An electrophysiological study of the mechanism of fatigue in multiple sclerosis

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Summary
Fatigue is a common and disabling symptom in multiple sclerosis, occurring at a time when there is minimal or no neurological disability (Krupp et al., 1988). As many as 40% claim it to be their most serious symptom (Murray, 1985). Several lines of clinical evidence suggest that fatigue is related to the underlying pathophysiology of multiple sclerosis. First, it is strongly temperature-dependent (Krupp et al., 1988). Secondly, fatigue may be the presenting symptom of multiple sclerosis, occurring at a time when there is minimal or no neurological disability (Krupp et al., 1988). Thirdly, acute episodes of fatigue may occur in isolation, similar to typical acute neurological relapses of multiple sclerosis (Freal et al., 1984; Murray, 1985). Fatigue may even herald typical relapses (Freal et al., 1984) or be a prominent symptom within these relapses (Geisser, 1985). Although some therapeutic agents have shown promise (Murray, 1985; Cohen and Fisher, 1989; Cohen and Fisher, 1989; Cohen and Fisher, 1989).

Introduction
Fatigue is a severe and disabling symptom in multiple sclerosis, affecting up to 87% of patients (Krupp et al., 1988). As many as 40% claim it to be their most serious symptom (Murray, 1985). Several lines of clinical evidence suggest that fatigue is related to the underlying pathophysiology of multiple sclerosis. First, it is strongly temperature-dependent (Krupp et al., 1988). Secondly, fatigue may be the presenting symptom of multiple sclerosis, occurring at a time when there is minimal or no neurological disability (Krupp et al., 1988). Thirdly, acute episodes of fatigue may occur in isolation, similar to typical acute neurological relapses of multiple sclerosis (Freal et al., 1984; Murray, 1985). Fatigue may even herald typical relapses (Freal et al., 1984) or be a prominent symptom within these relapses (Geisser, 1985). Although some therapeutic agents have shown promise (Murray, 1985; Cohen and Fisher, 1989; Cohen and Fisher, 1989; Cohen and Fisher, 1989).
Weinschenker et al., 1992; Polman et al., 1994), the treatment of fatigue in multiple sclerosis has been largely disappointing.

Sadly, fatigue is often not accepted as a legitimate symptom by the medical profession (Rolak, 1993) and may be dismissed as neurosis (Burnfield and Burnfield, 1978). One of the main reasons for this may be that there is no strict clinical definition of fatigue. For example, most multiple sclerosis patients describe a lack of physical energy (Krupp et al., 1988), which in physiological terms may have many causes. Depression and sleepiness are both associated with similar feelings (Krupp et al., 1988; Schapira, 1994). Because of this problem, we have focused in the present paper on one well-defined aspect of fatigue, the physiological definition being ‘inability of a muscle or group of muscles to sustain the required or expected force’ (Bigland-Ritchie et al., 1978). In many muscles of normal subjects, fatigue occurs because of a loss of force-generating capacity within the muscle itself (peripheral fatigue) (Merton, 1954). However, central fatigue (defined as an inability to sustain the central drive to spinal motoneurons) may also contribute (Gandevia et al., 1995).

Although there have been several reports of muscular dysfunction (Lenman et al., 1989; Miller et al., 1990; Kent-Braun et al., 1994; Vaz-Fragoso et al., 1995) or defects of neuromuscular transmission (Patten et al., 1972) in multiple sclerosis, it seems likely, given the nature of the illness, that much of the fatigue of multiple sclerosis should be central in origin. Demyelination is known to cause slowing of nerve conduction velocity and conduction block. In the latter, partially demyelinated central nervous system axons may conduct single or low-frequency electrical impulses faithfully but are unable to transmit trains at high-frequency (McDonald and Sears, 1970). This phenomenon, termed frequency-dependent conduction block (FDCB), was later shown in demyelinated single fibres to be occurring at affected nodal regions (Rasminsky and Sears, 1972). FDCB arises from hyperpolarization of the blocking node due to electrogenic sodium pumping which develops progressively during trains of stimuli until conduction block occurs (Bostock and Grafe, 1985).

FDCB is thought to underlie some of the symptoms of multiple sclerosis (Waxman, 1981) and, if it developed in central motor fibres during a sustained contraction, could contribute to the reversible fatigue experienced by patients. The question is whether or not central motor axons discharge at sufficiently high rates during sustained maximal contraction for conduction block to occur. In McDonald and Sears’ (1970) experiments on CNS axons, block occurred at frequencies over 290 Hz. Such discharge rates are seen in corticospinal axons during (i) phasic rapid voluntary contractions and (ii) transmission of repetitive I-waves following transcranial stimulation of the motor cortex. In both situations, FDCB has been documented in multiple sclerosis: the speed of the most rapid voluntary muscle contractions is reduced (van der Kamp et al., 1991) and I-waves may be lost after transcranial magnetic stimulation (TCMS) (Boniface et al., 1991). In contrast, current work on the primate pyramidal tract suggests that during maximal sustained contractions, the tonic discharge rate of corticospinal axons rarely exceeds ~100 Hz (Cheney and Fetz, 1980). Because of this, a role of FDCB in fatigue is questionable unless frequencies lower than those reported by McDonald and Sears (1970) are blocked during prolonged periods of activity. Some later experimental work suggests that this may be possible. Bostock and Grafe (1985) observed conduction block in the demyelinated ventral roots of rats when they were subjected to trains of 50 Hz impulses.

In addition to FDCB, McDonald and Sears (1970) showed with paired stimulation of experimentally demyelinated nerve fibres that the second of the two impulses was unable to traverse the demyelinated segment, i.e. it experienced conduction block. The longest interstimulus interval (ISI) at which conduction block of the second impulse occurred was termed the refractory period of transmission. They found that the normal refractory period of transmission of ~1 ms could increase to at least 4 ms in demyelination (McDonald and Sears, 1970). Rasminsky and Sears (1972) later showed that, preceding the conduction block, conduction of the second impulse was slowed compared with the first and slowed further as the ISIs got shorter. Both FDCB and an increased refractory period of transmission are thought to be due to the same mechanism (Bostock and Grafe, 1985). Both are dependent upon the severity of the lesion and the frequency and duration of stimulation (Rasminsky and Sears, 1972; Bostock and Grafe, 1985); conduction disturbances develop more quickly and at lower stimulation frequencies in more severe lesions.

The present study was undertaken to test whether the symptom of fatigue in multiple sclerosis is caused by early failure of normal physiological mechanisms. The specific goals of the study were (i) to establish whether excessive fatigue in a ‘physiological’ sense could be demonstrated, (ii) if so, to determine whether it is peripheral or central in origin and (iii) to test the hypothesis that FDCB in demyelinated central motor pathways is a contributing factor. If the latter can be shown, then treatment with aminopyridines, which are known to reverse FDCB partially (Bostock et al., 1981) could be beneficial.

Patients

Patients with clinically definite multiple sclerosis (Poser et al., 1983) complaining of excessive and disabling fatigue were recruited. Those with epilepsy, a pacemaker, intracranial metal, or significant weakness of the upper limb were excluded from the study. The symptom of fatigue was measured by the Fatigue Severity Scale (FSS) developed and validated by Krupp et al. (1989), a self-scored questionnaire that is independent of depression. An extra item on heat-sensitivity of the fatigue was included. Disability was measured by the Kurtzke Extended Disability Severity Score (EDSS; Kurtzke, 1983). Normal controls were recruited from the laboratory staff. All subjects gave informed consent,
Methods

Electrophysiological tests and equipment

All tests involved the right adductor pollicis muscle. Responses were recorded from the right adductor pollicis with silver–silver chloride, 9 mm diameter disc electrodes fixed to the skin with collodion, and taped securely. The active electrode was placed over the motor point of the muscle in the palm and the reference electrode on the proximal phalanx of the thumb adjacent to the metacarpophalangeal joint. EMG responses were amplified and filtered by Digitimer D150 amplifiers (Digitimer Ltd, Welwyn Garden City, Herts, UK) with a time constant of 100 ms and a low-pass filter set at 3 kHz. The force transducer bandpass was DC–400 Hz; force resolution was 0.03 kg. Signals underwent analogue-to-digital conversion through a CED 1401 (Cambridge Electronic Design, Cambridge, UK) with a sampling rate of 1000 Hz. Data were stored on a personal computer for later analysis.

Magnetic stimulation was performed with a custom-built device capable of delivering up to three stimuli in close succession. This device consisted of three D190 magnetic stimulators (Digitimer Ltd, Welwyn Garden City, Herts, UK), each of which discharged through a common output and a single coil. The output characteristics of each magnetic stimulator were similar when tested separately with a coil induction technique. The maximum field strength was 0.9 Tesla with a rise time of 340 µs. Using the same technique, a field strength of 1.66 Tesla with a rise time of 100 µs was calculated for a Magstim 200 (Magstim, Dyfed, Wales); the manufacturer quote values of 2.0 Tesla and 100 µs, respectively. Discharging the stimulators in sequence at 100% output and with ISIs as short as 1 ms, the measured output of each was the same. Each stimulator demonstrated linearity and reproducibility of output. Electrophysiological studies comprised both static and dynamic tests.

Static tests

Threshold determination

Subjects were seated comfortably in a chair with the arms supported on a pillow. To promote relaxation, the subjects viewed the EMG signal displayed at high gain on an oscilloscope and were given auditory feedback. Threshold was determined at rest with single TCMS delivered with a circular coil (inner diameter 10 cm) placed on the vertex. Resting threshold was defined as the smallest stimulus which produced a small (>100 µV) motor evoked potential (MEP) in 50% of trials with the target muscle relaxed (Kujirai et al., 1993), and was measured to the nearest 2.5% of the stimulator output. Active threshold was determined during a small contraction (a few percent of maximum); it was defined as the smallest stimulus that evoked a small, reproducible response distinguishable from the background EMG signal. The first of the three stimulators was used to determine threshold. It was considered unnecessary to test threshold separately for each stimulator because the output of each was similar when discharged sequentially at short ISIs. All magnetic stimuli in the study were delivered at an intensity of 120% of resting threshold, with the circular coil placed on the vertex.

Paired magnetic stimulation

Although only demonstrated in single nerve fibres so far, we attempted in this study to test the patients for evidence of disordered conduction of paired stimuli as indirect evidence of FDCB by delivering pairs of TCMS. If present, the MEP from the second stimulus might be abnormally small with a longer latency. However, this test situation is more complex than that previously employed (McDonald and Sears, 1970; Rasminksy and Sears, 1972; Bostock and Grafe, 1985). Following TCMS there are complex alterations in cortical excitability including periods of inhibition and excitation, both when the target muscle is at rest and when it is contracted (Day et al., 1989a; Claus et al., 1992; Kujirai et al., 1993; Duvey et al., 1994). Thus, the size of the MEP in response to the second stimulus might not only reflect alterations in conduction in the motor fibres but also the excitability of the motor cortex, that is, a certain refractoriness at the stimulation site. Nonetheless, any abnormality detected in the patient group indicating either excessive intracortical inhibition or impaired ability to transmit paired impulses could at least provide evidence of a possible physiological mechanism contributing to abnormal fatigue.

Each TCMS of the pair was at a stimulus intensity of 120% of resting threshold and the ISI between each stimulus of the pair were 2, 4, 6, 10 and 20 ms; each pair was delivered 3.6 s apart. At least 10 responses for each ISI were recorded and interspersed with blocks of five single stimuli at 120% of resting threshold, so that, by completion, there were equal numbers of responses to single (control) stimuli and paired (test) stimuli. MEP area was measured and the mean value for each condition was taken for analysis. At short ISI (2–10 ms), the responses to each of the TCMS pairs overlapped and it was not possible to separate them. Thus, for 2–10 ms ISIs, the area of the combined action potential was measured. At 20 ms ISI, the two responses were usually separated. Even so, a combined MEP measurement could not be made because of distortion of the first MEP by the artefact from the second stimulus. Thus, for the 20 ms ISI only the area of the second MEP was measured. The ratio of the test (second) MEP area to the control MEP area was calculated and designated the MEP ratio. Similarly, the onset latency of the second response could only be measured at the 20 ms ISI. Because the single and paired stimuli were not generated randomly, an attempt was made to minimize the effects of variability in the size...
of the control MEP; the mean control MEP used to calculate the MEP ratio for a particular paired stimulus ISI was calculated from those recorded at a time close to the relevant paired stimuli.

**Dynamic tests**

Before the fatiguing exercise (see below), the following baseline tests were undertaken, which were repeated after the exercise. The subject’s hand and forearm rested on a padded, flat board in the supinated position with the thumb suspended in an inelastic sling attached to a force transducer by a stiff wire; only adduction force was registered and in this direction the contractions were virtually isometric. The hand and wrist were secured to the board by Velcro straps to prevent movement.

**Central motor conduction**

Supramaximal electrical stimuli (rectangular pulse of 200 µs duration) were delivered to the ulnar nerve at the wrist by a bar electrode firmly secured by a strap around the wrist; this remained in place for the duration of the experiment. The M wave and at least 10 F waves were recorded from the right adductor pollicis. Ten MEPs were obtained with TCMS (at 120% of resting threshold) during facilitation by a small twitch force (as observed on a display oscilloscope), at 5–10% of maximum (MEPF). In some subjects, five MEPs were also recorded at rest. Peak-to-peak amplitude and area of the MEP were measured and expressed as a ratio of the M-wave size (MEP/M-wave amplitude or area ratio). Central motor conduction time (CMCT) was calculated from facilitated MEPs using the following formula (see Murray, 1992):

\[
CMCT = \text{cortical MEPF latency} - (\text{distal motor latency} + F\text{-wave latency} - 1)/2.
\]

**Rapid voluntary twitches (RVTs)**

Performing a brisk voluntary phasic movement depends upon a rapid rate of recruitment of motor neurons (van der Kamp et al., 1991). RVTs are performed more slowly in patients with multiple sclerosis and may serve as a marker of central motor pathway dysfunction (van der Kamp et al., 1991). The subjects performed brisk contractions of adductor pollicis, being instructed to make each as rapid a movement as possible. After a short practice and a period of rest, 10 RVTs were recorded, performed at a rate of about one every 1–2 s. The maximum rate of rise of force (maximum slope determined by force differentiation) and the twitch force were measured. The maximum rate of rise of force is linearly related to the force produced by the twitch (Miller et al., 1981), and so the data were normalized by expressing the former as a ratio of the latter. This was to eliminate the possibility that slow rates of force rise in patients could occur from weakness alone. Because RVTs are themselves fatiguing (Miller et al., 1993), only the first three acceptably reproducible RVTs were reviewed, and that with the maximal rate of force rise was taken for analysis.

**Baseline maximal voluntary isometric contraction (MVC)**

Three or more attempts at MVC were recorded, allowing ≥1 min between each attempt to minimize fatigue. Central activation was estimated using a modified twitch interpolation method, based on previously described techniques (Woods et al., 1987; Lloyd et al., 1991). At the peak of MVC force (as observed on a display oscilloscope), a paired supramaximal electrical stimulus (200 µs duration, ISI 10 ms) was delivered to the ulnar nerve at the wrist which was the cue for the subject to relax. A second paired stimulus was delivered at rest 1.5–2 s later to produce a stimulated control twitch. Where more than three attempts were made, the best three were selected and an average taken. Maximum force, force increment and stimulated twitch force were measured. Central activation was calculated using the following formula:

\[
\text{Central activation (K) = } 1 - (\text{force increment/stimulated twitch force}) \times 100,
\]

where force increment (kilogram) is the amount of extra force produced from paired supramaximal ulnar nerve stimulation during MVC, and stimulated twitch force (kg) is that evoked by the same paired stimulus at rest after the MVC (Lloyd et al., 1991).

**Fatiguing exercise**

Fatigue may be defined as an exercise-induced reduction in force-generating capacity (Bigland-Ritchie and Woods, 1984). To induce fatigue, the subjects performed 45 s of sustained MVC of adductor pollicis during which force was recorded. Although repeated submaximal contractions may have more closely simulated the normal situation (Lloyd et al., 1991), the hypothesis to be tested was the involvement of FDCB. We considered this would be best induced by sustained maximal activation of the central motor pathways. The upper limb was tested for several reasons; MEPs are easier to obtain in the upper limbs, RVTs could be assessed, and we expected intrinsic hand muscles to be less affected by inactivity. Furthermore, fatigue in adductor pollicis of normal subjects appears to be peripheral in origin (Merton, 1954; Bigland-Ritchie et al., 1982), giving greater opportunity to observe a difference between patients and controls. Both patients and control subjects were naive, in that they had not previously performed the test. During the exercise, they were loudly exhorted to maintain full effort throughout and visual feedback was given via a nearby oscilloscope.
displaying force output. Supramaximal paired electrical stimuli (ISI 10 ms) were given to the ulnar nerve at the wrist every 3 s during the fatiguing exercise to monitor central activation; the mean stimulated twitch force prior to exercise served as the control. At each nerve stimulus, force was measured and expressed as a ratio (of the maximum voluntary force determined before exercise). At the end of the exercise, three further paired electrical stimuli were given 1.5 s apart at rest, to measure electrical twitch force as well as M-wave size. The baseline tests of RVTs and MEP measurements (five at rest, 10 with facilitation as before exercise) were then repeated as quickly as possible in that order, beginning within 10 s of completion of the exercise. The first RVT after exercise was analysed to observe the maximal effect.

On a subsequent occasion, six patients who had demonstrated substantial central fatigue received TCMS (as above) every 5 s during the exercise test and immediately upon completion of the exercise during a weak contraction (5–10% maximum). CMCT, MEP size and MEP twitch force were measured.

Statistical analysis
Data comparisons before and after the fatiguing exercise within and between the two groups were made using paired or unpaired t tests or, where a non-Gaussian distribution of data was suspected, with the non-parametric Mann–Whitney and Wilcoxon rank sum tests. Multi-way analysis of variance (MANOVA) procedures were also used to check for differences in the behaviour of the two groups over time (e.g. pre- and post-exercise). Correlations in the patient group among clinical and electrophysiological data were tested with the Spearman rank-correlation procedure. P < 0.05 were considered significant.

Results
Patient characteristics
The clinical characteristics of the patients are given in Table 1. Twenty-one patients (nine males and 12 females) were studied, ranging in age from 26 to 55 (mean 39.8) years. The duration of disease ranged from 2 to 26 (mean ± SD = 10.3 ± 8.5) years. Thirteen patients suffered from relapsing–remitting multiple sclerosis, three from primary progressive and five from secondary progressive forms of multiple sclerosis. Disability scores (EDSS) ranged from 2.0 to 8.0 (5.4 ± 1.9). The control group of 19 subjects comprised eight males and 11 females, ranging in age from 22 to 40 years (mean 31.9 years).

Fatigue questionnaires
A FSS score of >4.0 was considered to be abnormal (Krupp et al., 1989). The mean FSS for the patients was 5.9 (range 2.7–7.0, SD 0.9) with all patients except one having an abnormal score of >4.0. Fatigue was reported as heat-sensitive in 15 patients, extremely so in 11.

Baseline tests
Dynamic tests
Data were obtained from 18 patients and 13 controls before and after exercise (Table 2). Prior to the fatiguing exercise, there was no significant difference between the two groups in the mean maximum force generated (Mann–Whitney), indicating that there was no impairment of strength in the patient group. Further confirmation of this was provided by the mean central activation which was 93.7 ± 10.5% for the patients and 97.2 ± 4.1% for the control subjects (P > 0.05, Mann–Whitney). The force of the stimulated twitches (produced by paired electrical stimulation of the ulnar nerve) was also similar; 2.06 ± 0.63 kg in patients and 2.00 ± 0.41 kg in controls. In contrast, the normalized peak rate of force rise in the RVTs was significantly lower in the patients compared with the controls (Table 2); (in patients, 11.4 ± 2.3; in controls, 14.2 ± 3.1; P < 0.01).

Static tests
TCMS thresholds. Three patients had relaxed thresholds exceeding 100% of stimulator output, two of whom also had no recordable MEP during a weak contraction of the right adductor pollicis. TCMS was contraindicated in another patient who had an incidental intracranial meningioma. The remaining 17 patients had resting thresholds which were not significantly different from the controls. The mean relaxed threshold in the patient group was 75.4 ± 13.4% compared with 67.8 ± 11.7% in the normal controls (Table 3). Activated thresholds on the other hand were significantly higher in the patient group; the mean active threshold for the patients was 61.1 ± 14.5% compared with 52.2 ± 8.3% in the normal controls (P < 0.05).

Central motor pathway conduction. CMCT was tested before and after the fatiguing exercise test in 12 patients (Table 3). CMCT and MEPF/M-wave amplitude and area ratios for the patients and normal controls are presented in Table 3. In the patients, the mean CMCT was 8.7 ± 4.3 ms, which was significantly longer than the mean CMCT in the controls of 4.4 ± 0.9 ms (P < 0.01). Based on mean ± 2.5 SD, the upper limit of normality for CMCT is 6.7 ms; eight of the 12 patients exceeded this limit before exercise. There were no significant differences between the patients and controls in mean MEPF/M-wave amplitude or area ratios. Based on mean ± 2.5 SD (after natural log conversion), the lower limit of normality for MEPF/M-wave amplitude ratio is 0.095 and for area is 0.143. Only two patients had a baseline MEPF/M-wave amplitude
Table 1 Clinical characteristics of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration (years)</th>
<th>Class</th>
<th>Type</th>
<th>EDSS</th>
<th>FSS</th>
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<td>37</td>
<td>F</td>
<td>2</td>
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<td>RR</td>
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<td>3.0</td>
<td>6.4</td>
</tr>
<tr>
<td>6</td>
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<td>8.0</td>
<td>5.4</td>
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<tr>
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<td>CDMS</td>
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<td>5.4</td>
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</table>

CDMS = clinically definite multiple sclerosis; LSDMS = laboratory-supported definite multiple sclerosis, according to Poser criteria (Poser et al., 1983). RR = relapsing-remitting; RP = relapsing progressive; PP = primary progressive; SP = secondary progressive; all refer to clinical type at the time of testing.

Table 2 Fatiguing exercise results for patients and control subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Controls</th>
<th>Baseline Patients</th>
<th>End/post-exercise Controls</th>
<th>End/post-exercise Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Force (kg)</td>
<td>5.0 ± 1.2</td>
<td>4.2 ± 1.2</td>
<td>4.0 ± 0.9</td>
<td>2.3 ± 1.2***</td>
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<tr>
<td>Force relative to baseline (%)</td>
<td>100</td>
<td>100</td>
<td>82.0 ± 14.5</td>
<td>54.7 ± 27.3***</td>
</tr>
<tr>
<td>Central activation (%)</td>
<td>97.2 ± 4.1</td>
<td>93.7 ± 10.5</td>
<td>90.6 ± 13.0</td>
<td>51.7 ± 28.4***</td>
</tr>
<tr>
<td>Stimulated twitch force (kg)</td>
<td>2.00 ± 0.41</td>
<td>2.06 ± 0.63</td>
<td>1.85 ± 0.43†</td>
<td>1.99 ± 0.61</td>
</tr>
<tr>
<td>CMAP amplitude (mV)</td>
<td>14.2 ± 4.3</td>
<td>13.4 ± 8.2</td>
<td>13.9 ± 4.5</td>
<td>14.8 ± 5.7</td>
</tr>
<tr>
<td>RVT, max. force increase</td>
<td>14.2 ± 3.1</td>
<td>11.4 ± 2.3**</td>
<td>10.3 ± 3.1</td>
<td>10.0 ± 2.6</td>
</tr>
</tbody>
</table>

Data from 18 patients and 13 controls (mean ± SD). Force ratio = force exerted as % of baseline maximal voluntary force; CMAP = compound muscle action potential (adductor pollicis); RVT = rapid voluntary twitches, normalized peak rate of force rise. **P < 0.01, ***P < 0.001: significance levels of comparisons between patients and controls (either t test or Mann–Whitney rank sum test as appropriate); all others are non-significant (P > 0.05). †P < 0.05: comparison between baseline and post-exercise.

Table 3 Central motor pathway conduction pre- and post-fatiguing exercise for patients and control subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Controls</th>
<th>Baseline Patients</th>
<th>Post-exercise Controls</th>
<th>Post-exercise Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting threshold (%)</td>
<td>67.8 ± 11.7</td>
<td>75.4 ± 13.4</td>
<td>4.6 ± 1.0</td>
<td>8.7 ± 4.0**</td>
</tr>
<tr>
<td>Activated threshold (%)</td>
<td>52.2 ± 8.3</td>
<td>61.1 ± 14.5*</td>
<td>33.8 ± 17.4</td>
<td>28.0 ± 23.0</td>
</tr>
<tr>
<td>CMCT (ms)</td>
<td>4.4 ± 0.9</td>
<td>8.7 ± 4.3**</td>
<td>45.7 ± 32.2</td>
<td>45.0 ± 3 4.4</td>
</tr>
</tbody>
</table>

Data from 12 patients and 12 controls (mean ± SD). MEPF/M = ratio between motor evoked potential (performed with facilitation by a small contraction of adductor pollicis) and M-wave amplitude or area; CMCT = central motor conduction time. *P < 0.05, **P < 0.01, ***P < 0.001: significance levels for comparisons between patients and controls; all others are non-significant (P > 0.05).
Fatigue in multiple sclerosis

Fig. 1 Results of (A) force output (expressed as a percentage of baseline maximal voluntary force) and (B) central activation during the fatiguing exercise tests. Mean results for patients (n = 18) and controls (n = 13) are shown. To simplify the data, three successive values are averaged (mean ± SD) in each period. Both groups fatigued during exercise, patients to a greater extent (P < 0.001) but only the normal subjects developed significant loss of central activation, i.e. central fatigue (P < 0.001).

Exercise test
Both the patients and controls showed a significant decline in force throughout the test (P < 0.001 for patients and P < 0.05 for controls; see Figs 1 and 2 and Table 2). However, the rate of force decline was significantly greater for the patients (P < 0.01). The mean final force produced by the patients was 54.7 ± 27.3% of baseline maximum force and by controls was 82.0 ± 14.5% (P < 0.001). Control subjects showed no significant change in central activation throughout the exercise; baseline mean central activation was 97.2 ± 4.1% and at completion of exercise was 90.6 ± 13.0%. In contrast, the patients showed a significant decline in central activation throughout the test; baseline mean central activation was 93.7 ± 10.5% and at
completion of exercise was 51.7 ± 28.4% (P < 0.001). The difference in central activation at the end of the test between patients and controls was statistically significant (P < 0.001). The decline in the force exerted and the degree of central activation throughout the exercise test showed a striking linear relationship in the patients (P < 0.001). The mean stimulated twitch force (which was similar in the two groups before exercise) was unchanged after exercise in the patient group, but was significantly smaller in the controls (P < 0.05). M-wave amplitudes and areas were also similar in the two groups before and after exercise and neither group showed a significant change with exercise. In summary, control subjects experienced only moderate fatigue which appeared to be peripheral in origin, i.e. no change in central activation and a reduced stimulated twitch force. Patients, however, experienced substantial fatigue which appeared to be largely central in origin, i.e. a parallel decline in central activation with no significant change in stimulated twitch force.

Post-exercise central motor conduction and RVTs
There was no significant change in either CMCT or MEP/M-wave size (amplitude or area) following exercise in either the patients or controls (Table 3). MEPs were also recorded at rest before and after exercise in nine patients and 12 controls. MEP/M-wave amplitude and area ratios at rest were not significantly different between the two groups before or after exercise. Both subject groups showed a significant change in the normalized peak rate of force rise of the RVT following exercise (Table 2). In patients, the values were 11.4 ± 2.3 before exercise and 10.0 ± 2.6 following exercise (P < 0.01). In controls, the value fell from 14.2 ± 3.1 before exercise to 10.3 ± 3.1 after exercise (P < 0.01); this change was greater than that in the patient group (P < 0.01). Thus, RVTs were performed more slowly after fatiguing exercise in both groups, but there was a greater degree of slowing in the controls. An illustrative example of the differences between patients and controls is presented in Fig. 2.

As mentioned in Methods, six patients on another occasion had TCMS performed during and immediately after the 45 s exercise. In their initial performance of the exercise test, these patients had demonstrated substantial central fatigue; the mean final force ratio was 57.1 ± 21.2% of baseline maximum and central activation had fallen from 94.0 ± 5.5% to 56.4 ± 23.2%. On the subsequent occasion, mean final force was 54.1 ± 23.3% of baseline maximum, confirming a consistent degree of excessive fatigue. When tested immediately after exercise on the second occasion, there was no prolongation of CMCT, reduction in MEPF size (area or amplitude) or loss of twitch force evoked by the MEP during a small contraction.

Paired TCMS at rest
Figure 3 depicts the MEP area ratio for each ISI obtained from the patients (n = 12) and control subjects (n = 17). MEP ratios for both groups were ~1 for the 2 ms ISI indicating that responses to the second TCMS were nearly totally inhibited, probably at a cortical level (Day et al., 1989a; Claus et al., 1992; Kujirai et al., 1993; Davey et al., 1994). At an ISI of 4 ms, the ratio was ~2, indicating recovery of the inhibition. The MEP ratio increased progressively thereafter up to an ISI of 20 ms, where facilitation was clearly evident. MANOVA analysis of the results at each ISI for the controls showed a significant effect of time (i.e. ISI) for both controls and patients (P < 0.001). However, there was no significant difference in the MEP ratios between the normal controls and the patients at any of the ISIs.

The mean latency of the MEPs to single stimuli was significantly longer in the patient group (21.6 ± 1.1 ms for controls and 24.6 ± 5.1 ms for patients; P < 0.05, MANOVA). Both groups showed a small significant decrease in the latency of the response to the second stimulus (ISI 20 ms) of ~1 ms (P < 0.02 for patients and P < 0.01 for controls), a change that was not significantly different between the two groups (MANOVA).

Thus, there was no apparent abnormality in the patients either in the short-term inhibitory and excitatory effects of TCMS on the cortex or in the ability of the central motor pathways to conduct paired TCMS.

Correlation of clinical findings with electrophysiological results in patients
Clinical-electrophysiological correlations were examined in the patients only. There was no correlation between the FSS and EDSS scores. Baseline central activation was not correlated with any baseline measurements of central motor

Fig. 2 Force output from a 45 s maximal voluntary contraction (MVC) of adductor pollicis for a representative control subject (A) and a multiple sclerosis patient (B). M-waves, MEPs, rapid voluntary twitches (RVTs) and electrical twitches before (left) and after (right) exercise are included. Superimposed twitches from electrical stimulation of the ulnar nerve (used to calculate central activation) from the beginning and end of exercise are shown at high gain. The control subject (A) demonstrated a progressive, mild decline in force output. The superimposed twitches show that the initial high level of central activation (no increment) was maintained to the end but the electrical twitch force was reduced, i.e. there was peripheral fatigue. In contrast, the multiple sclerosis patient (B) showed a progressive, more substantial decline in force output. The initial high level of central activation (little increment with superimposed twitch) declined in parallel so that by completion there was a large increment, and the electrical twitch force was unchanged, i.e. there was central fatigue. The M-wave and MEP size and CMCT remained unchanged after exercise in both subjects but RVT performance slowed.
conduction (CMCT, MEP size) nor with RVT performance. The force and central activation achieved at the end of the exercise test (both expressed as ratios of baseline values) were strongly correlated with each other ($P < 0.001$). These two parameters reflect the degree of fatigue produced by the exercise and the magnitude of the central component, respectively; lower ratios indicate greater (central) fatigue. Both final force and central activation ratios showed weak correlations with some aspects of the baseline RVTs ($P < 0.05$); the slower and smaller the RVTs, the greater the degree of subsequent (central) fatigue. However, this trend was not present when the rate of force rise was normalized to size of the RVTs. There was no correlation between the change (slowing) in the RVTs after exercise and either the degree of fatigue induced or the baseline performance of RVTs. There was a strong tendency ($P = 0.053$) for an inverse correlation between both final force and central activation ratios and the EDSS scores: the higher the EDSS score (the greater the disability), the greater the degree of central fatigue. EDSS did not correlate with any other electrophysiological tests, in particular, the MEP parameters. FSS did not correlate with any baseline electrophysiological parameter nor with any change in these after exercise. Neither did FSS correlate with the degree of exercise-induced fatigue. There was no correlation between CMCT and RVT performance before exercise. There was, however, a borderline significant correlation ($P = 0.051$) between pre-exercise CMCT and the degree of slowing of the normalized RVTs after exercise. In summary, the degree of exercise-induced (central) fatigue in patients was weakly correlated with the degree of global neurological disability but not with the symptom of fatigue. Only some aspects of the baseline performance of the RVTs had predictive value as to the degree of induced fatigue; the MEP parameters were not correlated. A longer baseline CMCT seemed to be associated with a greater impairment of RVT performance after exercise.

**Discussion**

Excessive fatigue is a common symptom among patients with a variety of central nervous system disorders including Parkinson’s disease (Friedman and Friedman, 1993), stroke and multiple sclerosis (Freal et al., 1984; Murray, 1985; Krupp et al., 1988). It also forms the basis of the chronic fatigue syndrome. In reporting fatigue, the patient may be describing many and varied physical as well as psychological symptoms. In this investigation, we have concerned ourselves with studying fatigue as defined physiologically (see Introduction). In everyday life this could manifest as an inability to sustain physical activity due to excessive and/or rapid loss of strength.

The normal subjects (and patients) in this study were capable of near-maximal voluntary activation of adductor pollicis. This agrees with the findings of Merton (1954) and suggests that they were highly motivated (Bigland-Ritchie and Woods, 1984). The exercise test produced a modest amount of fatigue (~20%) in the normal subjects. The lack of a significant change in the degree of central activation accompanied by a reduction in stimulated twitch force indicates that the fatigue was primarily peripheral in origin rather than central in the normal subjects. The amount of fatigue produced by the exercise protocol and its peripheral origin are in accordance with the findings of Merton (1954) and Bigland-Ritchie et al. (1982). Although the MVC was attempted for only 45 s in this study, Merton (1954) found no central fatigue after 2 min MVC of the right adductor pollicis that reduced the force to 20% of baseline. However, a variable degree of central fatigue has been reported in other
muscles, such as the biceps (Lloyd et al., 1991; Gandevia et al., 1995), quadriceps (Bigland-Ritchie et al., 1978), and diaphragm (Bellemare et al., 1984), so that it may depend on the muscle tested. Defective neuromuscular transmission has been suggested as a possible cause of peripheral fatigue of adductor pollicis in normal subjects (Stephens and Taylor, 1972). However, we and others (Merton, 1954; Bigland-Ritchie et al., 1982; Woods et al., 1987) found no change in M-wave size, suggesting that the mechanism lies beyond the neuromuscular junction.

Despite the fact that the patients’ maximal voluntary force was initially similar to that of the normal subjects, it declined much more rapidly than normal during the 45 s contraction. Since (i) central activation, as measured by twitch interpolation, declined at the same rate as voluntary strength and (ii) there was no change in the electrical twitch force of the muscle after exercise, it is probable that the fatigue was primarily central in origin in the patients. Indeed, the failing central motor drive to the motor pool during contraction may have ‘protected’ the peripheral neuromuscular apparatus from the fatigue observed in the normal subjects. Therefore, the symptom of excessive fatigue in multiple sclerosis is accompanied by an exercise-induced reduction in force-generating capacity, i.e. by physiological fatigue (Bigland-Ritchie and Woods, 1984). A practical implication of these results is that strength may be normal at the beginning of the contraction and only declines slowly over time. Thus, strength may be normal when tested clinically. Adequate clinical testing for fatigue requires a sustained MVC.

Other studies have shown excessive fatigue in multiple sclerosis, but of apparent peripheral (muscular) origin (Lenman et al., 1989; Miller et al., 1990). However, these studies tested the lower limbs and the muscular changes were attributed to the effects of inactivity (Lenman et al., 1989). The baseline stimulated twitch forces of our patients were not significantly different from those of controls, indicating that their peripheral neuromusculature was intact; one reason for using the upper limbs in this study was to avoid any secondary muscular changes resulting from inactivity (see Methods). Furthermore, the studies of Miller et al. (1990) and Lenman et al. (1989) used high-frequency tetanic electrical stimulation to induce fatigue rather than voluntary activation; this does not allow evaluation of central motor drive and is not strictly physiological (Bigland-Ritchie and Woods, 1984). In upper motor neuron lesions, muscle contractile properties more suitable to the lower firing rates can develop, allowing more efficient force generation (Rice et al., 1992); driving such fibres at faster rates electrically could produce excessive peripheral fatigue that may not occur with voluntary exercise. Defective neuromuscular transmission has been reported in multiple sclerosis (Patten et al., 1972) but we, and others (Kent-Braun et al., 1994), did not find evidence of this. The study of Kent-Braun et al. (1994) revealed some evidence of central fatigue in multiple sclerosis in which there was a small reduction in central activation during incremental submaximal exercise of ankle dorsiflexors; however, this trend was statistically non-significant and due mainly to marked central fatigue in a single subject.

**Mechanism of central fatigue in patients with multiple sclerosis**

Central fatigue develops because of failing central motor drive to spinal alpha motor neurons. Many factors determine the level of voluntary activation of a muscle including motivation, the integrity of the primary motor pathways, and the facilitatory and inhibitory effects of afferent feedback from the musculoskeletal apparatus, including pain. Since patients could activate their muscles fully at the start of contraction, the question to address here is whether or not FDCB in the central motor pathways could have contributed to the reduced central motor drive over the following 45 s.

Several lines of evidence indicate that conduction in the patients was initially abnormal. Many patients had impaired fine finger movements and hyperactive upper limb reflexes indicating upper motor neuron dysfunction. Furthermore, the mean CMCT to the target muscle in the patients was substantially longer than that in controls and RVTs were performed more slowly. Thus, with electrophysiological and clinical evidence that demyelination affecting central motor pathways to the upper limbs, there was opportunity for the development of FDCB. In fact, the impaired RVT performance before the exercise may have indicated that FDCB was already present (van der Kamp et al., 1991). The heat sensitivity of the fatigue in the majority of patients was further support for a contribution from FDCB. The responses of the patients to paired TCMS were no different from those of controls. Thus, there was no evidence to suggest an increased refractory period of transmission in the central motor pathways. As noted in Methods, any difference would have been difficult to interpret, given the complex changes in cortical excitability following TCMS (Claus et al., 1992; Valls-Solé et al., 1992). Indeed, there was evidence of substantial, presumably cortical, inhibition in the controls with ISIs <4 ms, possibly too long to recognize an increased refractory period of transmission or an abnormal delay in conduction of the second impulse. Nonetheless, the absence of a difference between patients and controls at least indicates that the cortex and primary motor pathways in these patients respond normally to paired TCMS. Thus, there appears to be no abnormality of the mechanisms governing intracortical excitability to explain the abnormal fatigue, at least at the ISIs used in this study. Using paired TCMS at a much longer ISI (200 ms), Claus et al. (1992) found excessive inhibition of MEP responses in patients with multiple sclerosis and postulated that this may contribute to fatigue in multiple sclerosis.

Electrophysiological evidence that might have suggested the development of (frequency-dependent?) conduction block during the fatiguing exercise include an increase in CMCT (Thompson et al., 1987; van der Kamp et al., 1991), a
reduction in MEP area or amplitude (facilitated or at rest) and further slowing of the RVTs. The alteration in TCMS parameters could occur with either total block of conduction in individual pyramidal fibres or simply blocking of some I-waves. However, these and the RVT parameters either did not change, or changed to a similar or lesser degree than normal controls. Sandroni *et al.* (1992) also found no difference in CMCT between the ‘rested’ and ‘fatigued’ states in patients with multiple sclerosis; however, these states were purely subjective and fatigue was not specifically induced with exercise. Similarly, CMCT was unchanged after a fatiguining contraction of the first dorsal interosseous in patients with chronic fatigue syndrome (Waddy *et al.*, 1990), in which others have demonstrated central fatigue (Kent-Braun *et al.*, 1993).

The decline in RVT performance after exercise in the patients might be evidence of increased dysfunction in the central motor pathways. RVTs also slowed after exercise in the controls and while this may have been evidence of central fatigue it might also be explained by the peripheral fatigue they developed. The patients showed no evidence of peripheral fatigue, possibly because the peripheral neuromusculature was somewhat ‘protected’ by the development of central fatigue. Therefore, the slowing of RVTs in patients could have been due to increased dysfunction of the central motor pathways; a correlation between the degree of RVT slowing following exercise and the baseline CMCT supports this notion. In summary, despite the development of substantial central fatigue, we found no conclusive evidence of increased conduction block or slowing of conduction in primary central motor pathways. The only accompanying change was increased slowing of RVT performance.

**Possible explanations for the negative TCMS findings**

Two general lines of reasoning may explain why TCMS parameters were unchanged despite central fatigue. The first concerns the possibility that fatigue may not have developed in the central motor pathways tested by TCMS and the second relates to limitations of the technique and methodology.

**Absence of fatigue in TCMS-activated pathways**

TCMS is thought to activate large-diameter, fast-conducting pyramidal fibres (Hess *et al.*, 1987). Clinical and electrophysiological studies from monkeys suggest that these pyramidal pathways are less important in a sustained power grip (‘tonic’) than in fine or fast (‘phasic’) hand movements (Evarts *et al.*, 1968; Lawrence and Kuypers, 1968; Hepp-Reymond and Wiesendanger, 1972; Hepp-Reymond *et al.*, 1974; Lemon *et al.*, 1986). In humans with multiple sclerosis, CMCT may be abnormal with normal strength (Hess *et al.*, 1987). Thus, if a sustained MVC in humans does not involve the fast-conducting pyramidal pathways to a significant degree, then TCMS might not be expected to show abnormalities with fatigue. Likewise, fatigue developing in the tonic (extrapyramidal?) motor pathways driving the sustained MVC would not necessarily be detectable by TCMS. These tonic pathways must have been capable of driving the motor neurons maximally in our subjects because of the initial high level of central activation.

Secondly, during a power handgrip, monkey pyramidal tracts may not be capable of firing at >100 Hz (Cheney and Fetz, 1980), which may be insufficient to induce FDCB. The minimum frequency at which FDCB was detected in the CNS by McDonald and Sears (1970) was 290 Hz, although we do not know the behaviour of CNS lesions of greater length or more severe demyelination, which may block at lower frequencies. Thus, even if the fast-conducting pyramidal fibres were significantly involved in the sustained MVC, FDCB may still not have occurred. On the other hand, Bostock and Grafe (1985) were able to demonstrate FDCB in demyelinated rat ventral roots after ~1 min of sustained stimulation at 50 Hz. Assuming that the pyramidal neurons fired at ≥50 Hz continuously throughout the exercise test, then the absence of apparent conduction block in these pathways might argue against involvement of these particular motor pathways in the fatigue. However, the issue of critical firing frequency becomes even more complex when one considers that the actual ISI between descending impulses arriving at a potential blocking node may have become cumulatively increased due to passage through partially demyelinated segments proximally (Rasminsky and Sears, 1972). Parenthetically, if a sustained MVC was not a suitable test for inducing fatigue in the large-diameter, fast-conducting pyramidal pathways, then the RVTs must have slowed for other reasons.

Thirdly, central fatigue may have developed in cortical pathways rostral to the pyramidal tracts. The pyramidal tracts may have continued to conduct normally in response to TCMS, whereas volitional drive to the descending motor pathways was reduced. This may well be the mechanism of central fatigue in normal subjects. During a fatiguing maximal voluntary contraction of biceps in normal subjects, Gandevia *et al.* (1995) found force increments in response to TCMS, despite the development of central fatigue. They concluded that central fatigue arose upstream from the primary motor cortex. A similar conclusion was reached by Lloyd *et al.* (1991) in another study of chronic fatigue syndrome, although abnormal fatigue was not demonstrated. The lack of correlation in our study between baseline electrophysiological measures of the integrity of the central motor pathways, such as CMCT or MEP size, and the degree of induced fatigue, is supportive of this hypothesis. Furthermore, it provides a central location for the increased impairment of the rapid voluntary movements (RVTs) after exercise. Possible mechanisms for the withdrawal of volitional drive include abnormal fatigue in the pathways directing the motor cortex, or in the facilitatory afferent pathways (Gandevia *et al.*, 1996); both mechanisms could still involve FDCB. Although
also possible, we do not believe that declining motivation was a factor for several reasons. Baseline strength and central activation was high and all patients appeared to be trying hard to exert full effort. Furthermore, the time course of the development of the central fatigue in the group was a smooth and strongly linear function ($P < 0.001$); motivation would not be expected to decline in such a way. Lastly, the six subjects in whom the test was repeated on a separate occasion showed virtually the same degree of fatigue each time; such consistency argues against a ‘voluntary’ failure of volition.

The possibility of defective afferent feedback deserves further discussion, since muscle afferent input to the cerebral cortex appears to play a role in motor control (Wiesendanger and Miles, 1982). During an MVC, facilitation from muscle afferents may contribute up to 30% of central motor drive (Gandevia et al., 1990; MacKeresfield et al., 1993) and feedback from cutaneous afferents is also facilitatory (Gandevia et al., 1990; Datta and Stephens, 1981). Such facilitation may occur at either the spinal or supraspinal level (Gandevia et al., 1996). At the same time, motor neuron firing is reflexly inhibited by afferent feedback from the muscle (Woods et al., 1987; Gandevia et al., 1990; Leonard et al., 1994) in such a way as to prevent high-frequency (peripheral) fatigue and to maximize force output (Bigland-Ritchie and Woods, 1984). This inhibitory input could be subject to central, possibly supraspinal control. Dysfunction in any of the sensory pathways that modulate motor neuron firing might impair the ability to produce or maintain maximal motor output and may be the mechanism of normal central fatigue in biceps (Allen et al., 1994; Gandevia et al., 1996). On the other hand, conditions involving pure sensory deficits (and no motor dysfunction) are not particularly associated with fatigue. Sensory feedback was sufficiently intact initially in our patients to allow them full activation of the muscle. An abnormal degree of fatigue developing in demyelinated central sensory afferents, possibly due to FDCB, could have resulted in central fatigue with an intact central motor pathway (as assessed by TCMS). Pain may also inhibit central activation (Stokes and Young, 1984; Gandevia and McKenzie, 1985; Rutherford et al., 1986), but none of our patients reported pain during the exercise test. As an extension of this argument, dysfunction in central sensory pathways could have contributed to the baseline and additional post-exercise impairment in RVT performance, as this may require intact peripheral sensory input (van der Kamp et al., 1991).

We attempted to test the hypothesis of abnormal afferent pathway fatigue by studying the recovery cycle of median sensory evoked potentials as a marker of FDCB in the cutaneous and muscle afferent pathways (Gandevia and Burke, 1988; Jones, 1993). The recovery cycle of the P11 component of median sensory evoked potentials (originating in the region of the dorsal root entry zone; Jones, 1993) was studied with paired median nerve stimulation in several patients. However, sensory evoked potentials with standard single stimuli were too impaired to allow confident identification of subcortical components. This evidence of involvement of the central sensory pathways due to demyelination at least supports the possibility that they could have been prone to abnormal fatigue.

In summary, fatigue might not have occurred in the large-diameter, fast-conducting pyramidal fibres that are activated by TCMS because (i) these pathways were not significantly involved in the sustained MVC, (ii) if involved, these pathways might not have fired at a frequency sufficient to provoke FDCB and fatigue, (iii) fatigue occurred in areas providing volitional drive to these primary motor pathways and (iv) fatigue occurred in sensory pathways that facilitate central motor drive.

**Technical and other limitations of the TCMS method**

First, even if conduction block did develop in the pyramidal pathways, MEP area and amplitude may not be a sufficiently sensitive measure of the integrity of the central motor pathways (Day et al., 1987; Rothwell et al., 1987; Thompson et al., 1987), partly because of the possibility of repetitive firing of motor neurons (Day et al., 1987; Day et al., 1989b; Hess et al., 1987). However, MEP twitch force was also unchanged in six subjects after substantial central fatigue was induced with the exercise test. Peri-stimulus time histograms might have revealed evidence of conduction block in the central motor pathways of individual motor units, such as the disappearance of I-waves (Boniface et al., 1991). However, this phenomenon was reportedly quite difficult to observe and, in any case, the technique was impractical with this protocol. FDCB might not have been detectable by TCMS because there is a latency period after the stimulus train is applied before it develops (McDonald and Sears, 1970; Rasminksy and Sears, 1972; Bostock and Grafe, 1985). Thus, a single TCMS, even with several I-waves, may not have been sufficient to provoke FDCB.

Secondly, exercise-induced FDCB in pyramidal pathways might have recovered by the time of re-testing [up to 10 s after exercise for the RVTs and 20–30 s for the (resting) MEPs]. This explanation is unlikely for three reasons. Firstly, one patient on a subsequent occasion performed MVCs immediately after the exercise test (which had induced substantial central fatigue) and did not recover full strength (baseline MVC force) or her baseline degree of central activation for several minutes indicating a slower recovery of the central fatigue. Secondly, TCMS performed during and immediately after the same exercise test in six of the multiple sclerosis patients produced no change in CMCT, MEP size or MEP-twitch force. Thirdly, although the hyperpolarization responsible for FDCB recovers after the stimulus is removed, it appears to do so over at least 1–2 min (see figs 6 and 7 in Bostock and Grafe, 1985).

Timing, however, may have been important with the resting MEPs. Following a fatiguing contraction, there is a biphasic
time course in resting-MEP changes; an initial facilitation followed by a period of inhibition (Samii et al., 1996). The resting MEPs after exercise may have been unchanged in both subject groups because they were tested in the transition period between facilitation and inhibition. MEPs performed immediately after exercise and continuing over a longer period of time might have revealed differences between the two groups.

Thus, single-stimulus TCMS and the MEP parameters measured may be too insensitive to observe conduction block in pyramidal pathways or else FDCB was too short-lived to be detected.

Of all these possibilities, we suspect that central fatigue in our patients originated upstream from the primary motor pathways and that this is the most likely explanation for the negative TCMS findings. As this appears to be the site of central fatigue in normal subjects (Gandevia et al., 1996), the physiological component of fatigue in multiple sclerosis could simply be an exaggerated form of normal fatigue. Determining the mechanism for the withdrawal of volitional drive could be difficult electrophysiologically, considering the possibilities. Although we cannot rule out a contribution from FDCB to central fatigue, we have no evidence that this occurs, at least not in the primary central motor pathways. Furthermore, although some patients described exercise-induced fatigue with a rapid recovery in their daily activities, as might be expected with exercise-induced FDCB, many reported, instead, a sustained fatigue lasting hours or days as well as delayed-onset fatigue.

TCMS may not help. If the central fatigue does originate upstream from the primary motor cortex, then TCMS delivered during the MVC may produce a force increment. On the other hand, if the fatigue is occurring ‘downstream’, in motor pathways not activated by TCMS, then TCMS may also produce a force increment resulting from stimulation of (non-fatigued) TCMS-activated pathways. If the TCMS-activated pathways fatigued as well, or if the fatigue was purely peripheral, then a force increment with TCMS may not occur.

Clinical–electrophysiological correlations

The degree of exercise-induced fatigue did not correlate with the severity of the symptom of fatigue as measured by the FSS. Therefore, although physiological, central fatigue probably contributes to the complaint of fatigue, other factors must also be operating. Immunochemicals, such as interleukins, have been implicated in fatigue in multiple sclerosis (Rosse, 1989) but refuted by others (Rudick et al., 1990). Lloyd et al. (1991) have commented that the symptom of fatigue in chronic fatigue syndrome could not be equated with failure of contractile force. Therefore, we have used the somewhat tautologous terms, ‘exercise-induced’ or ‘physiological’ fatigue, to distinguish this phenomenon from the symptom of fatigue. Another possible explanation for the lack of correlation is that most of the patients referred to either a generalized feeling of fatigue or fatigue predominantly involving their legs, whereas the upper limb was tested in this study (see Methods for explanation). Finally, a distorted perception of effort in the patients could contribute to a sensation of fatigue disproportionate to the actual loss of force-generating capacity. The perception of effort is partly dependent upon afferent feedback from cutaneous receptors (Gandevia and McCloskey, 1977a) and muscle spindles, as well as descending corollaries of motor commands (McCloskey et al., 1983). The latter may account for the increased perception of effort in pure motor strokes (Gandevia and McCloskey, 1977b). Any of these pathways could be affected by CNS demyelination; we did not specifically examine this aspect. It is apparent that the FSS provides a global evaluation of the sensation of fatigue, while the exercise test assesses only part of it.

We found no correlation between the degree of neurological disability assessed by the Kurtzke EDSS and the FSS. A poor correlation between fatigue and other physical disabilities has been described (Rolak, 1989; Fisk et al., 1994), but others have found that the degree of symptomatic fatigue was proportional to that of pyramidal tract involvement (de Castro et al., 1994). In our study, there was a borderline significant correlation between the degree of exercise-induced fatigue and the degree of general neurological disability (Kurtzke EDSS), suggesting some association between physiological fatigue and the severity of the disease. Although central fatigue did not correlate with baseline CMCT or MEP size, it did correlate (inversely) with some aspects of baseline RVT performance, suggesting that these two phenomena might share common pathophysiological mechanisms. However, central fatigue did not correlate with the RVT changes after exercise. In predicting central fatigue, baseline RVT performance appears to be better than baseline CMCT. Because our patients had essentially normal baseline strength, it was not possible to compare baseline weakness with the degree of exercise-induced fatigue. It would be interesting to see if greater fatigue developed in weaker subjects.

We have shown that abnormal central fatigue in patients with multiple sclerosis can be quantified by the exercise test used in this study. This provides a potential tool with which to evaluate therapies for fatigue. The aminopyridines have shown therapeutic promise for this and other symptoms in multiple sclerosis (Bever et al., 1994; Polman et al., 1994). By prolonging the action potential duration, aminopyridines increase the safety factor for conduction in demyelinated nerves, improving stable conduction block and FDCB (Bostock et al., 1981). If the latter mechanism contributes to physiological fatigue in multiple sclerosis then the aminopyridines could be beneficial. This would be so even if exercise-induced FDCB affected areas other than the primary motor pathways.

Conclusions

The conclusions that we may draw from this study are as follows. (i) Multiple sclerosis patients who complain of
excessive fatigue have demonstrably excessive ‘physiological’ fatigue, which is central in origin. However, there is no correlation between the amount of inducible fatigue and that of fatigue experienced in everyday life, suggesting that other factors contribute to this symptom. (ii) Despite central fatigue, there was no evidence of an increase in central motor dysfunction as tested by TCMS, and there is no firm evidence to support the role of FDCB in the generation of physiological fatigue in multiple sclerosis. (iii) The absence of a demonstrable increase in motor pathway dysfunction with central fatigue, as assessed by TCMS, may have several explanations but perhaps the most likely is that the site of fatigue is upstream from the primary motor pathways.

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