Sensory and cognitive event-related potentials in myalgic encephalomyelitis

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Abstract

Myalgic Encephalomyelitis (ME) is a form of post viral fatigue syndrome resulting in myalgia and fluctuating fatiguability. Symptoms reflecting central nervous system dysfunction are common and include muscle weakness, headache, sensory disturbances, poor short term memory and impairment of concentration. In view of the fact that sensory and cognitive disturbances are experienced by many patients objective evidence was sought with multi-modality sensory evoked potentials and auditory event-related cognitive potentials in a group of ME patients both with and without the enteroviral antigen, VP1 test positive. The auditory brainstem, median nerve somatosensory and pattern reversal checkerboard visual potentials were normal for all 37 patients tested. In contrast to the sensory potentials significant differences in the mean latencies of the cognitive potential N2 and P3 were found. Reaction times were also significantly prolonged but the performance in terms of error was not significantly affected. No significant difference emerged in any of the parameters for the VP1 test. P3 was abnormal in latency or amplitude in 36% of the VP1 positive patients for the frequency discrimination task and 48% for the more difficult duration discrimination task. The abnormalities indicate attentional deficits in some patients and slower speed of information processing in others. The prolonged latencies observed in these patients have not been observed in patients with depression in many other studies.

Myalgic Encephalomyelitis (ME) is a form of chronic post-viral fatigue syndrome which has in the past occurred in epidemic form in several places and has been variously referred to as Royal Free disease, Iceland disease, epidemic neuromyasthenia, and Akureyeri disease.¹⁻³ Its occurrence in epidemic form, and the absence of any abnormalities on clinical examination, normal routine laboratory investigations and concurrent neuropsychiatric symptoms cast doubt upon its organic basis.^{4,5}

However, the 1978 international symposium on ME at the Royal Society of Medicine³ concluded that this was a specific disease of viral origin with little evidence of it being a

hysterical phenomenon. More recently the use of the term post infection fatigue syndrome or chronic fatigue syndrome have been suggested^{6,7} with several reports⁸⁻¹⁰ linking this syndrome with evidence of recent infection by many viruses including Coxsackie A and B, varicella, influenza, and Epstein-Barr. Behan *et al*¹¹ have found antibodies to Coxsackie virus in 70% of their 50 cases and Calder *et al*⁸ found 46% in their 140 cases compared with 25% in controls. McCartney *et al*¹² found specific immunoglobulin (IgM) Coxsackie antibodies in 31% of 118 patients. Yousef *et al*¹³ reported an enterovirus-group-specific monoclonal antibody which detected enteroviral antigen in the circulation in 51% of their 87 cases. These studies suggest that there are a group of symptoms which are associated with evidence of persistent infection and immunological dysfunction.^{11,14,15}

The characteristic features of ME are fluctuating fatiguability and myalgia even after minor physical effort. Other symptoms vary from episode to episode in an individual and across patients.^{6,7} Symptoms which may reflect central nervous system dysfunction are common and include muscle weakness, headache, sensory disturbances, poor short term memory, impairment of concentration and sleep disorders.

Standard electromyography (EMG) has failed to show any definite abnormalities in ME, however, abnormally increased jitter potentials have been reported¹⁶ with single-fibre EMG but without any impulse blocking which according to Lloyd *et al*¹⁷ would not account for the symptom of muscle fatigue in this disorder. As many patients with ME experience some sensory and cognitive disturbances we decided to look objectively for evidence of this by using multi-modality sensory evoked potentials and auditory event-related cognitive potentials. These potentials result from the synchronous neural activity associated with a particular stimulus or process. Electrical activity time locked and influenced primarily by the physical characteristics of the eliciting stimulus is referred to as the exogenous sensory potentials. By providing information on the functional state of the specific pathways stimulated, auditory brainstem, somatosensory and visual evoked potentials have become extremely useful in clinical diagnosis especially in the separation of peripheral from central nervous system disorders, detection of space occupying lesions and

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demyelination (for reviews see Chiappa¹⁸ and Halliday¹⁹). The electrical responses which are primarily affected by the cognitive processes associated with task demands rather than the physical attributes of the stimulus allow inferences to be made regarding the sequence and timing of stimulus evaluation and response selection and execution.²⁰ Tasks which readily yield a cognitive potential consist of identifying a particular stimulus (target) in a series of randomly presented stimuli which differ in some form or dimension and classifying each according to a defined criterion.

The psychological processes involved in the identification and classification of a specific stimulus or event lead to the appearance of a characteristic response wave in the target average and is, usually referred to, by its polarity and modal latency as P300 or simply P3. It has been linked with memory mechanisms^{21,22} and its latency is affected by task complexity,²³ ageing²³ and is prolonged in patients with dementia.^{25,26} Considering the neuro-psychological disturbances in patients with ME, this study examined cognitive potentials, reaction time and performance measures to ascertain the patients' ability to conduct discrimination tasks of varying difficulty.

Methods

The control group consisted of 25 (16 female) subjects in the age range of 17 to 69 with mean of 39 years and the myalgic encephalomyelitis patient group comprised 25 patients (20 female) with enteroviral antigen (VP1) positive¹³ in the age range of 15 to 62 with a mean of 39 years and 12 patients (eight female) with VP1 antigen negative in the age range of 23 to 56 years with a mean of 39 years.

Diagnostic criteria

The diagnosis of ME was made by a neurologist (LJF) and was based on all of the following symptoms being present for over six months (mean duration of illness was 60 months) following a febrile illness: persistent or relapsing debilitating fatigue, myalgia which increases following exercise, poor concentration and memory. All patients had been referred to the neurological clinic at a district general hospital and were untreated at the time of testing.

The evoked potential testing was carried out independently (DKP and AS) at the National Hospital without reference to a diagnosis (blind assessment).

Patients were subdivided into those with and without VP1 positive¹³ because it was felt that the VP1 test may be defining a more homogeneous group. The group with VP1 test positive was compared with a control group and with the VP1 negative group. Other relevant conditions were excluded on a history, a normal examination, and a normal haematological and biochemical screen.

Procedure

Sensory Potentials

Subjects sat in a comfortable chair in a sound

attenuated room for their recording of brainstem, visual and somatosensory potentials using a Medelec Mistral EP system. Silver/silver chloride EEG electrodes were attached to the scalp with collodion and on the mastoids with double sided adhesive discs. Electrode impedance was reduced by slight abrasion of the skin with a blunt needle so that the impedance was below 3000 ohms.

Brainstem Potentials were recorded using alternating polarity click stimulation at a repetition rate of 10 Hz from Cz-A1 and Cz-A2 electrode positions with forehead as ground. Responses were amplified (50 000 times) and filtered (100–3000 Hz) before 1024 sweeps were averaged for both right and left ear stimulation. Response window was 10 ms with a cursor latency resolution of 0.02 ms per point.

Visual Potentials were recorded from three electrodes placed 5 cm on either side of a midline electrode 2 cm above theinion. All occipital (O1, O2 and O3) electrodes were referred to a midfrontal electrode with mastoid acting as ground. A checkerboard pattern reversal stimulus generated by the Mistral system was used to elicit the responses. The subject viewed the pattern (checksize = 20 mm, reversal rate 1 Hz) from a distance of one metre. Brightness and contrast were kept constant. Responses were filtered such that the bandpass was 1–125 Hz. Analysis time was set to 300 ms and 64 sweeps were averaged for each response. Latencies were measured under cursor control with a time resolution of 0.6 ms.

Somatosensory potentials were recorded to median nerve stimulation from cervical spine at Cv2 and 2 cm posterior to C3 and C4 electrode positions in the 10–20 system. All electrodes were referred to Fz with an earth strap attached proximal to the stimulation at the wrist on the arm being stimulated. Constant current electrical stimulation at a repetition rate of 2 Hz with a pulse duration of 0.3 ms at an intensity just above motor threshold was used to record the responses. Filter bandpass was set at 30–3000 Hz and an analysis window of 30 ms. Two hundred and fifty six sweeps were averaged for each response. Latencies quoted were measured with a time resolution of 0.1 ms.

Cognitive Potentials

Two auditory discrimination tasks were used to elicit cognitive potentials: 1) Frequency discrimination: 1.0 kHz versus 1.5 kHz tone burst of 100 ms and 2) Duration discrimination: 200 ms versus 100 ms tone burst of 1.0 kHz.

Subjects were seated in a comfortable chair and listened through headphones (TDH39) to a sequence of tone bursts presented at a rate of one every three seconds and their task was to press a response button as quickly as possible only when the target tone was heard. Reaction time from the onset of tone burst to the button press was recorded. The target for the frequency task was the higher frequency tone burst and for the duration task, the shorter duration burst. The discrimination of duration was judged by the majority of the subjects to be more difficult than the frequency discrimination task. For each task a total of 100 stimuli

Table 1 Mean (SD) of major component latencies of sensory potentials (ms)

Group	Controls		ME Positive		ME Negative	
VP1	—		25		12	
Number of patients	25		25		12	
Side	Left	Right	Left	Right	Left	Right
VEP P100	95.8 (7.4)	96.4 (7.3)	94.7 (7.1)	94.5 (7.5)	99.0 (10.4)	98.9 (9.9)
SEP N13	12.9 (1.0)	13.1 (0.9)	13.0 (1.0)	13.1 (1.2)	13.0 (0.96)	12.9 (0.73)
N20	18.5 (1.3)	18.6 (1.1)	18.6 (1.1)	18.7 (1.4)	18.3 (0.65)	18.4 (0.71)
ABR I	1.65 (0.16)	1.65 (0.16)	1.61 (0.15)	1.59 (0.13)	1.60 (0.13)	1.60 (0.16)
III	3.77 (0.18)	3.82 (0.19)	3.73 (0.26)	3.82 (0.15)	3.80 (0.15)	3.80 (0.25)
V	5.73 (0.19)	5.73 (0.22)	5.72 (0.24)	5.68 (0.20)	5.77 (0.19)	5.72 (0.19)

VEP = Visual Evoked Potential
SEP = Somatosensory Evoked Potential
ABR = Auditory Brainstem Responses.

were presented binaurally at 60 dBHL in a random sequence with a ratio of targets to non targets of 30/70. The subjects' performance for the number of targets correctly identified and the number missed and wrongly identified as targets was monitored. Reaction Time (RT) was recorded with a resolution of 0.1 ms.

Electrical activity was recorded from three electrode sites in the International 10:20 system, namely Fz, Cz, Pz with reference to the mastoid. Responses were amplified (50 000 times), filtered (0.3 Hz–32 Hz) and averaged using HP9836 computer. Seven hundred and sixty eight points were sampled at a rate of 1 kHz giving a window of 768 ms. Latencies quoted are those taken from the Pz electrode position.

Figure 1 Representative pattern reversal visual, median nerve somatosensory and auditory brainstem potentials from a patient with ME. All responses are within normal limits

Results

Mean and standard deviation of the latencies of brainstem, visual and somatosensory potentials are shown in table 1 for both control subjects and patients with ME. No significant differences in the major component latencies for any of the sensory potentials was found between controls and patients or between patients with VP1 positive and negative. None of the responses recorded from the patients lay outside the two standard deviation limit from the normal mean. Representative brainstem, visual and somatosensory potential recordings from one patient are shown in fig 1.

Cognitive event-related potential latencies for each component for both frequency and duration discrimination tasks for controls and patients with ME are shown in table 2. In contrast to the sensory potentials, significant differences in the mean latencies of the cognitive potential N2 ($p < 0.05$) and P3 ($p < 0.001$) were found between controls and patients with ME for the more difficult duration discrimination task but not for the standard "oddball" frequency discrimination task. Reaction time for both frequency and duration discrimination tasks were significantly ($p < 0.001$) prolonged compared with the control subjects. Performance measures of errors in identifying correct target or misclassifying a target (omission and commission) were not significantly increased for either frequency or duration tasks. A statistical comparison between the mean latencies of the major components of the cognitive potentials, reaction time and performance on the basis of the VP1 test is also shown in table 2. No significant difference emerges in any of the parameters with the VP1 test.

Further analysis has been carried out in the more homogeneous group of patients with the VP1 test positive.

Cognitive potential recordings of frequency discrimination task with their associated reaction time and error performance for all patients with ME (VP1 positive) are shown in fig 2 and those for the duration discrimination task in fig 3. A normal response is shown at the top of the respective figures for comparison. The more difficult duration task elicits a P3 with a longer latency than that obtained with the frequency task. All patients show a similar result. Mean and upper limit of normal P3 latency and reaction time are marked with vertical lines so that the responses falling outside the normal range can be clearly seen for both tasks. Analysis of individual responses for abnormality on the basis of response presence or absence and latency of P3 and RT (or errors in performance) being within the two standard deviation upper limit from the normal mean shows a significant proportion of patients to be outside the normal upper limit (table 3). Twenty (80%) of the 25 patients with VP1 positive had either P3, RT or performance abnormal on the duration task and 16 (64%) on the frequency task. Thirteen (52%) of the patients had an abnormality of P3, 12 (48%) of RT and eight (32%) of performance on either task. Nine (75%) of the 12 patients with VP1

Table 2 Comparison of Mean (SD) of latencies (ms) of Event-related potentials, reaction time and performance for frequency and duration discrimination tasks in ME and controls

	Control 25	ME 25 positive	ME 12 negative	Control vs ME positive p	Control vs ME negative p
N1F	110 (14)	110 (14)	107 (17)	0.61	0.64
N2F	231 (35)	239 (35)	241 (32)	0.49	0.88
P3F	327 (26)	345 (52)	353 (50)	0.17	0.67
RTF	351 (50)	425 (101)	462 (134)	0.002	0.42
PerF	0.76 (1.0)	2.9 (6.1)	4.0 (3.9)	0.096	0.54
N1D	107 (16)	109 (13)	112 (14)	0.61	0.51
N2D	257 (40)	288 (51)	313 (43)	0.032	0.18
P3D	398 (45)	450 (49)	458 (58)	0.001	0.70
RTD	443 (43)	513 (89)	562 (107)	0.001	0.20
PerD	1.28 (0.98)	3.6 (5.8)	5.7 (5.3)	0.063	0.31

Suffix F refers to Frequency Task and suffix D to the Duration Task. N1, N2 and P3 = cognitive potential components; RT = Reaction Time; Per = Performance. p = significance probability on Student's *t* test from independent samples with separate variance estimates.

negative had either P3, RT or performance abnormal on the duration task and eight (67%) on the frequency task. Abnormalities of the P3, RT and performance are considered further for the VP1 positive patients only.

Abnormalities of P3

For the frequency task nine (36%) patients had an abnormality of P3 with four (16%) patients

showing a delayed P3 and five (20%) having no identifiable P3 (fig 2). Seven of these nine patients with an abnormal P3 had normal RT and performance, only one each had an associated abnormality of RT or performance.

For the duration task 12 (48%) patients had an abnormal P3 of whom six (24%) were delayed and six (24%) absent (fig 3). Eight of the 12 patients with an abnormal P3 had no abnormality of RT or performance associated with it. The other four had associated RT prolongation and only one of these also had an impaired performance.

Abnormalities of RT

Reaction time was prolonged in 12 (48%) of the patients on the duration task, seven of whom also had a delayed RT on frequency task (fig 2 and 3). For the duration task only four of the 12 patients had an associated delay in P3 whilst the others had normal P3. Impairment of performance was associated with prolongation of RT in six of the 12 patients. For the frequency task only one of the seven patients with an abnormal RT had an abnormal P3 and impaired performance was only associated with four.

Figure 2 Frequency Task: Cognitive Event-related Potentials, reaction time (RT) and Performance (Perf) for all 25 patients with ME with a normal response at the top for comparison. Those marked with an asterisk were considered abnormal either in terms of amplitude or latency. Vertical lines indicate normal mean and 2SD limits.

Figure 3 Duration Task: Cognitive Event-related Potentials, reaction time (RT) and Performance (Perf) for all 25 patients with ME with a normal response at the top for comparison. Those marked with an asterisk were considered abnormal either in terms of amplitude or latency. Vertical lines indicate normal mean and 2SD limits.

Table 3 Number of patients with abnormal results

	Frequency Task		Duration Task	
	VP1 Positive	VP1 Negative	VP1 Positive	VP1 Negative
P3 absent	5	1	6	1
P3 delayed	4	3	6	3
RT	7	3	12	7
Performance	5	4	6	5

Abnormalities of performance

Errors of performance for incorrect target identification was impaired in five patients for the frequency task and six for the duration task. In the frequency task, of the five patients only one had an associated P3 abnormality whereas four had an RT prolongation but normal P3. Similarly, for the duration task only one patient had an abnormal P3 associated with impaired performance whereas all had RT prolongation.

P3 latency/RT Correlation

P3 latencies for all patients and control subjects plotted against reaction time (RT) for the frequency task are shown in fig 4 and those for the duration task in fig 5. Pearson correlation coefficients for P3 latency with RT for both frequency and duration tasks were compared for the control and ME (VP1 positive) group in table 4. P3 latency for the duration task was significantly ($p < 0.01$) correlated with RT in the normal control group. There were significant differences in the correlations for P3 and RT between the two groups. For the frequency task the correlation coefficient was 0.44 for the controls and only 0.18 for the ME patients, a similar difference was observed for the duration task with respective figures of 0.60 and 0.38.

P3 latency/Performance Error Correlation

There were no significant correlations between P3 latency and performance error scores for either task although the correlation coefficients for the ME group were much lower than those for the normal group (table 4).

RT/Performance Error Correlation

For the control group (table 4) there was no significant correlation ($r = 0.12$) between RT and performance for the frequency task but it was significant for the duration task ($r = 0.65$). For patients with ME similar results were obtained (table 4) in that the coefficient of correlation for the duration task was significant at $r = 0.59$ but not for the frequency task at $r = 0.33$.

Figure 4 Frequency Task: The relationship between P3 and RT for the VP1 positive patients and normal subjects is shown. The smaller rectangle indicates the upper limit for the range of P3 and RT. Those patients lying outside are either abnormal in P3 or RT.

Figure 5 Duration Task: The relationship between P3 and RT for the VP1 positive patients and normal subjects is shown. The smaller rectangle indicates the upper limit for the range of P3 and RT. Those patients lying outside are either abnormal in P3 or RT.

Effect of task difficulty

From the subjective reports of control subjects it is clear that the duration discrimination task is more difficult than the frequency task. This is also borne out by the differences in the mean latency of P3 and reaction times for the two tasks. In comparing the two tasks, it is clear that abnormality of one parameter (P3, RT or performance) on frequency task was mostly associated with an abnormality of the same parameter on the duration task. However, abnormalities on the duration task also occurred independently.

Discussion

The sensory potentials of the visual, auditory brainstem, and median nerve somatosensory systems remain unaffected in ME. This is in contrast to the abnormalities of evoked potentials observed in multiple sclerosis (MS),^{27,28} a disorder with known structural and functional abnormalities of the central nervous system. In the early stages of MS symptoms may be similar to those associated with ME which may pose a problem of differential diagnosis. Clearly sensory potentials provide a means of separating the two groups.

In contrast to the normal sensory potentials, there is clear objective evidence from this study that endogenous event-related potential, P3 is absent or significantly delayed in 52% of the patients. This finding is consistent with the universal complaint of these patients of impairment of cognitive functioning in the form of disturbances of memory and concentration. Furthermore the extent of cognitive potential abnormalities in the 12 patients who were VP1 test negative was not significantly different from those who were VP1 test positive. The psychological processes involved in the type of cognitive tasks used in this study require encoding of stimulus features, detection of relevant signal by comparison with memory and execution of response. The amplitude of P3 provides an indication of attentional capacity devoted to the task and its latency provides a measure of the speed of target detection.²⁰ In the ME group, P3 was delayed in some patients whilst in others the amplitude was diminished, sometimes to an extent that the response was labelled as "P3 absent". This implies two subgroups one with attentional deficits and the other with slower speed of information processing. Those with "P3

Table 4 Pearson correlation coefficient between P3 latency, RT, and performance for frequency and duration tasks

	Frequency Task		Duration Task	
	Controls	ME VP1 Positive	Controls	ME VP1 Positive
P3 latency/RT	0.44	0.18	0.60*	0.38
RT/Performance	0.12	0.33	0.65*	0.59*
P3 latency/Performance	0.15	0.03	0.48*	0.04

1-tailed Significance: * = 0.01.

absent" had normal performance and reaction time suggesting that the effect on P3 was not due to a diffuse effect on arousal or due to general fatigue. It is interesting that similar effects on P3 have been noticed with administration of scopolamine, a centrally active cholinergic blocking agent, which has a detrimental effect on recent memory and attention.²⁹ Hammond *et al*³⁰ showed that scopolamine abolishes P3 without affecting performance although the subject reported difficulty in maintaining attention. In a number of ME patients this precise effect was observed. In the study of Hammond *et al*³⁰ alteration in P3 also correlated with poor scores on tests of recent memory and at the end of the recording session, P3 and memory scores were restored to their original values indicating that the observed effects on P3 were not due to fatigue.

In terms of accuracy of performance there was no statistical difference in the error scores between the control and ME group. At most, 24% of the ME patients had impaired performance but this was not always associated with an abnormality of P3. Normal task performance with normal N1 and P2 peaks suggest that each stimulus is correctly categorised, and in terms of the response, it appears to be appropriately encoded as shown by N1/P2. Normal task performance also indicates accurate detection and categorisation processes but under these circumstances absence of P3 implies that these processes may not be occurring at the same time on each stimulus occurrence to generate a synchronous neural electrical field for generation of a P3.

Several studies have shown that specific psychological processes associated with the P3 component are attention,^{31,32} stimulus evaluation³⁰ and memory.^{34,35}

Thus, it appears that abnormalities of P3 reflect clearly the subjective difficulties of concentration and memory described by patients with ME and indeed provides corroborative evidence of deficiencies in the psychological processes involved. It has been suggested that symptoms associated with ME such as profound fatigue on physical and mental exertion can also be due to an affective disorder such as depression.³⁶⁻³⁸ Thus, it is significant that Pfefferbaum³⁹ in his review of studies⁴⁰⁻⁴³ evaluating abnormalities of P3 in mental disorders concluded that "for depressed patients there are almost no reports of significant changes in P3 latency, while amplitude reduction is a variable finding".

Further studies⁴⁴⁻⁴⁸ have confirmed that P3 latency is normal in patients with depression. It

would appear, at least on the basis of the cognitive potentials, that depression is not a factor responsible for the abnormalities detected in patients with ME. From the relationship of P3 abnormality, RT prolongation and task performance, it is clear that if general fatigue was an important factor in determining the abnormalities then all three parameters (P3, RT and Performance) should have been affected much more in association with one another than they actually were (table 4). Although RT was significantly prolonged in patients with ME compared with normal controls, RT prolongation was not always associated with prolongation or absence of P3 and in fact the correlation between P3 latency and RT in ME was much lower than in normals. There was a greater correlation of RT with performance than with P3 or of performance with P3. This implies that accuracy of performance is a factor of influence for RT but not for P3. It suggests further that although both P3 and RT are affected in patients with ME, they reflect separate processes. At its simplest, it may be argued that stimulus evaluation stages are affected in patients with an abnormal P3 but normal RT, whilst response activation and execution stages may be affected in those in whom RT was prolonged but P3 was normal as the influence of one parameter on the other appears to be minimal.

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