FATIGUE AND HUMAN PERFORMANCE

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Fatigue, which “at first sight might appear an imperfection of our body, is on the contrary one of its most marvelous perfections. The fatigue increasing more rapidly than the amount of work done saves us from injury […].”

Prof. Angelo Mosso, 1904

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ABSTRACT

Fatigue has been defined differently in the past depending on the field of research (e.g., psychology, exercise physiology, neuroscience, and medical fields), which has led to an inconsistent use of the term, thereby limiting scientific progress and communication. Hence, it is first of all important to differentiate between trait fatigue and state fatigue. Trait fatigue describes the fatigue experienced by an individual over a longer period of time (e.g., weeks and months), which is relatively stable and a symptom of various diseases (e.g., multiple sclerosis, chronic obstructive pulmonary disease, and rheumatoid arthritis). Activity-induced state fatigue, in turn, is characterized by an acute and temporary change in motor or cognitive performance (i.e., motor or cognitive performance fatigue, respectively) as well as the subjective experience of weariness or exhaustion (i.e., perceived motor or cognitive fatigue, respectively) that occur in the context of a specific motor or cognitive task.

In the context of this cumulative habilitation, seven studies investigating different aspects of activity-induced state fatigue were carried out and are presented in this scientific work. Three studies investigated basic mechanisms of state fatigue in response to motor and cognitive tasks. While the motor tasks included repetitive jumping until exhaustion and 2000-m rowing, the cognitive task consisted of performing an inhibition task for 90 min. The other four experiments tried to manipulate the determinants of motor task-induced state fatigue to gain insights into the contributing mechanisms. The applied interventions included endurance training, blood flow restriction exercise, dietary nitrate supplementation, and ischemic preconditioning. The results of the experimental studies have assisted in updating a recently published definition and framework of fatigue, which was addressed, among other things, in three narrative reviews included in this work.

Findings of the experimental studies and review articles belonging to this habilitation indicate that performance fatigue and perceived fatigue in response to motor and cognitive tasks as well as their determinants are task-dependent and interdependent. Therefore, the different aspects of these state fatigue dimensions should be considered in combination to unravel the psychophysiology underlying the performance during sustained motor and cognitive tasks. Consequently, there is no single factor primarily determining performance fatigue and perceived fatigue, but the relative weight of each determinant and their interaction depends on several modulating factors (e.g., age, sex, diseases, and characteristics of the task). Hence, a combined measurement of performance fatigue and perceived fatigue together with its (neuro)physiological correlates is necessary to decipher the psychophysiology of motor and cognitive task-induced state fatigue. This knowledge will assist to better understand the interactions between the different dimensions of state fatigue and their effect on human performance in health and disease. This is crucial to design and plan effective interventions for increasing exercise tolerance, which is of particular importance for vulnerable, deconditioned, and clinical populations.

1. INTRODUCTION

Performing intense and/or sustained motor and cognitive tasks is often required during daily, physical, vocational, and educational activities of humans. If these tasks are executed above a critical intensity or duration, various psychophysiological changes can occur resulting in a decrease in performance and/or alterations in the individuals' perceptions, which are typically summarized under the umbrella term fatigue. In the past, a variety of disciplines (e.g., psychology, exercise physiology, neuroscience, and medical fields) have specialized on selected aspects investigating either the changes in motor or cognitive performance, or the subjective perception of fatigue (Enoka und Duchateau 2008; Kluger et al. 2013; Enoka und Duchateau 2016; Tommasin et al. 2020; Venhorst et al. 2018a). Accordingly, fatigue was defined differentially in the respective scientific community leading to an inconsistent use of the term, which disregarded the dynamic interactions between the task-induced psychophysiological alterations and the perceptual, affective, and cognitive responses. This impeded the understanding of the phenomenon state fatigue in healthy and clinical populations as well as the development of effective interventions to increase exercise tolerance (Enoka und Duchateau 2016; Kluger et al. 2013). Therefore, it was argued that:

> *"[…] opportunities must be taken to discuss fatigue from a holistic perspective so that we can integrate different components of fatigue into a modern understanding*" (Marino et al. 2011).

This is not only important to increase the performance of athletes, but is also crucial for activities of daily life because state fatigue may pose a barrier for physical activity behavior of humans. Moreover, deconditioning due to a sedentary lifestyle and/or diseases can increase the extent of state fatigue and limit exercise tolerance resulting in a reduced capacity to perform daily activities, a low physical activity level, and a decline in quality of life (Kluger et al. 2013; Enoka und Duchateau 2016; Gruet 2018; Behrens et al. 2023).

In the course of this cumulative habilitation, seven experimental studies were conducted investigating the mechanisms of state fatigue and its impact on human performance. The following studies investigated basic mechanisms of state fatigue in response to motor and cognitive tasks (Behrens et al. 2015a; Husmann et al. 2017; Behrens et al. 2018).

1. **Behrens, M.**, Mau-Moeller, A., Wassermann, F., Plewka, A., Bader, R., Bruhn, S. (2015). Repetitive jumping and sprinting until exhaustion alters hamstring reflex responses and tibial translation in males and females. *Journal of Orthopaedic Research, 33* (11), 1687-1692, DOI: 10.1002/jor.22935. [IF_{2021}: 3.102]

2. Husmann, F., Gube, M., Felser, S., Weippert, M., Mau-Moeller, A., Bruhn, S., **Behrens, M.** (2017). Central factors contribute to knee extensor strength loss after 2000-m rowing in elite male and female rowers. *Medicine and Science in Sports and Exercise*, *49* (3), 440-449, DOI: 10.1249/MSS.0000000000001133. [IF_{2021}: 6.289]

3. **Behrens, M.**, Mau-Moeller, A., Lischke, A., Katlun, F., Gube, M., Zschorlich, V., Skripitz, R., Weippert, M. (2018). Mental fatigue increases gait variability during dual-task walking in old adults. *The Journals of Gerontology Series A: Medical Sciences*, *73* (6), 792-797, DOI: 10.1093/gerona/glx210. [IF_{2021}: 6.591]

Furthermore, basic mechanisms of activity-induced state fatigue were investigated via the modulation of potential determining factors. The interventions included endurance training, blood flow restriction exercise, dietary nitrate supplementation, and ischemic preconditioning (Behrens et al. 2015b; Husmann et al. 2018; Husmann et al. 2019; Behrens et al. 2020).

4. **Behrens, M.**, Weippert, M., Wassermann, F., Bader, R., Bruhn, S., Mau-Moeller, A. (2015). Neuromuscular function and fatigue resistance of the plantar flexors following short-term cycling endurance training. *Frontiers in Physiology*, 6:145, DOI: 10.3389/fphys.2015.00145. [IF_{2021}: 4.755]

5. Husmann, F., Mittlmeier, T., Bruhn, S., Zschorlich, V., **Behrens, M.** (2018). Impact of blood flow restriction exercise on muscle fatigue development and recovery. *Medicine and Science in Sports and Exercise*, *50* (3), 436-446, DOI: 10.1249/MSS.0000000000001475. [IF_{2021}: 6.289]

6. Husmann, F., Bruhn, S., Mittlmeier, T., Zschorlich, V., **Behrens, M.** (2019). Dietary nitrate supplementation improves exercise tolerance by reducing muscle fatigue and perceptual responses. *Frontiers in Physiology,* 10:404, DOI: 10.3389/fphys.2019.00404. [IF_{2021}: 4.755]

7. **Behrens, M.,** Zschorlich, V., Mittlmeier, T., Bruhn, S., Husmann, F. (2020). Ischemic preconditioning did not affect central and peripheral factors of performance fatigability after submaximal isometric exercise. *Frontiers in Physiology,* 11:371, DOI: 10.3389/fphys.2020.00371 [IF_{2021}: 4.755]

The results of the experimental studies have assisted in updating a recently published definition and framework of fatigue provided by Enoka and Duchateau (2016) (Behrens et al. 2021; Broscheid et al. 2021; Behrens et al. 2023). The related scientific works are the following:

8. **Behrens, M.***, Broscheid, K.-C.*, Schega, L. (2021). Taxonomie und Determinanten motorischer Performance Fatigability bei Multipler Sklerose [Taxonomy and determinants of motor performance fatigability in multiple sclerosis]. *Neurologie & Rehabilitation, 27* (1), 3-12, DOI: 10.14624/NR2101001. (* authors contributed equally to this work) [IF: -]

9. Broscheid, K.-C.*, **Behrens, M.***, Dettmers, C., Jöbges, M., Schega, L. (2021). Quantifizierung Motorischer Performance Fatigability bei Multipler Sklerose [Quantification of motor performance fatigability in multiple sclerosis]. *Neurologie & Rehabilitation, 27* (1), 13-22, DOI: 10.14624/NR2101002. (*authors contributed equally to this work) [IF: -]

10. **Behrens, M.**, Gube, M., Prieske, O., Chaabene, H., Zenon, A., Broscheid, K., Schega, L., Husmann, F., Weippert, M. (2023). Fatigue and Human Performance: An Updated Framework. *Sports Medicine*, *53* (1), 7-31, DOI: 10.1007/s40279-022-01748-2. [IF_{2021}: 11.928]

2. THEORETICAL BACKGROUND

2.1. Proposed Definition and Taxonomy of Fatigue

When defining fatigue, it is crucial to differentiate between trait fatigue and state fatigue. Trait fatigue describes the fatigue experienced by an individual over a longer period of time (e.g., weeks and months), which is relatively stable. Trait fatigue can be a symptom of various diseases (e.g., multiple sclerosis, chronic obstructive pulmonary disease, and rheumatoid arthritis) and is caused by primary disease-related mechanisms (e.g., neurodegeneration and inflammation) and secondary mechanisms (e.g., depression, sleep problems, and medication) (Kluger et al. 2013; Braley und Chervin 2010; Gruet 2018; Marrelli et al. 2018). However, trait fatigue is also experienced in a milder form by healthy people (Müller und Apps 2019). Activity-induced state fatigue, in turn, is characterized by an acute and temporary change in motor or cognitive performance as well as the subjective experience of weariness or exhaustion that occur in the context of a specific motor or cognitive task (Enoka und Duchateau 2016; Gruet 2018; Genova et al. 2013; Behrens et al. 2018; Behrens et al. 2021; Behrens et al. 2023).

In order to provide a holistic view of state fatigue, Enoka and Duchateau (2016) proposed a framework defining fatigue as a self-reported disabling symptom that limits physical and cognitive functions due to interactions between performance fatigability (i.e., decrease in an objective performance measure) and perceived fatigability (i.e., changes in the sensations that regulate the integrity of the performer). Both, performance fatigability and perceived fatigability depend on several factors that determine the decline in motor performance (i.e., muscle activation and contractile function) as well as the changes in the individuals' sensations (i.e., psychological and homeostatic state of the individual). In this framework, the interdependency of performance fatigability and perceived fatigability was highlighted and both contribute to the self-reported symptom state fatigue. This approach has the advantage that it can be applied to both healthy and clinical populations, given that it refers to the state fatigue mechanisms whose relative weight is subject- and task-dependent.

The definition and framework of fatigue suggested by Enoka and Duchateau (2016) served as a good starting point to decipher the psychophysiology of state fatigue. However, the authors have omitted some aspects (e.g., effort perception, affective valence, and self-regulation), which are regarded as important contributors to state fatigue induced by motor and cognitive tasks. Furthermore, the authors' definition of state fatigue comprised also a decline in cognitive performance, which was not embedded in their framework. Therefore, the definition and framework of state fatigue suggested by Enoka and Duchateau (2016) was updated during the habilitation phase (Behrens et al. 2021; Behrens et al. 2023).

On this basis, motor and cognitive task-induced state fatigue was defined as a psychophysiological condition that is characterized by a decrease in motor or cognitive performance and/or an increased perception of fatigue. The reduction in motor and cognitive performance can be termed *motor* and *cognitive performance fatigue*, respectively. Motor performance fatigue (e.g., decrease in maximal voluntary contraction force) depends, on the one hand, on the *muscle activation* characteristics, which can be impaired after fatiguing motor exercise. This includes a decrease in *voluntary activation* of muscles caused by alterations in *cortical* and/or *spinal motoneurons* resulting in changed firing frequencies and/or recruitment of motor units.

It is thought that the modulation of intrinsic properties of motoneurons, an increase in inhibitory *afferent feedback* from group III/IV muscle afferents, a decrease in facilitatory afferent feedback, and changes in neuromodulators contribute to the reduced muscle activation (Taylor et al. 2016). Moreover, the *activation patterns* of synergistic and antagonistic muscles can be modulated during fatiguing motor tasks, which can impair intermuscular coordination and thus force production capacity of muscles (Figure 1A) (Ebenbichler et al. 1998; Gagnon et al. 1992). Furthermore, motor performance fatigue depends on the *contractile function* of muscles, which is impaired by the accumulation of *metabolites* (e.g., inorganic phosphate, reactive oxygen species, and hydrogen ions) during fatiguing motor exercise. The involved processes include decreases in *sarcolemmal excitability*, *calcium (Ca^{2+}) release* from the sarcoplasmic reticulum, myofibrillar *Ca^{2+} sensitivity*, and in the *force-generating capacity* of the cross-bridges per se (Enoka und Duchateau 2016; Allen et al. 2008; Cheng et al. 2018; Gandevia 2001; Hunter 2018). In contrast, cognitive performance fatigue (e.g., decrease in reaction time) only depends on the *integrity of the central nervous system*, which is determined by changes in *brain activity*, *neurotransmitters*, and *metabolites* during fatiguing cognitive tasks (Figure 1A).

The motor and cognitive task-induced increase in the perception of fatigue can be labeled *perceived motor* and *cognitive fatigue*, respectively. These are determined by the *psychophysiological state* of an individual, which is influenced by several factors. The most important factors are *effort perception* and *affective valence*, given that they are thought to contribute to both perceived motor and cognitive fatigue (Venhorst et al. 2018a, 2018b; Kurzban 2016; Saunders und Inzlicht; Hockey 2013). Moreover, exercise-induced *pain/discomfort perception* might additionally contribute to perceived motor fatigue (Figure 1A) (Venhorst et al. 2018a; Behrens et al. 2021; Behrens et al. 2023). A detailed description of the contributing factors can be found in the narrative review included in this cumulative habilitation (Behrens et al. 2023) (see Appendix).

Motor and cognitive performance fatigue as well as perceived motor and cognitive fatigue are susceptible to perturbations in *body homeostasis*. Moreover, they are interdependent (Figure 1A) and depend on several *modulating factors* (e.g., characteristics of the subject, the task, and the environment) (Figure 1B). The extent of fatigue in the different dimensions can impair the motor and cognitive capacity of humans, which can be associated with a reduced quality of life, particularly in vulnerable, deconditioned, and clinical populations (Figure 1C) (Enoka und Duchateau 2016; Gruet 2018; Behrens et al. 2023).

The proposed updated definition slightly differs from that provided by Enoka and Duchateau (2016), who have characterized state fatigue as a self-reported disabling symptom derived from the interdependent attributes performance fatigability and perceived fatigability. However, this definition requires that state fatigue is assessed by self-report, which is also reflected by quantifying perceived fatigue in response to a specific motor or cognitive task (Micklewright et al. 2017). Moreover, performance might decrease without a concomitant increase in the perception of fatigue or vice versa. This selective change would not be captured by the definition of Enoka and Duchateau (2016). Furthermore, given that the suggested updated definition does not refer to state fatigue as a self-reported disabling symptom, the term fatigability is not necessary as it does not contribute any benefit compared to the term fatigue.

The psychophysiological changes during fatiguing motor exercise were interpreted as a protective mechanism, which regulates exercise behavior and ensures the preservation of homeostasis in the human body (Noakes 2012; Blain et al. 2016; Laurin et al. 2015).

This is in contrast to, the psychophysiological underpinnings of state fatigue resulting from sustained cognitive tasks. In this regard, some authors proposed that cognitive fatigue redirects behavior from the current to more rewarding and/or less effortful activities (Boksem und Tops 2008; Kurzban 2016), while others consider it as a protective mechanism assisting to stop the present activity in anticipation of future adverse, functional consequences (Benoit et al. 2019; Gergelyfi et al. 2021).

It is important to mention that the definition and taxonomy of state fatigue presented in this cumulative habilitation evolved during the habilitation phase and represents the current state of the art (Behrens et al. 2023). Therefore, in the following paragraphs, the proposed fatigue taxonomy was applied, even when the cited studies have not used this terminology.

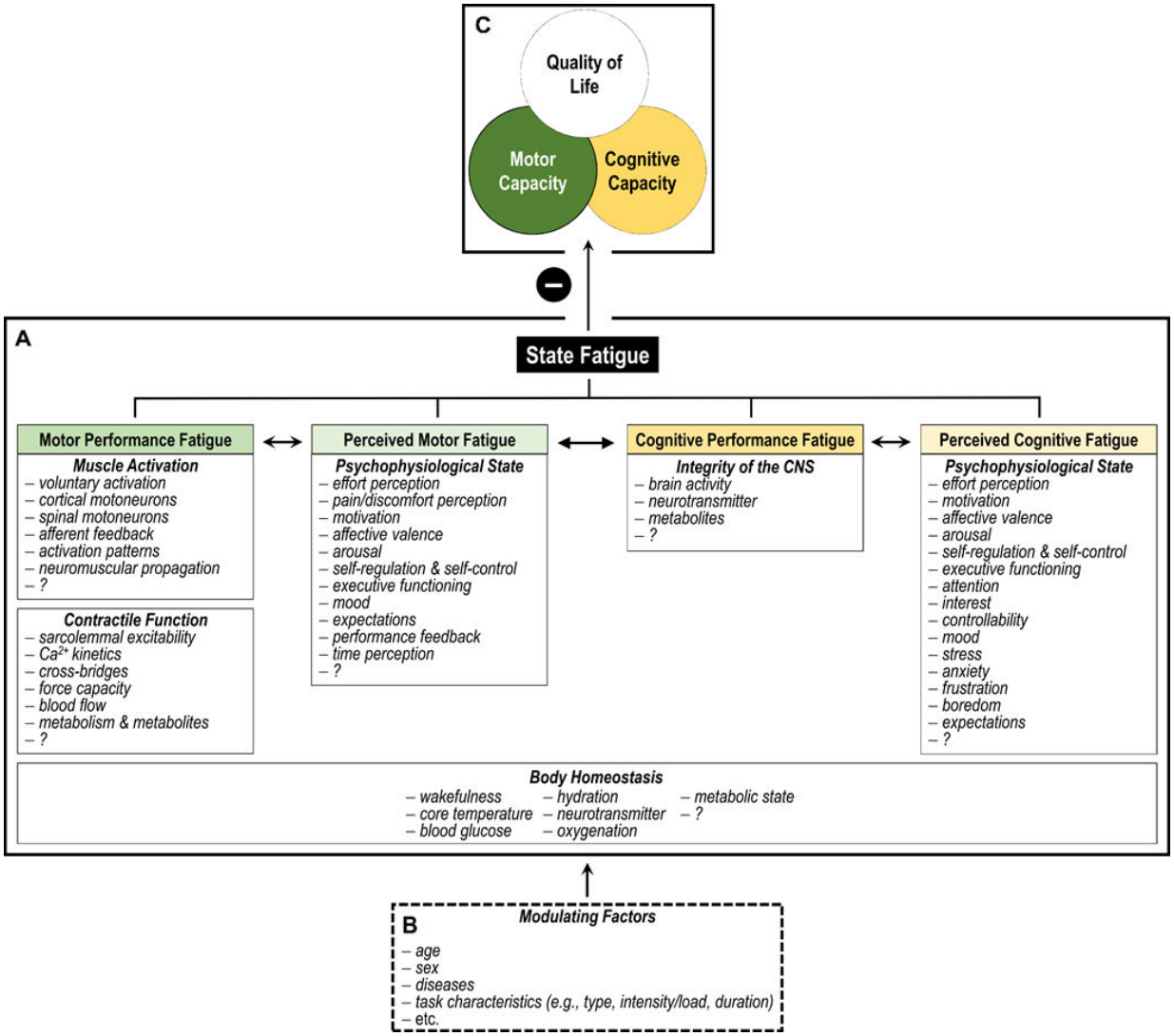

Figure 1. (**A**) Updated motor and/or cognitive task-induced state fatigue framework with its interdependent dimensions and the respective determinants first proposed by Enoka and Duchateau (2016). A detailed description of each determinant and their interactions is given in Behrens et al. (2023). The extent of state fatigue in the respective dimensions depends on (**B**) several modulating factors and has (**C**) negative consequences for the motor and/or cognitive capacity, which can impair quality of life. This is particularly the case in vulnerable, deconditioned, and clinical populations. The bidirectional arrows represent the interdependency between all dimensions. Please note that effort perception, affective valence, self-regulation, self-control, and time perception were added to the potential determinates of perceived motor fatigue compared to Enoka and Duchateau's framework (2016). Furthermore, cognitive performance fatigue, perceived cognitive fatigue, and the potentially contributing factors were added. CNS: central nervous system; ?: unknown factors that should be added in the future

2.2. Measurement of Motor Performance Fatigue as well as Perceived Motor and Cognitive Fatigue

In the following sections, only the methods applied in the experimental studies relevant for this cumulative habilitation were shortly described. Further information on the materials and methods used for the respective studies can be found in the published articles (see Appendix).

2.2.1. Measurement of Motor Performance Fatigue and its Determinants

Motor performance fatigue refers to the decline in an objective performance measure and can be quantified, for instance, as the change in maximal voluntary force/or torque production (Millet et al. 2011). Besides this, motor performance fatigue can also be assessed as a change in submaximal motor performance. In this context, an increase in the variation of mechanical signals (e.g., force fluctuations during submaximal isometric contractions or the coefficient of variation of kinematic gait parameters) is regarded to be indicative of motor performance fatigue (Enoka und Duchateau 2008, 2016; Behrens et al. 2018; Nagano et al. 2014).

To identify the origin of the performance-limiting adjustments within the neuromuscular system, further methods such as peripheral electrical nerve stimulation and electromyography (EMG) are required (Millet et al. 2011; Taylor et al. 2016). For instance, the application of peripheral electrical nerve stimulation during maximal voluntary contractions (MVCs) and at rest can be used to quantify fatigue-related changes at both the neural and muscular level. During this procedure, a superficial peripheral nerve innervating the muscle of interest is depolarized by paired electrical stimuli at 100 Hz during an isometric MVC, which evoke an additional torque output (i.e., interpolated twitch) (Figure 2) (Verges et al. 2009; Millet et al. 2011). The size of the interpolated twitch in relation to the control twitch torque, induced by the application of paired electrical stimuli at 100 Hz to the nerve when the muscle is relaxed, allows the calculation of voluntary activation in percent (interpolated twitch technique) (Behrens et al. 2017). A decrease in voluntary activation (i.e., muscle activation) after fatiguing exercise is typically interpreted as the reduced ability of the central nervous system to activate the muscle (Millet et al. 2011; Taylor et al. 2016; Taylor und Gandevia 2008).

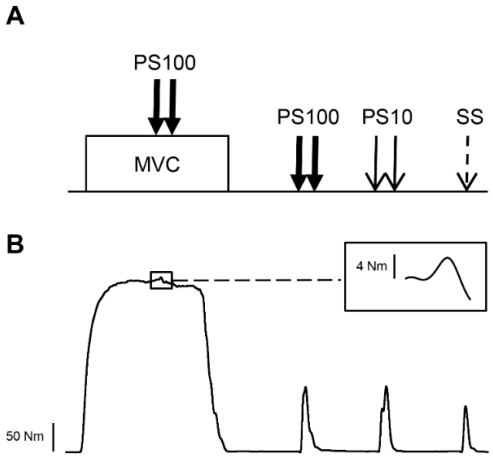

Figure 2. Neuromuscular testing procedure to identify changes in muscle activation and contractile function after fatiguing motor exercise. (**A**) The procedure consists of maximal voluntary contractions (MVC) of the quadriceps muscle combined with peripheral electrical stimulation of the femoral nerve to measure maximal voluntary torque, voluntary activation (via the interpolated twitch technique), and quadriceps maximal twitch torques in response to paired electrical stimuli at 100 Hz (PS100), 10 Hz (PS10), and with single stimuli (SS). (**B**) Typical torque-time-curve recorded during the neuromuscular testing procedure. An enlarged view of the interpolated twitch is presented in the box.

The twitch torques induced by electrical stimulations with different frequencies at rest (i.e., paired electrical stimuli at 100 Hz and 10 Hz as well as single stimuli) can be used to quantify the decrease in contractile function of muscles in the course of fatiguing exercise (Figure 2) (Verges et al. 2009; Millet et al. 2011; Froyd et al. 2013)

Moreover, the electrically evoked potentials recorded with EMG at rest and during exercise provide further insights into neural adjustments. For instance, the maximal muscle wave (M-wave) can be employed to measure changes in sarcolemmal excitability, while the Hoffmann reflex (H-reflex) and the volitional wave (V-wave) can be used to analyze modulations at the spinal level due to different interventions such as fatiguing exercise and training (Millet et al. 2011; Behrens et al. 2015b; Aagaard et al. 2002; Zehr 2002). The H-reflex and the V-wave are elicited, for example, when the posterior tibial nerve in the popliteal fossa is electrically stimulated and can be recorded via EMG in the soleus muscle (Aagaard et al. 2002). The H-reflex assesses the excitability of α-motoneurons via the Ia afferent pathway and/or presynaptic inhibition (Schieppati 1987; Zehr 2002), whereas the V-wave is a measure of the descending neural drive from the α-motoneurons to the muscle (Figure 3) (Aagaard et al. 2002).

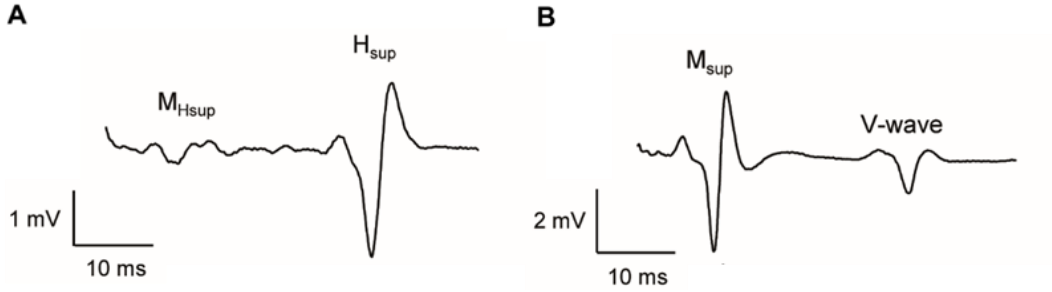

Figure 3. Evoked potentials recorded in the soleus muscle in response to electrical stimulation of the posterior tibial nerve. (**A**) H-reflex (H_{sup}) and (**B**) V-wave recorded during a maximal voluntary contraction (MVC). M_{Hsup}: submaximal M-wave evoked at H_{sup} intensity during MVC; M_{sup}: maximal M-wave during MVC.

Changes in neural function after fatiguing exercise can also be investigated using mechanical perturbations intended to elicit stretch reflex responses, which are of particular importance for the stabilization of joints (Wojtys et al. 1996; Melnyk und Gollhofer 2007; Behrens et al. 2013). These paradigms are often used to simulate injury mechanisms and to analyze the compensatory neural responses (Friemert et al. 2010; Melnyk et al. 2008; Gruber et al. 2006). For instance, to analyze the role of stretch reflexes in the hamstring muscles for the mechanical stability of the knee joint, the tibia can be mechanically translated in the anterior direction in standing subjects using a pulley system. Thereby, the anterior tibial translation can be measured using linear potentiometers (Figure 4) (Friemert et al. 2010).

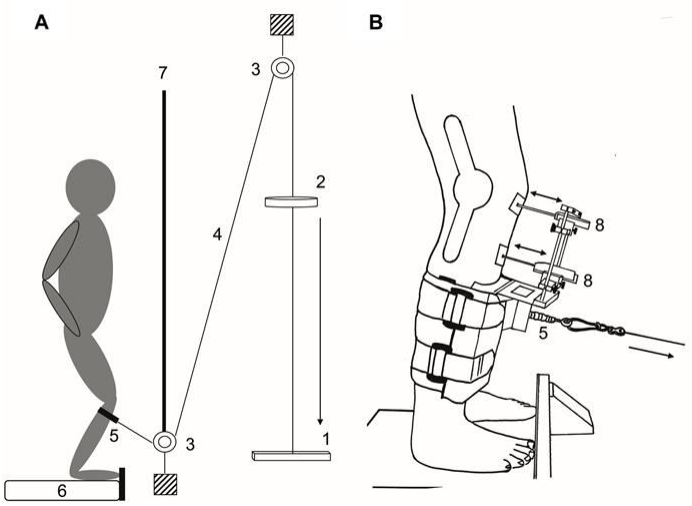

Figure 4. (**A**) Pulley system and (**B**) experimental setup to elicit and measure anterior tibial translation. 1: stopper, 2: falling weight, 3: pulley, 4: steel rope, 5: force transducer, 6: force plate, 7: visual cover, 8: linear potentiometer. Arrows indicate the direction of the force. Anterior tibial translation is measured by two linear potentiometers (8) placed on the patella and the tibial tuberosity. A force transducer (5) is used to record the force transmitted to the shank.

The movement of the tibia relative to the femur induces stretch reflexes that can be recorded via EMG. These are analyzed in different time frames representing the short-, medium-, and long-latency stretch reflex responses (Figure 5).

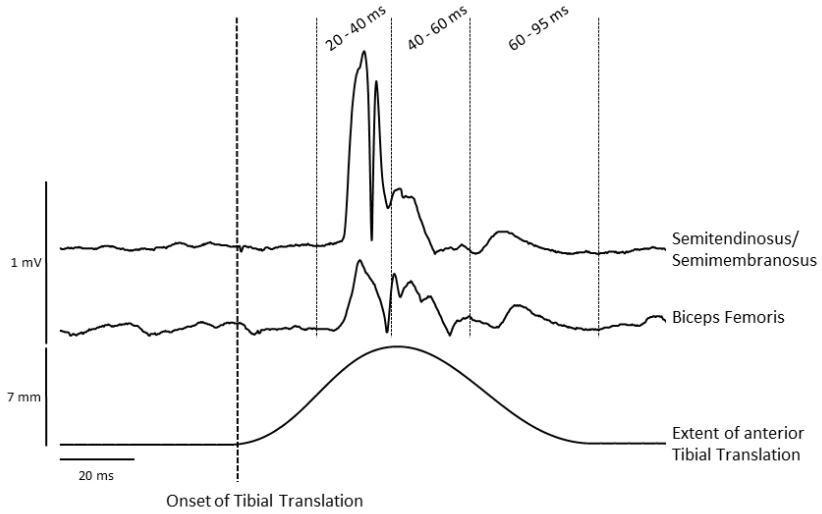

Figure 5. Exemplary electromyographic (EMG) and tibial translation data. Short-, medium-, and long-latency stretch reflex responses (20-40 ms, 40-60 ms, and 60-95 ms, respectively) of semitendinosus/semimembranosus and biceps femoris as well as the extent of anterior tibial translation of one subject. Please note that the EMG data was rectified. The vertical dashed line indicates the onset of anterior tibial translation.

The described neuromuscular assessments are typically performed before and immediately after exercise termination to identify the impairments induced by the respective motor task (Millet et al. 2011; Enoka und Duchateau 2016; Froyd et al. 2013; Behrens et al. 2013). Moreover, EMG and near-infrared spectroscopy (NIRS) data can be recorded to measure changes in neural function and muscle metabolism, respectively, during the development of motor performance fatigue in the course of fatiguing motor tasks (Enoka und Duchateau 2008; Ferrari et al. 2011; Behrens et al. 2023).

2.2.2. Measurement of Perceived Motor and Cognitive Fatigue and its Determinants

Perceived fatigue refers to the increase in the subjective perception of fatigue emerging during motor and cognitive tasks. It is often defined as a sensation of tiredness, weariness, lack of energy, and/or exhaustion (Vargas und Marino 2014; Boksem und Tops 2008; Skau et al. 2021) or the feeling of a need to rest or a mismatch between effort expended and actual performance (Skau et al. 2021). Perceived fatigue can be assessed, for instance, with the fatigue scale of the Profile of Mood States, the rating of fatigue scale, and visual analog scales (Behrens et al. 2018; Micklewright et al. 2017; Genova et al. 2013).

Moreover, effort perception and exercise-induced muscle pain perception should be quantified during fatiguing motor exercise, given that these are thought to contribute to perceived motor fatigue (Pageaux 2016; Mauger 2013; Venhorst et al. 2018a; Behrens et al. 2023). Effort perception and exercise-induced pain/discomfort perception can be measured with 15-point Borg scales and/or category ratio scales (e.g., CR-10 and CR-100). These measures should be applied together with standardized wording as described elsewhere (Pageaux 2016; Venhorst et al. 2018a, 2018b).

3. EXPERIMENTAL STUDIES

3.1. Study Overview

The seven experimental studies, included in this cumulative habilitation, investigated selected aspects of performance fatigue and/or perceived fatigue. Three studies investigated basic mechanisms of motor performance fatigue and perceived cognitive fatigue in response to motor and cognitive tasks. While the motor tasks included repetitive jumping until exhaustion and 2000-m rowing, the cognitive task consisted of performing an inhibition task for 90 min. The other four experiments tried to manipulate determinants of motor performance fatigue and perceived motor fatigue to gain insights into the contributing mechanisms. The applied interventions included endurance training, blood flow restriction exercise, dietary nitrate supplementation, and ischemic preconditioning. In the following paragraphs, a short description of the studies, including key-results and a short discussion of these, is presented. More information on the methods, results, and interpretation of findings can be found in the respective articles (see Appendix).

3.2. Studies Investigating Basic Mechanisms of Motor Performance Fatigue and Perceived Cognitive Fatigue

3.2.1. Repetitive Jumping and Sprinting Until Exhaustion Alters Hamstring Reflex Responses and Tibial Translation in Males and Females

Rupture of the anterior cruciate ligament (ACL) is one of the most common injuries during physical and sporting activities (Hootman et al. 2007), which is associated with a long rehabilitation period and high socio-economic costs. ACL injuries are more frequently observed in females than in males and the underlying mechanisms are not fully elucidated (Hewett et al. 2006). Nevertheless, it was suggested that differences in the passive and active stability of the tibiofemoral joint might be responsible for the higher injury rate in females. While the laxity of the ligaments and geometry of the articular surfaces contribute to the passive stability, muscle activity patterns, muscle reaction times, the patellar tendon-tibia shaft angle, time to peak torque, and muscle stiffness are thought to constitute active stability of the knee joint (Hughes und Watkins 2006). Epidemiological data indicate that the majority of injuries occur at the end of sports games (Hawkins et al. 2001; Price et al. 2004) suggesting that the risk of injury increases during fatiguing motor exercise. Indeed, it has been found that the magnitude and onset of stretch reflexes in the hamstring muscles after mechanically induced anterior tibial translation are modulated by fatiguing exercise (Wojtys et al. 1996; Melnyk und Gollhofer 2007; Behrens et al. 2013). Given that hamstring stretch reflexes are thought to contribute to the active stability of the knee joint (Friemert et al. 2010), their reduction might contribute to the pathomechanics of ACL injuries especially in females (Behrens et al. 2013). However, only the study published by Behrens et al. (2013) investigated the effect of fatiguing motor exercise on hamstring stretch reflexes and anterior tibial translation in standing subjects in a sufficient sample of young recreational active males and females. They only found a reduction in hamstring stretch reflex amplitudes and a concomitant increase in anterior tibial translation after repetitive jumps until exhaustion in females but not in males, which might be related to differences in muscle activation patterns during movements. Nevertheless, the used fatigue protocol, consisting of repetitive jumps until exhaustion, did not reflect the activity profile during sport games (e.g., a combination of sprinting and jumping is performed during basketball or handball games).

Therefore, hamstring stretch reflexes and anterior tibial translation were measured before and after repetitive jumping and sprinting until exhaustion in females and males. The protocol was performed until 50% of the maximal jump height was not achieved for three consecutive jumps or until the subjects reached an intolerable state of exhaustion or dyspnea. This protocol was previously used to investigate the effect of fatiguing motor exercise on knee joint kinetics and kinematics (Chappell et al. 2005; Tsai et al. 2009). It was conjectured that hamstring stretch reflexes decrease and anterior tibial translation increases after the fatiguing motor exercise in a sex-dependent manner.

Data analyses indicated that (i) stretch reflex onset latencies were delayed (see article) and (ii) the short-latency stretch reflex amplitudes were decreased in both females and males after the fatiguing motor exercise. Furthermore, (iii) anterior tibial translation increased in females and tended to increase in males (Figure 6).

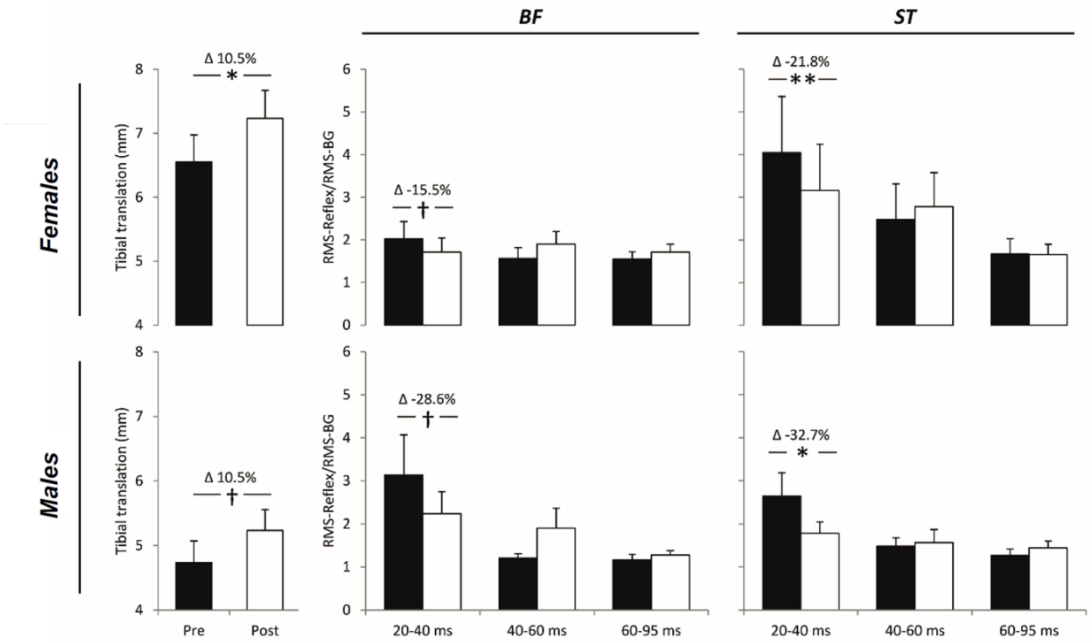

Figure 6. Effect of repetitive jumping and sprinting until exhaustion on tibial translation (**left**) and stretch reflex responses of the biceps femoris (BF, **middle**) and the semitendinosus/semimembranosus (ST, **right**). Data are displayed as means ± standard deviations. RMS-Reflex/RMS-BG: root mean square of the reflex components normalized to background muscle activity. *p ≤ 0.05; † p ≤ 0.10.

The findings of this study indicate that repetitive jumping and sprinting until exhaustion altered the latencies and amplitudes of the stretch reflexes in the hamstring muscles and anterior tibial translation in females and males. This might be due to increased firing rates of inhibitory group III/IV muscle afferents in response to the exercise-induced intramuscular metabolic perturbation, altered motoneuron properties, and/or a decrease in facilitatory afferent feedback over time (Taylor et al. 2016). Given that the hamstring muscles are crucial for maintaining knee stability and protecting the ACL during movements of the tibia relative to the femur (More et al. 1993; Friemert et al. 2010), the decreased latencies and stretch reflexes as well as the concomitant increase of anterior tibial translation might contribute to the pathomechanics of knee joint injuries in both females and males. These results are in contrast to those of Behrens et al. (2013), who have only found decreased hamstring stretch reflexes and an increased anterior tibial translation in females but not males after a different fatigue protocol consisting of repetitive jumps until exhaustion without intermittent sprinting as performed in the present study.

Consequently, it might be that the sex-specific changes in stretch reflexes and the mechanical stability of the knee depend on the kind and duration of the fatiguing motor exercise.

3.2.2. Central Factors Contribute to Knee Extensor Strength Loss after 2000-m Rowing in Elite Male and Female Rowers

The development of motor performance fatigue is task dependent and the relative contribution of neural (i.e., muscle activation) and muscular mechanisms (i.e., contractile function) to the performance decline differs depending on the tested muscle group, contraction mode, exercise intensity, and duration of the motor task (Enoka et al. 2011). This task dependency of motor performance fatigue has been extensively studied for single-joint exercise. For example, there is considerable evidence that the decline in MVC strength after low-force sustained voluntary contractions is mainly due to a decrease in muscle activation, whereas the strength loss after high-force contractions of short duration is rather due to a decrease in contractile function of muscles (Taylor und Gandevia 2008). Similarly, findings from studies investigating the neural and muscular mechanisms of motor performance fatigue during locomotor exercise (e.g., running and cycling) indicated a greater decline in contractile function of muscles after shorter, more intense compared to longer, less intense exercise (Lepers et al. 2001; Millet und Lepers 2004; Skof und Strojnik 2006; Thomas et al. 2016). This can be explained by the stronger metabolic disturbances within the muscle during high-intensity exercise (Jones et al. 2008; Thomas et al. 2016), which limit contractile force production of muscles. In contrast to that, a greater decline in muscle activation characteristics was typically found after low-intensity locomotor exercise of longer durations (Thomas et al. 2015; Thomas et al. 2016), which was attributed to increased firing rates of inhibitory group III/IV muscle afferents over time in response to the increasing intramuscular metabolic disturbances (Gandevia 2001). Nevertheless, the specific mechanisms of motor performance fatigue after fatiguing locomotor exercise are still discussed (Marcora 2008a). However, hardly anything is known about the impairments in muscle activation and contractile function after whole-body exercise such as rowing. During rowing, approximately 70% of the body's total muscle mass is involved, because of the synchronized activation of lower and upper body muscles during the rowing stroke (Steinacker 1993). In particular, the leg muscles are required for the propulsion of the rowing boat (Soper und Hume 2004), with a strong contribution of the quadriceps muscle to power production (Wilson et al. 1988; Guével et al. 2011).

Thus, this randomized, counterbalanced cross-over study investigated motor performance fatigue (i.e., decrease in MVC strength) and muscle activation changes (i.e., voluntary activation assessed with the interpolated twitch technique) during isometric and concentric MVCs of the knee extensors after a 2000-m rowing time trial and a passive control condition. Additionally, contractile function of muscles was assessed using electrical stimulation of the femoral nerve. Based on the findings presented above, it was hypothesized that the high-intensity and short-lasting 2000-m (6-7 min) rowing time trial would impair isometric and concentric MVC strength due to a large decrease in contractile function and a minor reduction in voluntary activation in competitive rowers.

The statistical analysis revealed that the 2000-m rowing time trial (i) induced motor performance fatigue indicated by the decline in isometric and concentric maximal voluntary torque, (ii) led to reductions in voluntary activation during isometric and concentric contractions representing a decrease in muscle activation, but (iii) has not significantly changed contractile function of the quadriceps muscle (Figure 7).

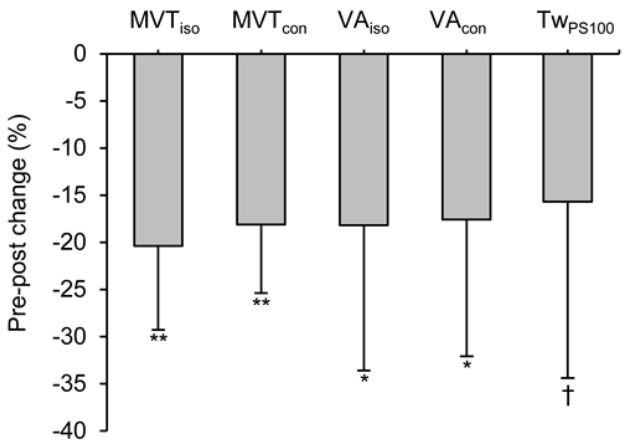

Figure 7. Effect of a 2000-m rowing time trial on percentage changes in maximal voluntary torque during maximal isometric and concentric contractions (MVT_{iso} and MVT_{con}), voluntary activation during maximal isometric and concentric contractions (VA_{iso} and VA_{con}), and contractile function of the quadriceps muscle (i.e., twitch torque induced by paired electrical stimuli at 100 Hz (Tw_{PS100})). **p ≤ 0.01, *p ≤ 0.05; † p ≤ 0.10.

The 2000-m rowing time trial induced considerable motor performance fatigue indicated by the large decline in maximal isometric and concentric MVC strength of the knee extensors. Interestingly, this decline in maximal motor performance after 6-7 min rowing was accompanied by a large decrease in voluntary activation, without a significant change in contractile function of the quadriceps muscle. This is in contrast to the results of previous studies, which have generally revealed that short-duration endurance exercise mainly impairs contractile function and not muscle activation characteristics (Thomas et al. 2015). The present findings might partly be a result of the great amount of active muscle mass involved in the rowing stroke, which might have increased the inhibitory feedback of metabosensitive group III/IV afferents to the central nervous system (i.e., at the spinal and supraspinal level). Consequently, the firing frequency and/or recruitment of α-motoneurons would have been impaired leading to a decrease in voluntary activation and voluntary force production (Rossman et al. 2014; Johnson et al. 2015; Sidhu et al. 2014) after the 2000-m rowing time trial in competitive rowers.

3.2.3. Mental Fatigue Increases Gait Variability During Dual-task Walking in Old Adults

Prolonged periods of demanding cognitive activity can result in cognitive performance fatigue (e.g., an increase in reaction times) and/or perceived cognitive fatigue (i.e., an increased perception of fatigue) (Boksem und Tops 2008; Behrens et al. 2023). Moreover, it was found that the execution of a sustained cognitive task did not only induce cognitive performance declines and/or an increase in the perception of fatigue (traditionally termed mental fatigue), but also impaired motor performance during subsequently conducted endurance-based and skill-based motor tasks (Marcora et al. 2009; Smith et al. 2016; Brown et al. 2020). Furthermore, it was hypothesized that performing a sustained cognitive task might also impair gait performance in older adults. This assumption was based on the results of studies that revealed relationships between poor cognitive functioning and a reduced gait performance in healthy older people (Grobe et al. 2017). The outcome of the study by Ben-Itzhak et al. (2008) point in the same direction. The authors have shown that the ingestion of methylphenidate increased cognitive performance and decreased gait variability (i.e., improved gait performance) in older adults underlining the link between cognitive functioning and successful walking.

Based on these findings, it might be that temporarily impairing cognitive functioning, due to a sustained cognitive activity intended to induce cognitive performance fatigue and perceived cognitive fatigue, results in a decrease in gait performance, especially during dual-task walking, which requires more cognitive resources (Leone et al. 2017). Given that aging is associated with structural and functional brain changes as well as impaired cognitive functioning (Harada et al. 2013; Murman 2015; Yogev-Seligmann et al. 2008), it might be that the effect of a sustained cognitive activity on gait measures is more pronounced in older compared to younger adults. However, there were no studies that have investigated the effect of a sustained cognitive activity on gait performance in young and old adults.

Therefore, this randomized, counterbalanced cross-over study assessed single- (walking) and dual-task walking performance (walking + serial subtractions by three) before and after a sustained cognitive activity intervention (90 min inhibition task) and a control intervention (watching a neutral video for 90 min) in young and old adults. It was hypothesized that the cognitive task induces cognitive performance fatigue and perceived cognitive fatigue as well as a decrease in gait performance, particularly during dual-task walking and in older adults.

Data analyses showed that the 90-min cognitive task induced (i) an increase in perceived cognitive fatigue (Figure 8) and (ii) a better cognitive task performance (see article) over time in both old and young adults, which might be related to a learning effect. Furthermore, (iii) the fatiguing cognitive exercise increased gait variability measures only in older adults during-dual task walking (Figure 9).

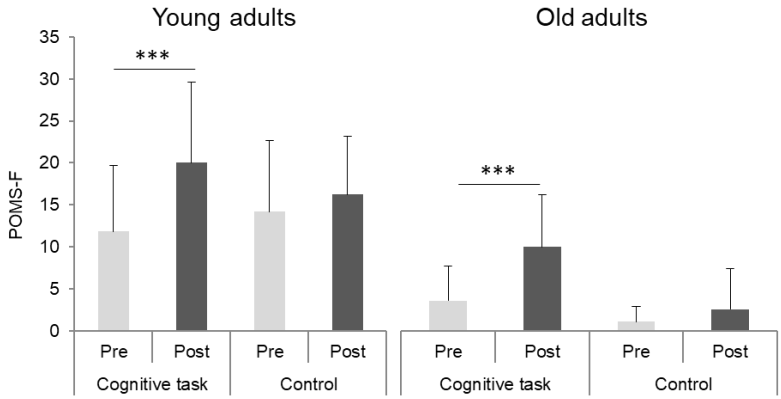

Figure 8. Perceived cognitive fatigue (Profile of Mood States-Fatigue, POMS-F) of the young and old participants before and after the sustained cognitive task (90 min inhibition task) and the control condition (watching a neutral video for 90 min). ***$p \leq 0.001$.

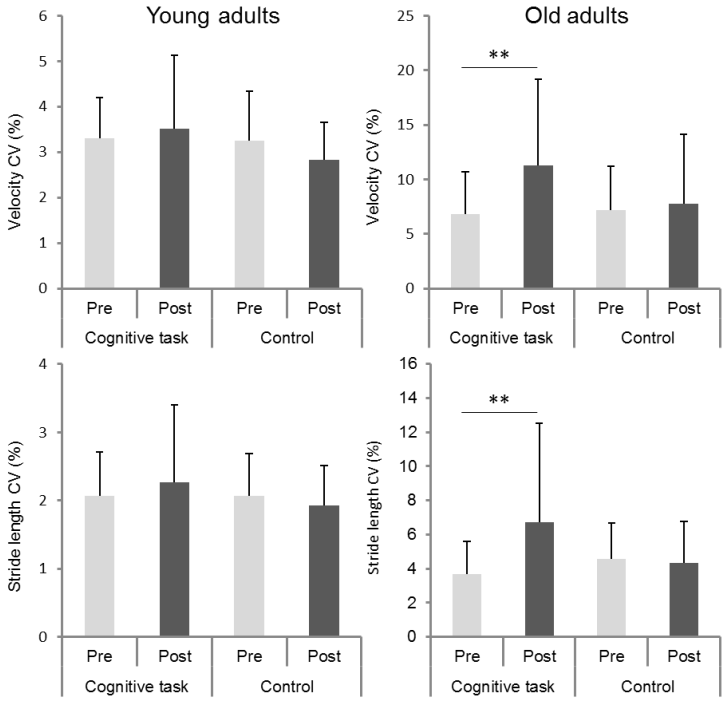

Figure 9. Coefficient of variation (CV) for the spatio-temporal dual-task gait parameters velocity (**top**) and stride length (**bottom**) recorded before and after the sustained cognitive task (90 min inhibition task) and the control condition (watching a neutral video for 90 min). **p ≤ 0.01.

Data of this study indicated that a sustained cognitive task performed for 90 min did not only increase perceived cognitive fatigue, but also gait variability during dual-task walking in older adults. This might be caused by the effect of aging on brain structure and function, which is also discussed as a contributor to an impaired dual-task gait performance in old compared to young people (Yogev-Seligmann et al. 2008). The utilization of these brain areas by performing a fatiguing cognitive task seems to increase gait variability during subsequent dual-task walking in the old age. This might be due to (i) a reduced processing capacity for the motor task (central capacity sharing model) and/or (ii) an impaired sequential neural processing of the motor and cognitive task during dual-task walking in old adults. Given that gait performance measures during dual-task walking, in particular the coefficient of variation, are predictors for falls in older people (Verghese et al. 2009; Muir-Hunter und Wittwer 2016), the susceptibility to the dual-task gait impairments after sustained cognitive activities might be regarded as a new intrinsic risk factor for falls in older people. Moreover, the potential influence of prolonged cognitive activity should be taken into account when dual-task gait analyses are performed in a clinical or scientific setting.

3.3. Studies Investigating Basic Mechanisms of Motor Performance Fatigue and Perceived Motor Fatigue via the Modulation of the Determining Factors

3.3.1. Neuromuscular Function and Fatigue Resistance of the Plantar Flexors Following Short-term Cycling Endurance Training

The findings of cross-sectional studies indicated that stretch reflex and H-reflex responses evoked at rest are higher in athletes performing long-term (several years) endurance training compared to those engaged in long-term power training (e.g., jumpers and sprinters) (Kyröläinen und Komi 1994a, 1994b; Maffiuletti et al. 2001). Furthermore, studies investigating the effect of short-term endurance training performed over several weeks have also shown increased stretch and H-reflexes in the soleus muscle (Pérot et al. 1991; Vila-Chã et al. 2012b). Therefore, it was hypothesized that endurance training can modulate the responsiveness of the α-motoneuron pool to the Ia afferent input and/or presynaptic inhibition of Ia afferents (Vila-Chã et al. 2012b). However, the studies on this topic had some limitations. For instance, Pérot et al. (1991) have not incorporated a control group in their study on the effects of short-term running endurance training on evoked reflex responses and the data were quite variable. In the same manner, Vila-Cha et al. (2012b) also had no “real” control group because they only investigated the effect of short-term cycling endurance training on H-reflexes and V-waves compared to strength training. In addition, and more relevant for the topic of this habilitation, previous studies have only examined the effect of short-term cycling endurance training on time to exhaustion during a defined submaximal contraction performed before and after the training period (Vila-Chã et al. 2012b, 2012a). However, this approach does not allow to capture the neural and muscular determinants of the improved time to exhaustion, which can be assessed with fatiguing motor exercise protocols of the same duration applied before and after the training combined with electrical stimulation of the posterior tibial nerve to elicit H-reflexes and V-waves in the soleus muscle.

Therefore, the effect of an 8-week cycling endurance training (two times per week) on MVC strength, electrically evoked potentials (i.e., H-reflex elicited at rest and during MVC, V-wave), and contractile properties of the soleus muscle was investigated in this randomized controlled trial. Of greater importance for this habilitation, the same fatiguing motor exercise protocol (i.e., load, repetitions, and range of motion), combined with peripheral nerve stimulation, was applied before and after the cycling endurance training. This approach was utilized to analyze the potential training-induced adaptations in neural and muscular function in response to the same fatiguing motor exercise. It was conjectured that the training intervention increases H-reflexes and the V-wave. Furthermore, it was expected that motor performance fatigue (i.e., decrease in MVC strength) as well as the neural (i.e., H-reflex elicited at rest and during MVC, V-wave) and muscular impairments in response to the same fatigue protocol are reduced after the training period.

The statistical analyses revealed that 8-weeks of cycling endurance training did not alter MVC strength, electrically evoked potentials, and contractile properties of the soleus muscle compared to the control group (see article). Moreover, motor performance fatigue as well as the neural and muscular impairments in response to the same fatigue protocol were not significantly different between the training and control group (Table 1).

Table 1. Comparison of percentage changes in motor performance fatigue (i.e. decrease in isometric voluntary torque), contractile function (i.e., peak twitch torques), and muscle activation indices (i.e., H-reflex and V-wave) in response to the same fatiguing motor exercise protocol performed before and after the training. Please note that analyses of covariance (ANCOVA) with baseline-adjustments were performed. Data are displayed as adjusted means ± adjusted standard deviations.

Parameter	Post			
	INT	CON	Diff. (95% CI)	*p*
Isometric maximum voluntary torque (%)	-4.4 ± 11.1	-10.4 ± 11.1	6.0 (-4.1 to 16.2)	0.229
Peak twitch torque (%)				
supramaximal single	-0.3 ± 10.8	-8.3 ± 10.8	8.0 (-1.7 to 17.7)	0.101
supramaximal doublet	-4.7 ± 12.7	-7.8 ± 12.7	3.1 (-8.4 to 14.5)	0.581
H-reflex intensity	-0.6 ± 15.1	-2.1 ± 15.1	1.5 (-12.4 to 15.5)	0.821
Evoked potentials (%)				
H_{max} *SOL*	10.2 ± 22.8	26.2 ± 22.8	-16.0 (-36.1 to 4.0)	0.110
M_{max} *SOL*	10.2 ± 15.8	3.5 ± 15.8	6.7 (-7.9 to 21.3)	0.346
H_{max}/M_{max} *SOL*	2.8 ± 23.9	24.0 ± 23.9	-21.2 (-43.3 to 0.9)	0.059
V-wave SOL	-23.4 ± 19.4	-34.7 ± 19.4	11.3 (-6.3 to 28.7)	0.195
M_{sup} *SOL*	-6.3 ± 11.7	-7.8 ± 11.7	1.5 (-8.9 to 12.0)	0.760
V/M_{sup} *SOL*	-18.8 ± 28.3	-26.6 ± 28.3	7.8 (-17.7 to 33.4)	0.527

INT: intervention group; CON: control group (CON); Diff. (95% CI): difference between means (95% confidence interval), H_{max}: maximal H-reflex, M_{max}: maximal M-wave, M_{sup}: maximal M-wave during maximal voluntary contraction, SOL: soleus.

In contrast to previous findings (Pérot et al. 1991; Vila-Chã et al. 2012b), this randomized controlled trial revealed that short-term cycling endurance training did not alter neural and muscular function of the soleus muscle. Surprisingly, the decline in motor performance as well as neural and muscular responses to a standardized fatiguing motor exercise protocol were also not significantly different between groups. These contradictory results are probably due to the fact that the other studies have not included a control group. In addition, the participants of these studies and the present experiment might have had a different adaptive responsiveness to the training stimulus. Given that running, but not cycling, involves the stretch-shortening cycle (Komi 2000), it seems likely that running endurance training rather than cycling endurance training induces the hypothesized increases in evoked reflex responses and an increase in motor performance fatigue resistance.

3.3.2. Impact of Blood Flow Restriction Exercise on Muscle Fatigue Development and Recovery

It has been shown that low-load resistance training with blood flow restriction (BFR) induces similar gains in muscle mass as high-load resistance training (Slysz et al. 2016; Lixandrão et al. 2018). BFR during exercise reduces arterial intramuscular oxygen delivery and blocks venous clearance of metabolites resulting in an increased metabolic stress (e.g., increased accumulation of inorganic phosphate, protons, and lactate). The increased metabolic perturbation is thought to trigger specific mechanisms that potentially promote muscle hypertrophy (e.g., increased hormone production, fast-twitch fiber recruitment, and cell swelling) (Takano et al. 2005; Manini und Clark 2009; Farup et al. 2015; Loenneke et al. 2012). Nevertheless, the higher metabolic disturbances induced by low-load resistance exercise combined with BFR also promote the development of motor performance fatigue. In this regard, Karabulut et al. (2010) were the first investigating the effect of low-load resistance exercise combined with BFR on muscle activation (i.e., voluntary activation assessed with the interpolated twitch technique) and contractile function of the knee extensors compared to work-matched low-load resistance exercise without BFR. They found a larger decrease in voluntary activation and contractile function after BFR exercise. However, the assessment of neuromuscular function only before and after exercise provides no information about the development and recovery of motor performance fatigue and its neural as well as muscular underpinnings in response to BFR exercise.

Therefore, this randomized, counterbalanced cross-over study investigated the development and recovery of motor performance fatigue (i.e., decrease in MVC strength) as well as of changes in muscle activation (i.e., voluntary activation assessed with the interpolated twitch technique) and contractile function of the quadriceps muscle after low-load resistance training with and without BFR (4 sets (30-15-15-15 repetitions) with 30% one repetition maximum). Additionally, effort and exercise-induced leg muscle pain perception during exercise were quantified. It was hypothesized that the development of motor performance fatigue is initially due to a decrease in contractile function of the knee extensors followed by an impaired voluntary activation. Moreover, it was conjectured that the recovery of neuromuscular function is delayed and that the perceptual responses are higher in the BFR condition compared to the control condition.

Data analyses indicated that (i) BFR accelerated motor performance fatigue development, (ii) the decrease in contractile function mainly contributed to the impaired motor performance with (iii) a delayed decrease in voluntary activation after all exercise sets (Figure 10). Interestingly, (iv) motor performance fatigue was substantially recovered at 2 min after BFR exercise mainly due to (v) a fast recovery of contractile function (Figure 10). Lastly, (vi) BFR exercise induced higher ratings of effort and exercise-induced leg muscle pain perception (Table 2).

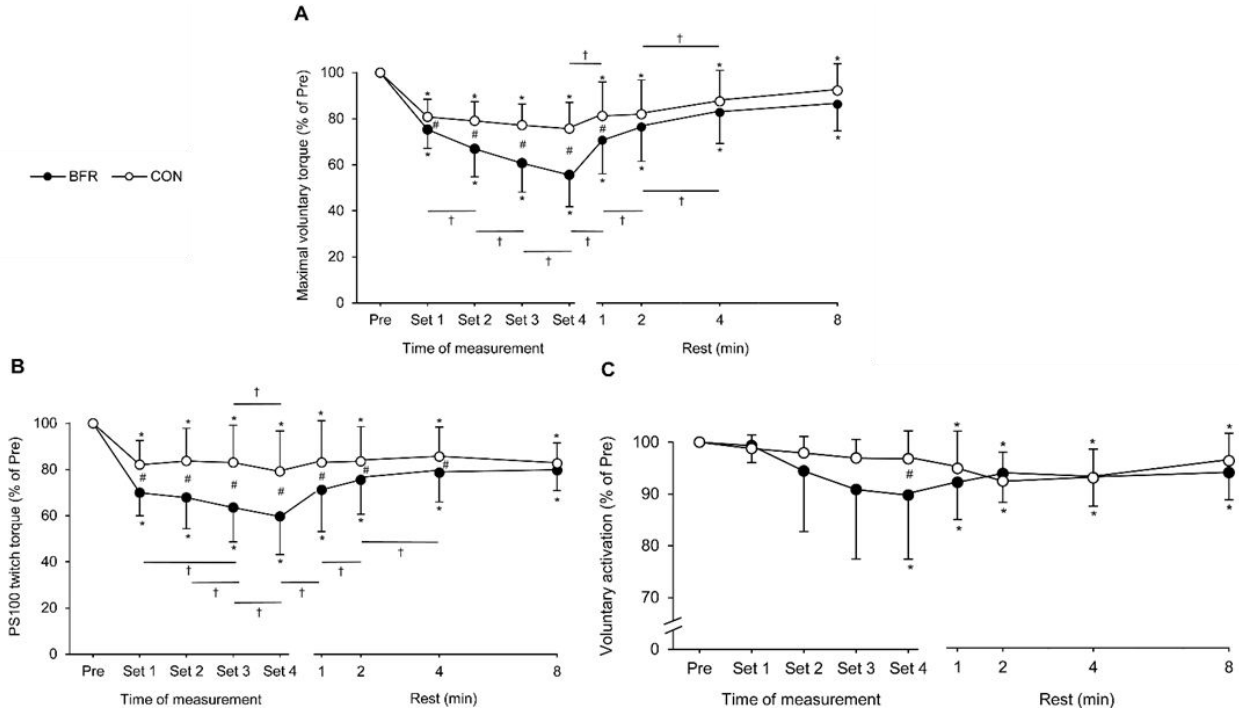

Figure 10. (**A**) Percentage changes from baseline values for maximal voluntary torque, (**B**) contractile function (i.e., PS100 twitch torque), and (**C**) voluntary activation of the quadriceps muscle. *p ≤ 0.050: significantly different from pre-values; †p ≤ 0.050: significantly different between time points; #p ≤ 0.050: significantly different between conditions. Values are expressed as means ± standard deviations. BFR: blood flow restriction condition; CON: control condition; PS100: paired stimuli at 100 Hz

Table 2. Effort and exercise-induced leg muscle pain perception during low-load resistance exercise with and without blood flow restriction (BFR). Data are means ± standard deviations.

Parameter	Condition	Set 1	Set 2	Set 3	Set 4
Effort perception					
	BFR	16 ± 2	16 ± 2*	18 ± 2*	18 ± 2*
	CON	15 ± 2	14 ± 2	15 ± 2	15 ± 2
Leg muscle pain perception					
	BFR	6 ± 2	6 ± 2*	7 ± 2*	8 ± 2*
	CON	5 ± 2	4 ± 2	5 ± 2	5 ± 2

CON: control condition without BFR. *p < 0.050: significantly different between conditions.

Low-load resistance exercise with BFR induced a higher motor performance fatigue in the knee extensors compared to the free blood flow condition, which is in line with previous findings (Karabulut et al. 2010). Interestingly, the initial and subsequent performance decline was mainly due to an impaired contractile function, which can be attributed to a reduced Ca^{2+} release from the sarcoplasmic reticulum, myofibrillar Ca^{2+} sensitivity, and force-generating capacity of the cross-bridges per se (Allen et al. 2008; Cheng et al. 2018). However, a reduced voluntary activation was also observed after 4 sets of BFR exercise suggesting that the increased metabolite accumulation enhanced the inhibitory feedback from group III/IV afferents to spinal and cortical motoneurons (Taylor et al. 2016). Interestingly, the higher motor performance fatigue in the BFR condition recovered quickly within 2 min after exercise due to a fast restitution of contractile function of the quadriceps muscle. These data indicate that low-load resistance exercise of the knee extensors combined with BFR provides a strong adaptive stimulus for muscle hypertrophy without long-lasting impairments in maximal motor performance, which is often present after high-load resistance training.

Consequently, low-load resistance exercise combined with BFR can be used during periods of high-frequency training for muscle hypertrophy. However, the higher effort and exercise-induced leg muscle pain perception during BFR exercise might compromise training compliance, especially in deconditioned people who cannot tolerate high levels of effort and exercise-induced pain/discomfort. Unfortunately, perceived motor fatigue was not queried during this experiment and therefore no statement can be made whether the higher perceptual responses during BFR exercise resulted in an increased perception of fatigue.

3.3.3. Dietary Nitrate Supplementation Improves Exercise Tolerance by Reducing Muscle Fatigue and Perceptual Responses

It has been found that dietary nitrate supplementation (e.g., in the form of beetroot juice) increases exercise tolerance during low- and high-intensity exercise (Bailey et al. 2009; Lansley et al. 2011; Thompson et al. 2014). This ergogenic effect is attributed to the increased bioavailability of the biological messenger nitric oxide (NO) after dietary nitrate ingestion (Lundberg und Govoni 2004), which is involved in the functional regulation of several physiological processes. These include but are not limited to mitochondrial respiration, vasodilatation, angiogenesis, and contractile function (Brown 1995; Ignarro 1989; Papapetropoulos et al. 1997; Kobzik et al. 1994). For instance, there is evidence that the ergogenic effect of dietary nitrate is related to a lower oxygen consumption during submaximal exercise resulting in a higher movement efficiency (Bailey et al. 2009; Larsen et al. 2007). This might be due to a more efficient mitochondrial adenosine triphosphate (ATP) synthesis (Larsen et al. 2011) and/or a better utilization of ATP during exercise (Bailey et al. 2010). Moreover, dietary nitrate has been shown to improve vascular control during exercise in rats resulting in an elevated oxygen delivery (Ferguson et al. 2013). Given that the integrity of these processes also determine contractile function of muscles during fatiguing motor exercise (Allen et al. 2008; Cheng et al. 2018), it was conceivable that dietary nitrate ingestion can modulate motor performance fatigue as well as its determinants during submaximal motor exercise. However, the impact of dietary nitrate supplementation on motor performance fatigue and its neural and muscular determinants was never investigated before.

Therefore, the effect of 5-days dietary nitrate or placebo supplementation on time to exhaustion during submaximal dynamic endurance exercise of the knee extensors was investigated using a randomized, counterbalanced, double-blind cross-over design. The participants, who improved their time to exhaustion after dietary nitrate supplementation, performed a time-matched motor exercise trial with the same duration achieved during the placebo condition. In addition, motor performance fatigue (i.e., decrease in MVC strength) as well as muscle activation (i.e., voluntary activation assessed with the interpolated twitch technique) and contractile function of the quadriceps muscle were quantified in each condition. During exercise, muscle activity, muscle oxygen saturation, and perceptual responses to exercise (i.e., effort and exercise-induced leg muscle pain perception) were recorded. It was hypothesized that motor performance fatigue is attenuated after dietary nitrate supplementation due to a lower reduction in contractile function of muscles after fatiguing motor exercise.

The statistical analyses revealed that dietary nitrate supplementation (i) increased time to exhaustion during dynamic submaximal knee extension exercise. Furthermore, the time-matched comparisons indicated that (ii) dietary nitrate reduced the extent of motor performance fatigue due to (iii) a better contractile function, while voluntary activation was not different between conditions (Figure 11A).

This was accompanied by (iv) a higher muscle oxygen saturation (Figure 11B) as well as (v) a lower effort and exercise-induced leg muscle pain perception during exercise in the dietary nitrate condition (Table 3).

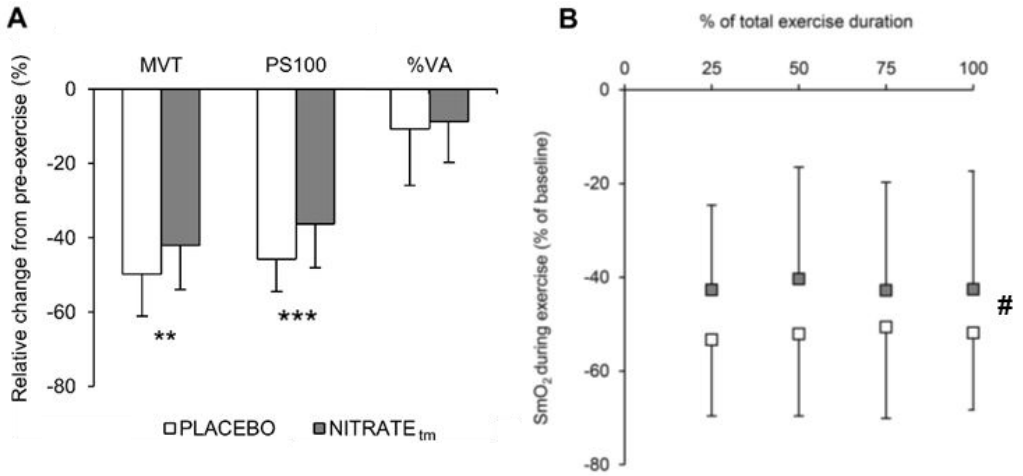

Figure 11. (**A**) Effect of dietary nitrate and placebo supplementation on percentage changes for maximal voluntary torque (MVT), contractile function (i.e., PS100 twitch torque), and voluntary activation (%VA) of the quadriceps muscle after fatiguing motor exercise. (**B**) Muscle oxygen saturation (SmO_2) during exercise. Please note that the data show the time-matched (tm) comparisons. Values are presented as means ± standard deviations. **$p \leq 0.010$, ***$p \leq 0.001$: significantly different between conditions; #$p \leq 0.050$: significant main effect for condition. PS100: paired stimuli at 100 Hz

Table 3. The means for effort and exercise-induced leg muscle pain perception represent the averages of all ratings during the fatiguing motor exercise trials. End-exercise values for both perceptual responses refer to the last ratings. Data are presented as means ± standard deviations.

Parameter	Condition	Mean	End-exercise
Effort perception			
	NITRATE$_{tm}$	16 ± 3*	18 ± 3*
	PLACEBO	17 ± 2	19 ± 2
Leg muscle pain perception			
	NITRATE$_{tm}$	4 ± 2*	5 ± 3
	PLACEBO	5 ± 3	6 ± 3

NITRATE$_{tm}$: time-matched dietary nitrate condition. *$p < 0.050$: significantly different between conditions.

Exercise tolerance was increased after dietary nitrate supplementation, which is in line with the findings of previous studies (Bailey et al. 2009; Lansley et al. 2011; Thompson et al. 2014). The lower performance and contractile function decline in the time-matched conditions indicate that dietary nitrate supplementation primarily modulated physiological processes at the muscle level. This is supported by the finding that muscle oxygen saturation during exercise was higher in the dietary nitrate condition indicating an improved vasodilatory vascular function, which could have resulted in a higher blood flow and a better oxygen supply (Ferguson et al. 2013). Moreover, it has been speculated that dietary nitrate is capable of reducing the ATP cost of muscle force production (Bailey et al. 2010). This assumption is supported by the finding of an improved intracellular Ca^{2+} handling and force production in response to low-frequency electrical stimulation after dietary nitrate supplementation (Hernández et al. 2012). These mechanisms might have collectively led to a lower metabolic disturbance during fatiguing motor exercise. Consequently, a reduced accumulation of inorganic phosphate, which is assumed to be a primary contributor to exercise-induced impairments in Ca^{2+} handling and Ca^{2+} sensitivity, might have preserved muscular force production. Interestingly, dietary nitrate supplementation also decreased effort and exercise-induced leg muscle pain perception during fatiguing motor exercise.

This is of particular importance, given that effort perception is considered as a key-determinant of endurance performance (Marcora und Staiano 2010) and was associated with perceived motor fatigue emerging during fatiguing motor exercise (Greenhouse-Tucknott et al. 2020). Additionally, muscle pain perception is also considered as a crucial determinant of endurance performance, which is underlined by the finding that an artificial increase in muscle pain perception during exercise reduced endurance performance (Mauger 2013; Astokorki und Mauger 2017). Therefore, dietary nitrate supplementation might be a suitable strategy to reduce exercise-related sensations, which are thought to contribute to the performance decline during fatiguing motor exercise (Behrens et al. 2023; Venhorst et al. 2018a). This might be a valuable strategy for deconditioned people with a low tolerance to higher levels of effort and exercise-induced pain/discomfort. Unfortunately, perceived motor fatigue was not queried in this study. Consequently, no conclusion can be drawn whether the lower perceptual responses during exercise after dietary nitrate supplementation resulted in a decreased perception of fatigue.

3.3.4. Ischemic Preconditioning Did Not Affect Central and Peripheral Factors of Performance Fatigability after Submaximal Isometric Exercise

Ischemic preconditioning (IPC) has been shown to increase human performance if applied to the exercising limb prior to fatiguing motor exercise (Incognito et al. 2016) and is characterized by repeated, short-term periods of vascular occlusion with subsequent reperfusion. Several studies have found improvements in endurance exercise performance including running, cycling, swimming, and sustained submaximal isometric contractions after the application of IPC (Bailey et al. 2012; Groot et al. 2010; Ferreira et al. 2016; Tanaka et al. 2016). The physiological underpinnings of the IPC-induced performance enhancements are still elusive, but it is thought that an improved metabolic efficiency and/or blood flow in the exercising muscles as well as neural adjustments might be involved (Incognito et al. 2016; Cruz et al. 2015). The (neuro)physiological changes after IPC are assumed to delay motor performance fatigue development and to enhance endurance-based task performance (Cruz et al. 2017; Tanaka et al. 2016). It was recently observed that time to exhaustion during a submaximal voluntary isometric contraction of the knee extensors (i.e., 20% MVC strength) increased after IPC. Moreover, an accelerated muscle deoxygenation response during exercise was observed, which was interpreted as an improved metabolic efficiency (Tanaka et al. 2016). However, this study did not thoroughly investigate the neural and muscular underpinnings of the endurance performance enhancement after IPC.

Therefore, the effect of IPC- and SHAM-application on time to exhaustion during isometric endurance exercise of the knee extensors at 20% maximal voluntary torque was investigated using a randomized, counterbalanced, single-blind cross-over design. The participants, who improved their time to exhaustion after IPC, performed a time-matched motor exercise trial (IPC_{tm}) with the same duration achieved during the SHAM condition. Motor performance fatigue (i.e., decrease in MVC strength) as well as muscle activation (i.e., voluntary activation assessed with the interpolated twitch technique) and contractile function of the quadriceps muscle were quantified in each condition. During exercise, muscle activity, muscle oxygen saturation, and perceptual responses to exercise (i.e., effort and exercise-induced leg muscle pain perception) were recorded. It was hypothesized that motor performance fatigue is attenuated after IPC and that this would be associated with adjustments in the neuromuscular system.

Data analyses revealed that IPC had no effect on time to exhaustion and motor performance fatigue as well as its neural and muscular underpinnings. Additionally, muscle activity, muscle oxygen saturation, and perceptual responses during exercise were not different between IPC and SHAM. Nevertheless, six participants improved their performance by > 10% after IPC compared to SHAM (Figure 12A). The time-matched comparisons (IPC_{tm} vs. SHAM) revealed that motor performance fatigue, its determinants (Figure 12C), and muscle oxygen saturation were not modulated by IPC (see article). However, effort perception during exercise seemed to be lower in the 'responders'. The longer time to exhaustion after IPC application in the 'responders' was also accompanied by a lower effort perception (Figure 13) and a larger motor performance fatigue as well as a more pronounced reduction in voluntary activation and contractile function (Figure 12B).

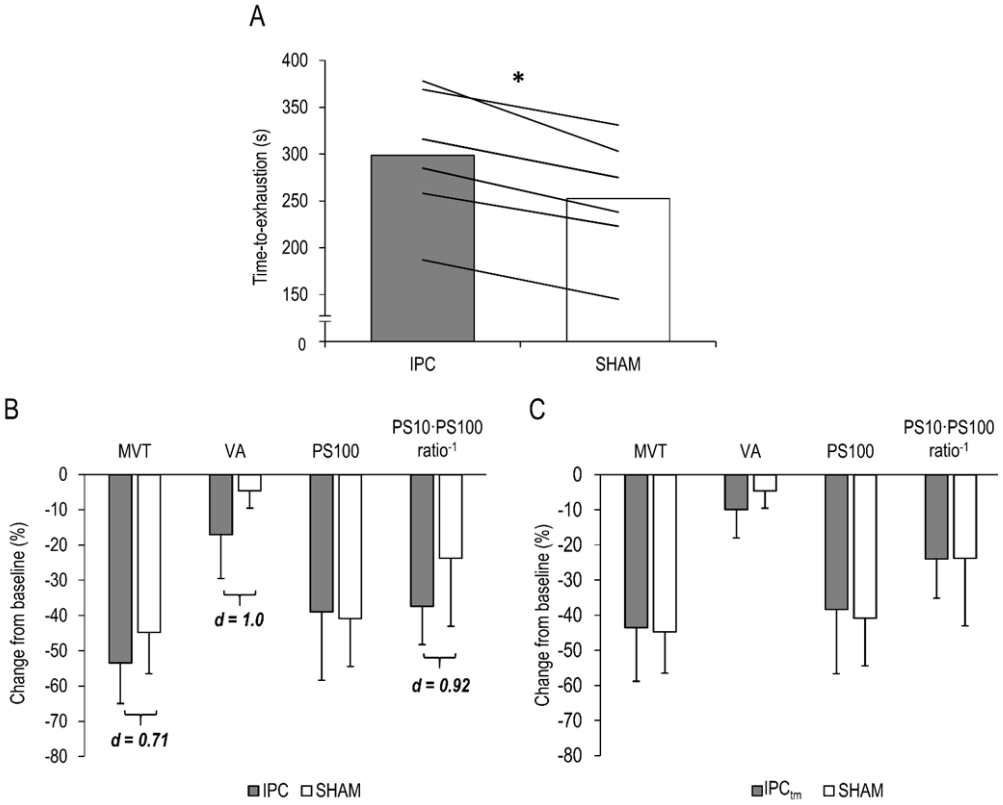

Figure 12. (**A**) 'Responders' mean values and individual data for the time to exhaustion tests for the ischemic preconditioning (IPC) and SHAM condition. (**B**) IPC vs. SHAM: Percentage change from pre-exercise values of the 'responders' for maximal voluntary torque (MVT), voluntary activation (VA), contractile function (i.e., twitch torque in response to paired electrical stimuli (PS100) and $PS10{\cdot}PS100^{-1}$ ratio. (**C**) Time-matched IPC trial (IPC_{tm}) vs. SHAM: Percentage change from baseline of the 'responders' for MVT, VA, PS100, and $PS10{\cdot}PS100^{-1}$ ratio. Values are presented as means ± standard deviations. d: effect size Cohen's d

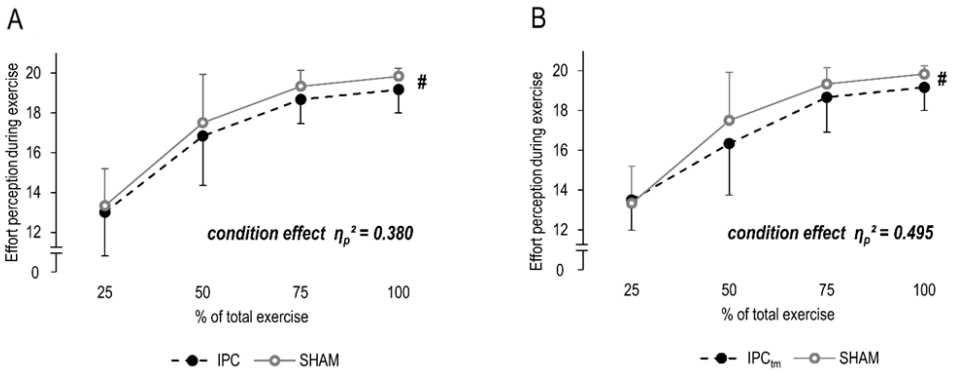

Figure 13. (**A**) IPC vs. SHAM: Effort perception during exercise of the 'responders' for the IPC and SHAM condition. (**B**) Time-matched IPC trial (IPC_{tm}) vs. SHAM: Effort perception during exercise of the 'responders' for the IPC_{tm} and SHAM condition. Values are presented as means ± standard deviations. #: large effect size for the main effect condition. η_p^2: effect size partial eta squared

IPC had no effect on exercise tolerance during submaximal isometric exercise, which is in contrast to the previously observed ergogenic effect of the same intervention on the same performance measure (Tanaka et al. 2016). Moreover, motor performance fatigue, its neural and muscular determinants, muscle activity, muscle oxygen saturation, and perceptual responses during exercise did not differ between the IPC and SHAM condition. However, IPC induced an endurance performance enhancement in a few subjects. The time-matched comparisons (IPC_{tm} vs. SHAM) revealed that motor performance fatigue, its neural and muscular determinants as well as muscle oxygen saturation were also not modulated by IPC in the 'responders'. This is in contrast to the assumption that IPC improves metabolic efficiency and/or blood flow in the active skeletal muscles during exercise (Incognito et al. 2016; Tanaka et al. 2016). Nevertheless, the longer time to exhaustion of the 'responders' after IPC was accompanied by a larger extent of motor performance fatigue (i.e., larger decrease in maximal voluntary torque) as well as a higher drop in voluntary activation and low-frequency twitch torque (i.e., an index of contractile function in response to submaximal electrical stimulation). Furthermore, data indicate that effort perception was lower during both IPC and IPC_{tm} compared to SHAM indicating a repeatable impact of IPC on effort perception during submaximal isometric exercise. Effort perception is considered as a key-determinant of endurance performance and is thought to be involved in processes related to self-regulation, exercise behavior, and task disengagement (Marcora 2008b; Marcora und Staiano 2010; Venhorst et al. 2018a; Behrens et al. 2021; Behrens et al. 2023). Hence, the IPC-induced lower effort perception might have enabled the subjects to perform the submaximal isometric task for a longer time and to tolerate larger motor performance fatigue as well as impairments in voluntary activation and contractile function. Regrettably, perceived motor fatigue was not queried in this study. Therefore, it is not known whether the lower effort perception during exercise in the 'responders' after IPC affected the perception of fatigue.

4. GENERAL DISCUSSION

4.1. Summary of Study Results

Three of the seven experimental studies were directed to investigate basic mechanisms of motor performance fatigue and/or the underlying neuromuscular and perceptual mechanisms in response to motor and cognitive tasks. The first study has shown that the changes in anterior tibial translation and hamstring stretch reflexes were similar in females and males after fatiguing motor exercise indicating that sex-differences in these measures might depend on the fatiguing motor task. Contrary to the expectation, the second study revealed that a 2000-m rowing time trial induced considerable motor performance fatigue via decrements in muscle activation, with minor impairments in contractile function, which might be attributed to the increased inhibitory feedback of metabo- and mechanosensitive muscle afferents. Study three revealed that a sustained cognitive task performed for 90 min did not only increase perceived cognitive fatigue, but also gait variability during dual-task walking in older adults, which might be regarded as a new intrinsic risk factor for falls in older people.

Four of the seven experimental studies were designed to investigate basic mechanisms of motor performance fatigue and perceived motor fatigue via the potential modulation of their determining factors. While cycling endurance training surprisingly did not modulate motor performance fatigue and its underlying neural and muscular changes, BFR exercise accelerated motor performance fatigue development mainly due to a decrease in contractile function, with a quick recovery of these impairments after exercise. Moreover, BFR increased the perceptual responses to exercise, which might compromise compliance to BFR training in some populations. Study six and seven investigated the effects of dietary nitrate supplementation and IPC application, respectively, on measures of motor performance fatigue and perceptual responses to exercise. Dietary nitrate supplementation increased exercise tolerance and the time-matched comparisons indicated that it lowered the extent of motor performance fatigue mainly due to a preservation of contractile function. This was probably related to the higher muscle oxygen saturation during exercise resulting in a lower accumulation of metabolites. Moreover, dietary nitrate supplementation lowered effort and leg muscle pain perception during exercise. In contrast, IPC had no effect on performance measures, its neuromuscular underpinnings, and the perceptual responses to exercise. However, data of the ‘responders’, who improved exercise tolerance after IPC, indicated that a lower effort perception after IPC might have enabled the subjects to perform the submaximal isometric task for a longer time.

The findings of these studies underline the notion that the effect of sustained activities on motor performance fatigue and the underlying mechanisms is task specific and depends on the involved muscle mass (Enoka et al. 2011; Enoka und Duchateau 2008; Rossman et al. 2014). Moreover, sustained cognitive activities can impair submaximal motor performance in an age-dependent manner, which is a new finding with potential high relevance for falls in older adults. Furthermore, the modulation of contractile function by the application of BFR and dietary nitrate has been shown to have large effects on the extent of motor performance fatigue as well as effort and exercise-induced leg muscle pain perception. The latter are thought to contribute to perceived motor fatigue (Greenhouse-Tucknott et al. 2020; Venhorst et al. 2018a; Behrens et al. 2023) and are considered as key-determinants of exercise tolerance (Marcora und Staiano 2010; Mauger 2013; Behrens et al. 2021; Behrens et al. 2023).

The findings for the 'responders' in the IPC study underline this notion, given that the increased time to exhaustion of the knee extensors was accompanied by a lower effort perception, which might has mediated the higher tolerance against motor performance fatigue.

When looking at these seven studies, it becomes apparent that they have only investigated selected aspects of state fatigue induced by motor or cognitive tasks. Nevertheless, a considerable methodological improvement is observable, when looking at the experimental studies belonging to this habilitation over time. Especially the last three studies dealing with the effect of BFR, dietary nitrate, and IPC on the outcome measures, provide good examples for investigating the interactions between determinants of motor performance and perceived motor fatigue. However, important aspects that might contribute to activity-induced state fatigue were not investigated. This applies in particular to perceived motor fatigue, which was not quantified during the experiments. Therefore, future studies should incorporate further measures to decipher the interactions between performance fatigue and perceived fatigue in response to motor and cognitive tasks.

4.2. Deciphering the Interactions between Motor Performance Fatigue and Perceived Motor Fatigue

There is extensive data on the contribution of changes in muscle activation and contractile function to the decline in motor performance, although not all mechanisms are fully understood (Taylor et al. 2016; Taylor und Gandevia 2008; Allen et al. 2008; Cheng et al. 2018). However, the mechanistic underpinnings of perceived motor fatigue and their interactions with motor performance fatigue is still insufficiently investigated. Consequently, not only the neuromuscular mechanisms of motor performance fatigue should be investigated, but also the diverse potential determinants of perceived motor fatigue as well as their (neuro)physiological correlates. The combination of this measures will help to decipher the motor task-induced performance and perceptual differences between individuals and exercise protocols (e.g., some people perceive exercise-induced muscle pain, whereas others experience breathing discomfort during the same motor task). This is of particular importance for clinical populations, which exhibit a high motor performance fatigue and perceived motor fatigue (e.g., multiple sclerosis, chronic obstructive pulmonary disease, and rheumatoid arthritis) (Kluger et al. 2013; Braley und Chervin 2010; Gruet 2018; Marrelli et al. 2018; Behrens et al. 2021).

Thereby, future studies should take the adapted three-dimensional dynamical system framework of perceived motor fatigue first proposed by Venhorst et al. (2018a) into account (Figure 14) to decipher the psychophysiological determinants of perceived motor fatigue (Behrens et al. 2023).

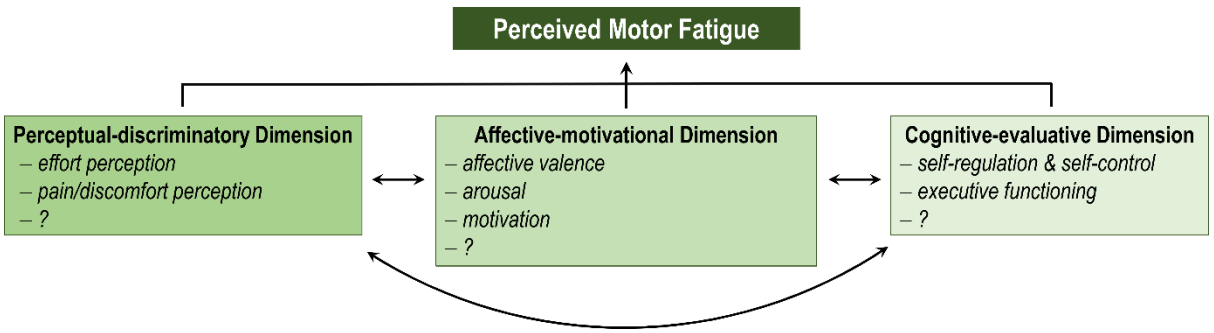

Figure 14. Adapted three-dimensional dynamical system framework of perceived motor fatigue (Behrens et al. 2023) first proposed by Venhorst et al. (2018a). The bidirectional arrows indicate the interdependency between the dimensions. ?: unknown factors that should be added in the future

In this framework, the perceptual responses to exercise (e.g., effort perception, exercise-induced muscle pain/discomfort perception) can be ascribed to the perceptual-discriminatory dimension. These perceptual responses increase during exercise and have a negative impact on the affective-motivational dimension (e.g., affective valence, arousal, and motivation). The perceptual and affective responses during motor tasks strongly influence the cognitive-evaluative dimension, in which the decision is made to slow down or speed up (pacing behavior) or even to terminate the motor exercise. These processes involve self-regulation, self-control, and executive functioning (Venhorst et al. 2018a; Hyland-Monks et al. 2018; Behrens et al. 2021; Behrens et al. 2023). Of note the interactions between these dimensions should not be regarded as hierarchical but interdependent.

There are already a few well-designed studies that have used such a combined approach (Greenhouse-Tucknott et al. 2020; Chatain et al. 2019). They measured motor performance fatigue as well as changes in muscle activation and contractile function together with perceived motor fatigue, effort perception, and affective valence to investigate their interactions. Greenhouse-Tucknott et al. (2020), for instance, investigated the effect of prior hand grip exercise on time to exhaustion and the perceptual and affective responses during a submaximal isometric contraction of the knee extensors. The authors revealed that prior submaximal hand grip exercise decreased time to exhaustion during the submaximal contraction of the quadriceps muscle but did not change neuromuscular function. In contrast, perceived motor fatigue and effort perception ratings were higher, while affective valence was lower, in the ‘prior exercise condition’ compared with the control condition. Interestingly, effort perception and affective valence were associated with time to exhaustion and perceived motor fatigue. These data indicate that hand grip exercise reduced subsequent knee extensor endurance performance mainly by the interactions between perceived motor fatigue, effort perception, as well as affective valence, and not changes in muscle activation and contractile function. Future studies should use similar approaches to decipher the interactions between motor performance fatigue and perceived motor fatigue in different populations and especially in those suffering from diseases.

Furthermore, the determining factors of motor performance fatigue and perceived motor fatigue can be manipulated to decipher their causal involvement in the development of state fatigue in different populations and during as well as after various motor tasks. This can be achieved by using interventions intended to modify the physiological and psychological mechanisms during fatiguing motor exercise. For instance, modulating cortical excitability with transcranial direct current stimulation can assist to examine how changed neural properties influence motor performance fatigue and perceived motor fatigue (Angius et al. 2019). Moreover, interventions, such as caffeine or dietary nitrate ingestion or IPC can be used to alter neural as well as muscular properties, which can modulate motor performance fatigue and perceived motor fatigue (Marcora et al. 2009; Husmann et al. 2019; Behrens et al. 2020; Backhouse et al. 2011). Psychological interventions intended to manipulate the psychological determinants of exercise tolerance have also been shown to alter motor performance and the perceptual responses to fatiguing motor exercise (McCormick et al. 2015). Therefore, these strategies might help to unravel the role of cognitive processes in the interpretation of perceptual responses, which contribute to a decreased affective valence during fatiguing motor exercise.

4.3. Deciphering the Interactions between Motor Performance Fatigue, Perceived Motor Fatigue, Cognitive Performance Fatigue, and Perceived Cognitive Fatigue

As shown above, a study, belonging to this habilitation, has revealed that a 90-min cognitive task increased perceived cognitive fatigue and impaired motor performance during dual-task walking in older adults. Similarly to that, performing a sustained cognitive task for 90 min has been found to impair endurance performance during constant-load cycling at 80% peak power (Marcora et al. 2009). Interestingly, the recorded physiological variables were not different compared to the control intervention (watching a documentary), but effort perception during exercise was higher. The authors concluded that the maximal tolerable effort level was reached earlier and the subjects subsequently terminated the exercise. Studies investigating the psychophysiological adjustments and performance changes in response to sustained motor-cognitive dual-tasks have also provided insight into the interactions between the different dimensions of activity-induced state fatigue (Yoon et al. 2009; Chatain et al. 2019; Mehta und Agnew 2012). The authors of these articles have observed that time to exhaustion during submaximal motor tasks was decreased, when a concurrent cognitive task had to be performed (e.g., arithmetic task and N-back task). In this regard, time to exhaustion during a fatiguing motor-cognitive dual-task was shorter when performing a high compared to the low cognitive load task. Interestingly, a higher reduction in muscle activation of the knee extensors (i.e., voluntary activation assessed with the interpolated twitch technique), an increased heart rate as well as a larger pupil diameter were observed in the dual-task conditions compared to the single motor task. Although cognitive effort perception scaled with the cognitive load level, effort perception during the motor task was enhanced in the high cognitive load condition compared to the single motor task condition (Chatain et al. 2019). These data impressively indicate that the different state fatigue domains interact with each other.

Given that the execution of fatiguing motor and cognitive tasks activate similar brain areas (e.g., prefrontal cortex, anterior cingulate cortex) (Schmidt et al. 2012; Müller und Apps 2019), it was supposed that these represent the mechanistic basis for these effects (Chatain et al. 2019; Aitken und MacMahon 2019). Consequently, the detrimental effects on performance and perceptions might be mediated by the degree of overlap between cognitive processes required for the respective cognitive and motor task (Müller und Apps 2019; Evans et al. 2016; Aitken und MacMahon 2019). Therefore, the influence of different types (e.g., inhibitory control, working memory, or cognitive flexibility task) and loads of cognitive tasks performed prior to or during motor exercise on performance fatigue and perceived fatigue measures should be investigated by future studies. Thereby, attention should be paid when measuring some perceptual responses to motor and cognitive tasks. This concerns in particular the quantification of perceived fatigue in response to motor, cognitive, or motor-cognitive dual-tasks, given that findings of studies indicate that perceived motor fatigue and perceived cognitive fatigue represent different perceptual domains (Völker et al. 2016; Dailey et al. 2015). The same is true for effort perception that should be inquired separately for the motor and the cognitive task (Chatain et al. 2019).

5. CONCLUSION

Data of the experimental studies belonging to this habilitation underline the notion that performance fatigue and perceived fatigue in response to motor and cognitive activity as well as their determinants are interdependent. Therefore, the different aspects of these state fatigue dimensions (Figure 1) should be considered in combination to decipher the psychophysiology underlying performance during sustained motor and cognitive tasks. Consequently, there is no single factor primarily determining activity-induced performance fatigue and perceived fatigue, but the relative weight of each determinant and their interaction depends on several modulating factors (e.g., age, sex, diseases, and characteristics of the task). Hence, a combined measurement of performance fatigue and perceived fatigue together with its (neuro)physiological correlates is necessary to decipher the psychophysiology of motor and cognitive task-induced state fatigue. This knowledge will assist to better understand the interactions between the different dimensions of state fatigue and their effect on human performance in health and disease. This is crucial to design and plan effective interventions for increasing exercise tolerance, which is of particular importance for vulnerable, deconditioned, and clinical populations.

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7. APPENDIX

1. **Behrens, M.**, Mau-Moeller, A., Wassermann, F., Plewka, A., Bader, R., Bruhn, S. (2015). Repetitive jumping and sprinting until exhaustion alters hamstring reflex responses and tibial translation in males and females. *Journal of Orthopaedic Research, 33* (11), 1687-1692, DOI: 10.1002/jor.22935. [IF_{2021}: 3.102]

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Repetitive Jumping and Sprinting Until Exhaustion Alters Hamstring Reflex Responses and Tibial Translation in Males and Females

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ABSTRACT: The incidence of anterior cruciate ligament injuries is considerably higher in females than in males and the underlying mechanisms are still under debate. Research indicates that the neuromuscular system of females and males might respond differently to the same fatigue protocol due to differences in muscle activation during movement tasks. This study analyzed sex differences in hamstring reflex responses and posterior-anterior tibial translation (TT) before and after fatiguing exercise. We measured the isolated movement of the tibia relative to the femur as a consequence of mechanically induced TT in standing subjects as well as muscle activity of the hamstrings before and after repetitive jumping and sprinting until exhaustion. Muscle fatigue delayed reflex onset latencies in females and males. A reduction in reflex responses associated with an increased TT was observed after fatiguing exercise for both sexes. Data indicate that the used fatigue protocol altered the latency and magnitude of reflex responses as well as TT in females and males. Based on the results of previous research and the outcome of this study, it might be that sex-specific effects of fatigue on reflex activity and mechanical stability of the knee depend on the kind of fatiguing exercise. © 2015 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 33:1687–1692, 2015.

Keywords: knee stability; ACL injury risk; stretch reflex; fatigue

Rupture of the anterior cruciate ligament (ACL) ranks among the most common injuries during physical and sporting activities.[15] These injuries are associated with long recovery times and high socio-economic costs. The incidence of ACL injuries is considerably higher in females than in males and the underlying mechanisms are still under debate.[14] It has been argued that differences in the passive and active stability of the tibiofemoral joint can account for the higher injury rate in females. The laxity of the ligaments and geometry of the articular surfaces constitute the passive stability of the knee joint, while active stability relies primarily on the patellar tendon-tibia shaft angle, muscle activity pattern, muscle reaction time, time to peak torque, and muscle stiffness.[16]

It has been argued that muscle fatigue can be a risk factor for ACL injuries.[14,16] There is evidence that muscle fatigue is associated with decreased joint proprioception and postural stability as well as increased joint laxity.[11,25,30] Furthermore, the control of lower extremity mechanics during landing, side-step cutting, and running is altered due to fatigue.[6,10,23,33] Epidemiological data indicate that injury rates tend to be higher at the end of matches,[13,28] suggesting fatigue could be related to injury. Therefore, fatigue may play an important role in the pathomechanics of knee joint injuries.[36]

It has been shown that hamstring stretch reflex responses play an important role with regard to the extent of posterior-anterior tibial translation (TT, mechanically induced movement of the tibia relative to the femur) in standing subjects. The reflex responses originate from primary and secondary spindle afferents in the hamstring muscles.[9] To our knowledge, only three studies have analyzed the effect of fatigue on reflex responses of the hamstring muscles and TT.[2,24,36] These studies have revealed that fatigue can modulate the timing and magnitude of reflex activity as well as increase TT. However, only the study by Behrens et al.[2] investigated sex-specific effects of fatigue on hamstring reflex responses and TT in a sufficient sample of young recreational active subjects. The authors have found a significant decrease in hamstring reflex responses and a corresponding increase in TT after repetitive jumps until exhaustion in females but not in males. They suggested that the neuromuscular system of females and males might respond differently to the same fatigue protocol because they activate their muscles differently according to the requirements of the movement task. In the study mentioned, repetitive jumps until exhaustion were used to induce muscle fatigue. However, in many sports, such as basketball or handball, a combination of sprinting and jumping is performed. The effect of this kind of physical activity, carried out until exhaustion, on neuromuscular function, and TT is unknown.

Therefore, the purpose of the present study was to analyze, for first time, sex differences in hamstring reflex responses and TT before and after a fatigue protocol consisting of jumping and sprinting until exhaustion. We assessed the isolated movement of the tibia relative to the femur in the sagittal plane as a consequence of mechanically induced TT in standing subjects. Muscle activity of the lateral and medial hamstrings was analyzed. It was hypothesized that

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reflex components of the hamstring muscles are impaired and TT is altered after fatiguing exercise. We assumed that the main outcome variables would show sex-specific differences.

METHODS

Subjects and Study Design

Based on the effect size for the fatigue-induced change in TT provided by a previously published study,[2] a given two-sided significance level of 0.05 and a power of 0.85 sample size calculation indicated that a total of 24 persons would be required. Therefore, 26 subjects (13 males: age: 26 ± 3 years, weight: 83 ± 12 kg, height: 181 ± 5 cm, body mass index: 25 ± 3 kg/m^2, physical activity per week over the last two months: 6 ± 3 h/13 females: age: 23 ± 1 years, weight: 64 ± 8 kg, height: 168 ± 4 cm, body mass index: 23 ± 2 kg/m^2, physical activity per week over the last two months: 6 ± 3 h) with no history of neurological disorders or injuries were invited to participate in this prospective comparative study (level of evidence II). The study participants were recreational active sport science students and their primary sporting activities included volleyball (males: 5/females: 6), basketball (males: 1/females: 1), football (males: 3/females: 0), handball (males: 0/females: 2), running (males: 2/females: 2), swimming (males: 1/females: 1), and strength training (males: 1/females: 1).

Before testing, subjects were instructed to refrain from consuming alcohol and caffeine in the 24 h preceding the experiment and not to perform any strenuous exercise in the 48 h prior to the measurements. All persons signed informed consent. The study was conducted according to the declaration of Helsinki and was approved by the ethics committee. During the experiment, participants were examined with regard to reflex responses and TT before and after fatiguing exercise consisting of repetitive jumping and sprinting until exhaustion. The measurements were performed using a knee arthrometer (Fig. 1).[2,4,12,24]

Measurement of Posterior-Anterior Tibial Translation

Participants were examined in bipedal stance with the knees in 30° flexion (0° = full extension). In order to standardize the stance position between the trials, subjects stood on a force plate (sampling frequency: 40 Hz, GKS 1000®, IMM Holding GmbH, Mittweida, Germany). Subjects were thereby provided with online feedback about their center of pressure. Furthermore, the subject wore ear protection to avoid the influence of acoustic signals (Bilsom Thunder T3 3M, Neuss, Germany). A device was attached to the tibia to secure two linear potentiometers (measuring accuracy: <0.01 mm, linearity: ± 0.7%, Type CLR13-50; Megatron, Putzbrunn, Germany) that were placed on the patella and the tibial tuberosity (Fig. 1). The knee arthrometer enabled us to measure the translational movement of the tibia relative to the femur in the sagittal plane. The interface pressure between the knee arthrometer and the subjects' tibia was controlled by an air pressure recorder (Kikuhime, TT Medi-Trade, Soro, Denmark) and was kept constant before and after the fatiguing exercise. The locations of the subjects' feet on the force plate, the stabilizing device and the linear potentiometers were marked in order to ensure the same positions before and after the fatigue protocol. A standardized force was applied to the proximal shank of the dominant leg (kicking preference) using a pulley system in order to induce TT. The applied force that induced TT was controlled using a force transducer (measuring range: 0–5000 N, sensitivity: −3.42 to 3.36 pC · N^{-1}, linearity: ± 0.2–0.3%; Kistler, Ostfildern, Germany). The force sensor was placed between the stabilizing device and the pulley system. TT was elicited

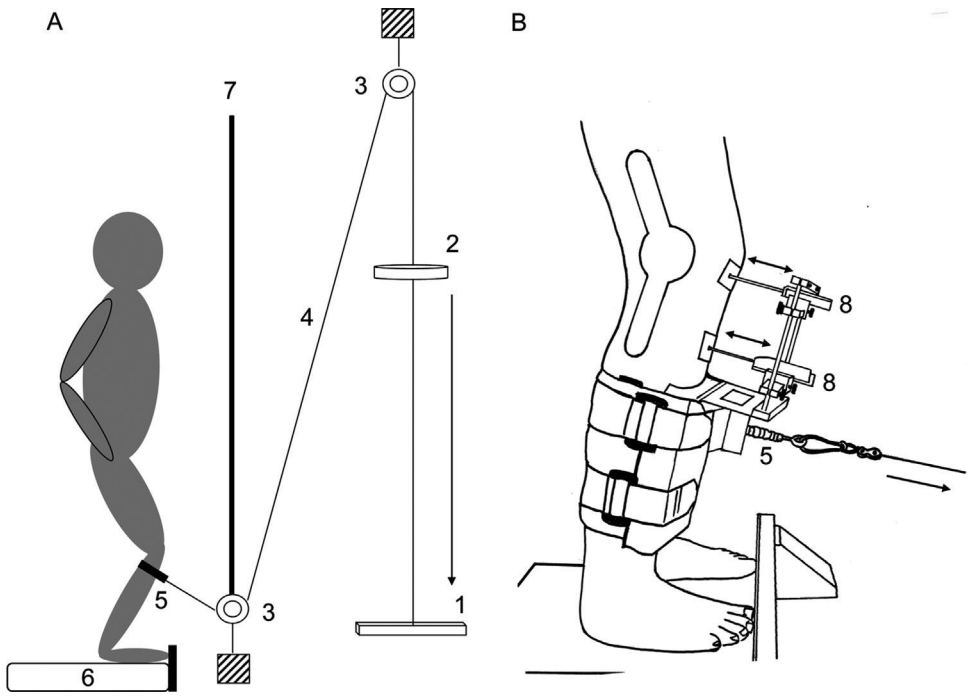

Figure 1. Schematic drawing of the experimental setup. (A) Experimental setup, (B) Measurement system | 1: stopper, 2: falling weight, 3: pulley, 4: steel rope, 5: force transducer, 6: force plate, 7: visual cover, 8: linear potentiometer. Arrows indicate the direction of the force. Posterior-anterior tibial translation was assessed by two linear potentiometers (8) placed on the patella and the tibial tuberosity. A force transducer (5) was used to measure the force transmitted to the shank.

15 times in order to familiarize the subject with the measurement. Thereafter, further 40 perturbations, with a break in between, were applied before and immediately after the fatigue protocol. The subjects had no information on the point in time of the perturbation and the inter stimulus interval was varied between ~6 s and ~8 s to avoid anticipation.

EMG Recordings

Surface EMG was recorded using bipolar electrodes (Ambu® Blue Sensor N, Bad Nauheim, Germany). The electrodes were attached to the shaved, abraded and cleaned skin over the biceps femoris (BF) and semitendinosus/semimembranosus (ST) of the dominant leg (resistance between electrodes <5 kΩ). The electrodes were applied with a center-to-center distance of 2 cm over the muscle bellies and in line with the presumed direction of the underlying muscle fibers. The reference electrode was attached to the patella. Signals were amplified (2500×), band-pass filtered (10–1300 Hz) and digitized (sampling frequency: 5 kHz) through an analog-to-digital converter (DAQ Card™ 6024E, National Instruments, Austin, TX). The EMG and linear potentiometer signals were stored on a hard drive for later analysis with custom built LABVIEW® based software (Imago, Pfitec, Endingen, Germany).

Fatigue Protocol

The fatigue protocol performed in this study was similar to that used previously.[5,33] Briefly, it consisted of five maximal countermovement jumps performed between ~90° and 0° knee flexion (0° = full extension) followed by a sprint over 30 m with a change of direction in between (Fig. 2). The fatigue protocol was performed until the subjects reached a fatigued state defined as the inability to reach 50% of their maximal jump height for three consecutive jumps or until the subjects reached an intolerable state of dyspnea or exhaustion. Heart rate was monitored during exhausting exercise (Polar S810i, Kempele, Finland) and rate of perceived exertion (RPE) was assessed using the Borg 6–20 scale.

Data Analysis

In order to analyze the data, the EMG signals of each subject were averaged. The EMG onset latencies were defined as the time between onset of TT and onset of significant muscular activity, e.g., the beginning of EMG deflection (average EMG baseline value measured over 100 ms ± 3 standard deviations). Muscle activity was analyzed as described previously.[2,4] Briefly, the deflection of the TT signal indicated the onset of perturbation and muscle activity was calculated over different time intervals relative to the onset of TT, i.e., 20–40, 40–60, and 60–95 ms using the root mean square of the EMG signal (RMS-EMG). In order to assess background activity before and after fatigue, RMS-EMG was calculated over 50 ms prior to the onset of TT. Consequently, reflex responses were normalized to background activity (RMS-Reflex/RMS-BG). Maximum TT was determined based on the TT curves.

Statistical Analysis

Data were checked for normal distribution using the Shapiro-Wilk test. Data were analyzed using repeated measures ANOVA with factors time (pre vs. post) and group (males vs. females). In case of significant F-values, post-hoc analysis was performed. In each case the level of significance was established at $p \leq 0.05$. SPSS 20.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Data are presented as group mean values ± standard deviations.

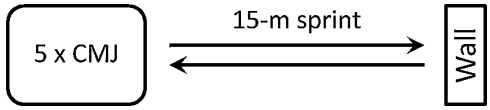

Figure 2. Setup of the fatigue protocol.

RESULTS

Females terminated exercise after 3:03 ± 0:38 min while males were exhausted after 4:32 ± 2:07 min. The difference in the time until exercise termination was significantly different between groups (independent t-test: $p = 0.043$). Mean heart rate during exercise was 178.1 ± 10.1 bpm for females and 184.0 ± 9.7 bpm for males (independent t-test: $p = 0.304$). Females rated their perceived exertion 17.5 ± 1.2 and males 17.1 ± 1.6 (independent t-test: $p = 0.445$).

The force applied to the proximal shank of the dominant leg remained constant during the pre- and post-test (Table 1). ANOVA revealed a significant main effect of time on reflex onset latencies of BF ($F = 9.255$, $p = 0.007$, $\eta^2 = 0.340$) and ST ($F = 10.460$, $p = 0.005$, $\eta^2 = 0.368$). Post-hoc analysis for females and males revealed significant delayed reflex responses for both muscles (Table 1).

Furthermore, ANOVA yielded a significant main effect of time on reflex responses of BF ($F = 6.133$, $p = 0.021$, $\eta^2 = 0.218$) and ST ($F = 16.446$, $p = 0.001$, $\eta^2 = 0.428$) in the time interval 20–40 ms. In addition, a significant main effect of time on TT was found ($F = 11.884$, $p = 0.002$, $\eta^2 = 0.351$). Post-hoc analysis for females revealed a tendency towards a significant decrease in reflex response of BF in the time interval 20–40 ms ($p = 0.098$) and a significant decrease in reflex activity of ST in the same time frame ($p = 0.024$). TT increased significantly after the fatigue protocol in females ($p = 0.015$). Post-hoc analysis for males revealed also a tendency towards a significant decrease in reflex response of BF in the time interval 20–40 ms ($p = 0.084$) and a significant decrease in reflex activity of ST in the time interval 20–40 ms ($p = 0.021$). TT showed a tendency towards a significant increase following fatigue in males ($p = 0.065$) (Fig. 3). We found no interactions of time and group for these parameters. Furthermore, no main effects or interactions were found for the reflex responses in the time intervals 40–60 and 60–90 ms in both sexes.

DISCUSSION

This study was directed to investigate sex-specific effects of fatigue, induced by repetitive jumping and sprinting, on reflex activity of the hamstrings and TT. Reflex onset latencies were delayed in females and males after fatiguing exercise. Furthermore, the results revealed a fatigue-induced reduction in reflex

Table 1. Force Applied to the Proximal Shank of the Dominant Leg and EMG Onset Latencies Before and After the Fatigue Protocol for Males and Females

	Males				Females			
Parameter	Pre	Post	% change	p	Pre	Post	% change	p
Force (N)	228.0 ± 28.5	225.8 ± 30.5	−1.0	0.477	224.2 ± 14.1	226.9 ± 12.1	−1.2	0.105
EMG onset latencies (ms)								
BF	22.3 ± 2.1	24.3 ± 3.7	9.0	0.054[b]	21.8 ± 1.3	23.2 ± 2.4	6.4	0.032[a]
ST	22.9 ± 1.7	24.8 ± 3.4	8.3	0.046[a]	21.7 ± 0.8	23.3 ± 2.3	7.4	0.037[a]

BF: biceps femoris, ST: semitendinosus/semimembranosus. Values are means ± standard deviations.[a]Denotes a significant difference to the pre-measurement, $p \leq 0.05$.[b]Denotes a tendency towards a significant difference to the pre-measurement, $p \leq 0.06$.

responses in the time interval 20–40 ms in both sexes. A significant increase in TT was observed in females, while TT in males showed a tendency towards a significant increase.

It has been proposed that the extent of joint laxity may be associated with an increased risk to sustain an ACL injury.[29] Several studies have shown that sports activities such as running or a regular workout in volleyball can increase anterior knee laxity.[17,20,21,27] However, only a study performed by Kvist et al.[21] has compared TT in females and males after exhausting exercise and found an increase of this parameter in males. Nevertheless, these studies measured anterior knee laxity while subjects were relaxed. In contrast, we have measured TT in a functional weight-bearing situation. In this condition, axial loading and forces due to muscle contraction could reduce rotation and translation compared to the passive condition.[22,34] The present study found a fatigue-induced increase in TT in females and a tendency towards a significant increase in males. Studies using a similar methodology have shown that an isokinetic fatigue protocol performed with a dynamometer can increase TT.[24,36] Wojtys et al.[36] have analyzed sex-specific differences in a very small sample (six males and four females) and reported no difference in any parameter. In a recently published study that used the similar methodology, it has been shown that a fatigue protocol, consisting of repetitive jumps until fatigue, led to an increase in TT in females but not in males.[2] During exercise, the laxity of ligamentous structures of the knee can increase which, in turn, put the athlete at

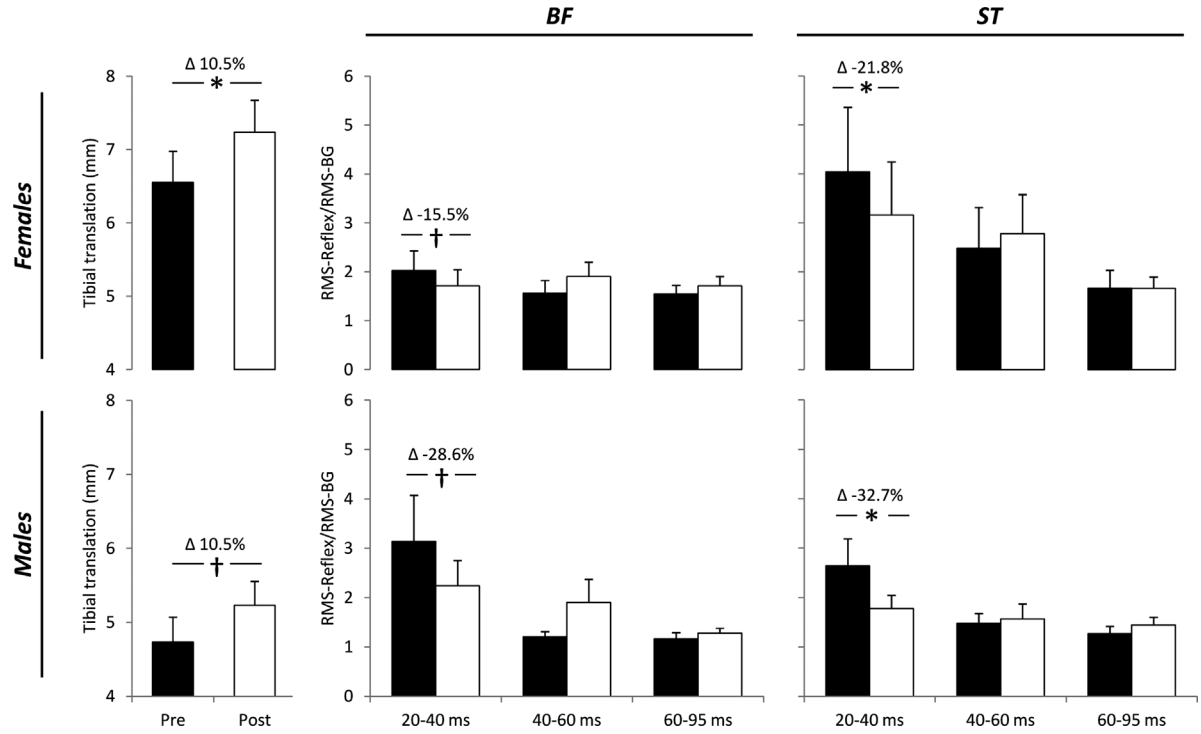

Figure 3. Effect of fatigue on tibial translation (*left*) and reflex responses (*middle and right*). Filled bars: Pre, open bars: Post, BF: biceps femoris, ST: semitendinosus/semimembranosus, RMS-Reflex/RMS-BG: root mean square of the reflex components normalized to background activity. Data are displayed as means ± standard deviations. *Denotes a significant difference compared to the pre-measurement, *$p \leq 0.05$. †Denotes a tendency towards a significant difference to the pre-measurement, $p \leq 0.10$.

risk to sustain ligamentous injury.[30] This is due to the fact that joint structures, particularly the ligaments, exhibit viscoelastic properties.[35] The cyclic stress of the ligamentous structures during exercise leads to time-dependent and stress-dependent modifications and therefore increased ligamentous laxity.[30,35] However, the muscles that cross the knee joint play a large role in maintaining physiological kinematics of the knee joint. Muscle activity is able to induce large changes in strains as well as forces experienced by the ACL.[32]

Therefore, the fast activation of muscles by means of reflexes may play a substantial role in the stabilization of the knee joint.[9] Because the direct reflex arc between the ACL and the hamstrings makes only a minor contribution to the biphasic reflex response observed in the hamstring muscles after a sudden TT,[8] it has been suggested that the reflex response is mainly generated due to the stretch of the hamstring muscles.[7]

In the present study, delayed reflex onset latencies were found in females and partially in males after repetitive jumping and sprinting until fatigue. This is in line with the results of Melnyk and Gollhofer[24] who reported an increased latency of reflex responses after submaximal isokinetic exercise of the hamstrings, but they did not analyze sex-specific differences. In contrast, Behrens et al.[2] observed delayed reflex responses of the hamstrings after fatiguing jumps until exhaustion only in females and not in males.

In this study, the reflex response of ST in the time interval 20–40 ms was significantly reduced in females and males after fatigue, whereas reflex activity of BF in the time interval 20–40 ms tended to a significant reduction. These results correspond with the results of Melnyk and Gollhofer[24] who found significantly decreased iEMG values for the short latency response and medium latency response of the hamstring stretch reflex after an isokinetic concentric-eccentric fatigue protocol. However, as mentioned above, the authors have not analyzed sex-specific differences. Behrens et al.[2] showed, by using a similar methodological approach, that repetitive jumps until exhaustion decreased reflex responses of the hamstrings in females but not in males. They concluded that the neuromuscular system of females and males might respond differently to the same fatigue protocol because they activate their muscles differently according to the requirements of the movement task. This assumption is based on the observation that trained females show greater hamstring muscle activity when landing from a jump and possess increased knee joint laxity as well as longer time to detect knee joint motion compared with males. It has been suggested that the greater EMG peak amplitude and area in females might be an attempt of the nervous system to compensate for the greater joint laxity and proprioceptive deficit. Furthermore, it has been argued that an interruption of this compensatory mechanism, for example due to fatigue, might increase joint laxity that may cause ligament injury.[31] In the present study, the subjects had to perform maximal countermovement jumps followed by a 30-m sprint with a change of direction in between. Although females seem to activate their hamstring muscles more than males when landing from a jump, muscle activity of the hamstrings during the support phase while sprinting is around 100% of that recorded during maximum voluntary contraction.[19] Therefore, the fatigue task used in the present study induced a decline in reflex responses in females and males.

The results of the present study show that repetitive jumping and sprinting until exhaustion altered the latency as well as magnitude of reflex responses of the hamstring muscles and TT in females and males. It has been suggested that the hamstring muscles play an important role in maintaining knee stability and protecting the ACL during movements of the tibia relative to the femur.[1,18,26] Therefore, decreased reflex responses of the hamstring muscles and in turn an increased TT might contribute to the pathomechanics of knee joint injuries. In contrast to the results of a previously published study,[2] reflex responses of the hamstrings were reduced and TT was increased in both recreational active females and males. Therefore, it might be that sex-specific effects of fatigue on reflex activity and mechanical stability of the knee depend on the kind of fatiguing exercise.

In this context, it has to be mentioned that we investigated reflex responses and TT of the dominant leg. However, it has been suggested that leg dominance might be an etiological factor with regard to ACL injuries in males and females.[3] The potential cause for this discrepancy should be investigated in future studies. Although the activity level was comparable and the kind of primary activities was relatively balanced between sexes, it might be that the significant difference between sexes regarding the time until exhaustion during the fatigue protocol has influenced our results. Even though sample size calculation indicated that we have recruited an appropriate number of subjects, it might be that the investigation of more subjects could have altered the results of the present study.

AUTHORS' CONTRIBUTIONS

MB, AMM, RB, and SB conceived and designed the experiments. MB, FW, and AP performed the experiments. MB, AMM, FW, AP, RB, and SB analyzed and interpreted the data. MB, AMM, FW, AP, RB, and SB drafted the paper and revised it critically. All authors have read and approved the manuscript.

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Central Factors Contribute to Knee Extensor Strength Loss after a 2000-m Rowing in Elite Male and Female Rowers

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BASIC SCIENCES

ABSTRACT

HUSMANN, F., M. GUBE, S. FELSER, M. WEIPPERT, A. MAU-MOELLER, S. BRUHN, and M. BEHRENS. Central Factors Contribute to Knee Extensor Strength Loss after a 2000-m Rowing in Elite Male and Female Rowers. *Med. Sci. Sports Exerc.*, Vol. 49, No. 3, pp. 440–449, 2017. **Purpose**: Despite growing interest in task-dependent alterations of central and peripheral fatigue after endurance exercise, little is known about the effect of rowing on quadriceps muscle fatigue. This study aimed to investigate central and peripheral mechanisms of fatigue after a 2000-m rowing time trial. **Methods**: Eight competitive rowers (four males and four females, 20 ± 4 yr) performed a 2000-m time trial on an indoor rower and a control condition (sitting). The neuromuscular function of the knee extensors was analyzed before and 3 min after each experimental condition. Maximal voluntary torque, voluntary activation, and normalized root-mean-square of the EMG signal were measured during isometric and concentric contractions. Furthermore, knee extensor twitch torque and maximal M-wave amplitudes in response to electrical nerve stimulation were assessed. **Results**: After the 2000-m rowing, there were significant reductions in isometric and concentric maximal voluntary torque of the knee extensors (−20% ± 9% and −18% ± 7%, respectively, $P < 0.01$). Both the voluntary activation of the knee extensors during isometric and concentric contractions decreased by 18% ± 15% ($P < 0.05$, respectively). The normalized muscle activity of rectus femoris was significantly reduced after rowing ($P = 0.007$), whereas vastus medialis and vastus lateralis muscle activities did not significantly differ from baseline values. No significant change was observed for knee extensor twitch torque in response to paired electrical stimuli after rowing. **Conclusion**: The 2000-m rowing time trial resulted in significant knee extensor strength loss. Quadriceps muscle fatigue after high-intensity rowing exercise was explained primarily by central factors that lead to large reductions in voluntary drive. **Key Words:** BIARTICULAR, CENTRAL FATIGUE, ENDURANCE, MONOARTICULAR, PERIPHERAL FATIGUE, QUADRICEPS, VOLUNTARY ACTIVATION

Muscle fatigue is commonly characterized as any exercise-associated reduction in maximal voluntary force produced by a muscle or muscle group (21). During exercise, the decline in the force-generating capacity of the neuromuscular system can originate from multiple physiological alterations along the motor pathway (21). Typically, a distinction is drawn between peripheral and central sites that contribute to muscle fatigue. Peripheral fatigue refers to exercise-related impairments that occur at or distal to the neuromuscular junction and can be measured by reductions in twitch force/torque produced by a muscle in response to transcutaneous stimulation (7). The underlying mechanisms encompass potential alterations in neuromuscular transmission and/or excitation–contraction coupling mainly caused by the accumulation of intramuscular metabolites and/or muscular damage (1). Central fatigue refers to the exercise-induced reduction in the voluntary activation of the tested muscle group and can be assessed by using the interpolated twitch technique (21). The impairment in voluntary activation can originate from several sites of the central nervous system (CNS). Thus, central fatigue involves any spinal and supraspinal alterations, which lead to impairments in motoneuron excitation (21).

The development of fatigue is generally considered to be task dependent. Specifically, the relative importance of central and peripheral mechanisms differs depending on the tested muscle group, the contraction mode, and the exercise intensity and duration (17). The task dependency of muscle fatigue has been extensively investigated during single-joint exercise. For instance, there is substantial evidence that long-duration, low-force voluntary contractions are predominantly limited by central factors, whereas near maximal voluntary contractions of short duration are rather limited by peripheral factors of fatigue (for a review, see Taylor and Gandevia [50]). In addition, further research interest focuses on task-specific alterations of central and peripheral fatigue after locomotor

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endurance exercise (43). Several studies have investigated the effect of locomotor endurance exercise (i.e., cycling and running) on central and peripheral aspects of fatigue after short (6–8 min [3,4,23]), medium (20–90 min [35,46]), and long exercise durations (3–5 h [37]). Together, findings from locomotor exercise studies suggest a greater contribution of peripheral impairments to reductions in voluntary force production after shorter, more intense locomotor exercise compared with longer, less intense exercise. Higher exercise intensities are shown to induce stronger metabolic disturbances within the muscle (31), which are likely responsible for the greater extent of peripheral fatigue (51,52). By contrast, a greater portion of central fatigue was typically demonstrated after a low-intensity locomotor exercise of longer durations. There is evidence suggesting that increased firing rates of group III/IV muscle afferents in response to intramuscular metabolic disturbances facilitate central fatigue (21). However, the distinct mechanisms of fatigue after locomotor endurance exercise are still controversially discussed (36).

Little is known about the origins of muscle fatigue after whole-body exercise such as rowing. In rowing, the leg muscles serve as important contributors to the propulsion of the rowing boat by pushing against the foot stretcher (47). Several studies have emphasized the major role of the quadriceps muscle to produce power during the rowing stroke (24,54). Furthermore, approximately 70% of total muscle mass is involved because of the fact that upper and lower body muscles work synchronized during the rowing stroke (48). There is growing evidence that the motor performance of the lower limb muscles can be affected when it is preceded by fatiguing contractions of the upper limbs (25,30). Therefore, rowing offers a unique possibility to assess the effect of simultaneously working upper body muscles on quadriceps muscle fatigue. To our knowledge, no previous study has investigated the effect of a simulated rowing race on quadriceps muscle fatigue. Therefore, the present study was designed to assess the effect of a 2000-m rowing time trial (~6–7 min) on indices of central and peripheral fatigue. We hypothesized that after termination of the 2000-m rowing time trial, both central and peripheral mechanisms would contribute to knee extensor strength loss.

METHODS

Subjects. Eight German heavyweight rowers, four males (mean ± SD; age = 19 ± 4 yr, height = 190 ± 4 cm, weight = 91 ± 6 kg) and four females (age = 20 ± 4 yr, height = 183 ± 3 cm, weight = 78 ± 5 kg), were recruited to participate in this study. At the time of the study, all subjects regularly participated in national and international-level championships. The average competitive rowing experience of the sample was 8.3 ± 3.5 yr. Subjects were asked to avoid caffeine and alcohol consumption for 24 h before the investigations. The study was approved by the university ethics committee and was conducted according to the declaration of Helsinki. All subjects were informed about possible risks and discomfort associated with the investigations before giving their written consent to participate.

Experimental procedure. All subjects participated in three experimental sessions at the laboratory. In the first session, subjects were familiarized with the procedures used to assess the neuromuscular function of the knee extensors. The second and the third sessions were separated by at least 1 wk and took place at the same time of the day. To control for potential effects of time and rowing warm-up on neuromuscular function, subjects randomly performed two experimental conditions: 1) a 2000-m time trial on an indoor rower and 2) a control intervention, in which the subjects rested on the indoor rower for a period similar to the time trial duration (Fig. 1). The period for the control condition was set according to the subjects' prediction of the race time. Before each experimental condition, participants performed their individual and standardized warm-up routine on the indoor rower (warm-up II) within a time window of 20 min. The warm-up period comprised low-intensity intervals of rowing with expanded resting periods in between. Between the warm-up period and each experimental condition, subjects rested for 5 min on the indoor rower. Before and 3 min after each experimental condition, neuromuscular tests were performed. The time lag of 3 min between exercise termination and neuromuscular testing was due to the time required for the preparation of postexercise measurements.

Before baseline measurements, subjects performed a short warm-up on a stationary bicycle (warm-up I; 5 min, 100 W, 80 rpm). Neuromuscular tests comprised supramaximal electrical stimulations of the femoral nerve during isometric as well as concentric maximal voluntary contractions (MVC) and at rest (Fig. 1). Contraction sequences were performed in a randomized order. All measurements were conducted on the quadriceps muscle of the right leg. During neuromuscular testing, subjects were comfortably seated and secured on a CYBEX NORM dynamometer (Computer Sports Medicine®, Inc., Stoughton, MA). The seating position was adjusted for each subject, and settings were documented for the subsequent sessions.

The 2000-m time trial. Time trial and rowing warm-up were performed on an instrumented Concept II rowing ergometer (Model E, Morrisville). The 2000-m time trial protocol was chosen according to the standard race distance of the Olympics and the World Rowing Championships. All subjects were familiar with both the ergometer and the test protocol used in this study. The 2000-m time trial started in the catch position. Drag factor was set at 140 for males and 130 for females. Mechanical data (i.e., power per rowing stroke) were recorded by using a force sensor fitted on the oar handle and a position sensor fitted on the flywheel (FES, Berlin, Germany). After finishing the time trial, subjects rated their perceived exertion using the Borg scale (9).

Torque recordings. A CYBEX NORM dynamometer was used to record instantaneous torques. Subjects were positioned on an adjustable chair with the hip fixed at 80° (0° = full extension). To avoid excessive movements during

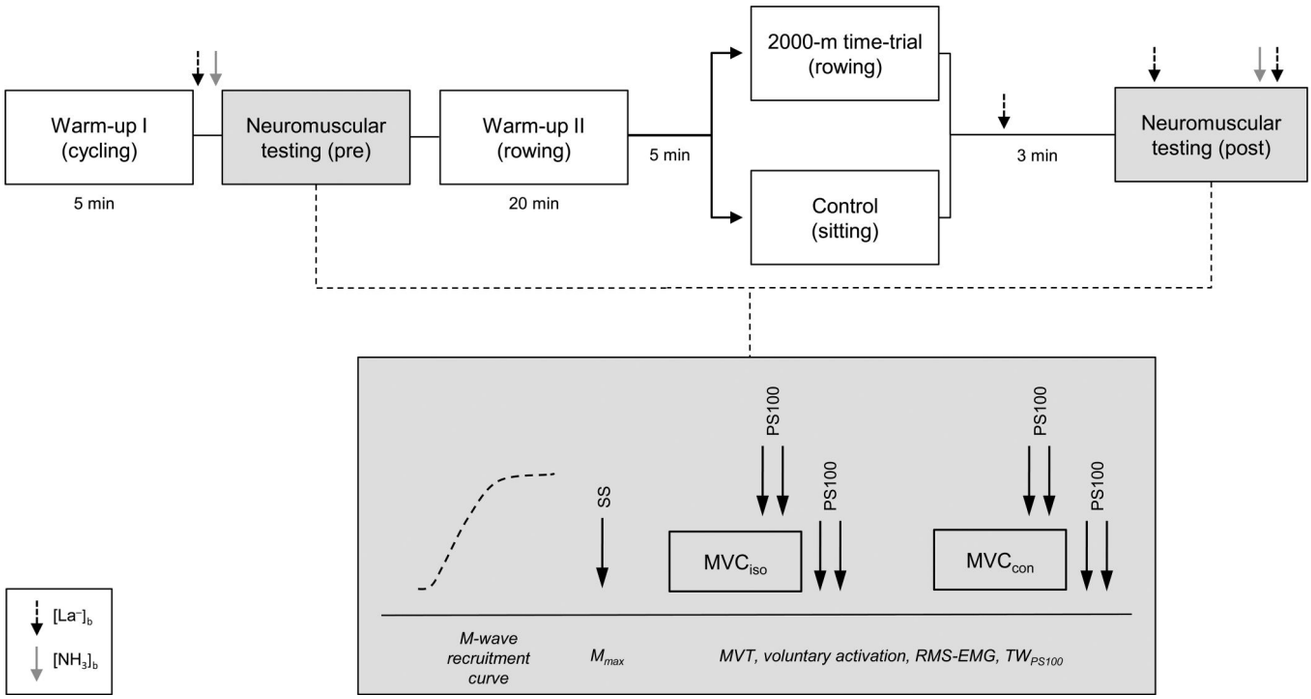

FIGURE 1—Illustration of the experimental procedure. For further information, see Experimental procedure section. $[La^-]_b$, blood lactate concentration; $[NH_3]_b$, blood ammonia concentration; SS, single electrical stimuli; PS100, paired electrical stimuli at 100 Hz; MVC_{iso}, maximal voluntary isometric contraction; MVC_{con}, maximal voluntary concentric contraction; M_{max}, maximum compound muscle action potential; TW_{PS100}, paired stimuli twitch torque.

contractions, straps were applied tightly across the subject's waist. The dynamometer rotation axis was aligned with the knee joint rotation axis, and the lever arm was fixed to the lower leg just above the lateral malleolus. Isometric MVC were performed at 80° knee flexion (0° = full extension). Concentric isokinetic contractions were performed at an angular velocity of $25°\cdot s^{-1}$ (5,6). After each contraction, participants were instructed to relax their knee extensor muscles, and the knee joint was passively extended via movement of the lever arm. During active and passive knee extension, the superimposed stimuli were automatically delivered at 80° of knee flexion. The range of motion was set at 85°, from 5° to 90° knee flexion. For each trial, subjects were instructed to cross their arms in front of their chest and to push as fast and as hard as possible against the lever arm of the dynamometer. Strong verbal encouragement was given to the participants by the investigator. Visual feedback of the torque–time curve was provided on a digital oscilloscope (HM1508, HAMEG Instruments, Mainhausen, Germany). Between each contraction, subjects recovered passively for 60 s. On average, three maximal attempts were performed for each contraction mode until the coefficient of variation of the maximal torque values was less than 5%.

EMG recordings. For a detailed description of the EMG recordings, we refer to a previously published study from our laboratory (6). Briefly, EMG signals from the vastus medialis (VM), rectus femoris (RF), and vastus lateralis (VL) were recorded using surface electrodes (EMG Ambu Blue Sensor N, Ballerup, Denmark). Myoelectrical signals were amplified (×2500), band-pass filtered (10–450 Hz), and digitized with a sampling frequency of 3 kHz by an analog-to-digital converter (NI PCI-6229, National Instruments, Austin, TX). EMG data were stored on a hard drive for further analysis using a custom-built LABVIEW based program (Imago, Pfitec, Endingen, Germany).

Electrical nerve stimulation. The femoral nerve was stimulated percutaneously using electrical stimulation to assess the neuromuscular function of the quadriceps muscle. Square wave pulses of 1-ms duration with maximal voltage of 400 V were delivered using a constant-current stimulator (Digitimer DS7A, Herfordshire, UK). A ball probe cathode (10 mm diameter) was pressed manually in the femoral triangle. The anode, a self-adhesive electrode (35 × 45 mm, Spes Medica, Genova, Italy), was affixed over the greater trochanter. After determining the optimal site for stimulation, the position was marked onto the subjects' skin to ensure repeatable measurements within each session. Individual stimulation intensity was progressively increased until the maximum compound muscle action potential (M_{max}) of VM and a plateau in knee extensor twitch torque was achieved. During the subsequent testing procedures, the stimulation intensity was increased by additional 40% to guarantee supramaximal stimulation. To ensure consistency of the effective stimulus intensity, VM M_{max} amplitude was redetermined after each experimental condition by using M-wave "mini-recruitment curves" (42). Three electrical single stimuli were used to elicit M_{max} amplitudes. As previously recommended for quantification of peripheral fatigue (40), potentiated peak twitch torques were evoked after isometric MVC using supramaximal

paired stimuli at 100 Hz (10 ms interstimulus interval). To determine the level of voluntary activation during isometric and concentric MVC, the interpolated twitch technique was used. Electrical paired stimuli were applied to the femoral nerve at 80° knee flexion. For the isometric condition, paired stimuli were delivered 2 s after torque onset (during the plateau phase) and 2 s after MVC. During concentric contractions, paired stimuli during MVC and at rest were automatically delivered at a knee angle of 80°. A LABVIEW based program (Imago, Pfitec, Erdingen, Germany) was used to trigger the electrical stimuli.

Physiological data recordings. All blood samples were drawn from the earlobe, with the site standardized for each subject. A portable analyzer (Lactate Scout, SensLab GmbH, Leipzig, Germany) was used for determination of blood lactate concentrations ($[La^-]_b$). Blood samples were taken before and 1, 5, and 10 min after finishing each experimental condition (Fig. 1). Blood ammonia concentrations ($[NH_3]_b$) were measured using an Ammonia Test Kit II for a PocketChem BA device (Arkay, Inc., Kyoto, Japan). Measurements for ammonia blood sampling were conducted before and 10 min after each experimental condition. Heart rate data were continuously recorded during the time trial using a Polar RS 800 heart rate monitor (Kempele, Finland).

Data analysis. All torque signals were corrected for the effect of gravity. Potentiated peak twitch torques (i.e., highest value of the torque–time curve) in response to paired electrical stimuli were determined and averaged for each trial. The three best isometric and concentric MVC trials were selected for further analysis. Isometric maximal voluntary torque (MVT), i.e., the highest torque value before the superimposed twitch, and concentric MVT, i.e., the torque value immediately before the superimposed twitch, were calculated. M_{max} amplitudes elicited by single stimuli were measured peak-to-peak and averaged over the three trials. Muscle activation during isometric MVC was estimated by calculating the root-mean-square of the EMG signal (RMS-EMG) over a time interval of 200 ms at MVT, i.e., 200 ms around the MVT for the isometric contraction and 200 ms before the superimposed stimuli for the concentric contraction. RMS-EMG of VM, RF, and VL were normalized to the corresponding M_{max} values ($RMS \cdot M^{-1}$). In addition, $RMS \cdot M^{-1}$ was averaged across VM, RF, and VL to estimate quadriceps muscle activation during isometric MVC ($Q\,RMS \cdot M^{-1}$). The level of voluntary activation for isometric MVC was calculated using a corrected formula: (1 − superimposed twitch $[T_b \times MVT^{-1}] \times$ control $twitch^{-1}) \times 100$ (49). MVT is the maximal torque level, and T_b is the torque value immediately before the superimposed twitch. The corrected formula is used to avoid the potential problem that the superimposed stimuli are not applied during the maximum torque level. For concentric MVC, voluntary activation was computed using the common formula: (1 − superimposed twitch × control $twitch^{-1}) \times 100$ (2).

Statistical analysis. All data were screened for normal distribution using the Shapiro–Wilk test. A two-way repeated-measures ANOVA, on time (before and after) and condition (time trial and control), was conducted for all neuromuscular parameters. Metabolic parameters were analyzed in separate repeated-measures ANOVA, on time (four measurement time points) and condition. *Post hoc* analyses were performed using Holm–Sidak tests. The effect size was determined by calculating partial eta squared (η^2). Values of 0.10 show small, 0.25 medium, and 0.40 large effects (11). Data were analyzed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL), and statistical significance was accepted at $P \leq 0.050$.

RESULTS

Exercise responses. Subjects completed the 2000-m rowing time trial in a mean time of 6:46 ± 0:32 min (range, 6:11 to 7:09 min). Mechanical, cardiovascular, and perceptual recordings during the time trial are provided in Table 1. Significant time–condition interactions were found for $[La^-]_b$ ($F_{1,7} = 53.72$, $P < 0.001$, $\eta^2 = 0.89$) and $[NH_3]_b$ ($F_{1,7} = 11.50$, $P = 0.012$, $\eta^2 = 0.62$). $[La^-]_b$ increased from 1.0 ± 0.4 $mmol \cdot L^{-1}$ at rest to 8.8 ± 2.3, 10.6 ± 2.5, and 10.3 ± 3.0 $mmol \cdot L^{-1}$ measured 1, 5, and 10 min after termination of the time trial, respectively (all $P < 0.001$). Compared with resting values (31.9 ± 22.4 $\mu mol \cdot L^{-1}$), $[NH_3]_b$ increased more than two times postexercise (77.4 ± 49.0 $\mu mol \cdot L^{-1}$, $P < 0.05$). As expected for the control condition, $[La^-]_b$ and $[NH_3]_b$ were not significantly different from baseline values for all times of measurement.

Maximal voluntary torque. Postexercise measurements were conducted with a mean time lag of 3:15 ± 0:17 min. There were significant time–condition interactions for isometric ($F_{1,7} = 22.52$, $P = 0.002$, $\eta^2 = 0.76$) and concentric ($F_{1,7} = 12.98$, $P = 0.002$, $\eta^2 = 0.65$) MVT. After rowing, isometric (−20.4% ± 8.9%, $P = 0.002$) and concentric (−18.1% ± 7.3%, $P = 0.002$) knee extensor MVT declined significantly from preexercise values (Figs. 2A and 2B). As expected for the control condition, no significant changes from baseline MVT levels were observed for isometric ($P = 0.477$) or concentric ($P = 0.872$) MVC (Table 2).

TABLE 1. Exercise measures during the 2000-m rowing time trial.

Exercise Time (mm:ss)	06:46 ± 00:32
Strokes	198 ± 10
Stroke rate (strokes per minute)	30 ± 1
Mean peak force (N)	
Race	797 ± 105
Start	874 ± 171
Steady-state phase	790 ± 98
Final spurt	808 ± 112
Mean power per stroke (W)	
Race	951 ± 191
Start	1145 ± 368
Steady-state phase	931 ± 173
Final spurt	1000 ± 207
Heart rate max (bpm)	190 ± 9
Heart rate mean (bpm)	184 ± 8
RPE (Borg scale)	15 ± 2

Values are expressed as means ± SD. Start: first 10 strokes. Steady-state phase: strokes 30–150. Final spurt: last 10 strokes.

Voluntary activation and RMS-EMG. The statistical analysis indicated significant time–condition interactions for voluntary activation during isometric ($F_{1,7} = 11.79$, $P = 0.011$, $\eta^2 = 0.63$) and concentric ($F_{1,7} = 10.03$, $P = 0.016$, $\eta^2 = 0.59$) MVC. Compared with preexercise values, there was a significant decay in isometric (−18.2% ± 15.4%, $P = 0.012$) and concentric (−17.6% ± 14.5%, $P = 0.013$) voluntary activation, respectively (Figs. 2C and 2D). As expected for the control condition, both isometric and concentric voluntary activation was not significantly different from baseline values ($P = 0.508$ and $P = 0.830$, respectively; Table 2).

Data analysis also revealed significant time–condition interactions for Q RMS·M^{-1} ($F_{1,7} = 9.88$, $P = 0.016$, $\eta^2 = 0.59$), RF RMS ($F_{1,7} = 6.43$, $P = 0.039$, $\eta^2 = 0.48$), and RF RMS·M^{-1} ($F_{1,7} = 21.33$, $P = 0.002$, $\eta^2 = 0.75$) during isometric MVC. After rowing, Q RMS·M^{-1} recorded during isometric MVC decreased significantly from preexercise values ($P = 0.001$; Fig. 2E). There were also significant reductions in RF RMS and RMS·M^{-1} during isometric MVC after rowing ($P = 0.049$ and $P = 0.007$, respectively; Fig. 3B). Conversely, there were no time–condition interactions for VM and VL RMS·M^{-1}. For the control condition, RMS·M^{-1} values for all muscles were not statistically different from baseline values (Table 2).

Electrically evoked twitch torque. No significant time–condition interaction was found for paired stimuli twitch torque ($F_{1,7} = 4.91$, $P = 0.062$, $\eta^2 = 0.41$) (Fig. 2F and Table 2).

Electrically evoked potentials. There was a significant time–condition interaction for RF M_{max} ($F_{1,7} = 12.75$, $P = 0.009$, $\eta^2 = 0.65$). However, there was no such interaction for VM and VL M_{max} amplitudes. After rowing, RF

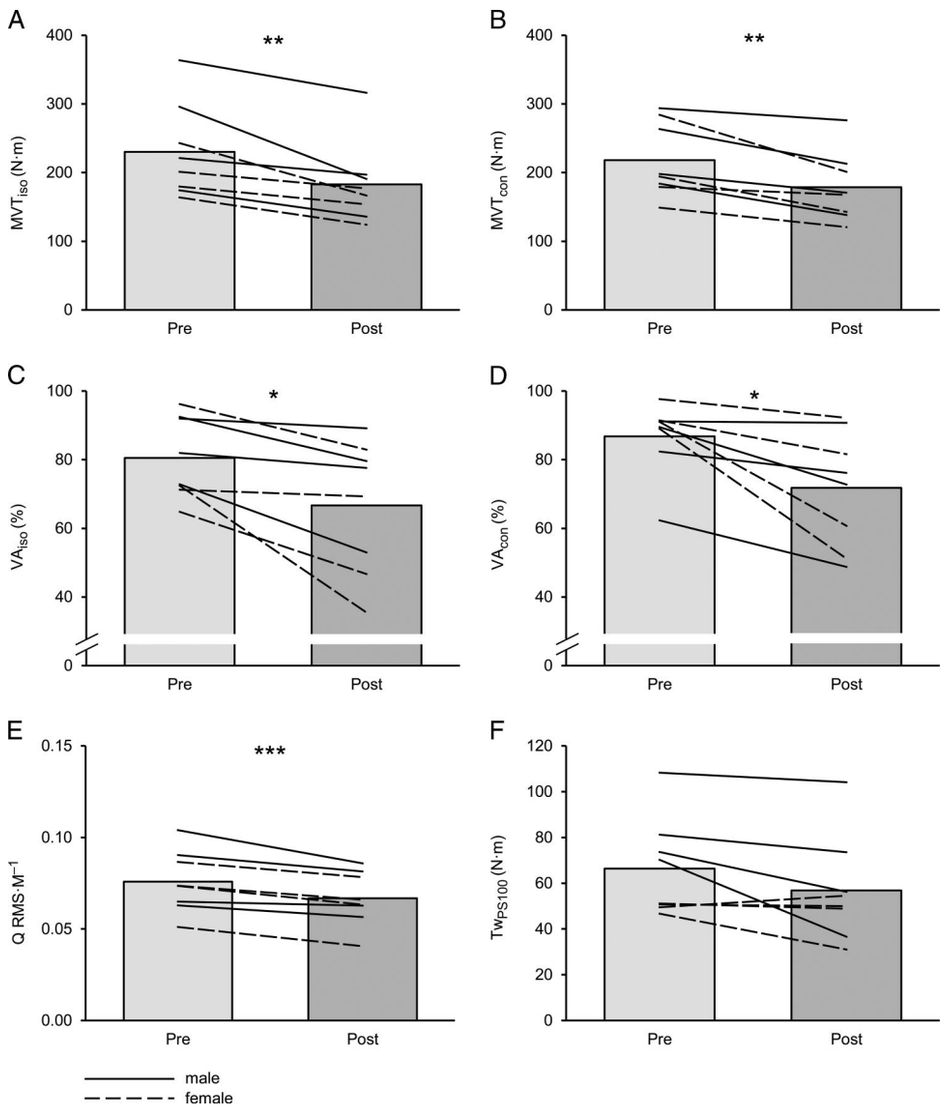

FIGURE 2—Neuromuscular function of the knee extensor muscles before and after the 2000-m rowing time trial. Mean values and individual data for MVT during isometric (MVT$_{iso}$) (A) and concentric contractions (MVT$_{con}$) (B), voluntary activation during isometric (VA$_{iso}$) (C) and concentric MVC (VA$_{con}$) (D), normalized RMS-EMG averaged across the superficial quadriceps muscles (Q RMS·M^{-1}) (E), and paired stimuli twitch torque (Tw$_{PS100}$) (F). Significant before and after change: *$P < 0.050$, **$P < 0.010$, ***$P < 0.001$.

TABLE 2. Neuromuscular function of the knee extensors before and after each experimental condition.

	Rowing		Control	
	Before	After	Before	After
MVT_{iso} (N·m)	230.4 ± 64.6	182.6 ± 55.8**	209.6 ± 69.1	216.8 ± 65.4
MVT_{con} (N·m)	218.3 ± 44.9	178.8 ± 31.2**	204.4 ± 49.8	203.4 ± 48.9
VA_{iso} (%)	80.5 ± 11.1	66.7 ± 18.1*	74.6 ± 18.5	76.8 ± 11.8
VA_{con} (%)	86.8 ± 10.7	71.8 ± 15.7*	85.6 ± 10.4	85.7 ± 9.7
VM RMS (mV)	0.626 ± 0.219	0.604 ± 0.220	0.597 ± 0.251	0.567 ± 0.182
RF RMS (mV)	0.330 ± 0.151	0.302 ± 0.132*	0.281 ± 0.086	0.281 ± 0.094
VL RMS (mV)	0.402 ± 0.163	0.378 ± 0.160	0.385 ± 0.212	0.352 ± 0.160
Q RMS·M^{-1}	0.076 ± 0.016	0.067 ± 0.014***	0.072 ± 0.016	0.075 ± 0.013
VM RMS·M^{-1}	0.061 ± 0.015	0.056 ± 0.015	0.057 ± 0.016	0.056 ± 0.007
RF RMS·M^{-1}	0.109 ± 0.034	0.090 ± 0.029**	0.101 ± 0.040	0.104 ± 0.033
VL RMS·M^{-1}	0.058 ± 0.024	0.054 ± 0.017	0.059 ± 0.021	0.068 ± 0.021
TW_{PS100} (N·m)	66.4 ± 20.0	56.7 ± 12.9	56.4 ± 19.1	64.6 ± 29.9
VM M_{max} (mV)	10.5 ± 3.4	10.9 ± 3.3	10.5 ± 2.3	10.3 ± 2.6
RF M_{max} (mV)	3.4 ± 2.0	3.8 ± 2.2**	3.2 ± 1.4	3.0 ± 1.3
VL M_{max} (mV)	7.9 ± 4.2	7.7 ± 4.1	7.0 ± 3.5	6.2 ± 2.8

Values are expressed as means ± SD.
*Significant difference before and after: $P < 0.050$.
**Significant difference before and after: $P < 0.010$.
***Significant difference before and after: $P < 0.001$.
MVT_{iso}, MVT during isometric contractions; MVT_{con}, MVT during concentric contractions; VA_{iso}, voluntary activation during isometric contractions; VA_{con}, voluntary activation during concentric contractions; Q RMS·M^{-1}, normalized RMS averaged across VM, RF, and VL; TW_{PS100}, paired stimuli twitch torque; M_{max}, maximum M-wave.

M_{max} amplitude increased significantly from preexercise values ($P = 0.012$; Table 2). For the control condition, M_{max} values for all muscles were not statistically different from baseline values (Table 2).

DISCUSSION

The present study investigated the effect of a 2000-m rowing time trial on indices of central and peripheral fatigue in elite male and female rowers. The main findings were as follows: (i) the torque-generating capacity of the quadriceps muscle significantly decreased after rowing as indicated by isometric (−20.4% ± 8.9%) and concentric (−18.1% ± 7.3%) MVT reductions; (ii) the rowing time trial induced significant declines in voluntary activation during isometric (−18.2% ± 15.4%) and concentric (−17.6% ± 14.5%) contractions; (iii) Q RMS·M^{-1} significantly decreased by 13.1% ± 4.1%; (iv) significant reductions in RF RMS·M^{-1} were found after rowing, whereas no significant changes were observed for the normalized muscle activity of VM and VL; and (v) no significant changes were found in paired stimuli twitch torque after rowing compared with preexercise values. Furthermore, because indices of central and peripheral fatigue remained unchanged after the control condition, we suggest an absence of any quadriceps muscle fatigue over time and due to the rowing warm-up.

Maximal voluntary torque. The loss in knee extensor strength, indicated by significant reductions in isometric and concentric MVT, demonstrates that quadriceps muscle fatigue occurred after the 2000-m rowing time trial. To the best of our knowledge, to date no study has shown quadriceps muscle fatigue after rowing exercise. The closest rowing can be compared with is cycling, as it involves predominantly concentric contractions of the knee extensor muscles. A similar decay in isometric knee extensor MVT (−18%) has been reported after high-intensity cycling time trials lasting approximately 6 min (52). On the contrary, several studies observed only minor reductions (8%–14%) in isometric knee extensor MVT after cycling time trials lasting 7–8 min (3,4).

Indices of central fatigue. Evidence for central fatigue after the 2000-m rowing is provided by reductions in voluntary activation during isometric (−18.2%) and concentric (−17.6%) contractions as well as decrements in Q RMS·M^{-1} during isometric MVC (−13.1%). Accordingly, both methods attested that the impaired voluntary drive to

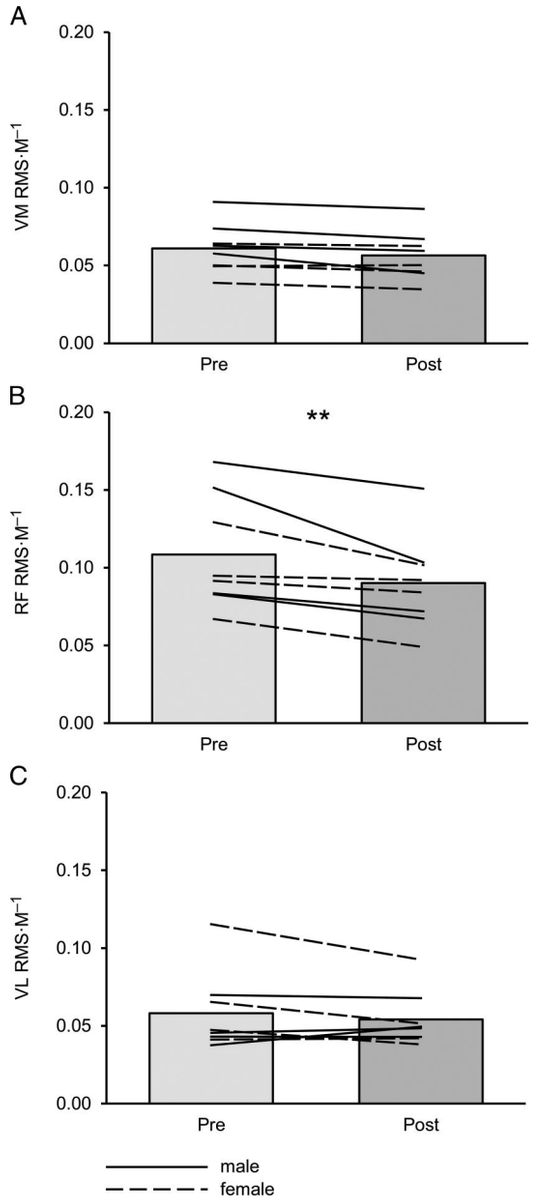

FIGURE 3—Normalized RMS-EMG (RMS·M^{-1}) recorded during isometric MVC. Mean values and individual data for VM (A), RF (B), and VL (C) before and after the 2000-m rowing time trial. Significant before and after change: **$P < 0.010$.

the quadriceps muscle contributed to the knee extensor strength loss after rowing.

In contrast to previous findings, which suggest that central fatigue is greater after longer compared with shorter exercise durations (18,52), we demonstrate a contribution of central factors to knee extensor strength loss already after short-duration endurance exercise (06:46 min). For instance, few comparable studies have shown no (3,4) or only minor reductions (5%−7% [22,52]) in voluntary activation after high-intensity cycling lasting 6–8 min. However, it should be noted that magnetic (3,4) and electrical (22,52) single stimuli were used to assess voluntary activation via the interpolated twitch technique. Because single stimuli have been suggested to produce less extra force and more variable twitch responses during MVC (13), these studies may underestimate the extent to which central fatigue is documented after exercise. Nonetheless, our findings lead us to the assumption that task-specific characteristics of a 2000-m rowing time trial might be responsible for the strong contribution of central factors to knee extensor strength loss after short-duration, high-intensity rowing exercise.

By using $RMS \cdot M^{-1}$, we were able to the estimate neural activation of individual knee extensor muscles. Interestingly, our data revealed significant reductions in RF $RMS \cdot M^{-1}$ during isometric MVC after rowing, whereas no significant changes in normalized muscle activity were observed for VM and VL. These findings suggest that the superficial muscles of the quadriceps were differentially affected by the rowing time trial. Such an observation is not unusual because previous studies have shown that the knee extensor muscles are not homogeneously activated and fatigued during different types of exercise (14,15). Our data seem to be in line with findings from Gerževič et al. (22), who have shown that the median power frequency (MDF) of the RF EMG signal progressively declined throughout a 6-min all-out test on an indoor rower, whereas the MDF of the vastii muscles did not significantly change. Because declines in MDF are thought to be indicative of muscle fatigue (13), these results might support the idea that RF is more fatigued after high-intensity rowing efforts than the vastii muscles. The increased RF muscle fatigue might be the consequence of its biarticular function and its biphasic activity pattern during the rowing stroke (18). RF has been shown to act as knee extensor during the early drive phase and as hip flexor during the early recovery phase (18), whereas the vastii muscles are only active in the former (24). Although single-joint studies have also suggested that RF is more susceptible to fatigue compared with the vastii (15,34), the results of investigations on multijoint leg extension exercise are rather contradictory. Several studies have shown that RF is less activated and does not increase its activity during fatiguing multijoint leg extension exercise, unlike the vastii muscles (10,15). Similar observations were also made by Guével et al. (24) during on-water rowing. However, the reasons for an attenuated RF activation during multijoint leg extension exercise are unclear. It has been suggested that the addition of hip extension leads to increased inhibitory and/or decreased excitatory input to the RF motoneuron pool (16). Finally, the exact causes for reductions in RF $RMS \cdot M^{-1}$ during isometric MVC after rowing remain unclear in the present study. Increased fatigability of the biarticular RF muscle during rowing and/or persistently altered neural input to the RF motoneuron pool might have played a role. Nevertheless, it should be emphasized that EMG data should be interpreted with caution, especially because amplitude cancellation of the EMG signal has been shown to increase during fatiguing exercise (32).

However, the attenuated RF muscle activation might not fully explain the greater reductions in voluntary activation after rowing compared with high-intensity, short-duration cycling exercise. One explanation refers to the additionally active muscle mass during rowing exercise. We propose, in this regard, that impairments in voluntary drive develop to a greater extent during rowing due to a spread of central fatigue from simultaneously working upper body muscles to the knee extensor muscles. This assumption is supported by recent findings from Johnson et al. (30), who found that central fatigue occurred more quickly during cycling when it is preceded by arm-cranking exercise. This effect was attributed to the inhibitory feedback of metabosensitive group III/IV afferents. Regarding to our results, it is conceivable that inhibitory muscle afferent feedback from simultaneously working upper body muscles led to further impairments in the voluntary activation of the remote quadriceps muscle. Evidence for metabosensitive muscle afferents as a contributor to a "spillover" of central fatigue was recently provided by Sidhu et al. (44), who reported a significant reduction in the cortical voluntary activation of the unexercised elbow flexors after high-intensity cycling exercise. This "spillover" of supraspinal fatigue was abolished after attenuating the group III/IV afferent feedback from the locomotor muscles using intrathecal fentanyl injections. Therefore, in addition to factors such as contraction mode, exercise duration, and intensity, the amount of active muscle mass involved in the task might affect the development of central fatigue during endurance exercise.

Besides inhibitory effects of metabosensitive afferents and reductions in RF muscle activation, several other mechanisms might be responsible for impairments in voluntary drive after rowing. In the present study, we found more a than twofold rise in $[NH_3]_b$ after rowing. Despite a lack of direct evidence, exercise-induced cerebral ammonia uptake is thought to be associated with central fatigue (38); hence, it cannot be ruled out that cerebral ammonia uptake has contributed to impairments in voluntary drive after rowing. Furthermore, brain neurotransmitter concentrations (33) and/or cerebral deoxygenation (53) might also affect the development of central fatigue. Nonetheless, by using motor nerve stimulation to assess the voluntary activation of the quadriceps muscle, we were unable to determine whether spinal and/or supraspinal sites contribute to impairments in motoneuron excitation after rowing.

Indices of peripheral fatigue. Despite strong impairments in the torque-generating capacity of the quadriceps muscle after rowing, no significant changes were observed for quadriceps twitch torque in response to paired electrical

stimuli. By contrast, previous studies have typically shown that quadriceps twitch torque in response to single stimuli was significantly decreased by 32%–40% after cycling time trials lasting 6–8 min (3,4,52), suggesting that considerable peripheral fatigue occurs after high-intensity, short-duration cycling exercise. Interestingly, although high levels of quadriceps contraction intensity were observed during the rowing stroke (24), the present data seem to reveal a lack of peripheral fatigue after the 2000-m rowing time trial. A physiological explanation for an absence of peripheral fatigue after rowing points toward the observation that the tolerance limit of peripheral fatigue seems to be regulated in a task-dependent manner (41,52). Particularly in regard to rowing exercise, the active muscle mass might play a role as a determining factor for the development of peripheral fatigue. Because Rossman et al. (41) have shown that increasing the amount of active muscle mass lowers the degree to which peripheral fatigue occurs after dynamic exercise, it might be conceivable that the great amount of active muscle mass during rowing limits the development of peripheral quadriceps fatigue. This assumption receives further support by recent findings from Johnson et al. (30), who reported less peripheral quadriceps fatigue after cycling when it is preceded by arm-cranking exercise. Rossman et al. (41) hypothesized, in this regard, that the CNS tolerates peripheral fatigue to a lesser extent when inhibitory feedback of group III/IV afferents originates from a greater amount of muscle mass.

However, it is important to emphasize that the rowing-induced changes in quadriceps twitch torque are characterized by large interindividual variability, which could also serve as an explanation for the lack of significance (Fig. 2F). Variability in quadriceps twitch response after rowing might be related to interindividual differences in the rowing technique. It is conceivable that subjects who have generated a large proportion of power during the rowing stroke by using their knee extensor muscles would have experienced more peripheral fatigue than participants who have predominantly used their upper body muscles as compensatory strategy to ensure adequate power output. Furthermore, because of a limited access to competitive rowers, our sample comprised both sexes. It has been shown that females are less fatigable compared with males when performing isometric fatiguing contractions. However, these sex-based differences are diminished during shortening contractions, suggesting that sex differences in fatigability are task dependent (28). Individual data from the present study reveal that three out of four female subjects have shown no changes in quadriceps twitch torque after rowing (Fig. 2F). This lack of peripheral fatigue would be in line with studies demonstrating a greater muscle perfusion during exercise (39) and a greater proportional area of type I fibers in females (45). However, present data on sex-specific differences in peripheral fatigue after the 2000-m rowing should be interpreted with caution because of the small sample size.

Interestingly, data revealed a significant rise in RF M_{max} amplitude after rowing, whereas no significant changes in M_{max} were observed for VM and VL. Because M-wave amplitude is commonly used as an index of changes in neuromuscular propagation, our data seem to indicate an exaggerated sarcolemmal excitability of the RF muscle. Similar to the twitch characteristics, the M-wave responses of a muscle depend on the contraction history (27) as well as the fiber type composition of a muscle (26). Because potentiation and fatigue-induced depression of M-wave amplitude have shown to be greater in muscles with a higher percentage of type II fibers (26), the higher proportion of type II fibers in RF (29) and a lower muscle activation during rowing compared with the vastii muscles (24) might be responsible for the increase in RF M_{max} amplitude after the rowing time trial. Nevertheless, as stated previously (12), the validity of M_{max} amplitude as an index of fatigue-related changes in neuromuscular propagation remains questionable.

LIMITATIONS

In the present study, neuromuscular testing was performed with a mean time lag of 03:15 min after exercise termination. Although this is common in studies investigating muscle fatigue induced by whole-body endurance exercise, Froyd et al. (20) have shown that substantial recovery in twitch torque occurs within 2 min after single-joint exercise. By contrast, a recent study by Blain et al. (8) has demonstrated persistent reductions in quadriceps twitch torque for at least 15 min after a high-intensity cycling time trial. On the basis of these ambiguous findings, one might suggest that the recovery process of twitch amplitude depends on the contraction history of the muscle group. Therefore, it cannot be ruled out that the lack of change in paired stimuli twitch torque might result from the recovery process within the time lag between time trial termination and postexercise measurements.

CONCLUSION

The 2000-m rowing time trial resulted in significant quadriceps muscle fatigue. Our data further revealed large impairments in voluntary drive to the knee extensors after high-intensity rowing exercise for 6–7 min. In particular, the neural drive to the RF muscle was significantly decreased after rowing whereas no changes were observed for the vastii muscles. Furthermore, the present results showed that there was no significant change in indices of peripheral fatigue after intense rowing in elite rowers. The present results are in contrast to previous findings, which have typically shown that short-duration endurance exercise primarily induces peripheral and rather less central fatigue (52). Therefore, we conclude that muscle fatigue of the knee extensor muscles after high-intensity rowing exercise was explained primarily by central factors that led to large reductions in voluntary drive. The attenuated the neural activation of the biarticular RF muscle and/or the great amount of active muscle mass might be responsible for the pronounced contribution of central factors to quadriceps muscle fatigue after the 2000-m rowing in elite male and female rowers.

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Brief Report

Mental Fatigue Increases Gait Variability During Dual-task Walking in Old Adults

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Abstract

Background: Mental fatigue is a psychobiological state induced by sustained periods of demanding cognitive activity and is characterized by feelings of tiredness which are common in everyday life. Recently, it has been hypothesized that mental fatigue might have an impact on gait performance in old adults. Therefore, the effect of mental fatigue on gait performance under single- and dual-task conditions was investigated in young and old participants.

Methods: Spatio-temporal gait parameters of 16 young and 16 old healthy participants were measured using a photoelectric system during single- and dual-task walking before and after a randomly assigned mental fatigue (performing a stop-signal task for 90 minutes) and control intervention (watching a video for 90 minutes), respectively. Changes in subjective fatigue, wakefulness, mood, arousal, and psychophysiological workload (heart rate variability indices) were assessed.

Results: Psychometric measures indicated increased subjective fatigue and arousal as well as decreased mood and wakefulness after the mental fatigue task. Heart rate variability indices revealed a higher psychophysiological workload during the mental fatigue intervention in old compared to young participants. Gait measures (coefficient of variation of speed, stride length, and stance time) revealed impaired dual-task walking performance following the mental fatigue intervention only in old participants.

Conclusion: Data indicate that mental fatigue, induced by sustained cognitive activity, can impair gait performance during dual-task walking in old adults. The susceptibility to mental fatigue could be a new intrinsic risk factor for falls in older people and should be taken into account when dual-task gait analyses are performed.

Keywords: Cognitive fatigue, State fatigue, Trait fatigue, Gait analysis, Aging, Cognitive-motor interference, Fall risk

According to Enoka and Duchateau (1) fatigue can be defined as a self-reported disabling symptom which is derived from two interdependent attributes: perceived fatigability and performance fatigability. Perceived fatigability is characterized by changes in the sensations that regulate the integrity of the performer, whereas performance fatigability is related to changes in objective measures of performance over a defined period of time. Based on this assumption, the symptom fatigue can only be measured by self-report and requires the individual to interpret relevant psychological and physiological factors. Similar to other symptoms, fatigue can be assessed as a trait characteristic or a state variable. While the trait level of fatigue comprises the fatigue experienced during the previous day(s), the state level of fatigue reflects the rate of change of fatigue during a fatiguing task (for reviews, see refs. (1,2)). In general, fatigue can emerge after physical as well as cognitive activity.

Prolonged and/or sustained periods of demanding cognitive activity can result in state fatigue, here termed mental fatigue. Some authors prefer the term cognitive fatigue to describe the psychobiological state associated with sustained cognitive activity. However, it has been recently proposed that the term mental fatigue is more

appropriate, since it also includes motivational and emotional aspects associated with task accomplishment and not only cognition (3). Mental fatigue can manifest subjectively (ie, feelings of tiredness or even exhaustion) and/or objectively (ie, change in cognitive and behavioral performance as well as physiological correlates) (3–5). The extent of mental fatigue largely depends on the amount of time spent on a given task (6) and is probably modulated by task complexity.

Recently, it was hypothesized that mental fatigue might have an impact on gait performance in old adults. This assumption is based on the outcome of studies that have shown an association between poor cognitive function and poor gait performance in healthy older people (7). Conversely, the acute increase of cognitive functioning, for example, by ingestion of methylphenidate, has been shown to decrease gait variability in old adults (8). Moreover, it has been revealed that the level of trait fatigue was associated with an attenuated increase in prefrontal cortex oxygenation from single- to dual-task walking as well as an altered trajectory of the oxygenation signal during the completion of repetitive dual-task walking trials (9). Based on the outcomes of the above-mentioned studies, temporarily impaired cognitive functioning due to mental fatigue could have distinct effects on gait performance especially during dual-task walking, for example, walking while simultaneously performing a cognitive interference task. Structural and functional changes within the brain have been observed with aging probably leading to a decline in cognitive performance which is particularly associated with dual-task gait measures (10). By contrast, the relationship between cognitive performance and dual-task gait measures was not observed in young adults (11). Therefore, it might be that the susceptibility to mental fatigue and the potential decline in gait performance is more pronounced in older compared to younger adults. To the authors' knowledge, no study exists that has investigated the impact of mental fatigue, induced by sustained cognitive activity, on single- and dual-task gait performance in young and old adults. In consideration of this, we assessed single- and dual-task walking performance in young and old participants before and after a randomly assigned mental fatigue and control intervention, respectively. It was hypothesized that mental fatigue impairs gait performance in old adults, in particular while performing a concurrent attention demanding cognitive interference task.

Methods

Participants

Sixteen young and 16 old participants without known history of neurological disorders and/or musculoskeletal injuries volunteered to participate in the present study. Demographic characteristics of the participants are given in Supplementary Table 1. All volunteers were informed about the experimental procedures and possible risks associated with the experiment before giving their written consent. The participants were asked to refrain from strenuous exercise as well as alcohol and caffeine consumption 48 hours prior to the experiments. The study was conducted according to the declaration of Helsinki and was approved by the local ethics committee.

Experimental Protocol

This study employed a randomized and counterbalanced cross-over design. The participants visited the laboratory on two different occasions with at least one week in between. They completed questionnaires and were instructed regarding the experimental procedures. During the experiments, participants completed two randomly assigned interventions on different days: (i) stop-signal task for 90 minutes to induce mental fatigue and (ii) control treatment consisting of watching a neutral video for 90 minutes. Before and after each intervention subjective fatigue, wakefulness, mood, arousal as well as gait performance under single- and dual-task conditions were recorded. The order of the gait tests was randomized.

Questionnaires

The Mini-Mental State Examination (MMSE) was applied to verify proper cognitive functioning of the participants (12). Furthermore, the Falls Efficacy Scale International (FES-I) was used as a measure of fall related self-efficacy in older persons (13). The Modified Fatigue Impact Scale (MFIS) was utilized to assess trait fatigue and the fatigue scale of the Profile of Mood States (POMS-F) was used to measure state fatigue (14). Moreover, the Multidimensional Mood Questionnaire (MDMQ) was employed to assess wakefulness, mood, and arousal (15).

Gait Analysis

Spatio-temporal gait parameters were measured using a photoelectric walkway (OptoGait, Microgate, Italy) as described previously (16,17). Briefly, participants walked in their own, flat shoes through a 6-m walkway at self-selected comfortable gait speed, starting and stopping each trial 2 m before and after the walkway. During the gait tests, the subjects wore always the same shoes. Two familiarization and five experimental trials were performed for the single- and dual-task condition, respectively. The order of the gait tests was randomized. The following parameters were calculated: speed normalized to height (speed × height^{-1}), step length and stride length normalized to height (step length × height^{-1}, stride length × height^{-1}), step time, single support time, double support time, stance time, and swing time. Furthermore, the coefficient of variation (CV), an index of gait variability and a predictor of falls in older adults (18), was calculated for each parameter (CV = standard deviation × mean^{-1} × 100).

Cognitive Interference Task

In addition to the single-task walking trials, gait parameters were also recorded while performing a concurrent attention demanding cognitive interference task (without explicit instructions regarding prioritization). The task consisted of serial subtractions by three, starting from a randomly selected number between 300 and 900. The results of this arithmetic task had to be recited verbally by the participants and the cognitive interference task performance was calculated by subtracting the number of mistakes from the total number of subtractions. The higher the value, the better the performance (19).

Psychophysiological Workload

Psychophysiological workload during the 90 minutes lasting mental fatiguing and control task was analyzed using heart rate variability. Inter-heartbeat intervals (RRI) were continuously recorded during both interventions using a heart rate monitor (Polar Electro, Finland). The root mean square of the successive differences of adjacent RRI (RMSSD) and the natural log-transformed power in the low frequency range (0.05–0.15 Hz) of the R-R frequency spectrum (lnLFP), both able to reflect mental effort (20,21), were calculated (Kubios HRV 2.2, University of Kuopio, Finland).

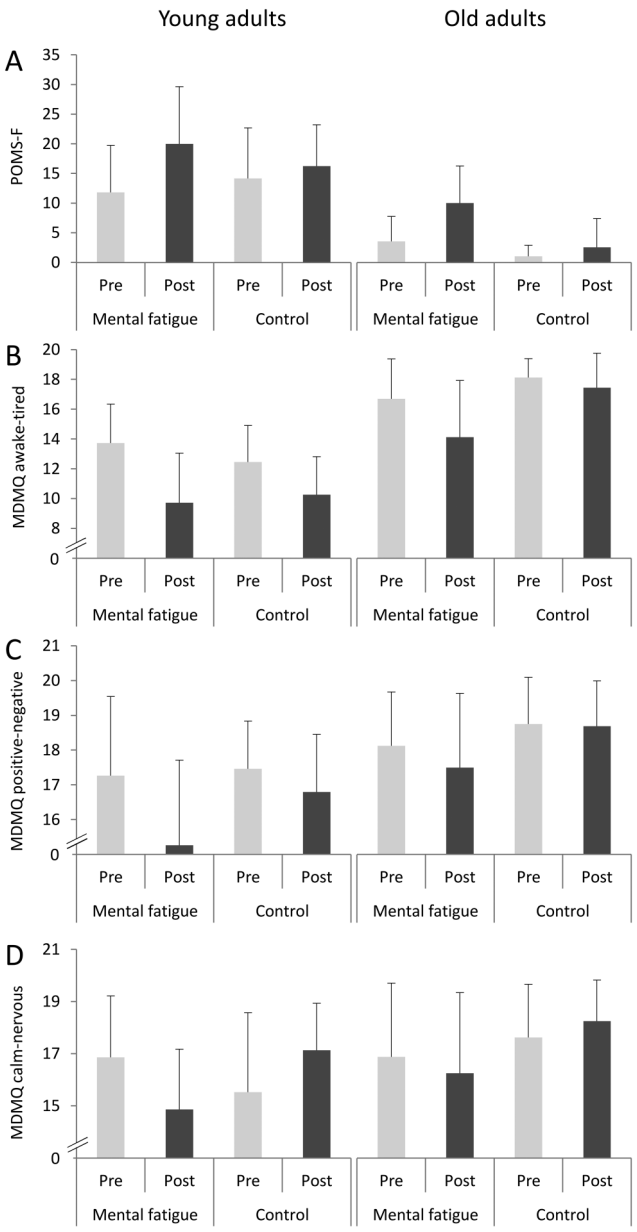

Figure 1. State fatigue (Profile of Mood States-Fatigue, POMS-F) (**A**) as well as the dimensions wakefulness (awake-tired) (**B**), mood (positive-negative) (**C**), and arousal (calm-nervous) (**D**) of the Multidimensional Mood Questionnaire (MDMQ) for the young and old participants before and after the mental fatigue and control intervention. Please note that the lower the value of the respective MDMQ score, the more tired, negative and nervous the participants felt. Time × condition interactions were observed for these variables indicating that mental fatigue was induced successfully in all participants.

Mental Fatigue and Control Intervention

During the mental fatigue intervention, participants had to perform a stop-signal task (22) for 90 minutes on a personal computer. This task is a commonly used laboratory measure of inhibitory control that consisted of presenting concurrent go and stop tasks. Participants had to press a button with the right or left hand as quickly and accurately as possible in response to the visual presentation of the letter X or O, respectively. The stop signal consisted of a delayed tone presented by headphones and, if it occurred, required stopping the ongoing response to the letter X or O. To increase engagement in and motivation for the stop-signal task, a cash prize was announced. The stop-signal reaction times were computed (23,24) to monitor performance during the mental fatiguing task. The average of this parameter was calculated for eight blocks during the stop-signal task. The control intervention consisted of watching the documentary "Earth" for 90 minutes on the same computer used for the mental fatigue task (25).

Statistical Analyses

Data were screened for normal distribution using the Shapiro-Wilk test. Data analysis of the performance measures during the mental fatigue task revealed missing values. To account for missing data, multiple imputation (10 imputed data sets) with the Markov Chain Monte Carlo method was used (26). Repeated measures analyses of variance (ANOVAs) with time of measurement (pre, post) as well as condition (mental fatigue, control) as within-subject variables and group (young, old) as between-subject variable were conducted for the average of each parameter. Due to the unequal distribution of males and females between groups, sex was entered as a covariate. In case of statistical significant interactions, Bonferroni-corrected post-hoc tests were carried out. Effect sizes were expressed as partial eta-squared (η_p^2). The level of statistical significance was set at $p \leq .050$. In addition, tendencies towards statistical significance were also interpreted ($p \leq .055$). Data were analyzed using the SPSS statistical package 22.0 (SPSS Inc., USA).

Results

Questionnaires

The scores of the MMSE (28.3 ± 1.6) and FES-I (18.3 ± 1.5) indicated that the old participants were cognitively healthy and without any serious concerns about falling. MFIS scores, a measure of trait fatigue, did not differ between groups (young: 14.6 ± 10.0, old: 11.4 ± 8.9, $p = .424$).

Significant main effects of time, condition, and group were found for the POMS-F, a measure of state fatigue. A time × condition interaction was observed for the POMS-F (Supplementary Table 2). Post-hoc analysis revealed that the POMS-F score increased significantly in both groups after performing the mental fatigue task (mental fatigue: $p < .001$, control: $p = .115$).

Several significant main and interaction effects of time, condition, and group were found for the MDMQ wakefulness, mood and arousal scores. Time × condition interactions were observed for the MDMQ wakefulness, mood and arousal scores (supplemental Table 2). Post-hoc analysis showed that the participants felt more tired following the mental fatigue task (mental fatigue: $p < .001$, control: $p < .001$). In addition, significant changes of the participants' scores towards negative mood (mental fatigue: $p = .001$, control: $p = .072$) and feeling nervous (mental fatigue: $p = .016$, control: $p = .286$) were only observed in the mental fatigue condition (Figure 1, Supplementary Table 3). No time × condition × group interactions were found.

Gait Performance

Single-task walking

Significant main and interaction effects of time, condition, and group were observed for several single-task gait parameters. Significant time × condition interactions were found for the parameters speed × height^{-1}, step length × height^{-1}, stride length × height^{-1}, step time,

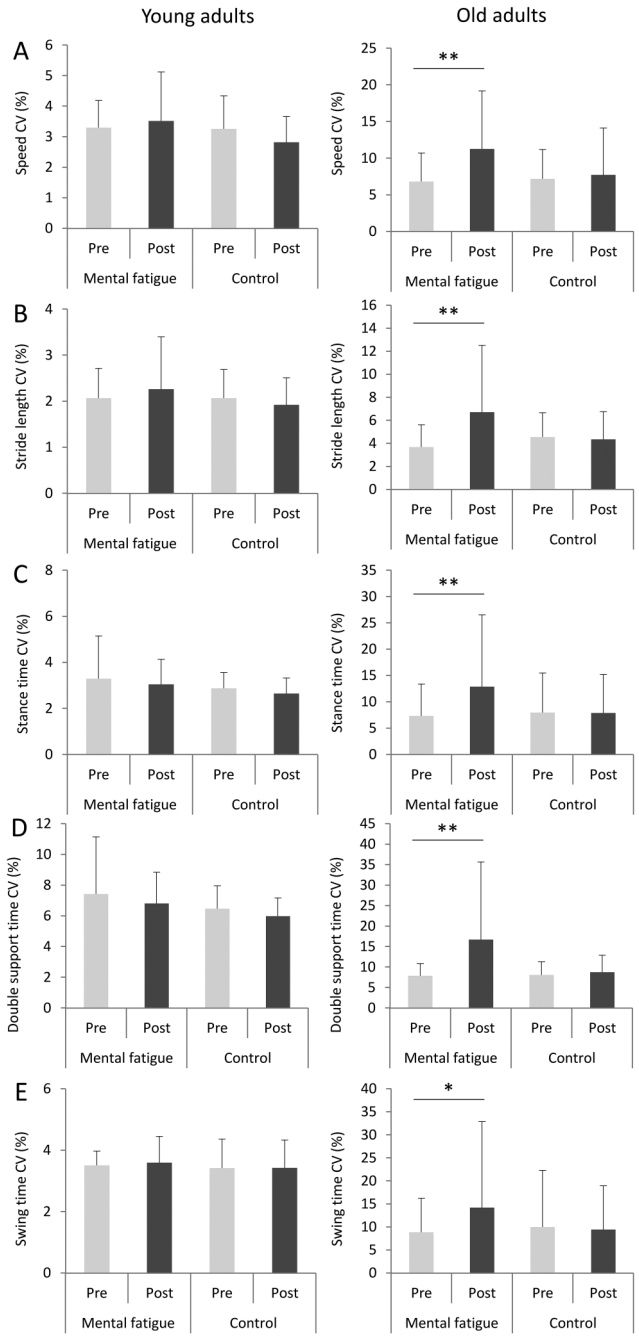

Figure 2. Coefficient of variation (CV) for the spatio-temporal dual-task gait parameters speed (**A**), stride length (**B**), stance time (**C**), double support time (**D**), and swing time (**E**) for the young and old participants recorded before and after the mental fatigue and control intervention, respectively. *p = .013, **$p \leq .008$.

double support time, $CV_{single\ support\ time}$, $CV_{stance\ time}$, and $CV_{swing\ time}$ (Supplementary Table 2). However, post-hoc analyses did not yield a significant change of any variable over time. No time × condition × group interactions were found (Supplementary Table 4).

Dual-task walking

Significant main and interaction effects of time, condition, and group were observed for several dual-task gait parameters. No time × condition interactions were found. Significant and tendential significant time × condition × group interactions were revealed for the parameters CV_{speed}, $CV_{stride\ length}$, $CV_{double\ support\ time}$, $CV_{stance\ time}$, and $CV_{swing\ time}$ (Supplementary Table 2). Post-hoc analyses yielded significant changes of these variables over time in the mental fatigue condition only for the old participants (Figure 2, Supplementary Table 5).

Cognitive Interference Task Performance

A significant main effect of group and interaction effects of time, condition, and group were observed for the cognitive interference task performance (Supplementary Table 2). A significant time × condition interaction was found for the cognitive interference task performance (Supplementary Table 2). Post-hoc analysis revealed that the performance index decreased significantly in both groups after performing the mental fatigue task (mental fatigue: p = .016, control: p = .286). No time × condition × group interactions were found (Supplementary Table 3).

Psychophysiological Workload

Significant main and interaction effects of time, condition, and group were found for the heart rate variability measures. Significant condition × group interactions were found for lnLFP and RMSSD (Supplementary Table 2). Post-hoc analyses revealed that, compared to the young participants, RMSSD (p = .022) and lnLFP (p = .002) in the old participants were lower during the mental fatiguing task but not during the control condition (p = .196 and p = .063) (Supplementary Table 3).

Performance Measure During the Mental Fatigue Intervention

Missing data amounted 8.5% and was refilled using multiple imputation (see statistical analyses). A significant main effect of group was observed for stop-signal reaction time (Supplementary Table 2). The stop-signal reaction times of the young and old participants did not change significantly over time and no time × group interaction was found (Supplementary Table 6).

Discussion

The present study was designed to investigate, for the first time, the effect of an increased level of state fatigue induced by sustained cognitive activity, that is, mental fatigue, on single- and dual-task gait performance in young and old adults. Changes in self-reported state fatigue as well as in self-reported wakefulness, mood, and arousal indicate that mental fatigue was induced successfully in our participants. This is in line with the results of studies that have used a similar computer-controlled task to provoke mental fatigue (25). Heart rate variability analyses implicate a stronger psychophysiological workload response and a higher cognitive effort during the mental fatiguing task in the old adults (20,21). However, performance measure during the stop-signal task did not change significantly. An increase in subjective measures of mental fatigue without a change in performance during the fatiguing task has been revealed in various studies. Therefore, it has been stated that mental fatigue does not necessarily lead to performance decrements during the fatiguing task (5). Recently, Holtzer et al. (9) analyzed the effect of trait fatigue, assessed over a 24-hour period, on dual-task gait measures in old adults. They could not reveal an association between subjective fatigue and dual-task gait performance. However, they have shown that stride velocity declined progressively during the completion of

repetitive dual-task walking trials but not during single-task walking trials. Thus, they suggested that the decrease in stride velocity during dual-task walking could serve as an index for objective mental fatigue during this motor task.

In accordance with our hypothesis, mental fatigue negatively affected gait variability. Interestingly, this was only observed for the old participants in the dual-task condition. Data indicate that dual-task gait variability, in terms of walking speed, stride length, stance time, double support time, and swing time, increased significantly following the mental fatiguing task only in the old participants. In addition, cognitive interference task performance was decreased following the mental fatiguing task in all participants.

It has been shown that specific brain areas (eg, prefrontal cortex, parietal areas) are more and/or additionally activated during dual-task compared to single-task walking. Moreover, brain areas implicated in dual-task walking are also involved in executive functioning, indicating that executive resources are essential for dual-task walking (27). Structural alterations of the brain, for example, in the prefrontal areas, have been observed with aging. This factor has been identified as a contributor to decreased gait performance under dual-task conditions in older people (10). Challenging these brain areas by means of a mental fatiguing task seems to increase gait variability during dual-task walking and impairs cognitive interference task performance in the old age. This effect of mental fatigue on gait variability during dual-task walking was not observed in young people. These results indicate that young adults can cope with the cognitive interference task in a mental fatigued state without attenuating (i) processing capacity for the motor task (central capacity sharing model) and/or (ii) sequential neural processing of the motor and cognitive interference task (bottleneck model) (27).

The following limitations should be considered when interpreting the results of the current study. First, although the effect of mental fatigue on dual-task gait performance of the old participants could be demonstrated, the sample size was relative small and a large number of measures was performed. Thus, further studies should be conducted to verify the present preliminary results. Second, although the old participants seemed to be active according to their self-reported physical activity level, the physical status was not quantified and its effect on the outcome measures is unknown. Third, it might be reasonably assumed that the dual-task gait parameters, which underwent a significant change, are highly related to each other. Thus, one of these parameters could be used as a surrogate in future studies. Although it is currently common, the present study was not notified to a clinical trial register and therefore lacks a trial registration number.

In conclusion, data indicate, for the first time, that mental fatigue, induced by sustained cognitive activity, can impair gait performance during dual-task walking in old adults. Therefore, the susceptibility to mental fatigue could be a new intrinsic risk factor for falls in older people. Moreover, the potential influence of mental fatigue on gait measures should be taken into account when dual-task gait analyses are performed in a scientific or clinical context. That is, state as well as trait fatigue should be assessed prior to the measurements and should be considered when interpreting the results. Future studies should investigate (i) the underlying neural mechanisms by using neurophysiological techniques, (ii) when aging starts to exert negative effects on dual-task gait performance during states of mental fatigue, and (iii) the dose-response relationship between the extent of mental fatigue and the increase in gait variability in older adults. The latter aspect is of particular importance due to the fact that the extent of mental fatigue largely depends on the amount of time spent on a given task (6) and is probably modulated by task complexity. Besides the effect of mental fatigue on dual-task gait performance in healthy older adults, the relevance of our findings for patient populations, particularly those with neurologic diseases showing a high prevalence and severity of fatigue symptoms, should be analyzed.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Conflict of Interest

None reported.

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Neuromuscular function and fatigue resistance of the plantar flexors following short-term cycling endurance training

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Previously published studies on the effect of short-term endurance training on neuromuscular function of the plantar flexors have shown that the H-reflex elicited at rest and during weak voluntary contractions was increased following the training regime. However, these studies did not test H-reflex modulation during isometric maximum voluntary contraction (iMVC) and did not incorporate a control group in their study design to compare the results of the endurance training group to individuals without the endurance training stimulus. Therefore, this randomized controlled study was directed to investigate the neuromuscular function of the plantar flexors at rest and during iMVC before and after 8 weeks of cycling endurance training. Twenty-two young adults were randomly assigned to an intervention group and a control group. During neuromuscular testing, rate of torque development, isometric maximum voluntary torque and muscle activation were measured. Triceps surae muscle activation and tibialis anterior muscle co-activation were assessed by normalized root mean square of the EMG signal during the initial phase of contraction (0–100, 100–200 ms) and iMVC of the plantar flexors. Furthermore, evoked spinal reflex responses of the soleus muscle (H-reflex evoked at rest and during iMVC, V-wave), peak twitch torques induced by electrical stimulation of the posterior tibial nerve at rest and fatigue resistance were evaluated. The results indicate that cycling endurance training did not lead to a significant change in any variable of interest. Data of the present study conflict with the outcome of previously published studies that have found an increase in H-reflex excitability after endurance training. However, these studies had not included a control group in their study design as was the case here. It is concluded that short-term cycling endurance training does not necessarily enhance H-reflex responses and fatigue resistance.

Keywords: explosive voluntary strength, maximal voluntary strength, H-reflex, V-wave, M-wave

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Introduction

Strength and endurance training are commonly used in physical training and rehabilitation programs. While a lot of studies have investigated and described neural and muscular adaptations

to strength training (Aagaard et al., 2002; Del Balso and Cafarelli, 2007; Andersen and Aagaard, 2010; Ekblom, 2010), there are only a few studies available that have analyzed the effect of short-term (several weeks) endurance training on neural plasticity at the spinal and supraspinal level at rest and during isometric maximum voluntary contraction (iMVC) (Vila-Cha et al., 2012b; Zghal et al., 2014).

The electrically evoked Hoffmann reflex (H-reflex) and the volitional wave (V-wave) can be used to analyze intervention-induced modulations at the spinal level (Aagaard et al., 2002; Zehr, 2002). These evoked potentials are elicited by electrical stimulation of the posterior tibial nerve in the popliteal fossa and their amplitudes can be recorded in the soleus muscle (SOL). The H-reflex assesses the excitability of α-motoneurons via the Ia afferent pathway (Schieppati, 1987) whereas the V-wave is a measure of the descending neural drive from the α-motoneurons to the muscle (Aagaard et al., 2002).

Cross-sectional studies have revealed that stretch reflexes and H-reflexes elicited at rest are higher in athletes engaged in long-term (several years) endurance training than in athletes engaged in long-term power training (Kyrolainen and Komi, 1994a,b; Maffiuletti et al., 2001). Furthermore, longitudinal studies indicate that even short-term endurance training is able to modulate stretch reflex and H-reflex excitability of SOL (Perot et al., 1991; Vila-Cha et al., 2012b). It has been argued that the increased H-reflex after endurance training is the result of an altered responsiveness of the α-motoneuron pool to the Ia afferent volley and/or changes in presynaptic inhibition of Ia afferents (Vila-Cha et al., 2012b).

However, Perot et al. (1991) have not included a control group in their study design in order to compare the results of the endurance training group to individuals without the training stimulus. The authors reported that 75% of the investigated subjects showed an increased stretch reflex and H-reflex excitability after endurance training while in the remaining subjects no change or even a decrease in these parameters was evident. The study performed by Vila-Cha et al. (2012b) compared the effect of two different training regimes, i.e., 3 weeks of either endurance training on a cycle ergometer or strength training, on neuromuscular function of the plantar flexors. Thus, this study was lacking a control group without any systematic training stimulus as well. Furthermore, although data of the cited studies indicate that the H-reflex at rest and during weak voluntary contractions is increased in response to short-term endurance training (Perot et al., 1991; Vila-Cha et al., 2012b), nothing is known about H-reflex modulation during iMVC. Even though it has been shown that V-wave responses of SOL and cortical voluntary activation of the knee extensors were unchanged following short-term endurance training (Vila-Cha et al., 2012b; Zghal et al., 2014), H-reflex modulation during iMVC is of particular interest because it has been revealed that endurance athletes possess a greater iMVC strength compared to sedentary subjects (Lattier et al., 2003). Therefore, it is not unlikely that endurance training alters the contribution of the Ia afferent pathway to the muscle activity during iMVC.

In addition, fatigue resistance following a period of endurance training was previously tested by sustained isometric contractions using a defined percentage of iMVC strength until task failure. With this approach it has been shown that time to task failure increases following endurance training (Vila-Cha et al., 2012a,b). However, the time to task failure does not provide information regarding neural and muscular contributions to improved resistance to fatigue. Therefore, we applied the same dynamic fatigue protocol, i.e., with the same load, repetitions and range of motion, before and after the training period to assess the changes in neuromuscular function of the plantar flexors. With this approach we wanted to find out if endurance training is able to reduce the performance decrements associated with fatigue.

Accordingly, we analyzed the effect of an 8-week cycling endurance training period on neuromuscular function of the plantar flexors in this randomized controlled study. In particular, isometric explosive and maximum voluntary strength of the plantar flexors, normalized muscle activity of the plantar flexors and tibialis anterior muscle (TA) as well as electrically evoked spinal reflex responses (H-reflex at rest and during iMVC; V-wave) of SOL and contractile properties of the plantar flexors were analyzed. In addition selected variables, representing neural and muscular function of the plantar flexors, were again tested after a defined fatigue protocol with the same load, repetitions and range of motion before and after the training period.

We hypothesized that cycling endurance training would increase the normalized H-reflex at rest and during iMVC. Furthermore, we expected a reduction of the fatigue-induced performance decrements with regard to neural and muscular factors in the training group.

Materials and Methods

Subjects

Twenty-two recreationally active subjects (moderate exercise <3 times per week, respectively, activities included swimming, strength training of the upper extremities and different sport games) with no history of neurological disorders or injuries volunteered for this study. The participants were randomly assigned to an intervention group and a control group using randomization by a computer-generated table of random numbers. The intervention group consisted of 11 subjects (6 females, 5 males, age: 24 ± 2 years, height: 172 ± 6 cm, body mass: 71 ± 8 kg), while 11 subjects were assigned to the control group (6 males, 5 females, age: 23 ± 2 years, height: 174 ± 6 cm, body mass: 70 ± 5 kg). Participants were not engaged in a systematic endurance training program in the 8 weeks prior to the study. The subjects were asked to avoid caffeine and alcohol consumption in the 24 h prior to the measurements. In addition, study participants were asked not to perform any strenuous exercise in the 48 h before the measurements. The study was conducted according to the declaration of Helsinki and was approved by the university's ethics committee.

Endurance Training

The subjects of the intervention group trained on a cycle ergometer (SP-SRP-3000, SportPlus, Hamburg, Germany) twice a week for 8 weeks with a total of 16 training sessions (at least 1 day rest between the training sessions). Each training

session lasted approximately 60 min and was supervised by experienced instructors. The endurance training was performed in accordance with a previously published study on neuromuscular function of the plantar flexors following endurance training (Vila-Cha et al., 2012b). Exercise intensity was regulated according to the approach used by Dimeo et al. (1997) (with maximal heart rate estimated by 220 minus age in years). Individual exercise intensity during the training sessions was permanently monitored by heart rate monitors (Polar S810i, Kempele, Finland). The prescribed exercise intensities during the training are displayed in **Table 1**. The control group was asked to maintain their individual level of physical activities.

Experimental Procedure and Fatigue Protocol

Neuromuscular function of the plantar flexors was measured prior to and after 8 weeks of either endurance training or a control period without the systematic training stimulus. The tests were performed under the same standardized conditions. To avoid H-reflex and M-wave potentiation no warm-up was utilized before neuromuscular testing (Folland et al., 2008). The measurements were performed on the triceps surae muscle and TA of the right leg. The participants were comfortably seated in a standardized position on a CYBEX NORM dynamometer during the testing sessions (Computer Sports Medicine®, Inc., Stoughton, MA, USA). Prior to neuromuscular testing, the subjects sat passively on the dynamometer for ∼5 min in order to minimize potentiation effects from walking to the laboratory.

TABLE 1 | Exercise intensity as a percentage of estimated maximal heart rate (HR_{max}) during the 8 weeks of endurance training.

Weeks	First training session		Second training session	
	Intensity	Duration (min)	Intensity	Duration (min)
1	80% HR_{max}	40	80% HR_{max}	40
2	80% HR_{max}	45	80% HR_{max}	45
3	80% HR_{max}	50	80% HR_{max}	50
4	70% HR_{max}	15	80% HR_{max}	55
	90% HR_{max}	10		
	70–80% HR_{max}	20		
5	70% HR_{max}	15	70% HR_{max}	15
	90% HR_{max}	10	90% HR_{max}	10
	70–80% HR_{max}	20	70–80% HR_{max}	25
6	70% HR_{max}	15	70% HR_{max}	15
	90% HR_{max}	15	90% HR_{max}	15
	70–80% HR_{max}	20	70–80% HR_{max}	25
7	70% HR_{max}	10	70% HR_{max}	10
	90% HR_{max}	10	90% HR_{max}	15
	70–80% HR_{max}	10	70–80% HR_{max}	10
	90% HR_{max}	10	90% HR_{max}	10
	70–80% HR_{max}	10	70–80% HR_{max}	10
8	70% HR_{max}	10	80% HR_{max}	55
	90% HR_{max}	15		
	70–80% HR_{max}	10		
	90% HR_{max}	10		
	70–80% HR_{max}	10		

Testing included different neuromuscular tests consisting of submaximal and supramaximal electrical stimulations of the posterior tibial nerve at rest and during iMVC (**Figure 1**).

Following this procedure subjects had to perform a standardized fatigue protocol consisting of dynamic plantar flexions in the isotonic mode of the CYBEX NORM dynamometer. Exercise intensity was 40% of iMVC strength and the subjects performed 35 contractions/min timed by a digital metronome. The fatigue protocol was stopped if the participants were not able to keep the metronome-guided contraction frequency or their individual range of motion for five consecutive contractions. After the fatigue protocol a further series of neuromuscular tests was performed (**Figure 1**). The same fatigue protocol, i.e., with the same load, repetitions and range of motion as before the training, was applied after the training intervention. With this approach we wanted to find out if endurance training is able to reduce the performance decrements associated with fatigue.

Electrical Stimulation

Electrical stimulation was performed as described previously (Behrens et al., 2015a,b). Briefly, the posterior tibial nerve was stimulated transcutaneously by two electrodes fixed in the popliteal fossa (cathode) and immediately distal to the patella on the anterior aspect of the knee (anode). A constant-current stimulator (Digitimer® DS7A, Hertfordshire, UK) in combination with a train/delay generator (Digitimer® DG2A, Hertfordshire, UK) allowed electrical stimulation (1 ms duration, 400 V maximal voltage). Identification of peak-to-peak maximal H-reflex (H_{max}) and maximal M-wave (M_{max}) of SOL was achieved by random stimulation (inter stimulus interval 7 s) with different current intensities. The H-reflex during iMVC (H_{sup}) was elicited 2 s after torque onset during the plateau of the torque-time curve with H_{max} intensity to record the small M-wave preceding H_{sup} (M_{Hsup}) and H_{sup}. M_{max} responses at rest and during iMVC (M_{sup}) as well as V-wave responses during iMVC were evoked with supramaximal stimulation intensity (140%).

Resting twitch torques were evoked using supramaximal single (1 ms duration, 400 V maximal voltage) and doublet stimuli (1 ms duration, 10 ms apart, 400 V maximal voltage). M_{max} amplitudes of TA were evoked by stimulating the peroneal nerve close to the fibular head with supramaximal stimuli. Following the fatigue protocol, a H-reflex mini-recruitment curve was established in order to adjust stimulation intensity for H-reflex, M-wave, V-wave and contractile properties testing as recommended (Rupp et al., 2010).

EMG and Torque Recordings

Surface EMG was recorded using bipolar EMG Ambu® Blue Sensor N electrodes (2 cm diameter) firmly attached to the shaved, abraded and cleaned skin over the muscle bellies of SOL, medial gastrocnemius, lateral gastrocnemius and TA of the right leg and the tibia of the ipsilateral leg (reference electrode). A digital multimeter (MY-68, McVoice, Braunschweig, Germany) was used to measure the resistance between electrodes (<5 kΩ). Signals were amplified (2500×), band-pass filtered (10–450 Hz),

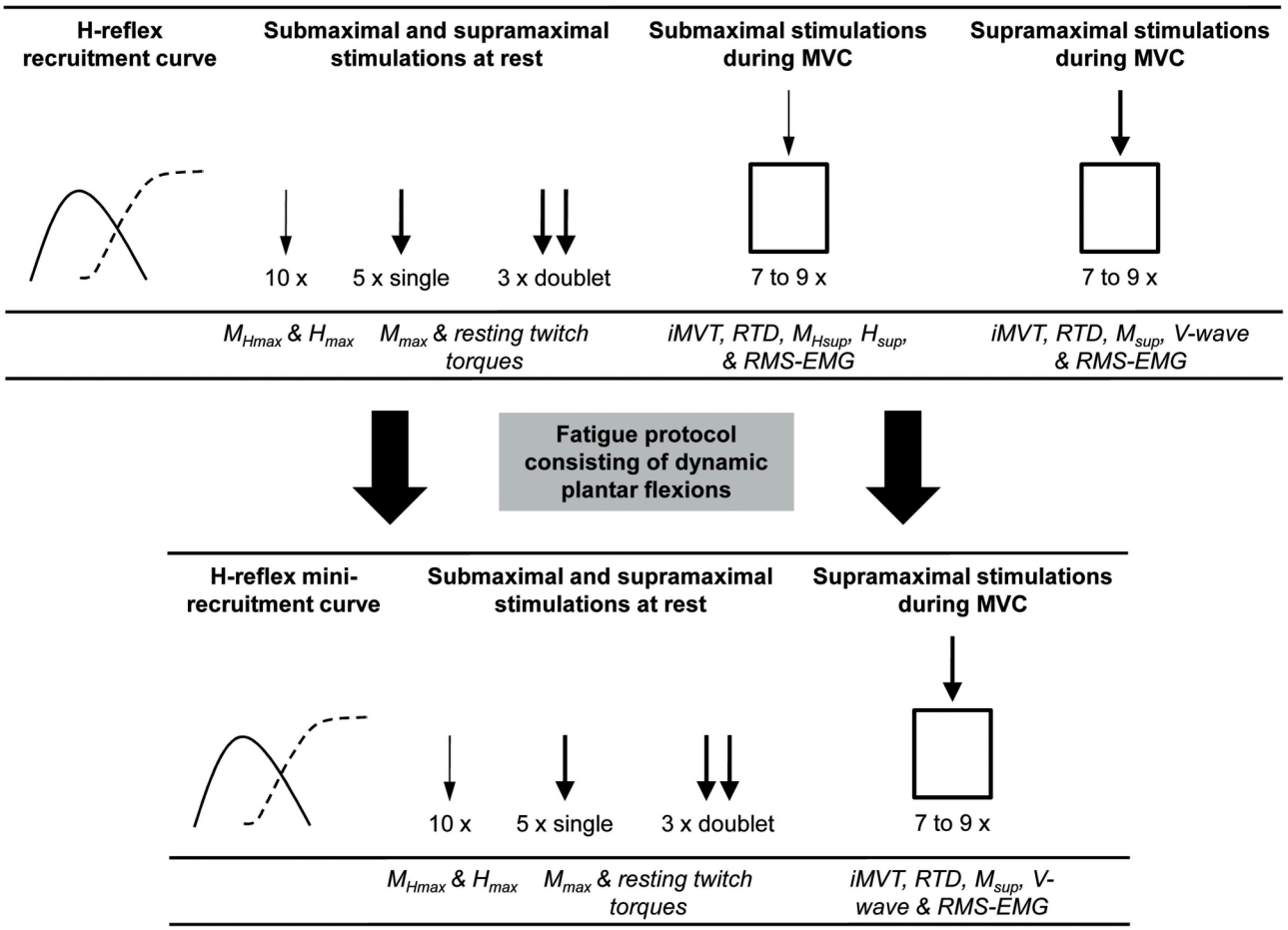

FIGURE 1 | An overview of the procedures carried out during neuromuscular testing and the extracted parameters. The *thin arrow* indicates stimulation at H_{max} intensity and the *thick arrow* indicates stimulation at supramaximal intensity. M_{Hmax}, submaximal M-wave evoked at H_{max} intensity; H_{max}, maximal H-reflex; M_{max}, maximal M-wave; M_{Hsup}, submaximal M-wave evoked at H_{sup} intensity during iMVC; H_{sup}, H-reflex during iMVC; M_{sup}, maximal M-wave during iMVC; iMVT, isometric maximum voluntary torque; RTD, rate of torque development; RMS-EMG, root mean square of the EMG signal.

and digitized with a sampling frequency of 5 kHz through an analog-to-digital converter (DAQ Card™-6024E, National Instruments, Austin, TX, USA). Both, the EMG and torque signals were sampled at 5 kHz and stored on a hard drive for later analysis with a custom built LABVIEW® based program (Imago, Pfitec, Endingen, Germany).

Torque signals were measured with a CYBEX NORM dynamometer (Computer Sports Medicine®, Inc., Stoughton, MA) equipped with a digital oscilloscope (HM1508, HAMEG Instruments, Germany) for instantaneous online visual feedback. Subjects were seated with their knees straight and their foot firmly attached to the adapter of the dynamometer using Velcro straps and a snowboard binding. Ankle and hip joint angles of 90 and 80° (0° = full extension) were maintained during the sessions and the ankle joint was aligned with the axis of the dynamometer. In order to prevent excessive movements and/or counter movements during recording of iMVC, straps across the thigh, waist and chest were used. For determination of isometric maximum voluntary torque (iMVT) subjects exerted maximal plantar flexions against the metal plate of the dynamometer for 3 s. A rest period of 1 min was allowed between the trials. The subjects performed three to five iMVC familiarization trials and testing was started once the coefficient of variance of three subsequent trials was below 5%. For H_{sup} and V-wave testing, seven to nine isometric maximal voluntary plantar flexions were performed, respectively (Behrens et al., 2015a,b).

Data Analysis

A gravity correction was applied to the torque signals and the mean of the signals recorded during the iMVC trials was used to calculate rate of torque development (RTD), iMVT and muscle activity. The average RTD over time intervals of 0–100 and 100–200 ms relative to the onset of contraction was calculated to give and index for explosive voluntary strength.

In addition, the root mean square of the EMG signal (RMS-EMG) in the same time intervals (0–100 and 0–200 ms

relative to the onset of the EMG signals) was calculated to analyze muscle activation during the early phase of contraction. RMS-EMG during the iMVCs ($RMS\text{-}EMG_{iMVT}$) was calculated over a 200 ms period at iMVT, i.e., 200 ms prior to the electrical stimulus. Muscle activities of SOL, medial gastrocnemius, lateral gastrocnemius and TA were normalized by dividing RMS-EMG by their respective M_{max} values ($RMS\text{-}EMG/M_{max}$). $RMS\text{-}EMG/M_{max}$ was averaged across SOL, medial gastrocnemius and lateral gastrocnemius to calculate triceps surae activation during the early phase of contraction and at iMVT ($RMS\text{-}EMG_{RTD}/M_{max}$ and $RMS\text{-}EMG_{iMVT}/M_{max}$, respectively). Torque and EMG onsets were identified manually according to the method of Tillin et al. (2010).

Peak-to-peak H_{max}, M_{Hmax}, M_{max}, H_{sup}, M_{Hsup}, M_{sup}, and V-wave amplitudes were averaged, respectively. The H_{max}/M_{max}-ratio, and H_{sup}/M_{sup}-ratio were calculated to detect modulations at the spinal level due to alterations in α-motoneuron excitability and/or presynaptic inhibition of primary muscle spindle afferents (Zehr, 2002). Furthermore, the M_{Hmax}/M_{max}-ratio and M_{Hsup}/M_{sup}-ratio were calculated to control for stimulation constancy, i.e., that the same proportion of α-motoneurons was activated by the electrical stimulation. The V/M_{sup}-ratio was calculated to assess changes in the neural drive from spinal α-motoneurons to SOL (Aagaard et al., 2002; Duclay and Martin, 2005). Resting twitch torques were analyzed regarding the highest value of twitch torque signal (peak twitch torque) and were averaged afterwards.

Statistical Analysis

Twenty-two subjects completed the study. Data of these participants were collected successfully. Data were checked for normal distribution (Shapiro-Wilk test). In addition, the statistical analysis comprised an analysis of covariance (ANCOVA) with baseline measurement and gender entered as covariates (Vickers and Altman, 2001; Egbewale et al., 2014). This approach provides an estimate for the difference between groups which is the variable of interest in randomized controlled trials (Vickers, 2005a). The level of significance was established at $P \leq 0.05$ and SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data obtained at baseline are presented as mean values ± standard deviations and those obtained after 8 weeks of training are given as adjusted means ± adjusted standard deviations. If appropriate, data are presented as difference between means (95% confidence interval).

Results

Findings at baseline are given in **Tables 2, 3**. The participants of the intervention group performed the fatigue protocol with a load of 52.6 ± 7.3 N·m before and after the endurance training, while the control group executed the fatiguing task with a load of 56.9 ± 6.5 N·m (independent *t*-test: $P = 0.181$). The training group terminated exercise after 250.8 ± 124.3 repetitions before and after the training period and the control group performed 232.7 ± 106.1 repetitions before and after the same time without the training stimulus (independent *t*-test: $P = 0.730$).

TABLE 2 | Peak twitch torques, evoked potentials, maximum and explosive voluntary strength, normalized muscle activity ($RMS\text{-}EMG/M_{max}$) during iMVC and the initial phase of contraction for the intervention (INT) and control group (CON) at baseline.

Parameter	Pre		
	INT	CON	Diff.
PEAK TWITCH TORQUE (N·m)			
Supramaximal single	13.1 ± 2.5	14.9 ± 1.7	−1.8
Supramaximal doublet	25.4 ± 5.1	26.7 ± 2.5	−1.3
H-reflex intensity	10.1 ± 2.3	10.9 ± 1.9	−0.8
EVOKED POTENTIALS			
H_{max} SOL (mV)	3.68 ± 1.96	2.70 ± 0.92	0.98
M_{max} SOL (mV)	6.50 ± 2.23	5.00 ± 1.60	1.50
H_{max}/M_{max} SOL	0.58 ± 0.19	0.57 ± 0.20	0.01
M_{Hmax}/M_{max} SOL	0.16 ± 0.13	0.17 ± 0.14	−0.01
H_{sup} SOL (mV)	3.92 ± 1.83	3.24 ± 1.43	0.68
M_{sup} SOL (mV)	6.50 ± 1.94	5.98 ± 1.87	0.52
H_{sup}/M_{sup} SOL	0.62 ± 0.12	0.52 ± 0.20	0.10
M_{Hsup}/M_{sup} SOL	0.20 ± 0.10	0.17 ± 0.05	0.03
V-wave SOL (mV)	2.42 ± 1.07	2.15 ± 0.78	0.27
V/M_{sup} SOL	0.38 ± 0.13	0.38 ± 0.14	0.00
M_{max} MG (mV)	4.39 ± 1.97	5.01 ± 2.06	−0.62
M_{max} LG (mV)	5.83 ± 1.96	6.84 ± 2.34	−1.01
M_{max} TA (mV)	4.45 ± 1.54	4.28 ± 1.03	0.17
Isometric maximum voluntary torque (N·m)	93.2 ± 19.9	102.0 ± 16.2	−8.8
$RMS\text{-}EMG_{iMVT}/M_{max}$			
TS	0.038 ± 0.009	0.043 ± 0.007	−0.005
TA	0.022 ± 0.017	0.021 ± 0.009	0.001
RATE OF TORQUE DEVELOPMENT ($N{\cdot}m{\cdot}s^{-1}$)			
0–100 ms	273.0 ± 71.6	293.9 ± 76.8	−20.9
100–200 ms	328.0 ± 64.9	355.8 ± 77.2	−27.8
$RMS\text{-}EMG_{RTD}/M_{max}$			
TS 0–100 ms	0.043 ± 0.015	0.044 ± 0.010	−0.001
TS 100–200 ms	0.047 ± 0.016	0.045 ± 0.008	0.002
TA 0–100 ms	0.021 ± 0.013	0.019 ± 0.007	0.002
TA 100–200 ms	0.026 ± 0.020	0.021 ± 0.010	0.005

Diff., difference between means; H_{max}, maximal H-reflex; M_{max}, maximal M-wave; M_{Hmax}, submaximal M-wave evoked at H_{max} intensity; H_{sup}, H-reflex during iMVC; M_{sup}, maximal M-wave during iMVC; M_{Hsup}, submaximal M-wave evoked at H_{sup} intensity during iMVC; SOL, soleus; MG, medial gastrocnemius; LG, lateral gastrocnemius; TS, triceps surae; TA, tibialis anterior. Data are means ± standard deviations.

No significant differences between groups in iMVT [4.3 N·m (−4.0 to 12.5 N·m, $P = 0.291$, $\eta_p^2 = 0.062$)], V/M_{sup} [0.04 (−0.07 to 0.13, $P = 0.508$, $\eta_p^2 = 0.025$)], H_{sup}/M_{sup} [0.00 (−0.21 to 0.22, $P = 0.974$, $\eta_p^2 = 0.000$)], triceps surae muscle activity [0.001 (−0.008 to 0.010, $P = 0.791$, $\eta_p^2 = 0.004$)], and TA muscle co-activity [0.002 (−0.008 to 0.012 N·m, $P = 0.694$, $\eta_p^2 = 0.009$)] were observed following the training (**Figures 2A–E**). Furthermore, the groups were not significantly different regarding the slope of the torque-time curve and the neural activation of muscles at the onset of contraction in the time intervals 0–100 and 100–200 ms (**Table 4**). The contractile performance as well as the remaining evoked

TABLE 3 | Fatigue-induced percentage change in peak twitch torques, evoked potentials, maximum and explosive voluntary strength, normalized muscle activity (RMS-EMG/M_{max}) during iMVC and the initial phase of contraction for the intervention (INT) and control group (CON) at baseline.

Parameter	Pre		
	INT	CON	Diff.
PEAK TWITCH TORQUE (%)			
Supramaximal single	−5.2 ± 9.0	−9.4 ± 12.5	4.2
Supramaximal doublet	−7.0 ± 10.1	−8.3 ± 9.5	1.3
H-reflex intensity	3.2 ± 11.2	2.1 ± 15.7	1.1
EVOKED POTENTIALS (%)			
H_{max} SOL	13.5 ± 18.7	16.5 ± 21.6	−3.0
M_{max} SOL	1.4 ± 13.0	10.1 ± 19.4	−8.7
H_{max}/M_{max} SOL	14.0 ± 20.1	12.0 ± 15.2	2.0
V-wave SOL	−37.0 ± 20.7	−27.1 ± 28.3	−9.9
M_{sup} SOL	−6.5 ± 15.0	−3.4 ± 10.5	−3.1
V/M_{sup} SOL	−32.6 ± 19.9	−25.1 ± 25.9	−7.5
Isometric maximum voluntary torque (%)	−13.6 ± 7.9	−8.6 ± 9.5	−5.0
$RMS\text{-}EMG_{iMVT}/M_{max}$ (%)			
TS	−26.5 ± 10.7	−27.8 ± 16.0	1.3
TA	−6.0 ± 6.2	−8.8 ± 7.5	2.8
RATE OF TORQUE DEVELOPMENT (%)			
0–100 ms	−23.7 ± 13.3	−24.6 ± 8.2	0.9
100–200 ms	−10.1 ± 11.2	−5.5 ± 10.3	−4.6
$RMS\text{-}EMG_{RTD}/M_{MAX}$ (%)			
TS 0–100 ms	−32.2 ± 14.3	−29.4 ± 13.5	−2.8
TS 100–200 ms	−27.0 ± 17.1	−22.2 ± 15.2	−4.8
TA 0–100 ms	−18.1 ± 9.6	−16.0 ± 7.2	−2.1
TA 100–200 ms	−13.8 ± 15.8	−12.7 ± 10.4	−1.1

Diff., difference between means; H_{max}, maximal H-reflex; M_{max}, maximal M-wave; M_{Hmax}, submaximal M-wave evoked at H_{max} intensity; H_{sup}, H-reflex during iMVC; M_{sup}, maximal M-wave during iMVC; M_{Hsup}, submaximal M-wave evoked at H_{sup} intensity during iMVC; SOL, soleus; TS, triceps surae; TA, tibialis anterior. Data are means ± standard deviations.

potentials revealed no statistical difference between groups (**Table 4**).

In addition, the change of crucial parameters following the same standardized fatigue protocol was analyzed before and after training to detect potential neural and/or muscular adaptations. These changes were not statistically different between groups with regard to iMVT, V/M_{sup} and contractile properties of the triceps surae assessed with doublet stimulation (**Table 5**). The same was true for the evoked potentials elicited at rest and during iMVC, the muscle activity during iMVC as well as for RTD and the neural activation of muscles at the onset of contraction (**Table 5**).

Discussion

The purpose of this randomized controlled study was (i) to analyze neuromuscular adaptations of the plantar flexors after short-term (8 weeks) cycling endurance training and (ii) to assess selected variables, representing neural and muscular function of the plantar flexors, after a defined fatigue protocol with the same load, repetitions and range of motion before and after the training period. The results indicate that cycling endurance training did not lead to a significant change in any variable of interest. Neither normalized evoked potentials elicited at rest and associated peak twitch torques, isometric explosive and maximum voluntary strength nor muscle activation at the onset of contraction and during iMVC were significantly different between the training and control group after a period of either cycling endurance training or no systematic cycling endurance training, respectively. Furthermore, no differences between groups were observed regarding the normalized evoked potentials elicited during iMVC and the changes of selected variables, representing neural and muscular function of the plantar flexors, after defined fatiguing exercise.

Previously published studies on the effect of endurance training on neuromuscular function of the plantar flexors have shown that stretch reflexes and H-reflexes of SOL were significantly increased after training (Perot et al., 1991; Vila-Cha et al., 2012b). These results conflict with the outcome of this study that could not confirm an increased recruitment of α-motoneurons via the Ia afferent pathway after a period of endurance training. Reasons for the discrepancy between the outcomes of the cited studies and our results could be that the investigated subjects responded differently to the training stimulus and/or the difference in the kind of endurance training. However, our subjects were recreationally active just like the subjects in the cited studies and it has been previously shown that an endurance training program performed on a cycle ergometer is effective in modulating spinal reflex responses (Vila-Cha et al., 2012b). Thus, another more probable explanation could be that both Perot et al. (1991) and Vila-Cha et al. (2012b) had not included a control group in their study design in order to compare the results of the endurance training group to individuals without the endurance training stimulus. In order to analyze our data as done in the studies mentioned, we have applied a paired statistical test (dependent *t*-test) for comparison of the normalized H-reflex at rest (H_{max}/M_{max}) before and after the training. The analysis yielded a significant increase in H_{max}/M_{max}-ratio ($P = 0.047$). Based on this result, we could also state that endurance training increases the normalized H-reflex. However, if we use an analysis of covariance (ANCOVA) with baseline measurement and gender entered as covariates, which is supposed to be the appropriate statistical test for analyzing the effect of an intervention compared to a control condition in randomized controlled trials (Vickers and Altman, 2001; Vickers, 2005a,b; Egbewale et al., 2014), no significant group difference can be revealed. Even Perot et al. (1991) observed that 75% of their investigated subjects showed an increased stretch reflex and H-reflex excitability after the endurance training whereas the remaining 25% of the subjects revealed no change or even a decrease in these parameters. Thus, it is rather likely that short-term endurance training does not necessarily enhance stretch and H-reflex responses. Based on our results and statistical analysis, an increased H-reflex excitability and/or changed presynaptic inhibition of Ia afferents after short-term cycling endurance training cannot be confirmed. Although it has been shown that endurance trained athletes (10–14 h endurance training per week

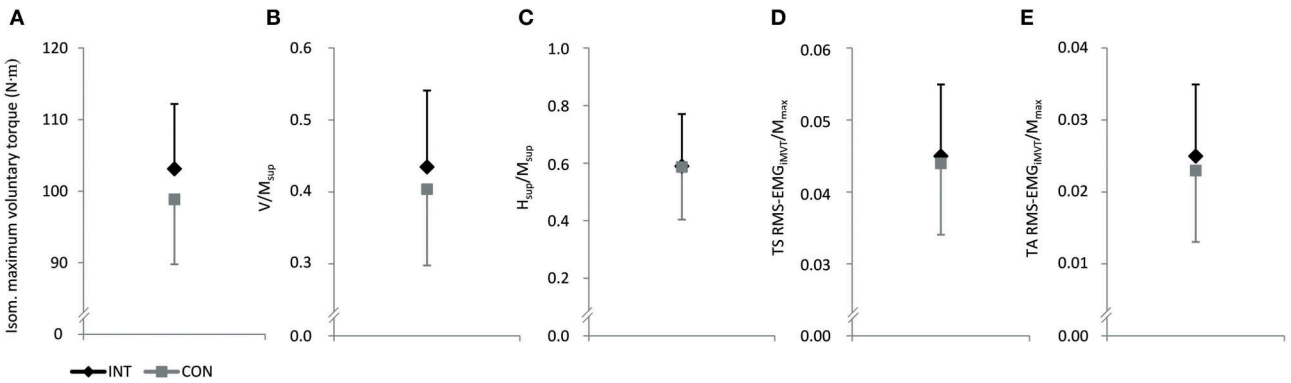

FIGURE 2 | Effect of endurance training (INT) on isometric maximum voluntary torque (A), normalized V-wave (V/M_{sup}, B), normalized H-reflex during iMVC (H_{sup}/M_{sup}, C) and normalized muscle activity during iMVT ($RMS\text{-}EMG_{iMVT}/M_{max}$, D and E). CON, control group; TS, triceps surae; TA, tibialis anterior.

TABLE 4 | Peak twitch torques and evoked potentials after training for the intervention (INT) and the control group (CON).

Parameter	Post			
	INT	**CON**	**Diff. (95% CI)**	***P***
PEAK TWITCH TORQUE (N·m)				
Supramaximal single	13.3 ± 1.8	12.9 ± 1.8	0.4 (−1.3 to 2.1)	0.626
Supramaximal doublet	24.6 ± 2.3	25.1 ± 2.3	−0.5 (−2.5 to 1.6)	0.629
H-reflex intensity	10.8 ± 1.9	10.0 ± 1.9	0.8 (−1.0 to 2.5)	0.363
EVOKED POTENTIALS				
H_{max} SOL (mV)	3.59 ± 1.12	3.49 ± 1.12	0.10 (−0.97 to 1.16)	0.853
M_{max} SOL (mV)	5.39 ± 1.60	6.35 ± 1.60	−0.96 (−2.54 to 0.63)	0.223
H_{max}/M_{max} SOL	0.67 ± 0.13	0.61 ± 0.13	0.06 (−0.06 to 0.18)	0.285
M_{Hmax}/M_{max} SOL	0.19 ± 0.09	0.18 ± 0.09	0.01 (−0.07 to 1.00)	0.696
H_{sup} SOL (mV)	3.80 ± 1.68	4.16 ± 1.68	−0.36 (−2.31 to 1.66)	0.723
M_{sup} SOL (mV)	6.56 ± 1.46	6.55 ± 1.46	0.01 (−1.31 to 1.34)	0.980
H_{sup}/M_{sup} SOL	0.59 ± 0.21	0.59 ± 0.21	0.00 (−0.21 to 0.22)	0.974
M_{Hsup}/M_{sup} SOL	0.14 ± 0.22	0.33 ± 0.22	−0.19 (−0.43 to 0.05)	0.114
V-wave SOL (mV)	2.69 ± 0.69	2.53 ± 0.69	0.16 (−0.47 to 0.78)	0.613
V/M_{sup} SOL	0.44 ± 0.11	0.40 ± 0.11	0.04 (−0.07 to 0.13)	0.508
M_{max} MG (mV)	4.73 ± 1.48	4.35 ± 1.48	0.38 (−0.95 to 1.71)	0.553
M_{max} LG (mV)	5.44 ± 1.40	6.37 ± 1.40	−0.93 (−2.20 to 0.34)	0.140
M_{max} TA (mV)	3.66 ± 1.42	4.01 ± 1.42	−0.35 (−1.63 to 0.92)	0.568
RATE OF TORQUE DEVELOPMENT ($N\cdot m\cdot s^{-1}$)				
0–100 ms	299.3 ± 47.3	263.9 ± 47.3	35.4 (−7.1 to 78.0)	0.097
100–200 ms	380.5 ± 39.6	386.8 ± 39.6	−6.3 (−42.1 to 29.5)	0.716
$RMS\text{-}EMG_{RTD}/M_{max}$				
TS 0–100 ms	0.046 ± 0.010	0.044 ± 0.010	0.002 (−0.007 to 0.011)	0.650
TS 100–200 ms	0.049 ± 0.013	0.052 ± 0.013	−0.003 (−0.014 to 0.008)	0.582
TA 0–100 ms	0.025 ± 0.013	0.022 ± 0.013	0.003 (−0.008 to 0.013)	0.648
TA 100–200 ms	0.026 ± 0.013	0.025 ± 0.013	0.001 (−0.011 to 0.013)	0.892

Diff. (95% CI), difference between means (95% confidence interval); H_{max}, maximal H-reflex; M_{max}, maximal M-wave; M_{Hmax}, submaximal M-wave evoked at H_{max} intensity; H_{sup}, H-reflex during iMVC; M_{sup}, maximal M-wave during iMVC; M_{Hsup}, submaximal M-wave evoked at H_{sup} intensity during iMVC; SOL, soleus; MG, medial gastrocnemius; LG, lateral gastrocnemius; TA, tibialis anterior. Data are adjusted means ± adjusted standard deviations.

for several years) have higher normalized H-reflexes than non-trained individuals (Maffiuletti et al., 2001), our data indicate that short-term endurance training performed on a cycle ergometer seems not to alter the recruitment threshold of α-motoneurons to Ia afferent input at rest. It can be assumed that a longer time of regular aerobic exercise is necessary to induce alterations in

TABLE 5 | Fatigue-induced percentage change in peak twitch torques, evoked potentials, maximum and explosive voluntary strength, normalized muscle activity (RMS-EMG/M_{max}) during iMVC and the initial phase of contraction after training for the intervention (INT) and control group (CON).

Parameter	Post			
	INT	CON	Diff. (95% CI)	*P*
PEAK TWITCH TORQUE (%)				
Supramaximal single	−0.3 ± 10.8	−8.3 ± 10.8	8.0 (−1.7 to 17.7)	0.101
Supramaximal doublet	−4.7 ± 12.7	−7.8 ± 12.7	3.1 (−8.4 to 14.5)	0.581
H-reflex intensity	−0.6 ± 15.1	−2.1 ± 15.1	1.5 (−12.4 to 15.5)	0.821
EVOKED POTENTIALS (%)				
H_{max} SOL	10.2 ± 22.8	26.2 ± 22.8	−16.0 (−36.1 to 4.0)	0.110
M_{max} SOL	10.2 ± 15.8	3.5 ± 15.8	6.7 (−7.9 to 21.3)	0.346
H_{max}/M_{max} SOL	2.8 ± 23.9	24.0 ± 23.9	−21.2 (−43.3 to 0.9)	0.059
V-wave SOL	−23.4 ± 19.4	−34.7 ± 19.4	11.3 (−6.3 to 28.7)	0.195
M_{sup} SOL	−6.3 ± 11.7	−7.8 ± 11.7	1.5 (−8.9 to 12.0)	0.760
V/M_{sup} SOL	−18.8 ± 28.3	−26.6 ± 28.3	7.8 (−17.7 to 33.4)	0.527
Isometric maximum voluntary torque (%)	−4.4 ± 11.1	−10.4 ± 11.1	6.0 (−4.1 to 16.2)	0.229
$RMS\text{-}EMG_{iMVT}/M_{max}$ (%)				
TS	−23.8 ± 11.1	−24.1 ± 11.1	0.3 (−9.7 to 10.3)	0.953
TA	−18.4 ± 16.3	−21.4 ± 16.3	3.0 (−11.9 to 17.9)	0.675
RATE OF TORQUE DEVELOPMENT (%)				
0–100 ms	−17.7 ± 16.2	−17.7 ± 16.2	0.0 (−14.7 to 14.4)	0.983
100–200 ms	−3.7 ± 12.6	−12.7 ± 12.6	9.0 (−2.4 to 20.5)	0.114
$RMS\text{-}EMG_{RTD}/M_{max}$ (%)				
TS 0–100 ms	−28.8 ± 17.2	−24.4 ± 17.2	−4.4 (−19.9 to 11.1)	0.560
TS 100–200 ms	−23.4 ± 17.4	−22.9 ± 17.4	−0.5 (−16.2 to 15.2)	0.950
TA 0–100 ms	−21.6 ± 16.1	−23.4 ± 16.1	1.8 (−13.0 to 16.6)	0.800
TA 100–200 ms	−18.5 ± 17.0	−16.6 ± 17.0	−1.9 (−17.4 to 13.5)	0.794

Diff. (95% CI), difference between means (95% confidence interval); H_{max}, maximal H-reflex; M_{max}, maximal M-wave; M_{sup}, maximal M-wave during iMVC; SOL, soleus; TA, tibialis anterior. Data are adjusted means ± adjusted standard deviations.

reflex responses. Moreover, as the contribution of stretch reflexes to overall muscle activity is greater during running, it is not unlikely that running training has stronger effects on spinal reflex responses than cycling training.

To the best of our knowledge H-reflex modulation during iMVC after a period of cycling endurance training was not tested before. In the present study we have found that the H-reflex evoked during iMVC (H_{sup}/M_{sup}) was unchanged after training. Therefore, short-term endurance training on a cycle ergometer is probably not able to alter the responsiveness of spinal a-motoneurons to Ia afferent input during isometric maximum voluntary strength tasks of the plantar flexors.

The training regimen had no effect on isometric explosive and maximum voluntary strength as well as muscle activation at the onset of contraction ($RMS\text{-}EMG_{RTD}/M_{max}$) and during iMVC ($V/M_{sup}$, $RMS\text{-}EMG_{iMVT}/M_{max}$). These results are in accordance with the outcome of a study by Vila-Cha et al. (2012b). The authors have shown that short-term endurance training on a cycle ergometer did not alter iMVC strength and neural activation of the plantar flexors assessed with the V-wave. Data of a recently published study on the effect of endurance training (running) on voluntary activation of the knee extensors support this view (Zghal et al., 2014).

The change in the resistance to fatigue following a period of endurance training was previously tested by sustained isometric contractions with a defined percentage of iMVC strength until task failure. With this approach, it has been shown that time to task failure increases following endurance training (Vila-Cha et al., 2012a,b). However, the time to task failure does not provide information regarding neural and muscular contributions to the improved resistance to fatigue. Therefore, we applied the same dynamic fatigue protocol, i.e., with the same load, repetitions and range of motion, before and after the cycling endurance training period and assessed the changes in neuromuscular function of the plantar flexors. With this approach, we wanted to find out if cycling endurance training is able to reduce the performance decrements associated with fatigue. Our data show that the percentage changes of these parameters following fatiguing exercise were not significantly different between groups after the training. However, the results indicate that the fatigue-induced reduction in iMVC strength, normalized V-wave and peak twitch torque in response to the same standardized fatigue protocol tended to be lower in the endurance-trained group compared to controls, but this change did not reach statistical significance (**Table 5**). Unfortunately, we have not measured cycling performance before and after the training. However, numerous studies have shown that cycling

endurance training with a similar intensity, as used in the present study, leads to an increase in endurance performance and corresponding physiological adaptations even in recreational active subjects (Ready and Quinney, 1982; Denis et al., 1984; Hickson et al., 1985; Coggan et al., 1990; Levine et al., 1992). We have compared the changes in iMVC strength due to the fatigue protocol before and after the training with a paired *t*-test ($P = 0.033$) indicating a significant reduction in the performance decrements. Based on this result, we could state that the performed cycling endurance training increased the fatigue resistance with regard to our specific fatigue protocol. However, if we use an analysis of covariance (ANCOVA) with baseline measurement and gender entered as covariates, which is supposed to be the appropriate statistical test for analyzing the effect of an intervention compared to a control condition in randomized controlled trials (Vickers and Altman, 2001; Vickers, 2005a,b; Egbewale et al., 2014), no significant group difference can be revealed. However, in this context it is noteworthy to illustrate the limitations of the present study regarding this issue: (i) we have not measured the effect of our training regimen on maximal oxygen uptake and cycling endurance performance, (ii) we have used a relative low training frequency of two times a week and (iii) SOL muscle activation during cycling is relative low (Rouffet and Hautier, 2008) and it might be that the training stimulus is not sufficient to induce neuromuscular adaptations in the SOL muscle of recreational active subjects.

In contrast to the outcome of previously published studies, the results of our randomized controlled trial indicate that short-term endurance training on a cycle ergometer seems not to alter the recruitment threshold of α-motoneurons to Ia afferent input and/or the extent of presynaptic inhibition of Ia afferents at rest. Furthermore, we have tested the responsiveness of spinal α-motoneurons to Ia afferent input during iMVC for the first time and have not found a modulation in α-motoneuron excitability and/or presynaptic inhibition of Ia afferents. The training regimen had no effect on isometric explosive and maximum voluntary strength as well as muscle activation at the onset of contraction ($RMS\text{-}EMG_{RTD}/M_{max}$) and during iMVC ($V/M_{sup}$, $RMS\text{-}EMG_{iMVT}/M_{max}$). Changes in iMVC strength, neural activation (V/M_{sup}) and muscles' contractile properties after the same standardized fatigue protocol applied before and after the training were not significantly different between groups.

Future research on the effect of short-term endurance training should analyze the impact of different training frequencies and types of activity, e.g., running, swimming, cycling, on evoked reflex responses and neuromuscular function. It is likely that changes in evoked spinal reflex responses depend on the kind of activity and its reliance on the stretch-shortening cycle. From this functional point of view, activities like running are more predestined to induce adaptations at the spinal level.

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Impact of Blood Flow Restriction Exercise on Muscle Fatigue Development and Recovery

FLORIAN HUSMANN[1], THOMAS MITTLMEIER[2], SVEN BRUHN[1], VOLKER ZSCHORLICH[1], and MARTIN BEHRENS[1]

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ABSTRACT

HUSMANN, F., T. MITTLMEIER, S. BRUHN, V. ZSCHORLICH, and M. BEHRENS. Impact of Blood Flow Restriction Exercise on Muscle Fatigue Development and Recovery. *Med. Sci. Sports Exerc.*, Vol. 50, No. 3, pp. 436–446, 2018. **Purpose**: The present study was designed to provide mechanistic insight into the time course and etiology of muscle fatigue development and recovery during and after low-intensity exercise when it is combined with blood flow restriction (BFR). **Methods**: Seventeen resistance-trained males completed four sets of low-intensity isotonic resistance exercise under two experimental conditions: knee extension exercise (i) with BFR and (ii) without BFR (CON). Neuromuscular tests were performed before, during (immediately after each set of knee extension exercise), and 1, 2, 4, and 8 min after each experimental condition. Maximal voluntary torque, quadriceps twitch torque in response to paired electrical stimuli at 10 Hz (PS10) and 100 Hz (PS100), PS10·PS100^{-1} ratio as an index of low-frequency fatigue, and voluntary activation were measured under isometric conditions. Perceptual and EMG data were recorded during each exercise condition. **Results**: After the first set of exercise, BFR induced significantly greater reductions in maximal voluntary torque, PS100, and PS10·PS100^{-1} ratio compared with CON. These parameters progressively declined throughout the BFR protocol but recovered substantially within 2 min postexercise when blood flow was restored. Neither a progressive decline in the course of the exercise protocol nor a substantial recovery of these parameters occurred during and after CON. Only at exercise termination, voluntary activation differed significantly between BFR and CON with greater reductions during BFR. **Conclusion**: At the early stage of exercise, BFR exacerbated the development of muscle fatigue mainly due to a pronounced impairment in contractile function. Despite the high level of muscle fatigue during BFR exercise, the effect of BFR on muscle fatigue was diminished after 2 min of reperfusion, suggesting that BFR has a strong but short-lasting effect on neuromuscular function. **Key Words:** CENTRAL FATIGUE, HYPOXIA, METABOLIC STRESS, PERIPHERAL FATIGUE, QUADRICEPS MUSCLE, VASCULAR OCCLUSION

It has been traditionally suggested that muscle growth can only be achieved with high-intensity resistance exercise (70%–80% one-repetition maximum [1RM]), whereas no significant hypertrophic effects were expected after low-intensity exercise. Mechanical stress was therefore considered as the essential stimulus for muscle hypertrophy (1). However, when low-intensity resistance exercise (20%–30% 1RM) was combined with blood flow restriction (BFR), similar gains in muscle mass were observed (2). BFR is used to limit intramuscular oxygen delivery and to prevent venous clearance of metabolites that, in turn, lead to increased metabolic stress (i.e., depletion of phosphocreatine, increased accumulation of inorganic phosphate, protons, and lactate). Even without heavy loads, metabolic stress is thought to trigger certain mechanisms (i.e., systemic hormone production, increased fast-twitch fiber recruitment, and cell swelling), which potentially mediate muscle growth (for a review, see [3]).

Besides the effect of metabolic stress as an obvious key stimulator for hypertrophic adaptations, disturbances in the intra- and extracellular environment induced by BFR exercise are strongly associated with a reduction in maximal voluntary force production (i.e., [4,5]). The impaired force or power-generating capacity of a muscle or muscle group is indicative of muscle fatigue, which stems from a decrease in neural activation of the muscle (i.e., commonly termed "central fatigue") and/or alterations at or distal to the neuromuscular junction that result in contractile dysfunction (commonly termed "peripheral fatigue") (6). Muscle fatigue

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is typically considered to be task dependent (i.e., exercise intensity, duration, contraction mode, active muscle mass) and particularly affected by local and systemic hypoxia (7,8). As might be expected, initial findings by Karabulut et al. (9) have demonstrated that BFR exacerbates the end-exercise level of muscle fatigue after work-matched low-intensity exercise. In detail, higher contributions of peripheral and central factors were responsible for the pronounced muscle fatigue as indicated by reductions in voluntary activation (−13%) and contractile twitch torque (−44%) after BFR exercise compared with the free blood flow condition (+4% and −19%, respectively).

Previous work investigating the effect of BFR on neuromuscular function is currently limited to pre- and post-exercise measurements (i.e., [4,9]). Considering the fact that the development and recovery of muscle fatigue heavily rely on the characteristics of the task (6,10), it is still unclear how the central and the peripheral sites of the neuromuscular system respond in the course of BFR exercise and how these sites acutely recover from such strong impairments. From a practical point of view, knowledge about the recovery process after low-intensity BFR exercise is crucial to understand the exercise–adaptation cycle to determine the optimal balance between training and recovery. Therefore, the present study was designed to provide mechanistic insight into the time course of changes in neuromuscular function during and after exercise under conditions of limited blood flow. By using various electrical stimulation methods at short time intervals during and after each exercise condition, we were able to investigate the effect of low-intensity exercise with BFR on central and peripheral aspects of muscle fatigue development and recovery.

METHODS

Subjects. Seventeen healthy males volunteered to participate in this study. A sample comprising exclusively male subjects was chosen based on the common finding that the level of muscle fatigue differs between sexes (for a review, see [11]). All subjects were physically active (training more than four times per week) and regularly engaged in a total body resistance training program for at least two times per week. Descriptive data of the subject characteristics are presented in Table 1. Participants were excluded if they were hypertensive (>140/90 mm Hg) or had more than one risk factor for thromboembolism (12). Subjects were asked to refrain from vigorous exercise, analgesics, caffeine, and alcohol consumption for 24 h before the investigations. The study was approved by the university ethics committee and was conducted according to the Declaration of Helsinki. All subjects were informed about possible risks and discomfort associated with the investigations before giving their written consent to participate.

TABLE 1. Subject characteristics.

Age (yr)	25 ± 4
Height (cm)	184 ± 6
Body mass (kg)	84 ± 6
Physical activity ($h \cdot wk^{-1}$)	9 ± 3
Resistance training ($h \cdot wk^{-1}$)	5 ± 2
SBP (mm Hg)	132 ± 9
DBP (mm Hg)	76 ± 8
Arterial occlusion pressure (mm Hg)	208 ± 25
BFR pressure (mm Hg)	125 ± 15
Unilateral 1RM (N·m)	240 ± 32

Values are expressed as means ± SD.
SBP, systolic blood pressure; DBP, diastolic blood pressure.

Experimental procedure. All subjects visited the laboratory on three different occasions. During the first visit, subjects' knee extension 1RM and arterial occlusion pressure were determined. Furthermore, subjects were thoroughly familiarized with the following procedures: (i) RPE and leg muscle pain, (ii) neuromuscular testing procedures comprising maximal voluntary contractions (MVC) and peripheral nerve stimulation, (iii) metronome pacing of knee extension exercise, and (iv) two submaximal sets (2 sets of 10 repetitions at 30% 1RM) of knee extension exercise under BFR at 60% arterial occlusion pressure. Furthermore, subjects' knee extension 1RM and arterial occlusion pressure were determined within the first session. Using a randomized, counterbalanced, within-subjects design, participants underwent two experimental conditions across two separate visits: four sets (30, 15, 15, and 15 repetitions; total exercise time, 315 s) of low-intensity knee extensions (i) with BFR and (ii) without BFR (CON). Testing sessions were separated by 7 ± 1 d and took place at the same time of the day. On the basis of the protocol previously used by Froyd et al. (13), neuromuscular tests were performed before, during (immediately after each set of knee extension exercise), and 1, 2, 4, and 8 min after each experimental condition (Fig. 1). Furthermore, RPE and leg muscle pain were assessed after each set. Electromyography (EMG) data were continuously recorded during each experimental trial.

Upon arrival at the laboratory, subjects' blood pressure and arterial occlusion pressure were determined. Before baseline measurements, subjects performed an initial warm-up on a stationary bicycle (5 min; 120 W; 90 rpm) followed by a specific warm-up on the dynamometer comprising two isometric contractions for 5 s at 50%, 70%, and 90% of maximal voluntary torque (MVT; determined during the familiarization session), respectively. Neuromuscular tests comprised supramaximal electrical stimulations of the femoral nerve during and after an isometric MVC (Fig. 1B and C). All measurements were conducted on the quadriceps muscle of the dominant leg (i.e., kicking preference). During knee extension exercise and neuromuscular testing, subjects were comfortably seated and secured on a CYBEX NORM dynamometer (Computer Sports Medicine®, Inc., Stoughton, MA). The seating position was adjusted for each subject, and settings were documented for the subsequent sessions.

Determination of arterial occlusion pressure. Arterial occlusion pressure was determined in a lying position using a handheld bidirectional Doppler probe (Hadeco Bidop ES-100V3, Kawasaki, Japan), which was placed over the posterior tibial artery. Pressure was automatically adjusted using a cuff inflator system (Heidi™; Ulrich Medical, Ulm, Germany).

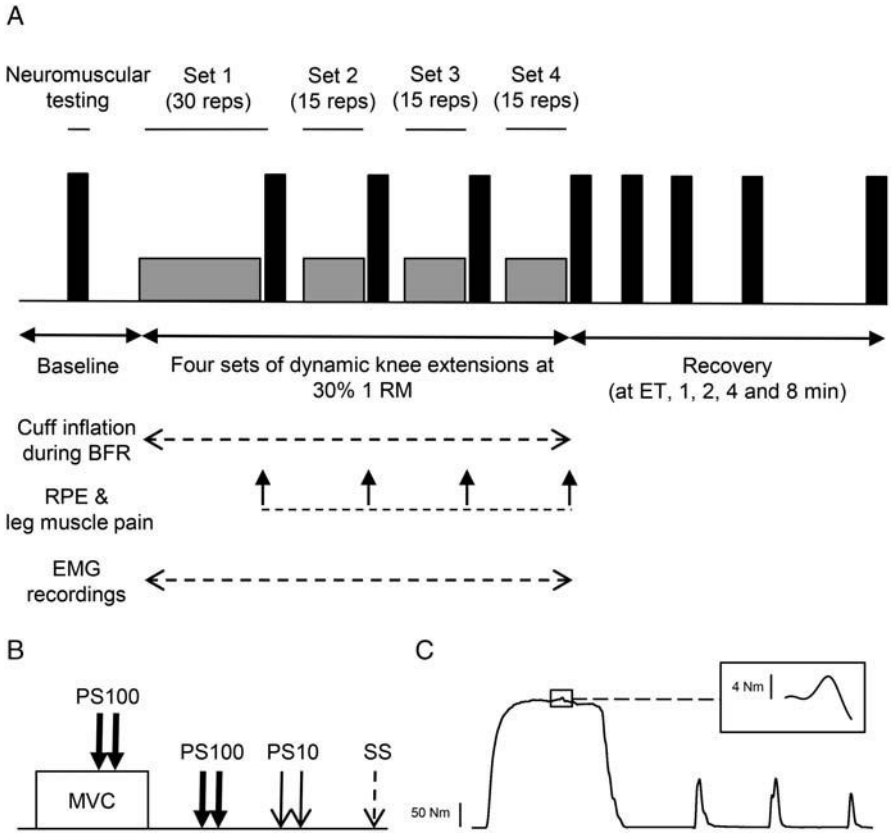

FIGURE 1—A. Illustration of the experimental design. Neuromuscular function was assessed before, during (immediately after each set of knee extension exercise), and 1, 2, 4, and 8 min after low-intensity exercise with and without BFR. Furthermore, RPE, leg muscle pain, and EMG data were recorded during each experimental condition. ET, exercise termination. B. The neuromuscular testing procedure comprised MVC of the quadriceps muscle combined with different electrical stimulation methods to assess MVT, voluntary activation (via the interpolated twitch technique), and quadriceps twitch torques in response to paired electrical stimuli at 100 Hz (PS100) and at 10 Hz (PS10) as well as single stimuli (SS). C. Typical torque recording of the neuromuscular testing procedure. An enlarged view of the interpolated twitch is presented in the box.

A 10 × 76-cm pneumatic cuff (Ulrich Medical) affixed to the most proximal part of the right thigh was incrementally inflated until the pulse of the tibial artery was interrupted. The inflation procedure was performed as described in detail by Loenneke et al. (14). Arterial occlusion pressure was determined within the familiarization session and again at baseline of each experimental condition to evaluate its reproducibility.

1RM. Subjects' unilateral knee extension 1RM was determined using the isotonic mode of a CYBEX NORM dynamometer (Computer Sports Medicine®, Inc.). 1RM was defined as the heaviest load that can be lifted through a controlled, full range of motion. Before isotonic testing, subjects performed an initial warm-up on a stationary bicycle (5 min, 120 W, 90 rpm). A second warm-up comprised six isotonic knee extensions with a submaximal load and two further contractions with a higher load. During the actual testing procedure, the load was progressively increased until 1RM was determined. Between each attempt, subjects rested for 90 s. All 1RM were determined within five attempts.

Torque recordings. A CYBEX NORM dynamometer (Computer Sports Medicine®, Inc.) was used to record instantaneous torques. Subjects were positioned on an adjustable chair with the hip fixed at 80° (0° = full extension). To avoid excessive movements during data recording, straps were fixed tightly across the subjects' waist and chest. The dynamometer rotation axis was aligned with the knee joint rotation axis, and the lever arm was attached to the lower leg just above the lateral malleolus. Isometric MVC were performed at 90° knee flexion (0° = full extension). For each trial, subjects were instructed to cross their arms in front of their chest and to push as hard and as fast as possible against the lever arm of the dynamometer. Strong verbal encouragement was given by the investigator. Visual feedback of the torque–time curve was provided on a digital oscilloscope (HM1508; HAMEG Instruments, Mainhausen, Germany).

EMG recordings. A detailed description of the EMG recordings can be found in a previously published study from our laboratory (15). Briefly, myoelectrical signals from the vastus medialis (VM), rectus femoris (RF), and vastus lateralis (VL) were recorded using surface electrodes (EMG Ambu Blue Sensor N). EMG signals were amplified (×2500), band-pass filtered (10–450 Hz), and digitized with a sampling frequency of 3 kHz using an analog-to-digital converter (NI PCI-6229; National Instruments, Austin).

Electrical nerve stimulation. To assess the neuromuscular function of the quadriceps muscle, the femoral

nerve was stimulated percutaneously using electrical stimulation. A constant-current stimulator (Digitimer DS7A, Herfordshire, UK) was used to deliver square wave pulses of 1-ms duration with a maximal voltage of 400 V. A ball probe cathode (10-mm diameter) was pressed in the femoral triangle always by the same investigator. The anode, a self-adhesive electrode (35 × 45 mm; Spes Medica, Genova, Italy), was affixed over the greater trochanter. After determining the optimal site for stimulation, the position was marked onto the subjects' skin to ensure repeatable measurements within each session. Individual stimulation intensity was progressively increased until the maximum compound muscle action potential (M_{max}) of VM, RF, and VL as well as a plateau in knee extensor twitch torque was achieved. During the subsequent testing procedures, the stimulation intensity was increased by additional 40% to guarantee supramaximal stimulation (~50 mA). Potentiated quadriceps twitch torque evoked by paired electrical stimuli at 100 Hz (PS100) and 10 Hz (PS10) and single stimuli (SS) were elicited 2, 4, and 6 s after MVC, respectively. As recommended previously (16), quadriceps twitch torque in response to PS100 was used to characterize changes in contractile function. To determine the level of voluntary activation during isometric MVC, the interpolated twitch technique was applied (17). Electrical paired stimuli were delivered to the femoral nerve at 90° knee flexion 2 s after torque onset (during the plateau phase) and 2 s after MVC.

Exercise protocol. The exercise protocol comprised 30 repetitions of unilateral isotonic knee extensions followed by three sets of 15 repetitions at 30% of 1RM. Each set was separated by 30 s of rest. This protocol was chosen because it is typically used for research purposes and practical applications in the context of BFR (2). A metronome set at 40 bpm was used to ensure a cadence of 1.5 s for concentric and 1.5 s for eccentric muscle actions. During the BFR condition, a pneumatic cuff applied to the subjects' thigh was inflated before the first set of exercise and deflated immediately after termination of the fourth set. The target pressure was set at 60% arterial occlusion pressure.

RPE and leg muscle pain. During the first session at the laboratory, subjects were thoroughly familiarized with RPE and ratings of leg muscle pain. Subjects' perception of effort was assessed by using the 15-point Borg scale. Before each testing session, participants received written instructions based on guidelines recently proposed by Pageaux (18). Briefly, instructions included the definition of effort, exercise-specific descriptions ("How hard is it for you to drive your leg?"), exercise anchoring (i.e., "Maximal exertion corresponds to the effort you experienced while you were performing a maximal voluntary contraction"), and the distinction of effort, pain, and other exercise-related sensations (18). Leg muscle pain was recorded using a modified category-ratio 10 (CR-10) scale as proposed by Cook et al. (19). RPE and CR-10 ratings were taken immediately after each set of knee extension exercise.

Data analyses. Peak twitch torques (i.e., highest values of the torque–time curve) were determined for SS, PS10, and PS100, respectively. The PS10·PS100^{-1} torque ratio was calculated as an index of low-frequency fatigue (20). Isometric MVT was defined as the highest torque value before the superimposed twitch. M_{max} amplitudes elicited by SS were measured peak-to-peak. Muscle activity during exercise was estimated by calculating the root mean square of the EMG signal (RMS-EMG) averaged for the first three and the last three repetitions of each set, respectively (21). Only EMG data during the concentric phase of each repetition were taken into account for analysis. RMS-EMG of VM, RF, and VL were normalized to the corresponding M_{max} values (RMS·M^{-1}). The level of voluntary activation was calculated using a corrected formula: [1 – superimposed twitch (T_b × MVT^{-1}) × control twitch^{-1}] × 100 (22). MVT is the maximal torque level and T_b the torque value immediately before the superimposed twitch. The corrected formula is used to avoid the potential problem that the superimposed stimuli are not applied during the maximum torque level. Our group has recently shown that voluntary activation of the knee extensors can be reliably assessed during isometric contractions using the corrected formula (23).

Statistical analysis. All data were screened for normal distribution using the Shapiro–Wilk test. A two-way (time and condition) repeated-measures ANOVA was conducted for all neuromuscular parameters. *Post hoc* tests for all time and condition comparisons were performed with Bonferroni adjustments. The effect size was determined by calculating partial eta squared (η_p^2). Differences in RPE and leg muscle pain (CR-10) across the experimental conditions were tested using Friedman's tests. *Post hoc* analyses with Wilcoxon signed-rank tests were conducted with a Bonferroni correction applied, resulting in a significance level of $P \leq 0.0125$. Absolute and relative intersession reliability of arterial occlusion pressure was computed using an Excel spreadsheet (24). Absolute reliability was determined by computing the coefficient of variation. Relative reliability was determined by calculating the intraclass correlation coefficient (low, <0.80; moderate, 0.80–0.90; high, >0.90) (25). Data were analyzed using the SPSS statistical package 22.0 (SPSS Inc., Chicago, IL), and statistical significance was accepted at $P \leq 0.050$.

RESULTS

All participants successfully completed both exercise protocols at the required cadence.

Intersession reliability of arterial occlusion pressure. Arterial occlusion pressure of the thigh was reliably assessed as indicated by an acceptable absolute (coefficient of variation = 5.5%) and a moderate relative intersession reliability (intraclass correlation coefficient = 0.80).

MVT. A significant time × condition interaction was found for MVT ($F_{8,16} = 12.47$, $P < 0.001$, $\eta_p^2 = 0.44$). Already after the first set of exercise, there was a significant group difference between BFR and CON ($P = 0.048$). This difference persisted up to and including the first min of recovery (all $P < 0.010$). A consistently greater MVT reduction was

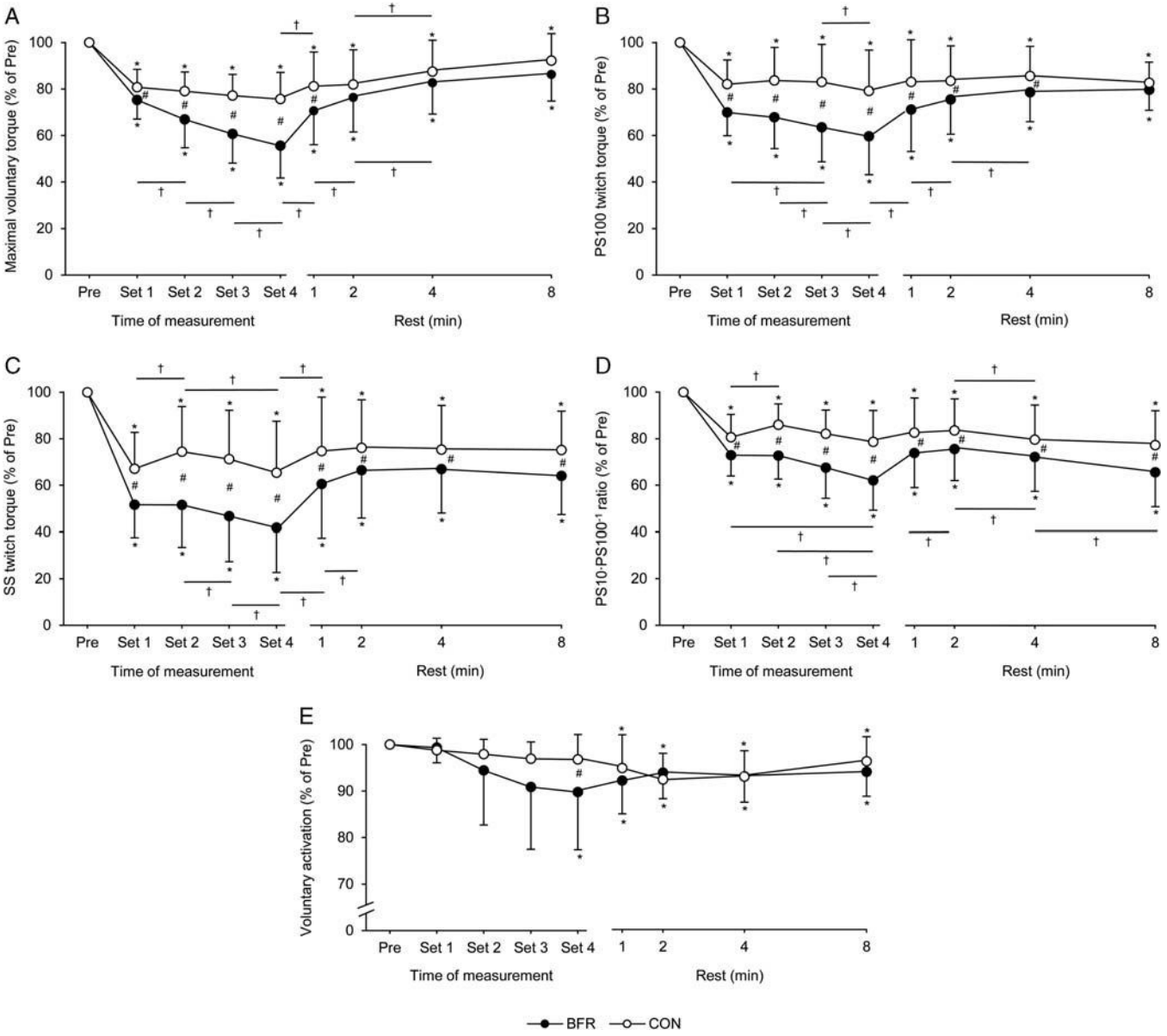

FIGURE 2—Percentage changes from baseline values for maximal voluntary torque (A), PS100 twitch torque (B), SS twitch torque (C), PS10·PS100^{-1} ratio (D), and voluntary activation (E) during and 1, 2, 4, and 8 min after each experimental condition. PS100, paired stimuli at 100 Hz; PS10, paired stimuli at 10 Hz; SS, single stimuli; PS10·PS100^{-1} ratio as an index of low-frequency fatigue; CON, control condition. Significantly different from Pre: *$P \leq 0.050$. Significantly different between time points: †$P \leq 0.050$. Significantly different between groups: #$P \leq 0.050$. Values are expressed as means ± SD. Please note that the statistics of the pairwise comparisons are presented in a reduced version to ensure clarity of the results.

observed during BFR (Fig. 2A). For both conditions, MVT differed significantly from baseline values until the eighth minute of recovery (all $P < 0.050$; Table 2). Immediately after exercise termination (set 4), there was a significantly greater decrease in MVT for BFR (−44.5% ± 14.1%) compared with CON (−24.3% ± 11.8%; $P < 0.001$). For the BFR condition, MVT progressively declined throughout the exercise protocol, recovered progressively within 4 min after exercise termination, but remained depressed by 13.4% ± 10.3% after 8 min of rest. During CON, there was a significant decrease in MVT after the first set of exercise but no further decline throughout the exercise protocol. After exercise termination, MVT values gradually recovered within 4 min postexercise but remained depressed compared with preexercise values after 8 min of rest. Absolute values and the percentage MVT changes during BFR and CON are shown in Table 2 and Figure 2A.

Electrically evoked twitch torque. There were significant time–condition interactions for PS100 ($F_{8,16} = 23.48$, $P < 0.001$, $\eta_p^2 = 0.60$), SS ($F_{8,16} = 26.54$, $P < 0.001$, $\eta_p^2 = 0.62$), and PS10·PS100^{-1} ratio ($F_{8,16} = 9.08$, $P < 0.001$, $\eta_p^2 = 0.39$). After the first set of exercise, there were significant group differences for PS100, SS, and PS10·PS100^{-1} ratio between BFR and CON (all $P < 0.001$; Fig. 2B–D). Group differences for SS and PS10·PS100^{-1} ratio persisted during

TABLE 2. Neuromuscular function of the quadriceps muscle before, during, and after each experimental condition.

			During Exercise				Rest			
		Pre	Set 1	Set 2	Set 3	Set 4	1 min	2 min	4 min	8 min
MVT (N·m)										
	BFR	292.0 ± 51.0	219.9 ± 44.5*	197.6 ± 54.3*	179.1 ± 52.4*	163.9 ± 51.4*	206.6 ± 50.5*†	222.1 ± 48.6*†	241.0 ± 48.0*†	251.4 ± 45.2*†
	CON	289.1 ± 41.6	233.3 ± 38.9*#	228.1 ± 36.0*#	222.1 ± 33.9*#	217.1 ± 36.6*#	234.3 ± 42.0*†#	236.3 ± 38.0*†	252.4 ± 38.6*†	265.7 ± 38.9†
PS100 (N·m)										
	BFR	102.5 ± 7.3	71.5 ± 10.7*	69.2 ± 13.6*	64.8 ± 14.9*	60.9 ± 16.7*	72.7 ± 18.3*†	77.3 ± 15.6*†	80.4 ± 13.5*†	81.4 ± 9.1*†
	CON	100.9 ± 11.1	82.5 ± 11.8*#	84.0 ± 14.3*#	83.0 ± 15.1*#	78.9 ± 15.2*#	83.1 ± 15.2*#	83.7 ± 12.7*#	85.9 ± 11.1*#	83.4 ± 11.5*
PS10 (N·m)										
	BFR	101.9 ± 9.8	53.1 ± 15.6*	51.9 ± 18.6*	46.1 ± 20.3*	39.9 ± 19.2*	56.3 ± 24.4*†	60.5 ± 23.2*†	59.8 ± 21.2*†	54.6 ± 18.4*†
	CON	99.2 ± 10.2	66.5 ± 17.8*#	72.5 ± 20.6*#	69.2 ± 23.2*#	63.9 ± 24.7*#	69.9 ± 25.0*†#	70.7 ± 22.1*†#	68.5 ± 19.3*#	64.0 ± 18.8*#
SS (N·m)										
	BFR	66.5 ± 5.7	34.2 ± 9.4*	34.1 ± 11.8*	30.9 ± 12.6*	27.6 ± 12.3*	39.1 ± 14.8*†	42.9 ± 13.3*†	43.3 ± 12.4*†	41.3 ± 10.9*†
	CON	65.4 ± 7.8	43.7 ± 10.7*#	48.5 ± 13.6*#	46.3 ± 13.9*#	42.7 ± 15.2*#	47.4 ± 12.9*#	48.3 ± 11.2*#	47.8 ± 9.7*#	47.6 ± 9.4*#
PS10·PS100^{-1} ratio										
	BFR	1.00 ± 0.09	0.73 ± 0.13*	0.73 ± 0.13*	0.68 ± 0.16*	0.62 ± 0.15*	0.74 ± 0.18*†	0.76 ± 0.18*†	0.73 ± 0.19*	0.66 ± 0.19*
	CON	0.99 ± 0.09	0.80 ± 0.14*#	0.85 ± 0.13*#	0.81 ± 0.15*#	0.78 ± 0.18*#	0.82 ± 0.18*#	0.83 ± 0.17*#	0.79 ± 0.18*#	0.77 ± 0.21*#
VM M_{max} (mV)										
	BFR	13.1 ± 2.8	12.7 ± 2.9	12.8 ± 2.9	12.8 ± 2.9	12.6 ± 2.9	12.7 ± 2.4	12.7 ± 2.4	12.6 ± 2.4	12.7 ± 2.5
	CON	13.1 ± 2.0	13.0 ± 2.0	13.1 ± 2.0	13.1 ± 2.0	13.2 ± 2.0	12.9 ± 1.7	13.0 ± 1.7	13.1 ± 1.8	13.0 ± 1.9
RF M_{max} (mV)										
	BFR	3.7 ± 1.1	3.8 ± 1.2	3.9 ± 1.2	3.9 ± 1.2	4.0 ± 1.2	3.9 ± 1.2	4.0 ± 1.2	3.9 ± 1.2	3.8 ± 1.2
	CON	4.1 ± 1.6	4.0 ± 1.4	4.2 ± 1.5	4.3 ± 1.4	4.3 ± 1.5	4.1 ± 1.4	4.2 ± 1.5	4.1 ± 1.5	4.0 ± 1.3
VL M_{max} (mV)										
	BFR	12.8 ± 3.8	12.7 ± 3.6	12.8 ± 3.5	12.8 ± 3.5	12.9 ± 3.6	12.3 ± 3.5	12.3 ± 3.5	11.9 ± 3.5	11.4 ± 3.5
	CON	12.9 ± 3.8	12.2 ± 3.9	12.4 ± 3.7	12.5 ± 3.6	12.6 ± 3.7	11.8 ± 3.6	11.7 ± 3.7	11.5 ± 3.8	11.2 ± 4.0
VA (%)										
	BFR	95.9 ± 3.3	95.2 ± 2.3	90.4 ± 10.7	87.1 ± 12.7	86.0 ± 11.2*	88.4 ± 7.7*	90.1 ± 6.7*	89.3 ± 6.9*	90.3 ± 6.5*
	CON	95.8 ± 3.2	94.6 ± 2.4	93.7 ± 2.2	92.8 ± 4.4	92.6 ± 4.4#	90.9 ± 4.0*	93.7 ± 2.2*	92.8 ± 4.4*	92.6 ± 4.4*

Values are expressed as mean ± SD. Note that the statistics of the pairwise comparisons are presented in a reduced version to ensure clarity of the results.
Significantly different from Pre: *$P \leq 0.050$.
Significantly different from exercise termination (set 4): †$P < 0.050$.
Significantly different between groups: #$P \leq 0.050$.
MVT, maximal voluntary torque; PS10·PS100^{-1} ratio, index of low-frequency fatigue; M_{max}, maximal M-wave; VA, voluntary activation; CON, control condition.

the entire recovery period (all $P < 0.050$; Fig. 2C–D). For PS100, group differences were still present up to and including 4 min postexercise ($P < 0.046$). At exercise termination, significantly greater reductions in PS100, SS, and PS10·PS100^{-1} ratio were found for BFR (−40.4% ± 16.9%, −58.2% ± 19.6%, and −38.0% ± 13.1%, respectively) compared with CON (−20.9% ± 17.6%, −34.6% ± 22.1%, and −21.4% ± 13.4%, respectively). For each stimulation method, twitch torques progressively declined throughout the BFR condition and recovered substantially within the first 2 min after exercise termination (Fig. 2B–D). Exercise-induced reductions in PS100 and SS persisted over the entire recovery period (all $P < 0.050$; Table 2). However, PS10·PS100^{-1} ratio progressively decreased from 2 to 8 min of recovery (Fig. 2D).

Electrically evoked potentials. No significant time–condition interactions were found for VM ($F_{8,16} = 1.32$, $P = 0.241$, $\eta_p^2 = 0.08$), RF ($F_{8,16} = 0.30$, $P = 0.964$, $\eta_p^2 = 0.02$), and VL M_{max} amplitude ($F_{8,16} = 0.9$, $P = 0.486$, $\eta_p^2 = 0.06$), respectively. Absolute values for M_{max} at each time point and condition are shown in Table 2.

Voluntary activation. A significant time–condition interaction was observed for voluntary activation ($F_{8,16} = 3.30$, $P = 0.002$, $\eta_p^2 = 0.17$). Significant group differences between BFR and CON were found after exercise termination ($P = 0.018$) with a greater reduction in voluntary activation for BFR (−10.2% ± 12.3%) compared with CON (−3.2% ± 5.5%; Fig. 2E). From the first to the eighth minute of recovery, voluntary activation for BFR and CON remained significantly reduced compared with baseline values (all $P < 0.050$; Table 2). Absolute values and percentage changes in voluntary activation during BFR and CON are presented in Table 2 and Figure 2E.

EMG recordings during exercise. There were significant time–condition interactions for VM RMS·M^{-1} ($F_{7,16} = 14.38$, $P < 0.001$, $\eta_p^2 = 0.47$) and VL RMS·M^{-1} during exercise ($F_{7,16} = 6.71$, $P < 0.001$, $\eta_p^2 = 0.30$). No significant time–condition interaction was found for RF RMS·M^{-1} ($F_{7,16} = 1.93$, $P = 0.071$, $\eta_p^2 = 0.30$). Regardless of the experimental condition, normalized muscle activity of VM and VL progressively increased during each exercise set (all $P < 0.01$; Fig. 3A and 3C). For normalized VM muscle activity, significant group differences between BFR and CON were evident for the last three repetitions of the first exercise set ($P = 0.015$); thereafter, significant differences could be documented for all time points with a consistently higher activation during BFR ($P < 0.001$; Fig. 3A). Significant group differences for normalized VL muscle activity were evident for the last repetitions of the second set ($P = 0.003$). In the following, significant differences between BFR and CON could be found for all time points with a higher activation during BFR (all $P < 0.010$; Fig. 3C).

RPE and leg muscle pain. There were significant changes in RPE over time for BFR ($\chi^2_3 = 33.28$, $P < 0.001$) and CON ($\chi^2_3 = 16.57$, $P = 0.001$). Except for the first exercise set ($P = 0.016$), RPE was significantly different between BFR and CON (all $P < 0.001$; Table 3). There were

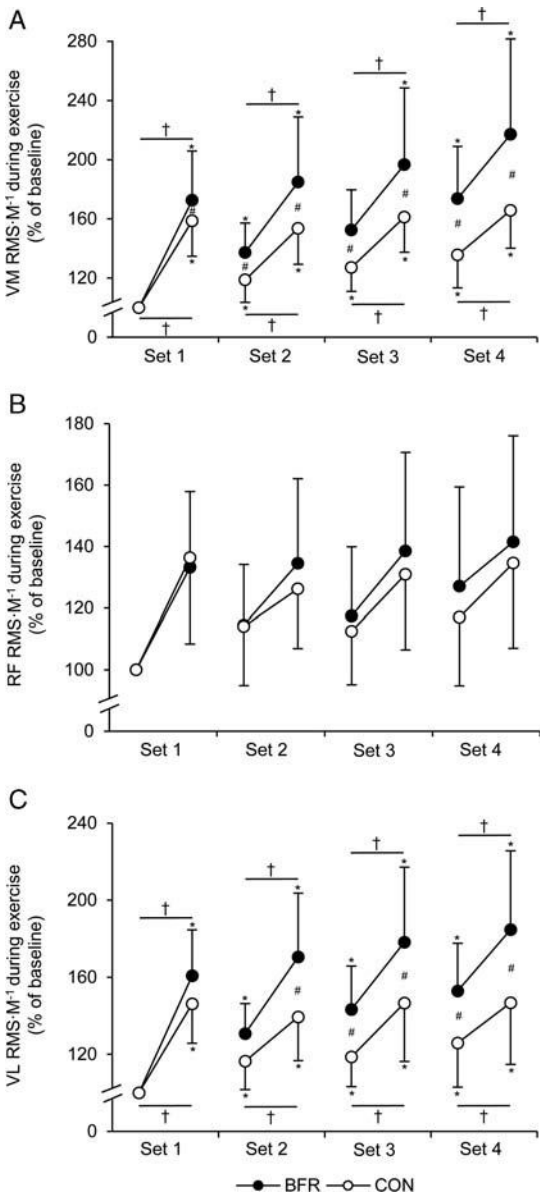

FIGURE 3—Percentage changes from baseline for the normalized muscle activity (RMS·M^{-1}) of VM (A), RF (B), and VL (C) averaged for the first three and the last three repetitions of each set. Baseline was defined as the average of the first three reps recorded during first set. RMS·M^{-1}, the root mean square of the EMG signal normalized to M_{max}; CON, control condition. Significantly different from baseline: *$P \leq 0.05$. Significantly different between time points: †$P \leq 0.050$. Significantly different between groups: #$P \leq 0.050$. Values are expressed as means ± SD.

also significant differences in leg muscle pain over time for BFR ($\chi^2_3 = 32.9$, $P < 0.001$) and CON ($\chi^2_3 = 13.90$, $P = 0.003$). Except for the first exercise set ($P = 0.040$), leg muscle pain was significantly different between BFR and CON (all $P < 0.001$; Table 3).

DISCUSSION

The present study investigated the time course and origin of changes in neuromuscular function during and after a bout of low-intensity exercise with and without BFR. The main findings were as follows: (i) BFR accelerated the exercise-induced development of muscle fatigue; (ii) peripheral factors mainly contributed to muscle fatigue during low-intensity BFR exercise with major impairments during the early phase of the exercise bout; (iii) neural factors also contributed to the pronounced end-exercise level of muscle fatigue under the condition of limited blood flow; (iv) BFR-induced muscle fatigue recovered substantially within 2 min after exercise termination; and (v) the initial recovery of muscle fatigue is mainly caused by a rapid restoration of contractile function. Interestingly, (vi) the effect of BFR on muscle fatigue was already diminished after 2 min of reperfusion. We also provide evidence that (vii) the augmented muscle activity during low-intensity BFR exercise compensated for the exacerbated contractile torque loss.

Development of muscle fatigue. As expected from other studies (i.e., [5,9]), the magnitude of muscle fatigue development during low-intensity exercise was exacerbated when blood flow to the working muscle was restricted. To our knowledge, this is the first study describing the development of muscle fatigue in the course of low-intensity exercise with and without BFR. In detail, we found a substantial loss in knee extensor MVT after the first set of exercise, irrespective of the condition. This large drop in knee extensor MVT is likely influenced by the greater number of contractions performed in the first compared with the following exercise sets (2). The exercise-induced MVT reduction was significantly greater for BFR compared with CON. In the course of the BFR condition, MVT progressively declined until exercise termination, whereas no further decrease in MVT was observed after the first set during CON. At exercise termination, there was a significantly greater MVT reduction for BFR (−45% ± 14%) compared with CON (−24% ± 12%). Studies using various exercise protocols reported BFR-induced MVT reductions of −30% to −62%, whereas minor reductions were observed for the free blood flow condition (−14% to −22% [4,9,26,27]). Discrepancies in acute responses to BFR exercise are likely due to methodological differences (i.e., cuff pressure, continuous or intermittent cuff application, exercise volume/intensity, and if exercise was performed to volitional task failure or not).

We also found that limited blood flow significantly increased the exercise-induced loss in quadriceps twitch torque, supporting previous observations that peripheral factors

TABLE 3. Perceptual responses during exercise.

		Set 1	Set 2	Set 3	Set 4
RPE					
	BFR	16 ± 2	16 ± 2	18 ± 2	18 ± 2
	CON	15 ± 2	14 ± 2*	15 ± 2*	15 ± 2*
Leg muscle pain					
	BFR	6 ± 2	6 ± 2	7 ± 2	8 ± 2
	CON	5 ± 2	4 ± 2*	5 ± 2*	5 ± 2*

Values are expressed as mean ± SD.
Significantly different between groups: *$P < 0.010$.
CON, control condition.

mainly contribute to muscle fatigue during low-intensity exercise with BFR (9,26). In detail, there was a substantial decrease in quadriceps twitch torque after the first exercise set, irrespective of the condition. Peripheral fatigue was more pronounced during BFR compared with CON. Throughout the BFR protocol, quadriceps twitch torque progressively declined until exercise termination, whereas quadriceps twitch torque during CON remained largely unchanged after the first set. Consequently, BFR resulted in a greater end-exercise level of peripheral fatigue as indicated by a twitch torque reduction of −40% ± 17% (PS100) from the preexercise value during BFR compared with CON (−21% ± 18%). Karabulut et al. (9), who also used work-matched exercise protocols, reported a similar reduction in quadriceps twitch torque (PS100) after BFR exercise (−44%) compared with the free blood flow condition (−19%). The fact that BFR exacerbated the exercise-induced accumulation of fatigue-related metabolites and prevented the recovery of contractile function within the interset rest periods might be the most obvious explanation for the pronounced development of peripheral fatigue. To our knowledge, this is the first study which investigated the etiology of peripheral fatigue after a bout of low-intensity BFR exercise. M-wave amplitude, commonly interpreted as an index of neuromuscular propagation (28), remained unchanged in the course of the exercise protocol in both conditions. By contrast, low-frequency fatigue (estimated via $PS10 \cdot PS100^{-1}$ ratio) was more pronounced during BFR compared with CON. Together, these findings suggest that low-intensity exercise combined with BFR exacerbated the contractile torque loss likely due to alterations distal to the sarcolemma, including the direct inhibition of the cross-bridge cycle, reduced myofibrillar sensitivity to calcium (Ca^{2+}), and/or impaired Ca^{2+} release from the sarcoplasmatic reticulum (SR) (29). As shown previously (30,31), the rate of phosphocreatine hydrolysis and concomitant inorganic phosphate accumulation is accelerated when exercise is performed under conditions of limited blood flow. The latter is thought to be the main contributor to exercise-induced impairments in Ca^{2+} handling (29) and the most likely explanation for the exacerbated development of peripheral fatigue during low-intensity BFR exercise. As recently described (32), a large portion of the initial drop in quadriceps twitch torque might be explained by impairments in myofibrillar function (i.e., direct inhibition of the cross-bridge cycle and reduced Ca^{2+} sensitivity), whereas the progressive decline in muscle function during the later phases of the exercise bout might be largely explained by impaired Ca^{2+} release from the SR.

The progressive loss in quadriceps twitch torque during exercise was accompanied by significant increases in VM and VL $RMS \cdot M^{-1}$ throughout both exercise protocols. Quadriceps muscle activity, as already observed by others (i.e., [21]), was significantly augmented in the course of exercise under conditions of limited blood flow. Higher muscle activation during BFR is commonly interpreted as an increased recruitment of type II muscle fibers, which is thought to be a potential rational for hypertrophic adaptations (3). Few researchers speculated that an increased inhibitory feedback of metabosensitive muscle afferents to the alpha motoneurons resulted in an augmented fiber recruitment to maintain adequate force output (21,33). However, the most plausible explanation is that the increased muscle activation during BFR compensates for the pronounced contractile force loss during BFR exercise (34). We also found that the augmented muscle activity was accompanied by higher RPE when exercise was performed under conditions of limited blood flow. Increased effort perception as a result of low-intensity work-matched exercise with BFR was frequently reported in the literature (i.e., [5]). It is well accepted that neuronal processing of sensory signals are involved in effort perception (35). In the present study, the stronger perception of effort during BFR exercise might result from an increased central motor command and a concomitant corollary discharge to compensate for the augmented contractile dysfunction (36) and/or from an increased afferent feedback from the working muscles due to stronger metabolic disturbances in the periphery (37,38). However, the exact sensory signals generating perception of effort are still debated (36).

Furthermore, by using the interpolated twitch technique, we found that central factors also contribute to the pronounced end-exercise level of quadriceps muscle fatigue during low-intensity BFR exercise. In contrast to the strong impairments in quadriceps twitch torque already observed after the first exercise set, the reduction in voluntary activation was not evident until the last set of BFR exercise (−10% ± 12%). After exercise termination, no significant changes in voluntary activation could be found during CON. This observation is in line with Karabulut et al. (9), who reported a 13% decline in voluntary activation at exercise termination induced by five sets of 20 dynamic knee extensions at 20% 1RM with BFR and a 4% increase after CON. Together, restricted blood flow appears to promote the development of central fatigue after multiple sets of work-matched low-intensity exercise. Although several mechanisms have been proposed to cause a reduction in voluntary activation (6), one mechanism that presumably accounts for decreased motoneuron firing rates under conditions of limited blood flow is the inhibitory feedback of group III/IV muscle afferents (39). A distinction is made between ergoreceptive group III/IV muscle afferents, which respond to low levels of interstitial ATP, H^+, and lactate associated with freely perfused, mostly aerobic exercise and nociceptive muscle afferents that are sensitive to high levels of metabolites associated with painful and/or ischemic exercise (40). The fact that higher ratings of leg muscle pain were recorded during BFR compared with CON might be a plausible but indirect indicator that nociceptive group III/IV muscle afferents were activated to a greater extent when exercise is performed under conditions of limited blood flow. Furthermore, it has been shown that group IV afferents can also be stimulated by venous distension (41); hence, it is conceivable that BFR-induced venous pooling itself has contributed to increased

discharge rates. Because group III/IV afferents are thought to decrease neural drive by acting at the spinal and/or supraspinal level, changes at spinal and/or supraspinal sites might have contributed to central fatigue after multiple sets of BFR exercise. However, by using peripheral nerve stimulation to assess voluntary activation, we were unable to determine whether spinal and/or supraspinal factors contributed to impairments in neural drive immediately after BFR exercise.

Recovery of muscle fatigue. To our knowledge, this is the first study investigating the time course and origin of neuromuscular recovery after fatiguing low-intensity exercise with and without BFR. We found a progressive but incomplete recovery of maximal voluntary quadriceps strength within 8 min postexercise, irrespective of the condition. Compared with CON, reperfusion after BFR exercise induced a markedly faster restitution of maximal voluntary quadriceps strength within the first 2 min after exercise termination. Despite the exacerbated muscle fatigue during BFR exercise, group differences were no longer evident after 2 min of rest, suggesting that the effect of limited blood flow on muscle fatigue was abolished shortly after reperfusion. However, MVT values did not recover completely within 8 min of rest. This observation is in accordance with Loenneke et al. (5), who measured maximal voluntary quadriceps strength 1, 24, and 48 h after the same BFR exercise protocol and found that MVT reductions persisted for 1 h postexercise and were no longer significantly different after 24 h.

The initial recovery of muscle fatigue after BFR exercise was mainly determined by peripheral factors as indicated by a rapid restitution of quadriceps twitch torque within the first 2 min after blood flow was restored. Despite the smaller extent to which muscle fatigue developed during CON, quadriceps twitch torque did not recover significantly after exercise termination. Interestingly, the effect of limited blood flow on contractile function was no longer evident after 8 min of reperfusion. The initial restitution of contractile function with reperfusion can be largely explained by the recovery of metabolically induced impairments in intracellular Ca^{2+} handling and/or sensitivity as indicated by a significant rebound of the $PS10{\cdot}PS100^{-1}$ ratio during the first 2 min after exercise termination. The fast initial restitution of quadriceps twitch torque might also be facilitated by a reactive hyperemic blood flow after cuff deflation (42), which, in turn, could have accelerated the removal of fatigue-related metabolites. However, contractile function did not recover completely within 8 min postexercise. This is not unusual because incomplete muscle function was shown to persist for some hours due to prolonged impairments in intracellular Ca^{2+} release from the SR or myofibrillar Ca^{2+} sensitivity (29). The exercise-induced production of reactive oxygen/nitrogen species has been recently linked to those prolonged impairments in contractile function (43).

It is important to emphasize that there was a progressive decline in $PS10{\cdot}PS100^{-1}$ ratio after 2 min of rest, whereas quadriceps twitch torque in response to SS and PS100 slightly increased or remained unchanged. This is in line with data from Froyd et al. (13), who also observed a decline in $PS10{\cdot}PS100^{-1}$ ratio after 2 min of recovery. This rather contradictory behavior might question the validity of the $PS10{\cdot}PS100^{-1}$ ratio as an index of low-frequency fatigue during the later phases of the recovery period after single-joint exercise.

Compared with the rapid restitution of quadriceps twitch torque shortly after reperfusion, there was no significant recovery of voluntary activation after BFR exercise. Group differences between BFR and CON were only evident at exercise termination and disappeared 1 min postexercise. Therefore, the present data suggest that voluntary drive is only affected when multiple sets of low-intensity exercise were performed under conditions of restricted blood flow and that this effect disappeared shortly after reperfusion. In line with the present findings, studies using postexercise ischemia to investigate the effect of group III/IV muscle afferents on central factors of muscle fatigue have demonstrated that the restoration of blood flow rapidly abolished the inhibitory effects of metabosensitive muscle afferents on voluntary activation (44,45). However, voluntary activation was significantly reduced 1 min postexercise, irrespective of the condition, suggesting that multiple sets of low-intensity dynamic exercise *per se* impaired neural drive to the quadriceps muscle, which, in turn, is not evident immediately after exercise termination. Reductions in neural drive persisted for the entire recovery period, irrespective of the condition. This is in line with studies showing a slow and incomplete recovery of voluntary activation after sustained low-intensity isometric contractions (for a review, see Carroll et al. [10]). Furthermore, because voluntary drive has been found to recover slowly after eccentric muscle actions (46), the eccentric portions might have contributed to the long-lasting depression of neural drive observed in the present study. The mechanisms underlying this delayed recovery of central fatigue after low-intensity contractions are currently unknown (10).

Limitations. A limitation to highlight is that the present findings are limited to male subjects. Previous research by Labarbera et al. (47) suggested that females are less fatigable compared with males, even when performing isotonic knee extensions under conditions of limited blood flow (47). Further studies are therefore needed to understand the role of sex during muscle fatigue in the time course of low-intensity BFR exercise.

CONCLUSION

The present study provides, for the first time, mechanistic insight into the etiology of muscle fatigue development and recovery when low-intensity exercise is performed under conditions of limited blood flow. We found that BFR accelerated the development of muscle fatigue mainly due to pronounced impairments in contractile function. The major change in contractile function occurred early during the BFR exercise bout, whereas the impairment in neural drive did

not play a significant role until exercise termination. Despite the pronounced level of muscle fatigue during BFR exercise, the effect of limited blood flow on muscle fatigue was diminished after 2 min of reperfusion, suggesting that BFR has a strong but short-lasting effect on neuromuscular function of the quadriceps muscle. The strong decline in neuromuscular function and the fast recovery after low-intensity BFR exercise seem to provide a strong adaptive stimulus for muscular growth without long-lasting impairments in motor performance, which are typically associated with heavy-load resistance training. From a practical point of view, low-intensity BFR exercise should be favored when applying high-frequency training regimes for muscle hypertrophy.

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Dietary Nitrate Supplementation Improves Exercise Tolerance by Reducing Muscle Fatigue and Perceptual Responses

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The present study was designed to provide further insight into the mechanistic basis for the improved exercise tolerance following dietary nitrate supplementation. In a randomized, double-blind, crossover design, twelve recreationally active males completed a dynamic time-to-exhaustion test of the knee extensors after 5 days of consuming both nitrate-rich (NITRATE) and nitrate-depleted beetroot juice (PLACEBO). Participants who improved their time-to-exhaustion following NITRATE performed a time-matched trial corresponding to the PLACEBO exercise duration with another 5 days of dietary nitrate supplementation. This procedure was performed to obtain time-matched exercise trials with ($NITRATE_{tm}$) and without dietary nitrate supplementation (PLACEBO). Neuromuscular tests were performed before and after each time-matched condition. Muscle fatigue was quantified as percentage change in maximal voluntary torque from pre- to post-exercise (ΔMVT). Changes in voluntary activation (ΔVA) and quadriceps twitch torque (ΔPS100) were used to quantify central and peripheral factors of muscle fatigue, respectively. Muscle oxygen saturation, quadriceps muscle activity as well as perceptual data (i.e., perception of effort and leg muscle pain) were recorded during exercise. Time-to-exhaustion was improved with NITRATE (12:41 ± 07:18 min) compared to PLACEBO (09:03 ± 04:18 min; $P = 0.010$). $NITRATE_{tm}$ resulted in both lower ΔMVT and ΔPS100 compared to PLACEBO ($P = 0.002$; $P = 0.001$, respectively). ΔVA was not different between conditions ($P = 0.308$). $NITRATE_{tm}$ resulted in reduced perception of effort and leg muscle pain. Our findings extend the mechanistic basis for the improved exercise tolerance by showing that dietary nitrate supplementation (i) attenuated the development of muscle fatigue by reducing the exercise-induced impairments in contractile muscle function; and (ii) lowered the perception of both effort and leg muscle pain during exercise.

Keywords: beetroot juice, central fatigue, contractile function, muscle pain, performance fatigability, peripheral fatigue

INTRODUCTION

The capacity to maintain physical activity (i.e., exercise tolerance) is crucial for endurance athletes, but is at least as important for the general population since it has been shown that poor aerobic fitness is linked to cardiovascular disease and overall mortality (Myers et al., 2002; Kodama et al., 2009). Exercise intolerance is known as a major symptom of various diseases [e.g., peripheral arterial disease (Leeper et al., 2013), chronic obstructive pulmonary disease (Pepin et al., 2007), or chronic heart failure (Mentzer and Auseon, 2012) with detrimental consequences for quality of life (Belfer and Reardon, 2009)]. It is therefore not surprising that its underpinning mechanisms have been extensively investigated for more than a century (McKenna and Hargreaves, 2007), but are still highly debated (Marcora and Staiano, 2010). As a multifactorial phenomenon, exercise tolerance is determined by various physiological [e.g., cardiovascular, respiratory, metabolic, and neuromuscular mechanisms (McKenna and Hargreaves, 2007)] and psychological factors [e.g., external motivation, mental fatigue (McCormick et al., 2015)]. Given its broad significance, many efforts have been made to identify possible interventions to improve exercise tolerance by utilizing, e.g., nutritional (Matson and Tran, 1993), pharmacological (Mauger et al., 2014), or psychological strategies (McCormick et al., 2015).

Dietary nitrate supplementation, commonly administered in the form of beetroot juice, has been demonstrated as a promising approach to improve exercise tolerance at low and high intensities (Bailey et al., 2009, 2010; Lansley et al., 2011; Thompson et al., 2014). The ergogenic effect of dietary nitrate on exercise tolerance is attributed to the actions of the biological messenger nitric oxide (NO), since dietary nitrate supplementation is thought to be an effective method to elevate its bioavailability (Lundberg and Govoni, 2004). NO is known for its regulatory function in various physiological processes including vasodilation (Ignarro, 1989), angiogenesis (Papapetropoulos et al., 1997), mitochondrial respiration (Brown, 1995), and contractile function (Kobzik et al., 1994). Several studies have shown that the ergogenic effect of dietary nitrate on exercise tolerance is associated with lower oxygen (O_2) cost of submaximal exercise (Bailey et al., 2009; Larsen et al., 2010, 2011), which might be related to a more efficient mitochondrial adenosine triphosphate (ATP) synthesis (Larsen et al., 2011) and/or a more efficient ATP utilization during skeletal muscle work (Bailey et al., 2010). Moreover, increased dietary nitrate intake has been shown to improve vascular (Ferguson et al., 2013), metabolic (Bailey et al., 2010), and skeletal muscle function in response to exercise (Hernández et al., 2012). Any of the physiological alterations associated with dietary nitrate are capable of modulating skeletal muscle function (Affourtit et al., 2015) and thus the development of muscle fatigue. Muscle fatigue [also referred to as 'performance fatigability' (Enoka and Duchateau, 2016)] is characterized by impairments in motor performance resulting from an exercise-induced decline in the force-generating capacity of the involved muscles and stems from a decrease in neural activation of muscles (traditionally termed 'central fatigue') and/or alterations at or distal to the neuromuscular junction that result in contractile dysfunction (traditionally termed 'peripheral fatigue') (Gandevia, 2001). The capacity of the neuromuscular system to generate the required power for the task is considered as critical factor of endurance performance (Burnley and Jones, 2018). However, the traditional assumption that exercise tolerance is exclusively limited by the inability to generate the power output required for the task despite maximal voluntary effort (also referred to as 'task failure') is highly debated (Enoka and Duchateau, 2016). Several authors suggest that endurance performance is rather regulated by a complex interplay of physiological and psychological factors (Marcora, 2008; Noakes, 2008; Venhorst et al., 2018). Particularly effort perception and muscle pain are considered as important factors that determine exercise tolerance (Noakes, 2008; Marcora and Staiano, 2010; Mauger, 2014).

To the authors' knowledge, no study to date has investigated the impact of dietary nitrate supplementation on central and peripheral mechanisms of muscle fatigue or its impact on effort and muscle pain perception during submaximal endurance exercise. The present study was designed to provide further insight into the mechanistic basis for the improved exercise tolerance after dietary nitrate supplementation by investigating key-determinants of endurance performance. Therefore, we quantified exercise tolerance via the use of single-joint endurance exercise, which provides a suitable model to investigate the underlying mechanisms of endurance performance without cardiorespiratory limitations typically associated with whole-body endurance exercise (Andersen et al., 1985). First, by using a randomized, counterbalanced, double-blind, crossover design, participants completed a high-intensity time-to-exhaustion test of the knee extensors after 5 days of dietary nitrate and placebo supplementation. Second, those who improved their time-to-exhaustion with dietary nitrate, performed a time-matched trial corresponding to the exercise duration of the placebo condition. The time-matched conditions were further examined to analyze the impact of dietary nitrate on (i) central and peripheral aspects of muscle fatigue; (ii) muscle O_2 saturation (SmO_2), (iii) electromyographic (EMG) activity, and (iv) perception of effort and leg muscle pain. To improve the validity of the present data, we also aimed to control for distinct factors (e.g., task motivation, trait and state fatigue), which are thought to affect both performance and perceptual measures during fatiguing exercise (Pageaux, 2014; Enoka and Duchateau, 2016).

We hypothesized that muscle fatigue development is attenuated with dietary nitrate supplementation.

MATERIALS AND METHODS

Subjects

An *a priori* sample size calculation was conducted based on the effect size of a previously published study investigating, amongst others, the impact of dietary nitrate on time-to-exhaustion during high-intensity knee extension exercise (Bailey et al., 2010). A two-sided significance level of 0.05 and a power of 0.95 indicated that 8 participants would be required. Based on the observation that not all participants improved their exercise

tolerance following dietary nitrate supplementation (Wilkerson et al., 2012; Coggan et al., 2018), 14 recreationally active males were initially recruited to participate in the present study. Given the fact that two participants did not reach exhaustion within the predefined time window (25 min) of the fatiguing task, a total of 12 subjects (age: 27 ± 5 years; height: 183 ± 7 cm; body mass: 85 ± 9 kg; physical activity: 6 ± 3 $h \cdot wk^{-1}$) was considered for analysis. Taking into account that muscle fatigue is thought to depend on sex [for a review see (Hunter, 2014)], we chose a sample comprising exclusively male subjects. All participants were familiar with high-intensity exercise. Subjects were asked to abstain from (i) vigorous exercise, analgesics, caffeine, and alcohol consumption for 24 h prior to the laboratory visits as well as (ii) nitrate-rich foods [i.e., leafy green vegetables, beetroot, and processed meats (Hord et al., 2009)] and (iii) antibacterial mouthwash during the entire study period (Bondonno et al., 2015). Furthermore, participants were instructed to record their diet 24 h prior to the first laboratory visit and to repeat this for all subsequent visits. The study was approved by the university ethics committee and was conducted according to the Declaration of Helsinki. All participants gave written informed consent in accordance with the Declaration of Helsinki.

Experimental Procedure

Subjects visited the laboratory on at least three different occasions. During the first visit, participants were thoroughly familiarized with the following procedures: (i) one-leg dynamic exercise (OLDE) of the knee extensors (for more details, see *One-leg dynamic exercise*); (ii) neuromuscular tests comprising maximal voluntary contractions (MVC), and peripheral nerve stimulation as well as (iii) ratings of perceived effort and leg muscle pain. Furthermore, an OLDE incremental test was performed to determine peak power output.

Using a randomized, counterbalanced, double-blind, crossover design, participants performed an OLDE time-to-exhaustion test of the knee extensors at 85% peak power output after 5 days of supplementation with dietary nitrate via beetroot juice (NITRATE; ∼6.5 mmol nitrate per 70 mL; Beet it, Heartbeet Ltd., Ipswich, United Kingdom) and nitrate-depleted beetroot juice (PLACEBO; ∼0.04 mmol nitrate per 70 mL; Beet it, Heartbeet Ltd., Ipswich, United Kingdom), respectively. The duration of the supplementation period was chosen based on data from Bailey et al. (2010), who have shown that time-to-exhaustion during high-intensity knee extension exercise was significantly improved following 4–6 days of dietary nitrate supplementation. For each experimental condition, subjects were instructed to consume 70 mL beetroot juice every morning and 2 h prior to the laboratory visits. The second and third occasion was separated by 7 ± 1 days and took place at the same time of the day (±2 h). Participants who improved their time-to-exhaustion following NITRATE by at least 8% performed a time-matched trial corresponding to the PLACEBO exercise duration after a 10 days wash-out period (Larsen et al., 2007) and another 5 days of dietary nitrate supplementation. This procedure was performed in order to allow comparison of neuromuscular, oxygenation, and perceptual data between time-matched exercise trials with ($NITRATE_{tm}$) and without dietary nitrate supplementation (PLACEBO). Time-to-exhaustion tests that do not differ by more than 8% between conditions were considered as time-matched. The worthwhile change for the time-to-exhaustion test was defined according to Pageaux et al. (2015) who reported a coefficient of variation of ∼8% for the intersession reliability of the OLDE protocol. Neuromuscular tests were performed before and immediately after exercise termination (<10 s) (**Figure 1A**). SmO_2 and EMG data as well as ratings of perceived effort and leg muscle pain were continuously recorded during each experimental condition.

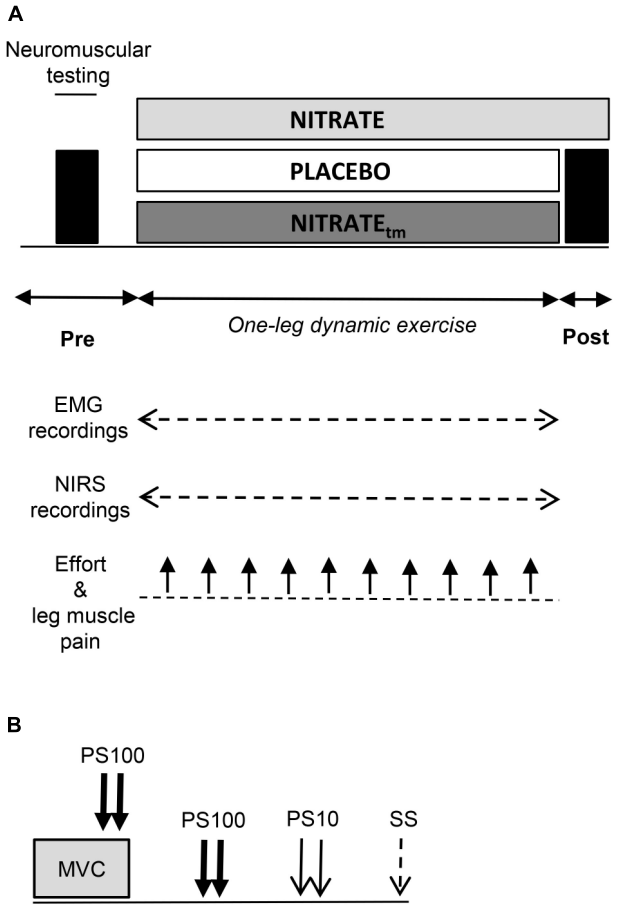

FIGURE 1 | (A) Illustration of the experimental design. A time-to-exhaustion test of the knee extensors was performed after 5 days of dietary nitrate (NITRATE) and PLACEBO supplementation. Neuromuscular function of the quadriceps muscle was assessed before and immediately after both PLACEBO and time-matched dietary nitrate condition ($NITRATE_{tm}$). Effort perception and leg muscle pain were recorded every min during exercise. Electromyography (EMG) and near-infrared spectroscopy (NIRS) data were continuously recorded during exercise. **(B)** The neuromuscular testing procedure comprised isometric MVC of the knee extensors combined with electrical stimulation to assess maximal voluntary torque (MVT), voluntary activation (via the interpolated twitch technique), and quadriceps twitch torques in response to paired electrical stimuli at 100 Hz (PS100) and at 10 Hz (PS10) as well as single stimuli (SS). A representative torque-time curve of the neuromuscular assessment procedure can be found in a previous publication from our group (Husmann et al., 2018).

Prior to pre-exercise measurements, participants performed an initial warm-up on a stationary bicycle (5 min; 100 W; 90 rpm) followed by a specific warm-up on a dynamometer comprising two isometric contractions for 5 s at 50, 70, and 90% of maximal voluntary torque interspaced by 60 s of rest (MVT; determined during the familiarization session), respectively. Neuromuscular tests comprised supramaximal electrical stimulations of the femoral nerve during and after an isometric MVC (**Figure 1B**). All measurements were conducted on the quadriceps muscle of the dominant leg (i.e., kicking preference). During OLDE and neuromuscular testing, subjects were comfortably seated and secured on a CYBEX NORM dynamometer (Computer Sports Medicine®, Inc., Stoughton, MA, United States). The seating position was adjusted for each participant and settings were documented for the subsequent sessions.

One-Leg Dynamic Exercise

One-leg dynamic exercise is an exercise protocol characterized by rhythmic isotonic contractions of the knee extensor muscles alternated with passive knee flexions. In contrast to whole body exercise, OLDE is not limited by cardiorespiratory function (Rossman et al., 2014). The OLDE protocol used in the present study was recently developed and proved as reliable to measure muscle endurance and to investigate central and peripheral mechanisms of muscle fatigue (Pageaux et al., 2015). It has been shown that OLDE induces severe levels of muscle fatigue (−40% MVT) with significant impairments in both peripheral (−40% contractile twitch torque) and central factors (−13% voluntary activation) (Pageaux et al., 2015). Furthermore, it allows bypassing the time lag between exercise termination and neuromuscular testing, which is typically associated with whole body endurance exercise. A more detailed description of the OLDE protocol used in the present study can be found elsewhere (Pageaux et al., 2015). Briefly, OLDE was performed on a CYBEX NORM dynamometer (Computer Sports Medicine®, Inc., Stoughton, MA, United States) with the range of motion set from 10 to 90° (0° = full knee extension). A metronome was used to ensure a cadence of 50 contractions per min (cpm), enabling an active knee extension with $\sim 106° \cdot s^{-1}$ and a passive knee flexion velocity of $\sim 180° \cdot s^{-1}$.

During the first visit, subjects were thoroughly familiarized with the OLDE protocol using torque and EMG feedback. An OLDE incremental test was performed afterwards to determine peak power output (89.5 ± 13.1 W). Testing started at an isotonic load of 4 N · m (∼7.4 W) for 1 min and was increased by 3 N · m every min (∼4.5 W) until exhaustion. Exhaustion was defined as a decline in cadence below 40 cpm for a period of ≥10 s despite strong verbal encouragement. On the second and third visit, subjects performed a 2 min warm-up at 10% peak power output followed by a high-intensity OLDE time-to-exhaustion test at 85% of peak power output (76.0 ± 11.1 W). Monetary rewards were announced for the three best performances (50 €, 30 €, and 20 €) in order to motivate the participants to exercise for as long as possible during the time-to-exhaustion test. Exhaustion was again defined as a drop in cadence below 40 cpm for a period of ≥10 s despite strong verbal encouragement. An upper time limit for the time-to-exhaustion test was set at 25 min.

Torque Recordings

A CYBEX NORM dynamometer (Computer Sports Medicine®, Inc., Stoughton, MA, United States) was used to capture instantaneous torques. Participants were seated on an adjustable chair with the hip fixed at 80° (0° = full extension). Straps were fixed tightly across the subjects' waist and chest to avoid excessive movements during data recording. The dynamometer rotation axis was aligned with the knee joint rotation axis and the lever arm was attached to the lower leg just above the lateral malleolus. Isometric MVC were performed at 90° knee flexion (0° = full extension). Isometric MVT was defined as the highest torque value prior to the superimposed twitch evoked by electrical stimulation. For each trial, subjects were instructed to cross their arms in front of their chest and to push as hard and as fast as possible against the lever arm of the dynamometer. Strong verbal encouragement was given by the investigator during MVC testing. Visual feedback of the torque-time curve was provided on a digital oscilloscope (HM1508, HAMEG Instruments, Mainhausen, Germany).

EMG Recordings

A detailed description of the EMG recordings can be found in a previously published study from our laboratory (Behrens et al., 2015). Briefly, myoelectrical signals of the vastus medialis (VM), rectus femoris (RF), and vastus lateralis (VL) muscles were recorded using surface electrodes in a bipolar configuration (EMG Ambu Blue Sensor N). EMG signals were amplified (2500×), band-pass filtered (10–450 Hz), and digitized with a sampling frequency of 3 kHz using an analog-to-digital converter (NI PCI-6229, National Instruments, Austin, TX, United States). Maximum compound muscle action potential amplitudes (M_{max}) elicited by electrical stimulation were measured peak-to-peak. Muscle activity during exercise was assessed by calculating the root mean square of the EMG signal (RMS-EMG) averaged for five contractions at the beginning, as well as at 25, 50, 75, and 100% of each trial, respectively. Only EMG data during the concentric phase of each repetition were considered for analysis. RMS-EMG of VM, RF, and VL was normalized to the corresponding M_{max} value ($RMS \cdot M^{-1}$). To estimate the total muscle activity of the quadriceps during knee-extension exercise, $RMS \cdot M^{-1}$ was averaged across VM, RF, and VL (Husmann et al., 2017).

Electrical Nerve Stimulation

Neuromuscular function of the quadriceps muscle was assessed by using electrical stimulation of the femoral nerve. A constant-current stimulator (Digitimer DS7A, Hertfordshire, United Kingdom) was used to deliver square-wave pulses of 1 ms duration with maximal voltage of 400 V. A ball probe cathode (10 mm diameter) was pressed in the femoral triangle always by the same experienced investigator. The anode, a self-adhesive electrode (35 mm × 45 mm, Spes Medica, Genova, Italy), was affixed over the greater trochanter. After determining the optimal

site for stimulation, the position was marked onto the subjects' skin to ensure repeatable measurements within each session. Individual stimulation intensity was progressively increased until M_{max} of VM, RF, and VL as well as a plateau in knee extensor twitch torque was achieved. During the subsequent testing procedures, the stimulation intensity was increased by additional 40% to guarantee supramaximal stimulation. Potentiated quadriceps twitch torques evoked by paired electrical stimuli at 100 Hz (PS100), 10 Hz (PS10), and single stimuli (SS) were elicited 2, 4, and 6 s after isometric MVC, respectively. Peak twitch torques (i.e., highest values of the torque-time curve) were determined for PS100, PS10, and SS, respectively. The $PS10 \cdot PS100^{-1}$ torque ratio was calculated as an index of low-frequency fatigue. A reduction of this ratio is thought to indicate impairments in excitation-contraction coupling (Verges et al., 2009). To determine the level of voluntary activation during isometric MVC, the interpolated twitch technique was applied. Electrical paired stimuli were delivered to the femoral nerve at 90° knee flexion 2 s after torque onset (during the plateau phase) and 2 s after MVC. The level of voluntary activation was calculated using a corrected formula: [1 − superimposed twitch ($T_b \times MVT^{-1}$) × control twitch^{-1}] × 100 (Strojnik and Komi, 1998). MVT is the maximal torque level and T_b the torque value immediately before the superimposed twitch. The corrected formula is used to avoid the potential problem that the superimposed stimuli are not always applied during the maximum torque level. As shown recently by our group, voluntary activation of the knee extensors can be reliably assessed during isometric contractions using the corrected formula (Behrens et al., 2017).

Muscle Oxygenation

Muscle oxygenation of VL was continuously monitored using a portable near-infrared spectroscopy (NIRS) device (Moxy, Fortiori Design LLC, Hutchinson, MN, United States). The Moxy monitor has been recently shown to allow reliable measurements of SmO_2 (Crum et al., 2017). SmO_2 reflects the balance between O_2 delivery and O_2 demand in the analyzed muscle (Ferrari et al., 2011). Prior to optode placement on the VL, subjects' skin was shaved and cleaned. The NIRS probe was attached at mid-thigh level, closely to the VL EMG electrodes. The optode was secured with tape and covered with a protective shell to avoid artifacts caused by motion and light. Reliable optode placement between sessions was assured by recording the distance to the patella, measured from the subject's patella to the greater trochanter. Furthermore, skinfold thickness above the VL was measured using a skinfold caliper (5 ± 1 mm). All signals were recorded with a sampling frequency of 2 Hz. A 4th order low-pass zero-phase Butterworth filter (cutoff frequency 0.2 Hz) was applied. NIRS-derived indices of muscle oxygenation were averaged across 5 s at 25, 50, 75, and 100% of each trial, respectively. Shortly after the OLDE warm-up, resting baseline values were averaged for 30 s prior to the start of the OLDE protocol. Baseline values were captured at rest in a seated position. SmO_2 and total hemoglobin (tHb) were reported as percentage changes from baseline (ΔSmO_2 and ΔtHb).

Ratings of Perceived Effort and Leg Muscle Pain

During the first visit at the laboratory, subjects were familiarized with ratings of perceived effort and ratings of leg muscle pain. Subjects' perception of effort was recorded by using the 15-point Borg scale (Borg, 1982). Prior to each testing session, participants received written instructions based on guidelines recently proposed by Pageaux (2016). Briefly, instructions comprised the definition of effort ("the conscious sensation of how hard, heavy, and strenuous a physical task is"), exercise-specific descriptions ("How hard is it for you to drive your leg?"), exercise-anchoring (e.g., "maximal exertion corresponds to the effort you experienced while you were performing a MVC"), and the distinction of effort, pain, and other exercise-related sensations (Pageaux, 2016). Leg muscle pain was defined as the intensity of pain perceived by the subject exclusively in the exercising quadriceps. A modified category-ratio 10 (CR-10) scale was used to quantify leg muscle pain during exercise (Cook et al., 1997). At the beginning of each minute, the participants were asked to rate their perceived effort and leg muscle pain. The average of all ratings across the entire exercise duration is reported as mean levels of effort and leg muscle pain. End-exercise levels of effort and leg muscle pain refer to the last rating of effort and leg muscle pain before exercise termination.

Task Motivation

Participants' motivation to successfully complete the time-to-exhaustion test was assessed by using the success motivation and task interest motivation subscales designed and validated by Matthews et al. (2001). On a 5-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = very much, 4 = extremely) subjects rated 8 items (e.g., "I wanted to succeed on the task" and "I was eager to do well"). Therefore, total scores range between 0 and 32. The questionnaire was presented to the participant prior to the start of each task. In order to control for potential differences in task motivation, total scores were compared across all experimental conditions. If there is a significant difference in task motivation between conditions, it is considered as a covariate in the statistical analysis.

Trait and State Properties of Fatigue

According to Enoka and Duchateau (2016), fatigue is defined as a disabling symptom which can be assessed by self-report and quantified as a state variable or as a trait characteristic. Both properties of fatigue are considered as modulating factors of human performance. The Modified Fatigue Impact Scale (MFIS), a self-reported measure of the impact of fatigue on cognitive, physical, and psychosocial aspects of daily activity, was utilized to assess the level of trait fatigue over the course of the last 7 days before each laboratory visit. State fatigue was examined by using the fatigue scale of the Profile of Mood States (POMS-F), which has been shown to provide a reliable and valid instrument to assess the level of state fatigue across a wide range of cohorts (O'Connor, 2004). Before each exercise trial, subjects were asked to complete both questionnaires. If there are significant differences in self-reported measures of fatigue

between conditions, they are considered as covariates in the statistical analysis.

Quantification of Muscle Fatigue

In the present study, muscle fatigue was quantified via the percentage change in MVT values from pre- to post-exercise (ΔMVT). Percentage changes in voluntary activation (ΔVA) and PS100 (ΔPS100) from pre- to post-exercise were used to quantify central and peripheral factors of muscle fatigue, respectively.

Statistical Analysis

All data were screened for normal distribution using the Shapiro–Wilk test. Differences in percentage changes from pre- to post-exercise of all neuromuscular parameters were tested using Student's paired *t*-tests. Cohen's *d* effect size was calculated for each paired comparison. Effect sizes of 0.20, 0.50, and 0.80 were considered small, medium, and large, respectively (Cohen, 1988). Two-way ANOVAs with repeated measures on time and condition were conducted for all parameters derived from EMG and NIRS recordings during exercise. *Post hoc* tests were performed with Bonferroni adjustments. The effect size was determined by calculating partial eta squared (η_p^2). Data were analyzed using the SPSS statistical package 22.0 (SPSS Inc., Chicago, IL, United States) and statistical significance was accepted at $P \leq 0.05$. Sample size was calculated with the statistical software package G*Power (version 3.1.4.).

RESULTS

Task Motivation

No differences in task motivation were found between PLACEBO (28 ± 3) and NITRATE (27 ± 3, $P = 0.156$). Furthermore, task motivation was not significantly different between time-matched conditions (PLACEBO: 26 ± 3; $NITRATE_{tm}$: 27 ± 5; $P = 0.282$).

Trait and State Properties of Fatigue

No differences in trait fatigue were observed between PLACEBO (12 ± 7) and NITRATE (11 ± 9, $P = 0.324$). Furthermore, trait fatigue was not significantly different between time-matched conditions (PLACEBO: 10 ± 6; $NITRATE_{tm}$: 9 ± 7, $P = 0.282$). No differences in state fatigue were found between PLACEBO (8 ± 7) and NITRATE (7 ± 6, $P = 0.386$). Furthermore, state fatigue was not significantly different between time-matched conditions (PLACEBO: 8 ± 6; $NITRATE_{tm}$: 7 ± 8, $P = 0.346$).

Exercise Tolerance

Time-to-exhaustion was significantly improved with NITRATE (12:41 ± 07:18 min) compared to PLACEBO (09:03 ± 04:18 min, $P = 0.010$, $d = 0.61$). Individual data are presented in **Figure 2**. Eight participants improved their exercise performance following dietary nitrate supplementation by at least 8% and completed another trial corresponding to the PLACEBO exercise duration. Exercise trials that do not differ by more than 8% from each other were considered as time-matched. Together, time-matched conditions of 11 subjects were taken into account for further analysis and are referred to as $NITRATE_{tm}$ and PLACEBO. Please note that two participants reached the upper time limit of 25 min during the NITRATE condition.

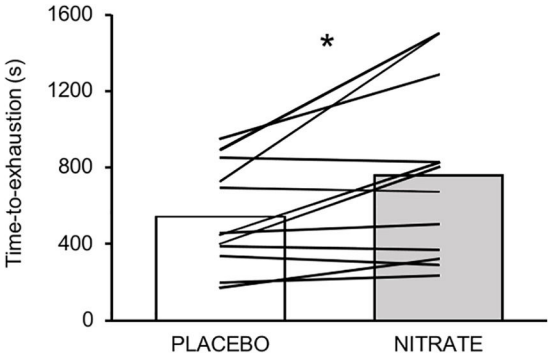

FIGURE 2 | Mean values and individual data for time-to-exhaustion (s) between experimental conditions. Please note that eight out of twelve participants improved their performance over a range from ∼9 to ∼51%. Significantly different between conditions: $^*P \leq 0.05$.

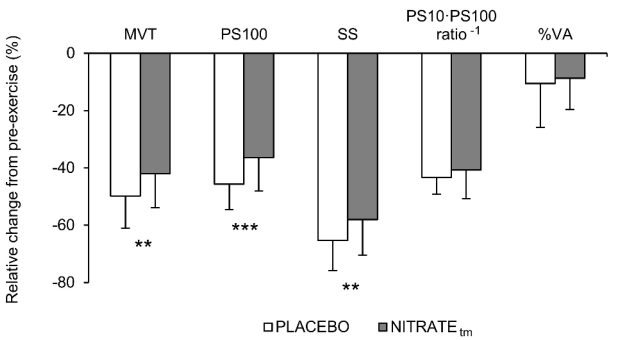

FIGURE 3 | Percentage change from pre-exercise values for maximal voluntary torque (MVT), twitch torque in response to paired (PS100) and single (SS) electrical stimuli, $PS10 \cdot PS100^{-1}$ ratio, and voluntary activation (%VA) across both PLACEBO and time-matched dietary nitrate condition ($NITRATE_{tm}$). Values are presented as mean ± SD. Significantly different between conditions: $^{**}P \leq 0.01$, $^{***}P \leq 0.001$.

Maximal Voluntary Torque

A significantly lower ΔMVT was found for $NITRATE_{tm}$ compared to PLACEBO ($P = 0.002$, $d = 0.66$; **Figure 3**). Absolute values for MVT are presented in **Table 1**.

Electrically Evoked Twitch Torque

A significantly lower ΔPS100 was found for $NITRATE_{tm}$ compared to PLACEBO ($P = 0.001$, $d = 0.91$; **Figure 3**). Furthermore, ΔSS was shown to be lower for $NITRATE_{tm}$ compared to PLACEBO ($P = 0.007$, $d = 0.64$). No significant differences for $\Delta PS10 \cdot PS100^{-1}$ ratio were found between $NITRATE_{tm}$ and PLACEBO ($P = 0.183$, $d = 0.31$; **Figure 3**). Absolute values for PS100, SS, and $PS10 \cdot PS100^{-1}$ ratio are presented in **Table 1**.

TABLE 1 | Neuromuscular function of the quadriceps muscle before and after each time-matched condition (n = 11).

		Pre	Post
MVT (N · m)			
	PLACEBO	304.7 ± 68.8	152.3 ± 47.4
	NITRATE$_{tm}$	300.6 ± 61.0	175.0 ± 55.3
PS100 (N · m)			
	PLACEBO	107.2 ± 24.1	57.6 ± 11.6
	NITRATE$_{tm}$	103.0 ± 21.4	65.0 ± 15.3
PS10 (N · m)			
	PLACEBO	103.9 ± 20.5	31.6 ± 6.8
	NITRATE$_{tm}$	103.6 ± 18.4	39.3 ± 13.2
SS (N · m)			
	PLACEBO	69.1 ± 16.6	23.3 ± 5.0
	NITRATE$_{tm}$	68.8 ± 16.4	28.3 ± 8.8
PS10 · PS100^{-1} ratio			
	PLACEBO	0.97 ± 0.05	0.55 ± 0.05
	NITRATE$_{tm}$	1.01 ± 0.06	0.60 ± 0.10
VM M_{max} (mV)			
	PLACEBO	12.5 ± 3.3	12.5 ± 3.3
	NITRATE$_{tm}$	13.2 ± 2.1	13.6 ± 2.2
RF M_{max} (mV)			
	PLACEBO	4.5 ± 2.1	4.0 ± 1.7
	NITRATE$_{tm}$	4.2 ± 1.7	3.9 ± 1.7
VL M_{max} (mV)			
	PLACEBO	9.9 ± 3.6	10.0 ± 3.7
	NITRATE$_{tm}$	9.3 ± 3.0	10.0 ± 3.4
VA (%)			
	PLACEBO	95.8 ± 2.8	85.9 ± 15.2
	NITRATE$_{tm}$	95.6 ± 3.6	87.3 ± 10.7

Values are expressed as mean ± SD. MVT, maximum voluntary torque; PS100, paired stimuli twitch torque at 100 Hz; PS10, paired stimuli twitch torque at 10 Hz; SS, single stimulus twitch torque; PS10 · PS100^{-1} ratio, index of low-frequency fatigue; M_{max}, maximum M-wave; VM, vastus medialis; RF, rectus femoris; VL, vastus lateralis; VA, voluntary activation; NITRATE$_{tm}$, time-matched dietary nitrate condition.

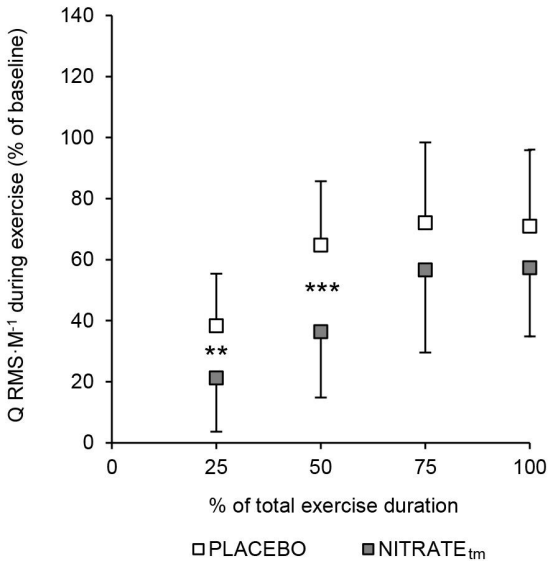

FIGURE 4 | Percentage increase from baseline for the normalized muscle activity of the quadriceps muscle (Q RMS · M^{-1}). To estimate the total muscle activity of the quadriceps muscle, RMS · M^{-1} was averaged across vastus medialis, rectus femoris, and vastus lateralis for five contractions at 25, 50, 75, and 100% of each trial, respectively. Baseline was defined as the average of the first five contractions. Values are presented as mean ± SD. NITRATE$_{tm}$, time-matched dietary nitrate condition; RMS · M^{-1}, the root mean square of the EMG signal normalized to M_{max}. Significantly different between conditions: $^{**}P \leq 0.01$, $^{***}P \leq 0.001$.

Electrically Evoked Potentials

No significant differences in ΔM_{max} between NITRATE$_{tm}$ and PLACEBO were observed for VM, RF, and VL (P = 0.215, d = 0.37; P = 0.297, d = 0.16; P = 0.448, d = 0.03, respectively). Absolute values for M_{max} are presented in **Table 1**.

Voluntary Activation

No significant differences between NITRATE$_{tm}$ and PLACEBO were found for ΔVA (P = 0.308, d = 0.14; **Figure 3**). Absolute values for voluntary activation are presented in **Table 1**.

EMG Recordings During Exercise

A significant condition effect was shown for RF ΔRMS · M^{-1} ($F_{1,10}$ = 6.85, P = 0.026, η_p^2 = 0.41) and VL ΔRMS · M^{-1} ($F_{1,10}$ = 5.56, P = 0.040, η_p^2 = 0.36), but not for VM ΔRMS · M^{-1} ($F_{1,10}$ = 2.34, P = 0.157, η_p^2 = 0.20). For RF ΔRMS · M^{-1}, significant differences between PLACEBO and NITRATE$_{tm}$ were found at 25% (P < 0.001) and 50% (P = 0.004), but not at 75% (P = 0.385) and 100% (P = 0.257) of total exercise duration. For VL ΔRMS · M^{-1}, significant differences between PLACEBO and NITRATE$_{tm}$ were found at 25% (P = 0.032) and 50% (P = 0.013), but not at 75% (P = 0.170), and 100% (P = 0.169) of total exercise duration. Furthermore, a significant condition effect was shown for Q ΔRMS · M^{-1} ($F_{1,10}$ = 6.59, P = 0.028, η_p^2 = 0.40). For Q ΔRMS · M^{-1}, significant differences between PLACEBO and NITRATE$_{tm}$ were found at 25% (P = 0.010) and 50% (P < 0.001), but not at 75% (P = 0.248) and 100% (P = 0.244) of total exercise duration (**Figure 4**). Absolute values of RMS · M^{-1} data across all muscles and time points are presented in **Table 2**.

Muscle Oxygenation During Exercise

There was no significant condition effect for ΔSmO_2 ($F_{1,10}$ = 5.09, P = 0.179, η_p^2 = 0.17) and ΔTHb ($F_{1,10}$ = 0.14, P = 0.714, η_p^2 = 0.01).

Please note that a subsample analysis of participants who improved their exercise tolerance following NITRATE (n = 8) revealed that there was a significant condition effect for ΔSmO_2 ($F_{1,7}$ = 5.84, P = 0.046, η_p^2 = 0.46). Absolute values for SmO_2 and THb during exercise are presented in **Table 2**.

Perception of Effort and Leg Muscle Pain

Mean and end-exercise levels of perceived effort were significantly lower during NITRATE$_{tm}$ compared to PLACEBO (P = 0.027, d = 0.47; P = 0.037, d = 0.36, respectively). Lower mean levels of leg muscle pain were documented during NITRATE$_{tm}$ compared to PLACEBO (P = 0.031, d = 0.43). End-exercise

TABLE 2 | Electromyography and near-infrared spectroscopy recordings during time-matched conditions (n = 11).

			Time (% of total exercise duration)			
		Baseline	25	50	75	100
VM RMS · M^{-1}						
	PLACEBO	0.038 ± 0.016	0.054 ± 0.023	0.062 ± 0.017	0.064 ± 0.017	0.061 ± 0.016
	NITRATE$_{tm}$	0.035 ± 0.014	0.047 ± 0.020	0.050 ± 0.016	0.056 ± 0.015	0.055 ± 0.012
RF RMS · M^{-1}						
	PLACEBO	0.065 ± 0.031	0.089 ± 0.045	0.096 ± 0.035	0.095 ± 0.038	0.094 ± 0.039
	NITRATE$_{tm}$	0.069 ± 0.030	0.087 ± 0.043	0.088 ± 0.042	0.098 ± 0.047	0.096 ± 0.045
VL RMS · M^{-1}						
	PLACEBO	0.036 ± 0.011	0.051 ± 0.018	0.054 ± 0.015	0.057 ± 0.015	0.055 ± 0.015
	NITRATE$_{tm}$	0.036 ± 0.012	0.045 ± 0.016	0.047 ± 0.013	0.052 ± 0.012	0.050 ± 0.012
Q RMS · M^{-1}						
	PLACEBO	0.044 ± 0.013	0.061 ± 0.023	0.070 ± 0.016	0.073 ± 0.018	0.073 ± 0.018
	NITRATE$_{tm}$	0.045 ± 0.014	0.055 ± 0.022	0.060 ± 0.018	0.068 ± 0.019	0.069 ± 0.018
SmO_2 (%)						
	PLACEBO	72.0 ± 7.3	33.4 ± 11.3	33.5 ± 14.0	32.8 ± 14.0	32.6 ± 12.3
	NITRATE$_{tm}$	69.5 ± 9.8	36.9 ± 15.7	37.6 ± 19.2	35.6 ± 19.5	35.8 ± 21.2
THb (g · dL^{-1})						
	PLACEBO	12.7 ± 0.4	12.6 ± 0.5	12.6 ± 0.5	12.6 ± 0.5	12.6 ± 0.5
	NITRATE$_{tm}$	12.6 ± 0.4	12.6 ± 0.4	12.6 ± 0.6	12.5 ± 0.6	12.6 ± 0.6

Values are expressed as mean ± SD. RMS · M^{-1}, root mean square of the electromyography signal normalized to the corresponding maximal M-wave; VM, vastus medialis; RF, rectus femoris; VL, vastus lateralis; Q RMS · M^{-1}, RMS · M^{-1} was averaged across VM, RF, and VL to estimate the total activity of the quadriceps muscle; SmO_2, muscle oxygen saturation; THb, total hemoglobin; NITRATE$_{tm}$, time-matched nitrate condition.

levels of leg muscle pain were not significantly different between time-matched conditions (P = 0.066, d = 0.34). Absolute values of perceived effort and leg muscle pain are presented in **Table 3**.

DISCUSSION

The present study was designed to provide further insight into the mechanistic basis for the improved exercise tolerance after dietary nitrate supplementation. We showed that dietary nitrate supplementation significantly improved exercise tolerance of the knee extensors during a high-intensity endurance task in two thirds of all subjects. Furthermore, by comparing time-matched exercise conditions with and without dietary nitrate supplementation, we found that dietary nitrate attenuated the development of muscle fatigue by reducing the exercise-induced impairments in contractile quadriceps function. Another important finding was that perception of effort and leg muscle pain was significantly lower following dietary nitrate supplementation.

TABLE 3 | Perceptual responses during exercise (n = 11).

		Mean levels	End-exercise
Effort perception			
	PLACEBO	17 ± 2	19 ± 2
	NITRATE$_{tm}$	16 ± 3*	18 ± 3*
Leg muscle pain			
	PLACEBO	5 ± 3	6 ± 3
	NITRATE$_{tm}$	4 ± 2*	5 ± 3

*Values are expressed as mean ± SD. The average of all ratings across the entire exercise duration is reported as mean levels of effort and leg muscle pain. End-exercise levels of effort and leg muscle pain refer to the last rating of effort and leg muscle pain before exercise termination. NITRATE$_{tm}$, time-matched dietary nitrate condition. Significantly different between conditions: *P < 0.05.*

Exercise Tolerance and Muscle Fatigue

In the present study, we found that exercise tolerance during high-intensity OLDE was improved after a 5 days dietary nitrate supplementation as indicated by a significantly increased time-to-exhaustion. Improved tolerance to low and high-intensity whole-body endurance exercise was also found in healthy adults after acute and short-term (4–6 days) dietary nitrate supplementation (Bailey et al., 2010; Lansley et al., 2011; Thompson et al., 2014). In the present study, however, only 8 out of 12 participants improved their exercise tolerance following 5 days of dietary nitrate supplementation. Interindividual differences in the responsiveness to dietary nitrate supplementation were also found by others (e.g., Wilkerson et al., 2012; Coggan et al., 2018). It has been suggested that the participant's training status (e.g., aerobic capacity), capillary density, endothelial NO synthase activity, and fiber type distribution can affect the impact of dietary nitrate supplementation on exercise performance (Jones, 2014b). Although we have not analyzed it, the interindividual variability in exercise performance could be further explained by differences in plasma [nitrate] and [nitrite] (Wilkerson et al., 2012; Coggan et al., 2018). As recently shown by Vanhatalo et al. (2018), this

might be due to differences in the nitrate reducing capacity of oral microbiota. Those who have not improved their exercise tolerance following 5 days of supplementation with ∼6.5 mmol nitrate per day, might have benefited from a higher daily dosage or a longer supplementation period. Further research is warranted to elucidate if there are 'non-responders' to dietary nitrate supplementation or whether individualized dosing strategies are necessary to achieve an ergogenic effect.

By comparing time-matched conditions, we showed that dietary nitrate supplementation attenuated the development of quadriceps muscle fatigue as indicated by a significantly lower ΔMVT during $NITRATE_{tm}$ (−42% ± 12%) compared to PLACEBO (−50% ± 11%). We found that ΔVA was not different between PLACEBO and $NITRATE_{tm}$, suggesting that dietary nitrate does not significantly affect central factors of muscle fatigue during high-intensity OLDE. However, we have shown, for the first time, that dietary nitrate attenuates the development of quadriceps muscle fatigue mainly by reducing the impairments in contractile quadriceps function during high-intensity OLDE. This was indicated by a significantly lower ΔPS100 during $NITRATE_{tm}$ (−36% ± 12%) compared to PLACEBO (−46% ± 8%). Increased dietary nitrate intake has been shown to improve vascular (Ferguson et al., 2013), metabolic (Bailey et al., 2010), and skeletal muscle function in response to exercise (Hernández et al., 2012; Haider and Folland, 2014). Any of the physiological alterations associated with dietary nitrate are capable of modulating skeletal muscle function during fatiguing exercise (Affourtit et al., 2015).

Bailey et al. (2010) have found that 4–6 days of dietary nitrate supplementation reduces the degradation of phosphocreatine (PCr) as well as the concomitant accumulation of adenosine diphosphate (ADP) and inorganic phosphate (P_i). The latter is thought to be a main contributor to exercise-induced impairments in Ca^{2+} handling and myofibrillar Ca^{2+} sensitivity (Allen et al., 2008). Consequently, a lower intracellular [P_i] associated with dietary nitrate supplementation seem to a plausible explanation for the reduced impairments in contractile function. On the one hand, data from Bailey et al. (2010) suggest that a reduction in the ATP cost of muscle force production might be responsible for the lower PCr degradation and accumulation of P_i following dietary nitrate supplementation. This assumption is supported by experiments in both humans (Haider and Folland, 2014; Whitfield et al., 2017) and mice (Hernández et al., 2012), showing that dietary nitrate enhances the contractile force production in response to low-frequency electrical stimulation. Hernández et al. (2012) have shown that the increased contractile force production results from an improved intracellular Ca^{2+} handling. On the other hand, there is data from experiments in rodents (Ferguson et al., 2013) and humans (Richards et al., 2018) suggesting that dietary nitrate increases muscle blood flow via local vasodilation, which in turn may improve oxygen delivery to the contracting muscles. It is generally well accepted that changes in O_2 delivery to muscles alter intracellular metabolism, metabolite accumulation and ultimately contractile muscle function during exercise (Amann and Calbet, 2007). Since the rate of PCr hydrolysis and concomitant intracellular accumulation of P_i have been shown to be slower under conditions of increased O_2 availability (Hogan et al., 1999), a higher O_2 availability during exercise might have contributed to the reduced impairments in contractile quadriceps function following dietary nitrate supplementation. Improvements in NIRS-derived indices of muscle oxygenation following dietary nitrate supplementation were found in healthy adults (Bailey et al., 2009) and patients with peripheral arterial disease (Kenjale et al., 2011) during whole body endurance exercise. Bailey et al. (2009) have shown that deoxyhemoglobin peak amplitude, an estimate of muscle fractional O_2 extraction, was significantly lower after beetroot juice consumption for 4–6 days when measured during moderate-intensity exercise. In the present study, however, there was no significant condition effect for ΔSmO_2 of the VL during exercise. Although conclusions should be drawn with caution, a subsample analysis of those who have improved their time-to-exhaustion with dietary nitrate has revealed a significant condition effect. Consequently, it cannot be fully excluded that an improved SmO_2 of the quadriceps muscle during exercise has contributed to the attenuated impairment in contractile function following dietary nitrate supplementation. Further studies are therefore needed to understand the exact causes for the reduced exercise-induced impairments in contractile function following dietary nitrate supplementation.

Furthermore, we found a significant condition effect for Q $RMS \cdot M^{-1}$ during exercise. Although only significant for the first half of the exercise protocol (see **Figure 4**), the exercise-induced increase in quadriceps muscle activity was lower during $NITRATE_{tm}$ compared to PLACEBO. A rise in muscle activity in the course of a submaximal motor task at a constant power output is commonly interpreted as an increased recruitment of additional motor units to compensate for the progressive loss in contractile muscle function (Devries et al., 1982; Moritani et al., 1993). Since we found that the exercise-induced loss in contractile torque production is lower following dietary nitrate intake, less muscle activation might be required to ensure the same power output.

Perceptual Responses During Exercise

In the present study, we found that $NITRATE_{tm}$ resulted in lower mean and end-exercise levels of effort perception compared to PLACEBO, suggesting that dietary nitrate reduces the perception of effort during a high-intensity endurance task of the knee extensors. This finding is of particular importance since effort perception is thought to be a key-determinant of endurance performance (Marcora and Staiano, 2010). Based on the psychobiological model of exercise tolerance (Marcora, 2008), it has been stated that participants disengage from a task as a result of an effort-based decision. There is evidence suggesting that tolerance to high-intensity aerobic exercise in highly motivated athletes is predominantly limited by effort perception but not by the inability of muscles to generate the required power for the task (Marcora and Staiano, 2010). Our participants can be characterized as highly motivated since we (i) documented high levels of task motivation during each experimental condition, (ii) announced a monetary reward for the best three performers, and (iii) provided strong verbal

encouragement during the task. Therefore, a reduced effort perception could be a significant contributor to the nitrate-induced improvements in exercise tolerance during high-intensity OLDE.

Although the exact physiological mechanisms underlying the perception of effort are still debated (Marcora, 2009), it is well accepted that neural processing of sensory signals in the brain is involved in effort perception (Noble and Robertson, 1996). Based on the corollary discharge model, it has been stated that effort perception reflects a centrally mediated feedforward mechanism in which an efference copy of the central motor command is sent from motor to sensory brain areas to enable a conscious awareness of processes associated with motor output (Poulet and Hedwig, 2007). During fatiguing contractions, the progressive rise in effort perception is thought to reflect the increase in central motor command which is necessary to compensate for the exercise-induced impairments in contractile muscle function in order to ensure adequate power output to maintain the task (de Morree et al., 2012). Consequently, the lower perception of effort following dietary nitrate supplementation could result from a reduced central motor command as a result of the preserved contractile function during exercise. By contrast, it has also been suggested that afferent feedback from working muscles contribute to the perception of effort (Amann et al., 2010). Although this assumption is highly debated (Marcora, 2009), it cannot be ruled out that an attenuated afferent feedback from the working muscles due to less metabolic disturbances in the periphery has contributed to the lower effort perception after dietary nitrate supplementation.

Although it is well accepted that perception of effort plays a crucial role in endurance performance (Marcora and Staiano, 2010), there is hardly any evidence for the impact of dietary nitrate on effort perception during endurance exercise. To the authors' knowledge, there is only one study that recorded ratings of perceived exertion during work-matched submaximal exercise (Cermak et al., 2012). Cermak et al. (2012) have found that ratings of perceived exertion during submaximal constant-load cycling were not significantly affected by 6 days of dietary nitrate supplementation. However, since the authors have not reported the underlying definition of exertion, it is possible that participants' rating included other exercise-related sensations than effort (e.g., discomfort and muscle pain) which are based on different neurophysiological mechanisms (Marcora, 2009). Therefore, it remains to be elucidated, if dietary nitrate supplementation also affects effort perception during submaximal, whole-body endurance tasks. Future studies investigating the mechanistic bases for the improved endurance performance following dietary nitrate supplementation should pay special attention on effort perception and its appropriate assessment [as recently proposed by Pageaux (2016)].

Furthermore, we found that 5 days of dietary nitrate supplementation resulted in lower mean levels of leg muscle pain during high-intensity OLDE, indicating that the participants had to tolerate less muscle pain in the course of exercise compared to PLACEBO. To our knowledge, there is no study to date assessing the impact of dietary nitrate on muscle pain during submaximal knee extension exercise. A previous study investigating patients with peripheral arterial disease has shown that dietary nitrate supplementation delays the onset of claudication pain during walking, which in turn resulted in an improved time-to-exhaustion (Kenjale et al., 2011). In healthy participants, exercise-induced muscle pain has also been proposed as an important factor in endurance performance (Mauger, 2013). Experimental evidence supporting this assumption is, however, scarce and often ambiguous (Stevens et al., 2018). Consequently, it cannot be ruled out that reductions in muscle pain perception contributed to the improved exercise tolerance.

While effort perception is likely centrally generated and seems to be independent of afferent feedback (Marcora, 2009), exercise-induced pain is thought to be related to feedback from nociceptive group III/IV muscle afferents about alterations associated with muscular contraction [e.g., increased intramuscular pressure, heat, high levels of metabolites, or deformation of tissue (Mense, 1993)]. As stated earlier, dietary nitrate supplementation has been shown to be associated with changes in local muscle perfusion, intramuscular metabolism, and reduced metabolite accumulation (Bailey et al., 2010). Given the fact that group III/IV afferents are sensitive to changes in metabolite concentration, it can be speculated that a reduced metabolite accumulation might attenuate the afferent feedback and thus lowers the perception of exercise-induced muscle pain. However, it should be noted that pain is not always directly related to the magnitude of the nociceptive signal, since pain is considered as subjective experience with a strong emotional component (Mauger, 2013). Further studies are necessary to better understand the impact of dietary nitrate on perception of exercise-induced muscle pain.

Limitations

Although single-joint endurance exercise provides an appropriate model to investigate underlying determinants of endurance performance, whole-body endurance exercise (e.g., cycling, running, and walking) has the advantage to better mimic real world activities and sport events (Pageaux and Lepers, 2016). Given the fact that whole-body exercise requires a greater amount of muscle work with concomitant higher cardio-respiratory demands, there is a greater potential for systemic responses (e.g., hyperthermia, respiratory muscle fatigue, and arterial hypoxemia), which might affect the fatigability of the neuromuscular system (Sidhu et al., 2013). Therefore, the impact of dietary nitrate ingestion on muscle fatigue, perceptual responses, and its implications for exercise tolerance is currently limited to single-joint exercise.

In line with other studies using high-intensity OLDE (Pageaux et al., 2015, 2016), we found a large interindividual variability in exercise duration of the time-to-exhaustion test (**Figure 2**). Considering that both muscle fatigue and the effectiveness of dietary nitrate with regard to endurance performance are thought to be task-dependent (Enoka et al., 2011; Jones, 2014a), the observed variability in duration and intensity might have affected the impact of dietary nitrate on muscle fatigue development.

CONCLUSION

The present findings extend the mechanistic basis for the improved exercise tolerance following dietary nitrate supplementation by investigating key-determinants of endurance performance. We showed, for the first time, that 5 days of dietary nitrate supplementation were associated with reduced levels of muscle fatigue compared to the time-matched placebo condition. Data indicate that the attenuated development of muscle fatigue following dietary nitrate ingestion was mainly due to lower exercise-induced impairments in contractile function (i.e., less peripheral fatigue). Therefore, dietary nitrate supplementation might be a promising approach to reduce muscle fatigue in situations (e.g., altitude) or populations (e.g., patients with peripheral arterial disease, type 2 diabetes, chronic heart failure) in which muscle fatigue is exacerbated and exercise tolerance is compromised. Another important finding of the present study was that dietary nitrate supplementation was accompanied by a lower effort perception during exercise. Based on the well-accepted corollary discharge model (Christensen et al., 2007; Poulet and Hedwig, 2007), we assume that the lower effort perception following dietary nitrate resulted from a lower rise in central motor command as an adjustment to the preserved contractile function compared to PLACEBO. We conclude that an attenuated development of muscle fatigue as well as lower levels of perceived effort and muscle pain have contributed to the improved exercise tolerance following dietary nitrate supplementation.

ETHICS STATEMENT

The study was approved by the university ethics committee and was conducted according to the Declaration of Helsinki. All subjects were informed about possible risks and discomfort associated with the investigations prior to giving their written consent to participate.

AUTHOR CONTRIBUTIONS

FH and MB designed the study and collected, analyzed, and interpreted the data. FH wrote the manuscript. MB, SB, TM, and VZ contributed to writing, reviewing, and editing of the manuscript. All authors approved the final version of the manuscript.

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Ischemic Preconditioning Did Not Affect Central and Peripheral Factors of Performance Fatigability After Submaximal Isometric Exercise

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The present study was designed to provide further insight into the mechanistic basis for the improved exercise tolerance following ischemic preconditioning (IPC) by investigating key-determinants of performance and perceived fatigability. Using a randomized, counterbalanced, single-blind, sham-controlled, crossover design, 16 males performed an isometric time-to-exhaustion test with the knee extensors at 20% maximal voluntary torque (MVT) after an IPC and a sham treatment (SHAM). Those who improved their time-to-exhaustion following IPC performed a time-matched IPC trial corresponding to the exercise duration of SHAM (IPC_{tm}). Neuromuscular function was assessed before and after exercise termination during each condition (IPC, IPC_{tm}, and SHAM) to analyze the impact of IPC on performance fatigability and its central and peripheral determinants. Muscle oxygenation (SmO_2), muscle activity, and perceptual responses (effort and muscle pain) were recorded during exercise. Performance fatigability as well as its central and peripheral determinants were quantified as percentage pre-post changes in MVT (ΔMVT) as well as voluntary activation (ΔVA) and quadriceps twitch torque evoked by paired electrical stimuli at 100 and 10 Hz (ΔPS100 and $\Delta PS10{\cdot}PS100^{-1}$ ratio), respectively. Time-to-exhaustion, performance fatigability, its determinants, muscle activity, SmO_2, and perceptual responses during exercise were not different between IPC and SHAM. However, six participants improved their performance by >10% following IPC (299 ± 71 s) compared to SHAM (253 ± 66 s, d = 3.23). The time-matched comparisons (IPC_{tm} vs. SHAM) indicated that performance fatigability, its determinants, and SmO_2 were not affected, while effort perception seemed to be lower (η_p^2 = 0.495) in those who improved their time-to-exhaustion. The longer time-to-exhaustion following IPC seemed to be associated with a lower effort perception (η_p^2 = 0.380) and larger impairments in neuromuscular function, i.e., larger ΔMVT, ΔVA, and $\Delta PS10{\cdot}PS100^{-1}$ ratio (d = 0.71, 1.0, 0.92, respectively). IPC did neither affect exercise tolerance, performance fatigability, as well as its central and peripheral

determinants, nor muscle activity, SmO_2, and perceptual responses during submaximal isometric exercise. However, IPC seemed to have an ergogenic effect in a few subjects, which might have resulted from a lower effort perception during exercise. These findings support the assumption that there are 'responders' and 'non-responders' to IPC.

Keywords: central fatigue, peripheral fatigue, muscle fatigue, contractile function, effort perception, muscle pain, pain perception, perceived fatigability

INTRODUCTION

Ischemic preconditioning (IPC) involves repeated, short-term periods of vascular occlusion with subsequent reperfusion and has been shown to increase human performance if applied to the exercising limb prior to physical activity (Incognito et al., 2016). For example, studies have found that IPC has ergogenic effects on a variety of endurance exercise modalities including running (Bailey et al., 2012), cycling (de Groot et al., 2010), swimming (Ferreira et al., 2016), and sustained submaximal isometric contractions (Tanaka et al., 2016). However, besides the observation of an enhanced performance, a number of studies have also reported no or even detrimental effects of IPC on endurance performance (Incognito et al., 2016; Sabino-Carvalho et al., 2017; Marocolo et al., 2019). Although the exact physiological mechanisms underlying the performance-enhancing effect of IPC still need to be clarified, improved metabolic efficiency and/or blood flow in the active skeletal muscles (Incognito et al., 2016) as well as neural adjustments (Cruz et al., 2015; Marocolo et al., 2019) have been discussed. The physiological alterations associated with IPC are thought to delay fatigue development and thereby increase endurance performance (Tanaka et al., 2016; Cruz et al., 2017). In this context, fatigue can be defined as a psychophysiological symptom that is characterized by an impaired physical and/or cognitive function as a result of interactions between performance and perceived fatigability. Performance fatigability can be characterized as the decline of an objective performance measure over time. In the present study, performance fatigability refers to the exercise-induced impairment in maximal voluntary torque-generating capacity of the involved muscles (traditionally termed muscle fatigue) caused by a decrease in voluntary activation of muscles and/or alterations at or distal to the neuromuscular junction that result in contractile dysfunction (traditionally termed central and peripheral fatigue, respectively). Perceived fatigability refers to the perceptual milieu during fatiguing exercise that emerges from homeostatic challenges of different physiological systems and the psychological state of the individual. During ongoing physical activity, perceived fatigability is thought to affect the integrity of the performer and thereby contributes to the regulation of exercise behavior and ultimately motor performance (Kluger et al., 2013; Enoka and Duchateau, 2016; Venhorst et al., 2018).

Recently, Halley et al. (2018, 2019) have found that IPC does not alter central and peripheral determinants of performance fatigability after maximal voluntary isometric and isokinetic exercise of the knee extensors compared to a sham treatment (SHAM). However, maximal voluntary contractions (MVC) induce complete or near-complete ischemia (Oranchuk et al., 2019), which renders modulations of blood flow due to IPC unlikely. To the authors' knowledge, there is no study to date that has investigated the impact of IPC on central and peripheral mechanisms of performance fatigability as well as its effect on determinants of perceived fatigability (i.e., perception of effort and exercise-induced muscle pain) during submaximal endurance exercise. Therefore, the present study was designed to provide further insight into the mechanistic basis for the improved exercise tolerance that has been shown following IPC. We have specifically chosen a time-to-exhaustion test that consisted of a sustained isometric knee extension at 20% maximal voluntary torque (MVT), because Tanaka et al. (2016) have found an improved exercise tolerance of 17.2% together with an accelerated muscle deoxygenation response during exercise after IPC using this protocol.

Based on the results of Tanaka et al. (2016), we hypothesized that performance fatigability, its determinants, and perceptual responses are affected by IPC compared to SHAM.

MATERIALS AND METHODS

Participants

An *a priori* sample size calculation was conducted based on the effect size of a previously published study investigating the impact of IPC on time-to-exhaustion during a sustained isometric knee extension (Tanaka et al., 2016). A two-sided significance level of 0.05, a correlation between groups of 0.5, and a power of 0.95 indicated that 13 participants would be required. To account for potential drop out, 16 recreationally active male subjects were recruited to participate in the present study (age: 26 ± 4 years, height: 183 ± 6 cm, body weight: 81 ± 8 kg, systolic blood pressure: 132 ± 6 mmHg, diastolic blood pressure: 77 ± 6 mmHg, training hours per week: 9 ± 3 h). Based on the common finding that performance fatigability depends on sex (for a review see Hunter, 2014), a sample comprising exclusively male participants was chosen. Subjects were excluded if they were hypertensive (>140/90 mmHg) or had more than one risk factor for thromboembolism (Motykie et al., 2000). All participants were familiar with endurance exercise. Subjects were asked to abstain from vigorous exercise, analgesics, caffeine, alcohol, and nitrate-rich food consumption for 24 h prior to the laboratory visits. The study was approved by the university ethics committee and was conducted according to the declaration of Helsinki. All subjects were informed about possible risks and discomfort associated with the investigations prior to giving their written consent to participate.

Experimental Procedure

All participants visited the laboratory on at least three different occasions. During the first visit, subjects' arterial occlusion pressure as well as their MVT of the knee extensors were determined. Furthermore, participants were thoroughly familiarized with the following procedures: (i) neuromuscular tests comprising MVCs combined with peripheral nerve stimulation, (ii) the fatigue protocol (a sustained isometric knee extension at 20% MVT) as well as (iii) ratings of perceived effort and exercise-induced leg muscle pain.

Using a randomized, counterbalanced, single-blind, sham-controlled, crossover design, participants performed a time-to-exhaustion test with a sustained unilateral isometric knee extension at 20% MVT following (i) an IPC protocol and (ii) a SHAM protocol, respectively. The experimental trials were separated by 7 ± 1 d. Participants who improved their time-to-exhaustion following IPC by at least 10% were considered as 'responders' and performed a time-matched IPC trial corresponding to the SHAM exercise duration (IPC_{tm}). The cut-off value of 10% was chosen because studies have shown that the coefficient of variation for time-to-exhaustion is ∼8% for submaximal isometric and dynamic knee extensions (Zech et al., 2008; Pageaux et al., 2016). In case IPC has an ergogenic effect on time-to-exhaustion, this procedure allows a time-matched comparison of neuromuscular data between IPC and SHAM (**Figure 1**). All conditions (IPC, IPC_{tm}, and SHAM) were further examined to analyze the impact of IPC on (i) performance fatigability, (ii) central and peripheral aspects of performance fatigability, (iii) muscle O2 saturation (SmO_2), (iv) electromyographic (EMG) activity as well as (v) perception of effort and exercise-induced leg muscle pain. This experimental procedure was chosen based on the observation that some people seem to respond to IPC but others not (Incognito et al., 2016; Marocolo et al., 2019).

Prior to the baseline measurements, participants performed an initial warm-up on a stationary bicycle (5 min, 100 W, 90 rpm) followed by a specific warm-up on a dynamometer comprising two isometric contractions for 5 s at 50, 70, and 90% of MVT interspaced by 60 s of rest (MVT was determined during the familiarization session), respectively. Baseline neuromuscular tests were performed before the IPC and SHAM protocols to exclude any effects of the study interventions on these measures. Neuromuscular tests consisted of supramaximal electrical stimulations of the femoral nerve during and after isometric MVCs. Afterward, subjects performed two to three short sustained isometric voluntary contractions at 20% MVT to acutely familiarize them with the exercise protocol. Participants were again familiarized with the ratings of perceived effort and exercise-induced leg muscle pain. During the study interventions, i.e., IPC and SHAM, the principal investigator left the room to rule out instruction differences between conditions due to the awareness of the protocol. An additional warm-up on a stationary bicycle (5 min, 100 W, 90 rpm) was performed before the fatigue protocol. SmO_2 as well as EMG activity were continuously recorded during each experimental condition. Every 30 s during the fatiguing protocol, participants were asked to rate their perceived effort and exercise-induced leg muscle pain. Neuromuscular tests were again performed immediately after (<10 s) exercise termination to investigate the development of performance fatigability.

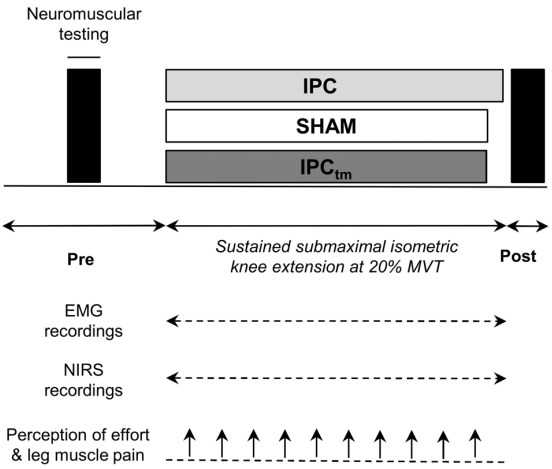

FIGURE 1 | Schematic representation of the experimental design. Participants performed an isometric time-to-exhaustion test with the knee extensors at 20% maximal voluntary torque (MVT) following ischemic preconditioning (IPC) and a sham treatment (SHAM). Those who improved their time-to-exhaustion following IPC were considered as 'responders' and performed a time-matched IPC trial corresponding to the SHAM exercise duration (IPC_{tm}). In case IPC has an ergogenic effect on time-to-exhaustion, this procedure allows a time-matched comparison of neuromuscular data between IPC and SHAM. Electromyography (EMG) and near-infrared spectroscopy (NIRS) data were continuously recorded during exercise. Effort perception and exercise-induced leg muscle pain were recorded every 30 s during exercise.

All measurements were carried out on the quadriceps muscle of the dominant leg (i.e., kicking preference). During neuromuscular testing and the fatiguing protocol, subjects were comfortably seated and secured on a CYBEX NORM dynamometer (Computer Sports Medicine®, Inc., Stoughton, MA, United States). The seating position was adjusted for each participant and settings were documented for the subsequent sessions.

Study Interventions

The IPC and SHAM protocols were applied to the participants in a supine position. Arterial occlusion pressure was determined as described in a previously published study from our laboratory (Husmann et al., 2018). Shortly, a pneumatic cuff (10 × 76 cm, Ulrich Medical, Ulm, Germany) was placed on the most proximal part of the thigh and was inflated using a cuff inflator system (Heidi^{TM}; UlrichMedical, Ulm, Germany) until the pulse of the tibial artery, which was monitored using a handheld bidirectional Doppler probe (Hadeco Bidop ES-100V3, Kawasaki, Japan), was interrupted (arterial occlusion pressure: 210 ± 20 mmHg). During the IPC and SHAM protocol, the cuff was inflated to 120% of subjects' arterial occlusion pressure (254 ± 24 mmHg) or 20 mmHg (SHAM) for three cycles of 5 min interspersed with 5 min of reperfusion. This protocol has been shown to increase exercise tolerance during a sustained isometric contraction at 20% of MVC in healthy young males by 17.2% (Tanaka et al.,

2016). No adverse effects were observed or reported during these procedures. The time interval between the study interventions and the start of the fatiguing task was 20 min. None of the participants had previously used or had knowledge about IPC. Furthermore, they were instructed that both IPC and SHAM increase exercise performance and that the aim of the study is to identify the most effective protocol.

Submaximal Fatigue Protocol

Exercise tolerance was quantified via the use of dynamometer-based single-joint endurance exercise, which provides a suitable model to investigate the underlying mechanisms of performance fatigability without a significant time delay for the assessment of neuromuscular function and cardiorespiratory limitations typically associated with whole-body endurance exercise. Therefore, the fatigue protocol comprised a sustained unilateral isometric knee extension at 20% MVT until exhaustion at 90° knee flexion (0° = full extension). The MVT recorded on the respective day served as the reference. This exercise protocol was chosen because it has been shown that time-to-exhaustion was improved during this task following IPC compared to a control condition (Tanaka et al., 2016). On each visit of the laboratory, subjects performed two to three short sustained isometric voluntary contractions at 20% MVT to acutely familiarize them with the exercise protocol. This was done after the neuromuscular baseline measurements and before the study interventions, i.e., IPC and SHAM. The participants were provided with visual feedback and had to match a target torque displayed on a digital oscilloscope (HM1508, HAMEG Instruments, Mainhausen, Germany). Exhaustion was defined as a decrease in torque by more than 10% for a duration of more than 5 s despite strong verbal encouragement by the principal investigator. Neither the participants nor the principal investigator who terminated the task were aware of the elapsed time. In order to motivate the participants to exercise for as long as possible during the time-to-exhaustion test, monetary rewards were announced for the three best performances (50 €, 30 €, 20 €). The subjects and the principal investigator did not get feedback about the performance until the completion of the study.

Torque Recordings

Electrically evoked and voluntary torques were measured using a CYBEX NORM dynamometer (Computer Sports Medicine®, Inc., Stoughton, MA, United States). Participants were seated on an adjustable chair with the knee and hip fixed at 90° and 80° (0° = full extension), respectively. In order to avoid excessive movements of the participants during data recording, they were fixed with straps at the waist and chest. The subjects' lower leg was affixed to the lever arm of the dynamometer and the dynamometer rotation axis was aligned with the knee joint rotation axis. During isometric strength testing, subjects were instructed to cross their arms in front of their chest and to push as hard as possible against the lever arm of the dynamometer. Strong verbal encouragement was given by the investigator and visual feedback of the torque-time curve was provided on a digital oscilloscope (HM1508, HAMEG Instruments, Mainhausen, Germany). Torque signals were digitized with a sampling frequency of 3 kHz using an analog-to-digital converter (NI PCI-6229; National Instruments, Austin). Data were saved on a hard drive for later analysis using a custom-built LABVIEW based program (Imago, Pfitec, Germany).

Electrical Nerve Stimulation

Electrical femoral nerve stimulation was utilized to assess neuromuscular function of the quadriceps muscle. A constant-current stimulator (Digitimer DS7A, Herfordshire, United Kingdom) was used to deliver square-wave pulses of 1 ms duration with maximal voltage of 400 V. After determining the optimal site for electrical stimulation in the femoral triangle, the position was marked onto the participants' skin to ensure repeatable measurements within each session. During neuromuscular testing, a ball probe cathode (15 mm diameter) was pressed into the femoral triangle always by the same experienced investigator to guarantee optimal electrical stimuli delivery. Individual stimulation intensity was progressively increased until the maximum compound muscle action potential (M_{max}) of vastus medialis (VM), rectus femoris (RF), and vastus lateralis (VL) muscles as well as a plateau in knee extensor twitch torque was achieved. During the subsequent testing procedures, the stimulation intensity was increased by additional 40% to guarantee supramaximal stimulation. A self-adhesive electrode (35 × 45 mm, Spes Medica, Genova, Italy) served as the anode and was affixed over the greater trochanter. Potentiated quadriceps twitch torques evoked by paired electrical stimuli at 100 Hz (PS100), 10 Hz (PS10), and single stimuli (SS) were elicited 2, 4, and 6 s following the isometric MVCs, respectively. Voluntary activation of the quadriceps muscle during isometric MVCs was quantified using the interpolated twitch technique. Therefore, electrical paired stimuli (PS100) were automatically delivered to the femoral nerve 2 s after torque onset (during the plateau phase) and 2 s after the MVCs.

EMG Recordings During Exercise

A detailed description of the EMG recordings can be found in a previously published study from our group (Behrens et al., 2015). Briefly summarized, myoelectrical signals of the VM, RF, and VL were recorded using surface electrodes (EMG Ambu Blue Sensor N). EMG signals were amplified (2500×), band-pass filtered (10–450 Hz), and digitized with a sampling frequency of 3 kHz using an analog-to-digital converter (NI PCI-6229, National Instruments, Austin, United States). Data were saved on a hard drive for later analysis using a custom-built LABVIEW based program (Imago, Pfitec, Germany).

Muscle Oxygenation During Exercise

SmO_2 reflects the balance between O_2 delivery and O_2 demand in the analyzed muscle (Ferrari et al., 2011). A portable near-infrared spectroscopy (NIRS) device (Moxy, Fortiori Design LLC, Minnesota, United States) was used to continuously monitor SmO_2 of the VL. The Moxy monitor enables reliable measurements of SmO_2 (Crum et al., 2017). The participants' skin was shaved and cleaned prior to optode placement. The NIRS probe was attached at mid-thigh level, closely to the VL EMG electrodes, and was secured with tape and covered

with a protective shell to avoid artifacts caused by motion and light. Reliable optode placement between sessions was ensured by documenting the distance to the patella, measured from the participants' patella to the greater trochanter. Additionally, skinfold thickness above the VL was measured using a skinfold caliper (4 ± 1 mm). Signals were recorded with a sampling frequency of 2 Hz.

Ratings of Perceived Effort and Exercise-Induced Leg Muscle Pain

The participants were briefed about how to rate perceived effort and exercise-induced leg muscle pain during the familiarization session as well as during the subsequent visits of the laboratory. The 15-point Borg scale (Borg, 1982) was used to quantify subjects' perception of effort. The participants received written instructions based on recently proposed guidelines (Pageaux, 2016) during each testing session. The instructions comprised the definition of effort ("the conscious sensation of how hard, heavy, and strenuous a physical task is"), exercise-specific descriptions ("How hard is it for you to drive your leg?"), exercise-anchoring (e.g., "maximal exertion corresponds to the effort you experienced while you were performing a MVC") and the distinction of effort, exercise-induced leg muscle pain, and other exercise-related sensations. Exercise-induced leg muscle pain was assessed using a modified category-ratio 10 (CR-10) scale (Cook et al., 1997). Leg muscle pain during exercise was defined as the perceived pain intensity exclusively in the exercising quadriceps muscle. The participants were asked to rate their perceived effort and exercise-induced leg muscle pain every 30 s during the fatigue protocol.

State Fatigue

It has been shown that state fatigue induced by sustained cognitive activity can be detrimental to subsequent endurance performance (Marcora et al., 2009). Therefore, state fatigue was quantified before each testing session using the fatigue scale of the Profile of Mood States (POMS-F) (Behrens et al., 2018). The POMS-F has been shown to provide a reliable and valid instrument to assess the level of state fatigue across a wide range of cohorts (O'Connor, 2004). In case of a difference between conditions, state fatigue would have been considered as a covariate in the statistical analyses.

Data Analyses

Time-to-exhaustion was defined as the time from the onset of exercise to task failure. Performance fatigability was quantified via the percentage change in MVT values from pre- to post-exercise (ΔMVT). Percentage changes in voluntary activation (ΔVA) and PS100 (ΔPS100) from pre- to post-exercise were used to quantify central and peripheral factors of performance fatigability, respectively. All torque signals were corrected for the effect of gravity. Isometric MVT was defined as the highest torque value prior to the electrically evoked superimposed twitch torque. Peak twitch torques (i.e., highest values of the torque-time curve) were determined for PS100, PS10, and SS, respectively. The PS10·PS100^{-1} torque ratio was calculated as an index of low-frequency fatigue and reduced values are thought to indicate impairments in excitation-contraction coupling (Verges et al., 2009). The level of voluntary activation was calculated using the corrected formula: [1 – superimposed twitch (T_b × MVT $^{-1}$) × control twitch^{-1}] × 100 (Strojnik and Komi, 1998). MVT is the maximal torque level and T_b the torque value immediately before the electrically evoked superimposed twitch torque. The corrected formula is used to avoid the potential problem that the superimposed stimuli are not always applied during MVT. As shown recently by our group, voluntary activation of the knee extensors can be reliably assessed during isometric contractions using the corrected formula (Behrens et al., 2017).

M_{max} amplitudes elicited by electrical nerve stimulation were measured peak-to-peak. Muscle activity during exercise was assessed by calculating the root mean square of the EMG signal (RMS-EMG) averaged for 10 s at the beginning, as well as at 25, 50, 75, and 100% of the shortest trial (IPC or SHAM), respectively. Data of the other trial was calculated for the same points in time. The same was done for the IPC_{tm} condition.

RMS-EMG of VM, RF, and VL were normalized to their corresponding M_{max} values (RMS·M^{-1}) and averaged to give an index of quadriceps muscle activation (Q RMS·M^{-1}) (Husmann et al., 2019).

A 4th order low-pass zero-phase Butterworth filter (cutoff frequency 0.2 Hz) was applied to the NIRS data. Indices of muscle oxygenation were averaged across 30 s before the start of the fatiguing protocol and across 10 s at 25, 50, 75, and 100%, respectively. Data analysis for the different conditions (IPC, SHAM, and IPC_{tm}) was the same as described for the EMG data.

Baseline values were captured at rest in a seated position. SmO_2 and total hemoglobin (tHb) were reported as percentage changes from baseline (ΔSmO_2 and ΔtHb).

Effort and exercise-induced leg muscle pain ratings across the fatiguing protocol were reported for 25, 50, 75, and 100%, respectively (the nearest rating was analyzed). Data analysis for the different conditions (IPC, SHAM, and IPC_{tm}) was the same as described for the EMG data.

Statistical Analysis

All data were screened for normal distribution using the Shapiro–Wilk test. Differences in time-to-exhaustion, state fatigue, ΔMVT, ΔVA, ΔPS100, ΔSS, ΔPS10·PS100^{-1} ratio, and ΔM_{max} values were tested using Student's paired *t*-tests. The effect size Cohen's *d* was calculated for each paired comparison. Effect sizes of 0.20, 0.50, and 0.80 were considered small, medium, and large, respectively (Cohen, 1988). A two-way (time × condition) repeated measure ANOVA was conducted for each variable recorded during exercise. *Post hoc* tests were performed with Bonferroni adjustments. The effect size was determined by calculating partial eta squared (η_p^2). Because only six 'responders' to the IPC protocol were identified, interpretation of their results on the basis of *P*-value statistics was not meaningful (du Prel et al., 2009). Therefore, as recommended, interpretation of the responders' data was based on effect sizes (Cohen's *d* for the pairwise comparisons and η_p^2 for the analyses using the

ANOVA) and mean differences with 95% confidence interval [diff. (95%CI)] (Rigby, 1999; Ranstam, 2012; Lakens, 2013; Lee, 2016; Abbott et al., 2018). Cohen's d values ≥ 0.70, representing a medium effect with the tendency to approach a large effect, were considered as meaningful. Partial eta squared values ≥ 0.200 which correspond to a Cohen's f value of 0.50, i.e., a large effect, were considered as relevant (Richardson, 2011). Furthermore, diff. (95%CI) was calculated for the pairwise comparisons and for the ANOVAs (for the latter only if the effect size exceeded the defined threshold).

Data were analyzed using the SPSS statistical package 25.0 (SPSS Inc., Chicago, IL, United States) and statistical significance was accepted at $P \leq 0.05$. Sample size was calculated with the statistical software package G*Power (version 3.1.4.).

RESULTS

Six participants were classified as 'responders' because they improved their exercise performance following IPC by at least 10% compared to SHAM and completed an IPC_{tm} trial. Therefore, the statistical results for the respective parameter are presented for the whole sample and for the 'responders' separately. The interpretation of outcomes of the whole sample is based on the P-values, while that of the 'responders' is based on the effect size and the diff. (95%CI) (Lakens, 2013). According to that, the order of the statistical parameters is different for the whole sample and the 'responders.'

Time-to-Exhaustion Test

Whole Sample

Time to-exhaustion did not significantly differ between IPC (234 ± 82 s) and SHAM (222 ± 66 s) [$P = 0.174$, diff.: 12 s (−6 to 28 s), $d = 0.39$] (**Figure 2A**).

Responders

Six participants improved their exercise performance following IPC (299 ± 71 s) by at least 10% compared to SHAM (253 ± 66 s) [$d = 3.23$, diff.: 46 s (31 to 62 s), $P < 0.001$] (**Figure 3A**) and completed an IPC_{tm} trial. During the IPC_{tm} trial, all 'responders' reached the SHAM exercise duration and reported that they were able to continue the submaximal isometric exercise.

State Fatigue

Whole Sample

There were no differences in state fatigue between IPC (12.1 ± 7.5) and SHAM (11.1 ± 6.9) [$P = 0.247$, diff.: 1.0 (−0.7 to 2.6), $d = 0.34$].

Responders – IPC vs. SHAM

There were no differences in state fatigue between IPC (14.5 ± 7.5) and SHAM (14.3 ± 6.5) for the six 'responders' [$d = 0.07$, diff.: 0.2 (−2.8 to 3.1), $P = 0.889$].

Responders – IPC_{tm} vs. SHAM

There were also no differences in state fatigue between IPC_{tm} (14.3 ± 9) and SHAM (14.3 ± 6.5) for the six 'responders' [$d = 0.00$, diff.: 0.0 (−5.4 to 5.4), $P = 1.000$].

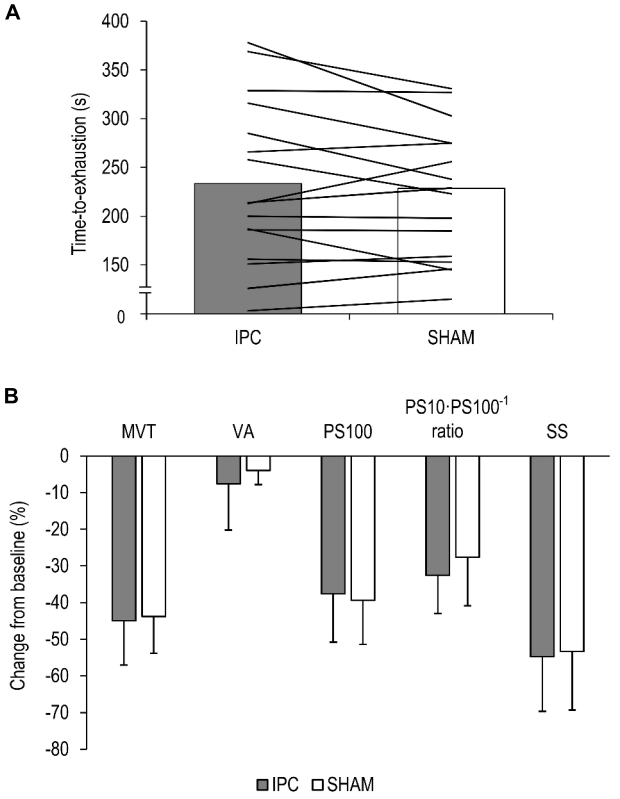

FIGURE 2 | (A) Mean values and individual data of all participants for the time-to-exhaustion tests for the ischemic preconditioning (IPC) and sham (SHAM) condition. **(B)** Percentage change from pre-exercise values for all participants for maximal voluntary torque (MVT), voluntary activation (VA), twitch torque in response to paired electrical stimuli (PS100), $PS10{\cdot}PS100^{-1}$ ratio, and twitch torque in response to a single electrical stimulus (SS). Values are presented as mean ± standard deviation.

Maximal Voluntary Torque

Whole Sample

The ΔMVT was not significantly different between IPC and SHAM [$P = 0.760$, diff.: 1.2% (−9.4 to 7.0%), $d = 0.08$]. Percentage changes and absolute values for MVT can be found in **Figure 2B** and **Table 1**, respectively.

Responders – IPC vs. SHAM

Based on the effect size and mean difference (95%CI), percentage changes in MVT differed between IPC and SHAM [$d = 0.71$, diff.: −8.7% (−35.3 to 17.9%), $P = 0.416$]. Percentage changes and absolute values for MVT can be found in **Figure 3B** and **Table 1**, respectively.

Responders – IPC_{tm} vs. SHAM

However, ΔMVT was not different between the conditions IPC_{tm} and SHAM [$d = 0.06$, diff.: 1.3% (−26.0 to 28.5%), $P = 0.905$]. Percentage changes and absolute values for MVT can be found in **Figure 3C** and **Table 1**, respectively.

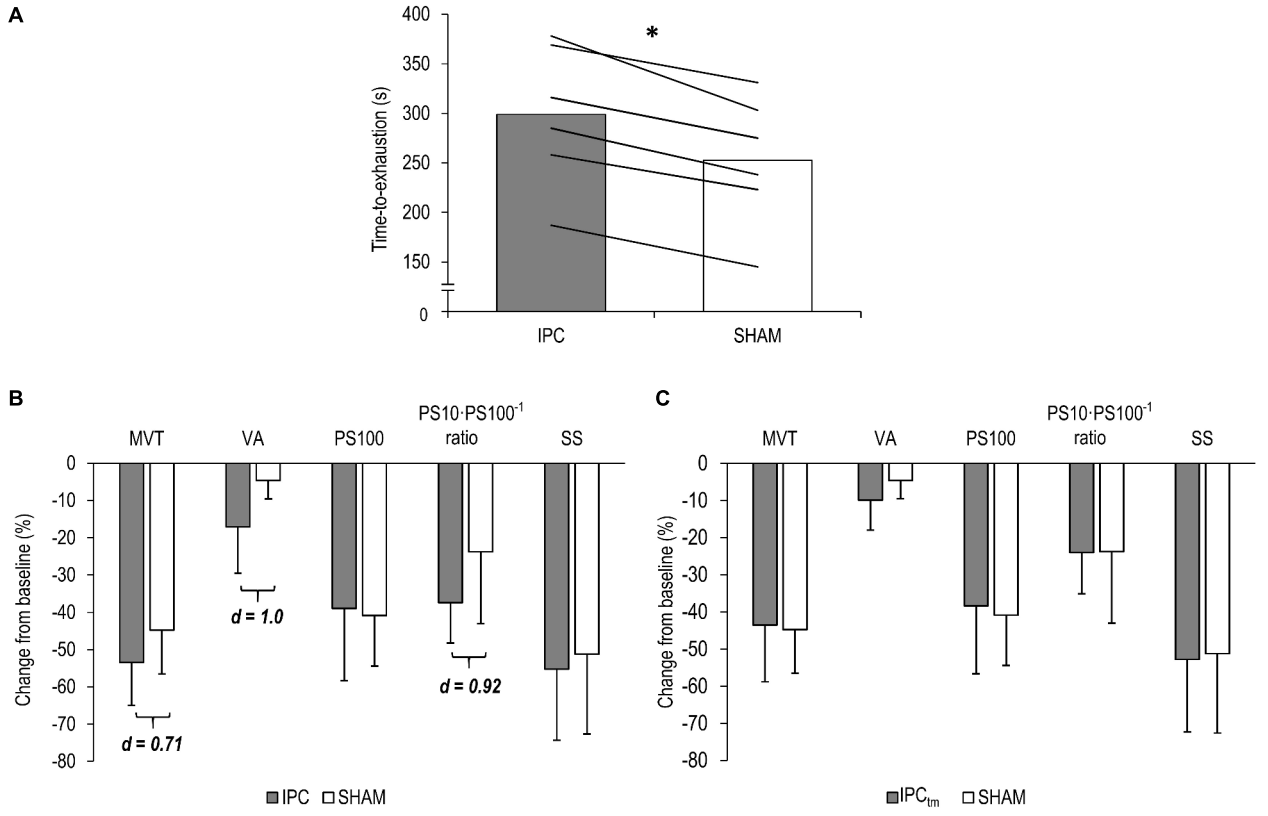

FIGURE 3 | (A) 'Responders' mean values and individual data for the time-to-exhaustion tests for the ischemic preconditioning (IPC) and sham (SHAM) condition. **(B)** *IPC vs. SHAM* – Percentage change from pre-exercise values of the 'responders' for maximal voluntary torque (MVT), voluntary activation (VA), twitch torque in response to paired electrical stimuli (PS100), PS10·PS100^{-1} ratio, and twitch torque in response to a single electrical stimulus (SS). **(C)** *Time-matched IPC trial (IPC$_{tm}$) vs. SHAM* – Percentage change from pre-exercise values of the 'responders' for MVT, VA, PS100, PS10·PS100^{-1} ratio, and SS. Values are presented as mean ± standard deviation. *$P < 0.001$.

Voluntary Activation

Whole Sample

No significant differences between IPC and SHAM were found for ΔVA [P = 0.291, diff.:−3.7% (−10.8 to 3.5%), d = 0.28]. Relative and absolute values for voluntary activation are presented in **Figure 2B** and **Table 1**, respectively.

Responders – IPC vs. SHAM

Based on the effect size and mean difference (95%CI), ΔVA differed between IPC and SHAM [d = 1.0, diff.:−12.4% (−27.7 to 2.8%), P = 0.086]. Relative and absolute values for voluntary activation are presented in **Figure 3B** and **Table 1**, respectively.

Responders – IPC$_{tm}$ vs. SHAM

The effect size for the percentage changes in ΔVA during IPC$_{tm}$ and SHAM did not reach the defined threshold of d = 0.70 [d = 0.67, diff.:−5.3% (−14.7 to 4.3%), P = 0.202]. Percentage changes and absolute values for VA are presented in **Figure 3C** and **Table 1**, respectively.

Electrically Evoked Twitch Torques

Whole Sample

There were no significant differences in ΔPS100 [P = 0.409, diff.: 1.8% (−2.8 to 6.4%), d = 0.22], ΔSS [P = 0.621, diff.: −1.4% (−7.2 to 4.4%), d = 0.12], and ΔPS10·PS100^{-1} ratio [P = 0.100, diff.: −5.0% (−11.1 to 1.1%), d = 0.46] between IPC and SHAM. Percentage changes and absolute values for PS100, SS, and PS10·PS100^{-1} ratio are presented in **Figure 2B** and **Table 1**, respectively.

Responders – IPC vs. SHAM

Based on the effect size and mean difference (95%CI), ΔPS10·PS100^{-1} ratio differed between IPC and SHAM [d = 0.92, diff.:−13.6% (−32.0 to 4.7%), P = 0.108]. This difference could not be observed for ΔPS100 [d = 0.19, diff.: 1.9% (−10.6 to 14.5%), P = 0.694] and ΔSS [d = 0.29, diff.:−4.0% (−17.8 to 9.8%), P = 0.466]. Percentage changes and absolute values for PS100, SS, and PS10·PS100^{-1} ratio are presented in **Figure 3B** and **Table 1**, respectively.

Responders – IPC$_{tm}$ vs. SHAM

There were no differences between IPC$_{tm}$ and SHAM for ΔPS100 [d = 0.45, diff.: 2.5% (−4.4 to 9.4%), P = 0.370],

TABLE 1 | Neuromuscular function of the quadriceps muscle before and after exercise following ischemic preconditioning (IPC) and the sham intervention (SHAM). Participants who increased their exercise tolerance ('responders') after IPC performed a time-matched IPC trial corresponding to the SHAM exercise duration (IPC_{tm}).

Parameter	Condition	*Whole sample*		Condition	*Responders*	
		Pre	Post		Pre	Post
MVT (N·m)						
	IPC	300.7 ± 64.1	165.9 ± 50.5	IPC	276.7 ± 65.7	127.3 ± 33.9
	SHAM	307.2 ± 60.0	171.4 ± 39.5	SHAM	297.3 ± 61.5	158.0 ± 15.7
				IPC_{tm}	276.7 ± 54.8	156.8 ± 58.1
PS100 (N·m)						
	IPC	93.3 ± 12.1	57.5 ± 10.3	IPC	95.4 ± 14.9	56.8 ± 14.8
	SHAM	94.7 ± 9.2	56.8 ± 8.9	SHAM	96.6 ± 11.1	56.1 ± 9.5
				IPC_{tm}	95.0 ± 15.6	57.8 ± 15.5
SS (N·m)						
	IPC	61.0 ± 8.9	27.1 ± 8.3	IPC	61.7 ± 12.0	26.6 ± 10.8
	SHAM	63.4 ± 6.9	29.1 ± 9.0	SHAM	66.3 ± 6.7	31.5 ± 12.0
				IPC_{tm}	63.7 ± 7.3	30.1 ± 12.3
PS10·PS100^{-1} ratio						
	IPC	1.01 ± 0.08	0.68 ± 0.11	IPC	1.03 ± 0.05	0.64 ± 0.12
	SHAM	1.02 ± 0.08	0.74 ± 0.16	SHAM	1.07 ± 0.03	0.82 ± 0.22
				IPC_{tm}	1.06 ± 0.02	0.80 ± 0.13
VM M_{max} (mV)						
	IPC	14.2 ± 2.2	13.3 ± 2.9	IPC	14.4 ± 1.3	13.1 ± 1.6
	SHAM	14.0 ± 2.0	13.5 ± 2.4	SHAM	13.3 ± 1.8	11.7 ± 2.0
				IPC_{tm}	13.7 ± 1.9	12.5 ± 1.6
RF M_{max} (mV)						
	IPC	3.5 ± 1.6	3.3 ± 1.3	IPC	3.7 ± 1.2	3.3 ± 1.3
	SHAM	4.1 ± 1.9	3.7 ± 0.7	SHAM	3.9 ± 1.0	3.4 ± 0.4
				IPC_{tm}	4.2 ± 1.4	3.7 ± 0.9
VL M_{max} (mV)						
	IPC	10.8 ± 4.4	10.5 ± 5.3	IPC	9.3 ± 4.1	7.5 ± 4.7
	SHAM	9.4 ± 4.2	8.7 ± 4.5	SHAM	7.9 ± 2.8	7.4 ± 3.1
				IPC_{tm}	7.0 ± 2.7	6.9 ± 2.6
VA (%)						
	IPC	96.1 ± 2.7	88.8 ± 12.0	IPC	96.0 ± 1.9	79.8 ± 13.3
	SHAM	95.6 ± 1.8	91.8 ± 4.3	SHAM	95.4 ± 1.8	91.0 ± 5.2
				IPC_{tm}	95.6 ± 1.5	86.2 ± 8.4

Values are expressed as mean ± standard deviation. MVT, maximum voluntary torque; PS100, paired stimuli twitch torque at 100 Hz; SS, single stimulus twitch torque; PS10·PS100^{-1} ratio, index of low-frequency fatigue; M_{max}, maximum M-wave; VM, vastus medialis; RF, rectus femoris; VL, vastus lateralis; VA, voluntary activation.

ΔSS [d = 0.33, diff.:−3.7% (−21.3 to 13.8%), P = 0.549], and ΔPS10·PS100^{-1} ratio [d = 0.02, diff.:−0.25% (−13.9 to 13.4%), P = 0.962] of the 'responders.' Percentage changes and absolute values for PS100, SS, and PS10·PS100^{-1} ratio are presented in **Figure 3C** and **Table 1**, respectively.

Electrically Evoked Potentials

Whole Sample

No significant differences in ΔM_{max} between IPC and SHAM were observed for VM, RF, and VL [P = 0.415, diff.:−2.8% (−10.0 to 4.4%), d = 0.22/P = 0.257, diff.: 4.6% (−3.8 to 13.1%), d = 0.30/P = 0.874, diff.: 1.2% (−15.4 to 17.9%), d = 0.04, respectively]. Absolute values for M_{max} are presented in **Table 1**.

Responders – IPC vs. SHAM

The effect sizes for the percentage changes of M_{max} for VM, RF, and VL recorded during IPC and SHAM did not reach the defined threshold of d = 0.70 [d = 0.19, diff.: 3.0% (−16.3 to 22.4%), P = 0.685/d = 0.56, diff.: 10.0% (−12.4 to 32.4%), P = 0.283/d = 0.67, diff.: − 14.4% (− 41.2 to 12.4%), P = 0.211, respectively].

Responders – IPC_{tm} vs. SHAM

The same was true for ΔM_{max} of VM, RF, and VL recorded during IPC_{tm} and SHAM [d = 0.39, diff.: 3.1% (−6.8 to 13.1%), P = 0.429/d = 0.03, diff.:−0.5% (−24.1 to 23.1%), P = 0.955/d = 0.39, diff.: 5.9% (−13.1 to 24.9%), P = 0.437, respectively]. Absolute values for M_{max} are presented in **Table 1**.

EMG Recordings During Exercise

Whole Sample

A time effect was found for ΔQ RMS·M^{-1} ($P < 0.001$, $F_{4,56} = 29.495$, $\eta_p^2 = 0.678$, *post hoc* analysis: all $P \leq 0.054$ compared to the first time point). No condition effect for ΔQ RMS·M^{-1} ($P = 0.497$, $F_{1,14} = 0.486$, $\eta_p^2 = 0.034$) or time × condition interaction was observed ($P = 0.125$, $F_{4,56} = 1.892$, $\eta_p^2 = 0.119$) (**Figure 4A** and **Table 2**).

Responders – IPC vs. SHAM

The effect size and mean difference (95%CI) for the main effect condition indicated that muscle activity was slightly higher during IPC compared to SHAM [$\eta_p^2 = 0.268$, diff.: 0.7% (−0.7 to 2.2%), $F_{1,5} = 1.827$, $P = 0.234$]. A time effect was found for ΔQ RMS·M^{-1} ($\eta_p^2 = 0.691$, $F_{4,20} = 11.174$, $P < 0.001$, *post hoc* analysis: all $P \geq 0.087$ compared to the first time point). No time × condition interaction was observed ($\eta_p^2 = 0.094$, $F_{4,20} = 0.520$, $P = 0.722$) (**Figure 4B** and **Table 2**).

Responders – IPC$_{tm}$ vs. SHAM

The effect size and mean difference (95%CI) for the main effect condition indicated that muscle activity was slightly higher during IPC$_{tm}$ compared to SHAM [$\eta_p^2 = 0.246$, diff.: 3.0% (−3.0 to 9.0%), $F_{1,5} = 1.630$, $P = 0.258$]. A time effect was found for ΔQ RMS·M^{-1} ($\eta_p^2 = 0.627$, $F_{4,20} = 8.408$, $P < 0.001$, *post hoc* analysis: all $P \geq 0.145$ compared to the first time point). The interaction of time × condition showed also a large effect size ($\eta_p^2 = 0.273$, $F_{4,20} = 1.879$, $P = 0.154$) (**Figure 4C** and **Table 2**).

Muscle Oxygenation During Exercise

Whole Sample

SmO_2 decreased ($P < 0.001$, $F_{4,60} = 39.099$, $\eta_p^2 = 0.723$, *post hoc* analysis: all $P \leq 0.001$ compared to the first time point) and ΔTHb increased ($P = 0.021$, $F_{4,60} = 3.183$, $\eta_p^2 = 0.197$, *post hoc* analysis: all $P \geq 0.621$ compared to the first time point) over time for both IPC and SHAM. No condition effects for ΔSmO_2 ($P = 0.428$, $F_{1,15} = 0.663$, $\eta_p^2 = 0.042$) and ΔTHb ($P = 0.180$, $F_{1,15} = 2.012$, $\eta_p^2 = 0.134$) or time × condition interactions for both parameters were observed ($P = 0.821$, $F_{4,60} = 0.382$, $\eta_p^2 = 0.025$/$P = 0.421$, $F_{4,60} = 0.874$, $\eta_p^2 = 0.063$, respectively) (**Figure 4A** and **Table 2**).

Responders – IPC vs. SHAM

A time effect was found for ΔSmO_2 ($\eta_p^2 = 0.787$, $F_{4,20} = 18.475$, $P < 0.001$, *post hoc* analysis: all $P \leq 0.157$ compared to the first time point) but not for ΔTHb ($\eta_p^2 = 0.129$, $F_{4,20} = 0.591$, $P = 0.674$). No condition effects for ΔSmO_2 ($\eta_p^2 = 0.032$, $F_{1,5} = 0.164$, $P = 0.703$) and ΔTHb ($\eta_p^2 = 0.009$, $F_{1,5} = 0.038$, $P = 0.855$) or time × condition interactions for both parameters were observed ($\eta_p^2 = 0.199$, $F_{4,20} = 1.243$, $P = 0.325$/$\eta_p^2 = 0.100$, $F_{4,20} = 0.447$, $P = 0.773$, respectively) (**Figure 4B** and **Table 2**).

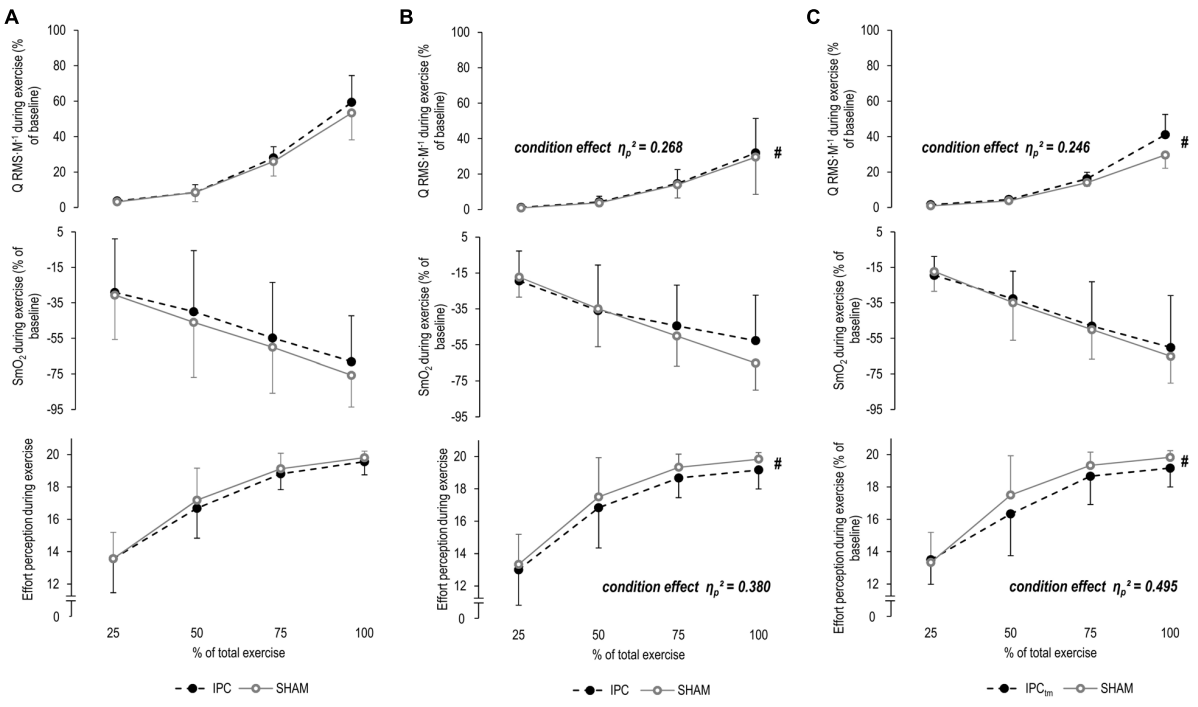

FIGURE 4 | (A) Percentage changes in normalized muscle activity of the quadriceps muscle (Q RMS·M^{-1}), muscle O_2 saturation of the vastus lateralis (SmO_2), and effort perception during exercise for the ***whole sample*** for the ischemic preconditioning (IPC) and sham (SHAM) condition. **(B)** *IPC vs. SHAM* – Percentage changes in Q RMS·M^{-1}, SmO_2, and effort perception during exercise of the ***'responders'*** for the IPC and SHAM condition. **(C)** *Time-matched IPC trial (IPC$_{tm}$) vs. SHAM* – Percentage changes in Q RMS·M^{-1}, SmO_2, and effort perception during exercise of the ***'responders'*** for the IPC$_{tm}$ and SHAM condition. Values are presented as mean ± standard deviation.

TABLE 2 | Electromyography, near-infrared spectroscopy recordings, and perceptual responses during exercise for the ischemic preconditioning (IPC) and sham condition (SHAM) as well as the time-matched IPC trial corresponding to the SHAM exercise duration (IPC_{tm}).

Parameter	Condition	Baseline	Time (% of total exercise duration)			
			25	50	75	100
			Whole sample			
Q RMS·M^{-1}						
	IPC	0.038 ± 0.007	0.039 ± 0.007	0.040 ± 0.008	0.045 ± 0.008	0.054 ± 0.012
	SHAM	0.034 ± 0.006	0.035 ± 0.006	0.036 ± 0.006	0.041 ± 0.005	0.047 ± 0.006
SmO_2 (%)						
	IPC	75.4 ± 9.3	55.1 ± 26.2	45.5 ± 28.5	32.9 ± 24.4	23.5 ± 21.5
	SHAM	75.6 ± 8.5	51.6 ± 20.7	39.0 ± 23.4	28.9 ± 19.3	17.4 ± 14.1
THb (g·dL^{-1})						
	IPC	12.75 ± 0.31	12.75 ± 0.36	12.76 ± 0.39	12.78 ± 0.45	12.82 ± 0.44
	SHAM	12.79 ± 0.36	12.80 ± 0.48	12.84 ± 0.50	12.87 ± 0.50	12.92 ± 0.49
Effort						
	IPC	–	13.6 ± 2.0	16.7 ± 1.8	18.8 ± 0.9	19.6 ± 0.8
	SHAM	–	13.6 ± 1.6	17.2 ± 1.9	19.1 ± 0.9	19.8 ± 0.4
Leg muscle pain						
	IPC	–	3.4 ± 1.6	6.3 ± 2.1	9.0 ± 2.2	10.0 ± 2.3
	SHAM	–	3.3 ± 1.8	6.5 ± 2.3	8.9 ± 1.4	10.6 ± 3.1
			Responders			
Q RMS·M^{-1}						
	IPC	0.037 ± 0.007	0.037 ± 0.007	0.039 ± 0.007	0.042 ± 0.007	0.048 ± 0.005
	SHAM	0.035 ± 0.004	0.036 ± 0.004	0.037 ± 0.004	0.040 ± 0.003	0.045 ± 0.004
	IPC_{tm}	0.038 ± 0.010	0.039 ± 0.010	0.040 ± 0.009	0.044 ± 0.009	0.051 ± 0.008
SmO_2 (%)						
	IPC	84.6 ± 3.8	68.2 ± 14.4	54.7 ± 22.7	47.4 ± 19.9	40.4 ± 22.0
	SHAM	84.2 ± 5.3	69.5 ± 9.4	55.6 ± 20.0	42.5 ± 15.5	29.9 ± 13.8
	IPC_{tm}	79.1 ± 7.2	63.1 ± 5.6	53.8 ± 14.6	41.8 ± 20.6	32.7 ± 23.7
THb (g·dL^{-1})						
	IPC	12.59 ± 0.33	12.52 ± 0.39	12.54 ± 0.47	12.52 ± 0.54	12.57 ± 0.55
	SHAM	12.62 ± 0.35	12.51 ± 0.49	12.57 ± 0.59	12.62 ± 0.64	12.66 ± 0.59
	IPC_{tm}	12.53 ± 0.25	12.51 ± 0.28	12.54 ± 0.32	12.55 ± 0.33	12.57 ± 0.35
Effort						
	IPC	–	13.0 ± 2.0	16.8 ± 2.3	18.7 ± 1.1	19.2 ± 1.1
	SHAM	–	13.3 ± 1.7	17.5 ± 2.2	19.3 ± 0.7	19.8 ± 0.4
	IPC_{tm}	–	13.5 ± 1.4	16.3 ± 2.4	18.7 ± 1.6	19.2 ± 1.1
Leg muscle pain						
	IPC	–	3.5 ± 0.8	6.5 ± 1.9	9.3 ± 0.5	9.8 ± 0.4
	SHAM	–	3.4 ± 1.2	6.5 ± 2.1	9.0 ± 1.2	9.5 ± 1.1
	IPC_{tm}	–	3.2 ± 0.7	5.8 ± 2.2	8.3 ± 1.8	9.2 ± 1.9

Values are expressed as mean ± standard deviation. Q RMS·M^{-1}, averaged root mean square of the electromyography signal normalized to the corresponding maximal M-wave of vastus lateralis, rectus femoris, and vastus medialis; SmO_2, muscle oxygen saturation; THb, total hemoglobin.

Responders – IPC_{tm} vs. SHAM

A time effect was found for ΔSmO_2 ($\eta_p^2 = 0.823$, $F_{4,20} = 23.210$, $P < 0.001$, *post hoc* analysis: all $P \leq 0.062$ compared to the first time point) but not for ΔTHb ($\eta_p^2 = 0.160$, $F_{4,20} = 0.760$, $P = 0.566$). No condition effects for ΔSmO_2 ($\eta_p^2 = 0.053$, $F_{1,5} = 0.281$, $P = 0.619$) and ΔTHb ($\eta_p^2 = 0.057$, $F_{1,5} = 0.240$, $P = 0.650$) or time × condition interactions for both parameters were observed ($\eta_p^2 = 0.136$, $F_{4,20} = 0.786$, $P = 0.548$/$\eta_p^2 = 0.120$, $F_{4,20} = 0.547$, $P = 0.704$, respectively) (**Figure 4C** and **Table 2**).

Perception of Effort

Whole Sample

There were increases in effort perception over time for both IPC and SHAM ($P < 0.001$, $F_{3,45} = 135.654$, $\eta_p^2 = 0.900$, *post hoc* analysis: all $P < 0.001$ compared to the first time point). No

condition effect (P = 0.101, $F_{1,15}$ = 3.046, η_p^2 = 0.169) or time × condition interaction was observed for effort perception (P = 0.492, $F_{3,45}$ = 0.541, η_p^2 = 0.046) (**Figure 4A** and **Table 2**).

Responders – IPC vs. SHAM

The effect size and mean difference (95%CI) for the main effect condition indicated that effort perception was lower during IPC compared to SHAM [η_p^2 = 0.380, diff.:−0.583 (−1.440 to 0.274), $F_{1,5}$ = 3.062, P = 0.141]. A time effect was found for effort perception (η_p^2 = 0.907, $F_{3,15}$ = 48.519, P < 0.001, *post hoc* analysis: all $P \leq 0.001$ compared to the first time point). No time × condition interaction was observed (η_p^2 = 0.048, $F_{3,15}$ = 0.250, P = 0.756) (**Figure 4B** and **Table 2**).

Responders – IPC_{tm} vs. SHAM

The effect size and mean difference (95%CI) for the main effect condition indicate that effort perception was lower during IPC_{tm} compared to SHAM [η_p^2 = 0.495, diff.:−0.583 (−1.261 to 0.094), $F_{1,5}$ = 4.900, P = 0.078]. A time effect was found for effort perception (η_p^2 = 0.921, $F_{3,15}$ = 58.116, P < 0.001, *post hoc* analysis: all P < 0.001 compared to the first time point). The interaction of time × condition showed also a large effect size (η_p^2 = 0.282, $F_{3,15}$ = 1.964, P = 0.203) (**Figure 4C** and **Table 2**).

Perception of Exercise-Induced Leg Muscle Pain

Whole Sample

Exercise-induced leg muscle pain perception increased over time during exercise for both IPC and SHAM (P < 0.001, $F_{3,45}$ = 128.337, η_p^2 = 0.895, *post hoc* analysis: all P < 0.001 compared to the first time point). No condition effect (P = 0.541, $F_{1,15}$ = 0.392, η_p^2 = 0.025) or time × condition interaction were found (P = 0.519, $F_{3,45}$ = 0.550, η_p^2 = 0.035) (**Table 2**).

Responders – IPC vs. SHAM

A time effect was found for exercise-induced leg muscle pain (η_p^2 = 0.916, $F_{3,15}$ = 54.243, P < 0.001, *post hoc* analysis: all $P \leq 0.031$ compared to the first time point). No condition effect (η_p^2 = 0.065, $F_{1,5}$ = 0.345, P = 0.582) or interaction of time × condition (η_p^2 = 0.074, $F_{3,15}$ = 0.399, P = 0.677) was observed (**Table 2**).

Responders – IPC_{tm} vs. SHAM

The effect size and mean difference (95%CI) for the main effect condition indicated that exercise-induced leg muscle pain was lower during IPC_{tm} compared to SHAM [η_p^2 = 0.562, diff.:−0.479 (−0.966 to 0.008), $F_{1,5}$ = 6.404, P = 0.052]. A time effect was found for exercise-induced leg muscle pain (η_p^2 = 0.875, $F_{3,15}$ = 35.142, P < 0.001, *post hoc* analysis: all $P \leq 0.083$ compared to the first time point). No time × condition interaction was observed (η_p^2 = 0.102, $F_{3,15}$ = 0.571, P = 0.565) (**Table 2**).

DISCUSSION

The present study was designed to provide further insights into the mechanistic basis for improvements in exercise performance that have been frequently observed after IPC by investigating key-determinants of performance and perceived fatigability. We have not found an improved exercise tolerance for the whole sample during a submaximal isometric voluntary contraction of the knee extensors at 20% MVT following IPC compared to SHAM. This result is in contrast to the finding of Tanaka et al. (2016) who observed an improved time-to-exhaustion of 17.2% during the same task following IPC. The authors have attributed the observed ergogenic effect of IPC to an accelerated muscle deoxygenation response during exercise, which was interpreted as an improved metabolic efficiency. However, our data on central and peripheral determinants of performance fatigability as well as muscle activity, SmO_2, and perceptual responses during exercise do not support this conclusion. Our results are in accordance with the outcomes of other studies that have neither found an increased exercise performance nor altered physiological and perceptual responses during and after submaximal and maximal exercise following IPC (Tocco et al., 2015; Sabino-Carvalho et al., 2017; Halley et al., 2018, 2019). Explanations for the discrepant outcomes of our study and that of Tanaka et al. (2016) might be that they have not performed a warm-up after the interventions (IPC and the control condition) and before the fatigue protocol. Therefore, the large improvement in time-to-exhaustion of 17.2% following IPC might be in part due to warming-up/priming effects (e.g., increased muscle temperature and improved muscle vascular O_2 kinetics) induced by the repeated, short-term periods of vascular occlusion with subsequent reperfusion, similar to that induced by prior exercise (Behnke et al., 2002; Burnley et al., 2005). Besides that, the missing SHAM condition and the awareness of the principal investigator regarding the treatment in the experiment of Tanaka et al. (2016) could be additional contributors the discrepant results.

However, it should be not ignored that six participants improved their time-to-exhaustion by more than 10% after IPC compared to SHAM. Although the subsample analysis of six participants should be interpreted with caution, the time-matched comparisons (IPC_{tm} vs. SHAM) suggest that performance fatigability and its central and peripheral determinants were not affected by IPC. Furthermore, SmO_2 data were also similar between all conditions. These data do not support the assertion that IPC improves metabolic efficiency and/or blood flow in the active skeletal muscles during exercise, which are thought to be the main mechanisms for the ergogenic effect of IPC (Incognito et al., 2016). Based on the effect sizes, it could be speculated that the longer time-to-exhaustion of the 'responders' following IPC was associated with greater impairments in neuromuscular function as indicated by a larger decrease in MVT, voluntary activation, and low-frequency twitch torque. Furthermore, data indicate that effort perception was lower and muscle activity was slightly higher during both IPC and IPC_{tm} compared to SHAM, suggesting a reliable impact of IPC on effort perception and muscle activity during submaximal isometric exercise.

An improved exercise performance and a lower effort perception during exercise in response to IPC has also been shown by others (Cruz et al., 2015; Paradis-Deschenes et al., 2018). In line with our data for the 'responders,' Cruz et al.

(2015) have found that the increased constant-load cycling performance after IPC was accompanied by a lower effort perception and higher muscle activity. There is a general finding that interventions which can reduce effort perception have the potential to increase endurance performance (McCormick et al., 2015). As a key-determinant of endurance performance, effort perception is thought to be involved in processes related to self-regulation, exercise behavior, and task disengagement (Marcora, 2008; Venhorst et al., 2018). Therefore, a lower effort perception following IPC might have enabled the participants to continue the submaximal isometric task for longer and allowed them to tolerate larger impairments in neuromuscular function. Although there is still controversy about whether effort perception results from a centrally mediated feedforward mechanisms (i.e., corollary discharge model) and/or afferent feedback from the working and respiratory muscles (i.e., afferent feedback or combined model), it is well accepted that neural processing of sensory signals in the brain is involved (Marcora, 2009; Pageaux, 2016). Since peripheral factors of performance fatigability (i.e., contractile function) and SmO_2 data were not altered by IPC at the same point in time, processes within the nervous system might have played a role in the reduced effort perception following IPC in the 'responders'. Recently, it has been speculated that IPC might desensitize small-diameter group III and IV muscle afferents leading to less inhibition at the supraspinal and/or spinal level during exercise. The authors proposed that these mechanisms might be responsible for the lower effort perception and higher muscle activity observed during constant-load cycling following IPC (Cruz et al., 2015, 2017). This assumption has been criticized for several reasons, e.g., the definition of effort perception in the experiment of Cruz et al. (2015) and the importance of small-diameter muscle afferents not only for inhibitory processes in the central nervous system but also for the upregulation of cardiovascular and ventilatory function during exercise (see Commentaries on Viewpoint of Cruz et al., 2017: Could small-diameter muscle afferents be responsible for the ergogenic effect of limb ischemic preconditioning?). An alternative explanation for the lower effort perception during exercise might be that periods of local ischemia increase the excitability of the corticospinal pathway at rest. McNulty et al. (2002) investigated the effect of 40 min of local ischemia on motor potentials of the first dorsal interosseous muscle evoked by transcranial magnetic stimulation. The authors have found that the motor-evoked potentials decreased progressively during the ischemic period but were significantly elevated for up to 20 min after the restoration of blood flow, which coincided with heightened afferent neural volleys. If the excitability of neurons at the supraspinal and/or spinal level of the respective muscle is increased, it might need to receive less input to generate the same muscle activation signal. In this case, a lower effort perception for a given torque output should be expected. However, currently it is not known if IPC increases corticospinal excitability at rest and/or during submaximal voluntary contractions and how long this effect persists. Due to the transient nature of these potential changes, only endurance tasks performed directly after the treatment might benefit from these acute neural adjustments.

Exercise-induced muscle pain perception of the 'responders' was not different between IPC and SHAM, but seemed to be lower during IPC_{tm} compared to SHAM. Because the IPC_{tm} trial was the last one for each 'responder', it might be that the repetitive application of IPC has altered pain perception and/or tolerance due to habituation to the noxious stimuli. This phenomenon was previously observed in response to high-intensity training (O'Leary et al., 2017).

CONCLUSION

IPC did neither affect exercise tolerance, performance fatigability, as well as its central and peripheral determinants, nor muscle activity, SmO_2, and perceptual responses during submaximal exercise. However, it should be not ignored that six out of 16 participants improved their time-to-exhaustion during the submaximal isometric endurance task following IPC. Our data suggest that this subsample of 'responders' was able to endure for longer and tolerated greater exercise-induced impairments in neuromuscular function after IPC. Interestingly, IPC seemed to be associated with a lower perception of effort during exercise. Since effort perception is considered as a key-determinant of endurance performance, a lower effort perception might have contributed to the improved time-to-exhaustion of the 'responders.' Future studies should aim to identify the underlying factors that contribute to inter-individual differences in the responsiveness to IPC, so that IPC can effectively be used as an ergogenic aid. The present findings support the assumption that there are 'responders' and 'non-responders' to IPC, which might contribute to the heterogeneous findings regarding the ergogenic effect of IPC on exercise performance.

Limitations

Although conditions were randomized, pre-exercise MVT values of the 'responders' were higher in the SHAM condition compared to IPC as well as compared to IPC_{tm}, which resulted in a slightly higher absolute load during the 20% MVT fatigue protocol in the SHAM condition. During SHAM, the 'responders' generated 55.9 ± 17.1 N·m (20.2 ± 0.6% MVT) compared to 53.0 ± 14.1 N·m (20.2 ± 0.5% MVT) in the IPC condition [d = 0.59, diff.:−2.9 N·m (−7.9 to 2.0 N·m), P = 0.191] and 54.1 ± 14.5 N·m (20.7 ± 0.8% MVT) in the IPC_{tm} condition [d = 0.52, diff.:−1.8 N·m (−5.8 to 2.1 N·m), P = 0.283]. However, muscle activity was slightly higher during both IPC conditions compared to SHAM and contractile function was not different between the time-matched conditions (IPC_{tm} vs. SHAM). Hence, the slightly higher absolute load during SHAM was probably not a significant contributor to the observed results of the 'responders'. Data of the remaining participants corroborate this assumption, because for six out of 10 subjects time-to-exhaustion was longer or similar despite higher pre-exercise MVT values, irrespective of the condition. Since our participants were young, healthy, and active males, conclusions for other populations should be drawn with caution. In addition, SmO_2 data were only captured for the VL and we cannot rule out that muscle oxygenation was different in the other muscles of the quadriceps after IPC.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee University of Rostock, St.-Georg-Str. 108, 18055 Rostock. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MB and FH designed the study, collected, analyzed, and interpreted the data, and wrote the manuscript. SB, TM, and VZ contributed to writing, reviewing, and editing of the manuscript. All authors approved the final version of the manuscript.

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Taxonomie und Determinanten motorischer Performance Fatigability bei Multipler Sklerose

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Zusammenfassung

Fatigue wurde in Abhängigkeit vom Forschungsfeld (z. B. Neurologie, Psychologie, Bewegungswissenschaft, Physiologie) unterschiedlich definiert. Das führte zu einer uneinheitlichen Verwendung des Begriffes, die den wissenschaftlichen Fortschritt einschränkt. Deshalb wird in diesem Beitrag eine Taxonomie vorgeschlagen, die ein besseres Verständnis von Fatigue bei Personen mit Multipler Sklerose (PmMS) befördert und somit eine eindeutige Charakterisierung des Phänomens und die Applikation effektiver Interventionen zulässt.

Zunächst sollte zwischen *Trait Fatigue* und *State Fatigue* unterschieden werden. Trait Fatigue beschreibt die Ermüdung/Erschöpfung eines Individuums über einen längeren Zeitraum, z. B. Wochen und Monate. State Fatigue hingegen bezeichnet die akute und transiente Veränderung der motorischen und/oder kognitiven Leistungsfähigkeit sowie verschiedener Wahrnehmungsqualitäten, die im Rahmen einer definierten anhaltenden motorischen und/oder kognitiven Aufgabe auftreten.

Die in diesem Beitrag thematisierte motorisch induzierte State Fatigue kann als ein beeinträchtigendes psychophysiologisches Symptom definiert werden, das durch die Abnahme der motorischen Leistungsfähigkeit (motorische *Performance Fatigability*) und/oder die erhöhte Wahrnehmung von Ermüdung/Erschöpfung *(Perceived Fatigability)* charakterisiert ist. Diese beiden Dimensionen sind interdependent, nicht separierbar und sollten deshalb simultan quantifiziert werden. Das Ausmaß der motorisch induzierten State Fatigue hängt von den Änderungsraten der motorischen Performance Fatigability sowie Perceived Fatigability ab und wird dadurch auf die Anforderungen der motorischen Aufgabe normalisiert. Die motorische Performance Fatigability wird durch neuronale (Muskelaktivierung) und muskuläre Faktoren (kontraktile Funktion) determiniert, während die Perceived Fatigability vom psychologischen Status des Individuums sowie der Homöostase abhängig ist. Durch den Bezug auf die zugrundeliegenden Mechanismen der motorisch induzierten State Fatigue kann die Analyse der Ursachen der belastungsinduzierten Veränderungen sowie die gezielte Beeinflussung der Mechanismen durch verschiedene Interventionen bei PmMS optimiert werden.

Schlüsselwörter: Fatigue, MS, Erschöpfung, Ermüdung, Perceived Fatigability

Fatigue, which »at first sight might appear an imperfection of our body, is on the contrary one of its most marvelous perfections. The fatigue increasing more rapidly than the amount of work done saves us from injury [...].«

Physiologie-Professor Angelo Mosso, 1904

Einführung

Multiple Sklerose (MS) ist eine chronische inflammatorische neurodegenerative Erkrankung des zentralen Nervensystems, die zu einer axonalen Demyelinisierung und Degeneration führt. Dadurch kommt es unter anderem zu einer veränderten Aktionspotentialweiterleitung und Synchronisation neuronaler Inputs an postsynaptischen Neuronen. Im Verlauf der Krankheit führt MS zu strukturellen Veränderungen der weißen und grauen Substanz auf kortikaler, subkortikaler und spinaler Ebene [36, 94], die die motorische, sensorische und kognitive Leistungsfähigkeit negativ beeinflussen können [16, 23, 24, 70, 76]. Zusätzlich zu diesen Einschränkungen leiden über 75 % der Personen mit MS (PmMS) unter der Fatigue-Symptomatik. Diese wird als das am stärksten limitierende Symptom wahrgenommen, das vor allem mit den Aktivitäten des täglichen Lebens konfligiert und die Lebensqualität von PmMS einschränkt [18]. Dabei wird Fatigue im MS-Kontext häufig als subjektiver Mangel an physischer und/oder mentaler Energie, der von der betroffenen oder der betreuenden Person als Beeinträchtigung üblicher und gewünschter Aktivitäten empfunden wird, definiert [39]. In Abhängigkeit vom Forschungsfeld (z. B. Neurologie, Psychologie, Bewegungswissenschaft, Physiologie) wurde Fatigue in der Vergangenheit jedoch sehr unterschiedlich charakterisiert. Einige Fachrichtungen haben primär auf die sub-

jektive Wahrnehmung von Fatigue reflektiert, während andere Fachdisziplinen Fatigue als Abnahme der motorischen oder kognitiven Leistungsfähigkeit definiert haben [30, 49, 90]. Die Vielzahl der differenten Definitionen führte und führt immer noch zu einer uneinheitlichen Verwendung des Begriffes Fatigue, die eine eindeutige Charakterisierung des Phänomens erschwert und damit den wissenschaftlichen Fortschritt sowie die Entwicklung effektiver Interventionen einschränkt [49].

Deshalb ist das Ziel dieses Beitrages, eine einheitliche Taxonomie zu etablieren, die ein differenziertes Verständnis von Fatigue bei PmMS befördert, eine eindeutige Charakterisierung des Phänomens zulässt und damit den wissenschaftlichen Fortschritt sowie die Entwicklung effektiver Interventionen unterstützt.

Taxonomie Fatigue und Fatigability

Definition Trait Fatigue und State Fatigue

Um Fatigue präzise definieren zu können, sollte zunächst zwischen *Trait Fatigue* und *State Fatigue* unterschieden werden. Dabei beschreibt Trait Fatigue die Ermüdung/Erschöpfung eines Individuums über einen längeren Zeitraum, z. B. Wochen und Monate, die relativ stabil ist. Konträr dazu bezeichnet State Fatigue die akute und zeitlich begrenzte Veränderung der motorischen und/oder kognitiven Leistungsfähigkeit sowie verschiedener Wahrnehmungsqualitäten, die im Rahmen einer definierten anhaltenden Aufgabe auftreten. Dabei kann die anhaltende Aufgabe beispielsweise motorischer und/oder kognitiver Natur sein [14, 35, 38].

In der Vergangenheit haben diverse Fatigue-Studien im MS-Kontext sowohl die subjektiv wahrgenommene Trait Fatigue mittels Fragebögen (z. B. Modified Fatigue Impact Scale) als auch die akute Veränderung der motorischen oder kognitiven Leistungsfähigkeit quantifiziert, die der State Fatigue zugeordnet wird [5, 20, 29, 78, 83]. Diese Experimente gewährten zwar Einblick in die Assoziation zwischen der überdauernden Wahrnehmung von Fatigue als Trait-Charakteristik und der akuten Änderung der motorischen oder kognitiven Leistungsfähigkeit als State-Variable. Sie berücksichtigten dabei jedoch häufig nicht, dass Trait Fatigue und State Fatigue verschiedene Aspekte von Fatigue darstellen, die unterschiedliche physiologische Mechanismen involvieren. Wahrscheinlich sind deshalb Trait Fatigue und die motorisch sowie kognitiv induzierte State Fatigue bei PmMS nicht hoch miteinander korreliert [52, 53]. Es wird vermutet, dass die Trait Fatigue bei PmMS multifaktoriell bedingt ist. Dabei spielen krankheitsspezifische Prozesse eine Rolle, wie z. B. Inflammation, Demyelinisierung, axonale Degeneration und Veränderungen in Neurotransmittersystemen (primäre Trait Fatigue). Hinzu kommen sekundäre Trait Fatigue-Mechanismen, die unter anderem mit Schlafproblemen, Depressionen, Schmerzen und der Einnahme von Medikamenten verbunden sind [18, 94].

Auch wenn diese Mechanismen der Trait Fatigue zum Teil zur Ausprägung der State Fatigue beitragen, sind andere physiologische Prozesse für die belastungsinduzierten akuten und kurzweiligen Veränderungen verantwortlich. Demnach erlaubt die Quantifizierung der subjektiv wahrgenommenen Trait Fatigue keine Aussage über die akuten Veränderungen im Rahmen verschiedener motorischer und/oder kognitiver Aktivitäten.

Im Folgenden werden wir ausschließlich auf die State Fatigue eingehen, die durch anhaltende motorische Aufgaben ausgelöst wird. Generell kann die motorisch induzierte State Fatigue als Schutzmechanismus interpretiert werden, der maßgeblichen Einfluss auf die Regulation des menschlichen Bewegungsverhaltens hat, um die Integrität der Homöostase des gesamten Körpers und vor allem der Arbeitsmuskulatur zu bewahren [17, 50, 65]. In Anlehnung an Kluger et al. [49], Enoka und Duchateau [31] sowie Gruet [38] wird die motorisch induzierte State Fatigue in diesem Beitrag als ein beeinträchtigendes psychophysiologisches Symptom definiert, das durch die Abnahme der motorischen Leistungsfähigkeit und/oder die erhöhte Perzeption von Fatigue charakterisiert ist. Die akute, durch motorische Aktivität induzierte Abnahme der physischen Leistungsfähigkeit wird dabei als motorische *Performance Fatigability* und die durch motorische Aktivität bedingte Modulation der Ermüdungs-/Erschöpfungswahrnehmung als *Perceived Fatigability* bezeichnet. Diese beiden Formen der State Fatigue sind interdependent und nicht separierbar **(Abb. 1A)**. Aufgrund des Bezuges auf Fatigability hängt das Ausmaß der State Fatigue von den Änderungsraten der motorischen Performance Fatigability und Perceived Fatigability ab und wird dadurch auf die Anforderungen der ausgeführten motorischen Aufgabe normalisiert. Damit wird eine klare Abgrenzung von Trait Fatigue möglich. Die Ausprägung und Gewichtung der motorischen Performance Fatigability und Perceived Fatigability ist von multiplen Einflüssen abhängig (z. B. Charakteristika des Individuums, Dauer und Intensität der Belastung) **(Abb. 1B)**. Das Ausmaß der motorisch induzierten State Fatigue bestimmt wiederum die Reduktion der *motorischen Kapazität* und kann negative Konsequenzen für das *psychosoziale Wohlbefinden* von PmMS haben **(Abb. 1C)**. Zur Verbesserung dieser Symptomatik können *akute und chronische Interventionen* genutzt werden **(Abb. 1D)**.

Motorische Performance Fatigability

Die motorische Performance Fatigability äußert sich als Abnahme der willkürlichen Kraftproduktionsfähigkeit im Verlauf körperlicher Belastungen, die durch neuronale und muskuläre Faktoren determiniert wird. In Abhängigkeit von der motorischen Aufgabe und von weiteren Faktoren, wie z. B. Krankheiten, können die zugrundelie-

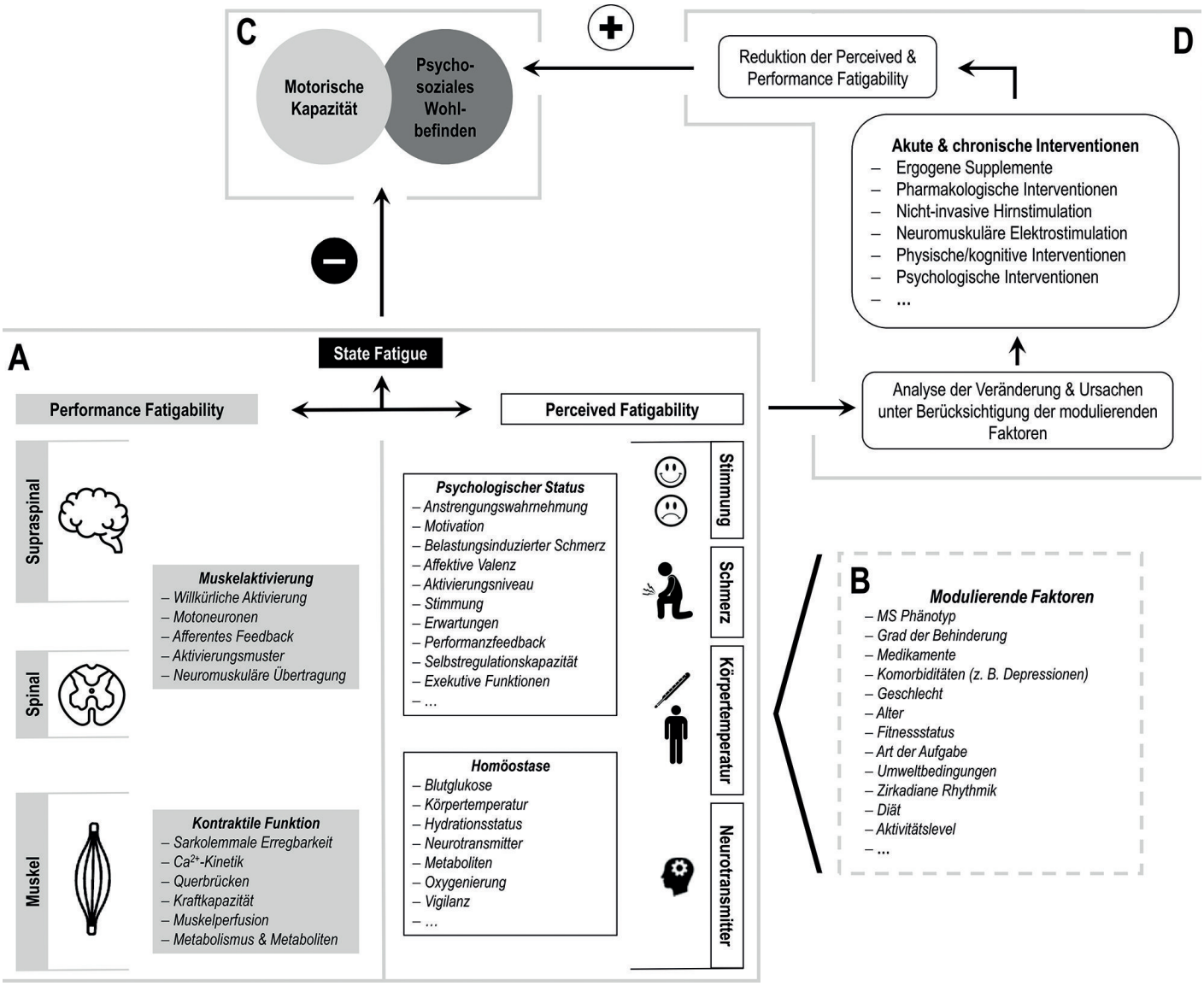

Abb. 1:

A: Modifiziertes Fatigue-Konstrukt nach Kluger et al. [49], Enoka und Duchateau [31] sowie Gruet [38]. Die Ausführung motorischer Aufgaben über einen längeren Zeitraum führt zu State Fatigue, die als ein beeinträchtigendes psychophysiologisches Symptom definiert werden kann. Motorisch induzierte State Fatigue kann sich als Abnahme der motorischen Leistungsfähigkeit und/oder als Veränderung der Wahrnehmung von Fatigue äußern und ergibt sich aus der Interaktion der Determinanten von Performance Fatigability und Perceived Fatigability. Durch den Bezug auf Fatigability hängt das Ausmaß der State Fatigue von den Änderungsraten der motorischen Performance Fatigability und Perceived Fatigability ab und wird dadurch auf die Anforderungen der ausgeführten motorischen Aufgabe normalisiert. Dadurch wird eine klare Abgrenzung von Trait Fatigue möglich.
Im Hinblick auf die Performance Fatigability tragen Veränderung im zentralen Nervensystem (hier als spinal und supraspinal definiert) zur Modulation der Muskelaktivierung bei, die von den darunter aufgeführten modulierenden Faktoren abhängig ist und die Abnahme der motorischen Leistungsfähigkeit befördert. Darüber hinaus führen anhaltende motorische Aufgaben zur Reduktion der kontraktilen Funktion, die ebenfalls zur motorischen Leistungsminderung beiträgt und von den darunter gelisteten Faktoren abhängig ist. Die Perceived Fatigability ist vom psychologischen Status des Individuums abhängig, der durch diverse Faktoren moduliert wird. Zudem spielen in dieser Hinsicht homöostatische Faktoren eine große Rolle, die wiederum auf den psychologischen Status des Individuums zurückwirken. Die Auflistung der verschiedenen Faktoren erhebt keinen Anspruch auf Vollständigkeit, sondern stellt eine Auswahl von bekannten Faktoren dar, die zu Performance Fatigability und Perceived Fatigability beitragen. Diese Liste sollte erweitert werden, sobald neue experimentelle Erkenntnisse vorliegen

B: Modulierende Faktoren, die die jeweilige Gewichtung der Fatigue-Kontributoren beeinflussen können

C: Potentielle Folgen von State Fatigue für das Leben der PmMS

D: Das Wissen um die Determinanten von State Fatigue ermöglicht die Anwendung gezielter und/oder die Entwicklung neuer Interventionen, die sich positiv auf das Leben der PmMS auswirken können

genden Mechanismen der motorischen Performance Fatigability verschiedene Schaltstellen im neuromuskulären System betreffen, die an der muskulären Kraftproduktion und damit an Bewegungen beteiligt sind. Dazu gehören unter anderem: (I) die Exzitabilität des motorischen Kortex, (II) die deszendierende kortikospinale Reizweiterleitung, (III) die Exzitabilität der spinalen α-Motoneuronen, (IV) die neuromuskuläre Übertragung, (V) die sarkolemmale Erregbarkeit, (VI) die Reizweiterleitung in die transversalen Tubuli, (VII) die intrazelluläre Calciumionen-(Ca^{2+})-Kinetik und (VIII) die Kraftproduktionen im Rahmen des Querbrückenzyklus [1, 21, 34]. Anhaltende motorische Aktivitäten können die Funktionsfähigkeit dieser physiologischen Prozesse einschränken und damit die motorische Leistungsfähigkeit beeinträchtigen. Um die Lokalisation der Modulationen feststellen zu können, hat sich eine Unterteilung in neuronale (zentrale) und muskuläre (periphere) Determinanten der motorischen Performance Fatigability etabliert.

Die neuronalen Faktoren umfassen Aspekte der *Muskelaktivierung,* die sich im Laufe einer anhaltenden motorischen Aufgabe ändern können **(Abb. 1A)**.Dazu gehören Veränderungen der *willkürlichen Aktivierung* individueller Muskeln, die mit Modulationen auf der Ebene des motorischen Kortex und/oder der spinalen *α-Motoneuronen* assoziiert sind. Diese führen zu einer aufgabenspezifischen Anpassung der Feuerfrequenz und/oder Rekrutierung motorischer Einheiten. In diesem Zusammenhang spielen weitere Prozesse eine Rolle, die unter anderem die Modifikation der intrinsischen Eigenschaften von Motoneuronen, die Erhöhung des inhibitorischen *afferenten Feedbacks* von Gruppe III und IV-Muskelafferenzen, die Abnahme von fazilitatorischem afferenten Feedback und die Veränderung von Neuromodulatoren umfassen. Darüber hinaus kann es auch zur Veränderung von *Aktivierungsmustern* kommen, die die intermuskuläre Koordination und damit die muskuläre Kraftproduktionsfähigkeit negativ beeinflussen [26, 33] (siehe Taylor et al. [85] für ein umfassendes Review zu den neuronalen Mechanismen der motorischen Performance Fatigability).

Zudem tragen muskuläre Faktoren, die die *kontraktile Funktion* betreffen, zum Ausmaß der motorischen Performance Fatigability bei **(Abb. 1A)**. Die Beeinträchtigung der kontraktilen Funktion hängt dabei maßgeblich vom *Metabolismus* und der *Muskelperfusion* ab. Wenn die aerobe Kapazität nicht mehr ausreicht, um den Energiebedarf für die Muskelarbeit zu decken, muss die Energiebereitstellung zunehmend durch den anaeroben Metabolismus gewährleistet werden. Dabei kommt es zur verstärkten Akkumulation von Stoffwechselend- und Zwischenprodukten (z. B. anorganisches Phosphat, Laktat und Wasserstoffionen), die die Kontraktionskraft eines Muskels beeinträchtigen können. Unter physiologischen Bedingungen ist jedoch primär das anorganische Phosphat und nicht Laktat und Wasserstoffionen für die Reduktion der kontraktilen Funktion verantwortlich [1, 2, 93]. Die wichtigsten Prozesse, die die Abnahme der kontraktilen Funktion und damit der Kontraktionskraft eines Muskels determinieren, sind die reduzierte *sarkolemmale Erregbarkeit*, die verminderte *Ca^{2+}-Ausschüttung* aus dem sarkoplasmatischen Retikulum, die verringerte myofibrilläre *Ca^{2+}-Sensitivität* sowie die Abnahme der Kraftproduktionsfähigkeit der *Querbrücken* per se [1, 21, 31, 34, 44] (siehe Allen et al. [1] und Cheng et al. [21] für umfassende Reviews zu den muskulären Mechanismen der motorischen Performance Fatigability).

Nach anhaltenden motorischen Aufgaben weisen PmMS häufig eine stärker ausgeprägte Performance Fatigability als gesunde Menschen auf, die zusätzlich vom Grad der Behinderung und den MS-Phänotypen beeinflusst wird **(Abb. 1B)**. Die erhöhte motorische Performance Fatigability äußert sich beispielsweise als größere belastungsinduzierte Abnahme der maximalen willkürlichen Kraft [77], die die maximale willkürliche Leistungsfähigkeit des neuromuskulären Systems repräsentiert. Wie oben beschrieben, wird diese Reduktion der motorischen Leistungsfähigkeit durch neuronale Faktoren (Muskelaktivierung) und muskuläre Faktoren (kontraktile Funktion) determiniert.

Die Muskelaktivierung kann valide durch die Kombination von Dynamometrie (Kraft- oder Drehmomentmessung) und neurophysiologischen Techniken quantifiziert werden. Eine der etabliertesten Techniken ist die Interpolated Twitch Technique, mit der die willkürliche Aktivierung von Muskeln in Prozent messbar wird. Dafür wird ein oberflächlich verlaufender peripherer Nerv während einer maximalen willkürlichen Kontraktion eines Muskels oder einer Muskelgruppe elektrisch stimuliert. Können die elektrischen Stimuli einen zusätzlichen Kraftanstieg produzieren, ist die willkürliche Aktivierung suboptimal [13]. Mittels dieser Technik wurde nachgewiesen, dass die Reduktion der willkürlichen Aktivierung nach einer anhaltenden motorischen Aufgabe bei PmMS häufig deutlich stärker ausgeprägt ist. Zudem konnte gezeigt werden, dass die belastungsinduzierte Abnahme der willkürlichen Aktivierung partiell vom Grad der Behinderung und dem MS-Phänotyp abhängig ist. Die Ursache für diese Beobachtungen wird in den krankheitsbedingten Veränderungen im zentralen Nervensystem gesehen, die die supraspinale und/oder spinale Ebene betreffen [24, 94].

Neben der Muskelaktivierung bestimmt jedoch auch die kontraktile Funktion die Abnahme der Leistungsfähigkeit während und nach anhaltenden motorischen Aktivitäten mit. Diese kann ebenfalls mithilfe der peripheren Nervenstimulation quantifiziert werden. Dazu wird ein oberflächlich verlaufender peripherer Nerv elektrisch stimuliert, während der Muskel inaktiv ist. In Kombination mit der Dynamometrie kann somit die Kontraktionskraft einer Muskelgruppe als Antwort auf einen definierten elektrischen Reiz erfasst werden

[12]. Unter Verwendung dieser Technik konnte gezeigt werden, dass anhaltende motorische Aufgaben generell eine Reduktion der kontraktilen Funktion induzierten. Die Ergebnisse sind jedoch heterogen und zeigten eine stärkere [40], gleiche [24] oder geringere [78] Abnahme der kontraktilen Funktion bei PmMS im Vergleich zu der jeweiligen gesunden Kontrollgruppe.

Zusammenfassend kann konstatiert werden, dass die häufig beobachtete stärkere Leistungsreduktion nach anhaltender körperlicher Aktivität bei PmMS primär durch neuronale und weniger durch muskuläre Faktoren bedingt ist.

Perceived Fatigability

Die Perceived Fatigability bezieht sich auf die Veränderung der subjektiven Ermüdungs-/Erschöpfungswahrnehmung im Rahmen einer motorischen Tätigkeit und kann mittels Skalen abgefragt werden [6, 14, 35, 43, 59]. Das Ausmaß der Perceived Fatigability ist dabei vom *psychologischen Status* des Individuums sowie von *homöostatischen Faktoren* abhängig **(Abb. 1A)** [31, 38]. Im Hinblick auf den psychologischen Status einer Person und dessen Auswirkungen auf die Perceived Fatigability sind diverse Faktoren relevant. Es wird angenommen, dass die ermüdungsbedingten Wahrnehmungsprozesse maßgeblich zur Regulation der selbstgewählten Belastungsintensität beitragen und damit einen limitierenden Faktor für die motorische Leistungsfähigkeit des Menschen darstellen [91].

Ein sehr wichtiger Faktor ist die *Anstrengungswahrnehmung* (effort perception) im Verlauf einer motorischen Tätigkeit, die mit der Perceived Fatigability assoziiert ist und diese beeinflusst [37, 85]. Zudem wird die bewegungsinduzierte Anstrengungswahrnehmung als wichtige Determinante für die Leistungsfähigkeit bei anhaltenden motorischen Aufgaben gesehen. Sie beeinflusst das Bewegungsverhalten, die Leistungsreduktion und den Abbruch einer motorischen Aktivität mit, die über einen längeren Zeitraum durchgeführt wird [54, 82, 91]. Die Anstrengungswahrnehmung ist neben der *Motivation* das Kernelement des psychobiologischen Modells der Ausdauerleistungsfähigkeit [54, 55]. Es konnte mehrfach gezeigt werden, dass Interventionen, die die Anstrengungswahrnehmung während einer motorischen Aufgabe reduzierten, die motorische Belastungstoleranz von Menschen erhöhten [15, 25, 46, 57, 79, 87].

Ein weniger untersuchter Faktor, der der Perceived Fatigability zugeordnet wird und diese beeinflussen kann, ist der *belastungsinduzierte Schmerz*. Dieser ist vor allem dann präsent, wenn eine motorische Tätigkeit intensiver ist und zur Akkumulation von Metaboliten in der Arbeitsmuskulatur führt. Neben weiteren Faktoren führt vor allem die Metabolitenakkumulation zur Aktivierung von Gruppe III und IV Muskelafferenzen, die zur belastungsinduzierten Schmerzwahrnehmung beitragen [56]. Es konnte gezeigt werden, dass Interventionen zur Reduktion des belastungsinduzierten Schmerzes die Leistungsfähigkeit bei anhaltenden submaximalen motorischen Aufgaben verbessern konnten [7, 46], während die artifizielle Erhöhung des belastungsinduzierten Schmerzes das Gegenteil bewirkte [81]. Diese Beispiele belegen eindrucksvoll die Interdependenz von Anstrengungswahrnehmung sowie belastungsinduziertem Schmerz und der motorischen Performance Fatigability.

Des Weiteren trägt der affektive Zustand einer Person ebenfalls zur Perceived Fatigability bei und bestimmt das Bewegungsverhalten, die Leistungsreduktion und den Abbruch einer anhaltenden motorischen Aufgabe mit [37, 42, 91]. Dieser wird über die beiden Dimensionen *affektive Valenz* und *Aktivierungsniveau* quantifiziert. Die affektive Valenz spiegelt wider, wie sich ein Mensch aktuell im Allgemeinen fühlt, d. h. von sehr gut bis sehr schlecht [28]. Es wird angenommen, dass diese Zustände subjektive Indikatoren des Homöostasestatus während einer motorischen Tätigkeit sind. Generell werden homöostatische Perturbationen interozeptiv aufgenommen und intrinsisch valenziert [22, 51]. Demzufolge

Taxonomy and determinants of motor performance fatigability in multiple sclerosis

M. Behrens, K.-C. Broscheid, L. Schega

Abstract

»Fatigue« has been defined differently depending on the field of research (e.g., neurology, psychology, exercise physiology), which has led to an inconsistent use of the term, limiting scientific progress. Therefore, this article proposes a taxonomy that promotes a better understanding of fatigue in people with multiple sclerosis (pwMS), allowing a clear characterization of the phenomenon and the application of effective interventions.
First, a distinction should be made between trait and state fatigue. Trait fatigue describes the fatigue experienced by an individual over a longer period of time, e.g. weeks and months. State fatigue, on the other hand, describes the acute and temporary change in motor and/or cognitive performance, as well as various perceptual qualities that emerge in the context of a defined sustained motor and/or cognitive task.
State fatigue, induced by sustained physical activity, can be defined as a disabling psychophysiological symptom characterized by a decrease in motor performance (motor performance fatigability) and/or an increased perception of fatigue (perceived fatigability). These two dimensions are interdependent, not separable, and should be quantified simultaneously. The magnitude of exercise-induced state fatigue depends on the rates of change in motor performance fatigability as well as perceived fatigability and is thus normalized to the demands of the motor task. Motor performance fatigability is determined by neural (muscle activation) and muscular (contractile function) factors, whereas perceived fatigability depends on the psychological status of the individual as well as the body's homeostasis. By referring to the underlying mechanisms of exercise-induced state fatigue, analysis of the etiology of the activity-dependent changes can be optimized. This knowledge can be used to apply acute and chronic interventions that specifically influence these mechanisms.

Keywords: fatigue, perceived fatigability, MS

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tragen homöostatische Perturbationen in den jeweiligen an der motorischen Aufgabe beteiligten physiologischen Subsystemen zur Ausprägung akuter negativer affektiver Valenz bei. Das passiert z. B. beim Übergang vom aeroben zum anaeroben Metabolismus [27, 72]. Aber auch andere homöostatische Perturbationen, wie z. B. Glykogendepletion, können die Entwicklung einer negativen affektiven Valenz während einer konstanten Ausdauerbelastung akzelerieren und die Zeit bis zum Abbruch einer submaximalen motorischen Aufgabe verkürzen. Interessanterweise war dabei die Abnahmerate der affektiven Valenz hoch mit der Zeit bis zum Abbruch der motorischen Aufgabe korreliert [42]. Dies untermauert wiederum die Interdependenz zwischen Aspekten der Perceived Fatigability und der motorischen Performance Fatigability und zeigt, dass diese beiden Dimensionen nicht separierbar sind.

Neben den zuvor genannten Kernelementen der Perceived Fatigability gibt es weitere Aspekte, die den psychologischen Status eines Individuums mitbestimmen und Auswirkungen auf die motorische Belastungstoleranz von Menschen haben können. Dazu gehören unter anderem die *Stimmung,* die *Erwartungen* und die Präsenz von *Performanzfeedback* [31, 56] sowie die *Selbstregulationskapazität* eines Individuums, die mit der Integrität der *exekutiven Funktionen* assoziiert ist [46]. Außerdem werden zunehmend weitere Faktoren untersucht und bekannt, die jedoch nicht Bestandteil dieses Artikels sind.

Die Regulation der Homöostase in den unterschiedlichen physiologischen Subsystemen hat ebenfalls Auswirkungen auf die verschiedenen Wahrnehmungsaspekte im Verlauf einer anhaltenden motorischen Aufgabe und somit auch auf die motorische Performance Fatigability **(Abb. 1A)** [31, 38]. Zu den wichtigsten Prozessen gehört die Regulation der intramuskulären Homöostase mittels Feedback der Gruppe III und IV Muskelafferenzen, die unter anderem zur Schmerzwahrnehmung beitragen [4, 17]. Außerdem konnte gezeigt werden, dass die Modulation homöostatischer Regulationsprozesse die Wahrnehmung von Beanspruchungsreaktionen sowie die motorische Leistungsfähigkeit bei anhaltenden motorischen Aufgaben negativ beeinflusste, z. B. durch Hypoglykämie [67], Hyperthermie [66], Dehydration [10], Hypoxie [73] und Schlafentzug [86]. In diesem Zusammenhang wird davon ausgegangen, dass die Interozeption der Beanspruchungsreaktionen über afferente Nervenfasern vermittelt wird, die den mechanischen, thermischen, chemischen, metabolischen und hormonellen Zustand verschiedener Gewebe detektieren. Durch ihre Projektionen zu verschiedenen Hirnarealen (z. B. anteriore Insula, anteriorer zingulärer Kortex) wird eine bewusste Wahrnehmung dieser Reize ermöglicht [22]. Diese Prozesse können als Schutzmechanismus des Körpers interpretiert werden.

Die belastungsinduzierte Perceived Fatigability sowie ihre Determinanten sind bei PmMS weniger gut untersucht. Einige Forschungsgruppen haben jedoch bereits eine Unterscheidung zwischen Trait Fatigue und State Fatigue auf der perzeptuellen Ebene vorgenommen. Beispielsweise haben Karpatkin et al. [48] die akute Veränderung der Ermüdungs-/Erschöpfungswahrnehmung bei PmMS quantifiziert, die einen kontinuierlichen und einen intermittierenden 6-Minuten-Gehtest absolvieren mussten. Sie stellten fest, dass die PmMS beim kontinuierlichen 6-Minuten-Gehtest weniger Strecke zurücklegten und eine höhere belastungsinduzierte Perceived Fatigability aufwiesen. Diese Ergebnisse deuten darauf hin, dass die Quantifizierung der Perceived Fatigability im Rahmen von anhaltenden motorischen Aktivitäten bei PmMS sensitiv für Belastungsvariationen ist. Eine kürzlich veröffentlichte Studie hat ebenfalls die mit der motorischen Aufgabe assoziierte Perceived Fatigability quantifiziert [6]. In dieser Studie mussten PmMS und eine gesunde Kontrollgruppe 20 Minuten auf dem Laufband gehen. Die Autoren haben die Ergebnisse zwar nur deskriptiv beschrieben, aber auf Basis der Mittelwerte kann kein Unterschied in der Perceived Fatigability zwischen den Gruppen festgestellt werden.

Wie oben beschrieben und in **Abbildung 1A** ersichtlich, gibt es verschiedene Wahrnehmungsaspekte, die zur Perceived Fatigability beitragen. Einer der wichtigsten Faktoren ist die Anstrengungswahrnehmung, die bei PmMS während submaximaler motorischer Aufgaben erhöht zu sein scheint [88]. Aufgrund der Tatsache, dass die belastungsinduzierte Anstrengungswahrnehmung das Bewegungsverhalten, die Leistungsreduktion und den Abbruch einer anhaltenden motorischen Aktivität mitbestimmt [54, 82, 91], könnte sie ein wichtiger Kontributor zur erhöhten motorischen Performance Fatigability bei PmMS sein. Eine neuere Studie hat neben der Anstrengungswahrnehmung auch die affektive Valenz bei einem 20-Minuten-Gehtest auf dem Laufband quantifiziert. Leider haben die Autoren diese Ergebnisse nur deskriptiv dargestellt, sodass keine statistisch gesicherte Aussage über die Unterschiede zwischen PmMS und der gesunden Kontrollgruppe vorliegt.

Zusammenfassend kann festgestellt werden, dass die belastungsinduzierte Perceived Fatigability und ihre Determinanten bei PmMS wenig untersucht sind. PmMS können jedoch eine erhöhte Anstrengungswahrnehmung während submaximaler Belastungen aufweisen. Diese wiederum könnte zur stärkeren Ausprägung der Performance Fatigability bei PmMS im Vergleich zu gesunden Menschen beitragen.

Modulierende Faktoren der motorischen Performance Fatigability und Perceived Fatigability

Wie in **Abbildung 1B** zu sehen ist, gibt es diverse modulierende Faktoren, die das Ausmaß der durch anhaltende motorische Aufgaben induzierten motorischen Performance Fatigability und Perceived Fatigability beeinflus-

sen. Auf diese Faktoren wird aufgrund des engen Fokus dieses Beitrages nur selektiv und in geringem Umfang eingegangen.

Im Hinblick auf PmMS haben die krankheitsbezogenen Aspekte, wie z. B. der *MS-Phänotyp,* der *Grad der Behinderung, Medikamente* sowie *Komorbiditäten,* einen Einfluss auf die motorische Performance Fatigability und Perceived Fatigability [88, 94]. Darüber hinaus spielen weitere Charakteristika des jeweiligen Individuums eine Rolle (z. B. *Geschlecht, Alter, Fitness-Status*) sowie die *Art der motorischen Aufgabe* (z. B. Belastungsdauer und -intensität, Kontraktionsform und -geschwindigkeit), die *Umweltbedingungen* (z. B. Temperatur, Sauerstoffverfügbarkeit), der Kontext (z. B. Wettbewerb) als auch akute und chronische Interventionen (z. B. Supplemente, Trainingsmaßnahmen) [31, 38, 44, 46, 85].

Einer der wichtigsten und gut untersuchten Einflussfaktoren für die aufgabenspezifische Ausprägung der motorischen Performance Fatigability ist die Art der motorischen Aktivität. Das ist darin begründet, dass unterschiedliche Bewegungen differente Beanspruchungen der verschiedenen physiologischen Subsysteme mit sich bringen. Im Hinblick auf die motorische Performance Fatigability ist das Ausmaß der Leistungsreduktion sowie der relative Beitrag der Veränderungen der Muskelaktivierung und kontraktilen Funktion von der Belastungsdauer und -intensität, der Kontraktionsform und -geschwindigkeit sowie der eingesetzten Muskelmasse abhängig [44, 45, 62, 69, 85].

Ein genereller Befund ist, dass hochintensive Belastungen von kurzer Dauer primär die kontraktile Funktion einschränken und mit einer geringen Reduktion der Muskelaktivierung einhergehen. Im Gegensatz dazu provozieren niedrigintensive Belastungen eher eine Abnahme der Muskelaktivierung und eine weniger starke Verringerung der kontraktilen Funktion [84, 85, 89]. Diese Intensitätsabhängigkeit ist unter anderem auf muskelmetabolische Faktoren, die sich bei hoch- und niedrigintensiven Belastungen unterscheiden, zurückzuführen (siehe Taylor et al. [84] und Taylor et al. [85] für umfassende Reviews zur Intensitätsabhängigkeit der motorischen Performance Fatigability).

Die Kontraktionsform eines Muskels moduliert ebenfalls den relativen Beitrag neuronaler und muskulärer Faktoren zur Leistungsreduktion nach anhaltenden motorischen Aktivitäten. Konzentrische Kontraktionen induzieren beispielsweise eine stärkere initiale Reduktion der kontraktilen Funktion als exzentrische Kontraktionen. Das kann auf die höhere Metabolitenakkumulation während konzentrischer Muskelarbeit zurückgeführt werden [69, 80]. Dagegen sind exzentrische Muskelaktionen häufig mit mikroskopischen Muskelschäden assoziiert, die die Kontraktionskraft längerfristig beeinträchtigen können [11].

Ein weiterer wichtiger Einflussfaktor ist die Kontraktionsgeschwindigkeit. Es konnte gezeigt werden, dass schnelle konzentrische Kontraktionen eine stärkere Reduktion der kontraktilen Funktion der Muskulatur, aber eine geringere Abnahme der Muskelaktivierung induzieren als langsame. Auch hier werden metabolische Faktoren als Ursache diskutiert [62].

Zudem ist das Ausmaß der eingesetzten Muskelmasse relevant. Es wurde nachgewiesen, dass die Reduktion der kontraktilen Funktion weniger und die der Muskelaktivierung größer ist, je mehr Muskelmasse zur Bewältigung der motorischen Aufgabe erforderlich wird. Es wird spekuliert, dass dieser Befund unter anderem auf das inhibitorische afferente Feedback von Gruppe III und IV Muskelafferenzen zurückzuführen ist, das beim Einsatz größerer Muskelmassen zunimmt [45, 75].

Die verschiedenen Determinanten der Perceived Fatigability unterliegen ebenfalls diversen Einflussfaktoren [57, 92]. Dabei spielen die homöostatischen Regulationsprozesse, die unter anderem stark von der Belastungsintensität abhängig sind, die größte Rolle. Eine Modulation dieser Regulationsprozesse, z. B. durch Supplemente wie Koffein oder diätetisches Nitrat, kann sich jedoch positiv auf die verschiedenen belastungsbegleitenden Wahrnehmungen (z. B. Anstrengungswahrnehmung und belastungsinduzierter Schmerz) auswirken [8, 46]. Darüber hinaus kann die Präsenz externer Stimuli (z. B. verbale Motivation, monetäre Anreize, Rückmeldung über die erbrachte Leistung oder auditive und visuelle Stimuli) sowie interner Stimuli (z. B. Selbstgespräche, Zwischenzielsetzung, Visualisierungsstrategien) die Interpretation sensorischer Signale und somit die Perceived Fatigability beeinflussen [57, 71, 87].

Diskussion und Fazit

Die hier vorgestellte Taxonomie erlaubt es, Trait Fatigue und die belastungsinduzierte State Fatigue bei PmMS besser voneinander abzugrenzen. Dadurch wird das Verständnis von motorisch induzierter State Fatigue bei PmMS befördert und eine eindeutige Charakterisierung des Phänomens möglich. Durch die Dimensionen motorische Performance Fatigability und Perceived Fatigability werden sowohl Veränderungen der motorischen Leistungsfähigkeit als auch der perzeptuellen Qualitäten berücksichtigt. Diese beiden Dimensionen beeinflussen sich gegenseitig, sind nicht separierbar und sollten deshalb simultan quantifiziert werden. Die Auflistung der jeweiligen Determinanten der motorischen Performance Fatigability (Muskelaktivierung und kontraktile Funktion) und der Perceived Fatigability (psychologischer Status und Homöostase) erlaubt eine zielgerichtete Analyse der Ursachen der belastungsinduzierten Veränderungen bei PmMS **(Abb. 1A)**. Dabei müssen jedoch die modulierenden Faktoren berücksichtigt werden **(Abb. 1B)**. Die wichtigsten krankheitsspezifischen Aspekte, wie der MS-Phänotyp sowie der Grad der Behinderung, haben einen großen Einfluss auf die belastungsinduzierte State

Fatigue. Darüber hinaus sind weitere Personencharakteristika von Bedeutung, wie z. B. die Einnahme von Medikamenten und Komorbiditäten.

Im Hinblick auf die Quantifizierung der motorischen Performance Fatigability ist vor allem die Art der motorischen Aufgabe von hoher Relevanz. Das Ausmaß der Leistungsreduktion sowie der relative Beitrag der Veränderungen der Muskelaktivierung und kontraktilen Funktion sind stark von der Belastungsdauer und -intensität, der Kontraktionsform und -geschwindigkeit sowie der eingesetzten Muskelmasse abhängig [44, 45, 62, 69, 85]. Deshalb ist die Auswahl eines geeigneten Belastungsprotokolls zur Quantifizierung der motorischen Performance Fatigability bei PmMS von enormer Bedeutung. Welche Protokolle bis dato verwendet wurden, stellen Broscheid et al. [19] in dieser Ausgabe der Neurologie & Rehabilitation vor. Zur Quantifizierung der zugrundeliegenden Mechanismen der Leistungsreduktion müssen weitere Methoden herangezogen werden. Für die Analyse neuronaler Veränderungen bieten sich z. B. die transkranielle Magnetstimulation, periphere Nervenstimulation, Elektromyographie, funktionelle Nahinfrarotspektroskopie und Elektroenzephalographie an [15, 60, 63, 74]. Die kontraktile Funktion lässt sich lediglich mittels der peripheren Nervenstimulation valide quantifizieren [60]. Es gibt jedoch weitere Methoden, die ein Monitoring muskulärer Veränderungen zulassen. Dazu gehören beispielsweise die muskuläre Nahinfrarotspektroskopie sowie die 31-Phosphor-Magnetresonanzspektroskopie [32, 58].

Neben der Quantifizierung der motorischen Leistung sollten auch perzeptuelle Qualitäten erhoben werden, um ein besseres Verständnis der Interdependenz von motorischer Performance Fatigability und Perceived Fatigability bei PmMS zu generieren. Zu den Kernelementen gehören die Ermüdungs-/Erschöpfungswahrnehmung (Perceived Fatigability), die Anstrengungswahrnehmung, die Motivation, der belastungsinduzierte Schmerz sowie die affektive Valenz. Diese Aspekte haben nachweislich einen Einfluss auf die Leistungsfähigkeit bei anhaltenden motorischen Aufgaben. Zudem spiegeln sie die belastungsinduzierte homöostatische Perturbation in verschiedenen physiologischen Subsystemen wider und sind somit ein Indikator für die körperliche Beanspruchung. Des Weiteren sollten Studien, die Zusammenhangsmaße zwischen Trait Fatigue und belastungsinduzierter State Fatigue bei PmMS quantifizieren wollen, nicht nur die motorische Performance Fatigability, sondern ebenfalls die Perceived Fatigability berücksichtigen. Es könnte möglich sein, dass die perzeptuellen Veränderungen im Rahmen einer anhaltenden motorischen Aufgabe ebenfalls oder eventuell sogar höher mit der subjektiv wahrgenommenen Trait Fatigue von PmMS korrelieren.

Das Wissen um die jeweiligen Determinanten der motorischen Performance Fatigability und Perceived Fatigability erlaubt es, *akute und chronische Interventionen* zielgerichtet zu applizieren. Dadurch können die motorische Kapazität und das psychosoziale Wohlbefinden von PmMS verbessert werden **(Abb. 1C und D)**. Akute Interventionen umfassen beispielsweise *ergogene Supplemente* wie Koffein oder diätetisches Nitrat. Koffein wirkt primär im zentralen Nervensystem und diätetisches Nitrat moduliert hauptsächlich Regulationsprozesse auf Muskelebene. Beide sind jedoch in der Lage, die Leistungsfähigkeit bei submaximalen anhaltenden motorischen Aufgaben zu verbessern und die Anstrengungswahrnehmung sowie die belastungsinduzierte Schmerzwahrnehmung bei gesunden Menschen zu reduzieren [8, 46, 64]. Chronische Interventionen hingegen umfassen die repetitive Applikation von Maßnahmen. Dazu gehören z. B. *pharmakologische Interventionen* [61], *nichtinvasive Hirnstimulation* [68], *neuromuskuläre Elektrostimulation* [3], *physisches Training* [41] und *kognitives Training* [9] **(Abb. 1D)**. Je nach Wirkungsweise der jeweiligen Intervention werden andere Determinanten der motorischen Performance Fatigability und Perceived Fatigability angesprochen und können somit eine Verbesserung der Symptomatik bei PmMS induzieren. Generell könnten multimodale Ansätze vielversprechend sein, die versuchen, verschiedene Determinanten simultan anzusprechen (z. B. die Kombination von motorischem und kognitivem Training).

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Interessenvermerk
Der korrespondierende Autor gibt an, dass kein Interessenkonflikt besteht.

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Quantifizierung motorischer Performance Fatigability bei Multipler Sklerose

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Zusammenfassung

Der Fokus dieser Übersichtsarbeit liegt auf der *motorischen Performance Fatigability* bei Personen mit Multiple Sklerose (PmMS), die die akute Reduktion der physischen Leistungsfähigkeit im Rahmen einer anhaltenden motorischen Aufgabe beschreibt. Das Ziel ist es, einen Einblick in die aktuell genutzten Testprotokolle zur Quantifizierung motorischer Performance Fatigability bei PmMS zu geben. Die bisher genutzten Testprotokolle können in isolierte Muskel- und Ganzkörperbelastungen untergliedert werden. Bei isolierten Muskelbelastungen ist das am häufigsten verwendete Testprotokoll eine isometrisch gehaltene maximale Kontraktion mit definierter Dauer. Der Parameter zur Quantifizierung der motorischen Performance Fatigability ist zumeist die Kraftabnahme, die sich aus dem Verhältnis zwischen maximal willkürlicher initialer und finaler Kraft ergibt. Bei Ganzkörperbelastungen wird vor allem der 6-min-Gehtest verwendet. Hier werden verschiedene Gangvariabilitäts- und Gangstabilitätsmaße zur Beurteilung der Leistungsabnahme herangezogen. Mit den meisten isolierten Muskel- und Ganzkörpertestprotokollen konnte bei PmMS und gesunden Personen ein Leistungsabfall nachgewiesen und zwischen den Gruppen unterschieden werden. Zudem wurde die Bedeutung verschiedener Kontextfaktoren, wie z. B. der Grad der Behinderung oder der MS-Phänotyp, betrachtet. Allerdings ist die Diversität der Testprotokolle groß und somit kein Goldstandard zur Quantifizierung der motorischen Performance Fatigability vorhanden. Für zukünftige Studien ist es entscheidend, zusätzliche Kontextfaktoren zu betrachten und die Veränderung der wahrgenommenen Ermüdung/Erschöpfung *(Perceived Fatigability)* stärker in die Quantifizierung der motorischen Performance Fatigability einzubeziehen.

Schlüsselwörter: Erschöpfung, Ermüdung, Fatigue, Assessment

Einleitung

Bisher haben die uneinheitlichen Taxonomien, die kaum bekannte Ätiologie und die vagen klinischen Beschreibungen die Quantifizierung der Fatigue-Symptomatik bei Personen mit Multipler Sklerose (PmMS) besonders im klinischen Kontext erschwert. Daher ist es nicht überraschend, dass aktuelle Behandlungen unspezifisch sind und zum Teil unbefriedigende Ergebnisse liefern [65].

Im ersten Teil »Taxonomie und Determinanten motorischer Performance Fatigability bei Multipler Sklerose« (Behrens et al. [5]) wurde in Anlehnung an Kluger et al. [40], Enoka und Duchateau [20] sowie Gruet [27] eine aktualisierte Taxonomie für Fatigue vorgeschlagen. Diese erlaubt eine bessere Systematisierung von Fatigue, die den wissenschaftlichen sowie auch klinischen Diskurs vereinfachen kann und die zugrundeliegenden Mechanismen in den Fokus stellt. Die Basis dieser Taxonomie ist zunächst die Unterscheidung zwischen *Trait Fatigue* und *State Fatigue*, wobei Trait Fatigue die Fatigue-Perzeption eines Menschen über einen längeren Zeitraum abbildet, z. B. Wochen und Monate, die relativ stabil ist. Im klinischen Kontext wird diese häufig mittels Fragebögen (z. B. Fatigue-Skala für Motorik und Kognition [55]) erfasst und in primäre (direkt MS-bedingt) sowie sekundäre (bedingt durch Zusatzfaktoren wie z. B. Depressionen und Medikamente) Fatigue eingeteilt [8]. Im Gegensatz dazu bezeichnet State Fatigue akute und transiente Veränderungen, die durch motorische und/oder kognitive Aufgaben induziert werden [3, 16, 25, 46].

In diesem Überblicksbeitrag beziehen wir uns auf State Fatigue, die im Rahmen der Ausführung einer anhaltenden motorischen Aufgabe auftritt. Dabei kann die motorisch induzierte State Fatigue als ein beeinträchtigendes psychophysiologisches Symptom charakterisiert werden, das durch die Abnahme der motorischen Leistungsfähigkeit und/oder die erhöhte Wahrnehmung von Fatigue gekennzeichnet ist. Die akute, durch anhaltende motorische Aufgaben induzierte Reduktion der physischen Leistungsfähigkeit wird dabei als *motorische Performance Fatigability* und die durch motorische Aktivität bedingte Veränderung der Wahrnehmung von Fatigue als *Perceived Fatigability* bezeichnet. Diese beiden Dimensionen der motorisch induzierten State Fatigue sind interdependent und nicht separierbar [20, 27]. Durch die Bezugnahme auf Fatigability ist das Ausmaß der State Fatigue von der Zustandsänderung der

Quantification of motor performance fatigability in multiple sclerosis

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Abstract

This article focuses on motor performance fatigability in people with multiple sclerosis (pwMS), which can be defined as the acute and temporary reduction in physical performance induced by a sustained motor task. Here, we provide an overview of the exercise protocols currently used to quantify motor performance fatigability in pwMS. The protocols used to date can be subdivided into isolated muscle and whole-body exercise protocols. The most commonly used isolated muscle exercise protocol is a sustained isometric maximal voluntary contraction of a defined duration. The parameter used to quantify motor performance fatigability is most often the force decrease, which is the ratio between initial and final maximal voluntary contraction force. For whole-body exercise protocols, the 6-min walk test is most often applied. Here, various gait variability and stability measures are used to assess motor performance fatigability in pwMS. By using isolated muscle and whole-body exercise protocols, a performance decline was demonstrated in pwMS as well as healthy subjects, and a differentiation between groups was possible. In addition, we considered the importance of different contextual factors, such as disability level or multiple sclerosis phenotype. However, the testing protocols used here are heterogeneous; no gold standard for analyzing motor performance fatigability is currently available. Future studies should consider additional contextual factors and should quantify perceived fatigability as well as its determinants. This knowledge could help to comprehensively understand motor performance fatigability in pwMS and to develop specific interventions.

Keywords: exhaustion, MS, fatigue, assessment

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motorischen Performance Fatigability und Perceived Fatigability abhängig. Dadurch wird eine Normalisierung auf die Anforderungen der ausgeführten motorischen Aufgabe und eine klare Abgrenzung von Trait Fatigue möglich (vergleiche **Abbildung 1** in Behrens et al. 2021 [5]).

Ziel dieser Übersichtsarbeit ist es, den aktuellen Stand des Wissens in Bezug auf die Quantifizierung der motorischen Performance Fatigability bei PmMS aufzuarbeiten. Die reliable und valide Quantifizierung der motorischen Performance Fatigability bei PmMS ist essenziell, um Interventionen (z. B. Bewegungstherapien und Medikationen) zu entwickeln, diese zu überprüfen und damit eine Verbesserung der Symptomatik zu schaffen.

Generell weist die motorische Performance Fatigability einen starken Kontextbezug auf und ist unter anderem von den Charakteristika des jeweiligen Menschen (z. B. Geschlecht, Alter, Fitness-Status), der motorischen Aufgabe (z. B. Belastungsdauer und -intensität, Kontraktionsform und -geschwindigkeit), den Umweltbedingungen (z. B. Temperatur, Sauerstoffverfügbarkeit) sowie akuten und chronischen Interventionsmaßnahmen (z. B. Supplemente, Trainingsinterventionen) abhängig [27, 32]. Speziell bei PmMS kommen hier noch weitere Faktoren hinzu, wie der Grad der Behinderung, zumeist wiedergegeben durch die Expanded Disability Status Scale (EDSS) und ihre Subkategorien [41], sowie der Phänotyp der Erkrankung. Letzterer wird je nach Quelle in rezidivierend-remittierende MS (RRMS), sekundär progressive MS (SPMS), primär progressive MS (PPMS) [47] oder in überwiegend schubförmige bzw. überwiegend progressive MS untergliedert [48]. Deshalb ist es in Abhängigkeit von der Zielstellung wichtig, ein adäquates Testprotokoll zur Quantifizierung der motorischen Performance Fatigability zu wählen. In der Vergangenheit wurden sowohl isolierte motorische Aufgaben einer Muskelgruppe als auch komplexe alltagsnähere funktionelle Ganzkörperbewegungen, wie z. B. das Gehen, zur Quantifizierung der motorischen Performance Fatigability genutzt. Für beide Herangehensweisen wird im Folgenden eine Übersicht gegeben.

Verfahren zur Quantifizierung motorischer Performance Fatigability

Isolierte Muskelgruppenbelastungen

In einem Review von Severijns et al. [69] wurden die verschiedenen Methoden zur Quantifizierung der motorischen Performance Fatigability bei PmMS mittels isolierter Muskelgruppenbelastungen zusammengestellt. Diese Belastungsprotokolle haben den Vorteil, dass der Einfluss der kardiorespiratorischen Kapazität auf die motorische Performance Fatigability minimiert wird und spezifische neurophysiologische Techniken appliziert werden können. Für diese Art der Quantifizierung von motorischer Performance Fatigability sind Dynamometer erforderlich, die die Messung der produzierten Kraft oder des generierten Drehmomentes eines Muskels bzw. einer Muskelgruppe ermöglichen (im Folgenden wird nur noch der Begriff Kraft verwendet, auch wenn das Drehmoment gemessen wurde). Bisher wurden zum einen isometrische (gehaltene und intermittierende) sowie zum anderen konzentrische und vor allem isokinetische Kontraktionsformen von Muskeln und Muskelgruppen der unteren sowie oberen Extremitäten verwendet. Beide Kontraktionsformen wurden je nach Zielstellung mit maximaler oder submaximaler Belastungsintensität durchgeführt. In diesem Kontext wird als Parameter zur Quantifizierung der motorischen Performance Fatigability zumeist die Kraftabnahme nach einer motorischen Aufgabe verwendet, die sich aus dem Verhältnis von maximal willkürlicher initialer und finaler Kraft ergibt. Dazu gehören unter anderem der absolute und prozentuale Kraftabfall, die Rate des Kraftabfalls sowie das Integral und die Steigung der Kraft-Zeit-Kurve, die das Ausmaß der motorischen Performance Fatigability beschreiben. Auf Basis dieser Parameter können zusätzlich verschiedene Fatigue-Indizes berechnet werden. Im Folgenden wird ein Überblick über die Studienlage zu den verschiedenen Testprotokollen und Ergebnisparametern gegeben.

Isometrische Testprotokolle

Die meisten Studien zu motorischer Performance Fatigability bei PmMS basieren auf isometrischen gehaltenen maximalen Testprotokollen. Die Dauer der maximal willkürlichen Kontraktion variierte von Studie zu Studie zwischen 15 [1] bis 180 Sekunden [56, 80]. Des Weiteren wurden Belastungsprotokolle ohne definierte Dauer verwendet, die abgebrochen wurden, wenn die Kraftabnahme einen gewissen Schwellenwert erreicht hatte [35]. Grundsätzlich wurde in den Studien nachgewiesen, dass zwischen PmMS und gesunden Kontrollpersonen differenziert werden kann und dass die Kraftleistungsminderung bei PmMS größer war. Bezug nehmend auf die oben herausgestellte Bedeutung des Kontextes haben Steens et al. [73] und Wolkorte et al. [82] mit einem ähnlichen isometrisch gehaltenen maximalen Kontraktionsprotokoll (Dauer 124 Sekunden) des M. interosseus dorsalis PmMS mit RRMS- bzw. SPMS-Phänotyp verglichen. Dabei wurden die letzten sechs Sekunden in Relation zur initialen Maximalkraft gesetzt, um die motorische Performance Fatigability zu beurteilen. Es konnte festgestellt werden, dass PmMS mit SPMS-Phänotyp nach Alterskorrektur einen größeren Kraftabfall aufwiesen als PmMS mit RRMS-Phänotyp. Dies könnte als ein Zeichen der weitaus stärker fortgeschrittenen Schädigung des zentralen Nervensystems betrachtet werden.

Ein anderer interessanter Aspekt ist weiterhin, inwieweit sich die motorische Performance Fatigability zwischen PmMS mit primärer und sekundärer Trait-Fatigue-Symptomatik unterscheidet. Um dies zu überprüfen, verwendeten Andreasen et al. [1] isometrische maximale willkürliche Kontraktionen des M. quadriceps femoris. Das Protokoll war zu Beginn intermittierend und bestand aus achtmal vier Sekunden maximaler Kontraktion mit jeweils zwei Sekunden Pause und wurde anschließend über 15 Sekunden gehalten. Nur zwischen PmMS und gesunden Kontrollpersonen konnte ein Unterschied in Bezug auf die motorische Performance Fatigability aufgezeigt werden, jedoch nicht zwischen PmMS mit primärer oder sekundärer Trait Fatigue-Symptomatik.

Neben den MS-Phänotypen und der Trait Fatigue-Ausprägung ist auch der Grad der Behinderung von zentraler Bedeutung für die Beurteilung der motorischen Performance Fatigability. Mittels eines isometrisch intermittierenden maximalen Belastungsprotokolls der Handgreifmuskulatur wurde nachgewiesen, dass sich der Abfall der maximalen willkürlichen Kraft der leicht betroffenen PmMS (EDSS 1,64 ± 1,02) nicht von dem der gesunden Kontrollpersonen unterschied [34]. Dies weicht von den Ergebnissen aus Untersuchungen sowohl der oberen Extremitäten bei schwerer betroffenen PmMS [63] als auch denen der unteren Extremitäten bei leicht bis schwer betroffenen PmMS [39] ab. Zusammenfassend weist die Datenlage darauf hin, dass die Funktion der oberen Extremitäten im Krankheitsverlauf länger erhalten bleibt. Zudem ist die motorische Performance Fatigability nach maximalen intermittierenden Belastungen zu Beginn der Krankheit weniger im Bereich der oberen Extremitäten als im Bereich der unteren ausgeprägt [80].

Auch Umweltfaktoren, vor allem die Temperatur (Uhthoff-Phänomen), haben bei PmMS einen Einfluss auf motorische Performance Fatigability. Durch eine Erhöhung der Körpertemperatur werden neurologische Symptome bei PmMS zeitweise verstärkt [28]. White et al. untersuchten die Auswirkungen passiver Wärme auf die motorische Performance Fatigability bei PmMS [81]. Dafür trugen die PmMS einen mit Wasser gefüllten Anzug. Das Wasser wurde über 45–60 Minuten auf 46 °C erhitzt, bis die Innentemperatur des Anzugs ca. um 0,6 °C anstieg. Das motorische Testprotokoll bestand aus einer drei Minuten isometrisch gehaltenen maximalen willkürlichen Daumenabduktion, bis die Personen nur noch 50 % der initialen Kraft erbringen konnte. Es wurde sowohl unter normalen Temperaturbedingungen als auch mit erhöhter Temperatur gemessen. Im Rahmen der motorischen Tätigkeit wurde die Veränderung der Fatigue-Wahrnehmung, d. h. die Perceived Fatigability, von den Teilnehmenden mittels visueller analoger Skala (VAS) beurteilt. Bei erhöhter Temperatur erzielten beide Gruppen eine signifikant höhere Perceived Fatigability, wobei diese bei PmMS ausgeprägter war. Durch das Uhthoff-Phänomen erklärbar, war die Perceived Fatigability bei PmMS durch die passive Wärmeeinwirkung allerdings bereits vor der motorischen Aufgabe erhöht. Zusätzlich konnte festgestellt werden, dass die Ausprägung der motorischen Performance Fatigability, also die Abnahme der maximalen willkürlichen Kontraktionskraft, nach Wärmeapplikation bei PmMS größer war.

Auf Basis der dynamometrisch erhobenen mechanischen Parameter können zudem statische und dynamische Fatigue-Indizes für maximale Belastungsprotokolle berechnet werden. Ein statischer Fatigue-Index wurde erstmals von Djaldetti et al. [18] publiziert und beschreibt das Verhältnis zwischen muskulärer Ausdauer während einer 30-sekündigen maximalen willkürlichen Kontraktion und der initialen maximalen willkürlichen Kontraktionskraft. Dieser Index basiert auf der Berechnung der Fläche unter der Kraft-Zeit-Kurve (Integral) über die gesamte isometrisch gehaltene Kontraktionsperiode von 0 bis 30 Sekunden. Das Integral während der 30 Sekunden wird durch das hypothetische Intergral geteilt, das sich ergeben würde, wenn die Person die maximale Anfangskraft während der gesamten 30 Sekunden aufrechterhalten könnte und somit keine motorische Performance Fatigability zeigen würde (statischer Fatigue-Index = 100 % * [1 - (Integral$_{0–30\,s}$/[$F_{max}{}^{0–5\,s}$ * 30 s])]). Der Vorteil des statischen Fatigue-Index ist, dass die maximale Kraft mitberücksichtigt wird. Es konnte gezeigt werden, dass PmMS mit pyramidalen Schädigungen (EDSS) einen höheren statischen Fatigue-Index aufwiesen als PmMS ohne diese Symptomatik. Beide

Subgruppen unterschieden sich zudem von den gesunden Kontrollpersonen.

In den Folgejahren wurden verschiedene Variationen des statischen Fatigue-Index eingeführt. Schwid et al. [64] stellten drei statische Indizes sowie einen dynamischen Fatigue-Index vor, die sich vor allem darin unterschieden, welcher Zeitausschnitt genutzt und ob die Maximalkraft oder das Integral betrachtet wurden. Des Weiteren wurde die Test-Retest-Reliabilität aller Fatigue-Indizes (auch der von Djaldetti et al. [18]) bei PmMS und gesunden Kontrollpersonen überprüft. Zum einen zeigten Schwid et al. [64], dass alle statischen Fatigue-Indizes, besser als der dynamische, eine Leistungsabnahme bei PmMS und gesunden Personen abbilden konnten und dass diese bei PmMS signifikant höher war. Es gab jedoch starke Variationen in der motorischen Performance Fatigability zwischen den untersuchten Muskelgruppen. Die Leistungsabnahme, gemessen anhand der statischen Fatigue-Indizes, unterschied sich im Hinblick auf die Greifmuskulatur, die Knieextensoren, die Dorsalflexoren und die Ellbogenextensoren zwischen PmMS und gesunden Kontrollpersonen. Zum anderen wiesen Schwid et al. [64] nach, dass die integralbasierten Verfahren reliabler sind. Der dynamische Fatigue-Index wies bei beiden Gruppen eine schlechte Reproduzierbarkeit auf, was eventuell an der Handgreifaufgabe und deren Durchführung gelegen haben könnte. Surakka et al. [74] entwickelten einen weiteren integralbasierten statischen Fatigue-Index, der den Zeitpunkt des maximalen Kraftwertes in den initialen fünf Sekunden berücksichtigt. Diese Ergebnisse ergänzen die Daten von Schwid et al. [64] und zeigten erneut, dass integralbasierte Verfahren zur Quantifizierung der motorischen Performance Fatigability der Knieextensoren und -flexoren bei PmMS reliabel sind. Weitere Studien [36–38] griffen diesen Index [74] ebenfalls auf und zeigten vergleichbare Ergebnisse. Die aufgeführten Studien wiesen zudem nach, dass motorische Performance Fatigability vom Behinderungsgrad (EDSS) abhängig ist.

Einige wenige Studien haben auch isometrisch gehaltene/intermittierende submaximale Testprotokolle angewendet. Latash et al. führten z. B. eine 60 Sekunden isometrische gehaltene Kontraktionen von 25 %, 50 %, 75 % und 100 % der maximalen willkürlichen Kontraktionskraft der Knieextensoren durch [44]. Es konnte beobachtet werden, dass es keine Unterschiede zwischen PmMS und gesunden Kontrollpersonen bei 25 % und 50 % der maximal willkürlichen Kontraktionskraft gab. PmMS zeigten aber sowohl bei 75 % als auch bei 100 % und die gesunden Kontrollpersonen erst bei 100 % einen Kraftabfall im Sinne der motorischen Performance Fatigability.

Thickbroom et al. nutzten ein 20 Minuten isometrisch intermittierendes submaximales Testprotokoll (40 % der maximalen willkürlichen Kontraktionskraft) bei einer Zeigefingerabduktion und quantifizierten die Kraftabnahme [75]. PmMS konnten zwar initial weniger Kraft aufbringen als die gesunden Kontrollpersonen, aber in beiden Gruppen wurde nach dem Belastungsprotokoll eine vergleichbare Kraftreduktion erfasst.

Zu einem ähnlichen Ergebnis kamen auch Severijns et al. [68], nur dass die motorische Aufgabe unterschiedlich war (isometrisch gehaltene submaximale Greifaufgabe; Intensität: 15 % und 25 % der maximal willkürlichen Kraft; Gesamtdauer: 18 min) und zur Quantifizierung der motorischen Performance Fatigability ein statischer und ein dynamischer Fatigue-Index [64] herangezogen wurden. Zusätzlich wurde das Ausmaß der Perceived Fatigability, induziert durch die motorische Aufgabe, mittels VAS (0–10) abgefragt. Diese war bei PmMS signifikant größer als bei den gesunden Kontrollpersonen.

Dynamische Testprotokolle

Neben den isometrischen wurden auch dynamische (konzentrische und isokinetische) Muskelkontraktionsprotokolle verwendet, um die motorische Performance Fatigability bei PmMS zu quantifizieren. Der Vorteil isokinetischer Protokolle ist, dass die Bewegung geschwindigkeitsfixiert und somit auch kontrollierter als bei anderen dynamischen Belastungsprotokollen ist. Zudem lassen sich durch diese Protokolle bewegungsgeschwindigkeitsabhängige Veränderungen der motorischen Performance Fatigability abbilden.

Das in diesem Kontext am häufigsten verwendete Protokoll zur Quantifizierung motorischer Performance Fatigability besteht aus der Durchführung einer vorher festgelegten Anzahl maximaler willkürlicher Kontraktionen (25–50) bei einer Winkelgeschwindigkeit von 180 °/s [10, 59]. Zudem gibt es Protokolle, die auf maximalen willkürlichen Kontraktionen basieren und so lange ausgeführt werden, bis ein Kraftabfall auf z. B. 50 % des Maximums erreicht ist [19]. Der am häufigsten berichtete Ergebnisparameter bei maximalen isokinetischen Belastungsprotokollen ist ein Fatigue-Index, der den prozentualen Rückgang der motorischen Leistung vom Beginn bis zum Ende des Protokolls darstellt [10, 59, 76]. Einige Autoren stellen jedoch die Reliabilität dieses Indexes infrage und präferieren die Steigung der Regressionslinie als Maß für den Kraftabfall und damit zur Beurteilung von motorischer Performance Fatigability [10].

In der Vergangenheit wurden reliable isokinetische motorische Performance Fatigability provozierende Testprotokolle für Personen mit verschiedenen neurologischen Beeinträchtigungen vorgestellt [42, 53]. Lambert et al. [42] sowie weitere Autoren [10, 54] postulierten, dass die motorische Performance Fatigability reliabler zu quantifizieren ist, wenn die gemittelte Arbeit über alle Kontraktionszyklen berechnet und nicht nur ein bestimmter Ausschnitt verwendet wird.

Lambert et al. nutzten das Standardprotokoll (180 °/s und 30 Wiederholungen) und konnten nachweisen, dass sowohl der Fatigue-Index der Knieextensoren und

-flexoren als auch die erbrachte mittlere Gesamtarbeit über alle 30 Kontraktionszyklen eine stärkere motorische Performance Fatigability bei PmMS im Vergleich zu gesunden Kontrollpersonen aufdeckten.

Moreau et al. [53] und Boudarham et al. [7] demonstrierten, dass motorische Performance Fatigability ebenfalls reliabel mit 50 konzentrisch intermittierenden maximalen Kontraktionen der Knieextensoren mit einer Winkelgeschwindigkeit von 60 °/s und einem passiven Zurückführen zur Ausgangsposition gemessen werden kann. Hameau et al. [30] wendeten dieses Protokoll bei PmMS an und zeigten, wie auch schon bei den isometrischen Verfahren beschrieben, dass moderat eingeschränkte PmMS (EDSS 4–6) einen höheren Grad an motorischer Performance Fatigability abbildeten als leicht betroffene PmMS (EDSS < 4).

Ganzkörperbelastungen: Gehen

Bei den im vorherigen Kapitel aufgezeigten Testverfahren wurden Belastungsprotokolle für isolierte Muskelgruppen vorgestellt, die ein Dynamometer zur Quantifizierung mechanischer Parameter benötigen und, durch die isolierte motorische Aktivität, keine alltagsnahen Bewegungen abbilden. Die Frage ist, inwieweit diese Erkenntnisse helfen, motorische Performance Fatigability bei komplexen Alltagsbewegungen zu verstehen, die mehrere Muskelgruppen sowie Gelenkkomplexe involvieren und höhere Anforderungen an die kardiorespiratorische Kapazität stellen. Deshalb wurde in der Vergangenheit versucht, alltagsnahe Testverfahren zur Quantifizierung der motorischen Performance Fatigability bei PmMS zu entwickeln. Die wichtigste Alltagsbewegung ist die bipedale Lokomotion, d. h. das Gehen, das erforderlich ist, um sozial integriert zu bleiben und eine hohe Lebensqualität zu erhalten [26, 57]. Allerdings gibt es bisher keinen Goldstandard, um die motorische Performance Fatigability von PmMS beim Gehen zu erfassen. Die Testverfahren zur Bestimmung motorischer Performance Fatigability beim Gehen sind sehr divers in Bezug auf das Setting, d. h. den Untergrund (Laufband vs. freies Gehen), die Dauer und die Zielparameter. Im klinischen Alltag werden vor allem kurze, möglichst kostengünstige und von der Expertise leicht umsetzbare Gehtests verwendet.

Leone et al. [45] haben deshalb, basierend auf dem klinisch etablierten 6-Minuten-Gehtest (6MGT), den Distance-Walked-Index entwickelt. Dieser wird aus der prozentualen Abnahme der Gehstrecke von der 1. zur 6. Minute berechnet. Nimmt die Gehstrecke um mehr als 15 % ab, wird dies als motorische Performance Fatigability bei PmMS bewertet. Diese Multicenter-Studie berücksichtigte nicht nur die Schwere der Erkrankung (EDSS), sondern auch den MS-Phänotyp. Mehr als ein Drittel der PmMS zeigten eine ganginduzierte motorische Performance Fatigability während des 6MGT, wobei die Leistungsabnahme bei stärker eingeschränkten Personen (bis zu 51 %) und bei Personen mit PPMS-/SPMS-Phänotyp (bis zu 50 %) am größten war. In einer neueren Veröffentlichung wurde der Grenzwert auf 10 % reduziert [77].

Phan-Ba et al. [57] führten in ihrer Arbeit den Dezelerationsindex ein. Dieser setzt die Gehgeschwindigkeit auf den letzten 100 m des 500-m-Gehtests zu der Gehgeschwindigkeit beim 25-Fuß-Gehtest mit dynamischem Start ins Verhältnis. Dieses Verhältnis zwischen der langsamsten und schnellsten Gehgeschwindigkeit war nur bei PmMS mit einem EDSS-Score von 4–6, einem pyramidalen oder zerebellären Funktionssystem-Score von 3 (EDSS) oder einer maximal berichteten Gehstrecke ≤ 4.000 m signifikant niedriger. Piérard et al. [58] definierten einen Grenzwert des Dezelerationsindex von 0,8, um auf motorische Performance Fatigability zu schließen. Sie stellten fest, dass PmMS mit einem Dezelerationsindex ≤ 0,8 und in Abhängigkeit vom Grad der Behinderung unterschiedliche Ausprägungen motorischer Performance Fatigability aufwiesen. PmMS mit einem EDSS ≤ 3 zeigten Variationen in der Schrittbreite, die als schlechtere dynamische Balance interpretiert werden kann, und bei PmMS mit einem EDSS > 3 wurde eine Reduktion der Gehgeschwindigkeit festgestellt.

Burschka et al. [11] fokussierten in ihrer Studie auf die Veränderung der Gehgeschwindigkeit beim 6MGT und 12-Minuten-Gehtest als Marker für motorische Performance Fatigability. Im Rahmen ihrer Studie untersuchten sie drei Gruppen: PmMS mit leichter (EDSS 0–3,5) und mittelgradiger Behinderung (EDSS 4–5) sowie eine gesunde Kontrollgruppe. Die Gesunden wiesen einen U-förmigen Verlauf der Gehgeschwindigkeit auf, das heißt, zu Beginn und am Ende war die Gehgeschwindigkeit am höchsten. Die MS-Gruppen zeigten bei beiden Gehtests eine lineare Abnahme der Gehgeschwindigkeit, wobei der Unterschied beim 6MGT bei der MS-Gruppe mit leichter Behinderung nicht signifikant unterschiedlich im Vergleich zu der gesunden Kontrollgruppe war. Weitere Studien wiesen ebenfalls eine signifikante Abnahme der Gehgeschwindigkeit als Indikator für motorische Performance Fatigability beim 6MGT nach, die vor allem die mittel bis schwer eingeschränkten PmMS betraf [21, 71]. Zusätzlich war in diesen Studien eine Abnahme der Schrittlänge, eine Zunahme der Schrittzeit, der bipedalen Phase, Schritt- bzw. Einbeinphasenasymmetrie [21] sowie eine erhöhte Schrittzeit- und bipedale Phasenvariabilität [71] zu beobachten.

Im Gegensatz zu diesen Studien stehen allerdings die Ergebnisse von Shema-Shiratzky et al. [70], die ebenfalls die kinematischen Gangparameter beim 6MGT gemessen haben, um motorische Performance Fatigability zu bestimmen. Dabei wurde jede Minute einzeln betrachtet und die PmMS in Abhängigkeit von der Schwere der Behinderung (EDSS) eingeteilt. Es konnte gezeigt werden, dass sich die Kadenz, die Doppelschrittzeitvariabi-

lität, die Doppelschritt- und Schrittregelmäßigkeit sowie die Gangkomplexität im Verlauf des 6MGT verschlechterten. Allerdings konnte auch herausgestellt werden, dass sich die Gehgeschwindigkeit und die Schwungzeitasymmetrie nicht signifikant veränderten und das auch nicht bei den schwerer betroffenen PmMS.

Abgesehen von diesen im klinischen Alltag bereits genutzten linearen Verfahren gibt es noch weitere nichtlineare Ansätze zur Ganganalyse. Zyklische Bewegungen, wie z. B. das Gehen, sind dynamische Systeme. Um motorische Performance Fatigability zu quantifizieren, wird überprüft, wie stabil/instabil (chaotisch) das System ist und wie sich dieser Zustand über den Verlauf der motorischen Aufgabe verändert. Der Vorteil gegenüber den linearen Verfahren ist, dass die Dynamik der kontinuierlichen Bewegung und deren Fluktuationen zur Bestimmung der Gangstabilität genutzt werden [50].

Eine nichtlineare Methode der Ganganalyse ist die Berechnung der lokalen dynamischen Stabilität [17], die auch zur Charakterisierung der motorischen Performance Fatigability herangezogen werden kann. Auf der Grundlage von 3-D-Beschleunigungsdaten wird der größte Lyapunov-Exponent bestimmt. Der Lyapunov-Exponent ist in einem dynamischen System ein Stabilitätsmaß und beschreibt, inwieweit sich zwei Trajektorien (hier Gangzyklen) über die Zeit annähern oder auseinanderentwickeln. Wird der Lyapunov-Exponent größer, wird das System instabiler [62]. Dieses Verfahren wird allerdings sehr kontrovers diskutiert, da bisher keine Einigung über die Platzierung der Sensoren (Füße, Rumpf), das Setting der Messung (Laufband, ebener Boden) und das Berechnungsverfahren gefunden wurde [29]. Nichtsdestotrotz wurde die lokale dynamische Stabilität für jede Minute des 6MGT bei PmMS und einer gesunden Kontrollgruppe berechnet [2]. Es konnte nachgewiesen werden, dass in den ersten drei Minuten kein signifikanter Unterschied zwischen beiden Gruppen existierte. In den letzten drei Minuten wiesen allerdings 60 % der PmMS ein instabiles Gangverhalten auf, das als motorische Performance Fatigability interpretiert wurde.

Eine weitere nichtlineare Methode ist der Fatigue-Index Kliniken Schmieder [67], der auf der Attraktor-Methode basiert [50]. Auch hier wird auf der Grundlage von 3-D-Beschleunigungsdaten eine Art Mittelwert aller Gangzyklen (Limit-Cycle Attraktor) und deren Variabilität berechnet. Für den Fatigue-Index Kliniken Schmieder wird die relative Veränderung dieser Limit-Cycle Attraktoren (deltaM) und der Variabilität der Gangzyklen um diese Attraktoren (deltaD) zwischen zwei Messzeitpunkten in Relation gesetzt. In der konkreten Umsetzung gehen die PmMS mit Wohlfühlgeschwindigkeit plus 10 % bis zu 60 Minuten oder bis zu einem Erschöpfungsgrad von 17 auf der Borg Skala [6] auf dem Laufband. Die erste Minute wird dann mit der letzten verglichen. Nur wenn beide Faktoren deltaM und deltaD sich deutlich verändern, wird dies als motorische Performance Fatigability interpretiert (Grenzwert ≥ 4). Bisher gibt es jedoch nur vereinzelte Studien, die den Fatigue-Index Kliniken Schmieder in diesem Kontext angewendet haben [15, 66].

Diskussion

Isolierte Muskelgruppenbelastungen

Zusammenfassend kann konstatiert werden, dass die Quantifizierung motorischer Performance Fatigability im Rahmen isolierter Muskelgruppenbelastungen am häufigsten mittels isometrisch gehaltener maximaler willkürlicher Kontraktionen erfasst wurde. Dies liegt vermutlich darin begründet, dass diese Protokolle gut standardisierbar sind, sodass die motorische Performance Fatigability schnell induziert und als Kraftabfall quantifiziert werden kann [72]. Zudem hat es sich als vorteilhaft erwiesen, eine vordefinierte Belastungsdauer zu nutzen und nicht die Kraftabnahme bis zu einem gewissen Prozentsatz der maximalen willkürlichen Kraft. Bei Letzterem spielen vor allem psychometrische Faktoren eine größere Rolle, die einen zusätzlichen Einfluss haben und die Reliabilität der Ergebnisse beeinflussen können [60]. Generell ist aber die Diversität der Belastungsdauer ein Problem, um eine Aussage über motorische Performance Fatigability bei PmMS treffen zu können. Je nach Intensität und Dauer der Kontraktion können der motorischen Performance Fatigability verschiedene Mechanismen zugrunde liegen [43, 82].

Weiterhin haben Studien gezeigt, dass die verschiedenen Fatigue-Indizes, die sich auf das Verhältnis der Kraftwerte am Anfang und Ende einer Kontraktion stützen, keine zufriedenstellende Reliabilität aufweisen [64, 74]. Dies ist wahrscheinlich auf die hohe Variabilität der Kraftwerte gegen Ende der Kontraktion zurückzuführen [14]. Im Gegensatz dazu haben sich integralbasierte Verfahren als reliabler herausgestellt [64, 74].

Zudem ist die Belastungsintensität der Testprotokolle wichtig. Anhand der aufgeführten isometrisch gehaltenen/intermittierenden submaximalen Protokolle wurde aufgezeigt, dass mit zu niedriger Belastungsintensität keine motorische Performance Fatigability induziert wird, unabhängig vom Grad der Behinderung oder des MS-Phänotyps [44, 68, 75]. Zu kritisieren ist allerdings, dass die Testprotokolle sehr kurz waren und eventuell die Belastungsdauer nicht ausreichend war, um motorische Performance Fatigability zu provozieren.

Es wurden jedoch nicht nur isometrische, sondern auch vereinzelt isokinetisch konzentrische maximale Belastungsprotokolle verwendet. Diese dynamischen Protokolle haben den Vorteil, dass sie den Kontraktionsformen, die im Alltag relevant sind, näher kommen als isometrische Kontraktionen [79]. Sie benötigen jedoch eine verhältnismäßig teure apparative Ausstattung.

Wie im ersten Teil »Taxonomie und Determinanten motorischer Performance Fatigability bei Multipler Skle-

rose« (Behrens et al. [5]) dargestellt, wird das Ausmaß der motorischen Performance Fatigability nach anhaltenden physischen Aktivitäten durch die Reduktion der Muskelaktivierung und kontraktilen Funktion determiniert. Die relativen Beiträge der neuronalen und muskulären Faktoren zur Leistungsabnahme können durch verschiedene neurophysiologische Techniken aufgeklärt werden, die sich methodisch am besten bei isolierten Muskelgruppenbelastungen umsetzen lassen. Durch die Nutzung der transkraniellen Magnetstimulation und peripheren elektrischen Nervenstimulation in Kombination mit der Dynamometrie und Elektromyographie lassen sich Veränderungen der Muskelaktivierung und kontraktilen Funktion sehr gut quantifizieren [4, 52]. Alternativ und/oder komplementär können weitere Techniken zum Monitoring neuronaler und muskulärer Veränderungen während anhaltender motorischer Aufgaben genutzt werden. Zur Quantifizierung von kortikalen Aktivitätsänderungen während anhaltender motorischer Aufgaben kann die funktionelle Nahinfrarotspektroskopie (NIRS) eingesetzt werden [61]. Sollen zusätzlich subkortikale Strukturen untersucht werden, bietet sich die funktionelle Magnetresonanzspektroskopie an [23]. Veränderungen in der Arbeitsmuskulatur lassen sich mit der muskulären NIRS abbilden [22]. Soll der Energiestoffwechsel im Detail untersucht werden, kann z. B. auf die 31-Phosphor-Magnetresonanzspektroskopie zurückgegriffen werden [51].

Ganzkörperbelastung: Gehen

Bei den Ganzkörperbelastungen fokussieren die meisten Testverfahren auf die Veränderung des Gehverhaltens beim 6MGT, der im klinischen Setting bereits vielfältig genutzt wird. Mit den verschiedenen Herangehensweisen konnten Veränderungen der Gangsymmetrie, der Gehgeschwindigkeit und einzelner spatio-temporaler Parameter sowie deren Variabilität nachgewiesen werden. Zum Teil sind die Ergebnisse allerdings widersprüchlich und werfen damit die Frage auf, ob die Abnahme der Gehgeschwindigkeit über den 6MGT ein aussagekräftiger Parameter zur Quantifizierung der motorischen Performance Fatigability ist [45, 70]. Durch Kompensationsmechanismen, wie z. B. des Oberkörpers [49], kann die Geschwindigkeit vereinzelt aufrechterhalten werden, auch wenn deutliche motorische Performance Fatigability vorliegt. Des Weiteren besteht die Möglichkeit, dass sich die motorische Performance Fatigability sehr divers auf die motorische Aufgabe auswirkt. Deshalb ist ein einzelner kinematischer Parameter, wie z. B. die Gehgeschwindigkeit, nicht ausreichend, um motorische Performance Fatigability zu quantifizieren.

Einige Studien, die nichtlineare dynamische Ansätze verwendet haben, konnten ebenfalls die motorische Performance Fatigability parametrisieren. In diesem Kontext ist jedoch anzumerken, dass diese Verfahren zeitlich aufwendig sind (Fatigue-Index Kliniken Schmieder), bisher keine Einigkeit zum optimalen Setting existiert (Laufband vs. freies Gehen) und die Verfahren aufgrund fehlender Vereinfachung in der Anwendung nicht problemlos im klinischen Setting durchgeführt werden können.

Insgesamt kann in Bezug auf die vorgestellten Verfahren zur Bestimmung der motorischen Performance Fatigability mittels Ganganalyse festgestellt werden, dass die Probanden zumeist ohne eine notwendige Gewöhnungsphase aus dem Stand starten. Diese ist nur bei der Bestimmung des Dezelerationsindex mit dynamischem Start vorgesehen. Es ist bekannt, dass dynamische Systeme gerade am Anfang wesentlich größere Oszillationen aufweisen und erst mit einer gewissen Einschwingzeit stabil werden. Dieses Phänomen wird auch als Transienteneffekt bezeichnet [78]. Folglich wäre es interessant, die oben beschriebenen Ansätze zur Ganganalyse mit einem dynamischen Start zu überprüfen und/oder die zweite mit der letzten Minute beim Gehen zu vergleichen.

Die genaue Quantifizierung der neuronalen und muskulären Beiträge zur motorischen Performance Fatigability beim Gehen gestaltet sich schwieriger als bei Belastungen isolierter Muskelgruppen. Unter Nutzung neurophysiologischer Techniken, wie z. B. der peripheren elektrischen Nervenstimulation, und der Dynamometrie könnten ganginduzierte Veränderungen in der Muskelaktivierung und kontraktilen Funktion durch einen Prä-/Post-Vergleich abgebildet werden. Das ist jedoch methodisch aufwendig und nur schwer umsetzbar. Zudem sind die neuronalen und vor allem muskulären Veränderungen durch anhaltende motorische Aufgaben sehr flüchtig und könnten nicht valide erfasst werden [24, 33], da die Probanden nach dem Gehprotokoll auf ein Dynamometer transferiert werden müssten.

Abgeleitet aus den zuvor genannten Argumenten zur mechanistischen Aufklärung der motorischen Performance Fatigability bieten alternative Techniken, wie z. B. die funktionelle NIRS, valide Möglichkeiten zur Quantifizierung kortikaler Aktivitätsveränderungen während einer anhaltenden Gehaufgabe. Im Vergleich zur Elektroenzephalographie ist die funktionelle NIRS robust gegenüber Bewegungsartefakten und erlaubt das Monitoring verschiedener am Gang beteiligter Gehirnareale (z. B. präfrontaler Cortex, motorische und sensorische Cortices). Bei PmMS wurde bisher vor allem die Aktivierung des präfrontalen Cortex beim einfachen Gehen und Gehen mit Zusatzaufgabe mittels funktioneller NIRS untersucht [12, 31]. Zudem konnte die Inter-Session-Reliabilität der funktionellen NIRS für ausgewählte Parameter während des einfachen Gehens bei PmMS nachgewiesen werden [9].

Zusammenfassend kann festgestellt werden, dass sowohl mit isolierten Muskelgruppen- als auch Ganz-

körperbelastungen Veränderungen in der Leistungsfähigkeit gemessen und zwischen PmMS und gesunden Kontrollpersonen unterschieden werden konnte. Allerdings existieren zahlreiche Belastungsprotokolle und es herrscht Uneinigkeit darüber, welche Parameter in den unterschiedlichen Settings die höchste Aussagekraft im Hinblick auf die Quantifizierung der motorischen Performance Fatigability haben. Einigkeit herrscht hingegen darüber, dass sowohl der mittels EDSS oder Teilaspekten des EDSS (z. B. pyramidale Schädigungen) bestimmte Behinderungsgrad, der MS-Phänotyp (RRMS, SPMS, PPMS bzw. überwiegend schubförmige, überwiegend progressive MS) als auch auch Umweltfaktoren (z. B. Temperatur [Uhthoff-Phänomen]) eine entscheidende Rolle in der Beurteilung der motorischen Performance Fatigability spielen und bei Messungen zwingend beachtet werden sollten.

Fazit

In dieser Übersichtsarbeit wird verdeutlicht, dass mit maximalen isolierten Muskel- bzw. Muskelgruppenbelastungen die motorische Performance Fatigability provoziert und damit zwischen PmMS und gesunden Personen differenziert werden kann. Die Befunde sind hinsichtlich der Ganzkörperbelastung Gehen heterogener. Das könnte unter anderem daran liegen, dass die Belastungsintensität beim Gehen häufig nicht ausreichend ist, um motorische Performance Fatigability zu induzieren. Dies wird sehr wahrscheinlich insbesondere bei PmMS der Fall sein, die einen geringen Grad der Behinderung und eine gute körperliche Verfassung aufweisen.

In der Zukunft sollte überprüft werden, ob alternative Ganzkörpertestprotokolle besser geeignet sind, um die motorische Performance Fatigability bei PmMS abzubilden. Dafür bieten sich z. B. fahrradergometrische Verfahren an, die ein Monitoring der mechanischen Leistung ermöglichen [13]. Damit könnten verschiedene Belastungsintensitäten in Relation zur maximalen Leistungsfähigkeit appliziert und auf ihre Aussagekraft zur Quantifizierung der motorischen Performance Fatigability bei PmMS überprüft werden. Aufgrund der starken Alltagsrelevanz des Gehens ist es dennoch wichtig, die existierenden Testprotokolle weiterzuentwickeln und neben der Geschwindigkeit verstärkt Gangvariabilitäts- und Gangstabilitätsmaßen zu quantifizieren.

Unabhängig vom gewählten Belastungsprotokoll ist es unerlässlich, Kontextfaktoren mit in die Betrachtung aufzunehmen und den Einfluss der eng verknüpften Perceived Fatigability intensiver zu untersuchen. Dafür sollten die wahrgenommene Ermüdung/Erschöpfung sowie ihre wichtigsten Einflussfaktoren sowohl vor und nach als auch während der Belastung quantifiziert werden. Diese werden in dieser Ausgabe der Neurologie & Rehabilitation von Behrens et al . [5] näher erläutert.

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REVIEW ARTICLE

Fatigue and Human Performance: An Updated Framework

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Abstract

Fatigue has been defined differently in the literature depending on the field of research. The inconsistent use of the term fatigue complicated scientific communication, thereby limiting progress towards a more in-depth understanding of the phenomenon. Therefore, Enoka and Duchateau (Med Sci Sports Exerc 48:2228–38, 2016, [3]) proposed a fatigue framework that distinguishes between trait fatigue (i.e., fatigue experienced by an individual over a longer period of time) and motor or cognitive task-induced state fatigue (i.e., self-reported disabling symptom derived from the two interdependent attributes performance fatigability and perceived fatigability). Thereby, performance fatigability describes a decrease in an objective performance measure, while perceived fatigability refers to the sensations that regulate the integrity of the performer. Although this framework served as a good starting point to unravel the psychophysiology of fatigue, several important aspects were not included and the interdependence of the mechanisms driving performance fatigability and perceived fatigability were not comprehensively discussed. Therefore, the present narrative review aimed to (1) update the fatigue framework suggested by Enoka and Duchateau (Med Sci Sports Exerc 48:2228–38, 2016, [3]) pertaining the taxonomy (i.e., cognitive performance fatigue and perceived cognitive fatigue were added) and important determinants that were not considered previously (e.g., effort perception, affective valence, self-regulation), (2) discuss the mechanisms underlying performance fatigue and perceived fatigue in response to motor and cognitive tasks as well as their interdependence, and (3) provide recommendations for future research on these interactions. We propose to define motor or cognitive task-induced state fatigue as a psychophysiological condition characterized by a decrease in motor or cognitive performance (i.e., motor or cognitive performance fatigue, respectively) and/or an increased perception of fatigue (i.e., perceived motor or cognitive fatigue). These dimensions are interdependent, hinge on different determinants, and depend on body homeostasis (e.g., wakefulness, core temperature) as well as several modulating factors (e.g., age, sex, diseases, characteristics of the motor or cognitive task). Consequently, there is no single factor primarily determining performance fatigue and perceived fatigue in response to motor or cognitive tasks. Instead, the relative weight of each determinant and their interaction are modulated by several factors.

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Key Points

Motor or cognitive task-induced state fatigue can be defined as a psychophysiological condition characterized by a decrease in motor or cognitive performance (i.e., motor or cognitive performance fatigue, respectively) and/or an increased perception of fatigue (i.e., perceived motor or cognitive fatigue).

Performance fatigue and perceived fatigue are interdependent, hinge on different determinants, and depend on several modulating factors (e.g., age, sex, diseases, characteristics of the motor or cognitive task).

The combined monitoring of performance fatigue and perceived fatigue measures as well as the investigation of the underlying mechanisms will help to unravel the interactions between the different dimensions of fatigue and their impact on human performance. This will contribute to assess the relative weight of each determinant and their interactions depending on several modulating factors.

1 Introduction

The capacity to maintain intense and/or sustained motor and cognitive tasks is important in human life and is required during daily, physical, vocational, and educational activities. The multitude of psychophysiological processes that inevitably accompany motor or cognitive activity above a certain intensity or duration can become a limiting factor for motor as well as cognitive performance and are typically summarized under the umbrella term fatigue. In the past, a variety of disciplines (e.g., psychology, exercise physiology, neuroscience, medical fields) have specialized on selected aspects investigating either the subjective perception of fatigue or changes in motor or cognitive performance [1–5]. Due to this fragmentation, a multitude of fatigue definitions emerged leading to an inconsistent use of the term and neglecting the dynamic interactions between the task-induced psychophysiological adjustments and the resulting perceptual, affective, and cognitive responses. Therefore, mechanistic insights into the psychophysiological processes associated with fatigue in healthy and clinical populations as well as the development of effective interventions were hampered [2, 3]. This is not only crucial to increase the performance of athletes and healthy people, but it is also important for vulnerable, deconditioned, as well as clinical populations due to fatigue-induced negative effects on the motor and cognitive capacity as well as quality of life.

To resolve the ambiguity of fatigue definitions, Enoka and Duchateau [3] proposed a framework defining fatigue as a self-reported disabling symptom that limits physical and cognitive functions due to interactions between performance fatigability (i.e., decrease in an objective performance measure) and perceived fatigability (i.e., changes in the sensations that regulate the integrity of the performer). Both performance fatigability and perceived fatigability depend on several factors that determine the decline in motor performance (i.e., muscle activation and contractile function) as well as the changes in the individuals's sensations (i.e., the psychological and homeostatic state of the individual). In their framework, the authors highlighted the interdependence of performance fatigability and perceived fatigability with both contributing to the self-reported symptom fatigue. The advantage of this framework is its applicability to both healthy and clinical populations, since it refers to the fatigue mechanisms whose relative weight is subject- and task-dependent.

Although the fatigue framework suggested by Enoka and Duchateau [3] served as a good starting point to unravel the psychophysiology of fatigue induced by motor and cognitive tasks, several important aspects were not included and discussed (e.g., effort perception, affective valence, self-regulation). Moreover, the authors' definition of fatigue comprised also a decline in cognitive performance, which was not adequately embedded in their framework in terms of the taxonomy and the underlying mechanisms. Finally, the interdependence of the mechanisms driving performance fatigability and perceived fatigability as well as the need to thoroughly quantify these aspects were not comprehensively discussed.

Therefore, the present narrative review aimed at (1) updating the framework and definition of fatigue proposed by Enoka and Duchateau [3] pertaining the taxonomy (i.e., cognitive performance fatigue and perceived cognitive fatigue were added) and important determinants that were not considered previously (i.e., effort perception, affective valence, self-regulation, and time perception), (2) discussing the mechanisms driving performance fatigue and perceived fatigue in response to motor and cognitive tasks as well as their interdependence, and (3) providing recommendations for future research on these interactions.

2 Taxonomy of Fatigue

To precisely define fatigue, it is first important to differentiate between trait fatigue and state fatigue. Trait fatigue describes the fatigue experienced by an individual over a longer period of time (e.g., weeks and months), which is

relatively stable. Trait fatigue is a symptom associated with many diseases (e.g., multiple sclerosis, chronic obstructive pulmonary disease, rheumatoid arthritis) and is a result of primary disease-related mechanisms (e.g., neurodegeneration, inflammation) as well as secondary mechanisms not directly caused by the disease but associated with it (e.g., depression, sleep problems, medication) [2, 6–8]. However, trait fatigue can also be present in a milder form in healthy people [9].

Activity-induced state fatigue, in turn, is characterized by an acute and temporary change in motor or cognitive performance as well as the subjective experience of weariness or exhaustion that occur in the context of a specific motor or cognitive task [3, 7, 10–12]. Inspired by the definition of fatigue proposed by Enoka and Duchateau [3], we suggest to define motor and cognitive task-induced state fatigue as a psychophysiological condition that is characterized by a decrease in motor or cognitive performance and/or an increased perception of fatigue. The acute reduction in motor and cognitive performance can be labeled as motor and cognitive performance fatigue, respectively. While motor performance fatigue (e.g., decrease in maximal voluntary force) depends on factors contributing to muscle activation and contractile function, the precise origin of cognitive performance fatigue (e.g., decrease in reaction time) remains disputed, but may depend on the integrity of the central nervous system. The motor and cognitive task-induced modulation of the perception of fatigue can be termed perceived motor and cognitive fatigue, respectively, which depend on the psychophysiological state of the individual. Motor and cognitive performance fatigue as well as perceived motor and cognitive fatigue further depend on factors related to body homeostasis, are interdependent, and hinge on different determinants (Fig. 1a). Thereby, the extent of motor and cognitive performance fatigue as well as perceived motor and cognitive fatigue depends on several modulating factors (e.g., characteristics of the subject and the task) (Fig. 1b) and can have detrimental effects on the motor and cognitive capacity of humans. In the long term, this can result in a reduced quality of life, particularly in vulnerable, deconditioned, and clinical populations (Fig. 1c) [3, 7].

Of note, this definition slightly differs from the taxonomy provided by Enoka and Duchateau [3], who have defined state fatigue as a self-reported disabling symptom derived from the interdependent attributes performance fatigability and perceived fatigability. However, this definition introduces the problem that state fatigue is assessed by self-report, which is also reflected by quantifying perceived fatigability (i.e., the task-induced rate of change in perceived fatigue [13]). In addition, performance may decrease without a corresponding increase in the perception of fatigue or vice versa. This potential selective change is not captured by the definition of Enoka and Duchateau [3]. In addition, since we do not refer to state fatigue as a self-reported disabling symptom, the term fatigability does not seem to be necessary as it does not contribute any benefit compared to the term fatigue. In fact, the term fatigue was also formerly used to describe a decrease in performance (e.g., muscle fatigue, cognitive fatigue), physiological function (e.g., central fatigue, peripheral fatigue), or an increase in the perception of fatigue (e.g., mental fatigue) [1, 10, 14–18]. The terms fatigability and fatigable could, however, be used synonymously as linguistic variations (e.g., when subjects have a high-performance fatigability or persons are highly fatigable). Of note, in the following paragraphs, the proposed fatigue taxonomy was applied, even when the cited studies have not used this terminology.

The psychophysiological alterations during fatiguing motor exercise can be interpreted as a protective mechanism that regulate exercise behavior to ensure the preservation of homeostasis of various physiological systems in the human body [15, 19, 20].

This is in contrast to fatigue resulting from sustained cognitive tasks, the psychophysiological underpinnings of which remain unclear. While some have proposed that the ultimate function of cognitive fatigue would be to redirect behavior from the current to more rewarding and/or less effortful activities [21, 22], others have argued, in closer agreement with motor fatigue, that it is a protective mechanism urging people to stop the present activity in anticipation of future adverse, functional consequences [23, 24].

3 Motor Performance Fatigue and Perceived Motor Fatigue

3.1 Motor Performance Fatigue

Motor performance fatigue (traditionally termed muscle or neuromuscular fatigue) can be quantified as a decrease in maximal voluntary force production capacity of the neuromuscular system, which is determined by neural and muscular factors [3]. Depending on the characteristics of the motor task (e.g., duration, intensity) and other factors (e.g., age, sex, diseases, fitness level), the underlying mechanisms of motor performance fatigue include changes at distinct levels within the neuromuscular system that are involved in muscular force production and thus movements. These include, but are not limited to: (1) excitability of the motor cortex, (2) descending corticospinal transmission of action potentials, (3) excitability of spinal α-motoneurons, (4) neuromuscular transmission, (5) sarcolemmal excitability, (6) propagation of action potentials into the transverse tubular system, (7) intracellular calcium ion (Ca^{2+}) kinetics, and (8) force production within the cross-bridge cycle [14, 25, 26]. Intense and/or sustained motor tasks can impair these

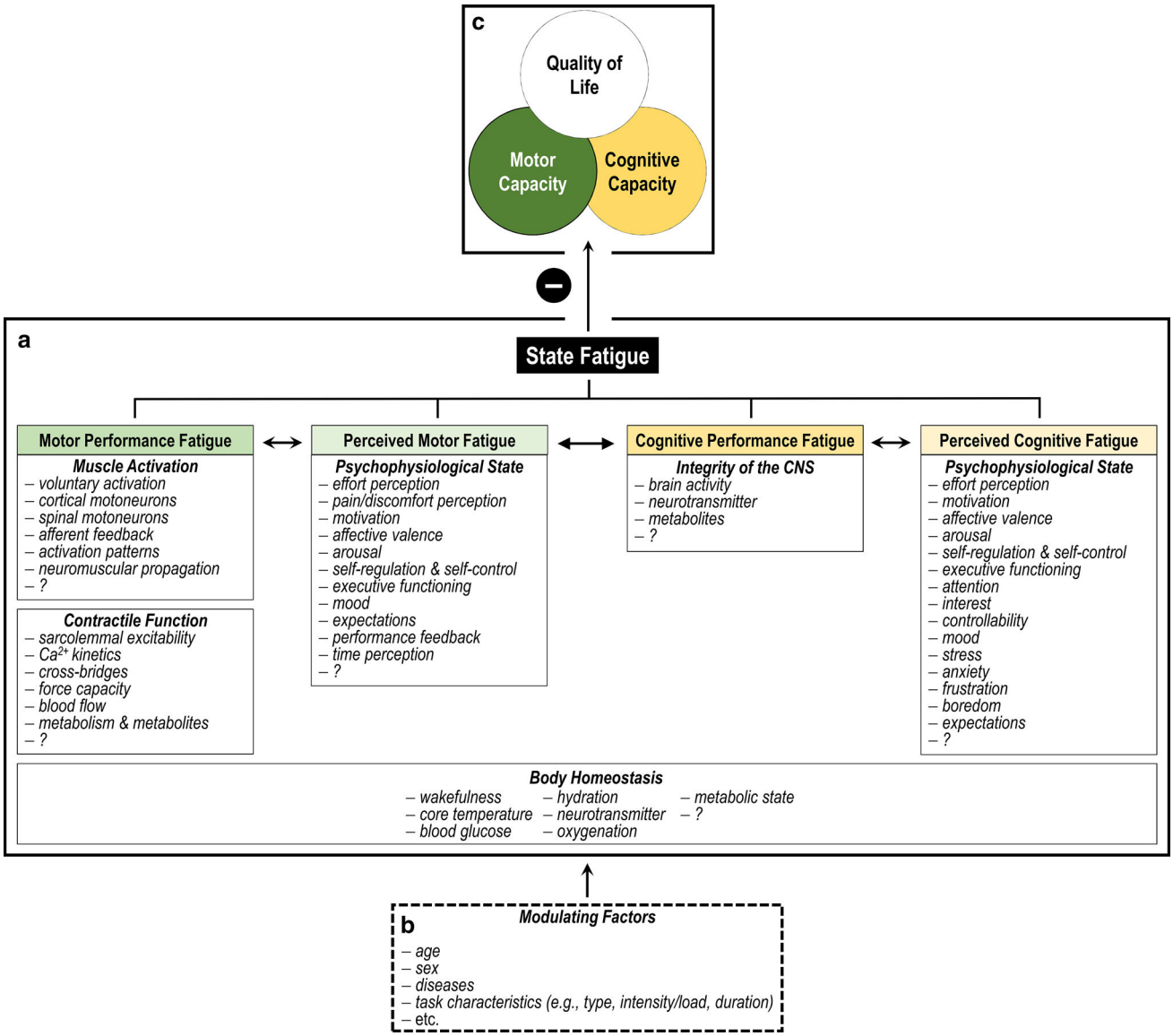

Fig. 1 Adapted motor and/or cognitive task-induced state fatigue framework with its interdependent dimensions and the respective determinants first proposed by Enoka and Duchateau [3] (**a**). The extent of state fatigue mirrored by these dimensions depends on several modulating factors (**b**) and can have negative consequences for the motor and cognitive capacity, which might negatively affect quality of life (**c**) particularly in vulnerable, deconditioned, and clinical populations. The bidirectional arrows indicate the interdependence between all dimensions. Please note that effort perception, affective valence, self-regulation and self-control, as well as time perception were added to the potential determinants of perceived motor fatigue compared to the framework of Enoka and Duchateau [3]. Furthermore, cognitive performance fatigue, perceived cognitive fatigue, and the potentially contributing factors were added to the framework. *CNS* central nervous system, *?* unknown factors that should be added in the future

physiological processes, which in turn, can contribute to a reduced motor performance. To determine the origin of these changes within the neuromuscular system, a distinction between neural (central) and muscular (peripheral) determinants of motor performance fatigue has been established. Neural determinants include aspects related to muscle activation (traditionally termed central fatigue) that can change during a motor task (Fig. 1a). These changes comprise decrements in voluntary activation of individual muscles associated with modulations in cortical motoneurons and/or spinal α-motoneurons. The exercise-induced neural as well as muscular alterations lead to task-specific adaptations in the firing frequency and/or recruitment of motor units. In this context, various processes play a role including the modulation of intrinsic properties of motoneurons, an increase in inhibitory afferent feedback from group III and IV muscle afferents, a decrease in facilitatory afferent feedback, and changes in neuromodulators [16]. In addition,

activation patterns of synergistic and antagonistic muscles can change during a fatiguing motor task, which in turn can negatively affect intermuscular coordination and thus force production capacity [27, 28].

Beside these neural determinants, changes in the contractile function of muscles can contribute to the extent of motor performance fatigue (Fig. 1a). The impairment of contractile function largely depends on muscle perfusion and the intramuscular metabolism. For instance, intense motor tasks lead to an increased accumulation of metabolites (e.g., inorganic phosphate, reactive oxygen species, hydrogen ions) that can impair contractile function of muscles. Under physiological conditions, inorganic phosphate seems to be primarily responsible for the reduction in contractile function, while reactive oxygen species seems to be involved in the prolonged force depression after exercise [25, 26, 29, 30]. The main factors that determine the decrease in contractile function and thus the contractile force of muscles are reductions in sarcolemmal excitability, Ca^{2+} release from the sarcoplasmic reticulum, myofibrillar Ca^{2+} sensitivity, and the force-generating capacity of the cross-bridges per se [3, 14, 25, 26, 31]. Importantly, the decrease in muscle activation and/or contractile function of muscles during and after exercise is sensitive to different homeostatic perturbations like hyperthermia [32], hypoxia [33], and hypoglycemia [34].

3.2 Perceived Motor Fatigue

Perceived motor fatigue refers to the increase in the subjective perception of fatigue emerging during a motor task that can affect motor task performance [5, 13]. It is often defined as a transient sensation of tiredness, weariness, lack of energy, or exhaustion [35, 36]. Recently, it was proposed to define perceived fatigue as the feeling of a need to rest or a mismatch between effort expended and actual performance [36].

Irrespective of the specific definition, the nature and extent of perceived motor fatigue depend on the psychophysiological state of the individual, which shapes the perceptual, affective, and cognitive processes during exercise (Fig. 1a). For example, exercising above an individual critical threshold (e.g., above critical power [37]) leads to metabolite accumulation resulting in a decline in contractile function of muscles [26]. Therefore, an increased muscle activation signal is necessary to maintain the submaximal force output, which is associated with an increased effort perception [38]. Besides this, exercise-induced pain and discomfort arise as a result of the enhanced metabolite accumulation, breathing rate, and body temperature [39]. These perceptual responses to exercise make a person feel increasingly bad and require regulatory cognitive processes to avoid slowing down or stopping the motor task [5, 40, 41]. Recently, Venhorst et al. [5] proposed a three-dimensional dynamical system framework to better understand these psychophysiological determinants of perceived motor fatigue. It allows the classification of some of the determining factors of perceived motor fatigue into three dimensions. Following this framework, the perceptual responses to exercise (e.g., effort perception, exercise-induced pain/discomfort perception) can be attributed to (1) the perceptual-discriminatory dimension. The intensity of these perceptions has an impact on (2) the affective-motivational dimension (e.g., affective valence, arousal, motivation). The motor task-induced changes in these dimensions strongly determine the processes in (3) the cognitive-evaluative dimension related to the decision to slow down or speed up (pacing behavior) or even to disengage from exercise. These processes involve, for instance, self-regulation, self-control, and executive functioning (Fig. 2). This three-dimensional dynamical system framework allows the comprehensive as well as specific assessment of the factors determining perceived motor fatigue and contributes to the understanding of the strain-perception-thinking-action coupling during fatiguing exercise [5]. However, the interactions between the perceptual-discriminatory dimension, the affective-motivational dimension, and the cognitive-evaluative dimension should not be regarded as hierarchical but as interdependent.

3.2.1 Perceptual-Discriminatory Dimension of Perceived Motor Fatigue

The effort perceived during a motor task can be attributed to the perceptual-discriminatory dimension and is associated with perceived motor fatigue [16, 42]. Moreover, motor task-related effort perception is considered an important determinant of exercise behavior and endurance performance

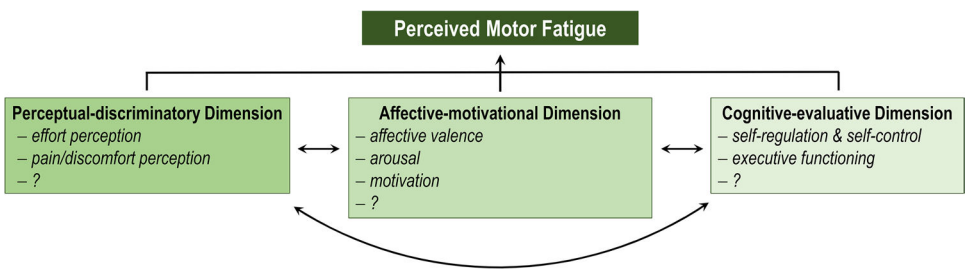

Fig. 2 Adapted three-dimensional dynamical system framework of perceived motor fatigue first proposed by Venhorst et al. [5]. The bidirectional arrows indicate the interdependence between the dimensions

[5, 43, 44]. Of note, there is controversy about whether effort perception results from centrally mediated feedforward mechanisms (i.e., corollary discharge model) and/or afferent feedback from the working and respiratory muscles (i.e., afferent feedback or combined model). However, it is well accepted that processing of sensory signals in the brain is involved [38, 45]. Effort perception, along with motivation, is one core element of the psychobiological model of endurance performance [43, 46] and it has been shown that interventions, which reduced effort perception during a sustained motor task, have subsequently led to an increased exercise tolerance (e.g., time to exhaustion during submaximal exercise) [47–52]. Conversely, effort perception during endurance exercise was higher and motor performance was reduced after interventions inducing homeostatic perturbations like hypoglycemia [34], hyperthermia [53], dehydration [54], hypoxia [55], and sleep deprivation [56].

A less studied factor that also belongs to the perceptual-discriminatory dimension and can influence perceived motor fatigue is exercise-induced muscle pain/discomfort. For instance, intense motor tasks lead to the accumulation of metabolites in the extracellular environment, resulting in an increased exercise-induced muscle pain perception, due to the activation of group III and IV muscle afferents [39]. Acute interventions aiming to reduce exercise-induced muscle pain have been shown to improve performance during sustained submaximal motor tasks [57], whereas artificially increasing exercise-induced muscle pain had the opposite effect [58]. These examples provide evidence for the importance of exercise-induced perceptual responses (e.g., effort and exercise-induced pain) for motor task performance.

3.2.2 Affective-Motivational Dimension of Perceived Motor Fatigue

The intensity of the perceptual responses (e.g., effort and exercise-induced pain/discomfort) has effects on the affective state and the motivation of an individual, which can be attributed to the affective-motivational dimension. The affective state of an individual also contributes to perceived motor fatigue and can influence exercise behavior as well as time to exhaustion during motor tasks [5, 42, 59]. It is thought that ratings of affective valence and arousal can mirror the affective state of individuals. Affective valence reflects how a person currently feels in general (i.e., from very good to very bad) [60]. These states are thought to be subjective indicators of the homeostatic status during motor tasks mediated by afferent nerve fibers that detect the mechanical, thermal, chemical, metabolic, and hormonal state of various tissues. Their projections to different brain areas (e.g., anterior insula, anterior cingulate cortex) enable conscious awareness of these stimuli and may serve as a protective mechanism for the body [61, 62]. Consequently, during fatiguing motor tasks, exercise intensity-dependent homeostatic perturbations in the respective physiological subsystems can contribute to the development of an acute negative affective valence. This is the case, for example, during the transition from the relative dominance of the aerobic to anaerobic muscle metabolism during exercise [40, 63]. Furthermore, other homeostatic perturbations, such as glycogen depletion, can also accelerate the development of negative affective valence during submaximal constant-load endurance exercise and shorten the time to exhaustion during this motor task [59]. Interestingly, the authors have found that the rate of decline in affective valence was highly and positively correlated with time to exhaustion. These findings again highlight the relevance of aspects of perceived motor fatigue for motor task performance.

3.2.3 Cognitive-Evaluative Dimension of Perceived Motor Fatigue

The changes in the perceptual-discriminatory and the affective-motivational dimensions influence processes within the cognitive-evaluative dimension with consequences for task performance during fatiguing exercise [5]. In this regard, the role of the self-regulation capacity of an individual for endurance performance has been discussed [41]. Self-regulation describes the process of bringing thinking and behavior in line with the desired goal. In certain circumstances, it requires self-control [64], which describes the process of overriding one's predominant (pre-potent, automatic) response tendencies in service of an overarching goal [65]. With regard to motor tasks, individuals have to continuously self-regulate different affective states induced by different perceptions (e.g., effort perception, exercise-induced pain perception), thoughts (e.g., related to task-termination or distractors), and behaviors (e.g., stopping the task or increasing the effort), with consequences for their motor performance. Self-regulation is effortful and relies on the integrity of executive functioning and in particular on the core executive functions, which can be classified into inhibitory control (i.e., response inhibition and interference control), working memory, and cognitive flexibility [66]. During endurance exercise, for instance, the performer has to block numerous distractors to achieve the goal attainment strategy retained in the working memory. Moreover, the individual has to resist the temptation to slow down when he/she is fatigued (inhibition) and might adjust his/her strategy for goal pursuit (cognitive flexibility) [41]. Recent findings support this view and have found that anodal transcranial direct current stimulation (tDCS) applied to the left dorsolateral prefrontal cortex improved Stroop task performance, a measure of inhibitory control, and time to exhaustion during submaximal constant-load cycling. Further, effort perception was lower, which was ascribed to the tDCS-induced increase in

neural excitability of the target areas [67]. Of note, there are also findings that tDCS did not modulate motor performance and exercise-related sensations [68].

In addition to the mentioned key-determinants of perceived motor fatigue, other important aspects contribute to the psychophysiological state of an individual and have an impact on perceived motor fatigue. These include mood, expectations, the presence of performance feedback, and time perception [3, 39, 69]. Besides, there are further factors contributing to perceived motor fatigue, which should be added to the list of determinants of perceived motor fatigue in the future, taking the three-dimensional dynamical system framework of perceived motor fatigue into account (Fig. 2).

3.3 Modulating Factors of Motor Performance Fatigue and Perceived Motor Fatigue

There are various modulating factors that can influence the extent of motor performance fatigue and perceived motor fatigue (Fig. 1b). The main subject-specific factors include age, sex, the presence of diseases, and the physical fitness level. The extent of fatigue in the different domains is further determined by the characteristics of the motor task (e.g., duration, intensity, contraction mode, and velocity), environmental conditions (e.g., temperature, oxygen availability), the context (e.g., competition), as well as acute and chronic interventions (e.g., ergogenic supplements, training interventions) [2, 3, 7, 16, 31, 51, 70–73]. In this article, we will only discuss the most studied subject- and motor task-specific factors that can modulate motor performance fatigue and perceived motor fatigue.

3.3.1 Subject-Specific Factors and Motor Performance Fatigue

In terms of subject-specific factors, it is well-known that motor function declines when people get older due to structural and functional changes within the neuromuscular system (e.g., decline in muscle quantity, quality, and function as well as neural drive) [74–76]. Interestingly, older adults often exhibit less motor performance fatigue during submaximal isometric contractions compared to young adults. This might be due to slower contractile properties requiring lower motor unit firing frequencies to reach a tetanic force output. Moreover, older adults possess a lower percentage of type II muscle fibers and a reduced reliance on glycolytic metabolism that preserves the contractile function of muscles during this type of exercise [71]. However, motor performance fatigue after fast concentric contractions is higher in older compared to younger adults [77]. This can most likely be attributed to the slower shortening velocity of muscle fibers, the loss of high-threshold motor units, less optimal muscle activation during rapid muscle actions, and impairment in skeletal muscle bioenergetics. Nevertheless, these age-related differences strongly depend on the muscle group under investigation [31, 71, 77, 78].

Furthermore, the extent of motor performance fatigue can differ between females and males during fatiguing isometric and dynamic tasks. Males usually show larger motor performance fatigue during single-joint isometric and slow-to-moderate velocity muscle actions as well as whole-body exercise compared to females [31, 79, 80]. It is thought that sex-related differences within the neuromuscular system are responsible for the lower motor performance fatigue of females. For instance, females possess a larger percentage of type I muscle fibers resulting in a higher capillarization and mitochondrial respiratory capacity, a lower glycogen utilization, as well as an increased muscle perfusion compared to males. These physiological differences lead to a slower accumulation of metabolites, and, in turn, a slower decline in contractile force and voluntary activation of muscles. However, the sex difference in motor performance fatigue is diminished when performing fast-velocity muscle actions and strongly depends on the investigated muscle(s) [31, 70, 81].

Motor performance fatigue after physical activity is often more pronounced in clinical populations compared with healthy controls leading to a reduced exercise tolerance and quality of life [2, 82]. The relative contribution of neural (i.e., muscle activation) and muscular factors (i.e., contractile function) to the larger motor performance decline strongly depends on the pathophysiology of the disease. For example, neurologic diseases like multiple sclerosis seem to be associated with a larger motor task-induced decrease in muscle activation characteristics [83, 84], while diseases affecting vascular and muscle functions can impair the contractile function of muscles to a larger extent compared to healthy controls [7, 8, 85]. Therefore, the relative contribution of neural (i.e., muscle activation) and muscular factors (i.e., contractile function) to motor performance fatigue in patients seems to depend on the disease-specific locus of the impairments in the body (primary mechanisms). However, secondary mechanisms related to these impairments, such as reduced physical activity, can also contribute to motor performance fatigue in these populations.

3.3.2 Characteristics of the Motor Task and Motor Performance Fatigue

One of the most important and extensively studied factors influencing the extent of motor performance fatigue are the characteristics of the motor task, which determine the stress imposed on the involved physiological subsystems. In this context, the magnitude of the decline in maximal voluntary force and the relative contribution of changes in muscle activation and contractile function strongly depend on the

duration and intensity of exercise, the mode and velocity of muscle action, and the involved muscle mass [16, 31, 86–90].

A general finding is that high-intensity exercise of short duration decreases maximal voluntary force primarily due to an impaired contractile function of muscles together with a small reduction in voluntary activation. In contrast, low-intensity exercise tends to provoke a substantial decrease in muscle activation and a smaller reduction in contractile function of the involved muscles. This is partly due to muscle metabolic factors that differ between high- and low-intensity exercise [16, 17, 89]. Further, the contraction mode of a muscle during a motor task can modulate motor performance fatigue and the relative contribution of neural (i.e., muscle activation) and muscular factors (i.e., contractile function) to the impairment in motor performance. For example, it has been shown that concentric contractions induce a greater initial reduction in contractile function than eccentric muscle actions. This was attributed to the higher metabolite accumulation during concentric contractions [86, 91]. In contrast, eccentric muscle actions are often associated with microscopic muscle damage impairing contractile force production [92, 93] and voluntary activation [94] over a longer period of time. Another important factor is the contraction velocity during exercise. It has been shown that fast concentric contractions induce a greater reduction in muscle contractile function but a smaller decrease in muscle activation compared with slow concentric muscle actions, probably due to different metabolic requirements [87]. Additionally, the amount of active muscle mass is of relevance. There is evidence that a higher amount of active muscle mass results in a lower drop in contractile function and larger impairments in voluntary activation. It was speculated that this is partly due to an increased inhibitory feedback from group III and IV muscle afferents associated with the larger active muscle mass [88, 95].

3.3.3 Subject-Specific Factors and Perceived Motor Fatigue

In line with motor performance fatigue, subject-specific factors like age, sex, and the presence of diseases might also modulate perceived motor fatigue and its determinants. While there are few data for perceived motor fatigue (i.e., rate of change in perceived fatigue assessed before and after or during motor tasks), the results of studies investigating age-related differences seem inconclusive for effort- and exercise-induced pain/discomfort perception [96–98]. For instance, it was shown that exercise-induced muscle pain during a graded arm crank ergometer exercise test was lower in older than in younger females [97]. In contrast, discomfort associated with breathing (i.e., exertional breathlessness) was higher in older than in younger adults of both sexes during a graded treadmill exercise test [98]. The same inconclusive results exist for sex differences in exercise-related perceptions. While effort perception seems to be similar for males and females during fatiguing exercise [99, 100], exercise-induced pain perception was lower in females during a graded cycle ergometer test [101]. However, discomfort associated with breathing (i.e., exertional breathlessness) was higher in older females than males during graded treadmill running [98]. Therefore, the age- and sex-related differences in perceptual responses to fatiguing motor exercise and their contribution to perceived motor fatigue might strongly depend on the origin of the sensory signal as well as the characteristics of the motor task.

Further, clinical populations might also have an increased motor task-induced perceived fatigue depending on the severity of the disease and the level of disability. For example, it was found that perceived motor fatigue (assessed with a visual analog scale) was higher in individuals with multiple sclerosis compared to healthy controls after low-intensity exercise of the non-dominant hand [102]. Moreover, it was shown that persons with multiple sclerosis had a higher effort perception during intermittent submaximal fatiguing exercise of the first dorsal interosseous muscle [103]. Similar results were found for effort perception during exercise in other patient populations, such as coronary heart disease [104] and females with type 2 diabetes [105]. Further, exercise-induced pain can be exacerbated in some diseases like fibromyalgia [106]. Overall, the larger perceptual responses during exercise might contribute to the increased perceived motor fatigue as well as motor performance fatigue observed in many clinical populations.

3.3.4 Characteristics of the Motor Task and Perceived Motor Fatigue

The characteristics of the motor task can also modulate the subjective feeling of fatigue and associated perceptions (e.g., effort, pain/discomfort) during motor task execution. It has been shown that perceived effort and exercise-induced pain were higher during fatiguing concentric compared to eccentric resistance exercise [107]. Furthermore, the amount of active muscle mass involved in a motor task can modulate the perceptual responses to fatiguing exercise. For instance, it was shown that single-leg incremental cycling was associated with a higher perceived effort and exercise-induced pain but lower discomfort associated with breathing (dyspnea) compared to double-leg incremental cycling [108]. The differences in the perceptual responses to exercise depending on the mode of muscle action and the involved muscle mass were always accompanied by different physiological adjustments [107, 108]. Furthermore, the motor task-specific homeostatic regulatory processes related to exercise intensity play an important role for the determinants of perceived

fatigue (e.g., effort perception, exercise-induced pain/discomfort, affective valence) [5].

The modulation of the regulatory processes within the involved subsystems (e.g., central nervous system and muscle), for instance, by supplements such as caffeine or dietary nitrate, has been shown to have a positive effect on the various perceptions during exercise (e.g., effort and exercise-induced pain) [51, 109]. In addition, the presence of external stimuli (e.g., verbal motivation, monetary incentives, feedback on performance, auditory and visual stimuli) as well as internal stimuli (e.g., self-talk, intermediate goal setting, visualization strategies) may influence the interpretation of sensory signals and thus the extent of perceived motor fatigue [48, 49, 110].

4 Cognitive Performance Fatigue and Perceived Cognitive Fatigue

4.1 Cognitive Performance Fatigue

Cognitive performance fatigue (traditionally termed objective cognitive fatigue) induced by sustained and/or intense cognitive tasks can be quantified as a decline in an objective cognitive performance measure during as well as after a cognitive task (e.g., change in reaction time, its variability, and/or accuracy) [4, 10, 111, 112]. The occurrence and extent of cognitive performance fatigue seem to depend on various modulating factors, for instance, subjects-specific factors (e.g., age, sex, diseases) and the characteristics of the cognitive task (e.g., type of task, duration, cognitive load) [113–118] (Fig. 1). Of note, performing prolonged cognitive tasks does not necessarily result in observable decrements in cognitive performance, which was often attributed to a learning effect or an increased compensatory cognitive effort [119–122].

The psychophysiological processes associated with cognitive performance fatigue are still under debate and include, but are not limited to, an altered brain activation, a loss of motivation, and the deterioration of cognitive resources (e.g., attention) [9, 21, 24, 119, 123]. It has been shown, for instance, that the activity of the dorso lateral prefrontal cortex, anterior cingulate cortex, and the insula can change during the execution of a sustained cognitive task [9, 21, 124]. One influential interpretation of these changes is that, with prolonged execution of a task, the invested effort becomes proportionally larger than the associated benefit/reward [23] and the motivation to engage in the task decreases, resulting in a reduction in performance [9, 21]. Furthermore, it has been argued that performing a prolonged cognitive task competes with the desire for control of action and therefore with other cognitive goals as well as basic emotional and biological needs (e.g., resting or doing nothing). Especially the latter are usually more potent in getting attention compared with cognitive goals, indicating their precedence for motivational processes [119]. This view is supported by experiments that have found a decrease in cognitive task performance with time-on-task, which was reversed by increasing motivation with task rewards [116]. However, this effect is not ubiquitous [125] and when comparing performance before and after fatigue induction under similar motivational conditions, there was no evidence for a recovery of task performance after providing rewards, indicating that motivational changes are not the only cause of cognitive performance fatigue [24, 126]. It has been proposed that the neural mechanisms involved in cognitive performance fatigue include changes in neural activity, neurotransmitters, and metabolites (Fig. 1a) [21, 116, 124, 127–131]. Nevertheless, it has been difficult so far to determine the significance of the observed changes in brain activation in relation to the development of cognitive performance fatigue, since they may reflect (1) a deteriorated function of the neural systems required for cognitive task performance, (2) the involvement of brain structures in the monitoring of effort and fatigue, (3) other time-dependent processes like learning, and/or (4) compensatory engagement of brain areas to maintain performance [132]. Of note, alterations in body homeostasis of individuals can modulate the neurophysiological adjustments and thus the cognitive performance changes during fatiguing cognitive tasks as shown, for instance, after inducing hyperthermia [133] and sleep deprivation [134] or after mouth rinsing with caffeine-maltodextrin [135].

4.2 Perceived Cognitive Fatigue

Perceived cognitive fatigue (traditionally termed subjective cognitive or mental fatigue) refers to the increase in the subjective perception of fatigue that develops during the execution of sustained and/or intense cognitive tasks [9, 10, 21]. It is often characterized as feelings of tiredness, weakness, or even exhaustion as well as an aversion to continue with the present task [9, 21]. Recently, it was proposed to define perceived cognitive fatigue as the feeling of a need to rest or a mismatch between effort expended and actual performance [36]. Regardless of the specific definition, the extent of perceived cognitive fatigue depends on the psychophysiological state of the individual that can change throughout a cognitive task and the body homeostasis (Fig. 1a). Similar to cognitive performance fatigue, it was proposed that perceived cognitive fatigue may arise as the consequence of the analysis of the costs and benefits of expending energy in a certain cognitive task [136], and would depend on modification in neurotransmitter release [21]. Performing a difficult sustained cognitive task requires cognitive effort, which would be perceived as increasingly aversive over time [22, 137] and would outweigh the potential task benefits/rewards

at a certain point in time (e.g., short- or long-term rewards, negative consequences if the task is terminated, or when the task is intrinsically motivating). Perceived cognitive fatigue would thus serve as a mechanism that would stop or change ongoing behavior when no longer beneficial. Of note, an alternative view on the origin and role of perceived cognitive fatigue is that of an anticipatory protection mechanism, akin to theories of motor task-induced fatigue [138–140]. According to this view, perceived cognitive fatigue would act in anticipation of future functional alterations induced by prolonged task performance, to divert behavior away from the taxing activity [23]. It is assumed that several factors contribute to perceived cognitive fatigue. However, to the best of the authors' knowledge, there has been no attempt so far to systematize these as was done for perceived motor fatigue with the three-dimensional dynamical system framework proposed by Venhorst et al. [5].

As mentioned above, one of the most relevant factors thought to contribute to perceived cognitive fatigue is the cognitive (or mental) effort invested in the task [9, 141]. It is thought that cognitive effort is associated with cognitive control, meaning that non-automated cognitive control-dependent processes, like the execution of difficult cognitive tasks, require cognitive effort [137]. As mentioned earlier, cognitive effort is perceived as costly as well as aversive and is only maintained or increased if it is expected to be beneficial. The costs of prolonged cognitive effort investment comprise the intrinsic costs related to cognitive control allocation per se as well as the opportunity costs that arise from forgoing other (more rewarding) behavior [137, 142]. However, there is also evidence that effort is not necessarily perceived as costly and can add value, meaning that the same outcome can be more rewarding when more and not less effort was invested [143]. It has been shown that several brain areas are activated when cognitive control and effort are exerted, which include the dorsal anterior cingulate cortex, anterior insula, lateral prefrontal cortex, and lateral parietal cortex [132, 144–146]. This is the case when a cognitive task has to be performed that requires sustained attention, maintenance of information in working memory, and/or the inhibition of prepotent responses. Similar to the perceived effort induced by motor tasks, cognitive effort perception and objective measures of effort investment during the same task can be modulated by homeostatic perturbations such as sleep deprivation [134] and heat stress [147], respectively.

It was argued that the costs of effort have a considerable impact on motivation, which drives the behavior of humans [9]. This interaction is intuitive, since motivation is not only directed towards a specific goal but also refers to the intensity (i.e., effort) with which this goal is pursued [143]. Müller and Apps [9] proposed that the psychophysiological processes associated with activity-induced state fatigue have an impact on motivation in two ways: they would cause direct changes in brain structures that motivate behaviors or would induce alterations in other systems, which are connected to or influenced by these brain areas.

Tasks that require sustained cognitive effort typically increase indices of sympathetic nervous system activity [148–150], which is interpreted to reflect an aversive affective response [143]. Indeed, it has been postulated that core affect, comprising affective valence (pleasure-displeasure) and arousal (activation-deactivation), changes during sustained cognitive tasks. This might occur at least in two ways: (1) increasing conflicts and errors during task execution result in negative affective valence leading to an increased effort to reduce conflicts and errors in order to achieve "cognitive comfort". Alternatively, (2) repeated conflicts and errors induce negative affective valence signaling that the current task is unrewarding. The latter is associated with perceived cognitive fatigue, which is thought to direct the individual to other more rewarding activities or to reduce effortful conflict monitoring, especially during externally mandated cognitive tasks [151]. This view is in line with the notion that negative affect signalizes inadequate progress towards goal achievement [152], which was also discussed in the context of perceived cognitive fatigue [119]. Furthermore, it was proposed that the increasingly aversive sensation with time-on-task results from the effort-induced accumulation of opportunity costs that arise from forgoing other and more rewarding behavior [22].

Similar to motor tasks, performing sustained cognitive tasks requires self-regulation [153], which describes the dynamic process of bringing thinking and behavior in line with the desired goal [154]. During sustained cognitive tasks, individuals have to continuously self-regulate different aversive sensations (e.g., cognitive effort, frustration, boredom [155]), thoughts (e.g., related to task-termination or distractors), and behaviors (e.g., stopping the task or increasing the effort), with consequences for their cognitive performance. Self-regulation per se requires effort and relies on the integrity of executive functioning and in particular on the core executive functions, which can be classified into inhibitory control (i.e., response inhibition and interference control), working memory, and cognitive flexibility [66]. There are several ways in which people can self-regulate themselves to modify their sensations, feelings, thoughts, and behaviors in service of a personal goal including effortful self-control [143]. Although self-regulation and self-control are often used interchangeably [153], it was proposed that they refer to distinct processes [64]. While self-regulation refers to more general processes of goal-directed thoughts and behaviors, self-control can be defined as the process of overcoming predominant (pre-potent, automatic) response tendencies in favor of the desired goal [65]. Self-control is exerted during the execution of sustained cognitive tasks and requires motivation as well as attention [64]. This is

in line with the view that performing a sustained cognitive task competes with motivational options (e.g., biological, emotional and/or alternative cognitive goals), which capture attention and have to be actively inhibited to maintain task performance [119].

In addition to these key-determinants, there are further important aspects that contribute to the psychophysiological state of an individual with potential consequences for perceived cognitive fatigue. For instance, it has been revealed that greater interest in a cognitive task resulted in less perceived cognitive fatigue despite a higher willingness to exert cognitive effort [156]. In the same manner, it was argued that the level of controllability modulates the aversive responses and perceived cognitive fatigue during sustained cognitive activities [119]. Furthermore, the execution of sustained cognitive tasks can be associated with changes in mood as well as with feelings like stress, anxiety, frustration, hopelessness, tension, and boredom [114, 141, 155, 157]. Some of these were shown to be related to cognitive task performance [155] and to modulate perceived cognitive fatigue [64, 119, 158]. For example, it was found that a task requiring the passive observation of strings of numbers resulted in higher boredom ratings, a steeper decline in affective valence, and higher perceived cognitive fatigue ratings compared to a cognitive task that consisted of adding three to each digit of a four-digit number [157]. Interestingly, passively watching strings of numbers was also rated as effortful, which was interpreted as the effort to keep paying attention. It was also proposed that boredom, caused by the low intrinsic attractiveness of the task itself, can also be responsible for a decrease in cognitive task performance [119], highlighting the interdependence between determinants of perceived cognitive fatigue and cognitive performance fatigue. Moreover, it was assumed that expectations based on previous experiences might influence the psychophysiological state and the psychophysiological adjustments during sustained cognitive tasks [159].

Alterations of an individual's body homeostasis can also modulate perceived cognitive fatigue and its determinants (e.g., cognitive effort perception) during cognitive tasks. For instance, this was shown in response to heat stress [133, 147], sleep deprivation [134], and mouth rinsing with caffeine-maltodextrin [135]. These sources of influence also highlight the similarity between the constructs of sleepiness and fatigue. Confusion between those concepts is very common and it remains unclear to what extent the subjective assessment measures allow researchers to clearly tease them apart [160]. Besides these, there are further factors contributing to perceived cognitive fatigue that are increasingly studied and should be added to the list of potential determinants in the future.

4.3 Modulating Factors of Cognitive Performance Fatigue and Perceived Cognitive Fatigue

Various modulating factors can influence the extent of cognitive performance fatigue and perceived cognitive fatigue (Fig. 1b). The main subject-specific factors include age, sex, the existence of diseases, and cognitive fitness. The extent of fatigue in the different domains is further determined by the characteristics of the cognitive task (e.g., type of task, duration, cognitive load), environmental conditions (e.g., temperature) as well as other homeostatic perturbations (e.g., thirst, sleep deprivation) [117, 133, 134, 143, 147, 161]. In the following sections, we will only discuss the most important subject- and cognitive task-specific factors that can modulate cognitive performance fatigue and perceived cognitive fatigue.

4.3.1 Subject-Specific Factors and Cognitive Performance Fatigue

Cognitive abilities, such as processing speed and executive functioning, decline with advancing age due to structural and functional changes within the brain (e.g., changes in white and gray matter volume, loss of synapses, dysfunction of neural networks) [162, 163]. It is thought that these age-related changes contribute to the increased (compensatory) brain activation observed during the execution of cognitive tasks [164], which was assumed to accelerate cognitive performance fatigue development [113]. However, the results of studies that have investigated the effect of age on cognitive performance fatigue are mixed and do not allow for a definite conclusion. For instance, it was found that reaction times remained constant in young and old adults after the execution of a working memory task performed for 60 min, while accuracy even increased in the elderly. The authors proposed that the potential decline in cognitive performance was countered by the learning effect [122]. This is in line with the results of Behrens et al. [11], who have found a progressive decline in reaction times with time-on-task, indicating a better task performance, during a 90-min inhibitory control task with no differences between young and old adults. In contrast, Terentjeviene et al. [113] found a similar progressively higher number of errors during an inhibition task performed over 120 min in younger and older males, which can be interpreted as cognitive performance fatigue. However, reaction times and intra-individual variability of reaction times only increased in young males indicating higher cognitive performance fatigue compared to the older males.

Since brain activation differs between sexes depending on the type of cognitive task [165, 166], it might be assumed that the extent of cognitive performance fatigue after a sustained cognitive activity is different between males and

females. However, the results of experiments on that topic are inconclusive. For instance, there were no sex-differences in the error rate and reaction times, which remained constant over time, after performing a continuous performance test for 51 min [114]. This is consistent with the results of Wang et al. [166], who have investigated sex-differences in brain activation in response to psychological stress induced by an arithmetic task (i.e., serial subtraction of 13 from a four-digit number). The authors did not observe differences in the number of errors and completed subtractions between males and females. However, the task lasted only 12 min and was possibly not long enough to induce cognitive performance fatigue. In contrast to these studies, Noreika et al. [167] have shown sex-specific cognitive performance changes during a 90-min mental rotation task. They have revealed that accuracy increased, and response times decreased to a larger extent in males compared to females with time-on-task. However, since cognitive performance increased over time, these results did not indicate cognitive performance fatigue and might be biased by the learning or practice effect.

Since the extent of cognitive performance fatigue strongly depends on the structural and functional integrity of the central nervous system, it might be assumed that cognitive performance fatigue development is accelerated in patient populations, especially in those with neurological diseases affecting the central nervous system. However, studies investigating cognitive performance fatigue in different patient populations (e.g., people with multiple sclerosis, traumatic brain injury, depression, chronic fatigue syndrome) have often found an increase in cognitive task performance (e.g., decrease in reaction time, increase in accuracy) with time-on-task, indicating a learning or practice effect, with no or minor differences compared to healthy controls [168–171]. Despite similar increases in cognitive task performance, patients showed heightened cerebral activation in specific areas and an increased perceived cognitive fatigue [10, 170, 172] indicating a lower efficiency. In contrast, a decrease in cognitive performance measures was revealed during the execution of a four-block paced auditory serial addition test with an earlier drop in performance in people with multiple sclerosis compared to healthy controls [173]. Analogous results were obtained by other studies that investigated the effects of sustained cognitive tasks on cognitive performance fatigue in multiple sclerosis and healthy controls [174, 175]. A decrease in cognitive task performance was also found in stroke survivors while performing a 60-min inhibition task, which was, however, comparable to the cognitive task performance reduction of the healthy control group [176]. Moreover, Jordan et al. [177] have revealed that cognitive task performance declined during the execution of different sustained cognitive tasks in patients with myasthenia gravis but not in the healthy control subjects.

The discrepant findings presented above indicate that the effect of age, sex, and diseases on cognitive performance fatigue seems to be strongly influenced by the task characteristics (e.g., type of task, duration, cognitive load) as well as the parameters and tasks used for the assessment of cognitive performance fatigue (e.g., reaction times and accuracy during the fatiguing task or a separate task performed before and after the fatiguing task).

4.3.2 Characteristics of the Cognitive Task and Cognitive Performance Fatigue

The occurrence and evaluation of cognitive performance fatigue strongly depend on the type of task (e.g., working memory task, response inhibition task), further characteristics of the cognitive task (e.g., duration, cognitive load), and the task used to quantify cognitive performance fatigue [116–118, 178, 179]. For instance, Smith et al. [118] have examined the effects of three different cognitive tasks, each performed for 45 min, on measures of cognitive performance fatigue: (1) psychomotor vigilance task, (2) AX-continuous performance task, (3) Stroop task. While the first task required only vigilance, the other two tasks additionally relied on response inhibition. Cognitive performance (i.e., reaction times, errors, misses) was recorded during each task and additionally using a 3-min psychomotor vigilance task performed before and after each task. Interestingly, cognitive performance monitored during the respective tasks deteriorated only for the psychomotor vigilance task (i.e., increased reaction times and misses). In contrast, pre- and post-cognitive performance assessments with the 3-min psychomotor vigilance task revealed increased reaction times only after the AX-continuous performance task and the Stroop task. These data indicate that the detection and extent of cognitive performance fatigue strongly depend on the type of task as well as the task used to assess the potential change in performance.

Besides the effect of the type of cognitive task, other task characteristics (e.g., duration, cognitive load) can also influence the extent of cognitive performance fatigue. Although several studies have not found a decline in cognitive performance with time-on-task, it was demonstrated that cognitive task performance decreased with increasing task duration [21, 116, 117]. Furthermore, it was proposed that the cognitive load induced by the task determines the extent of cognitive performance fatigue [117, 180, 181]. Studies on this topic manipulated the cognitive load either by increasing the difficulty of the task (e.g., N-back paradigm: 0-back task [low cognitive load] vs 2-back task [high cognitive load] [180]) or reducing the processing time for the stimuli presented during the cognitive tasks [117]. However, the results of these studies are inconsistent. For instance, during a 30-min working memory task, Shigihara

et al. [180] have observed an increase in reaction times with constant accuracy during the low cognitive load condition (0-back task), but not during the high cognitive load condition (2-back task). The authors have additionally tested the effect of the sustained cognitive tasks on the advanced trail making test performance and have found that the number of errors increased from pre to post for both conditions. These results again highlight the relevance of the cognitive tasks' characteristics and the performance measures used to assess cognitive performance fatigue. Moreover, the results of Borragàn et al. [117] indicated that not the difficulty of the task (e.g., 0-back task vs 1-back task) but the processing time interval for the stimuli determines the extent of cognitive performance fatigue, with shorter intervals producing larger cognitive performance declines. However, irrespective of the task characteristics, there is a general critique that laboratory cognitive tasks are not ecologically valid and exhibit low intrinsic motivational value. Therefore, controllability of these tasks is low, people experience them as increasingly aversive, and might disengage from the tasks because they are not sufficiently important for them [22, 64, 119, 159].

4.3.3 Subject-Specific Factors and Perceived Cognitive Fatigue

Subject-specific factors like age, sex, and the presence of diseases might also modulate perceived cognitive fatigue and its potential determinants. For example, Wascher et al. [182] have observed a higher increase in perceived cognitive fatigue in young compared to old adults while performing a Simon task requiring inhibitory control for 21 min. Interestingly, young adults showed also a concomitant larger decrease in self-reported motivation. This is in line with the results of Terentjeviene et al. [113], who have found a higher rise of fatigue ratings during an inhibition task performed for 120 min in young compared to old adults. This was accompanied by a higher perceived cognitive effort and temporal demand in the young participants during task execution. The young adults additionally reported increases in tension and confusion as well as a decrease in vigor, which were not found for the older participants. These data collectively suggest that younger adults perceive sustained cognitive tasks as more effortful, demanding, and fatiguing than older adults, which is corroborated by the larger decreases in motivation and vigor as well as the increased tension and confusion. Since laboratory cognitive tasks are often performed using a computer and older adults have less experience with digital technology [183], these differences might be related to the higher intrinsic attractiveness of the task for older people. Nevertheless, it was also shown that older people with a low frequency of technology use have higher levels of computer anxiety [183]. Contrary to the findings of age-related differences, it has also been observed that the increase in perceived cognitive fatigue induced by a 90-min inhibitory control task was not different between young and old adults [11].

Studies on sex-differences in perceived cognitive fatigue also revealed partially inconsistent results. Some studies have not found differences in perceived cognitive fatigue between males and females after performing a 45-min Stroop task and a 51-min continuous performance test, which require response inhibition and sustained attention. Similarly, no sex-differences in the changes in cognitive effort, vigor, energy, tiredness, tension, calmness, and further self-reported data recorded during these tasks were reported [114, 184]. Nevertheless, others have observed higher increases in fatigue ratings during a 90-min mental rotation task in females compared to males, which depended on the menstrual cycle phase [167]. It was additionally revealed that perceived cognitive effort and perceived task difficulty were higher in females compared to males during both a high and low cognitive load condition involving arithmetic tasks [166].

There is evidence that perceived cognitive fatigue development in response to sustained cognitive tasks is higher in some diseases, especially those affecting the central nervous system [10, 171, 175, 185]. Higher increases in fatigue ratings during cognitive tasks have particularly been observed in people with multiple sclerosis [171, 175, 185]. It was further reported that the perceived workload (e.g., effort, mental, temporal, physical demand) induced by a 60-min stop-signal task was higher in stroke survivors compared to an age-matched control group [176]. In contrast, studies on other patient populations, such as people with chronic fatigue syndrome, depression, and myasthenia gravis, have not found differential changes in perceived cognitive fatigue ratings compared with healthy controls during sustained cognitive tasks [171, 177]. The discrepant findings on the effect of age and sex on perceived cognitive fatigue may partially be related to the tasks' characteristics (e.g., type of task, duration, cognitive load), while task-induced perceived cognitive fatigue seems to be increased in some clinical populations such as multiple sclerosis.

4.3.4 Characteristics of the Cognitive Task and Perceived Cognitive Fatigue

It has been shown that perceived cognitive fatigue and its determinants can be influenced by the type of task (e.g., working memory task, response inhibition task) as well as other characteristics of the cognitive task (e.g., duration, cognitive load) [116, 117, 178]. The results of studies that have examined the effect of the type of cognitive task on perceived cognitive fatigue are inconclusive. For instance, O'Keefe et al. [178] have compared perceived cognitive fatigue after performing the AX continuous performance

test for 90 min, which requires attention and response inhibition, and the TloadDback task executed for 16 min, which is a working memory dual task. The latter was applied with constant processing intervals and with shorter individualized processing intervals based on the maximal performance determined during an incremental TloadDback task. Although the task duration differed greatly, all cognitive tasks induced perceived cognitive fatigue, assessed with a visual analog scale, with the highest increase in the individualized TloadDback task condition. However, the AX continuous performance test induced a higher increase in perceived cognitive fatigue and a larger decrease in vigor assessed with the Brunel Mood Scale. These results were accompanied by higher sleepiness ratings and a larger drop in task motivation compared to the TloadDback task condition. Another study on this topic has compared perceived cognitive fatigue as well as its recovery in response to a psychomotor vigilance task, an AX-continuous performance task, and a Stroop task each performed for 45 min [118]. The tasks differed regarding their demands on vigilance and response inhibition. Although all tasks increased perceived cognitive fatigue, the authors concluded that tasks requiring response inhibition appeared to induce perceived cognitive fatigue for a longer duration than a simple vigilance task.

With regard to other task characteristics, it was often found that perceived cognitive fatigue progressively increases with time-on-task [116, 185]. Moreover, it was shown that altering the cognitive load by the difficulty of the task (i.e., N-back paradigm: 0-back task [low cognitive load] vs 2-back task [high cognitive load]) resulted in comparable increases in the fatigue ratings after both tasks. In line with this, Borragàn et al. [117] found a similar increase in perceived cognitive fatigue in the low and high cognitive load condition, when the cognitive load was manipulated by the number of items to be processed during the task. However, when cognitive load was modulated by decreasing the processing interval for the stimuli, the high cognitive load condition induced a higher increase in perceived cognitive fatigue compared to the low cognitive load condition. The authors concluded that the processing time interval during cognitive tasks is more relevant for perceived cognitive fatigue development than the number of processed items. In contrast to this, it was also shown that perceived cognitive fatigue cannot only result from performing a sustained cognitive task (i.e., adding three to each digit of a four-digit number for 20 min) but also from passively observing strings of numbers intended to induce boredom [157]. More specifically, perceived cognitive fatigue was even higher in the boredom condition compared with the cognitive task condition despite lower cognitive effort ratings. This might be related to the steeper decline in affective valence ratings and the lower task interest ratings in the boredom condition. Indeed, higher interest in a task has been shown to induce less perceived cognitive fatigue [156]. These data highlight the importance of the characteristics of the cognitive task for the development of perceived cognitive fatigue and its determinants. Moreover, the individuals' attitude towards the cognitive task (e.g., interest) seems to modulate the perceptual, affective, and cognitive responses.

5 Unraveling the Interactions Between Performance Fatigue and Perceived Fatigue: Recommendations for Future Research

The updated framework covers the different dimensions of task-induced state fatigue and the involved mechanisms (Fig. 1). Thereby, the interdependence of performance fatigue and perceived fatigue as well as their determinants is acknowledged and highlighted. There is no single factor primarily determining performance fatigue and perceived fatigue in response to motor and cognitive tasks. Instead, the relative weight of each determinant and their interaction depends on several modulating factors (e.g., age, sex, diseases, fitness, characteristics of the motor and cognitive task).

5.1 Unraveling the Interactions Between Motor Performance Fatigue and Perceived Motor Fatigue

Although the mechanisms of motor performance fatigue are not yet fully elucidated, there are extensive data on the changes in the nervous system and muscle during motor tasks contributing to the decline in motor performance [16, 17, 25, 26]. In contrast, the mechanisms underlying perceived motor fatigue and their interactions with motor performance fatigue received less attention. Therefore, future research should not only investigate the neural and muscular mechanisms driving motor performance fatigue but also aspects of perceived motor fatigue and the corresponding (neuro)physiological correlates in detail. The combined measurement of changes in maximal and/or submaximal motor performance, their neural and muscular determinants as well as subjective perceptual, affective, and cognitive responses will help to understand state fatigue in different populations and in response to different motor tasks. This approach can assist in investigating the motor task-induced perceptual differences between individuals and exercise protocols (e.g., some experience exercise-induced muscle pain, whereas others primarily perceive breathing discomfort during the same motor task) and their effects on affective and cognitive processes as well as motor performance fatigue. This is of special importance for clinical populations suffering from an increased prevalence of motor performance

fatigue and perceived motor fatigue (e.g., multiple sclerosis, chronic obstructive pulmonary disease, rheumatoid arthritis) [2, 6–8, 12].

There are a few studies available that have assessed neural and muscular contributions to motor performance fatigue in parallel with ratings of perceived motor fatigue, effort perception, and affective valence to study their interactions [42, 186]. For instance, Greenhouse-Tucknott et al. [42] investigated the neuromuscular as well as perceptual and affective mechanisms responsible for the reduced endurance performance of the knee extensors following prior upper body motor activity. They have shown that prior submaximal hand grip exercise reduced the time to exhaustion during a submaximal isometric contraction of the knee extensors without altering neuromuscular function. However, they have found increased perceived motor fatigue as well as effort perception ratings and a reduced affective valence in the 'prior exercise condition' compared to a passive control condition. Thereby, effort perception and affective valence were correlated with time to exhaustion and the ratings of perceived motor fatigue. These findings indicate that prior handgrip exercise limited single-joint endurance performance of the knee extensors primarily by the interactions between perceived motor fatigue, effort perception, as well as affective valence and not by a decreased neuromuscular function. Similar approaches should be adopted in the future to investigate the interactions between motor performance fatigue and perceived motor fatigue in different populations, particularly in those suffering from diseases.

Besides the combined investigation of motor performance fatigue, perceived motor fatigue, and the underlying mechanisms, the determining factors can be manipulated to elucidate their causal involvement in the development of state fatigue in different populations and in response to various motor tasks. For that purpose, different interventions can be used aiming to modify the physiological and psychological regulatory processes during fatiguing motor exercise. For instance, neuromodulation techniques like tDCS are suitable to alter cortical excitability and to investigate the effects of changed neural properties on motor performance fatigue and perceived motor fatigue [67]. Furthermore, other interventions can be applied to modify neural as well as muscular properties (e.g., triggering 'mental fatigue' by a sustained cognitive task, supplements like caffeine or dietary nitrate, ischemic preconditioning) to investigate their effects on the different dimensions of motor task-induced state fatigue [18, 51, 52, 109]. Interventions aiming to modulate the psychological determinants of endurance performance have also been shown to induce changes in motor performance and the perceptual responses to fatiguing exercise [48]. These strategies could be used to investigate the role of cognitive processes in the interpretation of perceptual responses and the change in affective valence emerging during fatiguing motor exercise.

Motor performance fatigue can be assessed using maximal and submaximal motor performance measures. Maximal performance tasks (e.g., maximal voluntary contractions jumps) are suitable to monitor changes in the maximal capacity of the neuromuscular system to produce force or power in response to a fatiguing motor task [187, 188]. In addition, the variation of submaximal motor performance is also an indication of motor performance fatigue (e.g., force fluctuations during submaximal isometric contractions, coefficient of variation of kinematic gait parameters) [11, 189, 190].

The neural and muscular mechanisms contributing to motor performance fatigue can be investigated with different non-invasive techniques. Neural adjustments (i.e., muscle activation) can be quantified, for example, with transcranial magnetic stimulation, peripheral nerve stimulation, electromyography, functional near-infrared spectroscopy, and electroencephalography [187, 191, 192]. Moreover, functional magnetic resonance imaging is suitable to monitor changes within cortical and subcortical structures during motor exercise [193]. The contractile function of muscles can be validly quantified using peripheral nerve stimulation [187], while changes in muscle oxygenation and muscle metabolism can be measured with near-infrared spectroscopy and 31-phosphorus magnetic resonance spectroscopy, respectively [194, 195]

In addition to these measures, perceived motor fatigue as well as the contributing factors should be comprehensively assessed before, during, and after fatiguing exercise. For this purpose, different scales and questionnaires can be used according to the focus of the respective study. Perceived motor fatigue can be assessed with the ratings of fatigue scale [13], while effort perception and exercise-induced pain/discomfort perception can be quantified with 15-point Borg scales and/or category ratio scales (CR10 and CR100). These measures should be applied together with standardized wording as described elsewhere [5, 38]. Furthermore, the attentional focus during fatiguing motor exercise should be recorded as an index for the motor task intensity-dependent attentional shift from an external focus on the surrounding to an internal focus on the bodily sensations [196]. These aspects should be quantified in conjunction with affective valence and arousal, recorded with the feeling scale and felt arousal scale, respectively, as indicators of the motor task-dependent homeostatic perturbations [40, 60]. It has been shown that these aspects can influence perceived motor fatigue and performance during fatiguing motor tasks. Moreover, they reflect the motor task-induced homeostatic perturbations in various physiological subsystems and are thus indicators of the physical demands.

Besides these core measures of perceived motor fatigue, additional scales and tests should be used according to the aim of the respective study. This should be done to investigate the role of self-regulation capacity, executive functioning [41, 197, 198], and other determinants for motor performance fatigue as well as perceived motor fatigue.

5.2 Unraveling the Interactions Between Cognitive Performance Fatigue and Perceived Cognitive Fatigue

The interactions between cognitive performance fatigue and perceived cognitive fatigue have been investigated more comprehensively and in greater detail compared to those between motor performance fatigue and perceived motor fatigue. Accordingly, many studies in this field have recorded both changes in cognitive performance as well as in the perception of fatigue during and after sustained cognitive tasks. However, it must be pointed out that in studies which have measured cognitive performance on the same task as the one used to induce fatigue, evidence for a decline in cognitive task performance was frequently missing [119, 199]. The lack of a systematic decline in cognitive performance with time-on-task was often attributed to an increased compensatory cognitive effort or to a learning effect that would lead to a performance increase overcoming the performance decline induced by fatigue [119–122]. In contrast, increases in perceived cognitive fatigue with time-on-task have been shown very consistently across many different conditions (e.g., types and loads of cognitive tasks) [117, 118, 178, 180]. Therefore, future studies should use separate cognitive tasks to induce and measure cognitive performance fatigue as already done by some studies [23, 24, 118, 126, 180]. This approach might bypass the influence of a decreased motivation or learning effect and has typically led to more consistent correlations between the cognitive performance decline and perceived cognitive fatigue [24, 126].

Furthermore, the effect of distinct types (e.g., inhibitory control, working memory, or cognitive flexibility task) and loads of cognitive tasks on cognitive performance fatigue and perceived cognitive fatigue should be investigated in more detail. There is evidence that different cognitive tasks induce specific declines in performance measures depending on the assessment task. For instance, Smith et al. [118] have shown that performance decreased with time-on-task only for the psychomotor vigilance task, but not for the AX-continuous performance task and Stroop task, each performed for 45 min. On the contrary, pre and post cognitive performance assessments with a 3-min psychomotor vigilance task revealed only increased reaction times after the AX-continuous performance task and the Stroop task. However, perceived cognitive fatigue increased in all conditions, even though it tended to persist longer after the tasks requiring more response inhibition. Moreover, cognitive performance fatigue and perceived cognitive fatigue measures were also shown to be sensitive to the manipulation of the cognitive load [117, 200]. Consequently, future studies on this topic should not only examine the effects of diverse types of tasks on cognitive performance fatigue, perceived cognitive fatigue, and their neural correlates but also the influence of varying cognitive loads.

Furthermore, it is likely that the level of overlap between the fatiguing and the assessment tasks, in terms of the cognitive processes involved, is also crucial [201]. Therefore, it appears essential that future studies assess performance before and after the fatiguing cognitive task not only with cognitive tasks requiring similar cognitive processes, but also with tasks that involve different processes. These experiments should further take the impact of the cognitive load, the nature of the cognitive processes involved, and the degree of process overlap with the fatiguing task into account. As stated above, other important sources of influence are mood and emotional variables, like stress, anxiety, frustration, hopelessness, tension, and boredom [114, 141, 155, 157], which were shown to modulate perceived cognitive fatigue [119, 157, 158] and cognitive task performance [155]. Therefore, it seems mandatory to quantify these aspects and to analyze their effects on cognitive performance fatigue, perceived cognitive fatigue, and their neural correlates.

Due to the discrepant findings, the influence of subject-specific factors (i.e., age, sex, the presence of diseases) on cognitive performance fatigue and perceived cognitive fatigue also require further investigation. Nevertheless, it seems that cognitive task-induced perceived cognitive fatigue is higher in some patient populations [171, 175, 185].

To address the causal relationships, neurophysiological and psychophysiological determinants of cognitive performance fatigue as well as perceived cognitive fatigue can also be modulated experimentally. For instance, it was shown that anodal tDCS applied to the right parietal cortex counteracted the cognitive performance decline during a 40-min visual vigilance task in healthy controls and people with multiple sclerosis but had no effect on perceived cognitive fatigue [202]. Similar effects were observed in multiple sclerosis patients after stimulating the left dorsolateral prefrontal cortex with anodal tDCS [203]. In addition, investigating the effects of different neuromodulatory substances such as caffeine on cognitive performance fatigue, perceived cognitive fatigue [135], and its neurophysiological correlates can help to unravel their interdependence.

As outlined above, the detection and quantification of cognitive performance fatigue strongly depend on the assessment task and the considered variables (e.g., reaction times, accuracy, variability) [112, 118]. Perceived cognitive fatigue as well as other task-induced sensations and

emotions can be captured, for instance, using visual analog scales and/or standardized questionnaires on mood (e.g., Brunel Mood Scale), workload (e.g., NASA Task Load Index), and activation states (e.g., Activation Deactivation Adjective Check List) [10, 11, 112, 114, 118, 155, 157]. These measures should be combined with techniques suitable to record brain activity (e.g., functional magnetic resonance imaging, electroencephalography, functional near-infrared spectroscopy) [113, 125, 128] and autonomic nervous system function (e.g., heart rate variability, pupil diameter) [11, 204, 205] to learn more about the interactions of cognitive performance fatigue, perceived cognitive fatigue, and their neural correlates.

5.3 Unraveling the Interactions Between Motor Performance Fatigue, Perceived Motor Fatigue, Cognitive Performance Fatigue, and Perceived Cognitive Fatigue

Ample evidence points to the interactions between the different dimensions of activity-induced state fatigue. For instance, Marcora et al. [18] have shown that performing a 90-min response inhibition task decreased time to exhaustion in a subsequent constant-load cycling task at 80% peak power output without differences in the physiological variables compared to a control condition (watching a documentary). However, effort perception during exercise was higher after performing the sustained cognitive task leading the authors to the conclusion that the participants reached their maximal tolerable effort level earlier and subsequently disengaged from exercise. Moreover, it was observed that 60-min constant-load cycling at 90% ventilatory threshold resulted in higher reaction times during a 40-min visual working-memory vigilance test compared to the group that did not exercise before [206]. These data indicate that fatiguing cognitive or motor activities seem to modulate the performance and perceptions during a subsequent fatiguing motor or cognitive task, respectively. Evidence for the interactions between the different dimensions of activity-induced state fatigue also arises from experiments that have investigated the psychophysiological adjustments and performance changes in response to sustained motor-cognitive dual tasks [100, 186, 207]. These studies have found a decreased time to exhaustion during submaximal motor tasks when a concurrent cognitive task had to be executed (e.g., arithmetic task, N-back task). Additionally, time to exhaustion during a fatiguing motor-cognitive dual task tended to be shorter for a high compared to a low cognitive load condition. This was accompanied by a higher reduction in muscle activation of the knee extensors (i.e., voluntary activation assessed with peripheral nerve stimulation) as well as an increased heart rate and pupil diameter in the dual-task conditions compared to the single motor task condition. As expected, cognitive effort perception scaled with the level of cognitive load, but, surprisingly, effort perception associated with the motor task was greater in the high cognitive load condition compared to that recorded during the single motor task condition [186]. These data have impressively shown that the different domains of activity-induced state fatigue interact with each other. Since there is an overlap of brain structures involved during the execution of fatiguing motor and cognitive tasks (e.g., prefrontal cortex, anterior cingulate cortex) [9, 208], it was argued that these represent the mechanistic basis for the observed effects [186, 209]. Thereby, the degree of overlap between cognitive processes required for the respective motor and cognitive task might mediate the detrimental effects on performance and perceptions [9, 159, 209]. Consequently, future studies should investigate the effects of diverse types (e.g., inhibitory control, working memory, or cognitive flexibility task) and loads of cognitive tasks performed prior to or during motor exercise on performance fatigue and perceived fatigue measures. These effects should also be studied in relation to various motor tasks (e.g., whole-body and single-joint exercise in different intensity domains). Conversely, the impact of different fatiguing motor tasks performed prior to various fatiguing cognitive tasks relying on distinct cognitive processes should be examined.

The mechanistic basis for the interactions between motor performance fatigue, perceived motor fatigue, cognitive performance fatigue, and perceived cognitive fatigue can be probed with the methods mentioned in the respective paragraphs above. However, the quantification of some perceptual responses to motor and cognitive tasks requires specific scales and a clear description with standardized wording. This is of particular importance for the measurement of perceived fatigue and effort in response to motor, cognitive, or motor-cognitive dual tasks. Although it was proposed that the feeling of fatigue arising from exertion might be similarly induced by motor and cognitive tasks [9], results of studies indicated that perceived motor fatigue and perceived cognitive fatigue represent different perceptual domains [210, 211]. The same applies to effort perception, which can be related to either to the motor or the cognitive task [186].

6 Conclusion

Performance fatigue and perceived fatigue as well as their determinants are interdependent and should not be considered in isolation. Consequently, there is no single factor primarily determining performance fatigue and perceived fatigue in response to motor and cognitive tasks. Instead, the relative weight of each determinant and their interaction depend on body homeostasis (e.g., wakefulness, core

temperature) and several modulating factors (e.g., age, sex, diseases, characteristics of the task). Therefore, a combined assessment of performance fatigue and perceived fatigue measures as well as its (neuro)physiological correlates is required to unravel the psychophysiology of motor and cognitive task-induced state fatigue. This will help to better understand the interactions between the different dimensions of fatigue and their impact on human performance, which is necessary to design effective interventions for increasing exercise tolerance and human performance in healthy and clinical populations.

Declarations

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Conflict of interest Martin Behrens, Martin Gube, Helmi Chaabene, Olaf Prieske, Alexandre Zenon, Kim-Charline Broscheid, Lutz Schega, Florian Husmann, and Matthias Weippert declare that they have no conflicts of interest relevant to the content of this review.

Author contributions MB, FH, MG, and MW had the idea. MB, MG, FH, MW, and AZ wrote the first draft. All authors contributed and critically revised the content of the manuscript. All authors read and approved the final manuscript.

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