

## Auditory P300 Event-Related Potentials in Fibromyalgia Patients

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This study assessed the cognitive brain function measured by the cognitive P300 auditory event-related potentials (ERPs) in female fibromyalgia (FM) patients and compared the results with those from healthy age and education-matched controls. The relationship of the P300 potentials to the pain threshold of patients was also investigated.

The P300 component of the auditory ERPs were studied in 11 female FM patients and 10 age and education-matched healthy controls. None of the patients were taking antidepressants such as amitriptyline or serotonin-reuptake inhibitors.

The P300 latencies of the patients were not significantly different whereas the N2P3 amplitudes were significantly lower than the controls. The P300 latencies in the patients negatively correlated with the total myalgic scores (TMS) ( $r=-0.73$ ) and the control point scores (CPS) ( $r=-0.85$ ). On the other hand, the P300 amplitudes showed a significant correlation with the TMS ( $r=0.61$ ) and the CPS ( $r=0.60$ ). There was no significant correlation between the anxiety and depression scores with the P300 latency or amplitudes.

These results showed cognitive impairment, which was mainly expressed by the lower N2P3 amplitudes in patients with FM, and its clinical relevance requires further research.

**Key Words:** Fibromyalgia, auditory event-related potentials, P300

### INTRODUCTION

Fibromyalgia (FM) is one of the most common rheumatic diseases, which affects approximately 1-2% of the population. FM is a syndrome

characterised by pain, fatigue, joint stiffness, sleep problems, and memory difficulties. FM patients experience widespread musculoskeletal pain, multiple tender points, and increased pain during routine daily home and work activities.<sup>1-4</sup> Cognitive complaints, particularly difficulty with attention and short-term memory, are observed frequently in FM patients and cognitive behavioural therapy has generally been an effective treatment.<sup>5-8</sup>

The P300 component of the auditory event-related potentials (ERPs), which are elicited by a tone discriminating "oddball" paradigm, are objective measures related to information and cognitive processing. This allows the quantification of impaired cognitive brain functions.<sup>9,10</sup> The event-related P300 potentials closely reflect the special aspects of human information processing. They are test-retest reliable, and have been used successfully in a variety of clinical conditions (e.g., metabolic encephalopathies, dementia, obsessive compulsive disorders).<sup>9,11-13</sup>

In this study the cognitive brain function measured by the cognitive P300 auditory ERPs was evaluated in female FM patients and the results were compared with those from healthy age and education-matched controls. The relationship of the P300 potentials to the pain threshold of patients was also investigated.

### MATERIALS AND METHODS

Eleven female patients, aged 30-49 (mean 41.3  $\pm$  6.1), who met the 1990 American College of Rheumatology (ACR)<sup>1</sup> criteria for the classifica-

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tion of FM, and 10 healthy age and education-matched female subjects (aged 29 - 47, mean  $39.9 \pm 6.6$ ) were included in this study. The education level of the patients was  $7.2 \pm 3.2$  years (range 5 - 15), and that of the controls was  $7.5 \pm 3.3$  years (range 5 - 15). The inclusion criteria for the study group required a negative history for dementia, cerebrovascular disease, alcohol abuse, neurological diseases, and psychoactive medication. None of the patients were under anti-depressant therapy and those included into the study had not taken such drugs at least three weeks prior to the study. All subjects provided informed consent.

### Pain Pressure Threshold (PPT) measurements

The same physician performed the PPT measurements of the FM patients in the same room in the early afternoon. Prior to performing the measurements, the subjects were informed of the procedure. The pain threshold was explained as the amount of pressure adequate to induce a sensation of discomfort, and the subjects were warned that the aim of this procedure was to determine the pain threshold but not the pain tolerance.

Eighteen tender points (TP) accepted by the ACR for FM in 1990<sup>1</sup> and 3 control points (CP), which were generally agreed upon and used in previous studies, were evaluated. The three control points were the mid-forehead, the 2/3 distal portion of the dominant forearm and the dominant thumbnail. All of the points were algometrically measured by using a Fischer's dolorimeter, which is a manually operated mechanical device used for measuring the pain-pressure threshold. The apparatus has a force-pressure handle connected to a rubber disk and calibrated in  $\text{kg}/\text{cm}^2$ . The pressure was increased at a rate of 1  $\text{kg}/\text{sec}$ , after being vertically applied to the TP and in this course, the subjects were asked to state when pain was experienced. A positive tender point was defined as the point on where the subject experienced mild or great pain with less than 4  $\text{kg}/\text{cm}^2$  pressure. The sum of the PPTs of the 21 points (18 TPs and 3 CPs) were calculated as the total myalgic score (TMS in  $\text{kg}/\text{cm}^2$ ), and the sum of the PPTs of the CPs were recorded as the control point score (CPS in  $\text{kg}/\text{cm}^2$ ).<sup>14</sup> The measurements were repeated twice and the mean values were

used for the statistical analysis.

The Hamilton Depression Rating Scale (HDRS)<sup>15</sup> and the Hamilton Anxiety Rating Scale (HARS)<sup>16</sup> were used to evaluate the affective condition of the FM patients. The cut-off score for mild depression for the HDRS was 27.

### Auditory P300 event-related potentials

The P300 ERPs were recorded with Ag/AgCl electrodes (impedance 5 kOhm) on a Dantec Keypoint (Medtronic, Denmark) device by the same physician who was unaware of the subjects' clinical data. An active electrode was placed at the Cz (vertex) and was referenced to the linked earlobe A1 according to the international 10 - 20 system. The P300 evoked potentials were generated following a binaurally presented tone discrimination paradigm through a headphone with frequent (85%) tones of 1000 Hz and rare oddball stimuli (15%) of 2000 Hz at 80 dB. The subjects instructed to count the rare target tones at a 2000 Hz - stimuli, and in case of a discrepancy of more than 10% between the actual number of stimuli and the number counted by the subjects, the recordings were repeated. The frequency limits were 0.1 - 50 Hz and the total analysis time was 1 s. The latencies (ms) of the P300 peak and the amplitudes ( $\mu\text{V}$ ) of the N2P3 (potential difference between the N200 and P300 peaks) were recorded.

### Statistics

The data was analysed on a personal computer using SPSS software. Mann-Whitney U test was used for inter-group comparisons. The values were correlated using the Spearman rank correlation coefficients. A two tailed  $p$  value  $< 0.05$  was considered statistically significant.

## RESULTS

There was no statistically difference in age and education between the two groups. The P300 latencies of the patients were similar but the N2P3 amplitudes were significantly lower than the controls (Table 1). Patients had a mean of  $12.7 \pm$

1.9 (range 11-17) tender points and an average TMS of  $84.9 \pm 10.0$  (range 63.9-96.5) kg/cm<sup>2</sup>, and an average CPS of  $20.6 \pm 2.8$  (range 15-23.7) kg/cm<sup>2</sup>. The P300 latencies in the patients were negatively correlated with both the TMS ( $r=-0.73$ ,  $p=0.01$ , Fig. 1) and CPS ( $r=-0.85$ ,  $p=0.001$ ). On the other hand, the P300 amplitudes showed a significant correlation with both the TMS ( $r=0.61$ ,  $p=0.04$ , Fig. 2) and the CPS ( $r=0.60$ ,  $p=0.04$ ).

The FM patients had a mean HARS of  $25.2 \pm 7.5$  (range 15-37) and a mean HDRS of  $20.7 \pm 5.0$  (range 10-27). There was no significant correlation between either the HARS and HDRS with the P300 latency or amplitudes.

## DISCUSSION

In this study, the cognitive P300 auditory ERPs was measured in FM patients and compared with

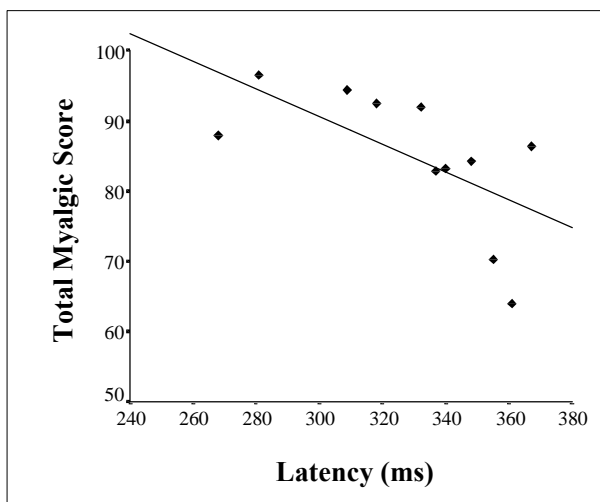


Fig. 1. Relationship between TMS and P300 latency ( $r=-0.73$ ,  $p=0.01$ ).

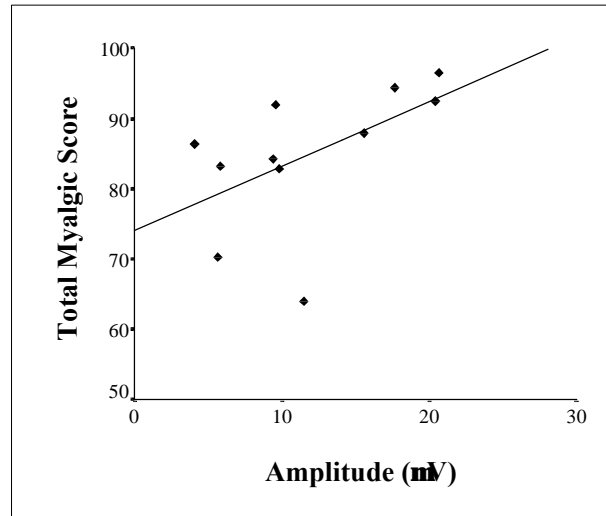


Fig. 2. Relationship between TMS and P300 amplitude ( $r=0.61$ ,  $p=0.04$ ).

the results of healthy aged and education-matched controls for the first time. In addition, this study also investigated the relationship between the myalgic scores, which in one respect reflects the intensity of the patients' symptoms, and the P300 latencies or amplitudes of FM patients. The P300 component of the ERPs has been shown to reflect sensitively certain aspects of human information processing<sup>9-11</sup> in a variety of conditions for diagnosis and longitudinal assessment.<sup>17-22</sup> In addition, the P300 component has also revealed a correlation with the psychometric tests.<sup>23,24</sup> This method of evaluating the cognitive functions is test-retest reliable<sup>11</sup> and has some advantages with respect to the psychometric tests i.e it is less prone to practice variations and is able to be performed in a blind manner.<sup>20</sup> On the other hand, there are some limitations in detecting the P300 ERPs, which must be controlled in a research environ-

Table 1. P300 Potentials of the Groups

	FM patients (n=11)		Controls (n=10)	
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
P300 latency (ms)*	$328.7 \pm 32.0$	268 - 367	$320.7 \pm 27.1$	262 - 349
N2P3 amplitude ( $\mu$ V) <sup>†</sup>	$11.8 \pm 5.9$	4.0 - 20.7	$18.5 \pm 5.3$	9.2 - 25.6

FM patients vs Controls (Mann-Whitney U test).

\*NS, not significant.

<sup>†</sup> $p < 0.05$ .

ment.<sup>25</sup> For example, the amplitudes may be influenced by the patients' age, the time of the day, the season of the year, recently ingested food and the personality type of the subject, whereas the latency may be influenced by age and body temperature.<sup>25-27</sup> Nevertheless, some reports have suggested that these effects do not basically restrict the clinical utility of P300.<sup>25,28,29</sup>

Gervais et al. suggested that an incomplete effort and the potential exaggeration of the cognitive deficits play a role in assessing patients with FM particularly those with medico-legal incentives.<sup>30</sup> It is important to be aware of the response bias during the assessment of memory impairment in FM especially in the context of a disability claim, and study group should exclude subjects with medico-legal incentives. An assessment of the P300 potentials have the advantage of being free of these exaggeration and response biases but does not give detailed information on the cognitive functions such as verbal fluency, verbal knowledge or free recall.

Park et al.<sup>8</sup> assessed the cognitive functions in FM patients in contrast to age and education-matched controls and just education-matched older controls. The cognitive functions were measured by means of information processing, recognition memory, working memory function, free recall, verbal fluency and vocabulary. The FM patients had a poor performance in all these measures with respect to age and education matched controls with the exception of the processing speed. The FM patients also had poorer vocabulary than the older controls. The authors also noted that the impaired cognitive performance in FM patients correlated significantly with the pain complaints measured using the Arthritis Impact Measurement Scales but not with the depression and anxiety scores. Previous studies have suggested that the P300 latency is a measure of the stimulus classification speed and the P300 amplitude is an index of the brain activity associated with the working memory performance.<sup>31-33</sup> In this study, the P300 latency and reduced amplitudes in the FM patients and the age and education matched controls were similar, which is in accordance with Park et al.'s results. A similar correlation was observed between the P300 potentials and the TMS and CPS but not

with the HARS or HDRS.

Our results showed cognitive impairment, which was mainly expressed by the lower N2P3 amplitudes in patients with FM. More research on this topic is needed in order to understand the clinical relevance of the P300 potentials in FM patients.

## REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, Bennet RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum* 1990;33:160-72.
2. Waylonis GW, Heck W. Fibromyalgia syndrome. New associations. *Am J Phys Med Rehabil* 1992;71:343-8.
3. Clauw DJ. Fibromyalgia. In: Ruddy S, Harris ED, Sledge CB, editors. *Kelly's Textbook of Rheumatology*, 6<sup>th</sup> ed. Philadelphia: WB Saunders; 2001. p.417-27.
4. Ozgocmen S, Cimen OB, Ardicoglu O. Relationship between chest expansion and respiratory muscle strength in patients with primary fibromyalgia. *Clin Rheumatol* 2002;21:19-22.
5. Keefe FJ, Caldwell DS. Cognitive behavioral control of arthritis pain. *Med Clin North Am* 1997;81:277-90.
6. Grace GM, Nielson WR, Hopkins M, Berg MA. Concentration and memory deficits in patients with fibromyalgia syndrome. *J Clin Exp Neuropsychol* 1999; 21:477-87.
7. Glass JM, Park DC. Cognitive dysfunction in fibromyalgia. *Curr Rheumatol Rep* 2001;3:123-7.
8. Park DC, Glass JM, Minear M, Crofford LJ. Cognitive function in fibromyalgia patients. *Arthritis Rheum* 2001;44:2125-33.
9. Goodin DS, Squires KC, Starr A. Long latency event-related components of the auditory evoked potential in dementia. *Brain* 1978;101:635-48.
10. Polich J, Ehlers CL, Otis S, Mandell AJ, Bloom FE. P300 latency reflects the degree of cognitive decline in dementing illness. *Electroencephalogr Clin Neurophysiol* 1986;63:138-44.
11. Taghavi A, Kugler CFA. The pattern flash elicited P300 potentials (PF-P300): A new method for studying cognitive processes of the brain. *Int J Neurosci* 1988;38: 179-88.
12. Goodin DS, Aminoff MJ. Electrophysiological differences between subtypes of dementia. *Brain* 1986;109: 1103-13.
13. Gottlieb D, Wertman E, Bentin S. Passive listening and task related P300 measurement for the evaluation of dementia and pseudodementia. *Clin Electroencephalogr* 1991;22:102-7.
14. Catal SA, Erdem HR, Okumus M, Ozgocmen S, Yorgancioglu ZR. The measurement of pain pressure threshold in patients with rheumatoid arthritis. *Pain*

- Clinic 2000;12:187-91.
15. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
  16. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50-5.
  17. Rahman A, Yoldas T, Ustundag B, Burma O, Uysal A, Cikim G, et al. Neurocognitive markers following coronary artery bypass grafting with and without cardiopulmonary bypass. *Proceedings of the 4th International Congress on Coronary Artery Disease*. 2001:741-6.
  18. Kugler CFA, Lotterer E, Petter J, Wensing G, Taghavy A, Hahn EG, et al. Visual event-related P300 potentials in early porto-systemic encephalopathy. *Gastroenterology* 1992;103:302-10.
  19. Towey J, Bruder G, Hollander E, Friedman D, Erhan H, Liebowitz M, et al. Endogenous event-related potentials in obsessive-compulsive disorder. *Biol Psychiatry* 1990;28:92-8.
  20. Weissenborn K, Wiltfang J, Schmidt FW, Kunkel H. Neurophysiological assessment of early hepatic encephalopathy. *Electroencephalogr Clin Neurophysiol* 1990;75:289-95.
  21. Kugler CFA, Vlajic P, Funk H, Raithel D, Platt D. The event-related P300 potential approach to cognitive functions of non-demented patients with cerebral and peripheral arteriosclerosis. *J Am Geriatr Soc* 1995;43:1228-36.
  22. Sanz M, Molina V, Martin-Loecheles, Calcedo A, Rubia FJ. Auditory P300 event related potential and serotonin reuptake inhibitor treatment in obsessive-compulsive disorder patients. *Psychiatry Res* 2001;101:75-81.
  23. Tachibana H, Takeda M, Sugita M. Short-latency somatosensory evoked potential and event-related potential in patients with multiple cerebral infarcts. *Int J Neurosci* 1991;61:1-8.
  24. Wright GM, Scott LC, Richardson CE, Rai GS, Exton-Smith AW. Relationship between the P300 auditory event-related potential and automated psychometric tests. *Gerontology* 1988;34:134-8.
  25. Polich J. P300 in clinical applications. Meaning, method and measurement. *Am J EEG Technol* 1991;31:201-31.
  26. Geisler M, Polich J. P300 and time of day: Circadian rhythms, food intake and body temperature. *Biol Psychol* 1990;31:1-20.
  27. Geisler M, Polich J. P300, food consumption, and memory performance. *Psychophysiology* 1992;29:76-85.
  28. Kugler CFA, Taghavy A, Platt D. The event-related P300 potential analysis of cognitive human brain aging: A review. *Gerontology* 1993;39:280-303.
  29. Kugler CFA, Petter J, Platt D. Age-related dynamics of cognitive brain functions in humans: An electrophysiological approach. *J Gerontol Biol Sci* 1996;51A: B3-16.
  30. Gervais RO, Russell AS, Green P, Allen LM III, Ferrari R, Pieschl SD. Effort testing in patients with fibromyalgia and disability incentives. *J Rheumatol* 2001;28:1892-9.
  31. Polich J. P300 clinical utility and control of variability. *J Clin Neurophysiol* 1998;15:14-33.
  32. Polich J. Attention, probability, and task demands as determinants of P300 latency from auditory stimuli. *Electroencephalogr Clin Neurophysiol* 1986;63:251-9.
  33. Kramer AF, Strayer DL. Assessing the development of automatic processing: an application of dual-track and event-related brain potential methodologies. *Biol Psychol* 1988;26:231-67.