Auditory-evoked potentials as a tool for follow-up of fibromyalgia

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Aim of the study

In this study, we assessed the value of auditory-evoked potentials (AEPs) as objective measurable reproducible tests for the follow-up of patients with fibromyalgia (FM) in response to pharmacologic and rehabilitative therapy.

Patients and methods

This study included 30 female FM patients and 10 age-matched female controls. All participants underwent a clinical examination, a psychiatric and functional assessment (sleep score, Fibromyalgia Impact Questionnaire, and Hospital Anxiety and Depression Scale) and measurement of AEPs elicited by tones of increasing intensity (60, 70, 80, and 90 dB) known as late cortical responses and cognitive auditory potentials (P300). Patients were subdivided into three equal groups. Group 1 received pregabalin, group 2 received fluoxetine, and group 3 included patients who performed a graded aerobic exercise program. Assessment was repeated at the end of the 8-week treatment period.

Results

Patients had significantly shorter N1 latencies at 60 and 70 dB, significantly shorter P2 latencies at all the studied intensities, and significantly higher N1P2 amplitudes at 90 dB.There was a statistically significant decrease in amplitude and a significant increase in P300 latency when compared with controls. Changes in AEP values before and after treatment were closely associated with the changes in psychiatric and functional assessment parameters.

Conclusion

Improvement in the clinical assessment of the different symptoms of FM goes hand in hand with the improvement in the late cortical and cognitive components of AEPs, which provides evidence of the value of AEP as a simple, noninvasive, objective, and reproducible follow-up tool for assessment of hypervigilance and cognitive function in FM patients.

Keywords:

auditory-evoked potential, cognitive function, fibromyalgia, hypervigilance, P300

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Introduction

Fibromyalgia (FM) is a chronic pain syndrome that is characterized by widespread musculoskeletal pain, tenderness, fatigue, disturbed sleep, depressed mood, cognitive problems, and a variety of psychosomatic symptoms originating from various organs in the absence of any explanatory organic disease. Patients with FM often also complain of tingling, numbness, burning pain, and cutaneous hyperalgesia [1].

Pain is the cardinal symptom in FM. On being subjected to the same amount of stimulation, patients show enhanced brain responses as compared with controls, providing evidence of central pain augmentation in this syndrome [2]. There is a growing body of evidence supporting central sensitization as the mechanism underlying chronic musculoskeletal pain in these patients [3].

Hypervigilance is a component of central sensitization of pain. Generalized hypervigilance hypothesis in FM describes a 'perceptual habit' that involves subjective amplification of a variety of unpleasant sensations, not only painful ones. It was reported that FM patients had higher levels of hypervigilance and lower pressure-pain threshold and tolerance, compared with healthy controls, as shown by reduced auditory noise tolerance in these patients as compared with normal individuals [4]. An approach that has proven useful for objective assessment of interindividual variability in perception is the examination of evoked cortical potentials by stimuli of increasing intensity (e.g. auditory). Few studies have applied this methodology in FM patients [5].

Auditory-evoked potentials (AEP) caused by noninvasive stimulation provide a unique opportunity for investigating the functional integrity and magnitude of the brain processing pathways in the cerebral cortex and can be used to test the cortical functional activity. The electrical waveforms generated can be divided into early cortical waves and

late components, where waveforms are designated by their polarity (P-positive, N-negative) and latency (timing of peak) after stimulus onset. In addition, the amplitude (the size of the voltage difference between the component peak and a prestimulus baseline) is also quantified [6].

Responses recorded after 50-200 ms from stimuli are response patterns due to activity in higher auditory portions of the brain, such as the cerebral cortex, and are called auditory late response. They appear to be generated from the primary cortex (ventral portion of the medial geniculate body and primary auditory and nonprimary areas in the auditory thalamocortical pathway) [7].

The use of auditory late response elicited by increasing tones of intensity in FM patients may be a subjective test of generalized hypervigilance to noxious stimulation and defective inhibitory mechanisms that may be crucial factors in the pathophysiology of FM [8].

The P300 response is essentially a component within an extended auditory late-response time frame, occurring in the 300 ms region (with positive voltage, hence P) after acoustic stimuli. It is usually recorded under special stimulus conditions. The target signal produces a positive wave in the latency region of 300 ms; these are called cognitive or event-related potentials (ERPs) [9].

ERPs are useful indices for assessing changes in cognitive brain functions. In particular, the P300 component of the ERP has been widely applied in the scientific study of age-related cognitive dysfunction because it reflects attention and memory processes. The P300 represents concurrent activity in multiple regions of the brain, including temporoparietal neocortical areas and higher limbic structures, and the P300 amplitude can thus be viewed as a measure of central nervous system activity that reflects the processing of incoming information when it is incorporated into memory representations of the stimulus and the context in which the stimulus occurs. P300 latency is an index of the processing time required before response generation; it is a sensitive temporal measure of the neural activity underlying the processes of attention allocation and immediate memory. In addition, P300 latency is negatively correlated with mental functions in normal individuals, with shorter latencies associated with superior cognitive performance [10]. Both components proved to be reliable tests [11].

Aim

In this study, we assessed the value of AEPs as objective measurable reproducible tests for the follow-up of patients with FM in response to pharmacologic and rehabilitative therapy.

Patients and methods

This study was conducted on 30 female FM patients attending the Outpatient Clinic of Physical Medicine, Rheumatology and Rehabilitation and Psychiatry Departments of Ain Shams University Hospitals, fulfilling the 1990 American College of Rheumatology criteria for the diagnosis of primary FM [12]. The inclusion criteria for the study group comprised a negative history for dementia, cerebrovascular disease, alcohol abuse, psychoactive drug treatment, and other neurological disorders. None of the patients had comorbid psychiatric disorders. Patients with rheumatologic (e.g. rheumatoid arthritis and SLE), neurological, endocrinal, and metabolic disorders, diagnosed malignancy, auditory and vestibular disorders, who were pregnant, who were using contraceptive pills, or who had rheumatic heart disease, congenital heart disease, respiratory and chest conditions, anemia, and other chronic debilitating diseases were excluded from the study. Written informed consent was taken from the patients. The study also enrolled 10 healthy age-matched and sex-matched volunteers as the control group. The study was approved by the ethical committee of the Faculty of Medicine, Ain Shams University.

All patients underwent thorough medical history taking and full clinical examination. Laboratory tests including complete blood count, erythrocyte sedimentation rate, C-reactive protein, liver function tests (AST and ALT), kidney function tests (serum creatinine and blood urea), glycated hemoglobin, free T3, T4 and thyroid-stimulating hormone, rheumatoid factor, and ANA were carried out.

Psychiatric and functional assessment was performed using the questionnaire of widespread pain, fatigue, and disability using a visual analogue scale (VAS) [13], ranging from 0 to 10, where 0 indicates no symptoms and 10 indicates severe symptoms. Sleep disorder assessment was performed using the 11-point numeric rating scale of sleep to assess sleep quality during the previous 24 h [14]. The Fibromyalgia Impact Questionnaire (FIQ), which is a 20-item patient-reported instrument containing 10 subscales, was used to yield a combined total score. A questionnaire on depression and anxiety was assessed according to the Hospital Anxiety and Depression Scale (HADS) [15].

Auditory-evoked potentials

Late-latency auditory-evoked potentials

Audiometry was performed before AEP recording to rule out the possibility of hearing deficiency. AEPs were, in all cases, recorded between 9 and 11 a.m. Patients had to have slept well the previous night and had to come to the laboratory without having breakfast or without smoking. They sat in a comfortable chair with their eyes closed in a darkened room and were instructed to listen to a series of tones through earphones. They were asked not to make eye and body movements. The AEPs were recorded during the presentation of five series of 1000-Hz binaural tones. Within each 90-stimulus series, tone intensity was constant (60, 70, 80, and 90 dB in successive series). Each tone was of a total duration of 50 ms (including 10-ms ramps at start and finish) and was presented at a rate of 0.7/s. Each series was separated from the next by an interval of 20 s. The signals were recorded at the vertex using the right earlobe as reference. It was amplified 20 000 times and filtered using a 1-30 Hz band-pass (EP Program 4.0; Bio-logic Systems). Impedances were kept at 5 kΩ or less. The signals were sampled at 257 Hz with a rest interval of length 700 ms, including 200 ms of prestimulus baseline. For each patient, two traces of five representative waveforms were obtained (one per intensity level).

All further analyses were performed using data extracted from these four average waveforms. For each of the four intensities, the N1 and P2 latency and the N1P2 peak-to-peak amplitude were measured. The N1 component was identified as the most negative peak within the 60-125-ms window and P2 as the most positive peak between 110 and 210 ms. As a measure of the intensity dependence of the AEPs, the slope of the N1P2 amplitude versus intensity plot (*A-I slope) was calculated for each patient.*

Extended late-latency auditory-evoked potentials (P300)

Late response of ERPs is called P300. Late ERPs were recorded with Ag/AgCl electrodes (impedance was held below 5 kΩ) on a DantecKeypoint (Medtronic, Denmark) device, in an electromagnetically isolated, sound attenuating room. The active electrode was placed at Cz (vertex) and referenced to the linked earlobe. P300-evoked potentials were generated after a tone was presented to both ears (binaurally) by two stimuli, one more common than the other. The patient was typically instructed to pay attention to the rare stimulus, ignoring the more common stimulus, which is called 'oddball' paradigm; the discrimination paradigm was performed through a headphone with frequent (85%) tones of 1000 Hz and rare oddball stimuli (15%) of 2000 Hz at 80 dB. Patients were instructed to count rare stimuli (target tones at 2000 Hz) and to report at the end of the session. When there was a discrepancy of more than 10% hits between the actual number of stimuli and the number reported by the patients, recordings were repeated. Latencies (ms) of the P3 peak and amplitudes (μV) of P3 were recorded.

After assessment, patients were randomly allocated to three groups: Group 1 included 10 patients who received 75 mg pregabalin tablets twice daily of a total dose of 150 mg/day for 8 weeks; group 2 included 10 patients who received fluoxetine capsules of 20 mg/day for 8 weeks; and group 3 included 10 patients who underwent only a graded aerobic exercise program for 8 weeks (16,17).

The psychiatric and functional assessment and AEPs were performed at the start of the study for all patients and at the end of the 8-week treatment period.

Statistical analysis was performed using a statistical software package 'SPSS' version 10. Descriptive quantitative data were expressed as ranges, mean, and SD and as numbers and percentages for qualitative data. Student's *t*-test was used to compare between two independent means, one-way analysis of variance test was used for comparison between the three study groups, and the paired sample t-test was used for comparison between results before and after treatment. A *P*-value less than 0.05 was considered significant and a *P*-value less than 0.01 was considered highly significant. All results were tabulated and statistically analyzed.

Results

The present study was conducted on 30 female patients with FM. Ten age-matched and sex-matched healthy volunteers were included in the study as the control group. The patients were classified into three groups: Group 1 included 10 patients treated with pregabalin 150 mg/day for 8 weeks; group 2 included 10 patients who received fluoxetine 20 mg/day for 8 weeks; and group 3 included 10 patients who performed a graded aerobic exercise program for 8 weeks. The demographic and clinical data of the patients are shown in Table 1.

Fifty percent of the patients had postural hypotension and 46.7% complained of morning stiffness (<30 min). Comparison between patients and healthy controls for laboratory data revealed a nonsignificant difference (Table 2).

An initial evaluation of the AEPs for all patients and controls was conducted, and the findings were compared. Late-latency AEPs N1 and P2 latencies

Table 1 Demographic and clinical data of the fibromyalgia patients

	Range	Mean ± SD
Age (years)	20–38	30.7 ± 5.03
Disease duration (months)	3–60	19.13 ± 15.35
Number of tender points	11–16	12.73 ± 1.44
Fatigue duration (months)	2–48	11.43 ± 10.29
VAS (mm)	7–9	8.17 ± 0,59
Sleep score	6–9	7.9 ± 0.92
FIQ	6–18	15.47 ± 2.06
HADS	10–14	12.03 ± 1.22

FIQ, fibromyalgia impact questionnaire; HADS, hospital anxiety and depression scale; sleep score, 11-point numeric rating scale of sleep; VAS, visual analogue scale.

Table 2 Comparison of mean and SD of laboratory data in patients and controls

	Groups	Mean ± SD	*t*	*P*	Significance
Hb (g%)	Patients	12.28 ± 0.54	0.341	>0.05	NS
	Controls	12.35 ± 0.53			
ESR (mm/h)	Patients	14.63 ± 3.13	0.207	>0.05	NS
	Controls	14.4 ± 2.95			
ALT (IU/mm)	Patients	22.27 ± 1.53	0.295	>0.05	NS
	Controls	22.1 ± 1.59			
AST (IU/mm)	Patients	22.77 ± 2.08	0.296	>0.05	NS
	Controls	23 ± 2.4			
Serum creatinine (mg/dl)	Patients	0.8 ± 0.15	0.338	>0.05	NS
	Controls	0.78 ± 0.19			
Blood urea (mg/dl)	Patients	34.57 ± 2.94	0.346	>0.05	NS
	Controls	34.2 ± 2.78			

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate.

were shorter in patients at all sound intensities tested. The N1P2 amplitude was significantly higher in FM patients. Cognitive auditory potentials (P300) showed longer latencies and lower amplitudes compared with those of controls (Table 3).

Patients in the three randomly divided groups did not show significant differences with respect to their clinical characteristics, mean values of laboratory data, and initial values of all AEP recordings (*P > 0.05) on comparison* using the analysis of variance test.

Group 1 results

Comparison between clinical data before and after treatment with 150 mg pregabalin daily for 8 weeks using the paired sample test revealed significant improvement in the sleep score and HADS *(P < 0.05), as well as highly significant improvement in the VAS and FIQ (P < 0.001)* (Table 4).

Late cortical responses N1 and P2 in group 1 patients at all sound intensities tested showed significantly longer

Table 3 Comparison of mean and SD of initial auditory-evoked potentials at different sound intensities in patients and controls

	Groups	Mean ± SD	*t*	*P*	Significance
N1 latency at 60 dB (ms)	Patients	115.5 ± 8.13	4.677	<0.001	HS
	Controls	128 ± 2.31			
N1 latency at 70 dB (ms)	Patients	110.5 ± 7.23	4.85	<0.001	HS
	Controls	122.3 ± 2.63			
N1 latency at 80 dB (ms)	Patients	101.87 ± 5.04	1.119	>0.05	NS
	Controls	103.8 ± 2.09			
N1 latency at 90 dB (ms)	Patients	97.87 ± 4.69	1.66	>0.05	NS
	Controls	100.4 ± 1.71			
P2 latency at 60 dB (ms)	Patients	141.73 ± 5.56	4.694	<0.001	HS
	Controls	152.3 ± 4.45			
P2 latency at 70 dB (ms)	Patients	141.53 ± 4.37	3.74	<0.001	HS
	Controls	149 ± 4.56			
P2 latency at 80 dB (ms)	Patients	141.4 ± 4.28	4.175	<0.001	HS
	Controls	150 ± 4.91			
P2 latency at 90 dB (ms)	Patients	142.27 ± 5.04	2.151	<0.05	S
	Controls	147.3 ± 5.41			
N1P2 amplitude at 90 dB (mV)	Patients	4.14 ± 0.39	4.32	<0.001	HS
	Controls	3.56 ± 0.31			
P300 peak latency (ms)	Patients	360.33 ± 27.69	2.926	<0.05	S
	Controls	334 ± 9.66			
P300 peak amplitude (mV)	Patients	10.84 ± 1.04	5.516	<0.001	HS
	Controls	13.15 ± 0.82			

HS, highly significant; S, significant.

latencies at the end of the study. N1P2 amplitude was significantly decreased after treatment. Cognitive auditory potentials (P300) showed shortening of the delayed latencies and increase in the diminished amplitudes after 8 weeks of treatment with pregabalin (Table 5).

Comparison of post-treatment results of group 1 with the results of the control group revealed improvement in all AEP recordings, whether late cortical responses or cognitive auditory potentials, with a resultant nonsignificant difference between FM patients and normal controls, except N1 latency at 90 dB, in which the increase in the shortened latency exceeded normal values to become significantly longer than that of controls (Table 6).

Group 2 results

Treatment with fluoxetine 20 mg/day for 8 weeks resulted in highly significant improvement in the VAS,

Table 4 Comparison of clinical data in group 1 before and after treatment

	Mean ± SD	*t*	*P*	Significance
VAS before	8 ± 0.67	8.820	<0.001	HS
VAS after	5.8 ± 1.03			
Sleep score before	7.7 ± 0.95	4.295	<0.05	S
Sleep score after	6 ± 1.05			
FIQ before	16.1 ± 1.1	9.127	<0.001	HS
FIQ after	12.3 ± 1.76			
HADS before	11.6 ± 1.26	3.375	<0.05	S
HADS after	9.8 ± 1.23			

FIQ, fribromyalgia impact questionnaire; HADS, hospital anxiety and depression scale; HS, highly significant; S, significant; sleep score, 11-point numeric rating scale of sleep; VAS, visual analogue scale.

Table 5 Comparison of auditory-evoked potential recordings before and after treatment in group 1

	Mean ± SD	*t*	*P*	Significance
N1 latency at 60 dB (ms) before	115.5 ± 8.64	7.236	<0.001	HS
N1 latency at 60 dB (ms) after	127.5 ± 6.77			
N1 latency at 70 dB (ms) before	110 ± 7.07	3.498	<0.05	S
N1 latency at 70 dB (ms) after	120.5 ± 4.97			
N1 latency at 80 dB (ms) before	103.7 ± 5.49	3.958	<0.05	S
N1 latency at 80 dB (ms) after	105.3 ± 5.96			
N1 latency at 90 dB (ms) before	100.1 ± 5.28	5.211	<0.001	HS
N1 latency at 90 dB (ms) after	104.4 ± 4.06			
P2 latency at 60 dB (ms) before	143.6 ± 3.69	6.384	<0.001	HS
P2 latency at 60 dB (ms) after	153.3 ± 4.57			
P2 latency at 70 dB (ms) before	140.1 ± 4.18	9.97	<0.001	HS
P2 latency at 70 dB (ms) after	149.7 ± 3.59			
P2 latency at 80 dB (ms) before	142.7 ± 3.47	6.987	<0.001	HS
P2 latency at 80 dB (ms) after	150.7 ± 3.65			
P2 latency at 90 dB (ms) before	144 ± 3.56	8.26	<0.001	HS
P2 latency at 90 dB (ms) after	147.7 ± 4.83			
N1P2 amplitude at 90 dB (mV) before	4.34 ± 0.32	7.372	<0.001	HS
N1P2 amplitude at 90 dB (mV) after	3.54 ± 0.51			
P300 peak latency (ms) before	363.5 ± 21.22	4.747	<0.001	HS
P300 peak latency (ms) after	341.2 ± 23.04			
P300 peak amplitude (mV) before	10.98 ± 0.95	12.036	<0.001	HS
P300 peak amplitude (mV) after	12.93 ± 0.91			

HS, highly significant; S, significant.

Table 6 Comparison of group 1 auditory-evoked potential results of patients and controls, after treatment

	Groups	Mean ± SD	*t*	*P*	Significance
N1 latency at 60 dB (ms)	Group 1	127.5 ± 6.77	0.221	>0.05	NS
	Controls	128 ± 2.31			
N1 latency at 70 dB (ms)	Group 1	120.5 ± 4.97	1.08	>0.05	NS
	Controls	122.3 ± 2.63			
N1 latency at 80 dB (ms)	Group 1	105.3 ± 5.96	0.751	>0.05	NS
	Controls	103.8 ± 2.09			
N1 latency at 90 dB (ms)	Group 1	104.4 ± 4.06	2.871	<0.05	S
	Controls	100.4 ± 1.71			
P2 latency at 60 dB (ms)	Group 1	153.3 ± 4.57	0.496	>0.05	NS
	Controls	152.3 ± 4.45			
P2 latency at 70 dB (ms)	Group 1	149.7 ± 3.59	0.239	>0.05	NS
	Controls	149 ± 4.56			
P2 latency at 80 dB (ms)	Group 1	150.7 ± 3.65	0.266	>0.05	NS
	Controls	150 ± 4.91			
P2 latency at 90 dB (ms)	Group 1	147.7 ± 4.83	0.158	>0.05	NS
	Controls	147.3 ± 5.41			
N1P2 amplitude at 90 dB (mV)	Group 1	3.54 ± 0.51	0.108	>0.05	NS
	Controls	3.56 ± 0.31			
P300 peak latency (ms)	Group 1	341.2 ± 23.04	0.911	>0.05	NS
	Controls	334 ± 9.66			
P300 peak amplitude (mV)	Group 1	12.93 ± 0.91	0.562	>0.05	NS
	Controls	13.15 ± 0.82			

S, significant.

FIQ and HAD scale *(P < 0.001), as well as significant improvement in the sleep score (P < 0.05)* (Table 7).

Eight weeks of fluoxetine treatment caused late cortical responses N1 and P2 in group 2 patients to show significant delay in the shortened latencies toward normal values. The N1P2 amplitude showed highly significant decrease after treatment. Cognitive auditory potentials (P300) showed shortening of the delayed latencies that did not reach significance and highly significant increase in the diminished amplitude by the end of the study (Table 8).

At the end of the 8 weeks, the AEP recordings in group 2 reflected an improvement in FM patients with a resultant absence of significant difference between patients and controls except for P2 latency at 60 dB, which, although improved, remained significantly less than that of controls, and N1 latency at 90 dB, which increased even further than that of controls to show significantly longer latency (Table 9).

Table 7 Comparison of clinical data in group 2 before and after fluoxetine treatment

	Mean ± SD	*t*	*P*	Significance
VAS before	8.2 ± 0.63	8.835	<0.001	HS
VAS after	5.9 ± 0.99			
Sleep score before	7.9 ± 1.1	3.791	<0.05	S
Sleep score after	6.2 ± 1.03			
FIQ before	15.9 ± 0.88	10.062	<0.001	HS
FIQ after	12.9 ± 1.37			
HADS before	11.7 ± 1.16	6.042	<0.001	HS
HADS after	9.8 ± 0.79			

FIQ, fibromyalgia impact questionnaire; HADS, hospital anxiety and depression scale; HS, highly significant; S, significant; sleep score, 11-point numeric rating scale of sleep; VAS, visual analogue scale.

Table 8 Comparison of group 2 auditory-evoked potential recordings before and after treatment

	Mean ± SD	*t*	*P*	Significance
N1 latency at 60 dB (ms) before	115.5 ± 6.43	12.72	<0.001	HS
N1 latency at 60 dB (ms) after	126.8 ± 5.79			
N1 latency at 70 dB (ms) before	112.5 ± 7.55	3.628	<0.05	S
N1 latency at 70 dB (ms) after	118.7 ± 5.49			
N1 latency at 80 dB (ms) before	99.5 ± 4.09	5.205	<0.001	HS
N1 latency at 80 dB (ms) after	105.1 ± 4.58			
N1 latency at 90 dB (ms) before	96.2 ± 4.34	11.129	<0.001	HS
N1 latency at 90 dB (ms) after	104.1 ± 4.58			
P2 latency at 60 dB (ms) before	140.8 ± 4.87	3.217	<0.05	S
P2 latency at 60 dB (ms) after	146.1 ± 3.69			
P2 latency at 70 dB (ms) before	142.1 ± 4.68	9.696	<0.001	HS
P2 latency at 70 dB (ms) after	149 ± 3.97			
P2 latency at 80 dB (ms) before	140.8 ± 4.69	3.586	<0.05	S
P2 latency at 80 dB (ms) after	146.8 ± 4.57			
P2 latency at 90 dB (ms) before	141.8 ± 4.87	2.641	<0.05	S
P2 latency at 90 dB (ms) after	144.6 ± 3.09			
N1P2 amplitude at 90 dB (mV) before	4.1 ± 0.39	5.217	<0.001	HS
N1P2 amplitude at 90 dB (mV) after	3.75 ± 0.42			
P300 peak latency (ms) before	369 ± 39.64	1.727	>0.05	NS
P300 peak latency (ms) after	341.5 ± 17.17			
P300 peak amplitude (mV) before	10.93 ± 1.04	12.429	<0.001	HS
P300 peak amplitude (mV) after	13.35 ± 1.06			

HS, highly significant; S, significant.

Table 9 Comparison between group 2 auditory-evoked potentials and the control group, after treatment

	Groups	Mean ± SD	*t*	*P*	Significance
N1 latency at 60 dB (ms)	Group 2	126.8 ± 5.79	0.609	>0.05	NS
	Controls	128 ± 2.31			
N1 latency at 70 dB (ms)	Group 2	118.7 ± 5.49	1.976	>0.05	NS
	Controls	122.3 ± 2.63			
N1 latency at 80 dB (ms)	Group 2	105.1 ± 4.58	0.817	>0.05	NS
	Controls	103.8 ± 2.09			
N1 latency at 90 dB (ms)	Group 2	104.1 ± 4.58	2.393	<0.05	S
	Controls	100.4 ± 1.71			
P2 latency at 60 dB (ms)	Group 2	146.1 ± 3.69	3.392	<0.05	S
	Controls	152.3 ± 4.45			
P2 latency at 70 dB (ms)	Group 2	149 ± 3.97	0	>0.05	NS
	Controls	149 ± 4.56			
P2 latency at 80 dB (ms)	Group 2	146.8 ± 4.57	1.153	>0.05	NS
	Controls	150 ± 4.91			
P2 latency at 90 dB (ms)	Group 2	144.6 ± 3.09	1.199	>0.05	NS
	Controls	147.3 ± 5.41			
N1P2 amplitude at 90 dB (mV)	Group 2	3.75 ± 0.42	1.177	>0.05	NS
	Controls	3.56 ± 0.31			
P300 peak latency (ms)	Group 2	341.5 ± 17.17	1.204	>0.05	NS
	Controls	334 ± 9.66			
P300 peak amplitude (mV)	Group 2	13.35 ± 1.06	0.468	>0.05	NS
	Controls	13.15 ± 0.82			

S, significant.

Group 3 results

Comparison of clinical data among group 3 patients before and after a rehabilitation program of graded aerobic exercise over 8 weeks using a paired sample *t*-test revealed significant improvement among all administered tools except the FIQ for which improvement did not reach statistical significance (Table 10).

Late cortical responses at all the intensities assessed and cognitive auditory potentials showed improvement in group 3 after the rehabilitation program in different degrees. All the recordings reached statistical significance, except for P2 latency at 60 and 90 dB, which showed a delay in the shortened latency toward normal; yet, the difference did not reach statistical significance (Table 11).

After the 8-week rehabilitation program, the AEP recordings of group 3 showed an improvement in all recordings; yet, the statistical difference between the FM patients and healthy controls was still present in P2 latency at 60, 70, and 90 dB (Table 12).

Table 10 Comparison of clinical data in group 3 before and after treatment

	Mean ± SD	*t*	*P*	Significance
VAS before	8.3 ± 0.48	4.63	<0.001	HS
VAS after	6.5 ± 1.27			
Sleep score before	8.1 ± 0.74	3.597	<0.05	S
Sleep score after	6.4 ± 0.97			
FIQ before	14.4 ± 3.13	1.449	>0.05	NS
FIQ after	12.9 ± 1.59			
HADS before	12.8 ± 0.92	6	<0.001	HS
HADS after	10.4 ± 0.84			

FIQ, fibromyalgia impact questionnaire; HADS, hospital anxiety and depression scale; HS, highly significant; S, significant; sleep score, 11-point numeric rating scale of sleep; VAS, visual analogue scale.

Table 11 Comparison of auditory-evoked potential recordings before and after treatment in group 3

	Mean ± SD	*t*	*P*	Significance
N1 latency at 60 dB (ms) before	115.5 ± 9.85	4	<0.05	S
N1 latency at 60 dB (ms) after	121.5 ± 7.47			
N1 latency at 70 dB (ms) before	109 ± 7.38	3.364	<0.05	S
N1 latency at 70 dB (ms) after	116.1 ± 7.67			
N1 latency at 80 dB (ms) before	102.4 ± 4.95	2.799	<0.05	S
N1 latency at 80 dB (ms) after	105.2 ± 3.39			
N1 latency at 90 dB (ms) before	97.3 ± 3.89	4.236	<0.05	S
N1 latency at 90 dB (ms) after	104.8 ± 4.87			
P2 latency at 60 dB (ms) before	140.8 ± 7.51	1.913	>0.05	NS
P2 latency at 60 dB (ms) after	142.5 ± 7.44			
P2 latency at 70 dB (ms) before	142.4 ± 4.33	3.207	<0.05	S
P2 latency at 70 dB (ms) after	149.2 ± 2.86			
P2 latency at 80 dB (ms) before	140.7 ± 4.72	3.85	<0.05	S
P2 latency at 80 dB (ms) after	146.9 ± 4.63			
P2 latency at 90 dB (ms) before	141 ± 6.34	2.216	>0.05	NS
P2 latency at 90 dB (ms) after	144.5 ± 3.69			
N1P2 amplitude at 90 dB (mV) before	3.99 ± 0.39	3.243	<0.001	HS
N1P2 amplitude at 90 dB (mV) after	3.8 ± 0.42			
P300 peak latency (ms) before	348.5 ± 14.15	5.468	<0.001	HS
P300 peak latency (ms) after	334.5 ± 9.26			
P300 peak amplitude (mV) before	10.6 ± 1.18	11.207	<0.001	HS
P300 peak amplitude (mV) after	12.21 ± 1.23			

HS, highly significant; S, significant.

Table 12 Comparison between group 3 auditory-evoked potentials and the control group, after treatment

	Groups	Mean ± SD	*t*	*P*	Significance
N1 latency at 60 dB (ms)	Group 3	121.5 ± 7.47	2.629	<0.05	S
	Controls	128 ± 2.31			
N1 latency at 70 dB (ms)	Group 3	116.1 ± 7.67	2.418	<0.05	S
	Controls	122.3 ± 2.63			
N1 latency at 80 dB (ms)	Group 3	105.2 ± 3.39	1.112	>0.05	NS
	Controls	103.8 ± 2.09			
N1 latency at 90 dB (ms)	Group 3	104.8 ± 4.87	2.696	<0.05	S
	Controls	100.4 ± 1.71			
P2 latency at 60 dB (ms)	Group 3	142.5 ± 7.44	3.575	<0.05	S
	Controls	152.3 ± 4.45			
P2 latency at 70 dB (ms)	Group 3	149.2 ± 2.86	0.118	>0.05	NS
	Controls	149 ± 4.56			
P2 latency at 80 dB (ms)	Group 3	146.9 ± 4.63	1.453	>0.05	Ns
	Controls	150 ± 4.91			
P2 latency at 90 dB (ms)	Group 3	144.5 ± 3.69	1.352	>0.05	NS
	Controls	147.3 ± 5.41			
N1P2 amplitude at 90 dB (mV)	Group 3	3.8 ± 0.42	1.454	>0.05	NS
	Controls	3.56 ± 0.31			
P300 peak latency (ms)	Group 3	334.5 ± 9.26	0.118	>0.05	NS
	Controls	334 ± 9.66			
P300 peak amplitude (mV)	Group 3	12.21 ± 1.23	2.011	>0.05	NS
	Controls	13.15 ± 0.82			

S, significant.

Discussion

FM is a common chronic widespread pain disorder. Extensive research suggests that the chronic widespread pain characteristic of FM is neurogenic in origin. The pain seems to result from neurochemical imbalances in the central nervous system that lead to a 'central amplification' of pain perception characterized by allodynia (a heightened sensitivity to stimuli that are not normally painful) and hyperalgesia (an increased response to painful stimuli) [18].

Furthermore, many FM patients experience sensitivity to loud noises, bright lights, odors, and chemicals. These symptoms of generalized sensitivity to multiple stimuli account for a significant number of FM patients who can be classified as having 'multiple chemical sensitivities' [19].

At present, there is neither a laboratory test nor an imaging technique that can set apart people who suffer from FM from healthy controls. This lack of an objective marker has hampered FM recognition and research. A biomarker is defined as a characteristic that can be

objectively measured and evaluated as an indication of normal or pathogenic processes or pharmacological responses to a therapeutic intervention [20]. AEPs are brain waves generated upon stimulation with sounds. They reflect the ability of the brain to discriminate, classify, and memorize the significance of exogenous stimuli [21].

Results of this study show a statistically significant shortening of latencies of the late AEPs at all studied sound intensities, except the mean values of N1 at 70 and 80 dB, at which the latencies, although shortened, did not reach statistical significance. We also report significantly higher N1P2 amplitudes at 90 dB in FM patients compared with healthy controls. Our findings agree with those of Carrillo *et al.* [22] and Hollins *et al.* [23]. These groups showed that FM patients generally have shorter latencies and larger amplitudes in all responses.

The latency reductions and higher amplitudes of late AEPs found in FM patients here suggest that FM patients may have increased attention or anticipation to auditory stimuli, a result that fits well with the generalized hypervigilance hypothesis. As originally defined, hypervigilance is 'a readiness to select out and respond to a certain type of weak or infrequent stimulus from the external or internal environment' (which is the same as in our study hypothesis; we use the infrequent type). On the basis of our findings and those of González *et al.* [4] with respect to the AEP amplitudes, we may conclude that FM patients are especially hypervigilant for intense stimuli [4].

Latency reduction and increased amplitude of AEPs in FM patients can also be in accordance with a consistent body of evidence pointing to deficient inhibitory mechanisms in FM patients, especially with respect to the modulation of sensitivity to pain. By means of conditioned stimulus, it has been shown that FM patients have deficient diffuse noxious inhibitory controls [24].

P300 is the late component of AEP, which is a repeatable, relatively inexpensive, and useful method for the assessment of cognitive ability in normal individuals and in patients with neuropsychiatric disorders [25]. Our study reports that there was a high statistically significant decrease in amplitude and a significant increase in P300 latency when compared with controls. These findings agree with the results obtained by Ozgocmen *et al.* [26]. Park *et al.* [27] confirmed the value of P300 in FM and its relation to cognitive abilities such as information processing, recognition memory, working memory function, free recall, verbal fluency, and psychiatric scales and provided evidence that longer latencies and smaller amplitudes of P300 as the late component of AEPS are found in FM patients as compared with age-matched controls, which reflects defects in these higher functions.

The three groups of patients showed no significant difference with respect to the clinical, laboratory, and AEPs, verifying the random choice of patients among the groups.

On comparing the clinical data in group 1 before and after treatment with 150 mg pregabalin daily for 8 weeks, we found significant improvement in the sleep score and HADS, whereas this improvement was highly significant with respect to VAS and FIQ. This is in accordance with the results of Häuser *et al.* [28] and of Siler *et al.* [29], who found significant improvement in patients with respect to sleep score, HADS, VAS, and FHAQ with pregabalin treatment. This may be because of the ability of pregabalin to improve pain, sleep, and psychological scores in FM patients [30,31].

Values of AEPS before and after treatment in group 1 showed significant improvement in N1 latency at 70 and 80 dB after treatment and a highly significant improvement in all other values, whether late-latency AEPs or P300.

This study shows that pregabalin 150 mg daily for 8 weeks improves the values of late-latency AEPs, rendering them closer to the values in healthy controls. Hence, after treatment with pregabalin all values of late AEPs showed nonsignificant difference as compared with control, except N1 latency at 90 dB, which exceeded normal values. This demonstrates the success of pregabalin in improving the hypervigilance, which is in accordance with the finding of González *et al.* [4]. Improvement in hypervigilance as a part of central sensitization by pregabalin is due to its mechanism of action that causes a decrease in excitatory neurotransmitters such as glutamate and substance P [32].

In this study, pregabalin significantly improved the amplitude and latency of the late component P300. Ozgocmen *et al.* [26] agreed with these findings and added that FM patients after treatments showed near-normal amplitude and latency of P300 together with an improvement in cognitive abilities and psychiatric scales of FM, reinforcing the evidence of the value of P300 as a follow-up tool for the assessment of cognitive performance in FM patients.

In FM patients who received fluoxetine 20 mg/day for 8 weeks (group 2), the clinical data before and after treatment revealed highly significant improvement with respect to VAS, FIQ, and HAD. There was significant improvement with respect to sleep score

as well. These findings are in accordance with those of Uçeyler *et al.* [33] and Wilcke and Clauw [34], who found that fluoxetine improves pain scores and impacts clinical scores and psychiatric scores significantly after treatment because of its mechanism of action that depends on slow reuptake of serotonin and norepinephrine. This confirms the effectiveness of fluoxetine in pain reduction and sleep improvement, besides its action as an antidepressant [35].

On comparing late-latencyAEPs before and after treatment, there was a highly significant improvement in the results after treatment with respect to N1 latency at 60, 80, and 90 dB, P2 latency at 70 dB, and N1P2 amplitude at 90 dB. In addition, there was a significant improvement with respect to N1 latency at 70 dB and P2 latency at 60, 80, and 90 dB.

Group 2 late-latency AEPs after treatment showed absence of significant difference compared with healthy controls at all studied values except P1 latency at 90 dB, for which the increase in latency exceeded normal, and at P2 latency after exposure to a sound of 60 dB intensity, for which improvement failed to reach statistical significance.

The cognitive response showed highly significant improvement in P300 amplitude and also an improvement that did not reach statistical significance in P300 latency. Yet, both P300 latency and amplitude were not statistically different from the values recorded in healthy individuals by the end of the study.

The results of group 2 demonstrate that treatment with fluoxetine caused marked improvement in the patients' values, which became close to control values. Hence, we can conclude that fluoxetine treatment in FM patients improves both hyperalgesia and cognitive function.

The effect of the rehabilitation program on FM patients who performed graded aerobic exercise for 8 weeks with respect to clinical data before and after treatment showed a highly significant difference with respect to VAS and HADS and a significant improvement in the sleep score, whereas improvement in FIQ did not reach statistical significance.

These results are in accordance with the findings of Häuser *et al.* [28] who reported that exercise may ease the symptoms of FM and improve pain scores and psychiatric scores, but in contrast to our results they found that exercise significantly improves the clinical impact of FM. This dissimilarity may be due to close observation in our study, as we used a detailed questionnaire and not the global effect of the disease as used by Häuser and colleagues, who applied the visual analogue scale to measure the effect of the disease. In addition, in our study we used a graded program tailored for each patient individually and not a fixed program as used by Häuser *et al.* [36] in their study.

With respect to the effect of the rehabilitation program on late AEPs, all studied recordings showed significant improvement, except P2 latency at 60 and 90 dB, in which increase in latency did not reach statistical significance. We found a highly significant difference with respect to P300 latency and amplitude. This indicates that exercise improves all intellectual function in FM patients (both hypervigilance and cognitive).

On comparing the post-treatment results of AEP values (both late latency and cognitive P300) with those of healthy controls, near-normal values were achieved with absence of significant difference except for N1 latency at 60 and 70 dB and P2 latency at 60 dB. N1 latency at 90 dB was even larger than normal readings to ensure improvement in all indicators of hypervigilance.

The use of rehabilitation alone in the treatment of FM resulted in the least improvement in both clinical parameters and AEP values among the three groups, suggesting the need for combining medication with rehabilitation in these patients.

Our findings in all three groups of patients and after studying the changes in AEP values before and after treatment, which happened together with the changes in clinical assessment parameters, suggest that both late and extended late AEPs can be used to monitor the patients' improvement in FM, as they reflect changes in hypervigilance and cognitive function successfully.

Conclusion

Improvement in the different symptoms of FM is closely associated with improvement in the late cortical and cognitive components of AEPs, which provides evidence of the value of AEP as a simple, noninvasive, objective, and reproducible follow-up tool for assessment of hypervigilance and cognitive function in FM patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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