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Fatigue Versus Activity-Dependent Fatigability in Patients With Central or Peripheral Motor Impairments

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Abstract

In the rehabilitation literature, fatigue is a common symptom of patients with any neurological impairment when defined as a subjective lack of physical and mental energy that interferes with usual activities. Some complaints may, however, arise from *fatigability*, an objective decline in strength as routine use of muscle groups proceeds. By this refined definition of fatigue, exercise or sustained use reduces the ability of muscles to produce force or power, regardless of whether the task can be sustained. Fatigability may be masked clinically because (1) the degree of weakening is not profound, (2) activity-induced weakness rapidly lessens with cessation of exertion, and (3) clinicians rarely test for changes in strength after repetitive movements to objectively entertain the diagnosis. The repetitive movements that induce fatigability during daily activities are an iterative physiological process that depends on changing states induced by activation of spared central and peripheral neurons and axons and compromised muscle. Fatigability may be especially difficult to localize in patients undergoing neurorehabilitation, in part because no finite boundary exists between the central and peripheral components of motor reserve and endurance. At the bedside, however, manual muscle testing before and after repetitive movements could at least put some focus on the presence of fatigability in any patient with motor impairments and related disabilities. Reliable measures of fatigability beyond a careful clinical examination, such as physiological changes monitored by cerebral functional neuroimaging techniques and more standardized central and peripheral electrical and magnetic stimulation paradigms, may help determine the mechanisms of activity-dependent weakening and lead to specific therapies. Testable interventions to increase motor reserve include muscle strengthening and endurance exercises, varying the biomechanical requirements of repetitive muscle contractions, and training-induced neural plasticity or pharmacologic manipulations to enhance synaptic efficacy.

Keywords

Fatigue; Muscle weakness; Stroke; Spinal cord injury; Neuropathy; Motor control; Spinal stenosis

Persons with neurological diseases often report feeling sluggish, weary, easily tired, sleepy, weak, and having a low level of energy and motivation.¹ This fatigue can be defined as a subjective lack of physical and mental energy that interferes with usual activities. Scales of

fatigue obtained at any time after hemiparetic stroke suggest that 20% to 40% of community dwellers experience these feelings. Pathologic fatigue, however, has been difficult to define other than by Likert-type subjective rating scales that ask about the presence and severity of symptoms. Some of these symptoms have been related to disorders of mood and psychological manifestations of disease and disability, as well as to neural and neuromuscular mechanisms. Self-reported fatigue may not, however, correlate with tests of physical performance. Patients frequently have difficulty separating and associating the effects of their disease-related neurological impairments and disabilities from their symptoms of fatigue.²

For rehabilitation studies and interventions, better distinctions need to be made among the psychological, mood-related, and physiological causes of fatigue.³ One category that can be culled out of the various perceptions of fatigue may have both central and peripheral nervous system causes. A patient's symptoms may arise from demonstrable *fatigability*—diminished strength as routine exercise of muscle groups proceeds. This fatigability may be masked clinically because the induced weakness may rapidly lessen after exertion ceases. Studies of fatigue almost never describe an attempt to demonstrate whether a patient evolves weakness with repetitive or sustained movements during tasks. Screening tools for rehabilitation needs do not include fatigability associated with exercise-related weakness among their questions.⁴ Better characterization of fatigability may improve our concept of what patients mean by their symptoms and open up additional directions for research and treatment.

THE PROBLEM

Fatigue after stroke, spinal cord injury, and in multiple sclerosis or amyotrophic lateral sclerosis, as well as diseases of peripheral nerve and muscle, may represent a problem of fatigability, equal to an exercise-induced reduction in the ability of muscles to produce force or power, regardless of whether a task can be sustained.⁵ Fatigability of motor output is often studied in the context of high-output short-term muscle contractions or lower output sustained contractions. The acute impairment of performance may be defined in terms of an increase in perceived effort to exert the desired force and then by the physical inability to do so.⁶ Variables that may influence the mechanisms of fatigability include subject motivation, the pattern of motor unit activation, intensity and duration of activity, use of continuous or intermittent activity, posture of the limb due to differences in the load placed on accessory muscles, the number of spared ascending and descending axons that can drive the spinal motor pools, and other elements of the upper motor neuron (UMN) syndrome. The UMN syndrome itself includes weakness, poor coordination in motor unit firing, hypertonicity, changes in the relative contributions to net muscle torque by synergistic muscles, as well as more peripheral alterations in muscle fiber typing, connective tissue and joint mobility, muscle atrophy, deconditioning, and diminished muscle oxidative capacity from nonuse. On top of these problems, older and sedentary persons in general can develop an underlying decrement in peak torques for most muscles, so onset of fatigue may vary with the task that requires those muscles. Superimposed factors for weakness and fatigue in patients with neurorehabilitative disorders include anemia, endocrinopathies, electrolyte dysequilibrium,

and medications that impair the neuromuscular system such as steroids or a statin-induced myopathy.⁷

More specifically, central causes of fatigability may arise from recruitment of higher threshold motor units, reduced numbers of units leading to less drive from cortical pyramidal cells, central conduction block when firing needs to rise above the capacity of residual descending fibers, and metabolically induced afferent inhibition of the spinal and cortical motor network.⁸ Frequency-dependent conduction block has been demonstrated in multiple sclerosis, compressive cervical myelopathy, and cerebral palsy. Some studies suggest that an interaction called muscle wisdom plays a role in fatigability. The wisdom represents a decline in force, relaxation rate, motor neuron discharge rate, and alterations in feedback from afferents that optimize muscle force to ensure an economical central nervous system (CNS) activation of fatiguing muscle. Peripheral fatigue is expected from impaired propagation of an action potential, some loss of coupling of excitation and contraction, abnormal neuromuscular junction function, and changes in muscle phosphocreatine and intracellular pH.⁹

Associations between fatigability and these pathophysiologies have been confounded by trying to relate, especially in patients with multiple sclerosis (MS), abnormalities of intracortical excitability with a scale of symptoms of fatigue. Patients with MS who have greater axonal injury by magnetic resonance imaging and spectroscopy and must recruit larger cortical regions than healthy individuals when performing a simple motor task to compensate for reduced motor control, however, do describe significantly greater symptoms on the Fatigue Severity Scale.¹⁰ Thus, both central conduction impairment and fewer axonal pathways in both the sensorimotor system and the frontal regions needed for motor planning and executive functions not only reflect the burden of the disease but also may reveal mechanisms for activity-dependent fatigability.

Attributions of psychological versus supraspinal versus peripheral fatigability, or of neural versus muscular causes, will be tenuous. In addition, patients and clinicians may not specifically appreciate fatigability because weakening of muscle forces may begin soon after the onset of sustained activity such as walking, even though an individual can continue performing the task. Not unlike people who are being exercised to their maximum level of effort, patients may push on with an activity by drawing upon evolutionarily important central drivers of the motor cortices, such as limbic inputs and midbrain and spinal locomotor circuits, to override the homeostatic mechanisms that could have stopped the fatiguing exercise.⁶

Fatigability, then, may go underestimated with moderate exertion or relatively brief use of the upper and lower extremities during activities of daily living at home and in the community. The groups that are most likely to bear the brunt of fatigability include the most task-related active muscles of the upper extremities or the girdle and flexor and extensor muscles of the proximal lower extremities during standing and walking. Repetitive use of the same spared central and peripheral pathways to these groups, as well as abnormal muscle coactivation and torque coupling of these groups, is common in patients with poor motor control after CNS lesions. The energy cost of mobility may rise, and neural reserve may be

taxed as repeatedly firing residual central and peripheral motor neurons and fibers and affected muscles try to compensate to maintain stability over the time of a task such as ordinary walking. The pattern of gait especially on uneven surfaces, walking speed, and safety may diminish. Although the workload may not be great enough at any central or peripheral site to prevent a routine activity, the patient compensates unconsciously by slowing the pace of movement, resting intermittently, or disengaging.

Measures of Fatigability

Experimental studies that test for the weakness associated with fatigue usually employ either maximal or submaximal repetitive nerve stimulation or voluntary exercise. Dynamometer measures of maximal strength or electromyographic motor unit responses during an isometric or dynamic set of concentric or eccentric muscle contractions test function across a single joint. To obtain a measure of fatigue, the maximum contraction is followed by brief rest, then a single contraction to look for a decline in torque or electromyography amplitude. Tetanic contractions induced by electrical stimulation, compared to voluntary muscle contraction, may offer insight into the rate of motor unit firing that leads to fatigue. Peripheral fatigue has been measured by comparing the force responses to nerve stimulation before and after a fatiguing exercise. The contribution of central fatigue, as opposed to peripheral causes, has been represented by the force response to a single supramaximal electrical stimulus to the nerve superimposed on a sustained maximal voluntary contraction. When the muscle force evoked by the stimulus exceeds the force that can be exerted voluntarily, the decline in muscle force has been apportioned to central fatigue. By transcranial magnetic stimulation (TMS), the component from central fatigue has been suggested by the size of the superimposed TMS-induced muscle-evoked response during a maximal voluntary contraction. All of these techniques pose technical problems and require well-controlled experiments. Many different adjustments have been found in motor units that were evoked during a fatiguing contraction. These depend on the experimental conditions, such as low- versus high-frequency trains of stimuli, large versus modest contractile forces, preferential excitation of high- versus low-threshold motor neurons, inhibition and excitation from sensory feedback to cortical and spinal neurons, differences in fatigue resistance in different muscles, and the nature of the voluntary motor task.¹¹

Models of fatigability in healthy individuals are a work in progress.¹² A key problem is that fatigue occurs prior to task failure and well before the peripheral failure of excitation-contraction coupling in experiments, so its physiological onset and severity are elusive to capture. Measurements used to quantify fatigue in patients with neurologic diseases have not been the subject of many reports. In an exploratory study, Schwid et al¹³ compared several methods to quantify fatigability in patients with MS. The most reliable approach for some but not all muscles tested came from integrating the area under a force-versus-time curve from 5 seconds after onset until the end of a 30-second isometric contraction.¹³ No relationship was found between the degree of weakness and fatigability in this small study. The diversity of central and peripheral factors already mentioned will likely confound finding any simple interaction.

SOLUTIONS

Self-reports about fatigue and measurable changes in central or peripheral activity are not likely to correlate very well if patients can compensate for evolving weakness by increasing their effort or central drive. Most research aims to discern the effects of strenuous muscle contractions on fatigability, rather than the fatigue that may accompany routine daily activities. Are patients who describe fatigue actually weak or weaker over the course of daily activities such as walking and reaching? The sine qua non of neuromuscular fatigability is weakness.

Diagnosis

Prospects for highly reliable methods to measure fatigability and to calculate its effects are wanting.

Clinical Bedside Tests—The most routine clinical way to assess for activity-dependent fatigability is by manual muscle testing after repetitive movements of functionally important muscles. Weakness is relative, so the examination needs to include manual muscle testing of specific proximal or distal muscles after rest, immediately after repetitive movements against light resistance, and again after 60 to 120 seconds of rest to retest for reversibility of weakness. Testing could help clinicians recognize and treat the symptoms and physical consequences of prolonged standing, walking, reaching, and repetitive use of a hand. The approach and its plausibility differ little from the test-retest strategy for assessing patients with myasthenia gravis or after the old-fashioned hot bath test for MS. Weakening is not disease-specific, however. Indeed, the rationale and value are consistent with watching the gait pattern decline and greater leg weakness develop transiently in people with symptomatic lumbar spinal stenosis. In these patients, the walking exercise-induced weakness from transient nerve conduction block by root or cauda equina compression or ischemia resolves within a minute of ceasing the activity. The test helps solidify the diagnosis as well as the highest spinal level of compression.

The manual muscle examination should be performed on the muscle groups most relevant to maintaining the task being tested. Thus, the examiner could choose 10 to 15 repetitions of (1) raising the extended arms overhead or reaching and lifting an item, followed by retesting the strength of the isolated deltoids at 60 degrees of abduction; (2) repetitive extension of the fingers against the modest resistance of an examiner's finger; (3) repetitive 30-degree hip flexor movements with the patient supine and leg extended at the knee followed by retesting strength of the iliopsoas at 20 degrees of hip flexion; (4) repetitive 20-degree hip extensor movements against gravity or a modest force with the patient prone; (5) repetitive 60-degree knee flexor movements while prone against only gravity or modest resistance, followed by retesting the hamstrings with the knee flexed 30 degrees, and so on. Retesting that reveals any decline from the initial torque and that resolves after a minute of rest would be consistent with exercise-induced fatigability. Testing requires very consistent within-subject technique and ought to be repeated several times to make sure that the individual is complying with the request to briefly offer maximal resistance at the pre- and posttest. The approach, however, does not allow comparisons across subjects or across visits, unless

fatigability completely resolves across office visits. A handheld dynamometer may be no more quantitative than the clinical exam, because use of a device adds its own confounders. Until quantitative testing is readily available, the primary advantage of manual muscle testing is that the demonstration of a decline in strength with activity points to therapeutic targets for rehabilitation to improve activity-related functioning.

Functional Neuroimaging—Functional magnetic resonance imaging (fMRI) and related techniques offer insight into the effort necessary to maintain a movement. Impaired functional integrity of the corticospinal tract after stroke can be characterized by the recruitment of secondary motor networks in both hemispheres, as well as within the spared and adapted motor network,^{14,15} in an attempt to produce enough output to the spinal motor neurons to perform a task. Activation within nonmotor regions can be interpreted as an increase in the central effort as fatigue evolves. For example, during a sustained finger force at 20% of the individual's maximum voluntary force that lasted for 4.5 minutes, the effort eventually activated the dorsolateral prefrontal cortex and several other regions in a study using positron emission tomography. These regions were not activated by a nonfatiguing repetitive or static force.¹⁶ The pattern of the cortical signal change during a sustained maximal voluntary contraction (MVC) is different from that induced by intermittent MVCs. For example, signals were higher and less affected by fatigue during repetitive MVCs. Differences in the cortical signals found for sustained and intermittent contractions are supported by single-cell recordings in the monkey that show distinct populations of neurons that only fire phasically before or tonically during a muscle contraction. This finding implies that more phasic neurons in the brain would participate in repetitive muscle activities, but a majority of cells in controlling a sustained contraction would belong to the tonic population.¹⁷ These studies offer insight into potential strategies for varying the pattern of muscle actions during tasks in patients with an injury along the sensorimotor projections.

A few fMRI, TMS, and near-infrared spectroscopy (NIRS) studies suggest that specific changes in the primary sensorimotor cortex (S1M1) accompany fatigability during more intensive exercise. NIRS detects changes in oxyhemoglobin and deoxyhemoglobin under a detector electrode, giving a measure of focal tissue oxygenation. Although far from definitive, a NIRS experiment during repetitive pinch at about half the force of a maximum voluntary contraction showed increased activation in the contralateral then ipsilateral S1M1 by 10 seconds after onset of exercise, then a synchronous decline in activation about 10 seconds prior to exhaustion, which occurred at about 40 seconds in healthy individuals.¹⁸ A maximum fatigue test using unilateral hand grip monitored by fMRI in healthy individuals has also revealed an uncoupling of functional connectivity among interhemispheric motor regions.¹⁹ TMS offers measures of changes in motor cortex excitation and inhibition over time that may provide additional insights into the effects of repetitive movement and drugs on central processing in the face of fatigability.²⁰

Thus, physiological imaging over the course of fatiguing exercise may serve as a measure of the time of onset of central fatigability for a particular movement and as an assay over time of the therapeutic effects of a rehabilitation or drug intervention.^{21,22} Also, a rehabilitation strategy, such as feedback during fMRI or NIRS or by motor imagery of a task, may enable individuals to more consciously engage and recruit the CNS's networks for motor control, in

turn increasing the ability to generate more force and sustained muscle activation during a task.

Therapeutic Strategies

If fatigability can be given an operational definition even from the bedside, then empirical strategies for rehabilitation can be tested.

Enhance Motor Learning—Engaging the motor network through training in specific tasks that improves motor learning may increase synaptic efficacy of the distributed motor system, improve motor control,²³ and perhaps enhance the reserve of the motor pathways during repetitive movements. Task-specific training, such as that used for the Spinal Cord Injury Locomotor Trial (SCILT)^{24–26} and the Extremity Constraint-Induced Therapy Evaluation (EXCITE) trial,^{27,28} aimed to optimize identifiable components for learning motor skills. Patients who received specific training not only improved over the course of that training but also continued to improve as they presumably practiced on their own. Some of that gain is likely to coincide with greater ability to sustain movements owing to kinematic and other compensatory changes, improved activity-dependent synaptic efficacy with skills learning, and greater ability to sustain repetitive movements that contributed to faster walking speeds and longer distances walked in SCILT and faster times performing Wolf Motor Function Test activities²⁹ using the affected upper extremity in EXCITE. These therapeutic strategies were associated with cerebral adaptations found by fMRI and TMS.²² Thus, a rehabilitation therapy, such as task or perhaps imagery-based practice, that helps individuals more consciously engage and recruit the CNS's networks for motor control to increase its ability to generate more force and sustained muscle activation during a task may have therapeutic utility.

Strengthen Muscle and Improve Fitness—The type of exercise that can increase muscle fiber volume and strength and improve aerobic conditioning is understood well enough to offer disabled patients a progressive exercise prescription.³⁰ The task-associated learning that is derived from exercise and may affect cerebral movement representations is the subject of considerable research. Between these 2 areas of interest for rehabilitation is the uncertainty of how to motivate patients to practice and what the central and peripheral limitations to repetitive muscle contractions may impose.

Vary the Requirements of Repetitive or Sustained Movements—Changing the position or orientation of a segment of the arm or leg and adding mechanical stability may enable patients to engage different muscles over the time of repetitive and sustained movements. Using different muscle groups to maintain a posture should lessen the impact of fatigability. This approach is also a form of energy conservation that is often employed by physical and occupational therapists. A systematic assessment of how tasks are performed and when they induce fatigue is required. An approach could be to compare 2 different types of biomechanical performance during a movement task to identify the adjustments that reduce fatigability and allow the task to be sustained during rehabilitation training and for community activities. For example, one aim could be to reduce abnormal torque couplings

in stereotypical movements of the shoulder abductors with the elbow flexors. Fatigability may also be reduced by varying the need for tonic and phasic neuron firing.

Pharmacologic Modulation—Much of the literature on drug therapy for fatigue centers on antidepressants and cortical activators that affect neurotransmitters. In a related line of thought, if a decrease in central excitability leads to fatigue and a decline in voluntary drive on muscle, then drugs that increase cortical excitability may reduce the fatiguing decline in force. That decline, in an experiment, could be represented by the size of a motor-evoked response.¹¹ Drugs that aim to increase cortical activation, attention, and wakefulness such as caffeine, modafinil, methylphenidate, amantadine, amphetamine, and others, however, have not been effective in neurophysiological studies but may lessen some symptoms on fatigue scales.

Drugs that can improve the computational speed of the distributed sensorimotor network by an increase in synaptic efficacy^{31,32} could obviate the fatigability of central origins. Training and biological and pharmacological interventions that can enhance learning, synaptogenesis, and axonal regeneration or sprouting may lessen both motor and cognitive impairments³³ and the fatigability that can be attributed to these impairments.

CONCLUSIONS

The identification of activity-dependent fatigability of key muscle groups is an opportunity for clinicians to lessen this impairment and its related disabilities. Measures of the decline in strength with sustained and repetitive movements have been difficult to standardize for both research and diagnosis. Perhaps simple manual muscle testing for activity-dependent decrements in strength in patients with neurological diseases can raise awareness of the problem. Solutions will come from reliable quantitative test techniques and clinical trials that focus on interventions that alter central and peripheral etiologies.

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