'Fatigue' in Patients With Multiple Sclerosis

Motor Pathway Conduction and Event-Related Potentials

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• **Ten patients with a definite diagnosis of multiple sclerosis and complaints of "fatigue" were studied using (1) reaction times and event-related potentials accompanying the performance of auditory memory tasks (target detection, verbal short-term memory) and (2) motor conduction velocities of the pyramidal tract elicited by cerebral and cervical magnetic stimulation. Patients were studied when "rested" and when fatigued. Reaction times of the patients when rested were significantly delayed in the short-term memory but not the target-detection tasks when compared with normal controls. When patients were fatigued, their reaction times became significantly longer in all tasks compared with when they were rested. Event-related potentials in these tasks consist of N_1/P_2 sensory components and P_{3a} and P_{3b} cognitive components. The N_1 component latency was longer and P_{3a} and P_{3b} amplitudes were reduced in patients compared with controls. Fatigue in patients with multiple sclerosis was accompanied by a shortening of P_{3a} latency and an increase in P_{3a} and P_{3b} amplitudes compared with these measures when patients were rested. Pyramidal tract conduction velocities did not differ between rested and fatigued conditions. Thus, fatigue in patients with multiple sclerosis was associated with a slowing of performance (reaction time) on memory tasks, whereas brain potentials reflecting neural events of stimulus encoding and classification were either unchanged or paradoxically speeded up in latency in the fatigued compared with the rested conditions. We postulate that, in patients with multiple sclerosis, fatigue affects neural processes acting after stimulus evaluation but before activation of the primary motor pathways.**
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Fatigue is a common experience that refers to a slowing and/or worsening of performance, usually brought about after prolonged activity.[1] While changes in muscle metabolism can follow prolonged exertion,[2] the experience of fatigue probably has multiple explanations, since it is experienced in a wide range of diseases (eg, hepatitis, cardiac failure, systemic infection) and in normal persons following effortful cognitive functions.[3] Patients with multiple sclerosis (MS) note fatigue as a major and often presenting symptom.[4,5] This experience is not restricted to motor acts but also affects cognitive activities.[6,7]

Techniques are available to quantify the function of the central pathways subserving both motor action using transcranial magnetic or electrical stimulation[8] and cognitive activity using event-related potentials recorded from surface electrodes.[9] Components of event-related potentials recorded during the performance of cognitive tasks are related to sensory processes,[10] stimulus evaluation, and stimulus classification.[11,12] Moreover, when these potentials are recorded from subjects engaged in tasks measuring particular cognitive functions, such as short-term memory, they can be related to specific activities, such as memorization,[13] maintenance of the memory trace,[14] and memory scanning.[15] Abnormalities of event-related potentials during cognitive tasks have been demonstrated in patients with MS,[16] raising the possibility that these alterations may also index altered cognitive functions accompanying fatigue. This study of patients with MS measured event-related potentials and performance (reaction time [RT] and accuracy) in tasks of auditory short-term memory (target detection to musical notes and auditory verbal short-term memory) when they were "rested" and when they were fatigued. The conduction times of the central motor pathways evoked by magnetic stimulation[8] were also measured in the rested and fatigued conditions.

SUBJECTS AND METHODS

Ten patients of both genders (two men, eight women) with a mean (±SD) age of 39.3 ± 4.4 years (range, 29 to 43 years) participated in the study. They had a "certain" diagnosis of MS based on the criteria of at least two separate clinical episodes with neurological signs and multiple periventricular lesions on magnetic resonance imaging. Clinical details regarding the patients are contained in Table 1. We selected patients with minimal weakness or sensory loss of the upper extremities to reduce the influence of such deficits on their ability to press a response button. They were cognitively intact on clinical assessment, with Mini-Mental State[17] scores averaging 28.9 (range, 26 to 30). The extent of their fatigue on the Krupp Fatigue Severity Scale[18] averaged 5.2 (range, 2.4 to 6.8), indicating that, in general, their degree of fatigue was high. Four of the 10 patients were slightly depressed: three of them were receiving antidepressant medications (amitriptyline, trazodone). Use of these medicines was discontinued 4 days before testing. Depression can be associated with the sense of fatigue. All patients were tested on two separate occa-

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Table 1.—Patient Profiles*

Patient No./ Age, y/y From Onset/Sex	Disability Score[47]	Symptoms (Main)	MRI Lesions	Krupp Scale[18]	Medication
1/40/18/F	4	Ataxia, vision	Periventricular	4.2	Azathioprine, prednisone, amitriptyline hydrochloride
2/29/5/F	7	Ataxia, bladder, paraparesis	Periventricular, cerebellum, brain stem	2.4	Azathioprine, prednisone, alprazolam
3/40/14/F	6.5	Ataxia	Periventricular, brain stem	5.3	Baclofen
4/42/10/F	3.5	Ataxia, affect, paraparesis	Periventricular, centrum semiovale	6.8	Prednisone, azathioprine
5/39/20/F	6.5	Bladder, ataxia, numbness LEs, paraparesis	Periventricular, spinal cord, centrum semiovale, brain stem	4.4	Azathioprine, prednisone, fluoxetine hydrochloride
6/43/4/M	5	Vision, affect, weakness	Centrum semiovale, optic nerve, brain stem	6.4	Prednisone, azathioprine, trazodone hydrochloride
7/44/20/M	4.5	Ataxia, bladder, weakness	Periventricular	5.3	Azathioprine, prednisone, amitriptyline
8/38/14/F	4.5	Ataxia, memory, vertigo	Periventricular, brain stem	6.2	. . .
9/35/5/F	4.5	Vision, memory	Periventricular	5.8	. . .
10/42/5/F	4.5	Ataxia, vision, numbness	Periventricular, centrum semiovale	5.1	Amantadine hydrochloride, triazolam

*MRI indicates magnetic resonance imaging; LEs, low extremities.

sions: once in a relatively rested state and the other in a relatively fatigued state, the latter usually being late in the day. A comparison of these two states was made by grading the continuum between rested and fatigued on a scale from 0 ("without fatigue") to 10 ("the most exhausted state ever experienced"). All of the patients had a minimum difference score of 4 between the two tests. We did not counterbalance the sequence of testing, as the initial test in eight of the patients was in the rested state. We believe the role of depression in the study was minimal, since patients were tested on two occasions, usually 1 week apart, in which the extent of fatigue differed while the state of depression did not change.

Brain Potential Recordings

Subjects were seated in a sound-attenuated room with scalp electroencephalography electrodes positioned at F_z, C_z, P_z, C_3, C_4, T_5, and T_6. Electrodes on each earlobe were linked together as the reference. Eye movements were monitored from electrodes positioned above and below the right eye to assist in data analysis during the subsequent averaging procedures. The interelectrode impedances were below 2 kΩ. Brain activity was amplified with a band pass of 0.1 to 100 Hz, digitized at 200 Hz, and stored on a computer for subsequent averaging and data analysis.

Experimental Procedures

Recordings were made with the subjects wearing earphones, sitting, and fixating on a point directly ahead. They were instructed to refrain from blinking during particular portions of the tasks. Two discrimination tasks were employed that have been described in detail elsewhere,[13] and only a brief account is presented herein. The first was an auditory target-detection test, in which the subject was instructed to press an RT button "as accurately and as rapidly as possible" when the target stimulus occurred. The stimuli consisted of 300 notes, 20% of which were of a high pitch (high D) representing the target, interspersed randomly among low-pitched notes (middle C, one octave below). Stimulus duration was 50 milliseconds, intensity was 60 dB normal hearing level, and the interstimulus interval was 2 seconds.

The second task was a short-term verbal memory test in which verbal items (the digits 1 through 9) were presented in the auditory modality for memorization followed by a probe item that the subject classified (by an appropriate button press) as being (in set) or not being (out of set) a member of the preceding memory set.[19,20] Two memory set lengths were used, containing one and five items. For each memory set length, two series of 20 trials were presented, providing a total of 20 in-set and 20 out-of-set stimuli. Stimulus intensity was 60 dB normal hearing level, with the memory items presented at 1.2-second intervals. A 2-second interval separated the last memory item from the probe. Three seconds intervened before the start of the next trial.

Event-Related Potentials

Averaged brain potentials were made to the probes in the short-term memory task and to the targets in the target detection task that had a correct response without an eye blink in the 1-second period surrounding the stimuli. The averages were 1 second in length for targets and 1.28 seconds in length for probes, and both included a 120-millisecond prestimulus baseline. The latencies and amplitudes of the averaged event-related potentials recorded at the P_z electrode to the targets were measured at the peaks close to 100 (N_1), 200 (P_2), 280 (N_2), and 300 milliseconds (P_{3b}). In the short-term memory tasks, the potentials to the probes at the P_z electrode were measured at the peaks close to 150 (N_1), 250 (P_2), 300 (N_2), and 450 milliseconds (P_{3b}), all slightly delayed compared with the peaks of the averaged potentials to the notes used in the target detection task. The P_3 components of the target and probe evoked potentials also have an early peak, P_{3a}, most prominent in the frontal lead from which peak measures were made. The P_{3b} components were also measured using an average amplitude in a 500-millisecond time window fixed from 450 to 950 milliseconds for the short-term memory task and in a 200-millisecond window for the target-detection task with the midposition adjusted for each subject to coincide with the peak of P_{3b}.

Motor Evoked Potentials

A magnetic stimulator coil (Cadwell MES-10, Cadwell Lab Inc, Kennewick, Wash; coil diameter, 9.5 cm) was used to activate the motor cortex and cervical roots. Recording electrodes were placed on the skin overlying the opponens pollicis muscle con-

Table 2.—Behavioral Measures*

	Tasks		
	TD	STM, 1 Item	STM, 5 Items
Reaction Time, ms			
Controls	368±110	562±93	764±128
Patients			
Rested	477±140	899±146†	1358±243†
Fatigued	556±178‡	1042±266‡	1425±257‡
Accuracy, %			
Controls	99.9±0.1	99.7±0.3	99.7±0.3
Patients			
Rested	99.9±0.1	98.2±0.5	92.7±1.6†
Fatigued	99.8±0.2	98.5±0.5	90.7±2.1

*TD indicates target detection; STM, short-term memory.
†$P<.05$, patients rested vs controls.
‡$P<.05$, patients fatigued vs patients rested.

tralateral to the cortex and ipsilateral to the root being stimulated. The magnetic stimulus duration was 0.07 milliseconds, and its intensity was gradually increased until a reproducible electromyographic potential was obtained both in a relaxed state and with minimal contraction of the opponens pollicis. The difference in latency between the electromyographic potential onset to cortical and to nerve root stimulation represents the conduction time of the central motor pathway.

Data Analysis

The results from a group of 10 young normal subjects (average age, 29 years; range, 18 to 45 years) previously tested with the same paradigms[13] were included in these analyses. The controls were approximately 10 years younger than the patients. While it is ideal to have no difference, studies of RTs using larger numbers of subjects over a wide age range are essentially no different across the decades for 20- to 30- vs the 30- to 40-year-olds.[21,22] Event-related potential amplitudes can decrease with age, but the differences only become significant with 30- to 40-year age disparities.[23] Measures of RT, accuracy, and the amplitudes and latencies of event-related potentials were tested for significance using analysis of variance for the factors of the patients' state (rested, fatigued), task type (short-term memory, one item; short-term memory, five items; target detection), and subject type (patients when rested, controls). The data for the in-set and out-of-set probes in the short-term memory tasks were combined since a separate analysis (analysis of variance) of the results from the short-term memory tasks showed no significant differences as a function of probe type. Significance level was set at $P<.05$ after adjusting with the Greehouse-Geisser correction factor. Significance of interactions in the analysis was evaluated using the Neumann-Keuls correction.

RESULTS

Behavior

Across all subjects, accuracy was almost perfect (>99%) in the target-detection and the one-item short-term memory tasks but decreased significantly ($P<.001$) from 96% in the five-item short-term memory task. The reduction in accuracy on the five-item task was due to the patients with MS, whose performance decreased to 92.8% correct when rested compared with the controls' accuracy of >99% ($P<.001$; Table 2, Fig 1). The patients' performance decreased to 90.8% when they were fatigued, but the change was not significantly different from their performance when they were rested.

Reaction times (Table 2) were significantly different

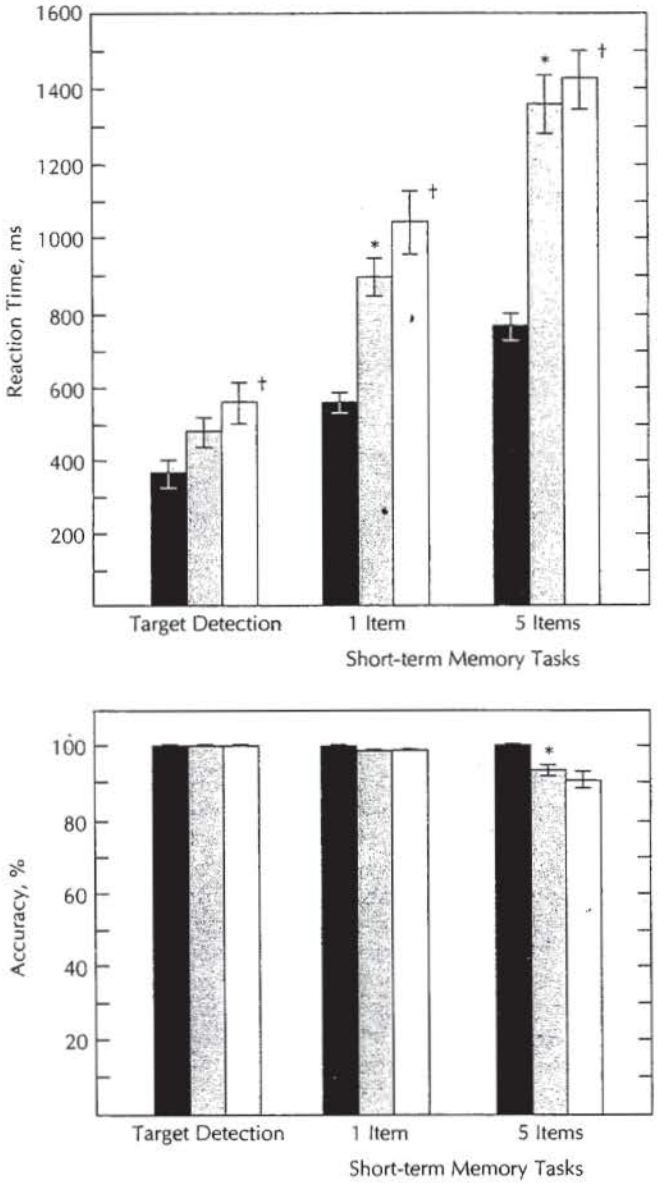

Fig 1.—*Bar graph of reaction times (RTs) and accuracy for controls (closed bars) and patients with multiple sclerosis (MS), rested (shaded bars) and fatigued (open bars), for the target-detection and short-term memory tasks. Asterisk indicates $P<.05$ for controls vs patients with MS when rested; dagger, $P<.05$, patients rested vs patients fatigued. Note the striking effect of task on RTs of the patients and the consistent lengthening of RT in patients when fatigued compared with when rested.*

($P<.001$) as a function of task, being longest with the five-item short-term memory task (1392 milliseconds), intermediate in the one-item task (971 milliseconds), and shortest in the target-detection task (517 milliseconds) across all subjects (rested patients and controls). Reaction times were significantly longer ($P<.01$) in patients with MS when rested compared with controls (Fig 1) for the short-term memory tasks (a difference of 337 milliseconds for one-item and 594 milliseconds for five-item task), but the difference (110 milliseconds) for the target-detection task did not achieve significance. For the patients, RTs increased significantly ($P<.05$) between the rested and fatigued states in all tasks, ranging on the average between 80 and 150 milliseconds. Thus, patients with MS when rested have significantly longer RTs as a group

compared with controls, and when patients with MS become fatigued, their RTs become even further delayed. An analysis of RT for each patient with MS showed that eight of 10 had longer RTs when fatigued compared with the rested condition for the short-term memory tasks and seven of 10 for the target-detection task.

In short-term memory tasks, RTs increase in a linear manner with memory load. The slope of this function, expressed in milliseconds per item, has been proposed as a measure of the time required to scan the contents of the short-term store before a response can be made.[19] In the control subjects of this study, scanning times averaged 50.5 milliseconds per item for auditory verbal material, while in the patients with MS scanning times increased significantly ($P<.05$), more than twofold, to 115 milliseconds per item without any further significant changes with fatigue (Fig 1).

Event-Related Potentials

Latency.—The evoked potentials to the stimuli used in these tasks consist of the initial short-duration negative/positive sensory complex (the N_1/P_2) between approximately 100 and 300 milliseconds, a subsequent negative wave, the N_2 (200 to 300 milliseconds), followed by a cognitive long-duration (500 milliseconds) positive component beginning at about 350 milliseconds. The latency of all the peaks differed significantly ($P<.001$) between tasks, being longer in the short-term memory tasks compared with the target-detection task (Table 3). The magnitude of the difference was approximately 50 milliseconds for N_1, P_2, and N_2, most likely reflecting differences in the rise times of the acoustic stimuli in the tasks: the digits used in the short-term memory tasks have an acoustic envelope with gradual rise times (up to 50 milliseconds), while the the notes used in target-detection had relatively fast rise times (5 milliseconds). Onishi and Davis[24] have shown the latency of the N_1/P_2 components to increase when rise times exceed 30 milliseconds. The latency difference for the P_3 components varied from 70 milliseconds for the frontal P_{3a} component to as much as 330 milliseconds for the parietal P_{3b} component. The magnitudes of these differences are unlikely to be due to the physical nature of the stimuli but, rather, to differences in the cognitive demands of the two tasks (target detection vs verbal short-term memory), as is evident in RT differences.

The latency of the event-related potentials differed significantly ($P<.05$) between controls and patients for only the N_1 component in all tasks, being approximately 15 milliseconds longer in the patients. A significant difference was noted in the latency of the P_{3a} component for all tasks as a function of the patients' state, ie, rested vs fatigued: P_{3a} was of shorter latency when the patients were fatigued compared with when they were rested, with the difference ranging from 15 milliseconds for target-detection to 29 milliseconds for short-term memory tasks. No other differences in peak latencies were defined.

The interval between N_1 and P_{3a} is a measure of the temporal pace of brain events accompanying the processing of acoustic stimuli reflecting the period between sensory processes (N_1) and cognitive evaluation (P_{3a}). This interval was approximately 250 milliseconds and did not differ significantly between tasks or between controls and patients with MS. The N_1 to P_{3a} interval in patients with MS was approximately 20 milliseconds less when they were fatigued than when rested in the short-term memory tasks, but the difference did not reach statistical significance.

In normal subjects, the latency of P_{3b} increases with memory load in a linear manner, with a slope of approximately 25 milliseconds per item,[13,25] approximately half that of the slope for RT. In the patients of this study, P_{3b} latency did not change significantly between the one- and five-item memory loads in distinction to the prolonged scanning rates apparent from RT measures.

Amplitude.—Only the amplitudes of the P_{3a} and P_{3b} components were significantly affected by the experimental variables: P_{3a} and P_{3b} significantly ($P<.001$) differed according to task, being larger for target-detection than for short-term memory tasks (Table 3). The patients had significantly ($P<.05$) lower amplitudes than the controls for P_{3b} (peak measure in the one-item short-term memory task; average amplitude in both the one- and five-item tasks). These differences are apparent in the grand averages plotted in Fig 2. Inspection of the individual averages in the short-term memory tasks also reveals that the sustained positivity, P_{3b}, characteristic of the normal subjects was of negative rather than of positive polarity in four of the 10 patients. The amplitude of the frontal P_{3a} component differed significantly as a function of the patients' state (rested vs fatigued) for all tasks, with P_{3a} amplitudes being larger when patients were fatigued than rested. The grand averages of the potentials recorded from F_z in the patients with MS when rested and fatigued are contained in Fig 3.

Motor Evoked Potentials

The motor potentials evoked by magnetic stimulation were tested in the rested and fatigued conditions in nine of the patients. In three of these patients, motor evoked potentials from stimulation of the motor cortex could only be obtained when the opponens pollicis was voluntarily contracted to a slight degree (facilitation). The central conduction times to the cervical cord were abnormal in three patients (>12.5 milliseconds without facilitation and >11 milliseconds with facilitation). The group average (Table 4) of 13.0±1.8 milliseconds without facilitation and 10.3±3.6 milliseconds with facilitation is slightly greater than the normal values from our laboratory (9.5±1.2 and 8.0±1.2 milliseconds, respectively). No significant difference was noted in central motor conduction times in the patients when rested and when fatigued. In addition, no significant correlation was found between central motor conduction times and RTs in each of the tasks.

COMMENT

The results of this study of a group of patients with MS show that performance and brain potentials were affected in different ways by fatigue. Reaction times were prolonged in a simple auditory discrimination task (distinguishing an infrequent high note, the target, randomly occurring during a sequence of frequent low notes requiring a go/no-go response) and in a complex auditory verbal short-term memory task (distinguishing whether a probe item was or was not a member of the preceding memory list, requiring a two-alternative forced-choice response). In contrast, the event-related potentials to the target or the probe were no different between the rested and fatigued conditions except for the cognitive component, P_{3a}. The latency of this component paradoxically

Table 3.—Evoked Potentials*

Peaks	Subjects	Tasks: TD	Tasks: STM, 1 Item	Tasks: STM, 5 Items
		Latency, ms		
N_1	Controls	102±13	157±18	150±13
	Patients			
	Rested	115±10†	165±24†	168±15†
	Fatigued	113±17	159±10	163±17
P_2	Controls	174±12	235±18	225±33
	Patients			
	Rested	185±17	242±29	239±21
	Fatigued	182±14	248±17	245±22
N_2	Controls	224±17	287±13	302±30
	Patients			
	Rested	231±18	310±37	327±50
	Fatigued	229±16	313±33	328±47
P_{3a}	Controls	333±18	403±30	407±29
	Patients			
	Rested	356±34	420±31	448±62
	Fatigued	340±39‡	396±27‡	419±62‡
P_{3b}	Controls	351±33	579±101	686±93
	Patients			
	Rested	359±34	670±51	686±38
	Fatigued	355±35	663±92	683±78
$P_{3a}-N_1$	Controls	231±25	246±39	257±34
	Patients			
	Rested	241±37	254±39	279±64
	Fatigued	226±37	237±29	256±66
		Amplitude, v		
N_1	Controls	−3.4±2.6	−4.4±2.4	−4.9±2.5
	Patients			
	Rested	−4.2±1.9	−4.4±2.8	−4.3±3.0
	Fatigued	−3.8±2.9	−4.2±2.5	−4.7±2.5
P_2	Controls	2.1±2.2	1.6±2.5	0.9±2.2
	Patients			
	Rested	3.4±2.8	1.6±2.8	2.5±2.3
	Fatigued	3.4±3.4	3.2±3.2	2.1±1.8
N_2	Controls	−1.3±2.4	−0.6±2.4	−2.8±1.8
	Patients			
	Rested	−0.7±3.2	−2.5±2.6	−2.8±2.1
	Fatigued	−0.9±4.1	−0.4±2.3	−2.0±1.6
P_{3a}	Controls	3.9±4.1	3.5±2.4	1.1±2.0
	Patients			
	Rested	5.8±3.6	3.6±2.9	1.1±2.5
	Fatigued	7.2±2.5‡	5.3±2.7‡	2.1±2.0‡
P_{3b}	Controls	14.2±5.1	11.2±3.5	10.0±4.5
	Patients			
	Rested	12.6±4.6	3.8±4.0†	5.2±5.0
	Fatigued	12.1±4.4	5.7±2.6	6.1±2.5
Average amplitude, P_{3b}	Controls	9.6±3.9	6.7±2.7	7.3±3.6
	Patients			
	Rested	8.1±3.7	1.4±3.6†	2.2±3.9†
	Fatigued	8.1±3.4	2.7±2.3	2.8±2.3

*TD indicates target detection; STM, short-term memory.
†$P<.05$, patients rested vs controls.
‡$P<.05$, patients fatigued vs patients rested.

decreased and its amplitude increased with fatigue in all of the tasks. Finally, the central conduction times of the pyramidal motor pathways were no different between the fatigued and rested states. Thus, fatigue in patients with MS is associated with a prolongation of RT without change in pyramidal tract conduction times.[8] Brain potentials reflecting neural events of sensory processes and stimulus evaluation[12] were generally no different between rested and fatigued states except for a particular frontal component, P3a, which was paradoxically shortened in latency and increased in amplitude with fatigue.

The P_3 components of event-related potentials can be divided into an early component, P_{3a}, maximal frontally, and a later component, P_{3b}, maximal parietally,[26,27] reflecting neural events underlying stimulus evaluation. The amplitudes of these components are dependent on factors

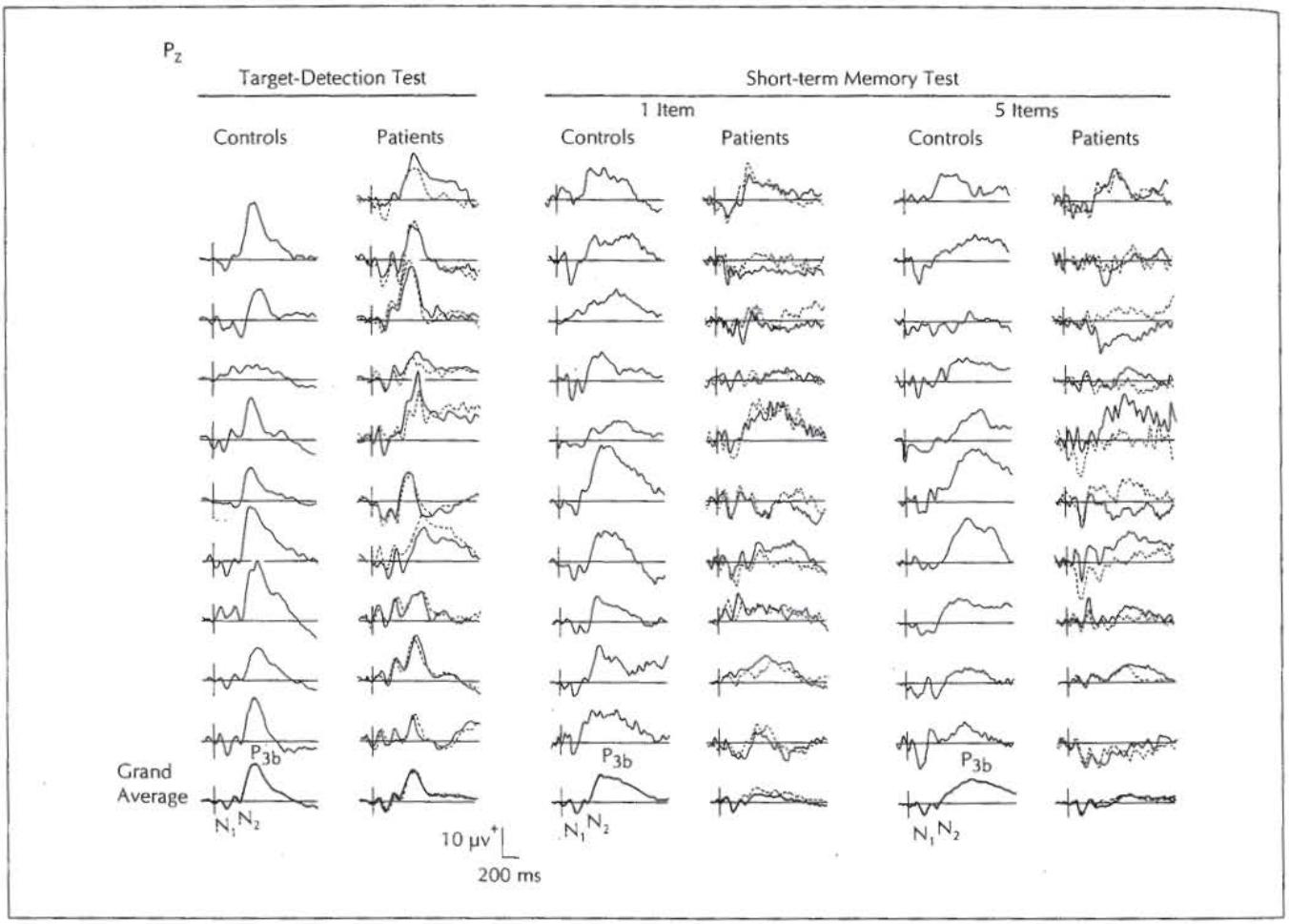

Fig 2.—*Individual and grand average evoked potentials recorded from the P_z electrode in target detection and short-term memory tasks for controls and for patients with multiple sclerosis (MS), rested (solid tracing) and fatigued (broken tracing). Note that the positive potential, P_{3b}, is smaller in amplitude in patients with MS than in controls in the short-term memory tasks but not in the target-detection task. There is no consistent difference across all tasks between the rested and fatigued conditions. Measures of latency and amplitude of the various peaks are given in Tables 2 and 3.*

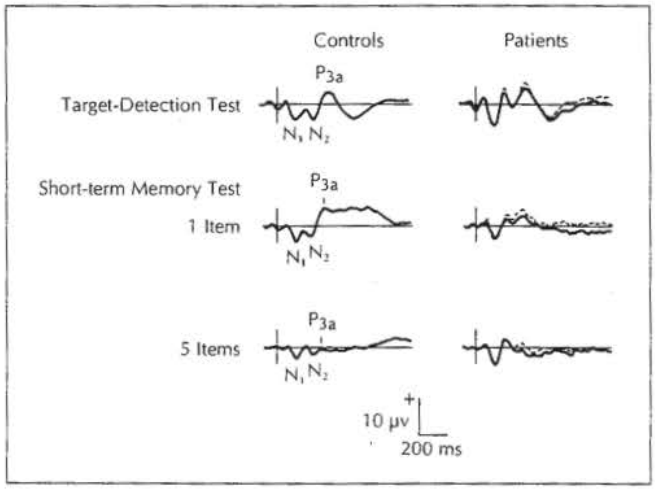

Fig 3.—*Grand-averaged evoked potentials recorded from the F_z electrode in controls and in patients with multiple sclerosis when rested (solid tracing) and fatigued (broken tracing). Note the increase in amplitude of the P_{3a} positive component in all three tasks when patients were fatigued compared with rested.*

Table 4.—Central Motor Pathway Conduction Times (ms), Cortex to Cervical Cord

	Patients		Normal Controls
	Rested	Fatigued	
Relaxed	13.0±1.8	13.6±3.9	9.5±1.2
Facilitated	10.3±3.6	11.6±4.7	8.0±1.2

of stimulus probability and task difficulty.[28] The amplitudes of the two subcomponents of P_3 behave differently, depending on the relationship between the stimulus and the subject's instructions. A P_{3a} can appear in response to a novel stimulus in the absence of any instruction to the subject to process that stimulus,[29] suggesting that it is associated with neural events subserving arousal. In contrast, the appearance of a P_{3b} requires the subject to process and respond to the stimulus.[30] The finding, in this study, that P_{3a} amplitude is increased and its latency shortened in patients with MS when fatigued compared with the rested state may reflect that fatigue involves neural systems regulating arousal. The failure to detect changes in the P_{3b} component indicates that neural

systems subserving stimulus classification appear to be relatively unaffected by fatigue.

Fatigue in patients with MS is accompanied by prolonged RTs without changes in P_{3b}, indicative that neural processes intervening between stimulus evaluation and the initiation of motor events are affected. This would encompass the period between the P_{3b} component, reflecting stimulus evaluation, and the period of activation of pyramidal tract neurons subserving motor systems used in the button press. In normal subjects engaged in the one-item memory-scanning task, we estimate this period to be approximately 160 milliseconds in duration, beginning with the onset of the P_3 component, which is at about 300 milliseconds after the probe's presentation, and ending just before the activation of pyramidal tract neurons used in the button press response (at about 460 milliseconds, 80 milliseconds before the actual RT of 540 milliseconds).[31,32] For the target detection task, the period intervening between the onset of the P_3 component, at approximately 250 milliseconds, and the activation of pyramidal tract neurons, at approximately 290 milliseconds, is only 40 milliseconds in duration. Using these same methods for the data from patients with MS, the period intervening between stimulus evaluation and motor pathway activation in the one-item memory-scanning task is threefold longer than in normal subjects, being almost 450 milliseconds in duration. When these patients are fatigued, the period increases even further, to 900 milliseconds. For the target detection task, the values are 150 milliseconds when rested and 225 milliseconds when fatigued. Thus, for patients with MS, the time intervening between brain events subserving stimulus evaluation and those involved in the initiation of motor responses is prolonged for simple and complex auditory discriminations, and these periods become further prolonged with fatigue.

There are several mechanisms by which fatigue could impair performance on the tasks used in this study. First, fatigue could affect attention, leading to impaired performance. We do not think this possibility is likely, since only RT and not accuracy changed between the rested and fatigued conditions.

A second possibility is that alterations in stimulus evaluation could lead to impaired performance, particularly when the subject is fatigued. Brain potentials accompanying the stimuli being evaluated differed considerably from those of normal subjects when rested.[16] It may be that performance based on altered neural processing of sensory information would be subject to additional impairment when subjects become fatigued. For example, for normal subjects performing discrimination tasks, P_3 latencies and RTs are prolonged when sensory stimuli are degraded compared with these measures when the sensory stimuli are clear.[33]

A third possibility is that core temperature is raised in patients with MS when fatigued, leading to alterations of nerve conductions in demyelinated fibers.[34] While we did not measure our patients' temperature, we do not think this possibility likely since pyramidal tract conduction velocities did not differ between the rested and fatigued states.

A fourth consideration is that a circulating neurohumoral factor is present in the brains of patients with MS that affects neural functions, leading to fatigue. An example of such a factor is interleukin 2, which has been discussed as participating in the symptoms of neural dysfunction in certain immune states.[35] Such a factor might act to "disconnect" neural systems subserving stimulus evaluation from response systems.[36] The sites of many of the lesions of MS are in the periventricular and subcortical white matter, well disposed to affect pathways interconnecting sensory, cognitive, and motor cortices involved in auditory discrimination tasks.[37-40] Changes in the synchrony of activity or the speed of conduction between these sites could account for the findings of delayed RTs in patients with MS accompanying fatigue.

The "readiness" or premovement potential reflects neural events underlying the initiation of motor responses.[41,42] In normal subjects, when a particular movement is fatigued with repetition, premovement potentials become larger, presumably reflecting increased central "effort" to accomplish the same motor task.[43] The analysis of such premovement potentials in patients with MS would appear to be an appropriate direction for investigation.

Fatigue is a frequent concomitant of a variety of illness, such as systemic viral infections,[44] depression,[1,45] or strokes.[46] The present study in patients with MS has provided measures of fatigue that could be examined in other disorders characterized by easy fatigability. For instance, in a recent study in patients with fatigue accompanying myalgic encephalomyelitis,[47] RT and P_3 components of event-related potentials were abnormally delayed compared with controls, findings that differed from this study of patients with MS. Finally, the experience of fatigue in normal subjects could also be examined to define if alterations in RTs or event-related potentials are present. In a preliminary study of two normal subjects, fatigued after sleep deprivation or overwork, RTs and brain potentials were unchanged.

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