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## Middle and Long Latency Auditory Evoked Potentials and Their Usage in Fibromyalgia and Schizophrenia

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### 1. Introduction

#### 1.1 Middle and long latency auditory evoked potentials and their usage in fibromyalgia

FM is a chronic syndrome that occurs predominantly in women and is marked by generalized pain, multiple defined tender points, fatigue, disturbed sleep, cognitive difficulty, and numerous other somatic complaints. The etiology and pathophysiology of FM remain unclear. Despite extensive research, no structural pathology has been identified in muscles or other tissues. The general and widespread nature of pain in FM strongly suggests the involvement of central mechanisms (Williams et al., 2006). Although psychological factors associated with chronic distress appear to be important for the development of FM in many patients, abundant evidence now indicates that pain in FM reflects abnormal pain processing in the central nervous system (ie. central sensitivity) (Herrero JF et al., 2000, Staud R. et al, 2001). Recent research suggested that FM patients might have deficiencies in central inhibitory mechanisms, such as diffuse noxious inhibitory control or the endogenous pain inhibitory system. Nevertheless, little is yet known about the brain mechanisms involved in the processing of nonpainful somatosensory information in FM (Monyoto P et al., 2006, Julien N. Et al., 2005).

Central mechanisms related to pathophysiology and hypervigilance have long been discussed for fibromyalgia. Nevertheless, research into this issue has been inconclusive so far. Our aim to design this study (Turker et al., 2008) was to determine whether central mechanisms played an important role in fibromyalgia via examining brain activity elicited by auditory evoked potentials in patients with FM and to assess relationship with clinical variables.

Middle latency evoked potentials (Middle Latency Auditory Evoked Potentials) are composed of several components that can be recorded from 10 to 50 msec after stimulus onset. The most stable components are Na and Pa, with latencies between 16-30 msec and 30-45 msec, respectively. Most of the MLAEP complex is thought to originate near the auditory cortex, although No, Po and Na may be generated by subcortical structures.

## 1.2 Patients and methods

33 female patients with a diagnosis of FM and 37 healthy women participated in the study. All patients met the American College of Rheumatology (ACR) criteria for FM (Wolfe et al., 1990).

Eighteen tender points accepted by the ACR for FM were evaluated. Each tender point was rated from 0 point (no pain) to 3 points (most severe pain). The sum of the 18 tender points was calculated as the total myalgic score (TMS). Other symptoms of FM were evaluated by using the Fibromyalgia Impact Questionnaire (FIQ) and Health Assessment Questionnaire (HAQ) (Küçükdeveci et al., 2004, Bennett et al., 2005). The HAQ functional disability index was used to assess functional status. The instrument asks 24 questions regarding 8 activities of daily living areas.

The FIQ is a 20-item, self report instrument that measures multiple symptoms, functioning, and overall well-being. The first 10 items comprise a physical functioning scale; each item is rated on a 3-point Likert-type scale. On items 11 and 12, subjects indicate the days that they feel well or miss work because of fibromyalgia symptoms. Items 14 through 20 rate the difficulty in performing their job responsibilities, pain, fatigue, morning tiredness, stiffness, anxiety, and depression on a 10-cm visual analog scales (VAS). All subscores with the exception of the two work-related scores and physical function score were summed to yield the total score of fibromyalgia impact, which ranges from 0 (no impact) to 70 (maximum impact). Global disease severity was assessed with visual analogue scale (VAS) (0=very good, 10=very poor). The Hamilton Rating Scale for Depression and Hamilton Rating Scale for Anxiety were used to evaluate the affective condition of patients with FM (Hamilton et al., 1967).

Patients were excluded if they had evidence of traumatic injury, inflammatory rheumatic disease, a history of seizure, head trauma, or cerebrovascular disease; a lifetime history of psychosis, or dementia; alcohol or substance dependence; if they received psychiatric treatment in the last 3 weeks or if there was a history of auditory impairment.

## 1.3 Evoked potentials recording procedure

All recordings of MLAEPs were performed at Dantec Keypoint. Electrode montage was adjusted as active electrode placed on ipsilateral mastoid and reference and ground electrodes at Cz and Fz, respectively. Silver surface electrodes were used for reference and ground electrodes. A scalp needle electrode was used as active electrode. Alternating clicks of 100  $\mu$ sec duration were used and polarity was adjusted as vertex. The frequency of stimulation was 10/sec and the filtering was chosen as 10 Hz–200 Hz. Analysis time (sweep length) and sensitivity were 100msec and 0,2  $\mu$ v/d, respectively. The intensity of the stimuli was chosen according to the auditory threshold. The ipsilateral ear was stimulated with an intensity of stimulus such as hearing threshold plus 60 DB, while the contralateral ear was masked with white noise. Averaging of 1000 signals was performed twice and overlapped for each ear. No, Po, Na, Pa, Nb, and Pb were sampled and latencies and amplitudes of each potential were determined and compared with age and gender matched controls. MLAEPs recordings were performed bilaterally i.e. 30 recordings were performed for patients and 30 recordings were performed for controls making a total of 60 recordings. No artifact rejection was employed. As hearing impairment can alter the MLAEPs, prior to beginning testing, the external ear canal was checked with an otoscope to assure that the canal was not blocked by cerumen. Patients with hearing problems assessed by otologic tests were excluded. MLAEPs

are known to be affected by medications, however all patients were under treatment and there was no other way to investigate them. Recordings of MLAEPs and LLAEPs (Long latency auditory evoked potentials) were performed for both patients and controls, using an active electrode placed on ipsilateral mastoid and reference and ground electrodes at Cz and Fz, respectively. Binaural stimulation was performed for LLAEPs. No, Po, Na, Pa, Nb, and Pb were sampled for MLAEPs. N1, P1, N2 and P2 were sampled for LLAEPs. Latencies and amplitudes of each potential were compared with those of controls and correlation between clinical and electrophysiological parameters were investigated statistically. Our study was approved by the local committee of ethics.

1.4 Statistical methods

Statistical evaluation of data was performed via using descriptive statistical methods such as mean and standard deviations while student T test was used for quantitative data showing normal statistical distribution. Pearson and Spearman’s correlation analysis methods were used to investigate the correlation between latencies of MLAEP and clinical parameters. The results were evaluated at a confidency interval of 95% and a statistical significancy of  $p < 0.05$ . Comparisons between groups were made using the chi-square test for categorical variables. No statistically significant differences were recognized in the comparison of demographical data (age, disease duration, education, occupation, education level and marital status) between the groups. Clinical measures of patients are shown in table 1.

Clinical parameter	Mean ± SD
HAQ (0-3)	0,87 ± 0,48
Number of tender points(11-18)	14,90 ± 4,14
Total myalgia score	35,09 ± 13,22
Anxiety score	23,06 ± 9,75
Depression score	19,15 ± 8,94
Global disease severity(0-10)	6,72 ± 1,89
	Mean ± SD
FIQ Total (0-70)	51,57 ± 15,08
Physical function score (0 – 30)	11,63 ± 5,49

HAQ: Health Assesment Questionary FIQ: Fibromyalgia Impact Questionaire

Table 1. Clinical measures of patients.

1.5 Results

The latencies of Na, Nb and Pb of MLAEPs in the patient group were statistically longer when compared with those of the healthy controls ( $p < 0.05$ ,  $p < 0.01$  and  $p < 0.01$  respectively). However No, Po and Pa did not show any statistical significant difference between the groups (Student t test). Latency of Na had statistically significant positive correlations with disease duration, FIQ total score, physical score and number of tender points ( $p < 0.05$ ). Latency of Pa had statistically significant positive correlations with age, disease duration, FIQ total score, physical score and FIQ 2, FIQ 3, FIQ 4 and FIQ 6 ( $p < 0.05$ ,  $p < 0.01$ ,  $p < 0.05$ ,  $p < 0.05$ ,  $p < 0.01$ , and  $p < 0.05$  for the rest respectively) (Figure 1). Latency of Nb had

statistically significant positive correlations with disease duration ( $p<0.05$ ) (Figure 2), FIQ total score ( $p<0.05$ ), FIQ 2 ( $p<0.01$ ), FIQ 6 ( $p<0.05$ ), global disease severity ( $p<0.05$ ). Latency of Pb had statistically significant positive correlations with FIQ total score ( $p<0.05$ ), FIQ 2 ( $p<0.05$ ) and global disease severity ( $p<0.05$ ) (Pearson and Spearman’s correlation tests). Evaluation of groups regarding parameters of LLAEP showed that latencies of P1, N2 and P2 were statistically longer when compared with those of the healthy controls ( $p<0.05$ ,  $p<0.01$  and  $p<0.01$  respectively) whereas N1 did not show any statistical significance between the groups (Student t test).

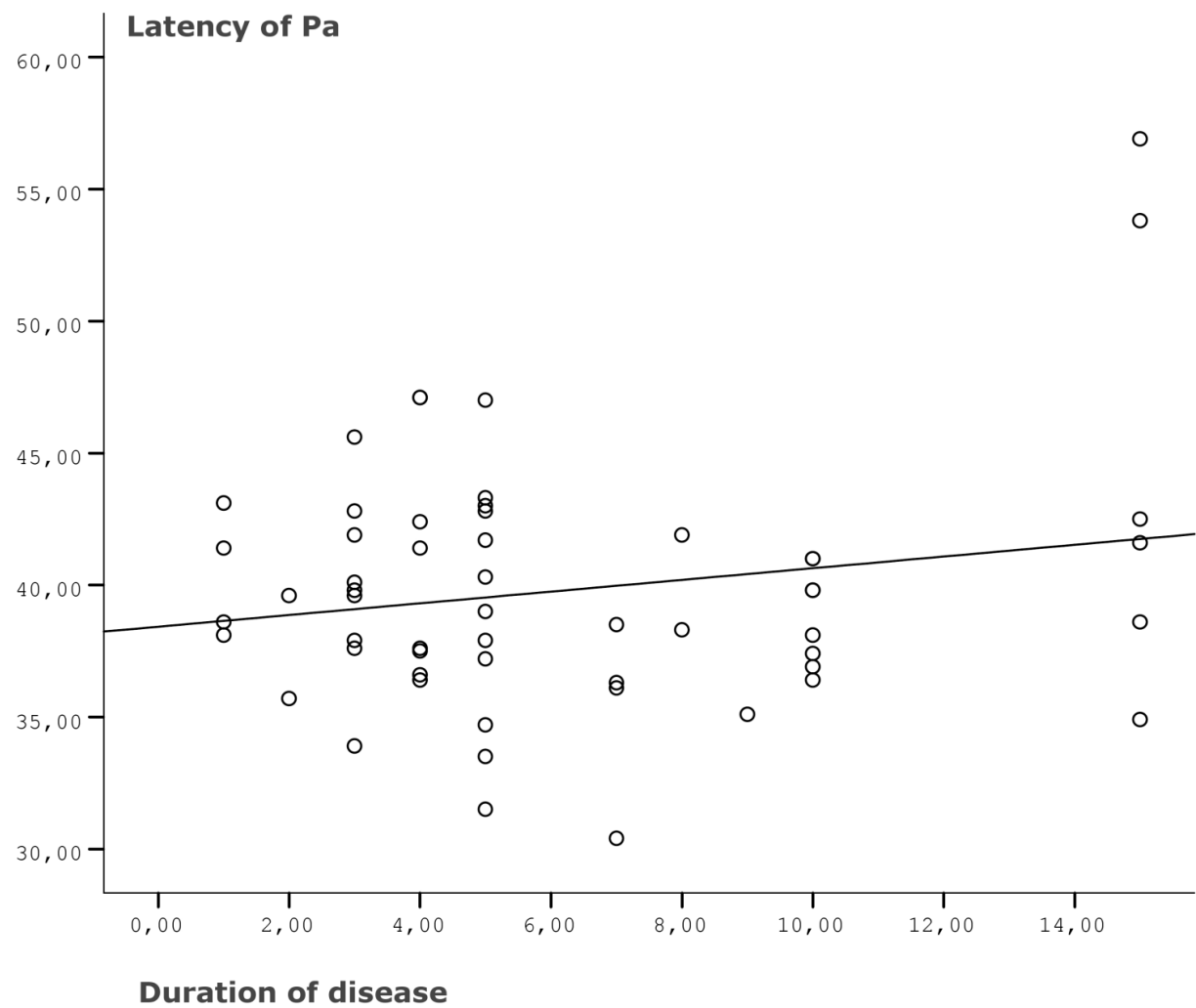


Fig. 1. Correlation analysis of Pa latency and disease duration.

Correlation studies of latencies of LLAEPs with clinical parameters showed that FIQ total score had a positive and statistically significant correlation with latency of N2 ( $p<0.05$ ), while the same was valid for physical score and FIQ2 with latency of N1 ( $p<0.05$ ). FIQ 5, 7 and 8 were positively correlated with latency of N2 ( $p<0.05$ ,  $p<0.01$  and  $p<0.01$  respectively), while FIQ 9 and 10 were positively correlated with latency of N1 ( $p<0.01$ ,  $p<0.05$  respectively). HAQ and anxiety score had positive correlations with latency of N2 ( $p<0.05$ ).

The amplitudes of Po, Pa and Nb of MLAEPs and P1, N1, P2 and N2 of LLAEPs in the patient group were statistically significantly very low when compared with those of the healthy controls ( $p<0.01$ ) (Student t test). However, there were not any statistical significant differences of amplitudes of MLAEPs and LLAEPs between patients having different disease durations. Patients suffering from fibromyalgia for five or more than five years did not show statistically higher or lower amplitudes when compared with patients having the disease for less than five years. Patients having myalgia scores equal or more than 40 also did not show any statistical differences of amplitudes of MLAEPs and LLAEPs when compared with patients having myalgia scores less than 40. Patients having anxiety scores equal or more than 25 were also compared with the ones having scores less than 25 and no statistically significant differences of amplitudes were found. Same results were obtained when patients were compared regarding latencies of both MLAEPs and LLAEPs.

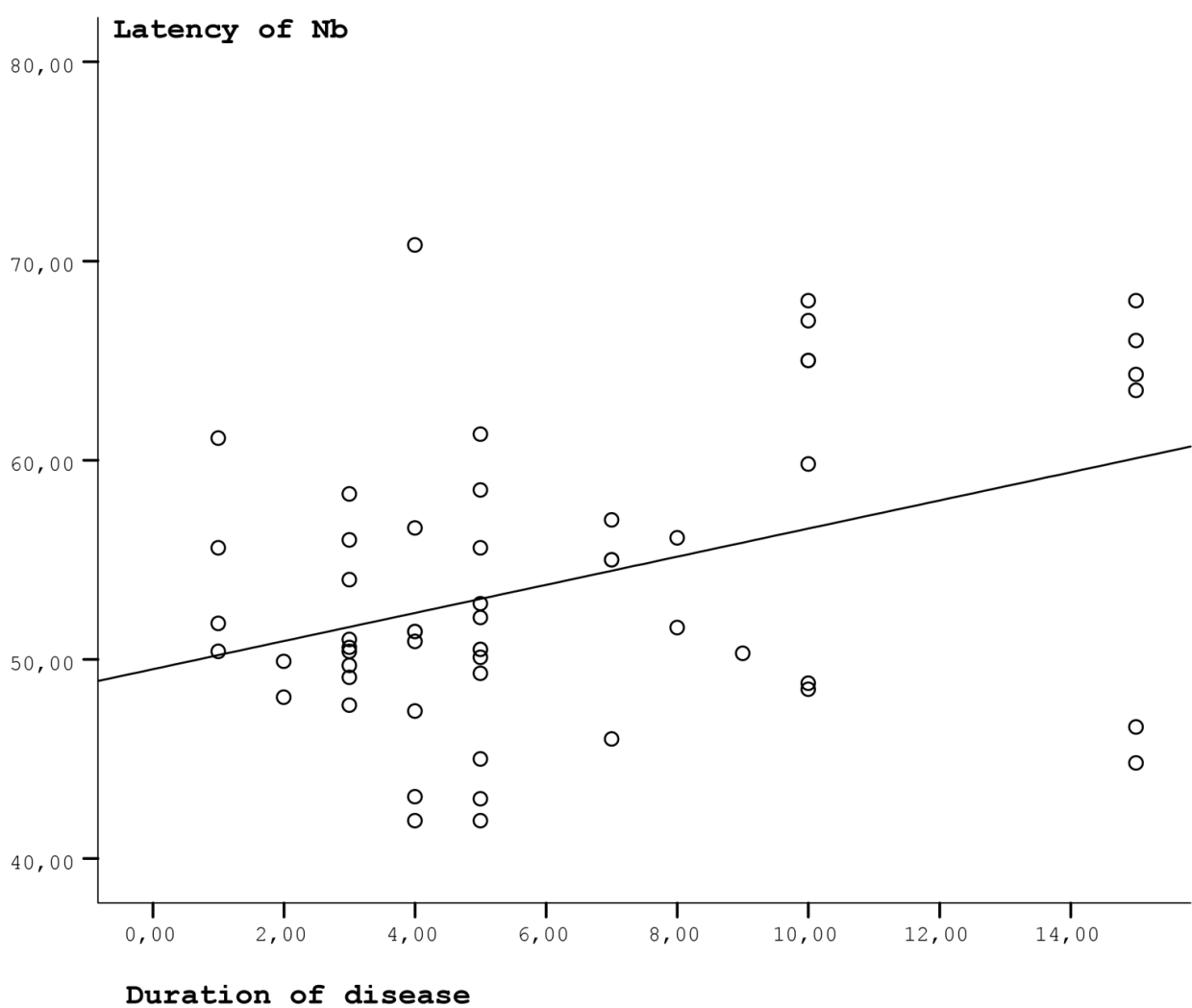


Fig. 2. Correlation analysis of Nb latency and disease duration.

A LLAEP trace of one of the patients with long latencies is shown in Fig. 3.

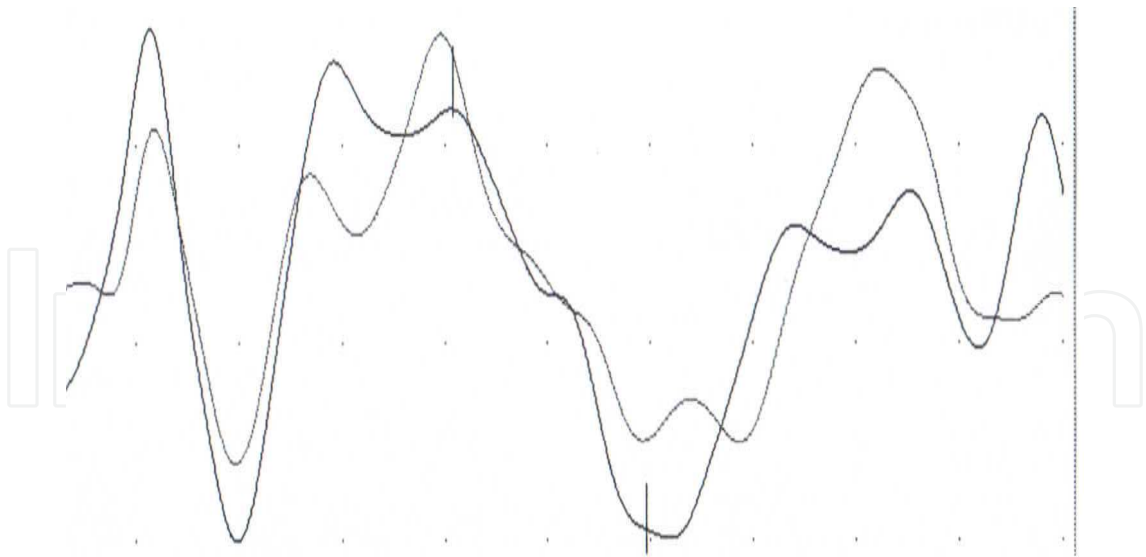


Fig. 3. A LLAEP trace of one of the patients with long latencies.

Correlation studies of amplitudes of LLAEPs with clinical parameters did not point out to any results of statistical significance, whereas only one electrophysiological parameter in MLAEP amplitudes did. Amplitude of No showed a negative correlation with number of tender points ( $p<0.05$ ) (Figure 4).

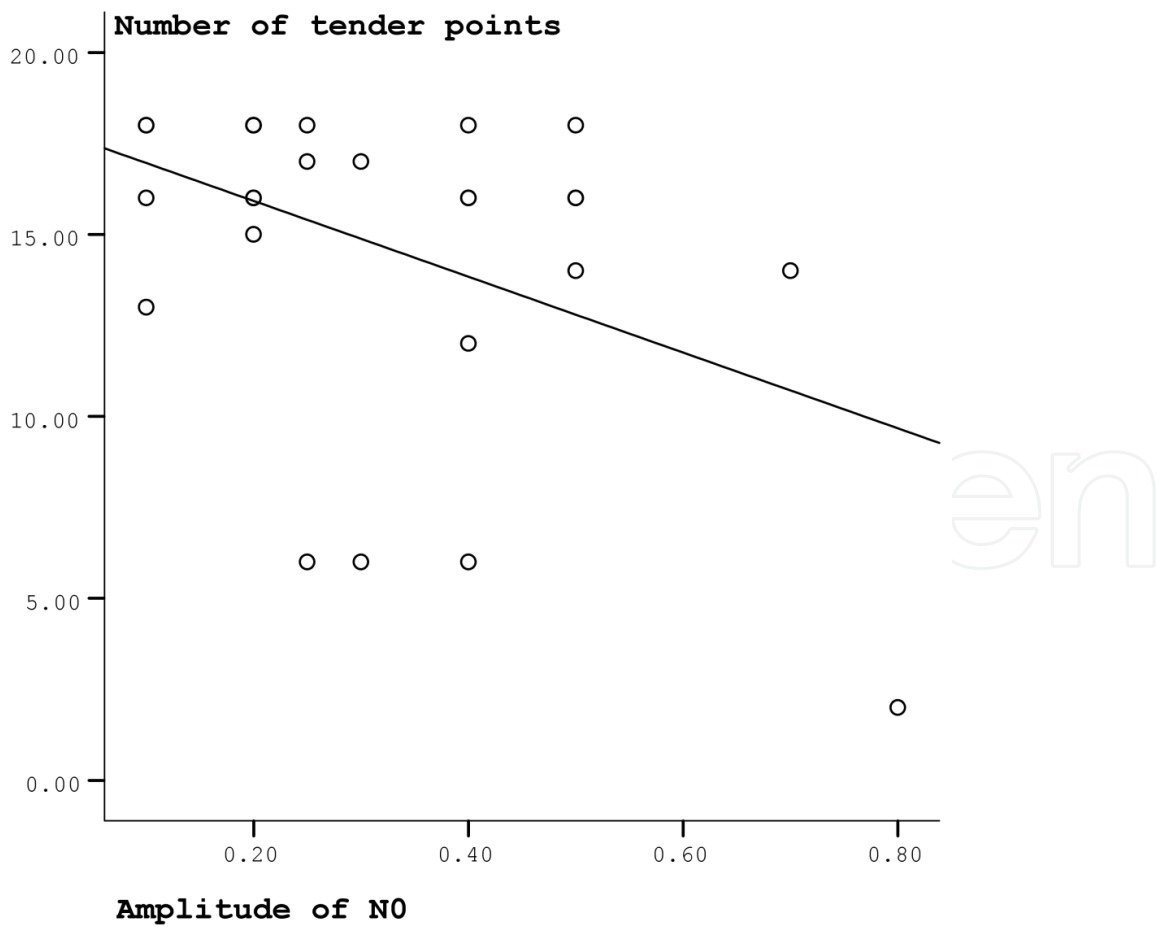


Fig. 4. Correlation analysis of number of tender points and amplitude of No.



Latencies of Na, Nb and Pb were statistically significantly longer in the patient group when compared with controls ( $p < 0.05$  and  $p < 0.01$  respectively).

The most important results for our study pointed out that Na, Pa and Nb latencies had positive correlations with disease duration which were statistically significant ( $p < 0.05$ ,  $p < 0.01$  and  $p < 0.05$  respectively) while the correlations between Na and HAQ and myalgia scores were positive although statistically insignificant ( $p > 0.05$ ). On the other hand, the number of tender points had a statistically significant positive correlation with Na ( $p < 0.05$ ). FIQ2 scores had negative and statistically very significant correlations with Pa and Nb ( $p < 0.01$  for both) while FIQ3 and FIQ scores had statistically positive correlations with Pa ( $p < 0.05$ ).

### 1.6 Discussion

Since 1990s, some possible explanations for the involvement of central pathways in fibromyalgia are discussed in various papers, though their number is still limited. To our knowledge, correlation of clinical parameters of fibromyalgia with MLAEPs has not been studied before.

In 1995, Johansson et al., reported significant focal flow decreases in dorsolateral frontal cortical areas of both hemispheres of fibromyalgic patients (Johansson et al., 1995). The AEPs also showed signs of dysfunction at least at the brainstem level. A large group of fibromyalgia patients were studied electrophysiologically by Rosenhall et al. in 1996 and significant differences were found in the study group regarding absolute and interpeak latencies in short latency AEPs, when compared with normals (Rosenhall et al, 1996). However sensorineural hearing loss was reported in 15% of patients. Bayazit et al., also studied short latency AEPs in fibromyalgia patients with and without cochleovestibular symptoms and reported no statistical difference of AEP abnormalities in these subgroups indicating that FM patients might complain of otologic symptoms without having a detectable ear disease and that a neural disintegration or some other events related to neural mediators might be the mechanism involved (Bayazit et al., 2002). Our group of patients did not have otological symptoms, however their MLAEPs showed statistically significant differences when compared with normal controls. This result of our study may be considered as being in agreement with the above study. Fann et al. studied MLAEPs in a similar patient group (chronic low back pain) and found a trend of increased latencies and lower amplitudes of P50 potential in the study group reporting also a decreased habituation of this very potential (Fann et al., 2005). Our study also indicated that Na, Nb and Pb (namely N16, N40 and P50 potentials) had longer latencies in the patient group when compared with normals. The origins of MLAEPs are still controversial. Most authors share the opinion that Pa potential (P30) is generated in the supratemporal auditory center of each hemisphere, but it is not clear that Pa represents the earliest cortical auditory response. Na and Pa are believed to be related with the activation of the primary auditory cortex. Some authors imply that Pa is generated in the auditory cortex while Na is originated subcortically. No, Po and Na have origins of subcortical structures while most other MLAEP potentials have origins generated from sites near the auditory cortex. In 1991 Erwin RJ et al. reported that P50 (Pb) was generated in thalamus (Erwin RJ et al., 1991). In a review of functional MRI (Magnetic resonance imaging) findings in FM, decreased rCBF (regional cerebral blood flow) in the thalamus and in the caudate nucleus was reported as results of various studies, nevertheless indicating the fact that this finding was not unique to FM.



Latency, on the other hand, has been shown to reflect the efficiency and speed of information processing in cognitive function (Gracely et al., 2002).

Thus results of our study may well be interpreted that FM patients show a slower speed of information processing in areas which are responsible for complex auditory perceptions related highly to cognitive functions. In 2006 Montoya et al. found significant amplitude reductions in FM patients for the auditory but not the somatosensory modality and suggested also that there was abnormal information processing in FM patients characterized by a lack of inhibitory control to repetitive nonpainful somatosensory information during stimulus coding and cognitive evaluation (Montoya et al., 2006). Roth et al. also stated that women with chronic pain were particularly vulnerable to cognitive dysfunction in a study designed as a cross-sectional survey (Roth et al., 2005).

### 1.7 Conclusion

Our results may be interpreted that central mechanisms may be important in the evolution of fibromyalgia. CNS dysfunction may be both an etiological factor in the fibromyalgia syndrome and a pathophysiological mechanism explaining the clinical symptoms and signs.

## 2. The relationship between middle latency auditory evoked responses, and the neuropsychological profile in patients with schizophrenia

### 2.1 Introduction

Although variable time ranges are described for MLAEPs, recent reliable sources report that the middle latency auditory evoked responses (MLAEPs) are far-field potentials that appear between 10-50 ms following an auditory stimulus and are recorded on vertex. The upper range limit is also reported as 80-100 ms in some sources (Buchwald et al., 1989; Buchwald et al., 1991; Erwin et al., 1986; Erwin et al., 1987; Mauguire et al., 2007). Far field potentials are generated by movement of the charge, but the electrode sees the moving front of depolarization and repolarization rather than the direct charge flow between regions of depolarization and repolarization. Most evoked potentials are generated by charge movement in nerve tracts to and from the relay nuclei and are far-field potentials because of the depth of the neural generators. The near-synchronous volley of action potentials in the nerve tracts produces far-field potentials that are recorded at scalp electrodes (Mauguire et al., 2007).

In literature, it has been assumed that MLAEPs are composed of six waves; No, Po, Na, Pa, Nb, Pb. No and Po are the the earliest responses. Pa and Pb (P1, P50) are defined as positive waves occurring in the 29 msec and 45 msec after a stimulus, while Na and Nb are negative deflections in the 25 msec and 50 msec, respectively. The neural sources of these waves are still controversial (Misulis et al., 2001, Cacace et al., 1990). Most of the MLAEP complex is thought to originate near the auditory cortex, although No, Po and Na may be generated by subcortical structures.

Among components of MLAEPs, the most commonly studied wave is the Pb (synonyms: P1 or P50). The P1 potential is blocked by the muscarinic anticholinergic drugs. It is present during waking and rapid eye movement sleep and does not exist during deep slow wave sleep. It has also been reported that the P1 component may be associated with cognitive processes, especially attention and state. Abnormalities of MLAEPs have been reported in some neurodegenerative and psychiatric diseases such as Alzheimer's disease, Parkinson's

disease, schizophrenia, Huntington disease and autism (Buchwald et al., 1989, Woods et al., 1987, Green et al., 1995).

It has been assumed that latency in evoked potential studies reflect the efficiency and speed of information processing. Thus, the prolonged latency may reflect that the information processing speed slowed. Amplitude abnormalities, on the other hand, refer to axonal loss in related areas and show the overall efficiency of neural structures mediating a response.

Over thirty years, various MLAEP studies have been performed in patients with schizophrenia. In most of these studies, the sensory gating paradigm has been investigated and they demonstrated the P1 habituating phenomenon, recovery cycle abnormalities and P1 suppression deficiency (Aminoff et al., 1990; Buchwald et al., 1992; Dickerson et al., 1991). However the relationship between the P1 latencies, amplitudes and neurocognitive status still remains unclear. In this study (Sahin et al., 2005; Turker et al., 2008) we investigated whether the MLAEPs correlated with the performances of neuropsychological tests in patients with schizophrenia and healthy controls.

## **2.2 Methods**

### **2.2.1 Subjects**

We examined 15 patients (8 female and 7 male) with schizophrenia, who met diagnostic criteria of DSM-IV for schizophrenia and compared them with control subjects (9 females and 6 males). Patients and control subjects were matched for age, gender, education levels and handedness.

Subjects who had other neurological or psychiatric disease, history of substance abuse and head trauma were not included in the study. All patients were psychiatrically stable (there were no psychotic symptoms and medication changes within at least two weeks prior to the assessment). Psychopathological symptoms severity in patients was assessed by Positive and Negative Syndrome Scale (PANSS) (First, 1997). Informed consent was obtained from patients and control subjects before the study.

### **2.2.2 Evoked potentials recording procedure**

All recordings of MLAEPs were performed at Dantec Keypoint. Electrode montage was adjusted as active electrode placed on ipsilateral mastoid and reference and ground electrodes at Cz and Fz, respectively. Silver surface electrodes were used for reference and ground electrode while a scalp needle electrode was used as active electrode. Alternating clicks of 100  $\mu$ sec duration were used and polarity was adjusted as vertex. The frequency of stimulation was 10/sec and the filtering was chosen as 10 Hz-200 Hz. Analysis time (sweep length) and sensitivity were 100msec and 0,2  $\mu$ V/d, respectively. The intensity of the stimuli was chosen according to the auditory threshold. The ipsilateral ear was stimulated with an intensity of stimulus such as hearing threshold plus 60 dB, while the contralateral ear was masked with white noise. Averaging of 1000 signals was performed twice and overlapped for each ear. No, Po, Na, Pa, Nb, and Pb were sampled and latencies and amplitudes of each potential were determined and compared with age and gender matched controls. MLAEPs recordings were performed bilaterally i.e. 30 recordings were performed for patients and 30 recordings were performed for controls making a total of 60 recordings. No artifact rejection was employed.

In MLAEP recording procedure, latency and amplitude measurements are usually done on the display, either manually or by an automatic peak detection algorithm that seeks the

maximum value between preset time values. The amplitude can be expressed as a peak to peak value between adjacent positive and negative components or the peak value can be measured against some baseline, usually taken just before the stimulus is presented. Latency for MLAEPs can be described as the time till the peak of the negative or the positive potential has evolved and this may be labelled on the display after the click (Erwin et al., 1987)

As hearing impairment can alter the MLAEPs, the external ear canal was checked with an otoscope to assure that the canal was not blocked by cerumen before the test. Patients with hearing problems assessed by otologic tests were excluded. MLAEPs are known to be affected by medications, however all patients were under treatment and there was no other way to investigate them.

2.2.3 Neuropsychological evaluation

An extensive neuropsychological test battery was used to assess the cognitive functions; attention, language, visuospatial functions, verbal and visual memory, executive functions (Table 3).

2.2.4 Statistical methods

The age, gender, handedness, education, the latencies and amplitudes of MLAEPs the neuropsychological test parameters of the patients and controls groups were compared with student-t test. The pearson correlation coefficient was used to determine the correlation between PANNS scores, the neuropsychological test parameters, and disease duration.

2.3 Results

The demographic features of patient and control groups are presented in Table 2. There were no statistically significant difference between age, gender, handedness, and education levels of patient and control groups.

	Patients (n = 15)		Controls (n = 15)	p
Age	32.9 ± 10.6	29.8±2.3	NS	
Education	12.1 ± 3.7	12.6±2.6	NS	
MMSE	28.1 ± 2.7	29.6±0.8	S	
Gender	8M. 7F	9M. 6F		NS
Duration of disease (month)	135.3± 112.1	(-)		(-)

Table 2. Demographic Features.

2.3.1 Neuropsychological tests

Results are summarized in Table 4. Generally, in all the neuropsychological tests, performance of the patient group was poor when compared to control group. MMSE scores of the patient group were statistically significantly lower than those of the control groups. There were statistically significant differences regarding the attention and the language tests. The scores of the tests assessing visuospatial functions, except BLO, were significantly different between patient and control groups. Also, patients got statistically significant lower scores on memory tests, and executive functions when compared with controls.

Mini mental state examination (MMSE)
Attention
WAIS-R Digit Span (DS)
Verbal Fluency (K-A-S Test)
Language
Boston Naming Test (30-items)
Visuo-spatial Functions
Benton’s Line Orientation Test (BLO)
Benton’s Facial Recognition Test (BFR)
WAIS-R Block Design (BD)
Hooper Visual Organization Test (HVOT)
Clock Drawing
Verbal Memory
California Verbal Learning Test (CVLT)
Visual Memory
WAIS-R subtest
Executive Functions
Wisconsin Card Sorting Test (WCST)
Stroop Test
Trail Making Test A and B (TMT A-B)

WAIS = Wechsler Adult Intelligence Scale.

Table 3. Neuropsychological Test Battery.

	Patients (n = 15)		Controls (n = 15)		p
	Mean	SD	Mean	SD	
MMSE	28.1	2.7	29.6	0.8	S
Attention					
WAIS-R DS-fwd	6	1.06	7.2	1.01	S
WAIS-R DS-bwd	3.6	1.29	5.2	1.08	S
Verbal Fluency (K-A-S Test)	35.07	13.96	48.47	12.18	S
K-A-S perseveration	0.67	0.81	0.07	0.25	S
Language					
Boston Naming Test (30-items)	27.60	2.79	29.27	1.28	S
Visuo-spatial Functions					
BLO	23.43	7.94	26.40	2.99	NS
BFR	18.07	3.38	21.93	2.63	S
BD	21.14	11.43	30.20	9.59	S
HVOT	17.79	4.04	21.00	1.89	S
Clock Drawing	9.26	0.79	9.93	0.25	S

		Patients (n = 15)		Controls (n = 15)		p
		Mean	SD	Mean	SD	
Verbal Memory						
CVLT						
Total of 5 trails	38.71	10.57	51.46	6.94	S	
Long-delay free recall	7.92	2.97	12.53	2.06	S	
Long-delay cued recall	8.21	2.96	13.20	1.65	S	
Perseverations	5	4.11	3.40	3.08	NS	
Free recall intrusions	2	2.21	1	1.81	NS	
Cued recall intrusions	1.21	1.67	0.67	1.11	NS	
Recognition	13.21	3.01	15.13	1.06	S	
Discriminability (%)	88.09	9	96	3.5	S	
False positive	1.5	1.6	0.46	1.06	S	
Visual Memory						
WAIS-R subtest	8	3.2	11.67	1.1	S	
Executive Functions						
WCST						
Total number of responses	117.50	18.25	95.6	15.37	S	
Total categories completed	3.57	2.10	5.93	0.25	S	
Number of perseverative responses	43.36	36.23	12.67	4.25	S	
Total number of errors	51.64	25.42	22.67	8.30	S	
Total number of correct responses	65.86	14.72	72.93	8.40	NS	
Stroop 3	14.3	4	11.1	2.7	S	
Stroop 5	27.9	9.6	25.1	8.2	NS	
TMT A	69.72	25.7	35.35	13.18	S	
TMT B	146.44	91.55	75.56	25.13	S	

Table 4. Neuropsychological Test Results.

2.3.2 Evoked potentials

The results indicated that most of the MLAEPs data elicited from the patients showed statistically significant differences from controls. The pathological responses from both sides of the brains of patients did not differ significantly from each other as both right and left sides generated MLAEPs which were statistically significantly different from controls (Table 5–6). Apart from NoR and PaL, all latencies of other parameters of MLAEPs were prolonged in the patient group (Table 5). Apart from PbR, amplitudes of parameters of MLAEPs were statistically significantly lower in the patient group when compared with the control group, (Table 6).

We also found no correlations between PANSS scores, the scores of neuropsychological tests, the duration of disease, and the latencies and amplitudes of MLAEPs.

	Patients (n=15)		Control (n=15)		p
	Mean	SD	Mean	SD	
No <sub>R</sub>	10.67	3.52	8.48	2.64	NS
No <sub>L</sub>	11.18	3.26	8.04	2.25	S
Po <sub>R</sub>	18.05	1.55	15.71	2.39	S
Po <sub>L</sub>	19.14	3.87	15.36	2.38	S
Na <sub>R</sub>	29.22	2.63	26.26	2.21	S
Na <sub>L</sub>	29.98	3.55	26.65	2.79	S
Pa <sub>R</sub>	40.16	3.32	37.70	2.64	S
Pa <sub>L</sub>	43.01	6.35	39.77	3.31	NS
Nb <sub>R</sub>	53.44	6.73	48.01	5.37	S
Nb <sub>L</sub>	55.66	10.09	48.97	3.58	S
Pb <sub>R</sub>	68.37	7.84	59.19	7.94	S
Pb <sub>L</sub>	66.54	11.07	59.35	5.76	S

Table 5. Latencies of MLAEPs (Millisecond).

	Patients (n=15)		Control (n=15)		p
	Mean	SD	Mean	SD	
No <sub>R</sub>	0.17	0.15	0.4	0.2	S
No <sub>L</sub>	0.22	0.15	0.47	0.27	S
Po <sub>R</sub>	0.22	0.13	0.49	0.25	S
Po <sub>L</sub>	0.22	0.15	0.56	0.32	S
Na <sub>R</sub>	0.39	0.35	0.86	0.50	S
Na <sub>L</sub>	0.39	0.29	0.76	0.34	S
Pa <sub>R</sub>	0.26	0.27	0.65	0.51	S
Pa <sub>L</sub>	0.26	0.25	0.58	0.33	S
Nb <sub>R</sub>	0.28	0.30	0.55	0.38	S
Nb <sub>L</sub>	0.25	0.22	0.50	0.33	S
Pb <sub>R</sub>	0.27	0.29	0.48	0.38	NS
Pb <sub>L</sub>	0.19	0.10	0.50	0.31	S

Table 6. Amplitudes of MLAEP Potentials (Microvolt).

2.4 Discussion

In this study we found that the many parameters of MLAEPs except No<sub>R</sub> and Pa<sub>L</sub> for latency and Pb<sub>R</sub> for amplidute, were significantly abnormal in the patient group. Also, the neuropsychological test performances of the patient group were poor when compared with normals.

According to our data, there were not any correlations between PANSS scores, the scores of neuropsychological test, the duration of disease, and the latencies and amplitudes of MLAEPs.

Although the neural sources of MLAEPs are still controversial, the studies suggest that Pa, Pb and Nb components of MLAEPs have a cortical generator (primary auditory cortex and adjacent areas) while No, Po, and Na have a brainstem-subcortical generator (medial



geniculate body, polysensory thalamic nuclei) (Deiber et al., 1988; Diaz et al., 1990) It is well-known that human Pb (P1) potential is blocked by scopolamine, muscarinic cholinergic antagonists, and due to lesions including cholinergic pedunculopontine nucleus (Diaz et al., 1990)

In patients with schizophrenia, the abnormalities in auditory evoked potentials have been reported by other studies. Erwin et al. reported that the recovery cycle of the P1 component of auditory midlatency evoked potential is abnormal (Erwin et al., 1991). Boutros and coworkers suggested that there were morphological abnormalities of the MLAEPs in schizophrenia patients (Boutros et al., 2004). Clementz et al. showed that P50 suppression was deficient in these patients, indicating sensory gating abnormality (Clementz et al., 1997). All these findings were interpreted by authors as a deficiency of generators of MLAEPs, underlying neural structures and neurotransmitter systems in patients with schizophrenia.

We investigated the latency and amplitude features of MLAEPs recorded on dominant and non-dominant hemisphere in patients with schizophrenia but not the recovery cycle and sensory gating features. All patients and control subjects were strongly right-handed according to Edinburgh Inventory (Oldfield et al., 1971).

Our results revealed statistically significant differences both in latency and amplitudes of MLAEP components in the patient group when compared with the normal group.

Lateralization seems to be important in schizophrenic patients since some symptoms of the disease emerge when specific parts of the brain are involved. It was hypothesized that hypermetabolism of the left temporal lobe seemed to occur only if the patient was actively hallucinating for example (Mesulam et al., 1990).

In our study the pathological responses elicited from both sides of the brains of patients did not differ significantly from each other as both right and left sides generated MLAEPs which were statistically significantly different from controls. We believe this is an important finding since all our patients and controls were strongly right-handed. Thoma et al. concluded in one of their studies that converging evidence from EEG, MEG and neuropsychological measures pointed to left hemisphere dysfunction related to the well established sensory gating in schizophrenia (Thoma et al., 2003).

It has been assumed that latency in evoked potential studies reflect the efficiency and speed of information processing. Thus, the prolonged latency may reflect that the information processing speed slowed.

Amplitude abnormalities, on the other hand, refer to axonal loss in related areas and show the overall efficiency of neural structures mediating a response.

Amplitude abnormalities in evoked potentials of patients with schizophrenia have been reported with much more consistency than latency abnormalities. Munkundan and coworkers observed amplitude and recovery abnormalities but normal latencies of MLAEPs in schizophrenia patients (Munkundan et al., 1986). Williams and coworkers similarly found no latency abnormalities in a group of medicated schizophrenia patients (Williams et al., 2000). However, Boutros and coworkers demonstrated that schizophrenia patients had significantly longer latencies for the P50 and N100 components (Boutros et al., 2004). Our findings agree with results of the researches in literature.

The many previous studies investigated the neuropsychological profile of the patients with schizophrenia. Almost all of these studies demonstrated the neuropsychological impairments in the multiple cognitive areas etc. memory, attention, language, executive functions (Bozikas et al., 2006; Brazo et al., 2005; Mohamed et al., 1999). However, it is still

unknown whether there is a relationship between the neuropsychological impairments and neuroanatomical changes. Also, it is unclear whether the negative and positive symptoms are associated with a specific brain region and/or neuropsychological deficits. Andreasen et al. and Weinberg et al. have reported that the negative symptoms reflected primarily frontal lobe dysfunction (Andreasen, 1986; Weinberger, 1987). Berman et al. observed that negative symptoms associated with poor performances on cognitive tests reflected poor frontal lobe functions while positive symptoms were associated with poor attention representing widespread neural network (Berman et al., 1997). Liu et al. demonstrated that the negative schizophrenic patients had executive function deficits and lower rCBF perfusion in left prefrontal lobes (Liu et al., 2002). On the other hand, Morrison-Stewart et al. found no correlation between frontal lobe assessing neuropsychological tests and negative symptoms (Morrison et al., 2002). Addington et al. reported that there was no relationship between attention and negative and positive symptoms (Addington et al., 1997).

The results of our study showed that the cognitive functions assessing the comprehensive neuropsychological test battery were statistically significantly worse in the patient group when compared with the control group.

Schizophrenia is a heterogeneous mental disease which is characterized with thought disorder, hallucination, delusion and cognitive deficits.<sup>45</sup> Postmortem studies showed low neuron density, cortical volume reduction, pyramidal cell disarray, neurotransmitter disturbances such as glutamate, GABA, dopamine, and acetylcholine (Harrison et al., 1998; Sarter et al., 1998; Simpson et al., 1998). The longitudinal studies support that schizophrenia is largely a static disorder while others suggest a deteriorating course (Harrison et al., 1998; Gur et al., 1998; Vita et al., 1997).

The spectrum of disease duration of our patients was fairly widespread (min: 50 months max: 440 months). In our study there were no correlations between the disease duration, severity of the disease (by PANSS), EP measures, and neuropsychological profiles. This may perhaps support that schizophrenia is a static disorder rather than progressive.

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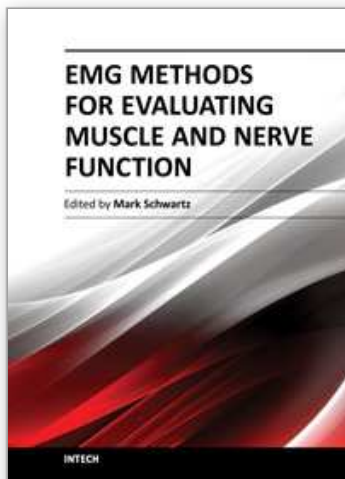
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