Review

Muscle fatigue – from motor units to clinical symptoms

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Abstract

Reductionist approaches have provided little insight on the fatigue experienced by humans during activities of daily living. Some of the reasons for this lack of progress include the persistence of outdated concepts, the misinterpretation of experimental recordings, and a failure to embrace a global perspective on fatigue. This paper summarizes the three examples of these limitations that were discussed in the 2011 Muybridge Award lecture: motor unit types and muscle fatigue, myoelectric manifestations of fatigue, and fatigue and fatigability. Although the motor units in a population do exhibit a range of fatigability values, there are not distinct groups of motor units and the concept that some motor units are resistant to fatigue emerged from protocols in which motor units were activated by electrical stimulation rather than voluntary activation. The concept of distinct motor unit types should be abandoned. The second example discussed in the lecture was the use of surface EMG signals to assess fatigue-related adjustments in motor unit activity. The critical assumption with this approach is that the association between surface EMG amplitude and muscle force remains constant during fatiguing contractions. Unfortunately, the relation does not remain constant and a series of computational studies demonstrate the magnitude of the discrepancy, including the absence of an association with the activation signal emerging from the spinal cord and that received by the muscle. The third example concerned the concepts of fatigue and fatigability. It has long been recognized that fatigue involves both sensations and impairments in motor function, and the final part of the lecture urged the integration of the two constructs into a single scheme in which fatigue can be modulated either independently or by interactions between perceptions of fatigue and the mechanisms that establish levels of fatigability. The expectation is that such critical evaluations of the concepts and approaches to the study of fatigue will provide a more effective foundation from which to identify the factors that contribute to fatigue in health and disease.

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1. Introduction

On the occasion of the 2011 Congress for the International Society of Biomechanics held in Brussels, I was recognized for career achievements in biomechanics and honored with the prestigious Muybridge Award. In recognition of the honor, I dutifully began the Muybridge Lecture by acknowledging the contributions to the field...
of biomechanics of the pioneer after whom the award was named, Eadward James Muybridge (1830–1904). The Society describes Muybridge as the “father of cinematography”. Although he did accumulate 20,000 images of animal and human locomotion over an 8yr period, he was more interested in the representation of motion from an artistic perspective than in analyzing its attributes. Rather, it was a contemporary of his who had the same initials and was born and died in the same years who contributed more than Muybridge to the scientific study of human motion. His name was Etienne-Jules Marey (1830–1904). The substantial contributions to the study of human motion by the venerable professor at the Collège de France and member of the Academy of Sciences are described in an excellent biography written by Marta Braun (1992). Marey and Muybridge were aware of each other’s work, and their relatively brief interaction is described in the proceedings of a conference to celebrate the 100 yr anniversary of the beginning of cinema (Delimata, 1996). Accordingly, the lecture was dedicated to EJM (1830–1904).

The purpose of the lecture was not to provide an historical account of key developments in biomechanics, but rather to discuss the difficulties associated with changing the ideas that define a contemporary issue. The topic chosen for the occasion was muscle fatigue, and the approach was to proceed from ideas on muscle fatigue that should be discarded through to challenges for the future. This was accomplished by discussing motor unit types and fatigue, myoelectric manifestations of fatigue, and the distinction between fatigue and fatigability.

2. Motor unit types and fatigue

The motor unit denotes the basic functional element of the central nervous system and muscle that produces movement. It comprises a motor neuron in the ventral horn of the spinal cord, its axon, and the muscle fibers that the axon innervates (Duchateau and Enoka, 2011; Sherrington, 1925). The central nervous system controls muscle force by varying the activity of the motor units in the muscle. The force exerted by each motor unit depends principally on the number of muscle fibers that are innervated by the motor neuron and the rate at which the motor neuron discharges action potentials. The motor unit population that innervates a muscle is heterogeneous, due to systematic variations in the properties of both the motor neurons and the muscle fibers. These systematic variations in the components of the motor unit have been used to distinguish different types of motor units.

Burke and colleagues developed the classic scheme for distinguishing motor unit types. In a study on experimental animals, single motor neurons were activated with brief electric stimuli and the force exerted in the muscle fibers innervated by the motor neuron was measured (Burke et al., 1973). They found that two contractile properties could be used to identify three types of motor units; the contractile properties were the profile of a submaximal tetanus and a measure of fatigability (Fig. 1). The protocol began by recording the twitch response of the motor unit to a single electrical stimulus and measuring the time from the onset of the increase in force to the peak force, which is a measure referred to as contraction time. Next, the motor unit was activated with a series of electric stimuli with an interstimulus interval of 1.25 × the contraction time of the unit. The resulting tetanus either exhibited a progressive increase in force or there was a slight decline that began soon after an initial peak force (Fig. 1). The decline in the tetanic force is known as the sag property. Burke and colleagues classified motor units that exhibited sag as fast (type F) units, whereas those that did not display sag were referred to as slow (type S) units. Sag appears to be caused by a transient reduction in the duration of the contractile state (Carp et al., 1999).

The other classification property was fatigability, which was assessed as the decline in the peak force in response to repeated activation of the muscle fibers with trains of electric stimuli. The fatigue test involved repeated submaximal tetani that were evoked once each second for several minutes. Each tetanus comprised the force elicited by 13 stimuli at 40 Hz for 330 ms. The tetanic force elicited by each 330 ms train of stimuli either declined minimally or substantially over the course of the fatigue test (Fig. 1). Those units whose tetanic force did not decline or decreased only slightly were described as fatigue resistant. In contrast, motor units that exhibited a marked decline in the tetanic force were characterized as fatigue sensitive or fatigable. The decline in tetanic force was quantified with a fatigue index, which was calculated as the force after 120 s relative to the initial force. The fatigue index for the fatigue resistant units was ≥ 0.75, whereas it was < 0.25 for the fatigable units.

On the basis of the sag and fatigue tests, Burke et al. (1973) identified three types of motor units: (1) type S–very fatigue resistant units with relatively slow twitch contraction; (2) type FR–fatigue resistant units with fast twitch contraction; and (3) type FF–fatigue sensitive units with relatively fast twitch contraction. Unfortunately, these descriptions are somewhat misleading because the type S and F units were distinguished on the basis of sag and not twitch contraction time. Indeed, the continuous distribution of twitch contraction times (Fig. 2) indicates that there were not distinct groups of slow- and fast-twitch motor units in the cat gastrocnemius muscle. Similarly, the time to peak force for motor units in the human tibialis anterior muscle as estimated with spike-triggered averaging exhibit a relatively normal distribution and argue strongly against the existence of distinct groups of slow- and fast-twitch motor units (Fig. 2).

The other significant constraint of the motor unit-typing scheme is the measure of fatigability. As indicated by Burke...
motor units (Burke et al., 1973). The human data (twitch force elicited by applying single electric stimuli to the axons of single activated during voluntary contractions in which the test motor unit discharged triggered-average estimates of contraction times for motor units that were et al. (1973), the stimulus frequency was selected to minimize the cat gastrocnemius muscle (top) and the human tibialis anterior muscle (bottom). Fig. 2. Frequency distributions of twitch contraction times for motor units in the cat gastrocnemius muscle (top) and the human tibialis anterior muscle (bottom). The cat data (n=117) were obtained by measuring the contraction time of the twitch force elicited by applying single electric stimuli to the axons of single motor units (Burke et al., 1973). The human data (n=528) comprise spike-triggered-average estimates of contraction times for motor units that were activated during voluntary contractions in which the test motor unit discharged action potentials at \( \leq 10 \text{pps} \) (Van Cutsem et al., 1997). The two histograms indicate that the contraction times did not cluster into distinct groups of slow- and fast-twitch motor units.

et al. (1973), the stimulus frequency was selected to minimize the failure of muscle fiber activation and thereby to stress the physiological processes distal to the muscle fiber action potential. Two of the significant outcomes of this approach are the functional relevance of the measure of fatigability and the interpretation that some motor units are fatigue resistant. One principle to emerge in the literature on muscle fatigue is the concept that the underlying mechanisms vary with the demands of the task being performed (Enoka and Stuart, 1992). Although the fatigability induced by some tasks can be attributed to mechanisms distal to muscle fiber action potentials, many tasks are limited by impairments in muscle activation (Enoka and Duchateau, 2008). Indeed, it is likely that limitations in activities of daily living are more related to activation issues rather than the capacity of muscle to develop force or power.

The second issue involves the fatigability of fatigue-resistant motor units. When human volunteers performed a series of 25 ramp-up and ramp-down contractions that were minimally fatigable (9% decline in maximal voluntary contraction [MVC] force), Farina et al. (2009) found that the adjustments were greatest for the first recruited motor units. As the target force for the ramp contractions was only 10% MVC force, the involved motor units were presumably fatigue resistant based on the motor unit-typing scheme. Nonetheless, the motor units that discharged action potentials for a greater proportion of the duration for the initial ramp contractions experienced greater declines in conduction velocity of muscle fiber action potentials and the proportion of the task during which action potentials were discharged. Furthermore, the recruitment thresholds of the least active motor units declined over the course of the 25 ramp contractions, which indicates that the earlier recruited motor units contributed less to the net muscle force as the task progressed. These results indicate that low-threshold motor units, presumably fatigue resistant, are actually fatigable during voluntary contractions.

Taken together, these findings indicate that motor units cannot be distinguished on the basis of twitch contraction times and that the characterization of motor unit fatigability with tests of imposed sequences of electrical stimulation does not provide a functionally useful metric of motor unit properties (Bigland-Ritchie et al., 1998). It is time that we abandoned the concept of motor unit types.

3. Myoelectric manifestations of fatigue

Voluntary contractions arise from the activation of a motor neuron pool by synaptic inputs that are provided by descending pathways, spinal interneurons, and peripheral afferent feedback. After these inputs have been integrated by the motor neurons, the activation signal sent from the spinal cord to muscle comprises trains of action potentials for the motor units that have been recruited for the action. The net motor unit activity, therefore, is reflected in the magnitude of the activation signal discharged by the spinal cord and can be related to the force exerted by the muscle. Consequently, selected properties of EMG signals have been used as an index of the fatigue-associated adjustments in motor unit activity during sustained and repetitive contractions (Molinari et al., 2006; Rainoldi et al., 2008; Watanabe and Akima, 2010). Such an interpretation, however, assumes a stable association between the EMG signal and muscle force. Unfortunately, muscle force can vary due to changes in motor unit twitch force and contraction velocity without changing EMG amplitude (Carpentier et al., 2001; Fuglevand et al., 1999; Thomas et al., 1991), and EMG amplitude can be modulated by changes in the shapes and propagation velocity of the motor unit action potentials (Dimitrova and Dimitrov, 2003; Keenan et al., 2005) without a concurrent change in muscle force.

3.1. EMG–force relation

To estimate the extent to which the EMG–force relation can be changed during fatiguing contractions, Dideriksen and colleagues developed a computational model (Fig. 3) based on an earlier model of motor unit recruitment and rate coding (Fuglevand et al. 1993a). The adjustments in motor unit activity during the fatiguing contractions were implemented with a compartment-model approach as functions of the metabolite concentration within each muscle fiber and in the extracellular space (Dideriksen et al., 2010a). The simulated concentrations were related to the decrease in conduction velocity of muscle fiber action potentials, increase in inhibitory afferent feedback, decline in twitch-force amplitude, and the progressive inability of the CNS to produce an output that matched the target force. The model (Fig. 3) is able to reproduce a number of the adjustments observed experimentally during fatiguing contractions: depression of motor unit action potentials, the relation between target force and time to task failure, size-dependent reductions in motor
The fatigue-related changes in the association between surface EMG amplitude and muscle force was examined with a computational model of motor unit recruitment and rate coding in which the time-varying accumulation of metabolites in a compartment model provided feedback that adjusted the conduction velocity of muscle fiber action potentials, inhibitory afferent feedback to the motor neuron pool, twitch-force amplitude, and the ability of the CNS to produce an output that matched the target force (Dideriksen et al., 2010a, b). The adjustments during the simulated contractions involved changes in the number of activated motor units and the rates at which they discharged action potentials (neural drive) and the total number of muscle fiber action potentials (muscle activation).

The model was used to simulate changes in EMG amplitude and muscle force for three representative fatigue protocols: (1) repeated ramp contractions to 100% of the maximal voluntary contraction (MVC) force; (2) contractions sustained at two target forces (30 and 60% MVC force) for a similar force-time integral and then followed by ramp contractions; and (3) contractions sustained at five target forces (20–80% MVC force) for longer than the time to task failure (Dideriksen et al., 2010b). The association between EMG amplitude and muscle force varied across the protocols being bounded by the relation in the absence of the fatigue and the adjustments observed when the simulated contractions were sustained longer than task failure (Fig. 4). Across the three representative fatigue protocols, therefore, the same muscle force was associated with EMG amplitudes that differed by up to 25% of the MVC value. A similar fatigue-related dissociation with muscle force presumably emerges for other properties of the EMG signal.

### 3.2. Fatigue induced depression of EMG amplitude

Dideriksen and colleagues subsequently used the computational model to determine the adjustments that are responsible for the depression of EMG amplitude when a low-force isometric contraction is sustained for as long as possible (Fuglevand et al., 1993b). The approach was to simulate the adjustments in motor unit activity that were required to sustain isometric contractions at target forces of 20, 40, and 60% of MVC force for as long as possible (Dideriksen et al., 2011). The depression of EMG amplitude at task failure of long-duration contractions was mainly caused by a decrease in muscle activation (number of muscle fiber action potentials) due to a decrease in net synaptic input to motor neurons, with less of an influence due to changes in the shapes of motor unit action potentials and no contribution by amplitude cancellation (Dideriksen et al., 2011). Significantly, EMG amplitude during the simulated fatiguing contractions was related to the number of muscle fiber action potentials (muscle activation), but not consistently to the number of motor unit action potentials (neural drive to the muscle). However, the slope of the relation between EMG amplitude and muscle activation was inversely related to mean muscle fiber conduction velocity.

The simulations by Dideriksen and colleagues indicate that the relation between surface EMG amplitude and muscle force is not constant during fatiguing contractions and that neither the amount of muscle activation (number of muscle fiber action potentials) nor the level of neural drive (number of motor unit action potentials) can be reliably estimated from EMG amplitude during fatiguing contractions.

### 4. Fatigue and fatigability

The fatigability of muscle is classically quantified as the decline in MVC force after performing some form of demanding physical activity (Enoka and Duchateau, 2008; Gandevia, 2001). At least since the observations of Mosso (1906), it has been known that the mechanisms responsible for the decline in MVC force depend on the characteristics of the task that induced the fatigue (Enoka and Stuart, 1992). Although the evidence clearly indicates that fatigue cannot be attributed to any single mechanism, it has proven difficult to ascribe the fatigue experienced under different conditions to specific sets of mechanisms.

Despite the emphasis in the fatigue literature on the impairment of physiological processes distal to the muscle fiber action potential (Ferreira and Reid, 2008; Fitts, 2008; Place et al., 2010), even actions that involve only a modest demand are accompanied by adjustments in motor unit activity (Farina et al., 2009). The magnitude of these adjustments is underscored by the influence of load compliance on the duration that a submaximal, isometric contraction can be sustained. For example, the duration that an individual can pull up against a rigid restraint with the elbow flexor muscles to match a target of 20% MVC force (force control) is approximately twice as long as when the same net muscle torque is used to support an inertial load while keeping the arm in the same position (position control) (Hunter et al., 2002). The briefer time to failure during position control was associated with greater adjustments in motor unit activity (mean discharge rate, variability in discharge times, and recruitment), undoubtedly due to differences in the synaptic input received by the motor neuron pool (Klass et al., 2008; Mottram et al., 2005; Rudloff et al., 2010). In addition to maintaining the requisite muscle force, however, the fatigue-related adjustments in motor unit activation also underlie the sensations that accompany fatiguing contractions and there is typically a strong association between fatigability.
and rating of perceived exertion (Enoka and Duchateau, 2008; Gandevia, 2001; Mosso, 1906).

In the clinical literature, however, perceptions of fatigue are often unrelated to measures of fatigability (Zwarts et al., 2008). Indeed, individuals can report being fatigued even in a rested state. For example, 243 of the 812 participants (65–102 yrs; mean 75 yrs) enrolled in the InCHIANTI study reported being fatigued in the absence of any physical activity (Vestergaard et al., 2009). Fatigue was conceptualized as “the awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity” and was assessed by two questions from the Center for Epidemiologic Studies–Depression Scale. There were no differences between the two groups of participants (fatigued and not fatigued) in most clinical conditions and the levels for a range of biomarkers (e.g., hemoglobin, C-reactive protein, IL-6, TNF-alpha, thyroid-stimulating hormone, thyroxine). However, those individuals classified as being fatigued (71 men and 172 women) reported worse sleep quality, lower self evaluations of health, and lower physical function scores, as indicated by handgrip strength, the Short Physical Performance Battery, average 400 m walking speed, the ability to walk 400 m, and self-reported difficulties with activities of daily living and instrumented activities of daily living.

Measures of fatigability in older adults have produced equally divergent observations, with some studies finding that old adults are less fatigable than young adults and other studies reporting the converse result. For example (Fig. 5), the time to task failure for an isometric contraction (force control) with the elbow flexor muscles sustained at 20% MVC for as long as possible was 22.6 ± 7.4 min for old men (67–76 yrs; n=8) and 13.0 ± 5.2 min for strength-matched young men (18–31 yrs; n=8), even though both groups experienced a similar decrease in MVC torque (–31.4 ± 10.6%) at task failure (Hunter et al., 2005). In contrast, the decline in the maximal torque exerted by the ankle dorsiflexor muscles during 5 sets of 30 maximal isokinetic (30˚/s) contractions was greater for old adults (72–87 yrs; n=16) compared with young adults (22–47 yrs; n=16) even though the initial maximal torque (38.3 ± 3.1 N m vs. 28.6 ± 1.3 N m) was greater for the young subjects (Baudry et al., 2007). The decrease

![Fig. 4.](image)

**Fig. 4.** The relation between the amplitude of the surface EMG signal and muscle force changes during fatiguing contractions. The changes in the associations between EMG amplitude and muscle force were examined with the computational model shown in Fig. 3 by simulating three representative fatigue protocols (Dideriksen et al. 2010b). One protocol (top) involved simulating contractions at five submaximal target forces (20, 35, 50, 65, and 85% of MVC force) beyond the point in time when the muscle can achieve the target force and both EMG amplitude and muscle force began to decline. The numbers on each trace (1, 2, 4, or 8) indicate a time point (min) in each simulated contraction. The bottom panel summarizes the simulated relations between EMG amplitude and muscle force from the three fatigue protocols. The blue line indicates the relation in the absence of fatigue, whereas the red line denotes the limit observed during the simulated protocol shown in the top panel. The other two protocols produced associations that ranged between these two boundaries. The results indicate that EMG amplitude was not uniquely related to muscle force during the simulated fatiguing contractions.

![Fig. 5.](image)

**Fig. 5.** The relative fatigability of young and old adults differs for isometric (top) and anisometric (bottom) contractions. The results in the top graph comprise the times to failure for strength-matched young and old men when they sustained an isometric contraction with the elbow flexor muscles at 20% MVC torque for as long as possible (Hunter et al., 2005). The time to failure of the old men (22.6 ± 7.4 min) was longer than that for the young men (13.0 ± 5.2 min), indicating that they were less fatigable with this task. In contrast, the rate of decline in maximal torque during 5 sets of 30 repetitions with maximal lengthening contractions with the ankle dorsiflexor muscles was greater for old adults (Baudry et al., 2007).
in maximal torque was greater for old adults than for young adults after both shortening (−50.2% vs. −40.9%, respectively) and lengthening (−42.1% vs. −27.1%) contractions. Consistent with these two examples, a subsequent meta-analysis concluded that old adults are generally less fatigable than young adults when the protocol involves isometric contractions, whereas the old adults are more fatigable when the protocol involves anisometric contractions (Christie et al., 2011).

Although the different observations on the relative fatigability of old adults can presumably be explained by the task-dependent demands on the underlying physiological processes, the critical issue is which tasks provide insight on the mechanisms responsible for the fatigue experienced by old adults. The lack of progress on this question suggests that it cannot be resolved by standard reductionist approaches, but that it requires a more global perspective (Knickert et al., 2011; Noakes et al., 2005; Nybo, 2008; Tucker, 2009). Such an approach needs to include both perceptions of fatigue and the mechanisms that define fatigability, where the perceptions include both homeostatic and psychological factors. The homeostatic factors involve those physiological processes required to maintain the energetic and physical integrity of the body and the psychological factors include expectations, arousal, motivation, and mood. The mechanisms that establish levels of fatigability correspond to the physiological processes that are impaired during the performance of various types of motor tasks. The fatigue experienced by an individual, therefore, depends on both perceptions of fatigue and the level of fatigability. With such a construct it is possible to align the fatigue experienced by individuals in the absence of exercise, such as older adults (Alexander et al., 2010; Eldadah, 2010; Vestergaard et al., 2009) and those afflicted with various disorders and diseases (Ament and Verkerke, 2009; Féasson et al., 2006; Zwarts et al., 2008), with that exercise-associated changes in fatigue.

As an example of this approach, Steens et al. (in press) compared the fatigue reported by 20 individuals (20–58 yrs; 13 women) with multiple sclerosis to that of 20 sex- and age-matched control subjects. Although the most common complaints of individuals with multiple sclerosis are fatigue and limitations in walking, symptomatic fatigue is often not associated with impairments in motor function (Hadjimichael et al., 2008; Patrick et al., 2009; Putzki et al., 2008). The patients in the study by Steens et al. (in press) were moderately impaired with Extended Disability Severity Scores (EDSS) of ≤ 5.5 (can walk without assistance) and a sense of fatigue (Fatigue Severity Scale [FSS] questionnaire) that was greater (5.3 ± 0.9) than that for the control subjects (2.9 ± 0.6). The purpose of the study was to examine the associations between the sense of fatigue (FSS scores) and the fatigability of a hand muscle. The patients were weaker than the control subjects, but the decline in MVC force during a sustained 2 min contraction did not differ between the two groups of subjects. Nonetheless, the sense of fatigue reported by the patients, but not the control subjects, was predicted ($r^2=0.45$) by the decline in MVC force ($r=0.37$), which was a measure of fatigability, and the initial MVC force ($r=0.35$). However, the sense of fatigue was more strongly predicted ($r^2=0.64$) by the combination of depression score (Hospital Anxiety and Depression Scale [HADS] questionnaire) and the normalized MVC force. The sense of fatigue experienced by the patients, therefore, was more strongly related to psychological factors and the strength of a hand muscle than it was to any measure of fatigability for the hand muscle.

Motivated by the lack of progress on translating observations on the mechanisms underlying laboratory measures of fatigability to the impairments experienced by individuals during activities of daily living, it seems necessary to question our current conceptualization of fatigue. A more global perspective seems appropriate in which fatigue can be influenced by both perceptions of fatigue and the mechanisms the establish levels of fatigability. Perhaps such a framework can provide a more effective foundation from which to establish the functional relevance of the diverse observations on fatigue.

Conflict of interest statement

None declared.

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