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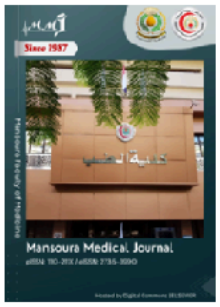

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Pre-attentive auditory responses in multiple sclerosis Patients

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- Mismatch negativity
- Multiple sclerosis
- Cognitive impairment

Abstract

Background :MS is characterized by impairment in cognitive domains. Sensory memory is one of the cognitive domains affected in MS. MMN allows the brain to detect (via a comparator mechanism) deviant events occurring within a stream of repetitive stimuli. The amplitude and latency of the MMN has been used to elucidate the nature of the sensory memory upon which it is based. Aim: This work was designed to evaluate and measure the MMN test results as regard its amplitude and latency in MS patients and to compare the results with normal age and gender matched control group in an attempt to declare the diagnostic and prognostic value of MMN in MS patients. Methods : Forty patients with multiple sclerosis (MS) were diagnosed and referred from the Neurology department. All participants in this study (forty MS patients and forty healthy subjects' sex and age-matched with MS patients) were subjected to basic audiological evaluation, mismatch negativity (MMN) recording using oddball paradigm with frequency variation, and Expanded disability status scale (EDSS) for MS patients. MMN amplitude and latency were measured in both MS patients and control subjects. MMN results were compared to MS and healthy control. Also, EDSS was measured in MS patients. The forty MS patients are divided into two subgroups: MS patients who produced an MMN wave and MS with absent MMN compared to the demographic data of both subsets. Results: A significant difference between the two subgroups in the duration of MS diagnosis was present. Also, there was a substantial difference between groups in sex. The subgroup with absent MMS was all male. Meanwhile, no considerable difference between both groups as regards age and EDSS. There is no difference in MMN latency and amplitude between MS patients with preserved MMN and control groups. Twenty percent of our MS patients have absent MMN, which is all-male reflecting cognitive impairment, cognitive fatigue, or central processing disorders. In contrast, there is no difference in latency and amplitude between recorded MMN in the study and control groups. Conclusions: The absence of MMN in some MS patients suggests affection of the central auditory processing abilities measured by MMN in those patients which need further research

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INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) within different degrees of disability [1]. MS is the most prevalent chronic inflammatory disease of the central nervous system which affects over two million people worldwide [*2]*.

Relapsing-remitting MS (RRMS) constitutes about 90% of patients, typically followed by a progressive course, while about 10% of patients are presented with primary progressive disease from the start [1]. MS doesn't follow a specific, expected path. Cortical affection in MS is associated with disease progression and cognitive impairment *[3]*.

The cause of MS is unknown, but some triggers and risk factors have been found to increase the risk of MS, such as family history, Epstein Bar virus, and vitamin D deficiency [*4]*.

MS symptoms are inconsistent. They include fatigue, abnormal sensations as paresthesia (tingling or "pins and needles"), muscle stiffness, tremors, numbness, dizziness, and even paralysis (usually in the legs*) [5]*. MS patients may be more likely to have hearing loss in the low (250-750 Hz) and high (3000-8000 Hz) frequencies *[6]*.

Event-related potentials (P300) showed abnormalities in MS patients suggesting impairment in cortical regions and dysfunction in cognitive processing, memory, attention, and auditory discrimination *[7]*. Mismatch negativity (MMN) is one of the cortical event-related evoked potentials. It is a brain response to violations of a rule established by a sequence of sensory stimuli (typically in the auditory domain) *[8]*. The MMN measures enable one to gain insights into the neurobiological substrate of central auditory processing, especially into auditory memory as well as to various attention-related processes controlling the access of auditory input to conscious perception and higher forms of memory [*9-11]*. About 40% to 70% of MS patients have varying degrees of cognitive impairment [12]. A study by Chinnadurai et al. [13] showed that cognitive fatigue is prevalent in MS patients and implies that MS may be a multifaceted entity. As the MS can affect cognitive abilities, it is assumed that the pre-attentive auditory responses could be affected in those patients.

MMN was recorded from MS patients in multiple studies with no conclusive results [14,15]. Accordingly, this study is designed to solve this point. Thus, the purpose of this study is to evaluate and to measure the MMN test results regarding the amplitude and latency in MS patients and to compare the results with average age and gender-matched control group to declare the cognitive function in MS patients.

Methods

This comparative study was carried out on MS patients at the Audiology Unit, Otorhinolaryngology Department, University Hospital.

Forty patients with MS (study group)

were diagnosed and referred from the Neurology department, University Hospital to Audiology Unit, in the period from November 2015 to March 2019. Patients were diagnosed according to the revised McDonald criteria of MS [16]. The inclusion criteria of patients in this study were 1) bilateral normal hearing sensitivity (normal audiogram from 250 to 8000 Hz) 2) bilateral type A tympanogram with intact acoustic reflex. Patients were excluded based on 1) the history of other neurological diseases, 2) those who have hearing impairments, and 3) the account of ototoxic drug intake.

Forty healthy subjects (control group) without any audiological or neurological disease were matched with the study group for gender and age to provide a normative database. The same exclusion criteria for the patients were applied.

Equipment included 1) Sound-treated room locally made; 2) Two-channel audiometer, Orbiter 922, Madsen electronic, version 2 (Denmark); 3) Immittancemeter, GSI middle ear analyzer, version 2 (USA); and 4) Biologic Auditory Evoked Potential, Navigator Pro, version 7.2.1 (USA).

All patients were treated with the same treatment according to the best current knowledge in clinical routine. The test session lasted for about one hour, including the basic audiological testing and auditory evoked response recording.

All participants gave a detailed clinical history, including full medical, audiological, and neurological history. They were questioned for the family history of audiological and neurological disorders. Otoscopic examination of the external auditory meatus and tympanic membrane was done.

All participants in this study were subjected to:

A) basic audiological evaluation including 1) air conduction thresholds (for an octave frequency ranging from 250 to 8000 Hz); 2) bone conduction for the frequency range 500-4000 Hz); 3) speech audiometry: including speech reception threshold and word discrimination score (WD); and 4) Immittancemetery including tympanometry and acoustic reflex thresholds.

B) MMN recording done using oddball paradigm (frequency variation paradigm) including:

1) stimulus parameters including i) tone burst 1000 Hz as a standard stimulus, and 1500 Hz tone burst as a deviant stimulus; ii) stimuli were presented at 70 dBnHL; iii) repetition rate (R.R) was 1.1/s with alternating polarity; vi) stimuli were presented monaurally to both ears via an ER3A -insert phone; v) sweep number was 50 sweeps and probability was 80% for the standard stimuli and 20% for the deviant stimuli; and iv) both standard and deviant tones had 10 ms of ascending and descending linear time, with 30 ms plateau;

2) recording parameters including i) electrode montage; four disposable electrodes were used after skin preparation as follows: one

high frontal Fz (positive electrode), one low frontal Fpz (ground electrode). The last two electrodes were placed on the left and right mastoids (as a negative electrode or reference electrode), and ii) recording time window was (0- 533 msec) with filtering 1 to 30 Hz;

3) The procedure of MMN recording was explained to all participants. Every participant was instructed to lie down calmly on a comfortable couch. They were introduced in a silent video. At the same time, they were told not to concentrate on the presented stimuli; and

4) data manipulated as the following: i) MMN calculated in the different waveform. The trace that occured in response to the standard stimulus alone was subtracted from the deviant stimulus response ready added to the new buffer presented within the oddball paradigm. The resulting difference between the standard and the deviant traces represents the MMN responses, identified visually as the most prominent negativity following N100 occurring between 100 and 250 ms, and ii) the response parameters of MMN determined as the following: a) MMN latency, that is the time from stimulus onset to the most negativity following N100 occurring between 100 and 250 ms, b) MMN amplitude, that is typically measured from the zero voltage of the trace to the most negative trough that follows N1 (figure 1).

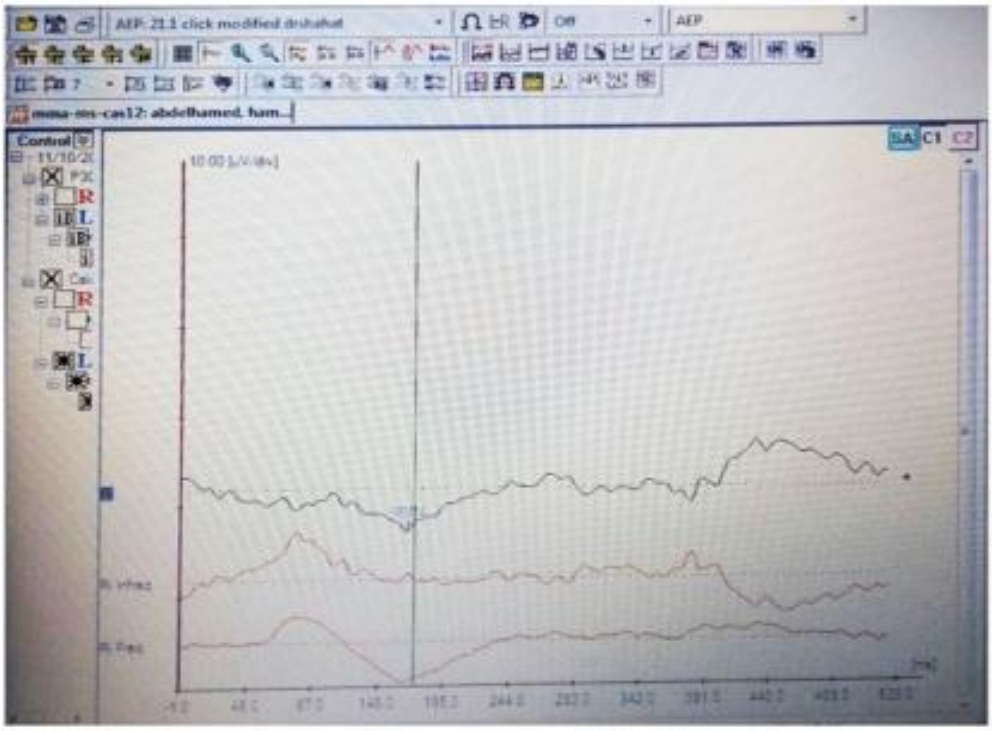

Fig. 1: MMN recordings in the Audiology Unit, Mansoura University Hospital (Biologic Auditory evoked potential navigator pro).

C) Expanded Disability Status Scale (EDSS) was measured in MS patients. EDSS consists of an ordinal rating method ranging from 0 (normal neurological status) to 10 (death due to MS) in 0.5 incremental intervals (when reaching EDSS). The lower values of the EDSS measure impairments based on the neurological evaluation. While > EDSS 6 measures MS patients handicapped. EDSS determination 4 – 6 is dependent on aspects of walking ability.

Statistical Analysis

Data tabulated, coded, and analyzed using the computer program SPSS (Statistical package for social science) version 23.0. Frequency, mean, standard deviation (SD), median, and minimum-maximum were used to describe data. Student's t-test (Unpaired) used to compare between means of two different groups of numerical (parametric) data. Student's t-test (Paired) is used to compare the mean of two related groups of numerical (parametric) data. Mann-Whitney test used to compare two different groups of numerical (non-parametric) data. The sign test is used to compare two related groups of numerical (non-parametric) data. Inter-group comparison of categorical data is performed by using chi-square test. Spearman's correlation coefficient test is used to correlate different parameters. The threshold of significance is p-value < 0.05.

Results

This study included 40 MS patients and 40 age and gender-matched persons were selected as a control group. The mean age of the study group was (32.2±5.97) years, while that of the control group was (29±6.5) years. Also, the number of subjects in the age group from 20-30 years in the study group was [8(20%)] and in the control group was [7(35%)]. The number of subjects of the age group from 23-40 years in the study group was [28(70%)] and in the control group was [22(55)], while the number of subjects of the age group from 20-30 years in the study group was [4(10%)] and in the control group was [4(10)]. The males in each group were 16(40), while the females in each group were 24(60). There is no statistical difference concerning age, gender, and age groups in study and control groups ($p > 0.05$).

The duration of MS illness (median-IQR) is 14 months (12.0-18.0). The EDSS of MS patients (mean ± SD) is 2.25 ± 1.50-3.50.

The study group was divided into two subgroups: MS patients who produced an MMN wave (group A) and MS patients with absent MMN (group B). As regards comparing the demographic data of (group A) and (group B). A significant difference between the two groups in the duration of MS diagnosis was present with a more extended period in group A. Also; there was a substantial difference between groups in sex. Group B was all male. Meanwhile, no considerable difference between both groups as regards age and EDSS. In our study, MMN components were absent in 20% of our MS patients. Meanwhile, it was detected in all healthy controls. As regards MMN latency, there

is no significant difference in MMN latency between the two groups (Table 1).

Table 1: Demographic & baseline data of studied groups of MS.

Item	Study group				P value
	Present MMN(A) n=32		**Absent MMN(B)** n=8		
Age (mean ± SD)	32.00 ± 6.39		33.00 ± 4.62		0.77
Gender **Male** **Female**	8(25%) 24(75%)		8(100%) 0(0%)		0.0001*
Duration of MS diagnosis (months) **Median** **Min-max**	14.00 12.00-18.00		6.50 1.00-12.00		0.049*
EDSS **median-** **Min-max** **]**	2.25 1.50-3.50		3.00 1.50-4.50		0.6
Total no (%)	32	80%	8	20%	40 (100%)

*P significant if p < 0.05 SD: Standard deviation

As regards gender there was not significant difference between the study and control groups in MMN latency (p>0.05) (figure 2).

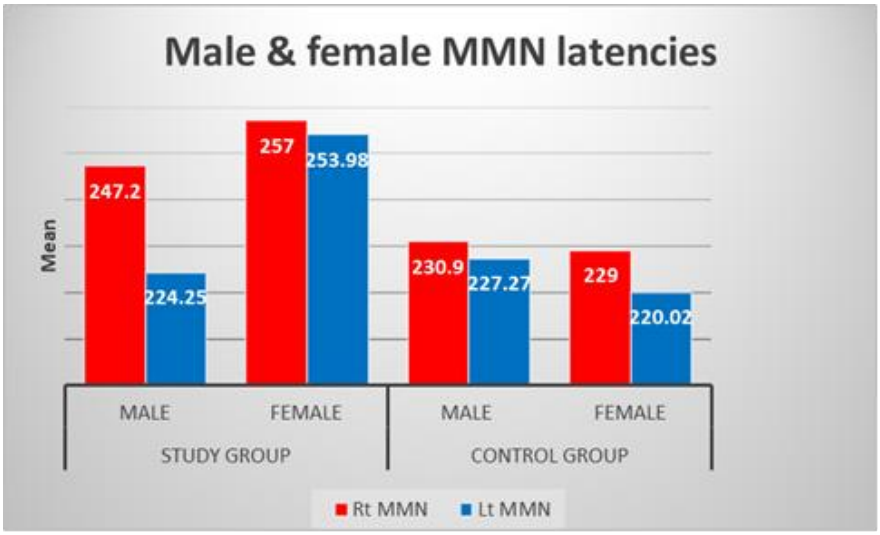

Fig. 2: Comparison between male & female according to MMN latency within studied groups.

There was no latency difference between MMN of the study and the control groups. Besides, there was no respectable difference of MMN latency in the right and left ear inside both groups, respectively (Table 2).

Table 2: Comparison between right & left ear in studied groups as regards MMN latency.

Item	Ear				P-value
	Rt		Lt		
	Mean	± SD	Mean	±SD	
Study	234.98	26.97	227.04	21.14	0.11
Control	238.20	26.73	233.60	27.54	0.27
p-value	0.7		0.4		

P significant if $p < 0.05$ SD: standard deviation

There was no statistically difference between the study and control groups in MMN amplitude. Besides, MMN amplitudes compared to the right and left ear inside each group showed no significant difference between the study and control groups, respectively (Table 3).

Table 3: Comparison between right & left ear in studied groups as regards MMN amplitude.

Group	Ear				P-value
	Rt		Lt		
	Median	Min-max	Median	Min-max	
Study	2.04	1.67-4.15	3.12	1.75-3.44	0.077
Control	1.89	1.65-3.37	1.89	1.50-2.30	0.11
p-value	0.80		0.16		

*P significant if $p < 0.05$

There was no statistically significant difference between gender in the study and control groups regarding MMN amplitude (Table 4).

Table 4: Comparison of MMN amplitude between male & female in studied groups

MMN amplitude	Study		p-value	Control		p-value
	Sex			Sex		
	Male	Female		Male	Female	
Rt Median	3.31	2.04	0.37	1.97	1.67	0.2
RT Min-max	1.78-4.84	1.55-3.60		1.89-2.69	1.59-4.30	
Lt Median	3.51	2.72	0.17	2.09	1.78	0.38
Lt Min-max	2.94-4.08	1.37-3.40		1.89-2.21	1.50-4.00	

P significant if $p < 0.05$

There was a moderate negative correlation between EDSS and MMN latency. A moderate negative correlation between MMN latency & amplitude, and also, duration of illness and EDSS. However, the correlation was statistically non-significant ($p > 0.05$) (Table 5).

Table 5: Correlation between duration of illness, EDSS, and MMN latency & amplitude.

Item		MMN Amplitude	Duration of illness (month)	EDSS
MMN latency	**R**	-.429	.209	-.466
	P	.098	.438	.069
MMN Amplitude	**R**		-.110	.295
	P		.684	.268
Duration of illness (month)	**R**			-.380
	P			.147

P significant if $p < 0.05$

Discussion

Cognitive impairment is a common finding in MS, mostly affecting attention, information processing speed, and recent memory. It occurs even in the absence of classically expected neurologic symptoms known as isolated cognitive relapses [17]. Multiple studies have revealed cognitive impairment progression over time in numerous MS disease courses, even in the absence of clinical disability [18].

MMN is one of the objective measures of auditory discrimination and sensory memory [8]. MMN may be useful for understanding the factors of cognition in various disorders and serves as an indicator of risk [19].

In this study, MMN was absent in 20% of the study group. Meanwhile, it was detected in all subjects of the control group. The presence of MMN in all healthy control subjects agrees with multiple studies [20-22]. The remaining 80% of the study group showed no significant difference in the latency and amplitude than in the control group.

This study results concur with Santos et al. [15]. They tested forty MS patients and found that MMN was absent in 40% of MS individuals using various duration protocols and 55% with multiple frequencies. In cases where MMN was present, there were no statistically significant differences in latencies and amplitudes compared to the control group. The present results also correlated with Jung et al. [14]who studied forty-six MS patients in which MMN was absent in 6.3% of MS patients that were

cognitively intact and absent in 16.6% of MS patients that were cognitively impaired when tested by a Paced Auditory Serial Addition Task (PASAT). The latencies of MMN were not statistically different between the study and control groups. Worth to mention that the MMN area in cognitively impaired patients was half of the MMN area in cognitively unimpaired patients. They also explained the absence of MMN in MS patients due to cognitive impairment indicated by the poor performance of PASAT.

The absence of MMN in MS patients could be explained by the assumption that cognitive impairment develops in MS patients, with larger impairment in cognitive domains of mood status, memory, and learning [23]. MMN is considered a secondary index for cognitive dysfunction [24]. An explanation that both Santos et al. [16] and Jung et al. [15] have adopted to interpret their findings. The differences in the methodology between our study and the previous two studies provide the power to improve our compatible results. The sample size of these studies was significant, they included all types of MS in their research, and the average EDSS was high.

Another possible explanation is whether the absence of the MMN wave is considered abnormal or not. Dijk et al. [25] observed that abnormality of ERPs is defined based on prolonged latencies, or absence of peaks. However, these changes were not harmonious and occurred in the patient and the control group. Bishop & Hardiman [26] have questioned the lack of mismatch response as an index of abnormality. It is believed that the presence of MMN is more relevant diagnostically rather than its absence. As some normal-hearing individuals also showed an absent MMN. However, Schwade et al. [22] recorded MMN in all studied healthy normal-hearing individuals. Interpretation of the presence of MMN in all healthy control groups strengthens the speculation of cognitive dysfunction in our MS group with absent MMN. Consequently, absent MMN in MS has an indicator of cognitive dysfunction in those patients.

A third possible explanation for the absence of MMN waves is (cognitive fatigue). It typically takes about one hour to record MMN waves, including preparations and electrodes for applications. Even in young adults, the MMN amplitude begins to attenuate after 1 to 2 hours on average [27]. Cognitive fatigue has been previously reported in MS, including temporal fatigue [13].

The insignificant difference detected in MMN latency and amplitude between study and control groups could be explained by the fact that MS plaque may not be affecting the generators of MMN (frontal and temporal). Another possible explanation is that even if the plaque is located on the generator site of MMN, the central auditory system has internal redundancy and compensatory mechanisms that may overcome any damage developed by slowly developing lesions [28].

Another explanation could be that the present study used an oddball paradigm using frequency deviance (Standard: 1000 Hz & Deviant: 1500 Hz). The auditory cortex has a tonotopic organization from low to high frequencies [29]. It assumes that even if the plaque is located over the temporal auditory cortex, it may be overlapping area neurons representing frequencies other than the frequencies used in the current study (1000 Hz, 1500 Hz).

In the running study, the MMN latency and amplitude compared right and left ears inside each group. Either study and control revealed no significant difference. This result follows the results observed by Schwade et al. [22] and Brückman & Garcia [30] who tested MMN in normal-hearing individuals and found no statistically significant difference between ears and no significant statistical difference between ears for both right-handed and left-handed groups.

The current study tested the effect of gender; there was no significant difference between males and females, which did not agree with Aaltonen et al. [31], who found that latency is longer in females than males. We explain this by the different stimuli used by the researchers as they used complex stimuli. In our study, absent MMN in male patients (20%). Lublin [32] stated that male MS has an unfavorable prognosis. This observation makes our assumption of poor prognostic outcome of MS patients with absent MMN.

The EDSS describes disease progression in MS patients and to assess the effectiveness of therapeutic intervention in clinical trials [33]. There was no correlation between the duration of MS illness or EDSS and the latency and amplitude of MMN in our study. Regarding the natural history of MS, Weinshenker [34] observed an average change of 0.5 points on the EDSS scale in a year in MS. A definite recommendation on interpreting varieties in EDSS value does not exist yet. EDSS changes by 1.0 points from a baseline EDSS equal or less than to 5.5. While 0.5 points over a baseline, 5.5 is commonly recognized as a clinical increase in disability. However, it is more accurate to define disability change as a sustained change for 12 weeks or, even more reliably for 24 weeks.

On the other hand, the current results are opposed to Newton et al. [35] Who observed that patients with a longer duration (average 10 years) of MS illness have significant physical and cognitive disabilities. This can be explained by noting that all our patients were RRMS and mean duration of disease (14 months).

In conclusion, twenty percent of our MS patients have absent MMN, all-male reflecting cognitive impairment, cognitive fatigue, or central processing disorders. While there is no difference in latency and amplitude between recorded MMN in study and control groups. We recommend the MMN test in the complementary diagnostic protocol and follow-up protocol of MS.

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