolescents, who were tripled and matched by age and gender with the SG). ►Table 1 shows the characteristics of the sample.

There was a marked presence of auditory hypersensitivity, as well as altered morphology, in the waves of the MMN in the SG. The description of each of these variables can be found in ►Table 1. There was no statistically significant correlation regarding morphology and wave latencies in

the right ear (RE; $p=0.38$) and left ear (LE; $p=0.35$), or between morphology and wave amplitude in the RE ($p=0.14$) and LE ($p=0.054$). In the comparative analysis between the RE and LE in the SG, no statistically significant difference in terms of wave latency ($p=0.399$) and amplitude values ($p=0.283$) was found, which indicates that the RE and LE had equivalent latency and amplitude values. Moreover, regarding gender, no statistically significant differences were found in the latency values of the for RE ($p=0.74$) and LE ($p=0.95$), neither in the amplitude values (RE: $p=0.24$; LE: $p=0.94$).

►Table 2 shows the results of the comparison of the latency and amplitude values of the MMN between the SG and CG, and statistically significant differences were observed for every analyzed variable.

►Table 3 and ►Table 4 show the same comparison made in Table 2, but considering only the children (►Table 3) and only the adolescents (►Table 4) in both groups, and statistically significant differences were observed. The latencies and amplitudes were increased compared with the results obtained from the comparison of the SG and CG. Thus, through the MMM test, we detected atypical auditory processing in sound discrimination in the SG.

Discussion

In the present study, the SG was composed of 17 children and adolescents of both genders diagnosed with ASD, and the CG was composed of 51 individuals triple-matched for gender and age with the SG. A systematic review of the literature containing reports on the pediatric population that most studies using MMN, which investigated auditory processing abnormalities in people who had specific disorders, have few individuals in the study sample. In addition, the authors found that most studies in the literature present the

Table 1 Characteristics of the study sample

Variable		Groups					
		Study group			Control group		
		n	%	Mean ± standard deviation	n	%	Mean ± standard deviation
Gender	Male	15	88.2		45	88.2	
	Female	2	11.8		6	11.8	
Age (years)	Total – range: 7–17	17	100	11.06 ± 2.65	51	100	11.06 ± 2.65
	Children – range: 7–11	7	41.18	9.3 ± 1.16	21	41.18	9.3 ± 1.16
	Teenagers – range: 12–17	10	58.82	13.57 ± 2.07	30	58.82	13.57 ± 2.07
Hypersensitivity	Yes	15	88.24				
	No	2	11.76				
Morphology of the mismatch negativity wave	Appropriate	9	52.94				
	Abnormal	6	35.3				
	Very abnormal	2	11.76				

Table 2 Results of the comparison between latency and amplitude of the mismatch negativity (MMN) wave

Ear	Variables	Groups				Difference between the mean values	p-value ^a
		Study group		Ccontrol group			
		n	Mean ± standard deviation	n	Mean ± standard deviation		
Right	MMN latency	17	246.65 ± 71.90ms	51	173.57 ± 29.67ms	73.08	< 0.001*
	MMN amplitude	17	6.41 ± 2.85µV	51	4.76 ± 1.04µV	1.65	< 0.001*
Left	MMN latency	17	242.06 ± 68.96ms	51	173.59 ± 29.79ms	68.47	< 0.001*
	MMN amplitude	17	5.76 ± 2.33µV	51	4.86 ± 1.13µV	0.9	< 0.001*

Notes: ^aStudent t-test; *statistically significant.

Table 3 Results of the comparison between latency and amplitude of the mismatch negativity (MMN) wave among children

Ear	Variables	Groups				Difference between the mean values	p-value ^a
		Study group		Control group			
		n	mean ± standard deviation	n	mean ± standard deviation		
Right	MMN latency	10	259.76 ± 69.9ms	30	187.41 ± 27.89ms	72.35	< 0.001*
	MMN amplitude	10	6.6 ± 2.77µV	30	5.13 ± 1.03µV	1.47	0.02*
Left	MMN latency	10	252.2 ± 64.76ms	30	186.25 ± 30.13ms	65.95	< 0.001*
	MMN amplitude	10	5.27 ± 2.06µV	30	5.17 ± 1.26µV	0.1	0.92

Notes: ^aStudent t-test; *statistically significant.

Table 4 Results of the comparison between latency and amplitude of the mismatch negativity (MMN) wave among teenagers

Ear	Variables	Groups				Difference between the mean values	p-value ^a
		Study group		Control group			
		n	Mean ± standard deviation	n	Mean ± standard deviation		
Right	MMN latency	7	227.84 ± 75.97ms	21	153.85 ± 19.43ms	73.99	< 0.001*
	MMN amplitude	7	6.18 ± 3.13µV	21	4.22 ± 0.81µV	1.96	0.015*
Left	MMN latency	7	227.48 ± 77.08ms	21	155.52 ± 17.88ms	71.96	< 0.001*
	MMN amplitude	7	6.54 ± 2.89µV	21	4.49 ± 0.76µV	2.05	0.002*

Notes: ^aStudent t-test; *statistically significant.

comparison of results between the study group and control group.³⁴

In the present study, there was a predominance of male subjects, which shows weak gender parity. It is known that there is a higher prevalence of ASD in males worldwide, with 4 to 5 times more cases than females.^{3,5,35–37}

Furthermore, in the present study, we found no statistically significant difference between the ears in terms of the latency and amplitude values of the MMN wave in the SG, which is in line with the findings of other studies^{20,35,38–40} with children and adolescents that used the same procedure as the one employed in the present research.

We did not find Brazilian studies using the MMN procedure in children and/or adolescents with ASD. However, we found international studies with different para-

digms and methodologies, such as a systematic review and meta-analysis by Schwartz et al.⁹ which assessed 38 publications on the MMN response in individuals with ASD. Of these, 15 studies were performed with children and adolescents, 11 studies only with children, 1 only with teenagers, and 4 with children, adolescents, and adults. A total of 15 of these studies were been published less than 10 years ago.

There was a wide variety of aims and conclusions in the studies included in the meta-analysis by Schwartz et al.⁹ and the samples of most of them contained less than 20 participants in both the study group and control group, which is also the case of the present study. It is believed that the small samples of the studies on the ASD population is justified by the difficulty in assessing behavioral and social issues in

individuals with this disorder, in addition to their inconsistent responses.^{9,41}

Moreover, analyzing the literature, we found that studies⁹ on auditory evoked potentials report no consistent abnormalities in autistic patients with mental retardation, showing contradictory results. Neurophysiological studies^{9,42} in which abnormalities have been reported suggest changes in cortical processing.

In the field of auditory electrophysiology, the study of the amplitude and latency of waves enables the measurement of neural activity in each place of the central auditory pathway and the observation the processing time of auditory information.⁴² In the present research, the MMN procedure was performed with tone burst stimulus and electrodes in the Fz position, and late latencies and increased amplitude among the SG were evident when compared with the CG. This demonstrates that the SG needed more time to understand the difference between frequent and rare stimuli. The latency delay to recognize the presented auditory situation and the increase in amplitude may indicate a greater number of neurons recruited for the task, which can suggest a disturbance in the auditory ability of temporal resolution, considering that it is defined as the minimum time required to segregate or solve acoustic events.⁴³

The findings about increased MMN latency in children and adolescents with ASD in the present study are described in ►Tables 3 and 4, and they corroborate those of previous studies.^{9,24,44–47} However, there are studies in which latency results do not show significant differences in MMN with pure tone stimulus in individuals with ASD compared with a control group. The results of a Finnish study did not show differences in MMN latency among high-functioning autistic children when they were tested with pure tone stimulus (presented in distinct levels of complexity) or vocal stimulus.²¹ Another study⁴⁷ also reported the absence of abnormalities in the MMN response in individuals with ASD when compared with a control group.

We believe that the delayed latency values found in the present study are a consequence of the heterogeneous sample, composed of individuals with different symptoms, deficits and ASD demonstrations. In studies on a specific group of individuals with ASD, such as high-functioning ASD patients, the case group can present findings similar to those of the control group.

Regarding amplitude, in the present study, the SG showed increased MMN values (►Tables 3 and 4). However, this finding goes against those of electrophysiology studies^{22–24,45,47} in children and adolescents with ASD with measurements of frequency-specificity. There are also studies that reported decreased amplitude, and others whose results were significantly different between the study and control groups.^{43,48}

The amplitude of the MMN wave demonstrates the extent of the neural allocation involved in cognitive processes.^{49,50} Some studies^{12,50,51} show MMN amplitude values usually lower than 5µV. However, it has been reported^{39,52} that, as well as the degree of discrepancy between the frequent stimulation and the increase of rare stimulus, MMN ampli-

tude can also be increased. Therefore, it is believed that this may be the reason why the amplitude values in the present study, as well those of other studies in the literature, were close to the maximum amplitude described.

Schwartz *et al.*⁹ reported that there are studies demonstrating that individuals with ASD had significantly decreased amplitude with the measurement of frequency-specificity. However, this variable did not show significant differences in the group with ASD when the MMN was tested with speech stimuli, which demonstrates that verbal stimuli with consonants and/or vowels can be processed differently than non-verbal stimuli, such as the tone burst stimulus, which was used in the present study. Schwartz *et al.*⁹ also reported substantial abnormalities in MMN responses in a group of ASD children, while, in an adult population with ASD, the responses were similar or with increased amplitude compared with control group.

Individuals with ASD can also present abnormal reaction or response to sensations, which is described as a defense, which reveals a neurological inability to properly process sensory stimuli, such as auditory stimuli.^{53–55} Auditory hypersensitivity, which consists of a psychoacoustic discomfort, is a quite common sensorial complaint in autistic individuals.^{32,56}

In the present study, 88.2% of the individuals with ASD had hypersensitivity according to self-reports and/or reports by the interviewed parent/guardian. Researchers⁵⁶ claim that these auditory sensory changes in this population can contribute to changes in the processing of the hearing in auditory discrimination, a skill tested in the MMN procedure.

The visual pattern of electrophysiological waves is called morphology. It indicates the involvement of neurons that reacted to auditory stimuli, the number of recruited neurons, and the extent of neural activation, and synaptic synchrony may interfere in this parameter.^{48,57} Thus, the maturation of the central auditory system is an essential factor for its analysis; however, it is important to mention that there are no standard classifications reported in the literature for the analysis of this parameter. No studies were found describing the morphology of MMN waves in patients with ASD, although there is a consensus in the literature that abnormalities in this parameter indicate atypical neural synchrony, which enables us to infer that individuals with ASD may present it, and, in the sample of the present study, there were abnormalities in 47,06% of the patients.^{48,58,59}

Even though the analysis of wave morphology has shown abnormalities in some patients in the SG, there was no statistically significant correlation with the results of wave latency and amplitude, which also demonstrates a heterogeneity and variability in ASD characteristics, with individual differences in MMN response in this population.

Therefore, these limitations expose gaps in the current literature regarding abnormalities in sound detection in ASD individuals. Thus, we suggest the performance of new studies in this population, with larger samples, to enable a reinforcement about auditory processing responses of these individuals to then provide subsidies for their assessment and contribute to the therapeutical follow-up.

Conclusion

The present study showed increased MMN latencies and amplitudes in the SG compared with the CG. In addition, abnormalities in the morphology of MMN waves were also found in ASD individuals. Therefore, we believe that the auditory processing skills of discrimination, involuntary attention, and sensory memory were impaired in the subjects with ASD who participated in the present study.

Conflict of Interests

The authors have no conflict of interests to declare.

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