Fatigue and fatigability in neurologic illnesses

Proposal for a unified taxonomy

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ABSTRACT

Fatigue is commonly reported in many neurologic illnesses, including multiple sclerosis, Parkinson disease, myasthenia gravis, traumatic brain injury, and stroke. Fatigue contributes substantially to decrements in quality of life and disability in these illnesses. Despite the clear impact of fatigue as a disabling symptom, our understanding of fatigue pathophysiology is limited and current treatment options rarely lead to meaningful improvements in fatigue. Progress continues to be hampered by issues related to terminology and assessment. In this article, we propose a unified taxonomy and a novel assessment approach to addressing distinct aspects of fatigue and fatigability in clinical and research settings. This taxonomy is based on our current knowledge of the pathophysiology and phenomenology of fatigue and fatigability. Application of our approach indicates that the assessment and reporting of fatigue can be clarified and improved by utilizing this taxonomy and creating measures to address distinct aspects of fatigue and fatigability. We review the strengths and weaknesses of several common measures of fatigue and suggest, based on our model, that many research questions may be better addressed by using multiple measures. We also provide examples of how to apply and validate the taxonomy and suggest directions for future research. *Neurology*® 2013;80:409–416

GLOSSARY

MG = myasthenia gravis; **MS** = multiple sclerosis; **PD** = Parkinson disease; **TMS** = transcranial magnetic stimulation.

Fatigue is one of the most common symptoms in neurology. Our understanding of the pathophysiology of fatigue is limited for most conditions. Even the term "fatigue" is used without standard definitions or means of measurement. Not surprisingly, current treatments are nonspecifically targeted to a vaguely defined symptom with unsatisfactory outcomes. In this article, we use the term fatigue to refer to subjective sensations and fatigability to refer to objective changes in performance. We briefly review the prevalence, impact, and treatment of fatigue in neurologic disorders before discussing problems with current terminology and proposing a unifying taxonomy. We conclude by providing examples of the use of the taxonomy, demonstrating how it relates to current fatigue measures, and proposing avenues for future research.

PREVALENCE AND IMPACT OF FATIGUE IN NEUROLOGIC ILLNESSES Community and primary care studies estimate 5%–45% of the population report fatigue as a debilitating symptom and 2%–11% report fatigue lasting at least 6 months.[1–5] These rates increase with age in some but not all studies.[6] Fatigue is also common in many chronic illnesses, including cardiovascular disease, cancer, inflammatory arthritis, and osteoarthritis.[7–10] It is thus critical for fatigue studies in neurologic populations to have an appropriate control group and assess for comorbid illnesses associated with fatigue, particularly when attempting to attribute fatigue to an underlying neurologic process.

The prevalence of fatigue is elevated in many neurologic illnesses beyond what would be expected solely on the basis of age and disability, including multiple sclerosis (MS),[11] Parkinson disease (PD),[12] traumatic brain injury,[13] myasthenia gravis (MG),[14] stroke,[15] amyotrophic lateral sclerosis,[16] and postpolio syndrome[17] (table 1). These studies have importantly shown that fatigue, however defined, is distinguishable from other related symptoms including sleepiness,[18] depression,[19] and apathy,[20] and that fatigue is largely a primary symptom of neurologic

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Supplemental Data

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Table 1 Estimated prevalence of fatigue in selected neurologic illnesses

Population	Estimated prevalence, %
Multiple sclerosis	38–83[e51–e53]
Parkinson disease	28–58[12,20,32,e54]
Stroke	36–77[15,e55–e57]
Myasthenia gravis	75–89[14,e58,e59]
Postpolio syndrome	27–91[74,e60,e61]
Amyotrophic lateral sclerosis	44–83[16,e62]
Traumatic brain injury	45–73[e63,e64]

illnesses and not secondary to medications,[21] mood disorders,[19] or sleep impairment.[18] Fatigue is associated with decreased quality of life and disability across numerous disorders, including MS,[22] PD,[23] and stroke,[24] even when controlling for other symptoms, such as depression. In MS, fatigue is reported by 40% of patients to be their most disabling symptom, more so than any other symptom including spasticity and weakness.[25] Similarly, one-third of patients with PD report fatigue to be their most disabling symptom.[26]

Fatigue treatments may be distinguished between those that treat the underlying disease and symptomatic therapies. Disease-modifying treatments in MS[27–29] and immunomodulatory and cholinergic medications in MG[30] may reduce perceptions of fatigue. Similarly, while some evidence suggests that levodopa therapy may reduce the incidence of fatigue in PD, the effect of levodopa on fatigue remains controversial.[31,32] Table 2 shows the results of selected trials of symptomatic treatments. Although there are several positive trials, the effect sizes are generally small and the benefit to individual patients is often negligible or inconsistent in clinical practice.[33] Pharmacologic trials have focused primarily on psychostimulants, although some other notable therapies have shown some efficacy, such as aspirin and amantadine in MS.[34,35] Antidepressant effects on fatigue, when noted, have generally been difficult to separate from their influence on depression.[36] Nonpharmacologic interventions for fatigue have been pursued mostly in MS and include exercise, mindfulness training, and energy management strategies.[37–40] These studies have shown some positive findings but have not been widely applied.

ISSUES IN THE CURRENT USAGE OF FATIGUE TERMINOLOGY Despite the apparent epidemiologic importance of fatigue, many fundamental questions remain unanswered, including an appropriate definition. Many studies fail to define fatigue, perhaps due to the assumption that the term is clearly known to all. Even among studies that define fatigue, there is a considerable range of definitions.[41] Attempts to remedy this situation by adding modifiers to the term fatigue are similarly limited by the lack of standards to anchor these terms. For example, "central fatigue" may be used to refer to subjective reports of fatigue, performance decrements on a cognitive task, changes in motivation, effects of fatigue on CNS function, or CNS causes of fatigability.[12,42–44] Without clear terminology and shared conceptual frameworks, clear communication, scientific

Table 2 Selected clinical trials of therapy for fatigue in neurologic populations

Intervention	Clinical population	Study design	Outcome
Amantadine[34]	MS (n = 93)	Double-blind RCT of amantadine vs pemoline vs placebo	Statistically significant improvement in MS Fatigue Scale for amantadine group; 79% of amantadine-treated patients preferred drug to no therapy
Aspirin[35]	MS (n = 30)	Crossover design	Statistically significant improvement in MFIS for aspirin vs placebo
Energy conservation course[e65]	MS (n = 169)	Single-blind wait list–controlled RCT	Statistically significant improvement in FIS for course vs wait list control
Aerobic training[e66]	MS (n = 54)	Single-blind usual activity–controlled RCT	No change observed in FSS
Progressive resistance training[e67]	MS (n = 31)	Double-blind usual activity–controlled RCT	Statistically significant improvement in FSS vs control group
Methylphenidate[e68]	PD (n = 36)	Double-blind placebo-controlled RCT	Significant change from baseline in MFI for methylphenidate but not different from placebo
Mindfulness training[38]	MS (n = 150)	Single-blind RCT of 8-week mindfulness training vs usual care	Statistically significant improvement in MFIS for mindfulness vs usual care
Modafinil[e69]	PD (n = 19)	Double-blind placebo-controlled RCT	No difference in MFI scores but modafinil group had less fatigue of finger-tapping rate
Modafinil[33]	MS (n = 39)	Retrospective case series	Fatigue response to modafinil was greater in those with EDS and fatigue (56%) than in those with fatigue alone (25%)
Vestibular rehabilitation[e70]	MS (n = 38)	Single-blind RCT of vestibular training vs exercise (bicycle/stretching) vs wait list	Statistically significant improvement in MFIS for intervention vs exercise or wait list controls

Abbreviations: EDS = excessive daytime somnolence; FIS = Fatigue Impact Scale; FSS = Fatigue Severity Scale; MFI = Multidimensional Fatigue Inventory; MFIS = Modified Fatigue Impact Scale; MS = multiple sclerosis; PD = Parkinson disease; RCT = randomized controlled trial.

progress, and the development of effective interventions are constrained. Memory is a motivating example of a field where transformation of a commonly used word into a rigorous scientific taxonomy, for example distinguishing between types of memory (e.g., working and procedural memory) and memory processes (e.g., retrieval and encoding), has led to scientific progress.

PROPOSAL FOR A UNIFIED TAXONOMY The term fatigue as used in the life sciences is not a unitary phenomenon and cannot be defined as such. Rather it is necessary to identify its distinct domains and to distinguish it from related phenomena. Our taxonomy may apply to clinical or research settings and is based on answering the following questions:

1. Is this fatigue or a related phenomenon?
2. Is the focus perception or performance?
3. Is it clinically significant?
4. Are there identifiable causal factors?
5. Is there a particular domain of task performance affected?

Is this fatigue or a related phenomenon? Altered perceptions of fatigue or fatigability may arise as either a primary or secondary manifestation of disease. Secondary causes include medications, chronic pain, physical deconditioning, anemia, respiratory dysfunction, depression, and sleep disorders. It is important to screen for these issues in patients complaining of fatigue and to treat when present. In both clinical practice and research, it is also critical to distinguish fatigue from potentially similar symptoms, including somnolence, depression, and apathy. Although there may be clinical overlap and interactions between these symptoms and fatigue, they are distinct phenomena. In PD, there is a clear dissociation between sleepiness and fatigue, suggesting different causes and hence the need for distinct treatments, whereas in MS there may be a more complex association between fatigue and sleep.[45,46] Even among patients with major depressive disorder, many report continued fatigue after successful treatment of their depressed mood.[47] From a research perspective, distinguishing fatigue from related phenomena can be accomplished by including measures of mood and sleepiness as covariates.

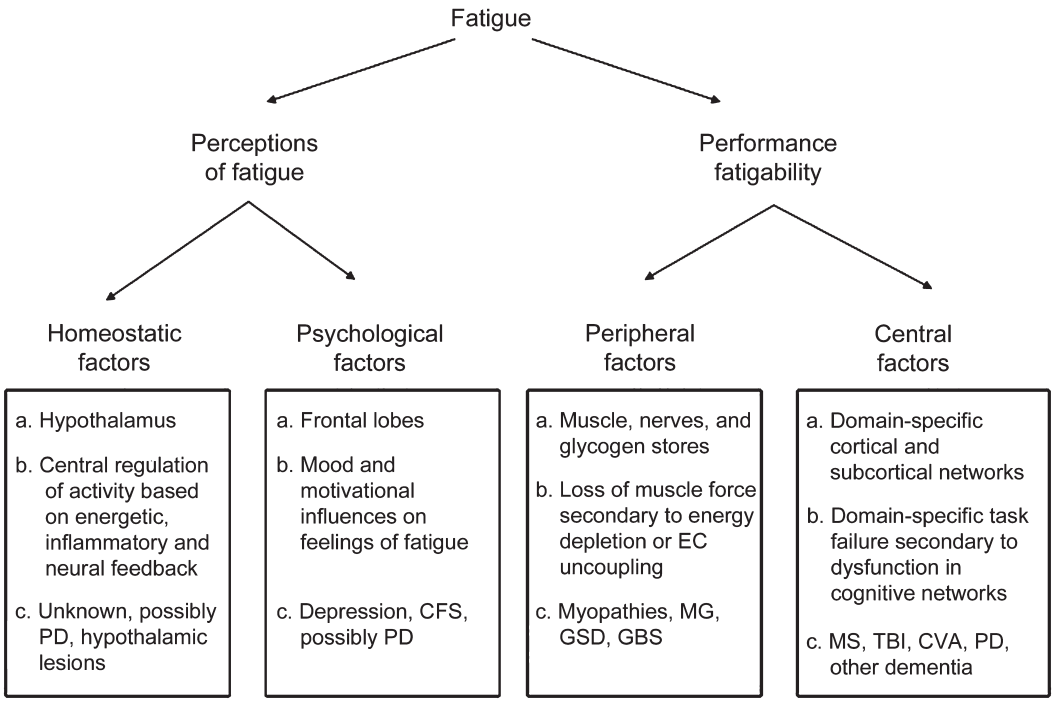
Is the focus perception or performance? One of the most important distinctions in a discussion of fatigue is that between perceptions of fatigue and performance fatigability. Perceptions of fatigue refer to subjective sensations of weariness, increasing sense of effort, mismatch between effort expended and actual performance, or exhaustion.[42,44,48] In contrast, fatigability is defined as the magnitude or rate of change in a performance criterion relative to a reference value over a given time of task performance or measure of mechanical output. Perceptions of fatigue and fatigability are not only distinct but also potentially independent. In PD, for example, Lou et al.[31] found objective decrements in motor performance did not significantly correlate with perceived fatigue. Similarly, in MS, changes in objective cognitive performance during prolonged testing can occur independently of changes in perceived fatigue.[49,50] In fact, establishing an association between fatigability and fatigue complaints is an important goal for clinical research but has proven difficult for most conditions.

Is it clinically significant? Perceptions of fatigue and fatigability are normal physiologic reactions to prolonged or intensive activity. In healthy adults, perceptions of fatigue and fatigability are predictable and transient phenomena typically brought about by prolonged exertion that diminish with rest and do not interfere with usual daily activities. In some disorders, particularly neurologic illnesses, perceptions of fatigue or fatigability may be chronic, vary in their response to exertion or rest, decrease quality of life, and cause disability,[51] and patients often report a qualitative difference in their experience of fatigue after acquiring a neurologic illness.[52] In clinical research, the term fatigue often implies a clinical syndrome of chronic or disabling fatigue, as when speaking about fatigue prevalence. Because perceptions of fatigue and fatigability also occur in healthy people, it is important to clearly define how clinical significance was determined.

There is currently no consensus on how to determine clinical significance. One common approach is to define fatigue on the basis of exceeding a particular score on fatigue questionnaires. Similarly, quantitative definitions of fatigability are typically based on a statistically significant difference from a control group. As knowledge of fatigue in neurologic disorders expands, clinical research may benefit from qualitative criteria such as those used in chronic fatigue syndrome or major depressive disorder.[53,54] For measures of both fatigue and fatigability, future research needs to determine the optimal test characteristics of these measures using ecologically valid activity level, disability, or quality of life outcomes.

Are there identifiable causal factors? Human and animal studies have identified many factors that can influence the perception of fatigue or fatigability. In discussing these causal factors, we first distinguish between those that can influence perceptions of fatigue and fatigability, and then identify relevant factors for each: homeostatic and physiologic factors based on phenomenology for perceptions of fatigue, and peripheral and central factors based on anatomy for fatigability (figure). While the fatigue experienced by an individual is certainly influenced by interactions between these factors, the purpose of this aspect of the taxonomy is to provide a framework

Figure Diagram of major factors contributing to the 2 domains of fatigue: perceptions of fatigue and fatigability



While separated in this diagram, is should be noted that perceptions of fatigue and performance fatigability have the potential to influence each other. Letters in boxes refer to the following: a) known neuroanatomic sites mediating this factor; b) normal function of this factor; c) pathologic states involving this factor. CFS = chronic fatigue syndrome; CVA = cerebrovascular accident; EC = excitation/contraction; GBS = Guillain-Barré syndrome; GSD = glycogen storage diseases; MG = myasthenia gravis; MS = multiple sclerosis; PD = Parkinson disease; TBI = traumatic brain injury.

for identifying and reporting which factors are most relevant in specific neurologic illnesses.

Homeostatic factors. Homeostasis refers to the tendency of an organism to maintain a stable functional state. This is accomplished by engaging feedback and feedforward pathways that constrain variation in 1 or more control variables. Within this context, perceptions of fatigue likely contribute to homeostasis through regulation of energy expenditure and protection from overuse injuries. Several metabolic stimuli are proposed to induce the sensation of muscle fatigue, including depletion of muscle glycogen and phosphocreatine and the accumulation of lactate, low pH, P_i, K+, ammonia, and ATP.[55,56] More recently, a unique population of dorsal root ganglion neurons has been discovered that specifically respond to low pH, ATP, and ammonia but not other painful stimuli.[57] Within the CNS, potential contributors to perceptions of fatigue may include cerebral glycogen depletion, increased brain temperature, accumulation of ammonia, inflammatory cytokines (particularly IL-6), increases in serotonin, and decrements in dopamine.[58–60,e1] Animal models demonstrate that the hypothalamus contributes to energy regulation and fatigue perception,[e2] similar to its role in hunger and thirst. Other brain areas, including frontal lobes and basal ganglia, are also likely important in regulating behavior relative to homeostatic factors and other cues.[43] One current hypothesis suggests that these CNS structures act as a "central governor" to limit energy utilization and avoid potential energetic collapse.[e3]

Although fatigue can be associated with lesions of the hypothalamus, it is difficult to attribute fatigue directly to these lesions as patients frequently have additional circadian rhythm and endocrine disturbances. However, disruption of the hypothalamic-pituitary-adrenal axis may contribute to other conditions associated with symptomatic fatigue.[e4,e5] While perceptions of fatigue and effort may be altered in PD and MS,[e6,e7] it is difficult to know whether these differences reflect changes in energy regulation vs other psychologic or physiologic factors. Research utilizing careful energetic measurements can test the role of homeostatic factors contribution to perceptions of fatigue in neurologic illness.[e8]

Psychological factors. Psychological factors that contribute to the perception of fatigue and fatigability among healthy volunteers include perceptions of effort, expectations, familiarity, motivation, temporal and performance feedback, arousal, and mood.[e9–e12] Some evidence suggests that these factors, particularly perceptions of effort, may be the primary factors limiting prolonged performance for many motor and cognitive

tasks in healthy adults.[e13] It is likely that similar psychologic processes contribute to fatigue in disease states. For example, depressed mood is frequently associated with fatigue in PD.[12] Similarly, the association between lesions in the ascending reticular activating system and fatigue in postpolio patients suggests that arousal may mediate some aspects of fatigue in this disorder.[e14]

Peripheral factors. Physiologic changes in muscle, the neuromuscular junction, and peripheral nerves contribute to fatigability in healthy humans and animals and can be referred to as peripheral factors on the basis of anatomical distinctions between the peripheral nervous system and CNS. However, even this distinction may lead to confusion as anterior horn cell bodies are part of the CNS, but the axon resides outside the CNS. Alternatively, the terms contractile factors and activating factors can be used to more specifically distinguish peripheral mechanisms within muscle and those providing the activating signal. Contractile factors include disruption of contraction-excitation uncoupling, alterations in cross-bridge function, changes in calcium conductance, and loss of intracellular energy stores.[41,e15,e16] Pathologic changes in the peripheral nervous system and muscle may also influence fatigability. Examples of pathologic mechanisms unique to neurologic diseases include energetic failure of muscle (glycogen storage disorders and mitochondrial myopathies), acetylcholine depletion at the neuromuscular junction (MG), and motor conduction block (multifocal motor neuropathy).[30,e17,e18]

Central factors. Fatigability during both motor and cognitive tasks is additionally driven by CNS mechanisms. Neurophysiologic studies of healthy human subjects using transcranial magnetic stimulation (TMS) and nerve stimulation reveal changes in motor cortex and spinal excitability associated with fatigability during motor tasks[e19–e22] and suggest that deficits in central drive are responsible for a significant percentage of fatigability depending on task demands.[e23,e24] TMS studies further show that perceptions of fatigue in MS are associated with delayed normalization of cortical excitability following a fatiguing motor task and impaired premovement facilitation.[e25,e26]

Chaudhuri and Behan[43] proposed that fatigue depends on intact basal ganglia and frontal lobe structures to maintain performance and on parietal areas to maintain sustained attention. This hypothesis is consistent with pathologic and neuroimaging studies from neurologic disorders.[e27] In MS, anatomic MRI identifies a number of correlates of self-reported fatigue and fatigability, including cortical thickness, lesion burden, or atrophy in frontal lobes, thalamus, or basal ganglia, and white matter connections between these regions.[e28–e31] fMRI measurements show increased activation in both motor and nonmotor regions, even prior to task engagement, which are associated with fatigability measured in motor and cognitive tasks.[e32,e33] It is hypothesized that this increased activity may represent compensatory activity followed by an inability to compensate for further changes causing accelerated performance decline.

Is there a particular domain of task performance affected? When measuring fatigability or momentary perceptions of fatigue, it is important to indicate the domain of performance examined and the task used to induce fatigability. Examples of domains of performance include sustained contractions, repetitive movements, skilled sequences, working memory, sustained attention, and verbal fluency. Although some causal factors, such as arousal, may influence performance across multiple domains, many aspects are domain-specific. For example, motor and cognitive tasks clearly induce fatigability at different rates and stress different physiologic factors. Even within well-defined motor tasks, subtle differences in performance strategy may influence the rate of fatigability.[e23] These differences have biological and clinical implications. For example, the sensitivity and specificity of a fatigability measure in MG would differ for tasks based on sustained visual attention vs repetitive motor actions.

EXAMPLES Our primary goal in proposing this taxonomy is to bring a greater level of clarity and consistency to clinical research on fatigue. First, it is necessary to establish clear definitions for perceptions of fatigue and fatigability that can be distinguished from related phenomena. Second, clinical studies need to specify how clinically relevant fatigue/fatigability is distinguished from normal physiologic fatigue/fatigability. Third, given the many factors that may contribute to fatigue/fatigability and the differences in fatigue/fatigability induced by specific tasks, it is critical that these factors and tasks are clearly identified.

To illustrate the utility of this taxonomy, we provide an example of its application. Compare the following 2 potential article titles: 1) "Peripheral fatigue in muscular dystrophy" vs 2) "Contractile factors associated with fatigability of muscle force during sustained muscle contractions in muscular dystrophy." The second title is more informative and precise. Reference to this taxonomy in articles will improve scientific communication and promote clarity in research questions related to fatigue in neurologic illnesses.

APPLICATION TO MEASUREMENT **Perceptions of fatigue.** Most clinical fatigue studies use self-report scales that can broadly be classified as measuring perceptions of fatigue. Available scales vary widely in how they measure fatigue, including questions regarding momentary (state) perceptions, chronic characteristics (trait perceptions), the impact of fatigue on function, ratings of

related constructs (e.g., tiredness), dimensions of fatigue (e.g., mental vs physical), and severity.[e34] Some scales have been designed for certain populations, but it is not clear that such scales offer advantages over general scales.[e35] Properties that distinguish scales include having clear cutpoints for moderate or severe fatigue (e.g., Fatigue Severity Scale) and demonstrating sensitivity to change over time for clinical interventions (e.g., Modified Fatigue Impact Scale).[39,e36] Related measures to be considered include fear of movement (kinesophobia) and ratings of perceived effort.[e37,e38] Clinical studies should consider normalizing measures of fatigue perceptions for activity levels as patients may restrict their activity levels in an attempt to minimize experiencing fatigue.[6]

Fatigability. Fatigability is primarily measured by quantifying the decline in 1 or more aspects of performance during continuous performance of a prolonged task or comparing performance on a probe task before and immediately after prolonged performance of a separate fatigue-inducing task. In the motor domain, fatigability is usually quantified as the decline in peak force (torque) after performing an exercise intervention, although declines in power, speed, or accuracy can also be examined.[e39–e41] In the cognitive domain, fatigability has been measured as declines in either reaction time or accuracy over time on continuous performance tasks, or a probe task given before and immediately after a fatiguing cognitive task.[50,e42,e43] Differing measures of fatigability can influence the results obtained in a target population. For example, older adults demonstrate less performance decrements than young adults when fatigability is quantified as decline in peak force during an isometric contraction, whereas the converse relation is observed when fatigability is measured as the decrease in peak torque during dynamic contractions.[e44] When characterizing the fatigability experienced by clinical populations, it is critical to use both a valid task and measure of fatigability. While there are scant data detailing task differences in specific neurologic illnesses, the initial choice of task can be made on the basis of current knowledge of neurophysiology in the illness of interest and data derived from tasks in healthy individuals.

Causal factors. Once valid measures of perceptions of fatigue or fatigability are identified, the challenge for the experimentalist is to identify causal factors. A number of technologies can monitor the adjustments during fatiguing contractions, including metabolic measures, electromyography, TMS, fMRI, structural MRI, PET, EEG, magnetoencephalography, and near infrared spectroscopy.[e28,e33,e45–e49] As with the requirements to select valid tasks and indices of fatigue, the technology should be capable of examining physiologic variables hypothesized to be responsible for the fatigue experienced by the target population. In the design of such experiments, it is important to ensure that factors causally related to fatigability may be distinguished from compensatory or other associated factors that may also change over the course of task performance. Specifically, causal factors should show correlations with performance decline rather than just change over time, retain a significant correlation with performance when controlling for other variables, and modulate fatigability when altered by specific interventions.

Clinical studies, especially those examining perceptions of fatigue, should account for important covariates, including depression, pain, weakness, and sleepiness. For example, Valko et al.[e50] found in MS that disease severity and depression were associated with self-reported fatigue, whereas disease duration and medications were correlated with sleepiness. Furthermore, it is often critical in clinical studies to include multiple measures to examine perceptions of fatigue, fatigability, and physiologic factors concurrently. Lou et al.[31] found that the combination of objective and perceptual measures was necessary to determine that fatigue complaints in PD were not related to fatigability or motor cortex excitability, suggesting that cognitive, homeostatic, or psychologic factors may be more important in perceptions of fatigue.

RECOMMENDATIONS FOR FUTURE RESEARCH

Future fatigue research should use clearly defined terminology. We recommend use of our taxonomy, but studies should minimally document the following:

1. How fatigue or fatigability is defined, operationalized, and distinguished from related phenomena.
2. Whether the focus is on perceptions of fatigue, performance fatigability, or both.
3. The quantitative (e.g., score on a fatigue scale, chronicity) or qualitative criteria (e.g., unpredictable, not improving with rest) used to determine clinical significance.
4. What causal or mechanistic factors were examined and how were they related to either perceptions of fatigue or fatigability.
5. What task was used to induce fatigability and how changes in performance were quantified.

Priorities for future research include the following:

1. Determining what physiologic, objective performance or homeostatic changes account for increased perceptions of fatigue in neurologic illnesses.
2. Creating valid, economical, and specific measures for components of fatigue relevant to specific neurologic illnesses.
3. As multiple types of fatigue and factors may be important within a specific population or even an individual, the concept of a fatigue battery may be helpful to define the relative importance of causal factors and to guide treatment.

4. Application of neuroimaging, neurophysiology, and neuropathologic measures to understand central factors related to fatigability and perceptions of fatigue.
5. Creation of empirically based criteria to identify, grade, and monitor clinically significant fatigue in neurologic populations.
6. Development of fatigue treatment strategies for specific neurologic illnesses based upon theoretical and empirical studies.

AUTHOR CONTRIBUTIONS

B.M.K.: design and conceptualization of the manuscript, writing of first draft, and revision of subsequent drafts. L.B.K.: assistance with conceptualization of the manuscript and revision of subsequent drafts. R.M.E.: assistance with conceptualization of the manuscript and revision of subsequent drafts.

STUDY FUNDING

Supported by the NIH (5 KL2 RR025779-03) and the US Army Research Laboratory and the US Army Research Office under contract number W911NF1010192.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received April 11, 2012. Accepted in final form August 28, 2012.

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