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Original Article

Automatic Pre-Attentive Auditory Responses: MMN to Tone Burst Frequency Changes in Autistic School-Age Children

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OBJECTIVE: Autism is a pervasive developmental disorder that includes deficits in socialization, communication, and adaptive functioning. The mismatch negativity (MMN) is a component of evoked response potentials that reflects pre-attentive change detection. The purpose of this study was to determine whether a group of autistic school-age children had abnormal changes in auditory MMN and to analyze and compare the results with an age-matched group of normal children.

MATERIALS and METHODS: This prospective study was carried out on 31 autistic school-age children. Thirty age-, gender-, and IQ-matched children served as a control group. The children were evaluated through diagnostic procedures that included psychometric and speech language tests and audiological assessments. Auditory MMNs were recorded from all participants, and the peak amplitudes and latencies were measured.

RESULTS: The mean ages were 11.3±2.8 and 11.2±3.2 years for the autistic and normal children, respectively. The MMN amplitudes obtained from the two groups were found to be statistically significantly different. The MMN amplitudes were reduced, and latencies were prolonged in autistic versus normal children.

CONCLUSION: Our results suggest that children with autism do have auditory changes at the level measured by MMN, mainly pre-attentive response, which argues for a doubt on affection of the supposed origin of auditory MMN in those children.

KEYWORDS: Auditory mismatch negativity, mismatch negativity, event-related potentials, autistic children, autism, auditory evoked potentials

INTRODUCTION

Autism was first described by Kanner, and since that time, extensive efforts have been made in describing the behaviors that define autism and to elucidate the underlying neural circuitry involved in autism through structural and functional neuroimaging [1]. It is a pervasive developmental disorder that includes deficits in socialization, communication, and adaptive functioning [2].

Its etiology has not yet been fully identified, but a variety of pathological events affecting brain development could be the cause [3]. Genetic factors might be incriminated for its etiology [4]. Children with autism often exhibit abnormalities in auditory processing and receptive language functioning [5]. It has been postulated that the deficits in attention processing contribute to many of the clinical features of autism [6].

Mismatch negativity (MMN) is a component of event-related potentials that reflects novelty discrimination. Although modulated by attention, it can be elicited, even if attention is not being paid to the stimulus; therefore, it reflects pre-attentive change detection [1]. MMN response has been elicited by changes in a variety of acoustic features, such as intensity, frequency, duration, and perceived location, and by changes in auditory patterns [7]. It can be reliably elicited in children, and the characteristics of the MMN elicited in simple paradigms from children are generally similar, although often somewhat longer in latency, to those elicited from adults [8].

This study was designed to investigate the auditory MMN event-related potential in autistic school-age children and to compare them with an age-matched group of normal children.

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MATERIALS and METHODS

Participants

This prospective study was conducted upon 31 school-age children at KFMMC Hospital (24 males and 7 females, mean age 11.3, range 6-15 years). The mean performance intelligence quotient (IQ) was 93.8±6.8. They were diagnosed with autism based upon the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR) [2]. Thirty children with normal language development were recruited as a control group (18 males and 12 females, mean age 11.2, range 6-17 years). The mean performance IQ was 95.1±5.8. They matched the study group in age, gender, and IQ. Approval of the hospital ethics and research committee was obtained, and informed consents were taken from the parents of the patients and normal children.

All participants were right-handed, and they were subjected to thorough history, ENT, medical, and neurological examinations. They had normal hearing by play or voluntary threshold on pure tone audiometric measurements. The hearing thresholds were equal or better than 20 dBHL at all tested frequency octaves from 250 to 8000 Hertz using an AC 40 pure tone audiometer (Interacoustics, DK-5610, Assens, Denmark) in a sound-treated booth. They had normal middle ear functions, as measured by immittancemetry on an AZ 26 (Interacoustics, DK-5610, Assens, Denmark).

Clinical Diagnostic Tools

The participants of both groups were subjected to the following:

1- Psychometric evaluations by:
   a. Non-verbal Marianne Frostig Developmental Test of Visual Perception to get performance IQ and mental age (MA) [9].
   b. Social age (SA) was obtained using Vineland Social Maturity scale [10].
   c. Autistic symptom severity was evaluated using the Childhood Autism Rating Scale (CARS) [11]. Children scoring below 30 were considered non-autistic, 30-36 was considered mild to moderate autism, while 37-60 was considered severe autism.

2- Language evaluation tests were performed for all participants [12]. This test ceiling covered until 8 years of language age. The chosen control group had a fully developed mastered language, so this test was applied to the autistic group of children only. The language test items included the following: receptive and expressive parts of semantics, receptive and expressive parts of syntax, pragmatics, prosody, and testing phonology by articulation test [13]. From the language test, the following measures were calculated: receptive and expressive language, pragmatic, prosodic, and total language age.

Auditory MMN Testing

Apparatus

All participants in this study were subjected to an auditory MMN electrophysiological study using evoked potential testing, using ICS Medical version 3.00 (CHARTR, IL, USA), coupled with a preamplifier. An output amplifier, computer, and insert earphones were used for both stimulation and recording of the auditory MMN event-related potentials. A sound-treated room, electrically shielded and meeting specifications for permissible ambient noise, served as the test environment.

Table 1. The mean±SD for age, gender, IQ, social age, and CARS scores of the autistic and normal children

	Autistic group		NC group			
	Mean	SD	Mean	SD	t test	p value
Age (in years)	11.37	2.8	11.2	3.2	0.8826	p>0.05
IQ	93.8	6.89	95.13	5.84	0.4202	P>0.05
MA (in years)	10.66	2.91	10.65	2.97	0.9968	P>0.05
SA (in years)	6.75	1.43	11.23	2.64	0.00021	P<0.001*
CARS score	33.7	2.3	20.2	4.1	0.00027	P<0.001*

* Highly significant, p<0.001; SD: standard deviation; IQ: intelligent quotient; MA: mental age; SA: social age; NC: normal children

Test Parameters and Procedure

The evoked potentials were recorded using surface electrodes placed on the left and right mastoid (A1 and A2, respectively) as reference electrodes. The active electrode was placed at Fz. The forehead served as a common electrode. The electrode impedances were kept below 5 KΩ. Insert earphones were used to deliver the stimuli at 75 dBnHL ipsi-laterally with a 1.1/s stimulus rate. The time window for recording was 512 ms of analysis time with 100 ms of pre-stimulus baseline recording. The filter was set at 1-100 Hz of band-pass filter (24 dB/octave). The MMN was evoked with an oddball paradigm pattern, which consists of the presentation of a stream of two different frequency tones; one of them was a rare deviant (1500 Hz tone bursts), and the others were frequent standards (1000 Hz tone bursts). The probability was 20% for the rare tone and 80% for the frequent tones. The average number of frequent and rare tones was 200 and 50, respectively. The tone bursts had a 50-ms plateau duration, and 10-ms rise/fall time. The amplifier was set to 50,000 gain, and the artifact sensitivity rejection was set to ±49 microvolts.

Two recordings were obtained for each participant. Children were seated in a reclining chair in the sound-attenuated chamber. They were given a pictured storybook to look at during the recording. Responses were separate averages and computed for standards and deviants. The averaged waveforms were digitally filtered and baseline-corrected. The MMN was observed by subtracting the waveform obtained to stimuli presented as standards from those obtained to deviants. The amplitude was measured at the peak latency obtained at Fz, and the peak latency was measured at the midpoint of the component peak. All reliable measures were included for analysis.

Statistical Analysis

The results were submitted to statistical analysis using a Statistical Package for the Social Sciences (SPSS) file version 17.0 (SPSS Inc., Chicago, IL, USA), this includes descriptive statistics (mean and standard deviation), correlation coefficient, and analysis of variance based on the t-test, adopting a significance level of < 0.05 and a highly significant level of <0.001. The statistical analysis was carried out in relation to psychometric, language, and audiological evaluations-mainly the latency and amplitude values for MMN components of autistic and normal children.

RESULTS

The data analysis followed two main lines:

A-Comparative analysis between the autistic group and the normal group as regards the results of the psychometric evaluation, language evaluation, and audiological evaluation (Tables 1, 2, 3, and 4).

Table 2. The mean±SD of the total language age delay and different language parameters in years for the autistic group

Language parameters	The mean delay (years)	SD
Total language age	7.25	2.81
Receptive language age	7.12	2.8
Expressive language age	8.62	2.73
Pragmatic age	9.64	2.8
Prosodic age	9.77	2.83

SD: standard deviation

Table 3. The mean latencies and amplitudes±SD of MMN recorded from the right and left mastoids for normal and autistic children

	Latencies in ms		Amplitude in µV	
	Mean	SD	Mean	SD
Autistic Children				
RM	173.1	19.7	2.1	0.59
LM	173.6	20.6	2	0.56
Total	173.3	20.1	2.1	0.5
Control				
RM	171.1	16.9	2.66	0.83
LM	170.4	17.8	2.63	0.77
Total	170.7	17.3	2.55	0.75

SD: standard deviation; ms: milliseconds; µV: microvolt; RM: right mastoid; LM: left mastoid

Table 4. *t-test* of autistic versus normal children, right versus left, and females versus males in autistic children as a function of latency and amplitude of auditory MMN

	Latencies	p value	Amplitude	p value
Autistic versus normal	0.44	>0.05	0.041	<0.05*
Autistic children				
Right versus left	0.9	>0.05	0.67	>0.05
Males versus females	0.79	>0.05	0.69	>0.05

* Significant p<0.05

B-Correlative analysis between the MMN results and different parameters of psychometric and language evaluations among the autistic group.

A-Comparative Analysis

1- Results of Psychometric Evaluation

The demographic data of the autistic and normal children are presented in Table 1. There were no statistically significant differences in age, sex, performance IQ, and MA between the two groups, whereas there were highly significant differences in SA and CARS scores between school-age autistic and normal children (p<0.001).

2-Results of Language Tests

The delay in total language age of the autistic children group was 7.25±2.81 years below the age-appropriate language performance level, as measured by standard language tests, whereas the delay in

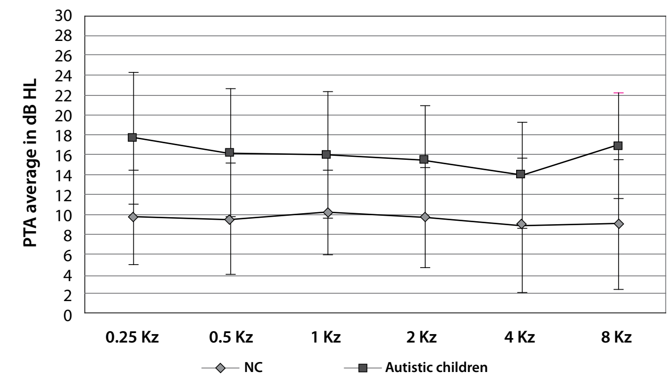

Figure 1. The mean pure tone audiogram of autistic and normal children. Error bars represent 1 SD above and below the mean
SD: standard deviation; NC: normal children

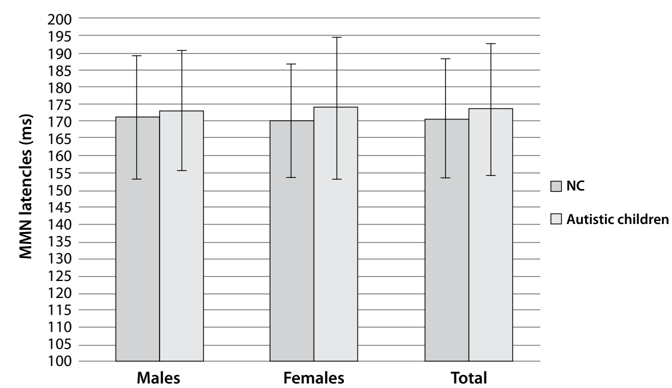

Figure 2. The mean MMN latencies measured from males and females and autistic and normal children. Error bars represent 1 SD above and below the mean
SD: standard deviation; ms: milliseconds; NC: normal children

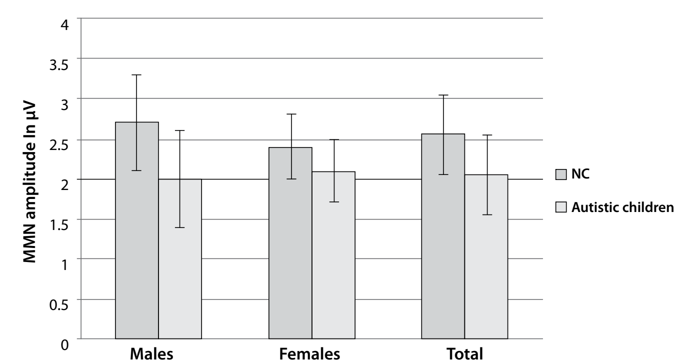

Figure 3. The mean MMN amplitudes measured from males and females and autistic and normal children. Error bars represent 1 SD above and below the mean
SD: standard deviation; µV: microvolt; NC: normal children

the receptive, expressive, prosodic, and pragmatic ages were as follows: 7.25, 8.62, 9.64, and 9.77, respectively, in these patients.

3- Results of Audiological Evaluation

The mean pure-tone audiogram for the autistic and normal children at frequency octaves 0.25 to 8 kHz as a function of hearing threshold level in dBHL is displayed in Figure 1. There were no statistically significant differences between the two groups (p>0.05). In this study, the mean latency of the MMN in normal children was 170.7±17.3 msec, while the mean amplitude was 2.55±0.75 µV. Figures 2 and 3

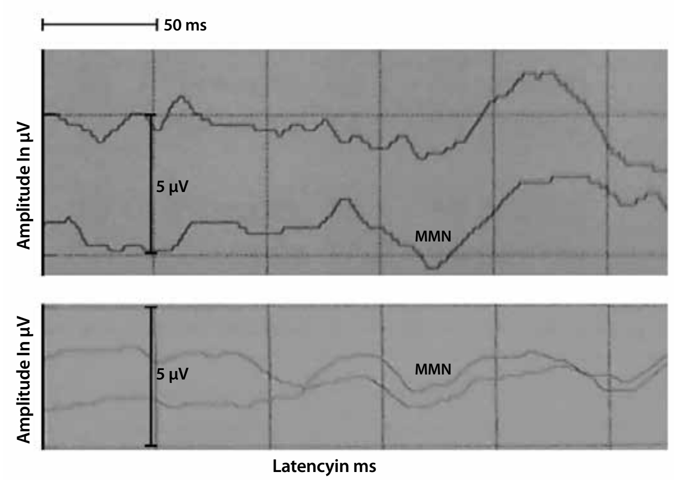

Figure 4. Mismatch negativity (MMN) waveform recorded from the left mastoid of a normal child on the upper trace, while the lower trace represents mismatch negativity (MMN) recorded from the right mastoid of an autistic child
µV: microvolt; ms: milliseconds

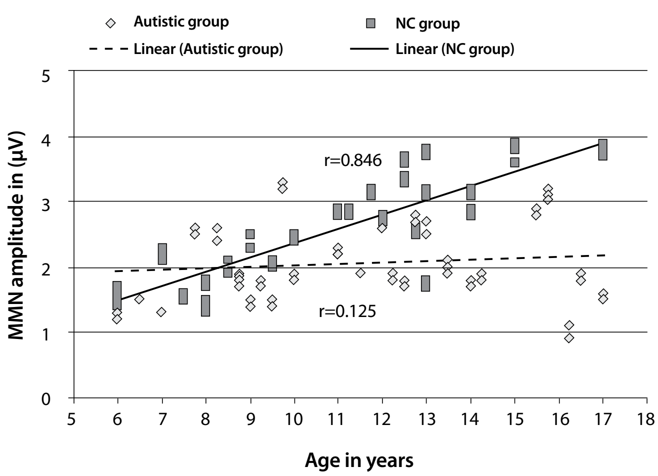

Figure 5. The correlation between MMN amplitudes and age in autistic and normal children
µV: microvolt; NC: normal children

show auditory MMN amplitudes and latencies for males and females of normal and autistic children. Figure 4 shows the auditory MMN waveform recorded from the left mastoid of a normal child on the upper trace, while the lower trace represents the MMN recorded from the right mastoid of an autistic child.

Table 3 shows the comparison between auditory MMN latencies and amplitudes recorded from the left and right mastoids in normal and autistic children. It was noticed that the amplitudes were lower and that the latencies were prolonged in autistic versus normal children. The reduced amplitudes were statistically significant at $p<0.05$. Table 4 shows the t-test of the autistic versus normal children and in the autistic group (right versus left and females versus males) as a function of latency and amplitude of auditory MMNs.

B- Correlative Analysis

Figure 5 reveals the correlation between MMN amplitude as a function of age for both groups. In the normal children group, the amplitude of MMN shows a trend to increase with age; this trend is not evident in autistic children. Figure 6 shows the correlation between MMN latencies as a function of age for school-age autistic and the normal age-matched group. The correlation between the MMN amplitude as a function of CARS score for normal and autistic children is shown in Figures 7 and 8, respectively. Figure 9 reveals the correlation between the MMN amplitude as a function of language age for autistic school-age children.

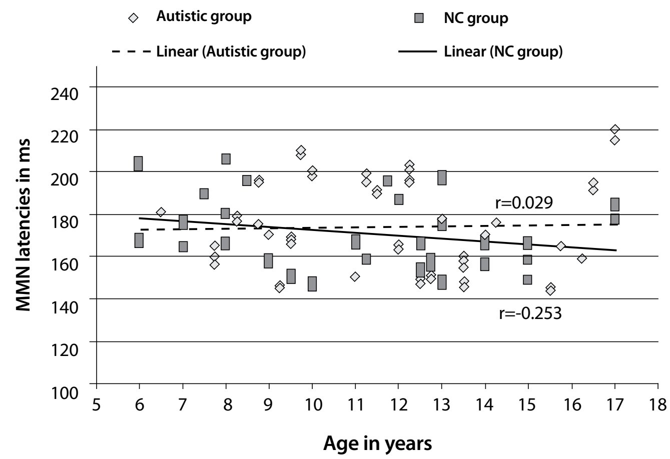

Figure 6. The correlation between MMN latencies and age in autistic and normal children
ms: milliseconds; NC: normal children

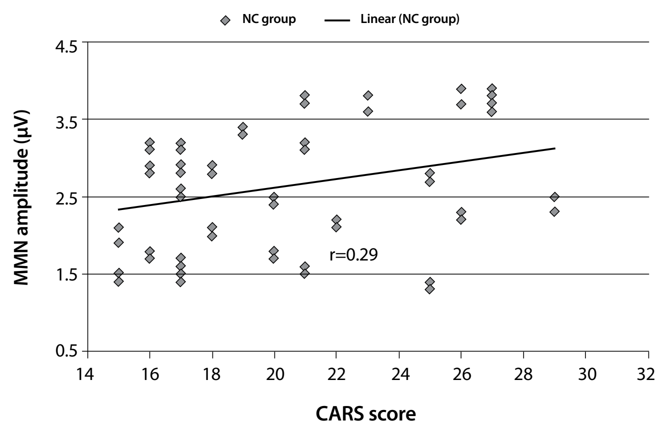

Figure 7. The correlation between MMN amplitudes and CARS score for normal children
µV: microvolt; NC: normal children

DISCUSSION

As MMN is a pre-attentive automatic response that can be elicited using a passive "oddball paradigm," it can be used as a tool for the evaluation of the pre-attentive process in children. In this study, MMN was used as an index of the presence or absence of pre-attentive process in autistic children to understand the nature of the problem and to compare them with normal chronological age-matched children.

The response of MMN represents some form of preconscious endogenous neural process in the brain, conditioned to respond to acoustic stimulus change [14]. It is a pre-attentive involuntary response that can be used as a tool for evaluating central auditory processing [15]. Sussman, 2007, postulated that as the MMN generation relies on multiple processing mechanisms that are part of a large system of

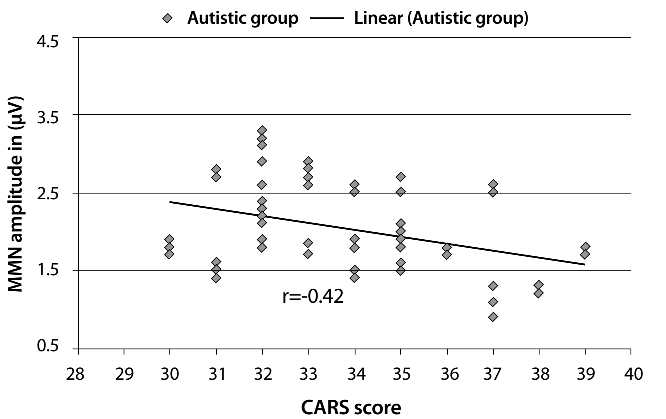

Figure 8. The correlation between MMN amplitudes and CARS score for autistic children
µV: microvolt

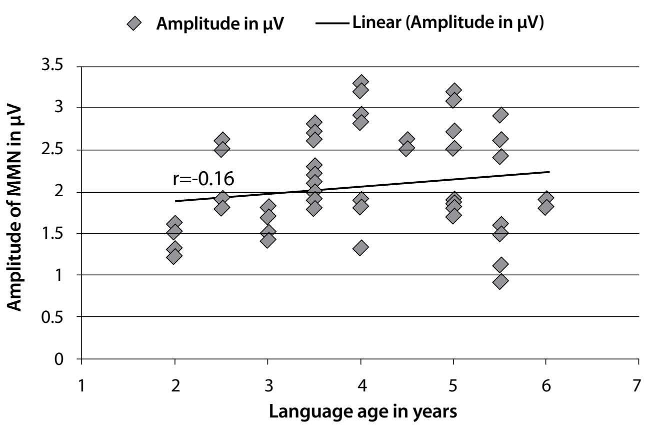

Figure 9. The correlation between the MMN amplitudes and language age for autistic children
µV: microvolt

auditory scene analysis, a new model proposes that the principal factor governing MMN is the sound context. In view of the fact that this large system can be modulated by attention, it can not be considered strictly pre-attentive. But, the direct attention influences on the deviance detection process are less clear, and the response is still considered an attention-independent process [16], and the MMN can be considered an auditory evoked response that is thought to represent the detection of stimulus change at a pre-attentive neurophysiological level [17].

In the present study, we addressed the relationship between the amplitudes of the auditory MMN with clinical scores for autism (CARS) and language parameters. In this study, there were highly significant differences between both groups in social age and CARS score ($p<0.001$). This is accepted and concurrent with the delayed language development and retarded social skills in autistic children as compared with non-autistic normal children.

In our study, all language parameters were delayed-mainly, the expressive, prosodic, and pragmatic skills. It has been postulated that children with autism have impaired ability to process rapid or brief sounds. They are less able to process rapid auditory information than children with normal spoken language skills. Deficits and/or differences in timing, magnitude, and topography of the neural activity associated with a child's auditory discriminative processes would have implications for higher-level cognitive processing of sound, which is necessary for language development [8].

Landa et al.[18] emphasized the importance of understanding the cognitive roots of pragmatics. The cognitive phenomenon that is most frequently investigated with language pragmatics in autism is the "theory of mind" deficit. It is the cognitive capacity necessary for understanding the mental states of another person [19]. Tager-Flusberg, in 1999, highlighted a close connection between the capacity of understanding other minds and the social use of language [20].

Our results suggest that children with autism do have auditory changes at the level measured by MMN, mainly the pre-attentive response. In this study, there were significant correlations between MMN amplitude and the language age, as well as CARS scores, for autistic children, and their latencies were prolonged. Finley et al. [21], 1985, used auditory event-related potentials in their investigation of children with cognitive disorders. They found that compared to normal subjects, children with organic cognitive problems had significantly longer latencies in event-related potentials than normal children. But, Gomot et al. [22], 2006, found shortened MMN latencies to pitch changes.

The results of this study agree with Dunn et al. [23], 2008, in which they found that the amplitude of MMN in children with autism was significantly smaller than in normal children in unattended conditions. Their findings support the idea of abnormal automatic auditory processing by children with autism. In a study by Ferri et al. [24], 2003, they found that MMN to a frequency deviant had a significantly larger amplitude in a group of mentally retarded autistic boys than in a group of age- but not IQ-matched boys. Gomot et al. [25], 2002, found earlier MMN in latencies to tonal deviants in children with autism than in normal children.

On the contrary, Ceponiene et al. [26], 2003, found that the MMN elicited from high-functioning children with autism was similar in amplitude to that elicited from normal control for frequency deviants in streams of synthesized vowels and complex and simple tones, suggesting that perhaps the MMN may be correlated to cognitive function in autism.

In the current study, we assumed that the auditory processing reflected by MMN responses was different in autistic compared with age-matched normal children. This suggests that their pre-attentive responses are unlikely the same as in normal children, but further studies are needed for both linguistic and nonlinguistic stimuli of various types to be presented and used as stimuli. Also, in addition to the evoked potential studies, further research involving simultaneous collection of behavioral and physiological data should also be considered.

In the present study, MMN amplitude was reduced in the autistic group in comparison with children with normal hearing and language development. This indicates that the neurophysiologic measures of auditory processing that reflect the pre-attentive response to tonal frequency changes in these children are different, hence, arguing for a doubt of the affection of the supposed origin of auditory MMN in autistic school-age children, which needs further research.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of ORL Department, Mansoura University, Egypt. & KFMMC Hospital, Dhahran, KSA.

Informed Consent: Written informed consents were obtained from the parents of all participated children in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: No conflict of interest was declared by the authors.

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