General features of motor fatigue – a review

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No conflict of interest to declare.

Summary

Fatigue is an ubiquitous phenomenon that has many definitions, and it is always multidimensional comprising physiological and psychological aspects. It ranges from a chronic symptom in somatic and psychiatric disorders to time-related physiological alterations of primary cortical areas, and to efferent and afferent pathways of the central and peripheral nervous system (CNS, PNS) in healthy exercise physiology. Thus, it is necessary to define the context when referring to fatigue. Fatigue can generally be defined as a difficulty in initiating or sustaining a voluntary activity, the latter also being named fatigability in a more strict sense of nomenclature. Fatigue in a clinical setting is best quantified by means of self-reported questionnaires, for example the Fatigue Severity Scale (FSS). The discrimination of accounts of depression, sleepiness, weakness, exercise intolerance and exhaustion relies however on a focused interview, clinical signs, and on the use of additional para-clinical investigations. Time-related physiological alterations during fatiguing tasks can occur at spinal and supraspinal sites, termed central fatigue, as well as at the neuro-muscular junction and in muscle fibres, termed peripheral fatigue. In exercise physiology, both central and peripheral fatigue can be assessed by electrophysiological techniques (e.g., transcranial magnetic stimulation, peripheral nerve stimulation, electromyography), pharmacological intervention, functional magnetic resonance imaging and laboratory tests. In the myriad of neurological disorders that cause fatigue, ranging from chronic fatigue syndrome and multiple sclerosis to neuro-muscular disorders and myopathy, different sites of pathological alterations are involved, all yielding to a patient complaining about excessive fatigue. This links the different aspects of fatigue, thus always calling for a multidimensional assessment of this intriguing phenomenon.

Key words: motor fatigue; exercise; chronic fatigue syndrome; muscle; muscle metabolism

Introduction

Fatigue is an everyday phenomenon, which we all experience. Yet, the definition of fatigue is difficult, since it is not a uniform phenomenon and has various appreciations depending on the context. When it is used in exercise physiology, we usually think of fatigue as an exercise-induced decrease of the maximal muscular force [1–4]. As such it is a normal phenomenon to a certain extent. In clinical routine, fatigue is interpreted as a pathological state of difficulty of initiation and sustenance of voluntary activity due to an altered experience of physiological fatigue [5]. It is distinct from sleepiness (physiological state between wakefulness and overt sleep, satisfied by sleep), tiredness (lack of energy and initiative, improved by rest but not by sleep; [6]), depression and muscle fatigability (see below). The lay notion of fatigue is rather less differentiated and comprises a spectrum of symptoms ranging between the aforementioned states. This short review summarises general aspects of motor fatigue with a focus on the multidimensional aspect.

In every day life, motor fatigue is intimately related to a sensation of muscle fatigue. The sensation of fatigue may be localised to the working muscle, but it may also be more generalised, giving rise to a general feeling of tiredness or loss of energy. The close general association of motor fatigability (i.e., exercise-related decrement of maximal muscle force) with the sensation of fatigue makes it difficult to distinguish between the two, for both patient and doctor. This may confuse their conception of the nature of the symptom. Pure motor fatigue is observed in endplate disorders like myasthenia gravis. However, a sensation of muscle fatigue is not usually present in myasthenia gravis, and therefore these patients do not usually complain about fatigue. On the other hand, the profound sensation of fatigue is the key symptom in the chronic fatigue syndrome. These patients usually insist on their increased muscular fatigue, yet objective tests of muscle performance do not substantiate their subjective perception. Finally, mental fatigue may be associated with muscular fatigue, which may additionally confuse the situation.

Chronic generalised (i.e., mental and bodily) fatigue is a frequent complaint in primary care. It can accompany diseases (e.g., anaemia), may be a main feature of the disease itself (e.g., in chronic fatigue syndrome), or may result from a psychiatric disorder (e.g., somatoform disorder) or as a side-effect of drug treatment [7]. This kind of fatigue may include aspects of time, task, activity, motivation, sleepiness, weakness, exercise intolerance and exhaustion. Since it is a multidimensional concept involving both psychological and physiological aspects, different – and sometimes overlapping – definitions are used. It is therefore important to define the context when referring to fatigue, and to distinguish other similar symptoms as mentioned above.

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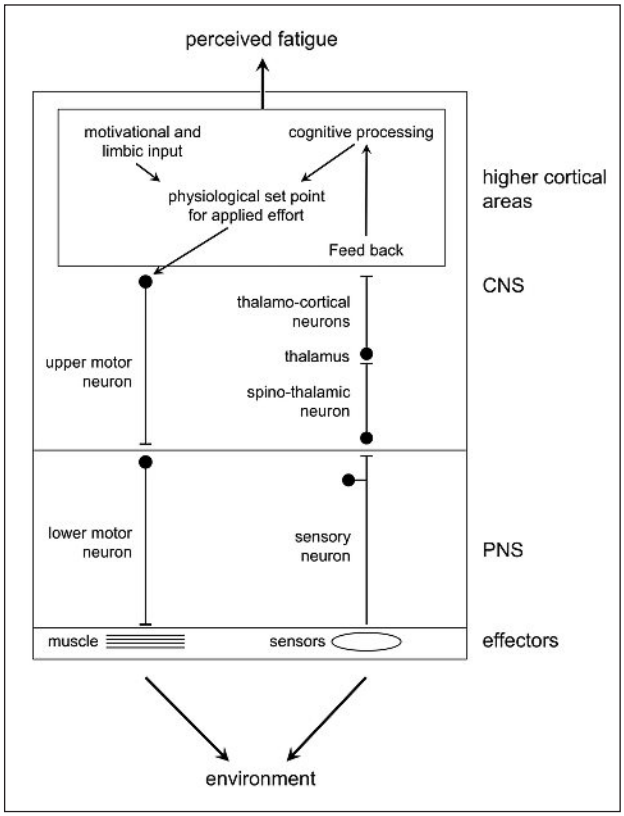
Physiological alterations leading to motor fatigue, here defined as a time-on-task motor performance decrement, may occur within the muscle and at the neuro-muscular junction (= peripheral fatigue). It is probable that changes also occur within the central nervous system, at spinal and supraspinal sites (= central fatigue). Both afferent and efferent pathways, and higher cortical areas for integration are involved, and in its basic concept, fatigue constitutes a feedback circuit [5] as depicted in figure 1. A variety of tests can be used to address the various aspects and the localisation of ongoing physiological alterations during fatigue.

Figure 1
Basic concept of fatigue (adapted from [5]).



Motor fatigue

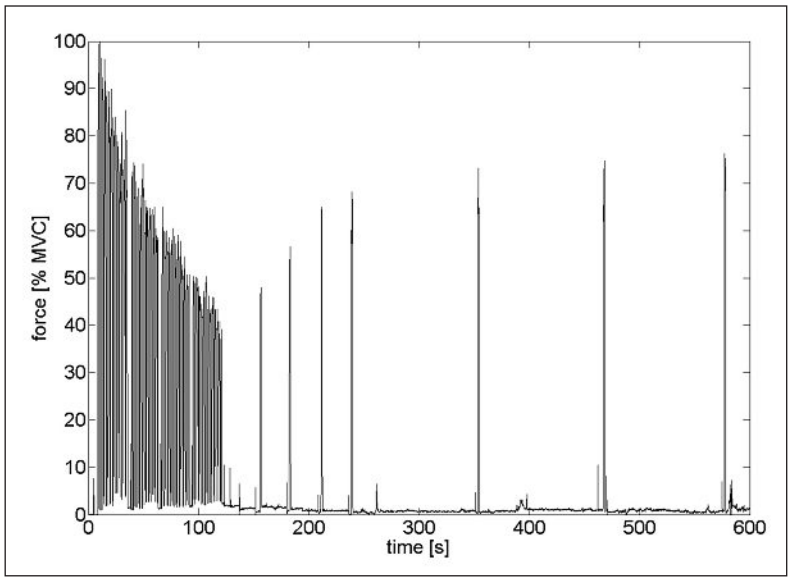
Motor fatigue can be defined as loss of force during sustained muscle work [1]. To measure the extent of motor fatigue, a great variety of methods have been developed. Many athletic disciplines may be considered fatigue measurements during a predetermined motor task. In a clinical situation, a sample of such an "athletic" performance may be the time needed to walk a given distance or by the time a subject is able to maintain a given level of force. Muscular fatigue can also be measured by electromechanical force transducers assessing the force output during single contractions (fig. 2). Such force measurements are difficult to do and are thus not readily applicable in clinical situations. All of the above-mentioned methods have the disadvantage of not allowing to discriminate between the physiological factors contributing to the fatigue.

Theoretically, the site of motor fatigue could be located in any of the structures between the motor cortex and myofibril. In healthy subjects, the primary site of motor fatigue appears to be within the muscle cell itself (for review see Fitts [8]; [9]). Alterations of the excitation-contraction (E-C) coupling and metabolic factors result in the loss of force during muscular work. These changes occur progressively with time and work intensity. Changes of electrolytes impair the E-C coupling: elevation of extracellular K^+ or intracellular H^+ occurs during intensive short-duration exercise, and the Ca^{2+} homoeostasis is disturbed by a disrupted sarcoplasmic reticulum in prolonged exercise. During long lasting endurance exercise, the depletion of muscular glycogen may further lead to a deterioration of muscle force.

A number of peripheral factors contributing to fatigue can be measured. Electromyographic measurements using surface electrodes allow conclusions on electrical changes at the sarcolemma, on recruitment of motor neurons, and on motor unit firing frequencies [10]. Muscular metabolism can be analysed during fatigue using magnetic resonance spectroscopy [11–13], blood oxygen level dependent imaging [14], and arterial spin labelling [15]. By measuring oxygenation, perfusion, and metabolites such as high energy phosphate, anorganic phosphate, myoglobin, creatine, lipids, glucose and pH, many key substances in oxidative and glycolytic metabolism can be assessed (fig. 3).

There are no doubts about the existence of a central fatigue component, but its quantitative contributions at spinal and supraspinal sites still remain elusive (for detailed discussion see [17]). Probably the earliest hint to a central fatigue component was the observation that muscular force was reduced when subjects had to perform excessive mental work prior to exercise [16]. Quantitative estimation of central fatigue is possible by recording the twitch force induced by maximal electrical nerve stimuli superimposed

Figure 2
Force recordings of abductor digiti minimi muscle recorded by an electromechanical force transducer. One subject performed a fatiguing exercise of intermittent maximal voluntary contractions (MVC) at 0.5 Hz for 2 minutes, followed by a recovery period of 6 minutes. Exercise was interrupted every 30 seconds for short periods to allow for electrophysiological measurements (see fig. 4).



to a maximal voluntary contraction. This "twitch interpolation technique" demonstrates that a subject is usually not able to voluntarily drive a muscle to its maximum. During fatiguing exercises, the amplitude of the interpolated twitch decreased, suggesting that corticospinal output increases progressively during fatigue [17]. Using transcranial magnetic stimulation (TMS), both excitatory and inhibitory responses can be elicited by activating different neuronal circuits. Many TMS studies have revealed that muscle fatigue is associated with changes in both excitatory and inhibitory responses to TMS. Motor evoked potentials (MEPs) increase in size during exercise [18, 19], indicating an increased excitability of motor cortical neurons ("post-exercise facilitation", see fig. 4). During recovery, however, MEPs are depressed for as long as 30 minutes ("post-fatigue depression"; [18, 20]. The cortical silent period (EMG silence after TMS) lengthens during exercise, suggesting an increase in intracortical inhibitory mechanisms [21]. It is not clear to date, how much these phenomena contribute to the muscle fatigue experienced by the subject.

Figure 3 In vivo measurement of metabolites involved in high energy turnover using functional MR spectroscopy. Sequential 1H-spectra of tibial anterior muscle in one subject at rest, during 2 minutes of imposed tetanic stimulation (Stim.) of the peroneal nerve, and during recovery. Note the drop of the spectroscopic signature of total creatine (Cr2 and Cr3) during exercise. AcCt = acetylcarnitine, TMA = trimethylamine, ppm = parts per million. Courtesy of PD Dr A.C. Nirkko, Inselspital Bern).

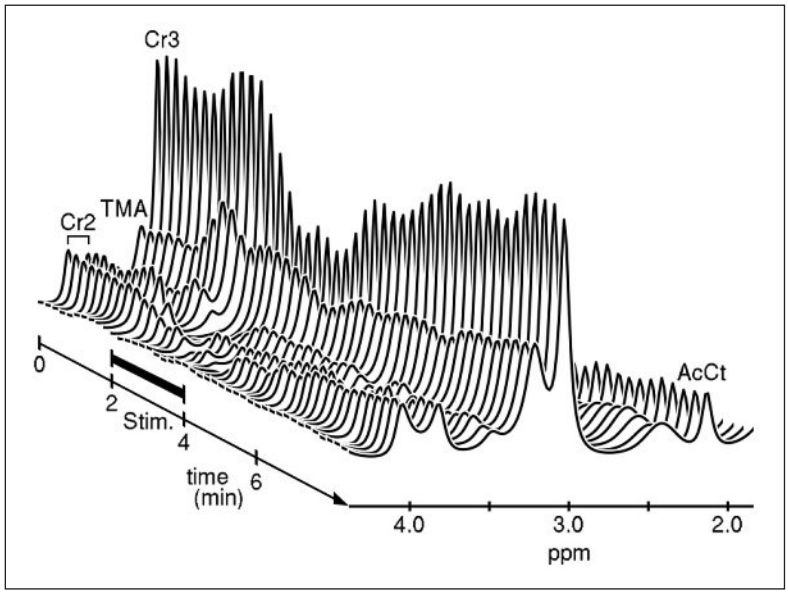
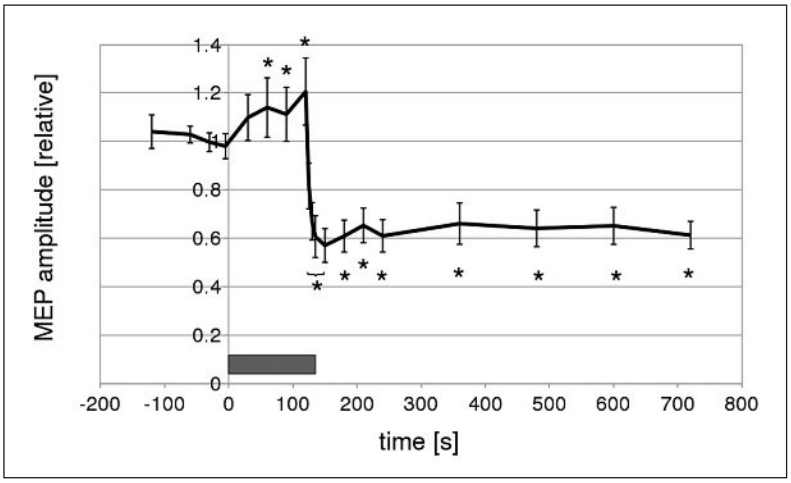


Figure 4 Relative size of the MEP amplitudes during exhausting exercise (horizontal grey bar, same exercise protocol as in fig. 2) compared to baseline measurements in 10 healthy subjects. Note an increase of the MEP amplitude until the end of the exercise (= post-exercise facilitation), and a long-lasting decrease during recovery (= post-fatigue depression). Error handles depict standard errors of the mean, asterisks significant changes from baseline values ($p < 0.05$, Mann-Whitney-U test).



Fatigue in PNS disorders

PNS disorders may be associated with symptoms such as muscle weakness, muscle wasting, fasciculations and pain. Even in the absence of blunt muscular weakness, exercise intolerance as a form of motor fatigue is often present in neuro-muscular disorders. The prime example of these diseases is myasthenia gravis, in which a defect of neuromuscular transmission causes excessive loss of muscle force during an exercise. As mentioned above, these patients usually do not complain about muscular fatigue but rather about muscular weakness. In myasthenia gravis, the sensation of muscle fatigue may not develop because the endplate failure prevents intramuscular fatigue to occur. Muscular fatigue as a consequence of metabolic insufficiency is a prominent feature of many metabolic muscle disorders. Central adaptive processes to maintain force output have been suggested [22], as they can lead to excessive perceived exertion. Even when peripheral factors resolve, central fatigue may persist as shown in patients with Guillain-Barré syndrome [23]. Failure of central activation in disorders of the PNS have also been reported in patients suffering from post-polio syndrome [24]. However, the central adaptive processes in PNS disorders still remain elusive.

Fatigue in CNS disorders

In a clinical setting, fatigue can be assessed using self-reported questionnaires. In the last decade, over 15 fatigue specific scales have been reported in the literature [25], among which the Fatigue Severity Scale (FSS) is the most popular. Several CNS diseases are associated with abnormally increased fatigue. In multiple sclerosis (MS), fatigue is a predominant and disabling symptom. Fatigue in MS is not usually characterised by pure motor fatigue but includes a generalised sensation of bodily and mental lack of energy. The pathophysiology of fatigue in MS is elusive. Using MR spectroscopy, widespread axonal dysfunction was related to fatigue in MS patients [26]. Applying TMS during fatiguing exercises has revealed enhanced corticomotor excitability when compared to normal subjects [27]. There appears to be an increased recruitment of cortical areas and pathways during fatiguing exercises, leading to a greater perceived exertion. Further influences on fatigue in MS patients are motivational deficits, depression and general physical impairment [28]. Excessive fatigue can also occur in Parkinson's disease and may be linked to abnormal corticomotor

excitability [29]. Surgical studies have identified the basal ganglia as important structures in the pathogenesis of fatigue [30]. In post-stroke patients, an involvement of brain-stem and thalamic structures in the generation of fatigue were suggested by neurobehavioural changes [31].

Fatigue as a disease

Unexplained "idiopathic" fatigue is a relatively common clinical problem. It may result in disabling impairment of daily functioning and is referred to as chronic fatigue syndrome (CFS) when lasting six months or more. The typical clinical complaint is the perception of persistent, generalised fatigue even before muscular exertion has begun. Hence, although the patients estimate their capacity to perform mentally and physically as greatly reduced, the subjective feeling of fatigue is unrelated to exertion, and it is not substantially relieved by rest either. Conclusive evidence of an impairment of the efferent structures involved in force generation is lacking. Thus, it may be that CFS is a disease of impaired fatigue perception. There has been a long and controversial debate about the etiology and pathophysiology of this entity (for review see [32]). There are cases where the syndrome seemed to be triggered by an infection, which is why it is also sometimes referred to as post-viral fatigue syndrome, but a causative agent has so far not be convincingly identified.

Conclusion

Motor fatigue remains a complex phenomenon regarding 1) the definitions, 2) the contributing mechanisms, especially the interplay of psychological and (patho-)physiological mechanisms, 3) the assessments, both in healthy and diseased states, and consequently, 4) the therapeutic possibilities. The context must always be defined when referring to fatigue as it is always multidimensional, and it must be clearly distinguished from other similar symptoms such as fatigability, tiredness, depression and sleepiness. A broad classification of fatigue in cognitive versus motor fatigue is helpful, the latter additionally divided into peripheral versus central motor fatigue. While alterations in all structures from the motor cortex to the myofibril may contribute to motor fatigue, an altered physiological setpoint of the experience of task performance is predominant for the more cognitive definition of fatigue in clinical practice.

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