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Fatigue in multiple sclerosis: Current understanding and future directions

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Abstract—Fatigue is a very common symptom of multiple sclerosis (MS). Theoretically, fatigue may be related to neuromodulation by soluble products of the autoimmune process or by disruption of central nervous system pathways necessary for sustained activity, but little empirical evidence supports these possibilities. Amantadine, pemoline, and modafanil improved fatigue in placebo-controlled clinical trials, but these studies all had significant limitations. Difficulty measuring fatigue has impeded studies of its characteristics, mechanisms, and therapeutics. Most studies have relied on self-report questionnaires. These may be inappropriate, however, because they can be easily confounded by other symptoms of MS, they are entirely subjective, and they require patients to make difficult retrospective assessments. Studies of fatigue would be improved by including measures of more rigorously defined, quantifiable components of fatigue. For example, motor fatigue can be measured as the decline in strength during sustained muscle contractions. Cognitive fatigue can be measured as the analogous decline in cognitive performance during tasks requiring sustained attention. *Lassitude* is defined as a subjective sense of reduced energy, and it can be measured with the use of a visual analog diary. These measures provide reproducible results and demonstrate significant differences between MS patients and healthy controls. Dividing fatigue into these components can provide objective assessments that are less likely to be confounded by other symptoms of MS, such as weakness, spasticity, cognitive impairment, and depressed mood.

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INTRODUCTION

Fatigue is defined as a state with reduced capacity for work following a period of mental or physical activity. In casual use, however, patients often use the term "fatigue" to describe a much broader range of symptoms. This article reviews the evidence that fatigue is a common symptom of multiple sclerosis (MS). It also reviews measures of fatigue in MS, possible mechanisms and treatments for fatigue, and the need to develop more objective and quantifiable methods of measuring fatigue severity.

CURRENT MEASURE OF FATIGUE IN MS

Fatigue was rarely listed as a symptom of MS in studies performed prior to the 1980s, for example, Kurtzke (1). This changed in 1984 when Freal et al. published an influential report in which 78 percent of 656 MS patients surveyed listed fatigue as one of their symptoms (2). This was striking not only because of its difference from prior reports, but also because fatigue was the single most common symptom of MS in these patients and the most likely symptom to interfere with activities of daily living. This assessment was made by having patients endorse items on a mailed symptom list; fatigue was not defined for the

patients. A follow-up questionnaire was sent to the fatigued patients to obtain more detailed information about this unexpectedly common symptom. Respondents provided narrative descriptions of their fatigue, which most often included some facet of "weakness, tiredness, and/or the need to rest" (71 percent of patients). Patients were also given a list of descriptions to endorse, which provided similar information (**Table 1**). Many patients (28 percent) stated that their fatigue made "symptoms more apparent." Many patients thought that fatigue was similar to (43 percent) or exactly the same (11 percent) as an MS exacerbation, which was defined as "a worsening of MS symptoms lasting more than 24 hours." These observations suggest that patients may not have been distinguishing between fatigue and other symptoms.

In 1985 Murray published results of a similar questionnaire, in which 96 percent of patients at the Dalhousie MS Research Center (Halifax, Nova Scotia) listed fatigue as a symptom (3). Most patients (76 percent) felt that their fatigue was "abnormal," and 40 percent described it as their major complaint. Again fatigue was undefined. It is not clear whether all of these patients were experiencing the same symptom or whether it was distinct from motor impairment, cognitive impairment, depression, and other common symptoms of MS. Furthermore, both the Freal and Murray studies failed to include a control group to determine how healthy patients would respond to these questions.

Krupp et al., recognizing many of the limitations of these studies, interviewed 32 MS patients and 33 healthy adults to more rigorously assess the characteristics of fatigue in MS patients and the relationship of this symptom to disease activity, neurologic disability, and depression (4). They defined fatigue as "a sense of physical tiredness and lack of energy, distinct from sadness or weakness." They found that 88 percent of MS patients and 51 percent of controls stated that they were "bothered by fatigue." Twenty-eight percent of MS patients considered fatigue their most troubling symptom. On average, fatigue was more severe in MS patients than controls based on visual analog scale ratings. They also found that fatigue ratings were unrelated to neurologic impairment/disability measured by the Expanded Disability Status Scale (EDSS) or to depression measured by the Center for Epidemiologic Studies Depression (CES-D) scale. The characteristics that distinguished fatigue in MS patients and controls are presented in **Table 2**.

Based on this study, Krupp et al. devised the Fatigue Severity Scale (FSS), a nine-item questionnaire (see **Figure 1**) in which patients rate their agreement with statements that distinguished fatigue in MS patients from healthy controls (5). The questionnaire demonstrated good internal consistency, test-retest reliability, and responsiveness to treatment effects. Construct validity was supported by dem-

Table 1.
Description of fatigue.

Description	*n*	%
Tiredness or the need to rest	278	90
Sleepiness	132	43
A worsening of MS symptoms not otherwise experienced	148	48
Other	69	22

Source: See Freal et al. (2).

Table 2.
Characteristics distinguishing fatigue in MS patients and healthy controls.

Characteristic	MS %	Control %	*P*
Heat worsens it	92	17	<0.001
Prevents sustained physical functioning	89	0	<0.001
Comes on easily	82	22	<0.001
Interferes with physical functioning	79	28	< 0.01
Interferes with responsibilities	67	0	<0.001
Causes frequent problems	63	17	< 0.01

Source: See Krupp et al. (4).

1. My motivation is lower when I am fatigued.
2. Exercise brings on my fatigue.
3. I am easily fatigued.
4. Fatigue interferes with my physical functioning.
5. Fatigue causes frequent problems for me.
6. My fatigue prevents sustained physical functioning.
7. Fatigue interferes with carrying out certain duties and responsibilities.
8. Fatigue is among my three most disabling symptoms.
9. Fatigue interferes with my work, family, or social life.

Figure 1.
The Fatigue Severity Scale. Each item is rated on a 7-point Likert scale, with results averaged. Source: See Krupp et al. (5).

onstration of associations between FSS scores and a visual analog scale rating of fatigue severity. Correlations were modest, however (r = 0.47 in MS patients, r = 0.50 in healthy adults). Validity was further supported by demonstrating that FSS scores were higher in patients with MS or systemic lupus erythematosus compared to healthy controls, and that FSS scores were unrelated to depressive symptoms rated by the CES-D.

This study demonstrated that the FSS is a valid instrument for distinguishing the fatigue experienced by patients with medical illness from fatigue experienced by healthy controls. It did not fully establish that the FSS is a good measure of fatigue severity. Several FSS items address the quality of fatigue, rather than the quantity (Items 1, 2, 3, 4, 6). Other items rate motor, cognitive, and social consequences of fatigue rather than fatigue itself (Items 5, 7, 9). These items are particularly problematic in patients with confounding reasons for such consequences, including motor and cognitive impairment from MS. The remaining item compares the severity of fatigue to other MS symptoms, without directly addressing fatigue quality or quantity. Thus the FSS has limited face validity as a measure of fatigue severity.

In a subsequent study, the same research group performed factor analysis on the 29-item Fatigue Assessment Instrument (FAI), which includes the nine items from the FSS, in 198 patients with Lyme disease, chronic fatigue syndrome, post-Lyme chronic fatigue, systemic lupus erythematosus, MS, or dysthymia, and 37 healthy controls (6). They identified four distinct dimensions underlying these items: fatigue severity, situation specificity, consequences of fatigue, and responsiveness to rest/sleep. Eight of nine FSS items were principally related to the fatigue severity dimension. Nevertheless, the fact that these items cluster together and have good internal consistency does not necessarily mean that they provide a valid measure of fatigue severity.

Fisk et al. developed the Fatigue Impact Scale (FIS) in a similar way, starting with interviews of 30 MS patients to suggest questionnaire items, followed by a validation study in 105 patients with MS, 145 patients with CFS, and 34 hypertensive controls (7,8). The FIS was designed "to assess the problems in patients' quality of life that they attribute to their symptoms of fatigue." It has separate subscales in which patients rate the impact of fatigue on physical (10 items), cognitive (10 items), and psychosocial functions (20 items). Fatigue was never defined, however, so it is unclear whether patients might have also considered motor dysfunction, cognitive dysfunction, depressed mood, and so forth, when making these determinations. FIS subscales had good internal consistency, and each subscale was higher (worse) in MS and CFS patients than in hypertensive controls. There was no association between FIS and EDSS scores. The authors stated that this observation showed the FIS was measuring fatigue rather than neurologic impairment/disability. Because the EDSS has limitations as a measure of disability, however, such a conclusion may not be warranted.

Despite these limitations, the FSS has become one of the most commonly used measures of fatigue severity in MS patients as well as other medical disorders. A modified version of the FIS (21 items instead of 40) has been incorporated into the MS Quality of Life Inventory developed by the Consortium of MS Centers. Many other self-report fatigue scales have been proposed as well, but their use, particularly in studies of MS patients, has been more limited. These are the Chalder Fatigue Scale (9), Fatigue Assessment Instrument (6), Multidimensional Assessment of Fatigue (10,11), Checklist of Individual Strengths (12–14), Multidimensional Fatigue Inventory (15), and the Fatigue Descriptive Scale (16). Some, but not all, have demonstrated good internal consistency and test-retest reliability; few have demonstrated responsiveness to change over time or to therapeutic effects. They all have similar limitations. First, they ask patients to rate fatigue without clearly defining it. As a result, it is not clear whether patients are commenting on a distinct symptom. Second, they are entirely subjective. Even if patients are appropriately rating the intended symptom, it is not clear that they can accurately assess fatigue any better than they could assess motor impairment, cognitive impairment, or other facets of their disease. For this reason, self-report scales may be particularly prone to placebo effects. Third, they require retrospective assessments of fatigue over relatively long periods. This makes self-report scales subject to recall bias.

PATHOPHYSIOLOGICAL MECHANISMS OF FATIGUE

The pathophysiology of fatigue in MS is not known. Potential mechanisms include (1) neuromodulation by soluble products of activated leukocytes participating in the autoimmune process and (2) demyelination and axonal

loss in central pathways necessary for sustained neural activity. While these possibilities have intuitive rationales, little direct evidence supports them. Alternatively, fatigue may have an indirect cause that is not specifically related to the disease process but secondary to other common consequences of MS, such as depression or sleep disturbance. The etiology of fatigue is most likely multifactorial, but the evidence for each of these mechanisms will be examined separately.

Several lines of evidence suggest that fatigue may be related to proinflammatory cytokines from activated leukocytes participating in the autoimmune process. Many proinflammatory cytokines known to be elevated in MS lesions cause fatigue and somnolence when administered exogenously. These include IL-1, IL-2, IL-6, IFNγ, and TNFα (17–21). There are receptors for IL-1 on hypothalamic neurons, but it is unknown whether neurons possess receptors for the rest of these cytokines, so it is unclear whether these effects occur through direct or indirect neuromodulation.

Furthermore, patients with other conditions associated with fatigue are known to have altered levels of cytokines in the peripheral circulation, generally skewed toward Th1 proinflammatory mediators. Patients with chronic fatigue syndrome have elevated serum levels of TNFα, IFNγ, and IL-6, as well as reduced levels of TGFβ (22–26). Patients with sleep apnea have increased levels of TNFα and IL-6 (27), and TNFα rises during dialysis in patients with postdialysis fatigue (28). In a study of experimental motor fatigue in mice injected with Corynebacterium antigen, C57BL/6 mice that respond with a Th1-mediated inflammatory response had significant increases in motor fatigue. On the other hand, Balb/c mice that respond with a Th2-mediated response exhibited less antigen-induced fatigue (29).

Although these studies are consistent with the hypothesis that fatigue in MS is related to proinflammatory cytokines, previous studies have failed to demonstrate relationships between markers of inflammatory disease activity and self-reported fatigue in MS patients. Rudick and Barna measured IL-2 and soluble IL-2 receptor (sIL-2r) in 8 patients with debilitating fatigue from MS and 50 healthy controls (30). IL-2 levels were undetectable in all patients and only one patient had an elevated level of sIL-2r. Bertolone et al. measured IL-1β, IL-6, beta-2 microglobulin, sIL-2r, and soluble CD8 in 30 patients with severe fatigue from MS participating in a double-blind, placebo-controlled, parallel group study of amantadine and pemoline. They found that patients reporting a treatment response had corresponding decreases in IL-1β and IL-6, but that nonresponders had no change in cytokine levels (31). The relevance of this observation is unclear, however, because the treatment effects for responders were relatively small and were likely caused by a psychostimulatory rather than anti-inflammatory effect. Giovannoni et al. (32) compared levels of serum C-reactive protein, urinary neopterin, and soluble intercellular adhesion molecule-1 (sICAM-1) to FSS and Fatigue Questionnaire Scale (33) scores in 38 MS patients. They found no association between the markers of inflammation and fatigue as measured by these scales.

An important limitation in all of these studies is that the inflammatory markers assessed are, at best, indirect indicators of disease activity in individual patients with MS, resulting in substantial overlap in marker levels in patients with and without active disease. Of the markers assessed, only sICAM-1 appears to vary with other signs of MS activity, such as the occurrence of gadolinium-enhancing lesions on brain MRI or clinical exacerbations (34). To avoid this problem, Mainero et al. focused on blood-brain barrier breakdown visualized with monthly gadolinium-enhanced MRI, which provides more direct assessment of CNS inflammatory activity (35). They found that FSS scores in 11 patients with relapsing MS were unrelated to enhancing lesion activity. Like all studies of fatigue in MS patients, however, these results must be interpreted cautiously because self-report questionnaires may not adequately measure fatigue severity.

It is also possible that fatigue may be related to demyelination and axonal loss. Consistent with this possibility, fatigue is more common in patients with progressive MS (a more advanced stage in general) rather than relapsing disease (36,37). In contrast, studies of the relationship between self-reported fatigue and neurologic disability have found either no association or modest associations (4,5,38,39), and there are no longitudinal studies demonstrating that fatigue worsens over time. Furthermore, Bakshi et al. found no difference in semiquantitative global and regional measures of MS lesion burden and atrophy in 46 fatigued (FSS $\geq$ 5.0) and 20 nonfatigued (FSS $\leq$ 4.0) MS patients (40). On the other hand, Roelcke et al. used PET to demonstrate that glucose metabolism was reduced in white matter adjacent to prefrontal cortex, premotor cortex, and basal ganglia of 19 fatigued (FSS > 4.9) compared to 16 nonfatigued (FSS

< 3.7) MS patients (41). These conflicting results must be interpreted cautiously because of the relatively small numbers of patients studied, because they relied on semiquantitative regional measures of pathology, and because the FSS may not be adequately assessing fatigue severity.

Finally, fatigue may be related to secondary consequences of MS, such as depression, or sleep disturbance. Depressive symptoms are common in patients with MS (42). These include lassitude, psychomotor retardation, decreased physical activity, decreased motivation, and other symptoms that overlap with what has commonly been considered fatigue. Fatigue is one of the criteria for a Major Depressive Episode according to DSM-IV, although fatigue is not defined there (43). As a result, most fatigue scales include items that could be influenced by depression (see **Figure 1**), and most depression scales include items that could be influenced by fatigue. Despite this overlap, studies of the relationships between fatigue and depression scales have yielded mixed results. FSS scores, for example, were associated with CES-D scores in patients with systemic lupus erythematosus ($r = 0.46$, $p < 0.05$), but not in small numbers of patients with MS ($r = 0.26$, $p > 0.05$) or healthy controls ($r = 0.20$, $p > 0.05$) (5). Higher fatigue ratings on a visual analog scale were associated with more depressive symptoms on the CES-D in a group of patients with MS and healthy controls ($r = 0.45$, $p < 0.01$), but not when the groups were analyzed separately (4). Measures of depression that assess mood and vegetative symptoms of depression separately, such as the Chicago Multiscale Depression Inventory, may allow more meaningful evaluation of these relationships (44).

Like depression, sleep disorders are common in patients with MS and are associated with lassitude, somnolence, and other symptoms that overlap with fatigue (45). Fatigue is listed as a symptom of Primary Insomnia in symptoms of Primary Insomnia in DSM-IV (43). Excessive sleepiness, one of the main symptoms of Primary Hypersomnia, Breathing-Related Sleep Disorder, and Circadian Rhythm Sleep Disorder, may be difficult for patients to differentiate from fatigue. The Epworth Sleepiness Scale, one of the more commonly used measures of self-reported sleepiness, asks patients to rate their probability of falling asleep in a variety of situations (46). Associations between this scale and self-reported fatigue have not been assessed.

EVIDENCE-BASED TREATMENT OF FATIGUE

Treatment of fatigue in MS has relied on nonspecific approaches because the underlying mechanisms are not known. In general, management begins with identification and amelioration of other factors contributing to it, such as depression, pain, sleep disorders, and comorbid medical conditions. Nonpharmacologic treatments, including graded exercise training, “energy management” strategies, and cooling therapy may be helpful, but evidence supporting their effectiveness is limited (47–49). Several pharmacologic treatments have been tried as well. The only treatments demonstrated to have an effect on fatigue in placebo-controlled clinical trials are amantadine, pemoline, and modafinil. As described in the following paragraphs, these studies all have significant limitations.

Amantadine has effects on cholinergic, dopaminergic, adrenergic, and glutamatergic neurotransmission, but its mechanism of action for MS fatigue is unknown. Five randomized, placebo-controlled trials of amantadine have been published (3,50–53). All of these trials had relatively small sample sizes (10 to 32 patients treated with amantadine), brief treatment periods (1 to 6 weeks), and four used a crossover design. They used different self-report measures of fatigue severity as their primary end points, generally showing a modest but statistically significant benefit of amantadine over placebo.

Pemoline is a CNS stimulant with dopaminergic rather than sympathomimetic effects. Two randomized, placebo-controlled trials of pemoline have been published (53,54). Limitations of these studies are similar to those for the amantadine trials, and one of the studies did not detect any difference between pemoline and placebo.

Modafanil has α_1-adrenergic properties, but is not a classic sympathomimetic. Modafanil has been used in one trial in MS patients, in which 72 blinded patients crossed over from placebo to modafanil and back to placebo over 9 weeks (55). During treatment, FSS and Multidimensional Fatigue Index Scale (MFIS) scores improved significantly. However, the design of this study does not adequately rule out the possibility that period effects confounded the results.

3,4-diaminopyridine and 4-aminopyridine are potassium channel blockers. They improve neurotransmission through demyelinated pathways by enhancing action potentials, but clinical effects have not been demonstrated definitively. They have been used in several randomized,

placebo-controlled trials in MS patients in which positive effects on fatigue were noted informally (56). One open-label study in eight patients focused on fatigue as the primary treatment target, demonstrating improvement in FSS scores and motor fatigue (57).

The effects of disease-modifying agents, such as interferon-*ß*, on fatigue in MS patients have not been adequately addressed. In clinical trials of interferon-*ß*1a and interferon-*ß*1b, "malaise" and "asthenia" occurred more often in patients treated with interferon than those receiving placebo, but it is not clear how those adverse experiences relate to fatigue (58–61). In one trial there was no difference in FSS scores between treated and placebo groups after 2 years of treatment (39), but none of the other pivotal trials measured fatigue severity. Metz et al. monitored patients starting interferon (n = 86) or glatiramer acetate (n = 136) at the Calgary MS clinic for 6 months, administering the FIS at baseline and after 6 months of treatment (62). More patients had at least 1.0 standard deviation improvement in FIS scores during glatiramer treatment (25 percent) than interferon treatment (12 percent), but these results must be interpreted cautiously because patients were not randomly assigned to treatment and there was no control group.

FUTURE DIRECTIONS: ALTERNATIVE WAYS TO MEASURE FATIGUE

Because of the limitations of self-report questionnaires used to assess fatigue severity, more rigorously defined, quantifiable measures are needed. Investigators often divide questionnaire items into subscales, either based on their clinical impressions or factor analysis. One of the most common divisions used separates motor and cognitive aspects of fatigue. Other authors have focused on the overwhelming lassitude that can be associated with fatigue, separate from motor, cognitive, or depressive qualities (63). An alternate way to assess fatigue severity would be to assess these distinct facets of MS fatigue separately, using objective methods when possible.

Motor Fatigue

Motor fatigue is defined as a decline in motor performance during sustained muscle activity (64). It has been provoked by a variety of experimental techniques and can be quantified based on measured decrements in force generated during these procedures. Sustained isometric contractions generally elicit larger reductions in force than intermittent ones, but neither method is clearly superior or more valid. Isokinetic techniques have also been used, but these require more costly and complex equipment (65). Electrically stimulated muscle contractions have been studied, but it is not clear whether these produce fatigue in the same way as voluntary contractions, which are more clinically relevant (66). The simplest method is to compare the maximal strength at the beginning and the end of the contraction (67). Alternatively, Bigland-Ritchie et al. found that force generated by an intrinsic hand muscle declines linearly during a sustained muscle contraction (68). The slope of the decline indicates the rate of fatigue. This method may be unsuitable for some muscles, however, because force generation does not show a consistent linear decline (see **Figure 2**). This problem can be overcome by integrating the area under the force versus time curve (69). The observed area is compared to the theoretical curve that would be seen if there was no fatigue (i.e., as if maximal initial force were sustained throughout the contraction).

The reliability of different methods for assessing fatigue in patients with MS had not been determined previously. Therefore, we considered four different models to measure the decline in motor output during sustained contractions, calculating a Motor Fatigue Index using each model, and comparing results for their test-retest reliability and ability to discriminate between fatigue experienced by MS patients and controls (70). We assessed motor fatigue during 30-second sustained maximal voluntary isometric contractions of the dominant elbow extensors, hand grip, knee extensors, and ankle dorsiflexors in 20 ambulatory MS patients and 20 age- and sex-matched healthy controls. Force versus time curves were obtained by having patients in standardized positions pull against a strap attached to an adjustable frame (71). A force transducer connected in series with the strap provided continuous data for calculation of peak force and area under the force versus time curve. Averaged MS and control force versus time curves for each muscle are shown in **Figure 2**.

We found that an analysis model based on area under the force versus time curve has several advantages compared to other models that we examined. First, the area under the curve (AUC) model does not require an assumption that force declines linearly during a sustained contraction. Second, the AUC model produced more

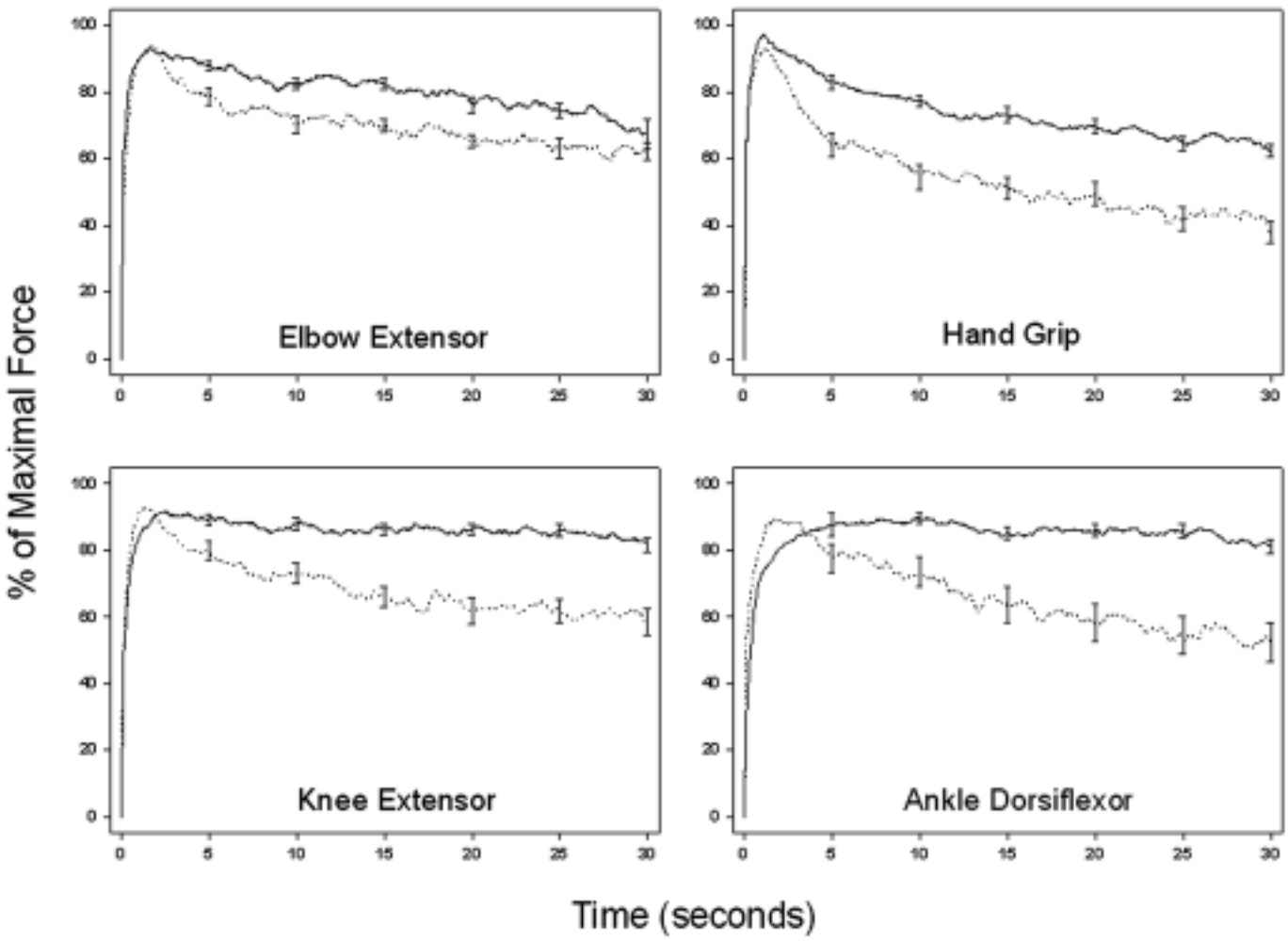

Figure 2.
Mean percent of maximal voluntary isometric contraction force plotted against time during 30-s sustained contractions of elbow extensors, hand grip, knee extensors, and ankle dorsiflexors on dominant side in MS patients (dotted lines) and healthy controls (solid lines). Error bars represent one standard error of the mean and are only shown at certain time points to improve visualization of the curves. MS patients had greater decrements in contraction force than controls in all muscles tested. Source: See Schwid (70).

reliable results than models based on the difference between initial and final strength. Motor Fatigue Index calculations based on the AUC model provided the best test-retest reliability (intraclass correlation coefficients 0.71 to 0.96, depending on the muscle tested). Third, the AUC model detected more separation between fatigue in healthy controls and the excess fatigue detected in patients with MS (**Table 3**). Fourth, AUC measures could be reliably obtained during brief muscle contractions, allowing several muscles to be tested in a single testing session. This may be critical in a variable disease like MS, in which different muscle groups are often affected in different and somewhat independent ways.

Fatigue in one muscle tended to correlate with fatigue in other muscles (r = 0.33 to 0.60), but motor fatigue was not significantly associated with weakness or ambulatory impairment, suggesting that fatigue and weakness are distinct features of motor dysfunction. We also attempted to measure fatigue during repetitive muscle contractions and ambulation, but found that those methods were not reliable. In a subsequent study of 23 ambulatory MS patients, we found that the Motor Fatigue Index was not associated with self-reported fatigue (FSS scores) or lassitude (Rochester Fatigue Diary [RFD] scores); (72). Motor fatigue was associated with trends toward greater neurologic impairment/disability (EDSS,

Table 3.
Motor Fatigue Index, calculated using AUC model, in MS patients and healthy controls.

	Motor Fatigue Index (AUC Model)				
	MS		Control		
Muscle	**Mean**	**SD**	**Mean**	**SD**	***p*-value**
Elbow Extensor	26.8	16.3	19.0	8.0	0.06
Hand Grip	49.2	14.5	30.4	8.0	<0.0001
Knee Extensor	28.0	13.0	9.4	11.2	<0.0001
Ankle Dorsiflexor	31.6	24.3	9.1	10.1	0.001

Source: See Schwid et al. (70).

time to walk 5 feet, maximum distance walked, and Functional Independence Measure) but was not associated with handicap (London Handicap Scale). Both self-reported fatigue and lassitude, on the other hand, were associated with handicap but not neurologic impairment/disability. Thus motor fatigue and lassitude are distinct components of fatigue, and self-reported fatigue does not adequately measure either. These data support the test-retest reliability and construct validity of the Motor Fatigue Index in MS patients.

These results generally agree with observations from other investigators. For example, motor fatigue during intermittent voluntary submaximal contractions of the tibialis anterior muscle was associated neither with self-reported fatigue in MS patients nor with overall neurologic impairment/disability, but it was associated with pyramidal signs on examination (69,73). Furthermore, motor fatigue worsened during MS exacerbations involving the motor system and improved during remission, but it did not change during exacerbations in which the motor system was unaffected (69).

The pathophysiologic basis for motor fatigue in MS patients remains unclear. Studies focusing on exercise-induced biochemical changes in muscle suggest that peripheral mechanisms are involved, producing alterations in muscle metabolism similar to those seen in sedentary patients (74–76). Analogous observations have been made in patients with chronic fatigue syndrome and fibromyalgia, in which there is no known neurologic pathology (77). On the other hand, studies using transcranial magnetic stimulation have suggested that there may also be decreased central activation as fatigue occurs in MS patients (78,79). Divergent observations may have occurred because fatigue was examined in different muscles that may have been affected by disuse and altered neural conduction in different ways. Despite somewhat conflicting results, these studies suggest that the mechanisms of fatigue can be examined more effectively if it is divided into more rigorously definable and measurable components.

Cognitive Fatigue

Cognitive fatigue is defined as a decline in cognitive performance during sustained cognitive activity. Prior attempts to objectively measure cognitive fatigue in MS patients have assessed a battery of neuropsychological tests before and after an intervening fatiguing task. A pilot study that used physical exercise between the administration of two neuropsychological batteries did not show a decline in cognitive function (80). Subsequent studies used a cognitively fatiguing task between test sessions (81–84). This paradigm has several drawbacks, however. Results have been confounded by practice effects so that both MS patients and controls frequently performed *better* after the intervening task, rather than worse. Different levels of cognitive impairment may also complicate results from this paradigm, since more impaired subjects may take longer to complete the tests, thus having greater opportunity to fatigue. Even if cognitive fatigue could be demonstrated with the use of this paradigm, these methods would not be conducive to therapeutic trials for cognitive fatigue because the assessment would take several hours and might not be adequately reproducible.

An alternate method would be to assess cognitive fatigue *during* the performance of a cognitive task. In this paradigm, fatigue can be measured as an inability to maintain initial levels of performance. Preliminary data using this paradigm comes from the administration of the Paced Auditory Serial Addition Test (PASAT-3 second version), a commonly used test that requires sustained attention and rapid information processing for 3 minutes. Thirty MS patients (EDSS 2.5–6.5) were evaluated (85). Cognitive fatigue was measured as the percent decrement in correct responses during the first 10 items of the PASAT compared to the last 10 items. Self-reported fatigue was measured with the Fatigue Severity Scale (FSS), and lassitude was measured with the RFD for 3 consecutive days. Motor fatigue was measured during 30-s sustained contractions of four lower extremity muscle groups. Total PASAT score was 44.4 ± 12.8 (mean ± standard deviation), with 8.3 ± 2.2 correct on the first 10 items and 6.8 ± 2.6 correct on the last 10. Patients

experienced an average decline in correct responses of 17.8 percent during this task ($p < 0.0001$, **Figure 3**). Individual declines in cognitive function were unrelated to cognitive impairment (total PASAT score), neurologic impairment/disability (EDSS), self-reported fatigue, lassitude, or motor fatigue. These data provide preliminary evidence that cognitive fatigue can be measured in MS patients with the use of the PASAT and that cognitive fatigue appears to be distinct from cognitive impairment, neurologic impairment/disability, self-reported fatigue, and other components of fatigue.

Lassitude

Lassitude is defined as a subjective sense of reduced energy. Unlike motor and cognitive fatigue, it cannot be measured objectively. Many investigators have considered lassitude to be synonymous with fatigue. As a result, measures of lassitude employed previously are essentially the same self-report questionnaires described in the previous section. As already discussed, these questionnaires contain items that may be assessing other components of fatigue as well as other neurologic and nonneurologic aspects of MS symptoms in variable ways. Visual analog scales may address lassitude more directly if the associated question directs patients to rate their "energy level" rather than "fatigue." The specific question addressed by visual analog scale ratings are rarely reported, however, making results difficult to interpret. Krupp et al. performed repeated measurements of fatigue in 25 MS patients using a visual analog scale, as well as the FSS and FIS (86). They found that test-retest reliability was adequate for the visual analog scale ($r = 0.60 – 0.98$), and that the visual analog scale was more responsive to changes in fatigue medications than the questionnaires.

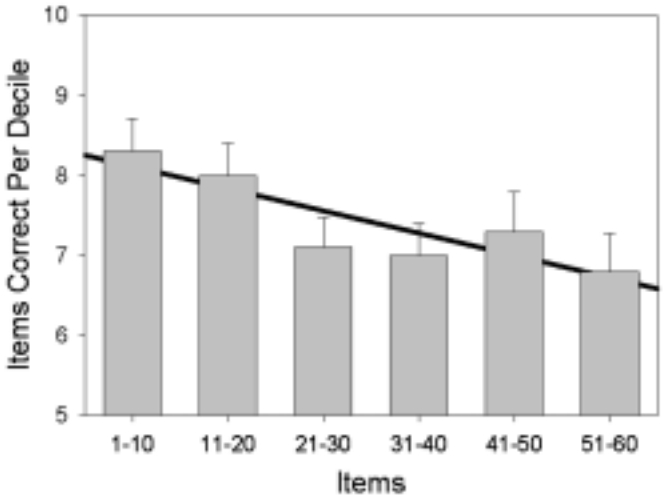

Figure 3.
Mean number of items correct in each decile of items on PASAT (3-s version) administered to 30 patients with MS (with standard error bars). Correct responses declined steadily from beginning to end of test. Diagonal line indicates least-squares regression of decile versus items correct. Source: See Schwid et al. (85).

To improve on these features, we have developed the Rochester Fatigue Diary (**Figure 4**). It consists of a single page with 24 vertical bars for subjects to rate fatigue severity on a visual analog scale every hour for 1 day. The location of each hourly mark is translated to a 0 (maximal fatigue) to 100 (no fatigue) scale and averaged to provide a daily mean fatigue severity. Sleep is assigned a score of 0, so a subject who had no fatigue and slept 8 hours would have a score of 66.67. This approach integrates fatigue while subjects were awake and the amount of sleep required into a single score, without requiring assumptions about the timing of duration of sleep. Compared to other subjective measures of fatigue severity, the RFD has the advantage that it specifically assesses lassitude (a low energy level) rather than other aspects of fatigue and neurologic dysfunction (87). Furthermore, it is less subject to recall bias and better able to discern temporal changes in lassitude than assessments in which patients must summarize longer periods of time.

For the initial validation of the RFD, 23 ambulatory MS patients (EDSS 2.5–6.5) participating in a natural history study of ambulatory impairment completed the RFD on 7 consecutive days immediately following a comprehensive neurologic evaluation. Of 161 possible diaries, 139 (86 percent) were analyzable, defined as no more than 3 hours in each day left blank or indeterminate, demonstrating that patients were willing and able to complete the RFD. The mean RFD score for a 24-hour period was 37.3 ± 13.1 (range 16.4–68.6). A circadian pattern was clear, with energy levels rising through the morning, peaking at 10–11 a.m., then falling through the afternoon (**Figure 5**). The intraclass correlation coefficient was 0.74 for single days, 0.85 for 2 days, and 0.89 for 3 days. RFD scores were modestly correlated with FSS scores ($r = 0.40$, $p = 0.05$), demonstrating that these measures of subjective fatigue reflect different constructs.

RFD scores were not associated with measures of impairment or disability but were correlated with handicap as measured by the London Handicap Scale ($r = –0.52$, $p = 0.009$). For comparison, the mean RFD score for a group of age- and gender-matched healthy controls ($n = 14$) was 54.9 ± 9.7 (range 36.3 − 70.9).

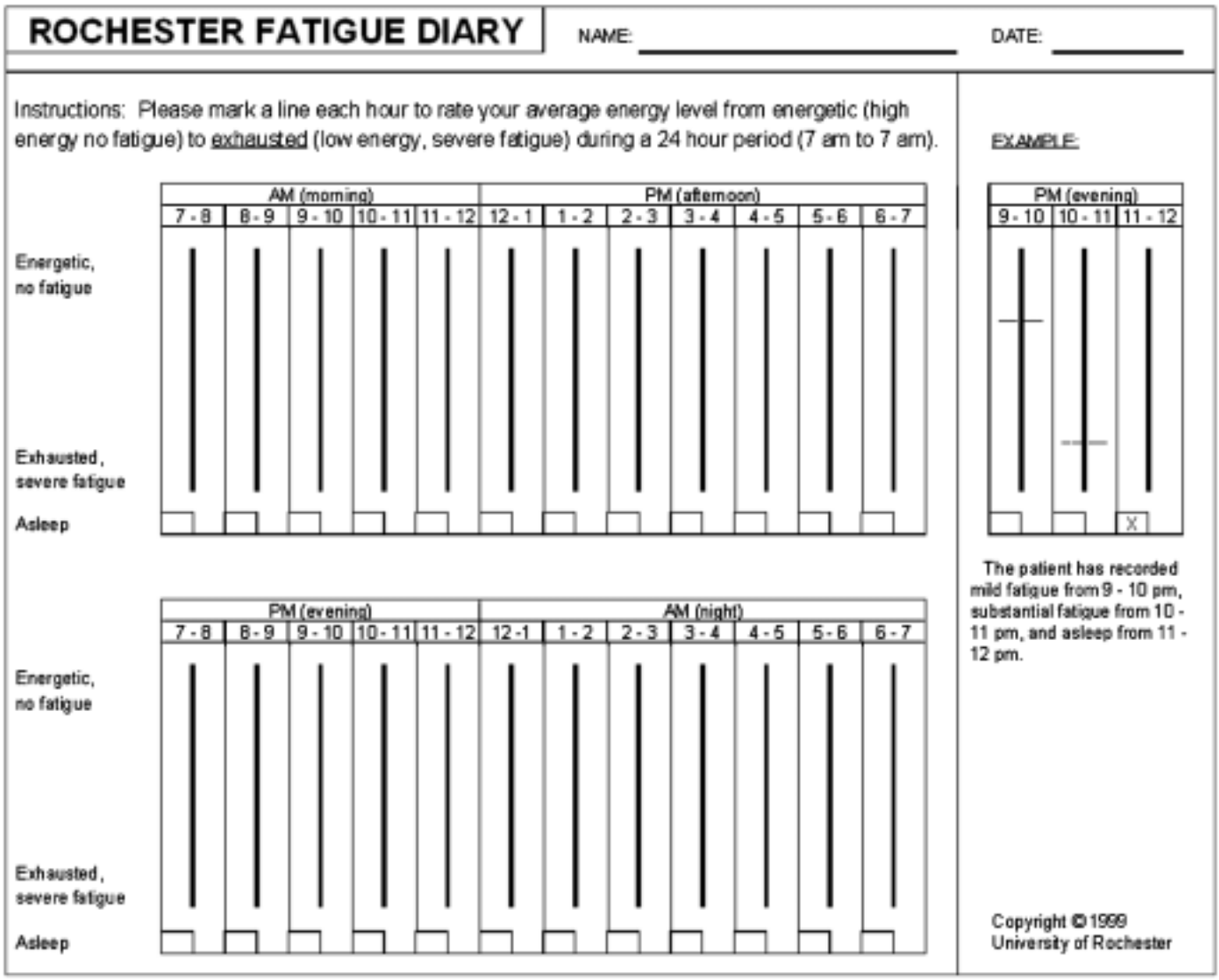

Figure 4.
The Rochester Fatigue Diary. Source: See Schwid et al. (87).

These preliminary data suggest that the RFD is a feasible, reproducible, and valid measure of excess lassitude in MS patients.

Subsequently, the RFD was used as a measure of fatigue severity in a multicenter trial of cooling vests in MS patients (55). Following several cooling sessions in clinic, 74 MS patients (EDSS 0–5.5) were randomly assigned to use a cooling vest (Lifetime Enhancement Technology, Sunnyvale, CA) 1 hour each morning or to continue with their normal activities for a month. After a 1-week washout period, patients crossed over to the alternate treatment. During the evaluation period, patients completed the RFD for 2 consecutive days each week. At the end of each month, patients were assessed with the MFIS and the Multiple Sclerosis Functional Composite (MSFC). Of 1,184 possible diaries, 1,100 (92.9 percent) were analyzable, defined as no more than 3 hours in each day left blank or indeterminate. The intraclass correlation coefficient was 0.69 – 0.90 ($p < 0.0001$) for 2 consecutive days, and 0.67 ($p = 0.0008$) for an entire month. RFD scores were modestly associated with self-reported fatigue (RFD versus MFIS, $r = –0.40$, $p = 0.001$) but were not associated with neurologic impairment/disability (RFD versus

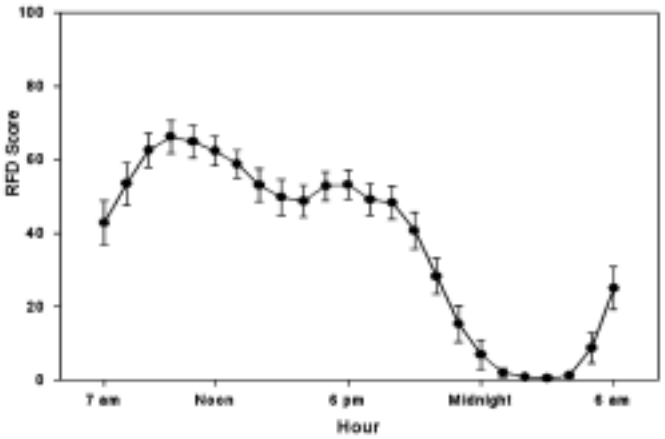

Figure 5.
Hourly RFD ratings. Each point represents mean of 23 patients averaged over 7 consecutive days with standard errors. Source: Schwid et al. (98).

MSFC, $r = 0.05$, $p = 0.35$). Mean RFD scores were significantly higher (less lassitude) during the cooled month than the noncooled month (36.3 versus 34.2, $p = 0.001$).

CONCLUSIONS

Most research on fatigue in MS patients has relied on self-report questionnaires to quantify fatigue severity. These questionnaires may not be adequate for this purpose, however, because they can be confounded by other symptoms of MS, they are entirely subjective, and they require patients to make difficult retrospective assessments. Research on the mechanisms and therapeutics of fatigue in MS patients has been impeded by reliance on these questionnaires. Even generally accepted conclusions about the incidence and clinical correlates of fatigue that are based on self-report questionnaires deserve reappraisal. Dividing fatigue into more rigorously defined and quantifiable components may improve the assessment of fatigue characteristics and severity as a critical step toward amelioration of this disabling symptom.

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