Review Article

Fatigue in Healthy and Diseased Individuals

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Josef Finsterer, MD, PhD[1], and Sinda Zarrouk Mahjoub, PhD[2]

Abstract

Objectives: Although fatigue is experienced by everyone, its definition and classification remains under debate. **Methods:** A review of the previously published data on fatigue. **Results:** Fatigue is influenced by age, gender, physical condition, type of food, latency to last meal, mental status, psychological conditions, personality type, life experience, and the health status of an individual. Fatigue may not only be a symptom but also a measurable and quantifiable dimension, also known as fatigability. Additionally, it may be classified as a condition occurring at rest or under exercise or stress, as physiologic reaction or pathologic condition, as spontaneous phenomenon or triggerable state, as resistant or irresistant to preconditioning, training, or attitude, as prominent or collateral experience, and as accessible or inaccessible to any type of treatment or intervention. Fatigue may be the sole symptom of a disease or one among others. It may be also classified as acute or chronic. Quantification of fatigability is achievable by fatigue scores, force measurement, electromyography, or other means. Fatigue and fatigability need to be delineated from conditions such as sleepiness, apathy, exhaustion, exercise intolerance, lack of vigor, weakness, inertia, or tiredness. Among neurological disorders, the prevalence of fatigue is particularly increased in multiple sclerosis, amyotrophic lateral sclerosis, Parkinson disease, traumatic brain injury, stroke, and bleeding and also in neuromuscular disorders. Fatigue may be influenced by training, mental preconditioning, or drugs. **Conclusions:** Fatigue needs to be recognized as an important condition that is not only a symptom but may also be quantified and can be modified by various measures depending on the underlying cause.

Keywords

fatigue, fatigability, tiredness, muscle performance, review

Introduction

Fatigue is a widely used term that refers to several different meanings, causalities, and domains.[1] Fatigue is a normal response to physical exertion or stress but can also be a sign of a physical disorder. In the common sense, fatigue is a condition known to everyone from his or her own experience, irrespective of his or her age, gender, or health (acute, physiologic fatigue).[2] In healthy individuals, fatigue is a physiologic reaction to prolonged, intense activity.[3] It is predictable and transient. It reduces with rest and usually does not interfere with the daily activities.[3] Fatigue in diseased individuals is of different character. Diseased individuals describe fatigue as an overwhelming sense of tiredness at rest, exhaustion with activity, lack of energy that precludes daily tasks, inertia or lack of endurance, or as loss of vigor.[2] In diseased individuals, fatigue may persist for >6 months (chronic fatigue),[1] may be variable in response to exercise or resting, may disrupt quality of life, may have a negative impact on emotional, social, or occupational functioning,[4] and may cause disability.[5] Pathologic fatigue is an important public health problem. Fatigue has a negative impact on emotional, social, or occupational functioning and causes serious disruption in the overall quality of life, with an estimated annual cost of US$126 billion for the US employers.[4] The subjective domain of fatigue refers to the sensation of weariness (perceived fatigue, sense of effort).[1] Additionally, fatigue may occur during a given performance task known as fatigability. Fatigability is a domain of fatigue defined as a 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, electrical, metabolic, or psychological output.[3] Fatigability may manifest as rapid rise in the score on one of the fatigue scales without task failure or reduction in maximal voluntary contraction. Fatigue can be a body's signal to prevent unnecessary strain on the muscle to prevent damage from muscle injury.[6] This minireview gives an overview about the current knowledge and future perspectives concerning definition, taxonomy, classification, prevalence, etiology, quantification, and treatment of fatigue.

Definition and Taxonomy

Although a number of definitions are available and have been applied in various studies, an appropriate, widely accepted, and

[1] Krankenanstalt Rudolfstiftung, Vienna, Austria
[2] Laboratory of Biochemistry, UR "Human Nutrition and Metabolic Disorders" Faculty of Medicine Monastir, Monastir, Tunisie

Corresponding Author:
Josef Finsterer, MD, PhD, Krankenanstalt Rudolfstiftung, Postfach 20, 1180 Vienna, Austria.
Email: fifigs1@yahoo.de

Table 1. Definitions of Fatigue.[2,7,8]

General
Progressive decline in the ability to activate the muscle voluntarily
Progressive loss of ability to generate MVC during or following repeated or sustained muscle contraction
Loss of force generation during a task
Difficulty in initiating or sustaining voluntary activity
Mismatch between expended effort and actual performance or exhaustion
Reduced force production (weakness)
Loss of exercise capacity (reduced endurance)
Increased sense of effort or overperception of force
Decreased power (reduced velocity of muscle contraction)
Loss of peak force (torque) >50%
Mental
Perception of the feeling to be cognitively fatigued after performing demanding cognitive activities that involve concentration
Central
Motor cortex failure to recruit muscle, particularly loss of high threshold motor units
Reduced central drive from increased inhibitory interneuron input to the cortex
Central conduction block from demyelination of neurons
Increased negative feedback from muscle afferents via type 3 + 4 sensory neurons
Loss of positive feedback from muscle spindle type I sensory afferents
Poor coordination of motor unit firing
Delayed conduction and impairment of dynamic recruitment
Changes in synergistic muscle contraction to net force
Loss of coherence between CNS motor neurons
Changes in joint mobility from spasticity
Peripheral
Progressive decline in MVC produced by a muscle
Progressive loss of MVC or decline in MVC during a task
Sense of exhaustion and lack of energy to perform repeated or sustained muscle contractions during a task
Long-lasting reduction in the activity to contract and to exert force
Incapacity to maintain the required or expected force
Diminished ATP production due to deconditioning
Disuse muscle atrophy secondary to inactivity
Muscle atrophy due to loss of innervation

Abbreviations: ATP, adenosine triphosphate; CNS, central nervous system; MVC, maximal voluntary contraction.

comprehensive definition remains eligible (Table 1). Even between studies there is a considerable range of definitions.[9] Definitions of fatigue may have a general aspect or may focus on general, central, peripheral, or mental fatigue (Table 1). Possible definitions describe fatigue as difficulty in initiating or sustaining voluntary activities[10,11] or as mismatch between expended effort and actual performance or exhaustion (Table 1). Central fatigue may be defined as reduced central drive from the motor cortex due to increased inhibitory interneuron input to the cortex, influences of propriospinal structures, reduced muscle spindle input, increased tendon organ input, increased type III and IV afferent input, presynaptic modulation of afferent input, or due to intrinsic motor neuron properties (Table 1).[12] Central fatigue may also be defined as loss of maximal voluntary contraction (MVC) during isometric, isokinetic, or dynamic exercise without task failure. Muscle fatigue may be defined as a progressive decline in production of MVC in a single muscle or muscle group (Table 1), as progressive loss of MVC during a task,[2] as long-lasting reduction in the activity to contract and to exert force, or as incapacity to maintain the required or expected force.[6] Muscle fatigue occurs after prolonged, strong muscle activity.[6] As an alternative, it is proposed to identify distinct domains of fatigue (eg, perceived fatigue, fatigability) and to distinguish them from related phenomena.[3] Fatigue is described with a range of terms that depend on education and cultural background.[13,14] To define the different aspects of fatigue, the term needs to be delineated from a number of expressions that suggest a similar meaning or understanding, such as sleepiness, apathy, exhaustion, exercise intolerance, drowsiness (feeling that sleep is necessary), tiredness, easy tiring, lack of vigor, weakness, inertia, overtraining (fatigue from an excessive load of training both in volume and in intensity),[15,16] task failure, lethargy, or somnolence (impaired consciousness).[17] In the present article, the term fatigue is used as a subjective sensation on one hand (perceived fatigue) and as an objective and quantifiable change in performance (fatigability) on the other hand.[3]

Classification of Fatigue

Fatigue may be classified as physiologic or pathologic.[2] A healthy individual may experience fatigue during or after running, but the same individual may perceive even more fatigue when running during an infectious disease. Additionally, fatigue may occur at rest or during or after exercise (exercise-related fatigue).[3] Fatigue may also be classified as acute or chronic (duration >6 months), as localized or generalized, and according to whether it occurs as an isolated condition or together with one or more other symptoms (Table 2).[11] Fatigue may be a subjective sense (perceived fatigue) or an objective, measurable phenomenon (fatigability). Fatigue has also been classified as primary (neurological) or secondary (nonneurological).[18] Fatigue may be further delineated as physical or mental (psychiatric).[19,21] It is also important to know whether fatigue dimensions represent a single symptom (multidimensional concept) or expression of several phenomena but indeed separate symptoms (multisymptom concept).[21] According to the inducibility of fatigue, it may be classified as a spontaneous phenomenon or as triggerable (Table 2). Furthermore, fatigue may be differentiated into treatable or nontreatable (Table 2).

Muscle Force

Muscle force is usually the parameter that is most strongly affected by fatigue. Muscle force depends on the number, type, and size of motor units recruited.[2] Motor units consist of a single type of muscle cell and are innervated by a single α-motoneuron. Three types of muscle cells, type I, type IIa, and type IIb, exist. Type I fibers have a high capacity of oxidative phosphorylation (OXPHOS), high capillary density, and high resistance to fatigue.[22] Type IIa fibers depend on OXPHOS and glycolysis. Capillary density and fatigue properties resemble those of type

Table 2. Classification Criteria.

Domain	Classification criteria	Reference
Pathogenicity	Physiologic/pathologic	2
Performance	At rest/during or after exercise	3
Acuity of occurrence	Acute/chronic (duration > 6 m)	1
Location	Localized/generalized	11
Causality	Primary (neurological) /secondary (nonneurological)	18
Origin	Physical/mental (psychological, psychiatric)	19
Origin	Central (spinal + supraspinal)/peripheral	20
Association with other	Isolated/one among various others	11
Measurability	Perceived fatigue (subjective sense)/measurable (fatigability)	3
Concept	Single symptom/several phenomena (multisymptom)	21
Inducibility	Spontaneous/triggerable	(J Finsterer, oral communication, 2013)
Reaction to treatment	Treatable/untreatable	(J Finsterer, oral communication, 2013)

I fibers. Type IIb fibers depend on glycolysis, have a low capillary density, and fatigue quickly.[2] Contraction properties of individual motor units depend on the fiber type that constitutes the motor unit. According to the fiber types, 3 types of motor units are differentiated, slow twitch, fatigue-resistant (type I fibers), fast twitch, fatigue-resistant (type IIa fibers), and fast twitch, fatigable (type IIb fibers) fibers.[2] Muscles with a high content of type IIb fibers fatigue more quickly than those with a small amount of type IIb fibers. Loss of type II fibers results in increased function of type I fibers but for a shorter period than normal, while endurance time may remain unchanged.[22]

Muscle force can be measured by measuring MVC, power (velocity of muscle contraction), or torque (peak force).[23] Muscle strength may be defined as a measure of how much force a muscle can exert, while endurance is a measure of how many times a muscle can repeat a specific exertion of force. Which of these correlate most with fatigability is unknown. That strength diminishes with age, whereas fatigue hardly does, may be attributable to changes in the type I and type II fiber composition[24-26] or changes in noncontractile muscle elements[27] with age. Strength also depends on the number of motor units firing, the firing rate, synchrony of firing, activation of antagonists, and on the coherence between electroencephalography (EEG) and electromyography (EMG). In healthy individuals, muscle strength is correlated with the cross-sectional muscle area (0.827 for males and 0.657 for females), while this relation is lost in frail elderly individuals, being attributed to replacement of contractile elements by fat or other noncontractile elements or to central fatigue.[28,29] Training often increases muscle strength and reduces fatigue before muscle mass which is important, since many studies on exercise last less than 8 weeks.[30-32]

Prevalence of Fatigue

In the general, healthy population fatigue is reported in 5% to 45% of the cases, depending on the study.[3,33,34] It is estimated that up to 38% of the community-dwelling individuals experience significant fatigue.[33,35] Fatigue lasting >6 months (chronic fatigue) is reported by 2% to 11% of the general population.[36–38] Among the diseased population, fatigue is common in neurological disease, malignancy (one of the most commonly reported symptoms of cancer),[5,39] cardiovascular disease, hematologic disease, dialysis, chronic fatigue syndrome (CFS, fatigue lasting >6 months without an underlying cause), fibromyalgia, asthma, or acute or chronic infections (Table 3).[3,59] Among primary care patients, up to 42% report significant fatigue.[60] These rates are highest among patients with inflammatory disease such as rheumatoid arthritis (Table 3).[61] Fatigue affects up to 60% of the patients with diabetes.[62] Among neurological patients, the prevalence of fatigue

Table 3. Prevalence in Healthy and Diseased Individuals.

Population	Prevalence, %	Reference
General population		
Temporary	5–45	3,7,34
Chronic fatigue (>6 m)	2–11	36–38
Patients with		
Postpolio syndrome	27–91	40–42
Myasthenia gravis	75–89	43–45
Multiple sclerosis	38–83	46-48
Amyotrophic lateral sclerosis	44–83	49,50
Motor neuron disease	−83	42
Stroke	36–77	46,51–53
Traumatic brain injury	45–73	54,55
Diabetes	60	62
Parkinson disease	28–58	14,56–58
Cancer		
Cancer survivors	30	(J Finsterer, oral communication, 2013)
Cancer treatment	70–80	(J Finsterer, oral communication, 2013)
Advanced cancer	90–100	(J Finsterer, oral communication, 2013)

is particularly increased in multiple sclerosis (MS),[63] amyotrophic lateral sclerosis (ALS), postpolio syndrome, Parkinson disease (PD), traumatic brain injury (TBI), myasthenia gravis, stroke (poststroke fatigue), and neuromuscular disorders.[3] Fatigue is the most frequent disabling symptom in MS. Fatigue is reported by 40% of the patients with MS more so than spasticity or weakness.[64] Fatigue is the most frequent disabling symptom in 33% of the patients with PD .[3] Among the patients with drug-naive PD, 36% reported fatigue.[7] The prevalence of fatigue in PD increases with the disease duration.[65]

Age and Gender Dependency

Age. At least some aspects of fatigue are age dependent. Fatigue perception and fatigability increase with age.[6] Age, on the contrary, does not reduce the ability to recruit motor units or central drive, but there is greater variability in motor neuron firing rate with age.[2] Recent data suggest that older individuals are not more fatigable than younger individuals.[66]Older individuals have a reduced strength from sarcopenia, but experience less fatigue during standard sustained contractions.[67] Old adults demonstrate less performance decrement than young adults when fatigability is quantified as a decline in peak force (torque) during an isometric contraction, whereas the opposite is the case when fatigability is quantified as a decline in peak force (torque) during a dynamic contraction.[68] Type I muscle fibers are preserved with aging, whereas type II muscle fibers are reduced with aging.[2] Younger individuals have more type IIb fibers than older individuals.[2] The OXPHOS does not change with age.[69]

Gender. Concerning differences between the genders, there are some studies that reported differences and some which did not.[70] Males experience more pronounced peripheral neuromuscular changes manifesting as greater reduction in quadriceps peak force (torque) after exercise than females.[71] Females on the other hand experience a more pronounced reduction in the quadriceps motor-evoked potential (MEP) amplitude when compared to males.[71] Reduction in the central neural drive of the quadriceps and preservation of the knee-extension peak force (torque) may increase the risk of knee injury in females.[71]

Causes of Fatigue

The origin of fatigue stems from the cerebral cortex to muscular crossbridge cycling.[2] Causes of fatigue may be categorized as depicted in Table 2. Typical causes of physiologic fatigue include tiredness after exercise, tiredness after work, mental stress, overstimulation or understimulation, jet lag, active recreation, boredom, and sleep deprivation. Causes of pathologic fatigue include mental or physical disease (Figure 1).[11,19] Physical disease can be further subdivided into neurological or nonneurological disorders (Table 4 and Figure 1).[11] Neurological disorders manifesting with fatigue may be further divided into central nervous system (CNS) disorders and peripheral nervous system

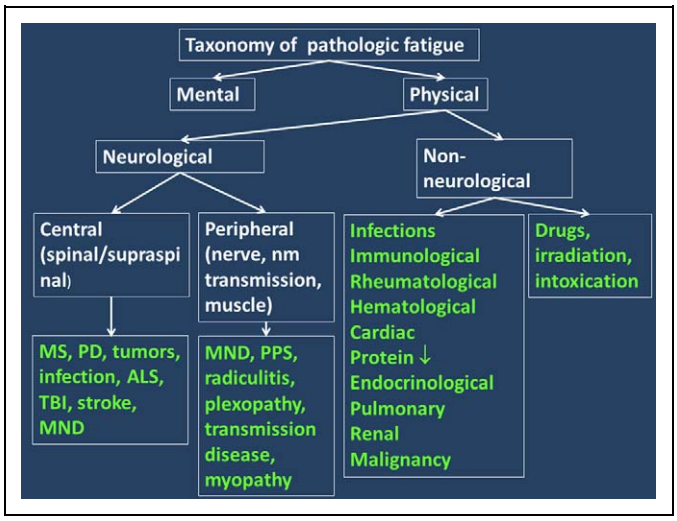

Figure 1. Taxonomy of pathological fatigue.

(PNS) disorders (Table 4 and Figure 1). When attributing fatigue to an underlying process, it is important to distinguish it from other related conditions (comorbidities) or other causes. In an individual not only 1 mechanism of fatigue but more than 1 cause of fatigue may be present.[2] Covariates (comorbidities), which need to be taken into account when examining perception of fatigue or fatigability, include drugs, depression, pain, preexisting weakness, sleepiness, smoking, alcohol consumption, decreased attention or concentration, or inflammation.[6] Characteristics of causal factors include (1) a strong correlation with performance decline rather than just a change over time, (2) retain a significant correlation with performance decline when controlling for other variables, and (3) modulation of fatigability when alternating specific interventions.[3]

Mental Causes. Mental fatigue may be defined as the perception of the feeling to be cognitively fatigued after performing demanding cognitive activities that involve concentration, attention, endurance, or alertness.[7] Mental causes of fatigue may be divided into psychological and psychiatric disorders. Psychological factors of fatigue include attitude, motivation, will, endurance, flexibility, inertia, persistence, concentration, and alertness. Psychiatric disease manifesting with fatigue includes minor and major depression, psychosis, addiction, or burnout syndrome.[2]

Physical Causes

Neurological Causes. Neurological fatigue may be classified as central or peripheral.[10] Central fatigue may be further categorized as spinal or supraspinal (Figure 1).[11] Neurological disorders may cause temporary or chronic fatigue.

Central. Central fatigue is generated at sites proximal to the peripheral nerves and referred to as progressive decline in the ability to activate muscles voluntarily.[11] It is due to impaired muscle performance that arises from the CNS (cerebrum or spinal cord).[2] Mechanisms of central fatigue on the cortical

Table 4. Primary Causes of Physiologic or Pathologic Fatigue.

Physiologic fatigue
Postprandial, postsleep, presleep, postexercise, and physical deconditioning
Pathologic fatigue
Mental
Psychological
Psychiatric
Physical
Neurologic (primary)
Central nervous system disease
Multiple sclerosis, ischemia, hypoxia, amyotrophic lateral sclerosis, and traumatic brain injury
Peripheral nervous system disease
Neuromuscular disorder, rhabdomyolysis, muscle ischemia
Nonneurological disease (secondary)
Disease
Immunologic disease
Hematological disease (anemia, hemochromatosis)
Rheumatological disease
Cardiac disease
Renal disease
Malnutrition (eating disorder, hypoproteinemia)
Endocrinological (hypothyroidism, Addison, hypopituitarism, diabetes)
Lung disease (COPD, asthma)
Chronic fatigue syndrome (fatigue + 4-8 other symptoms without explanation)
Malignancy
Other
Drugs (benzodiazepines, neuroleptics, antispastics, antiepileptic drugs, antihistamines, narcotics)
Irradiation
Chronic pain
Depression
Sleep disorder

Abbreviation: COPD, chronic obstructive pulmonary disease.

level include reduced central drive from increased inhibitory interneuron input to the motor cortex, delayed central conduction due to central conduction block from demyelination or motor neuron dropout, poor coordination of motor unit firing (loss of recruitment of high threshold motor units, declining motor unit firing rate during MVC), or loss of coherence among CNS motor neurons or between cortical and α-motoneurons.[2] Mechanisms of central fatigue on the spinal level include increased negative feedback from muscle afferent type 3 and type 4 sensory neurons, loss of positive feedback from muscle spindle type 1 sensory neurons,[2] poor coordination of motor unit firing, impaired dynamic recruitment of motor units, or impaired synergistic muscle contribution to net force. Central fatigue is determined by added force imposed by single or multiple supramaximal electrical stimuli during MVC.[2] Supraspinal fatigue is responsible for 15% to 25% of force loss causing physical fatigue during sustained contraction.[11] Supraspinal rather than spinal fatigue accounts for a significant portion of central fatigue at the end of exercise, irrespective of the type of exercise.[72] The central drive is different for each muscle.[2] Voluntary activation is less with the diaphragm compared to the biceps.[2] On the contrary, twitch force (measured by motor nerve stimulation or transcranial magnetic stimulation [TMS]) during MVC is higher in the diaphragm compared to the limb muscles.[2] Voluntary activation of a single muscle is reduced when multiple muscles are simultaneously contracted.[73] Voluntary activation is reduced by surgery, pain, and skin stimulation over the muscle or joint effusions.[2] This likely occurs from feedback inhibition to α-motoneurons.[74] Immobilization reduces voluntary activation, whereas training increases it.[2,8] Muscle atrophy secondary to inactivity from central fatigue or from loss of innervation may enhance fatigue as well as changes in joint mobility from spasticity or diminished adenosine triphosphate (ATP) production due to deconditioning. CNS disorders that go along with fatigue include stroke, MS and other immunological disorders, PD and other movement disorders, narcolepsy, ALS, mitochondrial disorders, hereditary spastic paraplegias (HSPs), spinocerebellar ataxias, CNS infections, TBI, or CNS tumors.[2] Fatigue in ALS or after stroke (poststroke fatigue) may not only have a central but also a peripheral component.[75]

Central fatigue is strongly influenced by psychological factors. A motivational input activates a facilitation system to increase motor output from the primary motor cortex in order to overcome supraspinal fatigue.[11] Additionally, a sensory input from the peripheral system activates an inhibition system to limit motor output from the primary motor cortex during exercise (supraspinal fatigue).[11] Obviously, the motor output from the motor cortex is primarily determined by the balance between these inhibition and facilitation systems.[11] As a muscle becomes fatigued, a progressive increase in the voluntary effort to enhance the facilitation system is added until the physical task requires a maximal effort.[11]

Peripheral Causes. Mechanisms of peripheral fatigue are usually attributable to a neuronal or muscular origin. In reality, central and peripheral mechanisms often go hand in hand (eg, marathon runners).[2] Neuronal mechanisms of peripheral fatigue include axonal loss, demyelination, or conduction block. Muscular mechanisms include loss of electrical conduction along the muscle membrane to the T-tubule system, impaired release of calcium from the sarcoplasmic reticulum (excitation–contraction uncoupling), impaired interaction between actin and myosin during crossbridge cycling, impaired reuptake of calcium, or bioenergetic failure due to impaired OXPHOS or glycolysis.[2] The PNS diseases that may go along with fatigue include motor neuron disease, polyradiculitis, plexopathy, polyneuropathy, neuromuscular transmission disease, myopathy, or rhabdomyolysis. Peripheral fatigue may affect a single muscle, several muscles of a region, or all muscles.[76] Muscle fatigue may be associated with accumulation of intracellular lactate and protons, with depletion of glycogen, ATP, phosphocreatine (PCr), failure of calcium release from the endoplasmic reticulum, and the effects of reactive oxidative species (ROS).[11]

Not only the head, trunk, or limb muscles but also the respiratory muscles may be affected. Affected inspiratory muscles may contribute to the development of respiratory failure.[76] Additionally, inspiratory muscle fatigue may indirectly contribute to the development of perceived fatigue. Recognition of inspiratory

Table 5. Technologies to Measure Fatigue Performance.[3]

Blood chemical values (biomarkers)
NCS
EMG
Mechanography
EEG
Structural/functional MRI, MRS
TMS
High-frequency paired-pulse evoked response
CMEP
PET
MEG
NIRS (tissue oxygenation index and oxygenation [OxyHb])

Abbreviations: CMEP, cervicomedullary evoked EMG potentials; EEG, electroencephalography; EMG, electromyography; MEG, magnetic encephalography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NCS, nerve conduction studies; NIRS, near-infrared spectroscopy; PET, positron emission tomography; TMS, transcranial magnetic stimulation.

muscle fatigue requires a rigorous and integrative methodological approach.[76] To assess respiratory muscle fatigue, it has to be induced by various methods such as inspiratory resistance loading, whole-body exercise, or hypercapnia.[76] Under normoxia or mild-to-moderate hypoxia, peripheral mechanisms contribute more to fatigue than central mechanisms, whereas under severe hypoxia, supraspinal mechanisms contribute more to fatigue than peripheral mechanisms.

Nonneurological Causes. Nonneurological disorders may cause temporary or chronic fatigue. A common nonneurological cause of temporary fatigue is a common cold or a fight of the immune system against an infection. Causes of chronic fatigue include chronic infectious diseases (human immunodeficiency virus (HIV), mononucleosis, Borreliosis, and chronic pancreatitis), hematologic disease (anemia and hemochromatosis), dehydration, immunological disease (celiac disease), rheumatological disease, cardiac disease (heart failure and cardiomyopathy), endocrinologic disorder (diabetes, Addison's disease, hypopituitarism, and hypothyroidism), renal disease (insufficiency and dialysis), lung disease (chronic obstructive lung disease and asthma), malnutrition (poor diet, irritable bowel disease, eating disorder and hypoproteinemia), liver disease, chronic pain, CFS, fibromyalgia, malignancy (cancer, sarcoma, lymphoma, and leukemia), Gulf War disease, poisoning, mineral or vitamin deficiencies, drugs, or irradiation (Table 4).[2,3,77] Drugs known to cause fatigue include benzodiazepines, neuroleptics, antispastics, some antiepileptic drugs, antihistamines, alcohol, or narcotics. The exact mechanism of how nonneurological disease causes fatigue is not fully understood. There are indications, however, that peripheral proinflammatory cytokines signal the CNS to initiate fatigue or other behavioral changes.[78]

Methods to Identify Causes of Fatigue

To identify the causal factors of fatigue, a number of technologies can be applied to monitor or to measure adjustments during fatiguing performances (Table 5). These include blood chemical investigations, nerve conduction studies (NCS),[76] EMG (surface or needle EMG interference pattern amplitude and frequency changes during a task), mechanography,[79] EEG, structural magnetic resonance imaging (MRI), TMS (differentiates supraspinal from spinal fatigue), high-frequency paired pulse-evoked response,[80] transmastoid stimulation of the spinal cord,[20] functional MRI (fMRI), positron emission tomography (PET), magnetic encephalography (MEG), or near-infrared spectroscopy (NIRS, determines the amount of muscle blood volume, the oxygenation (OxyHb), and the tissue oxygenation index[79,81] (Table 5).[3,6] Any of these technologies is capable to investigate physiologic variables hypothesized to cause fatigue experienced by the target cohort.[3] The most important of these methods are the measurement of force, blood chemical investigations, EMG, TMS, MRI, and magnetic resonance spectroscopy (MRS).

Maximal Voluntary Contraction . Fatigue of limb muscles may manifest as decline in intermittent MVC during submaximal isometric contractions. When comparing this rate with the decline in twitch force, central fatigue shows a greater decline of MVC than twitch force (increased twitch force relative to MVC during a task), whereas peripheral fatigue shows the same decline of both MVC and twitch force.[2]

Laboratory Findings (Biomarkers of Muscle Fatigue). There are no global, generally available, or cheap biomarkers of central or peripheral fatigue. However, single aspects of muscle fatigue may be monitored by determination of specific markers of the skeletal muscle's metabolism or function. Muscle fatigue is particularly associated with depletion of glycogen, ATP, or PCr, effects of ionic changes on the muscle membrane action potential, failure of the calcium release from the endoplasmic reticulum, and the effects of ROS.[82] Potential biomarkers of muscle fatigue thus include serum lactate, ammonia, oxipurines, thiobarbituric acid reactive substances, isoprostanes, protein carbonyls, glutathione, glutathione peroxidase, catalase, total antioxidant capacity, interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α).[17] Markers of inflammation such as C-reactive protein, IL-6, TNF-α, or neopterin may be associated with fatigue in patients with diabetes mellitus[83] or cancer.[39] In patients with cancer, fatigue may be particularly associated with high levels of IL-6.[4]

During low-intensity exercise, lactate is metabolized for energy production, which prevents its accumulation in the muscle and releases into the circulation. If exercise intensity exceeds the anaerobic threshold, which is the case at 60% of maximum oxygen consumption, oxygen for phosphorylation becomes limited and lactate accumulates, which is associated with fatigue.[84] Maximum oxygen consumption is determined by the cardiac output, pulmonary function, and capacity of the muscle to extract oxygen.[85] Exercise raises cardiac output and enhances OXPHOS by increasing muscle capillary supply, myoglobin content, amount of myosin heavy chains (MHC), and mitochondrial density and function.[2] Metabolic fatigue, as reflected by intramuscular acidosis, accumulation of

inorganic phosphate (Pi), and reduction in PCr, occurs before excitation–contraction uncoupling during high-intensity exercise. Uncoupling is the main cause of muscle fatigue during low-intensity exercise and due to impaired release and uptake of calcium by the endoplasmic reticulum.[86] Uncoupling lasts longer posttask than metabolic fatigue and reduces twitch force without activation failure.[2] Uncoupling reduces MVC despite recovery of PCr, pH, or Pi postexercise. Compound muscle action potentials remain normal with uncoupling. Muscle contraction and relaxation times with nerve stimulation are slow with uncoupling. Neuromuscular efficiency is delayed during recovery.

Nerve Conduction Studies and Electromyography. When central fatigue derives from impaired firing or recruitment of α-motoneurons, various EMG parameters may be altered (eg, spectral frequency, reduced amplitude, density of interference pattern).[2] The NCS may be helpful to determine the muscle twitch force. Phrenic nerve stimulation, ventilatory measurements, and EMG may be of help to assess fatigue of the inspiratory muscles.[76]

Transcranial Magnetic Stimulation (Motor-Evoked Potential). During maximal or submaximal fatiguing contractions, voluntary activation, as measured by TMS, decreases (supraspinal fatigue).[87] When exploring the relation between central and peripheral fatigue by inhibition of muscle recovery through blood pressure cuff occlusion and arterial blood flow, muscle ischemia maintains type 3 and type 4 sensory afferents in an active state and delays muscle recovery thereby maintaining fatigue.[2] Ischemia on the other hand does not prevent the MEP or the silent period (latency during which the cortex cannot be stimulated) to recover, whereas the inhibitory sensory input from the muscle appears to reduce the α-motoneuron activity but not the cortical activity.[5,88] The TMS shows that the excitability of the motor cortex increases, as fatigue develops during sustained single-joint contractions.[89] In contrast, sustained cyclic exercise does not increase motor cortex excitability.[89] The response to TMS not only depends on motor cortex excitability but also on the responsiveness of spinal motor circuits (including α-motoneurons).[20] Since the MEP amplitude increases throughout a fatiguing contraction, excitability of the corticospinal output increases, even though the muscle force declines.[20] Transmastoid stimulation (directly activates corticospinal axons), however, shows that cervicomedullary-evoked EMG potentials (CMEP) decline during a maximal contraction, suggesting that contrary to the cortical output, the spinal motor output becomes less excitable as fatigue progresses.[20] Small CMEP during the silent period of TMS during a fatiguing contraction compared to normal CMEP during a nonfatiguing contraction further suggest that the volitional drive of the corticospinal output increases to compensate for the reduced spinal excitability during fatigue.[20] Inability of voluntary output to produce MVC during a fatiguing contraction may result from normal voluntary cortical motor drive but reduced spinal excitability, from volitional effort increasing the cortical output above the nonfatigued levels but nonetheless failure of maximal muscle activation because of dropped spinal motor excitability, or from both reduced cortical output and reduced spinal excitability.[20] EMG studies and responses to paired-pulse TMS stimuli confirm that impaired α-motoneuron responsiveness rather than intracortical inhibition may contribute to central fatigue.[87]

Magnetic Resonance Imaging. Activation of the muscle by exercise results in enhancement with contrast medium on T2-muscle MRI postexercise. Postexercise enhancement is directly correlated with the production of protons (acidosis) and Pi.[90] In glycolytic defects (eg, McArdle disease), there is no acidosis and thus little T2 enhancement of postexercise . Reduced T2 enhancement also indicates that less muscle is activated to achieve the same amount of force.[2] The MRI is also suitable to measure the cross-sectional area (CSA) of a muscle.

Magnetic Resonance Spectroscopy. The MRS is important to understand and assess the muscle bioenergetics.[2] The MR spectra assess muscle metabolism at rest, during activity, or during recovery. Evaluated peaks include Pi, PCr, and 3 peaks for ATP.[91] During high-intensity exercise, PCr is reduced and Pi increases. Reduction in ATP occurs only at very high-intensity exercise. The aerobic capacity is measured as ratio of PCr-Pi or Pi-PCr, which are determined by fiber OXPHOS capacity. Reduction in pH and increase in Pi result from glycolysis.[91] High-intensity exercise will reduce the PCr levels by 80% and muscle pH from 7.0 to 6.2. In healthy individuals, reduction in force during exercise correlates best with acidosis and Pi rather than PCr levels.[91] Acidosis and depletion of PCr correlate with reduced neuromuscular efficiency (F/EMG amplitude).[92] In trained individuals, resistance training produces smaller changes in pH and less increase in Pi/PCr than in sedentary individuals. Short-term training (<8 weeks) reduces Pi/PCr per work output before increase in muscle CSA as measured by MRI or forearm blood flow.[93,94]

Quantification of Fatigue

Fatigue is difficult to define but even more difficult to measure.[14]

Measurement of Perceived Fatigue. Fatigue perception is most frequently measured by application of self-report scales. Scales available to quantify perceived fatigue are listed in Table 6. To assess perceived fatigue in muscle disease, questionnaires and scales are also used.[95] Generally, scales may be unidimensional (evaluates a single property) or multidimensional (evaluates multiple properties).[7] Dimensions assessed by fatigue scales include momentary (state) perception, chronic perception (trait perception), the impact of fatigue on function, ratings of related factors such as tiredness, dimensions of fatigue (eg, mental, physical fatigue), or the severity of fatigue.[3] The various scales differ with regard to their end points for moderate or severe fatigue (eg,, fatigue-sensitive scales), their sensitivity to change over time for clinical interventions (eg, modified fatigue impact scale), and their ability of demonstrating sensitivity to change over time for clinical interventions (Table 6).[3] Related

Table 6. Scales to Assess Fatigue.

Scale	NI	PE	IC (CA)	TRR	Validated in	COS	NPMC	Reference
Most frequently applied								
FSS	9	Uni	Excellent	Excellent (0.8)	PD	VAS	1741	7
FAI	29	Uni	good (0.7-0.91)	Moderate	Sarcoidosis	FSS	655	7
PesdsQL multidimensional fatigue scale	np	Multi	satisfactory (>0.7)	Good	Healthy	np	561	96
D-FIS	8	Uni	very good (0.93)	Good	PD	GBS, VAS	228	7
FIS-25	25	Multi	good (0.84)	0.7-0.85	COPD	FIS	159	3
PFS-16	16	Multi	good (0.93-0.98)	Satisfactory	PD	np	113	7
FACIT fatigue scale	16	Uni	excellent (0.94)	0.81	IBD	IBD	77	97,98
ISDI	np	Multi	good (0.76–0.82)	0.52–0.88	PD	FSS	25	7
SRF scale	18	Multi	good (0.81)	np	CMSI	np	7	99
Other scales								
Visual analog scale of fatigue							1653	7
Rating of perceived exertion (Borg scale)							1057	100
Subjective symptoms of fatigue test							553	101
Jadad score							331	59
Nonmotor symptom questionaire							216	7
Self rating numeric scale							172	102
Piper fatigue scale							125	103
CFS severity score							87	104
Chalder fatigue scale							80	105,106
Global impressive scale							25	7
PRISM							9	107
EORTC computer-adaptive test							2	108
Quick Piper fatigue scale							np	103

Abbreviations: NI, number of items; PE, properties evaluated; uni, unidimensional; multi, multidimensional; IC, internal consistency; PP, psychometric properties; TRR, test–retest-reliability; CA, Croisbach's alpha; COS, compared with other scales; NPMC, number of pubmed citations; PRISM, Pictorial representation of self and illness measure; CMSI, chronic multisystem illness; IBD, inflammatory bowel disease; np, not provided; FSS, fatigue severity scale; PD, Parkinson's disease; VAS, visual analogue scale; FAI, fatigue assessment inventory; PesdsQL, pediatric quality of life inventory; D-FIS; fatigue impact scale for daily use; GBS, Guillain-Barré syndrome; FIS-25, Modified fatigue impact scale; COPD, chronic obstructive pulmonary disease; FIS, fatigue impact scale; PFS-16, Parkinson fatigue scale; FACIT, Functional Assessment of Chronic Illness Therapy; ISDI, Iowa fatigue scale; SRF, self regulatory fatigue; EORTC, European Organisation for Research and Treatment of Cancer.

measures that have to be considered include fear of movement (kinesophobia) and ratings of perceived fatigue. Often, it is critical to include multiple measures to assess perception of fatigue or fatigability. In a study of patients with PD, the combination of objective and perceptual measures was necessary to determine that fatigue perception is related to cognition and homeostatic or psychological factors but not to fatigability or motor cortex excitability.[3] Perception of fatigue and fatigability was also independent of each other in a study on patients with PD who showed objective decrement in motor performance, which did not correlate with perceived fatigue.[109] Measuring fatigue perception needs effort to be normalized, as patients may restrict their effort level in an attempt to normalize or minimize experiencing fatigue.[110] The sense of effort can be viewed as a "central governor," which avoids catastrophic muscle damage.[111] Sense of effort is strongly dependent on the psychological status of a proband. Rating of perceived exertion is higher in patients with anxiety, depression, or neuroticism and lower among those with an extroverted personality.[112] As fatigue progresses to task failure, a progressive overmatching of force and increased sense of force exerted occurs.[113-115] Hemiparetic individuals will overmatch force on the ipsilateral side. Sense of force is distinct from sense of effort. Individuals can ignore effort during a task to selectively match force.[92] The main determinant of force perception is the level of central drive and corollary feedback to the sensory cortex.[91]

Table 7. Quantification of Fatigability.

Motor domain
Decline in peak force (torque) after exercise
Decline in power
Decline in speed of performance
Accuracy of performance
Cognitive domain
Decline in reaction time
Decline in accuracy on continuous performance tasks or a probe task given before and immediately after a fatiguing cognitive task

Measurement of Fatigability. To quantify fatigability, it is essential to select only those factors for measurement, which are causally related to fatigability and to distinguish them from compensatory mechanisms or other related factors that may change over the course of task performance.[3] For properly assessing fatigability, it is critical to use a valid task as well as a valid measure of fatigability. Mechanisms that cause fatigue are task dependent.[2] Variables that influence task dependency include exercise type, exercise intensity, exercise load (force or peak-force [torque]),

Table 8. Treatment of Fatigue.

Agent	Disorder	Design	Effect	Reference
Nonmedication based				
Elimination of the cause	na	na	na	(J Finsterer, oral communication, 2013)
Balanced food	na	na	na	(J Finsterer, oral communication, 2013)
Sufficient rest and sleep	na	na	na	(J Finsterer, oral communication, 2013)
Occupational therapy	PD	na	Mild	121
Acupuncture	Cancer, MS	RCT	Ineffective	122,123
Yoga	Cancer	Meta-analysis	Small	59
Avoidance of irradiation	na	na	na	(J Finsterer, oral communication, 2013)
Vestibular rehabilitation	MS	RCT	Improvement	124
Transcranial magnetic stimulation	na	na	na	2
Exercise				
Progressive resistance training	MS, cancer	PRCIT	Mild	125
Energy conservation courses	MS	RCT	Beneficial	126,127
Mindfulness training	MS	na	na	128
Aerobic training	MS, PH	na	Beneficial	129
Medication-based				
Drugs				
Amantadine	MS	BACT	1/3 responds on FSS	123,130
Acetylsalicylic acid	MS	RDBPC	Some on MFIS	131
Methylphenidate	PD	RPC	Sign. effect on FSS	132
Modafinil	PD, MS	Retrospective	Beneficial if sleepiness	133,134
Thiamin	IBD	Pilot	Beneficial on CFSS	135
Ginseng	MS	RDBPC	Beneficial on MFIS	136
Cyproheptadine	HIV	Review	Limited	137
Avoiding fatigue-inducing drugs	na	na	Effective	(J Finsterer, oral communication, 2013)

Abbreviations: MS, multiple sclerosis; PH, pulmonary hypertension; PD, Parkinson disease; IBD, inflammatory bowel disease; HIV, human immunodeficiency virus; PRCIT, prospective randomized controlled intervention trial; BACT, before/after clinical trial; RDBPC, randomized, double-blind placebo-controlled; RPC, randomized, placebo-controlled; RCT, randomized controlled trial; FSS, fatigue severity scale; MFIS, modified fatigue impact scale; CFSS, chronic fatigue syndrome scale; na, not available.

location of the tested muscle, physical environment (eg, temperature), and duty cycle.[2] Fatigability is measured by quantifying the decline in one or more aspects of performance during a continuous, prolonged task or by comparing performance of a probe task before and after prolonged performance of a fatigue-inducing task (Table 7).[3] Aspects of performance include strength, endurance, sustained contractions, repetitive movements, or skilled sequences in the motor domain and working memory, sustained attention, or verbal fluency in the cognitive domain.[2,3] In the motor domain, fatigability is usually quantified as a decline in peak force (torque) after performing an exercise. Additionally, decline in power (velocity of muscle contraction), speed of performance, fatigue index (force change over time), sense of effort, perception of effort, or accuracy of performance can be assessed.[2,9,116,117] In the cognitive domain, fatigability can be measured as a decline in the reaction time or as a decline in accuracy on continuous performance tasks or as a probe task given before and immediately after a fatiguing cognitive task.[118-120] The result of fatigability measurement is very much dependent on the measure applied.[3] Muscle fatigue can be assessed by measuring force, power, or torque.[23] Muscle fatigue may also be measured by various surface EMG models.[23] Peripheral fatigue may be gauged by comparing muscle force with the EMG amplitude.[2] When MVC declines, the CNS recruits more and larger motor units, while the EMG amplitude increases.

Treatment of Fatigue

Treatment of fatigue needs to be delineated from treatment of the underlying disorder. However, treatment of the underlying disorder may also have a beneficial influence on perception of fatigue. Treatment of fatigue may be divided into drugs and nonmedication-based treatment (Table 8). Treatment of fatigue has been most frequently investigated in patients with MS and cancer and rarely in patients with PD, inflammatory bowel disease, or human immunodeficiency virus (Table 8). Compounds that have been shown to exhibit a beneficial effect on fatigue include amantadine, acetylsalicylic acid, methylphenidate (increases dopamine levels in CNS), modafinil, ginseng, or thiamine (Table 8).[3] Nonmedication-bound measures, which have been shown to improve fatigue, include any form of exercise,[2] progressive resistance training,[125] energy conservation courses, mindfulness training,[128] or TMS.[2] Further nonmedication treatments include elimination of the underlying cause, sufficient rest and sleep, balanced food, vestibular rehabilitation,[124] occupational therapy,[121] acupuncture,[122] yoga, or avoidance of irradiation (Table 8). No beneficial effect was reported from aerobic training[129] or carnitine.[138]

Despite several trials showing a beneficial effect on fatigue, the size of the effect is generally small, and the individual effect is often negligible.[3] The MVC improves within days after starting exercise, whereas muscle mass increases not

earlier than after weeks.[30] Exercise is beneficial, since it improves OXPHOS in the muscle, increases muscle mass, and increases the production of fast MHC isoforms.[2,139-142] Peripheral changes with resistance training account for 40% of increased strength.[143] With resistance training, the velocity of muscle contraction also increases.[2] With fatigue, α-motoneurons become less responsive to descending input, while firing rates diminish and extra cortical drive is needed to maintain motoneuron activity and muscle force.[72]

Clinical Implication and Future Perspectives

Fatigue is a physiologic or pathologic reaction that requires further investigations with regard to its pathogenesis, causal factors, assessment, and treatment. The various dimensions of fatigue must be clearly delineated and distinguished from related phenomena. The effect of cortical and spinal excitability on muscle performance should be assessed, and all available techniques should be applied to understand how CNS factors or peripheral factors influence fatigue perception and fatigability. Empirical criteria should be identified to grade and monitor fatigue in neurological and nonneurological disorders and to develop strategies upon theoretic and empirical studies for the treatment of fatigue.

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