

ABSTRACT: The functional implications of central motor impairment and peripheral muscle alterations in multiple sclerosis are unclear. Muscle strength, central and peripheral activation, and symptomatic fatigue were investigated in 16 patients with multiple sclerosis (MS) and 18 control subjects. Voluntary and electrically stimulated isometric contractions were obtained from the ankle dorsiflexor muscles. Maximal voluntary contraction (MVC) was 27% lower in MS patients than controls, although electrically stimulated force was similar. Muscle fat-free cross-sectional area (CSA) was similar in both groups. These data indicate central activation impairment in MS. Such impairment in MS was further demonstrated by decreased foot-tap speed, rate of voluntary force development, and central activation ratio. Peripheral activation changes in MS patients were modest. Although stimulated tetanic force was similar, force relaxation was slower in MS patients compared to controls, resulting in a left-shifted force–frequency relationship in MS. Motor function changes were not associated with fatigue but were associated with impaired ambulation. Thus, weakness and walking impairment, but not fatigue, were related to impaired central activation in MS. These findings may help optimize rehabilitation strategies designed to improve function in persons with MS.

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FUNCTIONAL RELATIONSHIPS OF CENTRAL AND PERIPHERAL MUSCLE ALTERATIONS IN MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that can result in impaired muscle function leading to weakness, fatigue, and decreased ambulatory ability. Self-reported or symptomatic fatigue, which can be independent of muscle fatigue,^{15,45} is also a significant problem in many patients with MS.^{11–13,25}

Central motor impairment can be a primary consequence of MS, and significant peripheral changes may arise from chronically altered central motor function.^{20,37,42} Various central and peripheral alter-

ations in MS during or after fatiguing exercise have been described,^{5,20,27,39,45,46} but few studies have systematically, in the same subjects, examined the physiological or functional effects of chronically altered central and peripheral muscle function on muscle strength, symptomatic fatigue, or measures of ambulation in the absence of fatiguing contractions.^{18,42}

Muscle weakness in MS is of central origin,⁴² resulting from both decreased motor unit discharge rates and incomplete motor unit recruitment. However, muscle strength is also related to muscle fat-free cross-sectional area (CSA),⁴¹ and this peripheral relationship can also explain any weakness in MS.¹⁸ Previous studies have not examined central and peripheral contributions to weakness simultaneously. In addition, it has been suggested that impaired central motor activation³⁷ is associated with the symptomatic fatigue of MS even in the absence of overt muscle fatigue. However, the evidence supporting such a relationship is equivocal.^{27,45,46}

Altered peripheral muscle function in MS includes the slowing of muscle contractile proper-

Abbreviations: ANOVA, analysis of variance; CAR, central activation ratio; CI, confidence interval; CMAP, compound muscle action potential; CSA, fat-free muscle cross-sectional area; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; MVC, maximum voluntary contraction; T_{1/2}, half-relaxation time; VAFS, Visual Analog Fatigue Scale

Key words: central activation; central motor drive; fatigue; multiple sclerosis; muscle strength

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ties,^{20,42,45,46} decreased muscle oxidative capacity,^{18,19} possibly impaired excitation–contraction coupling,^{20,45} and an altered muscle metabolic response to exercise.^{20,35,45} These changes appear to be secondary to central nervous system impairment and may be related to disuse.^{20,36,42} These peripheral alterations, however, are not universally observed,^{5,6} and it is not known to what degree peripheral changes in muscle are related to functional capacity in persons with MS.

The purpose of this study was to systematically, and in the same subjects, investigate the consequences of central motor impairment and altered peripheral muscle properties to functional capacity in MS. Voluntary muscle strength and symptomatic fatigue, measured by questionnaires,²⁶ and 25-ft walk-time were our primary functional measures. Muscle specific strength (muscle force/muscle cross-sectional area) and electrically stimulated tetanic force were obtained to provide insight into the central and peripheral contributions to strength. Measures of the adequacy of central motor drive included: (1) foot-tap speed²¹; (2) rate of voluntary force development^{21,34}; and (3) central activation ratio.¹⁷ Both the foot-tap speed and rate of voluntary force development are central motor functions related to the ability to rapidly develop and coordinate maximal motor unit discharge rates and recruitment during voluntary contractions.^{7,34} The central activation ratio is an indication of the completeness of voluntary muscle activation.¹⁷

To gain insight into mechanisms of symptomatic or chronic fatigue, we examined the relationships between self-reported symptomatic fatigue and physiological and clinical measures. We did not measure muscle fatigue in these studies. Measures of peripheral muscle function included: (1) the compound muscle action potential (CMAP), to indicate neuromuscular junction and muscle membrane activation; (2) muscle twitch and tetanic force and their respective contractile properties, which can indicate intramuscular Ca^{++} function or relative changes in muscle fiber types; and (3) the electrically evoked muscle force–frequency relationship, which can reflect changes in muscle contractile behavior.

METHODS

Subjects. Eighteen volunteers with MS (12 women, 6 men) were recruited from the San Francisco Bay area. All MS subjects were free from any other disease that might affect muscle function (e.g., cardiovascular or metabolic disorders) based on a health questionnaire and comprehensive neurologic exam-

ination by a neurologist. All subjects were examined by a neurologist to confirm the diagnosis of MS using the diagnostic criteria of Poser et al.⁴⁰ and to establish their clinical status. One man smoked, and the rest were nonsmokers. Twelve subjects were ambulatory without assistance, 4 used a cane or crutch, and 2 used a walker or wheelchair.

Eighteen healthy control subjects without MS (12 women, 6 men) were also recruited from the surrounding community. Control subjects were selected to be of similar age to those in the MS group, and were also free from chronic disease. One man smoked, and the rest were nonsmokers. To recruit relatively sedentary control subjects, these volunteers did not participate in more than one formal exercise session of 20 minutes per week in the 3 months prior to enrollment in the study. All subjects provided signed informed consent approved by the Committees on Human Research of the University of California, San Francisco, and the California Pacific Medical Center.

Muscle Force and Electromyographic Measurements.

The measurement methods used have been described previously.²⁰ Muscle testing occurred with the subject seated and both legs extended. The right leg was studied unless there was some contraindication for doing so (such as bunions). The leg to be studied was stabilized with a knee brace inserted into the leg apparatus and the foot angle fixed at 120° plantarflexion. Dorsiflexor isometric force was measured by a transducer mounted under a footplate at the end of a Lexan tube, which further stabilized the leg. The transducer signal was amplified (TE-4 electromyograph, Teca, White Plains, NY) and coupled to a computer that provided visual feedback during voluntary contractions. Force and electromyographic data were collected using LabView software (National Instruments, Austin, TX) and subsequently transferred to a spreadsheet for analysis.

The surface CMAP from the tibialis anterior muscle was measured during stimulated contractions using circular electrodes (10-mm diameter). The active electrode was placed on the thickest part of the belly of the muscle, the reference electrode was placed on the medial malleolus, and a copper ground plate was placed on the calf. Such an electrode arrangement maximized the CMAP amplitude in a muscle with multiple endplate anatomy.³¹ For all electrically evoked contractions, stimulating electrodes were placed over the peroneal nerve, approximately 1 cm distal to the fibular head. Supramaximal stimulation was achieved with an NS6 stimulator (Teca). Filter settings for the CMAP were 1.6 Hz and 16 kHz. The

CMAP and corresponding twitch data were collected at 2500 Hz. All other data were collected at 500 Hz.

Central Motor Function. To investigate the impact of central nervous system disturbances on dorsiflexor muscle function, we measured central motor function in three ways¹⁷: (1) the number of foot-taps performed in 10 s; (2) the rate of voluntary force development; and (3) the central activation ratio (CAR).

Foot-Tap Speed. Foot-taps were performed seated with the hip and knee angle at approximately 90°. Subjects started with their feet flat and were instructed to keep their heel on the floor while rapidly tapping the ball of their foot to the floor as many times as possible in 10 s. The same investigator measured the foot-taps of all subjects.

Rapid Voluntary Contractions. Following three maximal voluntary contraction (MVC) measurements, described later, subjects performed rapid, voluntary contractions to 40% MVC. Subjects were instructed to perform these contractions as quickly as possible. Practice trials were allowed until the subjects could accurately achieve the desired submaximal force. Three to four successful trials were recorded with 1 min of rest between each trial, and the contraction from the trial closest to 40% MVC was used for analysis. Because the force level achieved can affect the rate of contraction,³³ all raw data were expressed as percent peak force/millisecond. To further control for differences in force development as the result of peripheral factors (e.g., muscle fiber type), the maximal rate of voluntary force development was scaled to the maximal rate of force developed during the 50-Hz tetanic stimulation (i.e., voluntary rate/tetanic rate). In this way, any difference in voluntary force development speed was due to differences in central motor drive.

Central Activation. To assess whether voluntary activation was complete during the MVC, a 0.5-s train of 50-Hz supramaximal stimulation was superimposed during the third MVC. The CAR was determined as the ratio of the maximal voluntary force produced to the total force produced,¹⁷ where total force was the sum of voluntary force plus any "added force" from the superimposed stimulation; that is, $CAR = MVC / (MVC + \text{superimposed force})$. If activation was complete, and there was no superimposed stimulated force, then $CAR = 1.0$.

Muscle Strength and Cross-Sectional Area. *Maximal Voluntary Force.* Three MVCs were obtained, each during a voluntary 3–5-s maximal dorsiflexion. Verbal encouragement was given to all subjects. One

minute of rest separated each MVC measurement. The greatest force of the three trials was recorded as the MVC.

Magnetic Resonance Imaging. These methods have been described in detail previously.¹⁸ The fat-free cross-sectional area (CSA) of the anterior leg compartment, which contains the dorsiflexors, was obtained with T1-weighted proton magnetic resonance imaging (MRI). A scout image was obtained followed by 33 interleaved axial slice acquisitions (slice thickness 4 mm, echo time 14 ms, repetition time 510 ms, flip angle 70°, field-of-view 210 mm, 256 × 256 matrix). Echo and repetition times were optimized to provide the greatest signal-intensity contrast between muscle and fat. The slice with the greatest anterior compartment cross-sectional area was further analyzed to obtain the fat-free area. A program written in Matlab (MathWorks, Natick, MA) was used to outline the muscles of the anterior compartment. A signal intensity threshold for fat was determined from a histogram plot of an area consisting primarily of fat. The signal from fat was then subtracted from the anterior compartment, resulting in the muscle fat-free CSA. All images were analyzed three times by the same investigator and averaged. The average within-subject variability (SD/mean) for the measure of muscle CSA was 2.9%.

Specific Strength. To determine whether differences in strength were explained by differences in contractile mass, specific strength was calculated as MVC/muscle CSA and compared between groups.

Symptomatic Fatigue. In both the MS and control groups, we obtained measures of subjective symptomatic fatigue using: (1) the Fatigue Severity Scale (FSS²⁶), a scale from 0 to 7 where increasing numbers represent increasing subjective fatigue; and (2) the Visual Analog Fatigue Scale (VAFS²⁶), which is an analog scale from 1 to 10 of increasing fatigue. Both scales are questionnaires that assess self-reported chronic fatigue, a major symptom in MS. For the FSS, the total score from each subject was averaged and used to calculate the group mean. These questionnaires were administered prior to any muscle testing.

Peripheral Muscle Function. *CMAP and Muscle Twitch Force.* After electrode placement, and prior to the MVC measurements, the CMAP and corresponding twitch force were obtained in response to a single supramaximal stimulus of 0.2-ms duration. Supramaximal stimulus intensity was obtained by using a voltage 10–15% greater than that associated with the highest peak-to-peak CMAP amplitude.

Table 1. Symptomatic fatigue and ankle dorsiflexor function during voluntary contractions in control and MS groups.

Measure	Control	MS	95% CI	P
Fatigue Severity Scale	2.9 ± 0.2	4.9 ± 0.3	1.1 to 2.8	<0.01
Visual Analog Fatigue Scale	3.3 ± 0.5	6.3 ± 0.6	1.5 to 4.6	<0.01
MVC (N)	157 ± 12	115 ± 15	4 to 80	0.03
Muscle cross-sectional area (cm ²)	9.8 ± 0.6	8.5 ± 0.5	0.29 to 2.89	0.11
Specific strength (N/cm ²)	16.0 ± 0.7	13.2 ± 1.4	-0.33 to 5.8	0.08
Foot taps (number in 10 s)	48 ± 2	26 ± 3	15 to 29	<0.01
Maximal rate of voluntary force development (% peak tetanic/ms)	0.77 ± 0.02	0.61 ± 0.05	0.05 to 0.27	<0.01
Central activation ratio	0.96 ± 0.03	0.86 ± 0.23		0.04

For voluntary force measures, control = 18 and MS = 16 subjects. Data are mean ± SE. Analysis of central activation ratio by Mann-Whitney U-test. 95% CI, confidence interval. MS, multiple sclerosis; MVC, maximal voluntary contraction.

Three CMAPs and twitches were obtained, each 1 min apart. Peak-to-peak amplitude (mV) and duration of the negative peak (ms) were measured for each CMAP and averaged. Peak force (N) and time-to-peak force (ms) were measured from each muscle twitch. Contractile data reported were those associated with the highest twitch force.

Force-Frequency Relationship. The stimulated force-frequency relationship of the dorsiflexors was investigated by measuring peak muscle force during a train of electrically evoked contractions of 1-s duration at 1, 5, 10, 20, and 50 Hz. The peak force produced by the 50-Hz stimulation is referred to as tetanic force. These measurements were obtained after the twitch and CMAP measurements and were also separated by 1 min of rest. Force data were expressed relative to those obtained from the 50-Hz stimulus train. We also calculated the maximum rates of tetanic force development (% peak force/ms), relaxation (negative % peak force/ms), and half-relaxation time ($T_{1/2}$, ms). The $T_{1/2}$ of the 50-Hz stimulation was calculated as the time in which force fell to 50% of maximal, as determined from the time of the last stimulus artifact.

Data Analyses. The CAR was analyzed with the nonparametric Mann-Whitney U-test. Two-factor (group, gender) analysis of variance (ANOVA) was used to test for differences in means for all other individual variables. If there were no within-group gender effects, including interactions, then the data for both genders were combined. In the event of a gender × group interaction, pairwise comparisons were used to determine where the differences occurred. To examine the stimulated force-frequency relationship, we tested for differences between groups in relative muscle force at each frequency using a repeated-measures ANOVA with two “between” factors (group and gender) and one “within”

factor (stimulation frequency). Because the force from the 50-Hz stimulus train was used as a normalizing variable, this data point was excluded from the analysis. Pearson product-moment correlations were used to examine relationships among fatigue measures and other physiological or clinical measures of interest. Analyses were performed using Systat software (Systat, Evanston, IL). For all statistical analyses, differences were considered significant at $P < 0.05$. Descriptive data are reported as median (range). All other data are reported as mean ± SE, with confidence interval (CI).

RESULTS

Subjects. One man and one woman with MS were not able to produce appreciable ankle dorsiflexor force. Because it was important to obtain systematic measures of both central and peripheral muscle function in all subjects, these two subjects were excluded, leaving a total of 16 MS subjects for study. Subjects with MS were similar in age (control vs. MS: 44 ± 2 vs. 47 ± 1 years; $P = 0.24$), height (169 ± 2 vs. 169 ± 3 cm; $P = 1.00$), and weight (73.7 ± 3.4 vs. 67.2 ± 3.6 kg; $P = 0.20$) to control. The MS group ranged from those minimally affected by their disease to several with significant limitations in mobility and activities of daily living. The following are the median (range) values for the patient group ($n = 16$) in measures of clinical status: Expanded Disability Status Scale (EDSS), 3.2 (1.5–6); Ashworth Spasticity Scale, 1.5 (1–3; normal, 1); MRC manual muscle test scale, 4.2 (0–5; normal, 5); and deep tendon reflex (ankle), 3.3 (2–4; normal, 2). Eleven patients had a Babinski sign. The mean (range) values for the 25-ft walk-time was 6.4 (3.1–13.0) s and number of steps in 25-ft was 12.2 (9–18). Half were diagnosed as having relapsing-remitting disease and half as having primary or secondary progressive disease. The

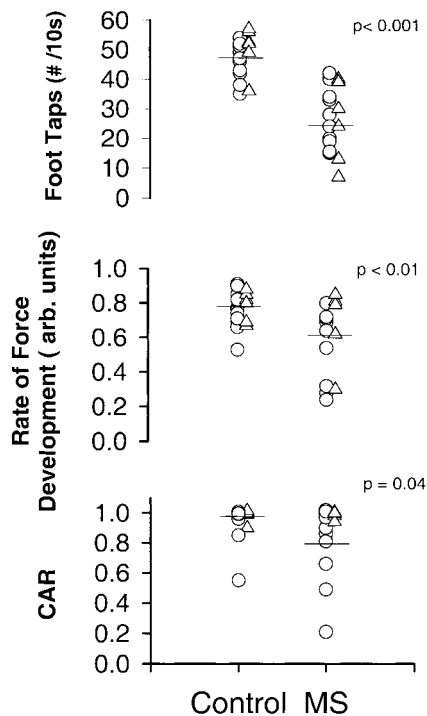


FIGURE 1. Individual values for speed of rapid foot-taps (number in 10 s) (**top**), maximal rate of voluntary force development (normalized to maximal rate of tetanic force development) (**middle**), and central activation ratio (CAR) for control and MS men (triangles) and women (circles) (**bottom**). The horizontal bars indicate combined group means. The MS group demonstrated significant impairment in central motor function compared to controls for the speed of rapid foot-taps, the maximal rate of voluntary force development, and CAR.

MS group had greater symptomatic fatigue than controls for both measures of perceived fatigue (Table 1). Thus, the overall clinical characteristics of this patient group ranged from mild to severe.

Central Motor Function. Measures of central motor function during voluntary contractions are presented in Table 1 and Figure 1. The MS subjects were able to perform only about half the number of foot-taps in 10 s compared to control subjects. The maximal rate of force development during a single, rapid submaximal isometric contraction was slower in the MS group than in controls (Table 1). Finally, the MS group had a lower CAR compared to controls (Table 1), indicating an inability to maximally activate the dorsiflexor muscles during a single maximal voluntary isometric contraction.

Muscle Strength and Cross-Sectional Area. The MS group was significantly weaker than the control group (Table 1). Not surprisingly, men were stronger than women, with no interaction ($P = 0.88$)

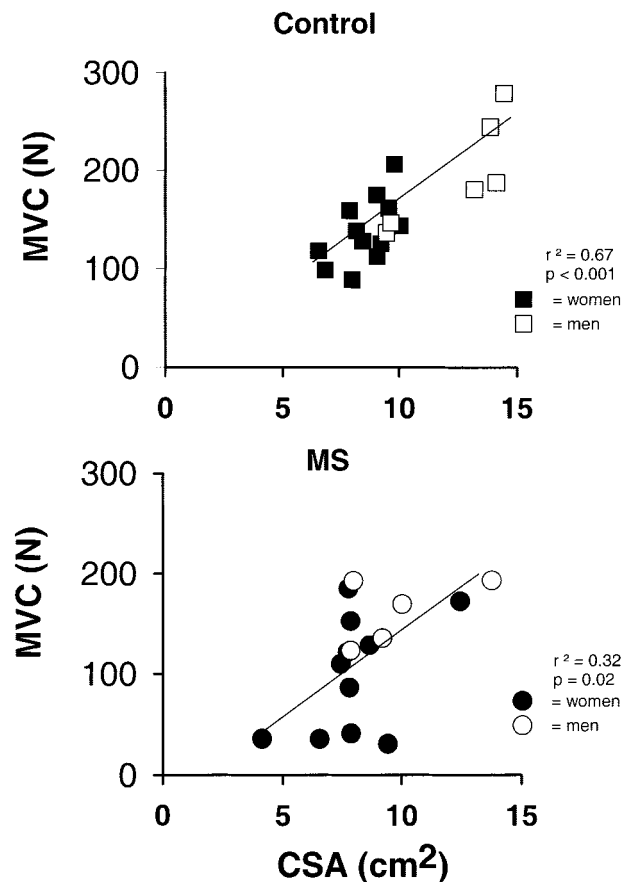


FIGURE 2. Relationship between dorsiflexor maximal isometric voluntary contraction force (MVC) and anterior compartment fat-free cross-sectional area (CSA) in controls and MS men and women.

between the MS and control groups (men = 180.8 ± 14.2 N, women = 119.8 ± 10.4 N; 95% CI = 24.5–97.5; $P = 0.01$). Although MS subjects were weaker, dorsiflexor muscle CSA was similar in MS compared to controls (Table 1). Men had a larger CSA than women (men = 11.2 ± 0.8 cm²; women = 8.2 ± 0.3 cm²; 95% CI = 1.5–4.5; $P < 0.001$), with no interaction ($P = 0.13$). Despite similar muscle CSA, much less of the variance in voluntary force production was explained by the muscle CSA in MS patients compared to controls (Fig. 2). When MVC was expressed relative to CSA, there was a tendency for the MS group to have lower specific strength than controls ($P = 0.08$). There was no gender difference in specific strength.

Correlations between Physiological, Clinical, and Functional Measures. Within the MS group, correlation analysis indicated significant ($P < 0.05$) relationships between the two measures of symptomatic

Table 2. Peripheral skeletal muscle function in 18 control and 18 MS subjects.

Measure	Control	MS	95% CI	<i>P</i>
CMAP amplitude (mV)	7.8 ± 0.4	6.9 ± 0.4	−0.3 to 2.1	0.14
CMAP duration (ms)	15.9 ± 0.6	16.1 ± 0.5	−1.9 to 1.4	0.80
Twitch force (N)	13.6 ± 2.3	18.7 ± 3.1	−12.9 to 2.7	0.19
Twitch time (ms)	120.3 ± 2.0	117.0 ± 4.0	−5.5 to 12.1	0.45
Tetanic force (N)	122.1 ± 11.3	125.9 ± 12.8	−38.5 to 31.0	0.82
T _{1/2} tetanic relaxation (ms)	127.5 ± 8.9	388.7 ± 83.2	−420.9 to 99.5	<0.01
Maximum rate tetanic force development (% peak force/ms)	0.49 ± 0.02	0.48 ± 0.02	−0.05 to 0.07	0.71
Maximum rate tetanic force relaxation (% peak force/ms)	−0.59 ± 0.03	−0.43 ± 0.05	−0.28 to 0.04	<0.01

Analysis was by two-factor ANOVA (group, gender). Data are mean ± SE. ANOVA, analysis of variance; CI, confidence interval; CMAP, compound muscle action potential; MS, multiple sclerosis.

fatigue (FSS and VAFS; $r = 0.92$). Neither the FSS nor VAFS was significantly associated with central motor function or any other physiological or clinical measure. The speed of foot-taps correlated with the maximal rate of voluntary force development ($r = -0.80$), MVC ($r = 0.56$), specific strength ($r = 0.55$), 25-ft walk time ($r = -0.78$), and number of steps in the 25-ft walk ($r = -0.86$). There was a tendency toward a correlation with the rate of tetanic force relaxation ($r = -0.45$; $P = 0.08$). In addition to foot-taps, the maximal rate of voluntary force development was also correlated with MVC ($r = 0.61$), specific strength ($r = 0.56$), peripheral contractile measure of maximal rate of tetanic force development ($r = 0.56$), 25-ft walk time ($r = -0.58$), and number of steps in the 25-ft walk ($r = -0.89$). Finally, the CAR was correlated with MVC ($r = 0.66$) and specific strength ($r = 0.74$).

Peripheral Skeletal Muscle Function. *CMAP and Muscle Twitch.* Electrically stimulated CMAP and force measurements are presented in Table 2. Control and MS groups had similar CMAP amplitude and duration, although there was a tendency for MS patients to have a smaller CMAP amplitude than controls ($P < 0.07$). Twitch force and contraction times were also similar between groups, as were peak tetanic force and the rate of tetanic force development. Despite similar peak tetanic force and rate of force development, the MS group demonstrated slowed force relaxation, whether measured as the tetanic force T_{1/2} or the maximal rate of tetanic force relaxation (Table 2). One control subject did not participate in this portion of the study ($n = 17$).

Force–Frequency Relationship. The force–frequency relationship was shifted to the left in MS subjects compared to controls (main effect, $P = 0.03$; Fig. 3). Because there was no gender effect

($P = 0.52$), data from men and women were combined. Differences ($P < 0.05$) between MS and control subjects were statistically significant with stimulation at 5, 10, and 20 Hz.

DISCUSSION

To determine how long-term changes in central motor drive affect muscle function in MS, we quantified central motor drive, muscle force, and peripheral motor function of muscle in MS patients and healthy controls. Voluntary and electrically stimulated isometric contractions were produced in the unfa-

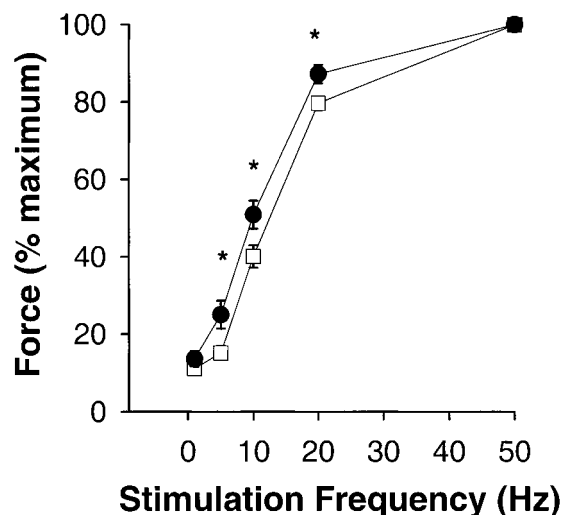


FIGURE 3. Ankle dorsiflexor muscle force–frequency relationships for control (open squares) and MS (filled circles) groups. Force data (mean ± SE) are expressed relative to maximum stimulated force. The MS group exhibited a left shift in the force–frequency relationship compared to control, suggesting relatively greater summation of force at lower frequencies in MS vs. control. *Pairwise differences between MS and control ($P < 0.05$).

tigued ankle dorsiflexor muscles. All measures of central motor function indicated central impairment in the MS group. Weakness in the MS group during the MVC was primarily the result of central impairment because there was no decreased force during stimulated contractions. Although central impairment was related to other clinical and functional measures such as walking, it was not related to symptomatic fatigue, as measured by questionnaires. Altered peripheral function was indicated by the slowing of the maximal tetanic force relaxation rate and the $T_{1/2}$ of force relaxation. In addition, slower muscle relaxation resulted in a left-shifted force–frequency curve. These measures quantify the impairment of central motor drive and indicate its primary role in the weakness of MS.

Central Motor Function. The inability to fully activate motor units during MVC in MS was indicated by a decreased CAR compared to control. This finding confirms previous studies using the same or similar techniques.^{6,27,42,45} However, because the central impairment of MS is likely to be manifest in both velocity- and strength-dependent motor function, the speed of foot-taps and the maximal rate of voluntary force development were obtained. The maximal rate of voluntary force development of a target submaximal force has not been reported before in MS and is an integrated measure of central motor function that incorporates coordination as well as velocity-dependent force generation. The slowed voluntary force development observed in MS was normalized to the rate of tetanic force generation to account for any change in peripheral muscle function. There was no difference in the rate of tetanic force development, which is a peripheral measure of muscle function. Thus, the slower rate of voluntary force development in MS was the result of central alterations in motor function.

The reduced speed of foot-taps and rate of voluntary force development indicate that the ability to rapidly modulate force at submaximal force levels is impaired in MS patients compared to controls. The ability to perform rapid successive foot-taps is dependent on effective modulation of both motor unit recruitment and rate coding.³⁴ The maximal rate of voluntary force production is characterized by the ability to rapidly develop high motor unit discharge rates.⁷ A reduced capacity to perform rapid voluntary contractions has been associated with other upper motor neuron disorders,^{2,3,21,50} but not with lower motor neuron disorders.^{28,32}

The impaired rapid successive voluntary contractions, as indicated by foot-tap speed, are likely a

function of the slowed rate of maximal voluntary force development as well as spasticity. The high correlations between the rate of maximal voluntary force development and foot-tap speed are consistent with this idea. Together, these data indicate that muscle weakness and impaired velocity-dependent motor function in MS coincide with abnormal central motor function, consistent with the central nervous system deficit of MS.

Weakness in MS. Measurements of MVC indicate that the MS group was ~32% weaker than an age- and gender-matched control group. This weakness is within the range that has been reported previously.^{5,20,45} The positive correlations between CAR, as well as maximal rate of voluntary force development, with both MVC and specific strength, suggest that impaired central activation contributes to weakness in MS. Findings based on MRI and strength confirm that impaired central activation contributes to weakness in MS. It is unlikely that changes in peripheral or intrinsic muscle function resulted in significant weakness in the MS subjects because similar electrically stimulated tetanic and twitch forces were measured in both groups. Muscle fiber atrophy can account for a portion of the weakness in MS.¹⁸ However, weakness in our MS group was not accounted for by whole-muscle atrophy, as muscle CSA was similar in both groups. In controls, muscle strength was directly related to the CSA of muscle (Fig. 2). A lack of strong association between CSA and MVC in MS (Fig. 2) with a trend toward decreased specific strength in the MS group, indicated that, although some persons with MS exhibited normal specific strength, others did not. Together, these MRI and strength findings, along with measures of central impairment, indicate that central activation impairment was responsible for much of the weakness in MS.

In addition to weakness, measures of central motor function (reduced speed of foot-taps, decreased maximal rate of voluntary force generation) were associated with decreased walking ability, as measured by the 25-ft walk speed and number of steps. These relationships attest to the functional importance of central motor function to ambulation as well as weakness.

Symptomatic Fatigue. Our measures of symptomatic fatigue (FSS, VAFS) confirmed the significant fatigue often reported in MS.^{11–13,26} Although common in MS, the mechanisms of symptomatic fatigue are elusive. It has been suggested that increased central drive to compensate for decreased central

activation could have a correlate in the symptomatic fatigue of MS.³⁷ As reported here and by others, symptomatic fatigue does not consistently correlate well with central activation, weakness (MVC), or any other clinical or muscle function measure, including muscle fatigue.^{14,45–48}

Depression has been shown to influence symptomatic fatigue by some^{1,4,24,43} but not all investigators.^{11,26,48,49} Finally, there is some evidence that symptomatic fatigue may be associated with alterations in cardiovascular autonomic control.^{22,30,35} Together, the current findings suggest that the fatigue in MS is multifactorial and not tightly linked to specific measures of impaired motor control.^{11,15}

Peripheral Function. In MS, peripheral changes in muscle function may occur secondary to changes in central motor drive and decreased physical activity. Muscle contractions, caused by stimulation of a peripheral nerve, allow for contractile function to be examined in the absence of central influences. The CMAP characteristics of our subjects were consistent with intact peripheral neuromuscular activation, consistent with previous studies.⁴⁶ The similarity between MS and control groups in CMAP and twitch data contrast with some of our previous results^{20,45} and likely result from population differences.

As previously discussed, the weakness of MS was not the result of changes in intrinsic muscle function, as twitch, tetanic force, and CSA were similar in MS and control subjects. In contrast, patients with lower motor neuron disorders have demonstrated substantially lower tetanic force^{21,44} compared to controls. Although intrinsic force production was preserved, prolonged force relaxation was present in the patients studied.

The observed slowing of force relaxation is similar to what has been reported previously for MS,^{20,42,45} postpolio syndrome,⁴⁴ and amyotrophic lateral sclerosis.²¹ This slowing of contractile properties is not likely explained by changes in muscle fiber type, as observed previously in MS¹⁸ or spinal cord injury.^{16,29} In such conditions, fiber types change toward a higher proportion of fast fibers (i.e., type II) that would promote a shift toward faster, not slower contractile properties. Furthermore, in MS, when fiber types were normalized to fiber cross-sectional area, the ratio of slow to fast fibers was similar to control muscle.¹⁸ As such, the slowing of force relaxation in MS might result from chronically reduced motor neuron discharge rates, similar to the effects of experimental low-frequency stimulation,¹⁰ or from altered sarcoplasmic Ca^{++} reuptake.²³ Although not measured, decreased maxi-

mal motor neuron discharge rates in MS have been reported by other investigators.⁴² Muscle relaxation properties are not always slowed in the quadriceps⁵ nor are they in the adductor pollicis muscle⁶ in patients with MS. These populations studied by other investigators^{5,6} had similar disability levels (EDSS) as subjects in our study. Differences between our study and earlier ones could reflect differences between the muscle groups studied, in the case of the adductor pollicis, or differences in population samples. Despite the observed slowing of muscle relaxation properties, the similar tetanic force in both groups and the greater weakness during MVC indicate that most of the muscle weakness observed in MS was due to impaired central, not peripheral, motor function.

We have emphasized how central motor changes were primarily responsible for the slowing of foot-taps, but prolonged muscle relaxation in MS could also be important. Slowed muscle relaxation could lead to an impaired ability to rapidly modulate torque across a joint. The moderate correlation of the rate of tetanic force relaxation with foot-tap speed is consistent with a contribution of peripheral factors to foot-tap speed.

A consequence of prolonged relaxation in the unfatigued muscle of persons with MS was the left shift of the electrically evoked force–frequency relationship (Fig. 3). This indicated that the MS patients produced greater relative force at a given electrical stimulation frequency than control subjects. This left-shifted force–frequency relationship follows from the slowing of muscle relaxation, which would result in greater summation for a given motor unit discharge rate. Such a left-shifted force–frequency relationship may serve to optimize muscle contractile properties to motor-neuron discharge rates in MS⁴² and could be considered adaptive. A left-shifted force–frequency relationship has previously been described in a single MS patient,⁴² but has not been shown to be characteristic of MS until now. de Ruyter and colleagues found no altered force–frequency relationship of the adductor pollicis in patients with MS compared to a control group,⁶ but they did not detect any alteration of adductor pollicis contractile properties.⁶

Altered peripheral function in MS may be secondary not only to long-term changes in central drive but to chronically decreased muscle activity. Slowed muscle contractile properties have been observed in studies of disuse or deconditioning.^{8,9} Physical activity in MS has been reported previously to be about 35% lower than sedentary control subjects.³⁶ Although the importance of regular exercise in MS

is recognized,³⁸ we do not know the extent to which changes in central or peripheral muscle function can be reversed or stabilized with exercise training.

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