Neuromuscular responses to fatiguing locomotor exercise

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Abstract

Over the last two decades, an abundance of research has explored the impact of fatiguing locomotor exercise on the neuromuscular system. Neurostimulation techniques have been implemented prior to and following locomotor exercise tasks of a wide variety of intensities, durations, and modes. These techniques have allowed for the assessment of alterations occurring within the central nervous system and the muscle, while techniques such as transcranial magnetic stimulation and spinal electrical stimulation have permitted further segmentalisation of locomotor exercise-induced changes along the motor pathway. To this end, the present review provides a comprehensive synopsis of the literature pertaining to neuromuscular responses to locomotor exercise. Sections of the review were divided to discuss neuromuscular responses to maximal, severe, heavy and moderate intensity, high-intensity intermittent exercise, and differences in neuromuscular responses between exercise modalities. During maximal and severe intensity exercise, alterations in neuromuscular function reside primarily within the muscle. Although post-exercise reductions in voluntary activation following maximal and severe intensity exercise are generally modest, several studies have observed alterations occurring at the cortical and/or spinal level. During prolonged heavy and moderate intensity exercise, impairments in contractile function are attenuated with respect to severe intensity exercise, but are still widely observed. While reductions in voluntary activation are greater during heavy and moderate intensity exercise, the specific alterations occurring within the central nervous system remain unclear. Further work utilising stimulation techniques during exercise and integrating new and emerging techniques such as high-density electromyography is warranted to provide further insight into neuromuscular responses to locomotor exercise.

Key words: Cycling, fatigue, neurostimulation, neuromuscular physiology, running

Introduction

The study of exercise-induced fatigue has captivated academics within the field of sport and exercise for centuries, with research into the topic dating back as far as the 18th century through the pioneering work of Alessandro Mosso, documented in his book *La fatica*. Today, fatigue remains the subject of considerable research attention, with over 3000 scientific publications on this topic in the last 20 years. Despite this interest, a strict definition of fatigue remains elusive, likely due to the numerous divisions within sport and exercise science providing definitions which best suit their individual discipline. Recent efforts have been made to provide a universal definition of fatigue, applicable to both athletic and clinical populations, which encompasses the interdependent physical and cognitive processes that occur with numerous chronic health conditions, and during and following strenuous exercise [1]. To this end, Enoka and Duchateau [1] define fatigue as a debilitating symptom of tiredness and weakness, dictated by interactions between performance fatigability, which involves an acute exercise-induced reduction in force or power output of the involved muscles, and perceived fatigability, involving changes in sensations that accompany fatigue. The definition of fatigue as a sensation of tiredness and weakness, underpinned and/or modulated by a myriad of physiological and psychological processes, is used for the purposes of this review.

In sport and exercise science, considerable research has focused on the effect of fatiguing exercise on objective measures of performance, such as alterations in the force and/or power generating capacity of muscle (i.e. the 'performance fatigability' aspects) [2-4]. Such endeavours are logical given that the ability of the muscle to exert force is imperative to successful sporting performance. During high-intensity or prolonged exercise, the force generating capacity of the muscle is reduced [5]. This reduction in muscle force during exercise, and the neurophysiological changes which accompany it, are integral contributors to fatigue and impaired exercise performance, and also possibly increase injury risk [6,7]. Consequently, understanding exercise-

induced impairments in muscle force generating capacity, and the mechanisms which elicit these impairments, is a pertinent area of research.

Voluntary force is produced through a complex chain of events which occur throughout the neuromuscular pathway, from brain to muscle. As every step along this pathway is susceptible to change during fatiguing exercise, determining the alterations within the neuromuscular pathway that occur during exercise can facilitate understanding of the causes of reduced muscle force, and in turn exercise performance [1]. Using peripheral nerve stimulation, it is possible to differentiate between the contribution of alterations within the muscle and central nervous system (CNS) to impaired neuromuscular function and force generating capacity during exercise. Peripheral contributors to reductions in muscle force involve disturbances at sites at or distal to the neuromuscular junction and can be assessed by measuring involuntary evoked responses to electrical stimulation on relaxed muscle. This technique offers a method to assess the manifestation of biochemical and histological changes occurring within muscle fibers through changes in the resting twitch force. Other methods, such as muscle biopsies and Ultrasound, can be used to provide further insight into biochemical and histological alterations occurring during locomotor exercise [8,24]. Central contributors to fatigue involve processes occurring proximal to the neuromuscular junction, resulting in an impairment in the capacity of the CNS to voluntarily activate the muscle, and can be examined through evoked responses to electrical or magnetic stimulation during submaximal and maximal voluntary contractions (MVCs) [5]. Moreover, exercise-induced alterations in the corticospinal tract, which represents the primary motor pathway for control of human movement, can be further segmented through the use of transcranial magnetic stimulation (TMS), with concurrent spinal stimulation enabling the differentiation between cortical and spinal components of the motor pathway [8,9]. Other techniques, such as the assessment of stretch-reflex responses following physical perturbations, can also be used to monitor natural reflex responses [10], though the application of

these methods in response to fatiguing locomotor exercise is limited. While many of these techniques permit the assessment of neuromuscular function at a segmented level, it should be noted that the peripheral and central contributors to impairments in neuromuscular function are not mutually exclusive. For example, changes occurring within the muscle influence the activation signal discharged by motor neurons during voluntary contractions, while sensory feedback ~~is~~ transmitted from the muscle travels to various sites within the CNS, and can influence the behaviour of cortical and spinal neurons [1,11,12].

A common approach when studying neuromuscular responses to fatiguing exercise is to deliver electrical and magnetic stimuli during fatiguing single-limb, isometric exercise protocols. While this approach is convenient because participants are not required to manoeuvre to the designated apparatus for the fatiguing task (i.e. the equipment used to measure isometric force), the 'real-world' applicability of the findings from these studies is questionable due to a lack of ecological validity. That is, the type of exercise being performed differs substantially from that performed in a sport and exercise environment, where dynamic, locomotor exercise is performed with multiple limbs, and the systemic and local responses are considerably different to that of isometric exercise. Given the well-established importance of task dependency in determining the aetiology of exercise-induced fatigue [13], extrapolations from findings using isometric exercise models in the context of locomotor activity should be made with caution [14], and there is a requirement to assess neuromuscular function in response to locomotor exercise itself. As such, a plethora of research over the last two decades have documented neuromuscular responses to locomotor exercise of varying intensities, durations and modes, both during and in the recovery period following exercise [15-17]. While a number of reviews exist in the literature on corticospinal excitability during locomotor exercise [8,18], neuromuscular function responses to repeated sprints [19] and extreme endurance exercise [20], a comprehensive review of the literature describing neuromuscular responses to locomotor exercise is lacking.

An understanding of how locomotor exercise impacts the neuromuscular system has implications for those working with both athletic and clinical populations. Accordingly, the aim of this review is to summarise literature examining neuromuscular responses during and following fatiguing locomotor exercise, with a focus on the role of locomotor exercise intensity, duration, and mode on the modulation of neuromuscular function.

The role of exercise intensity and duration on neuromuscular responses to fatiguing exercise

Research has demonstrated that the intensity and duration of locomotor exercise has a profound influence on the aetiology of impairments in neuromuscular function [21-23]. Exercise intensity during locomotor exercise can be categorised into distinct domains demarcated by physiological thresholds. Specifically, four intensity domains have so far been established; moderate (power output below lactate threshold), heavy (power output between lactate threshold and critical intensity, defined as the asymptote of the relationship between intensity and time, and the maximum sustainable exercise intensity), severe (power output above critical intensity that can be sustained until VO_{2max} is reached) and extreme (supra-severe intensity in which exercise intensity is so great that VO_{2max} cannot be reached before exhaustion) [24]. Each intensity domain is characterised by differences in VO_2 kinetics, muscle metabolic, and blood acid-base responses [25]. In turn, the exercise intensity domain and the distinct physiological responses within these domains are proposed to influence the mechanisms responsible for impairments in neuromuscular function. In addition, many sporting activities are characterised by intermittent bouts of maximal or severe intensity exercise interspersed with periods of recovery or moderate and heavy intensity exercise, such as in team sports. Thus, this form of activity imposes a unique challenge to all physiological systems, including the neuromuscular

system, in that it is of prolonged duration, spans the four exercise intensity domains, and is characterised by substantial mechanical demands.

Neuromuscular responses to 'all-out' exercise

Muscle force generating capacity, voluntary activation and contractile function

Short-duration, maximum intensity exercise (30-60 s), in which there is maximum effort and a considerable decrease in performance, is referred to as 'all-out' exercise [26]. This form of exercise is commonplace during sprint interval training, which is regularly implemented as a means of improving health [27] and sports performance [28], as well as the Wingate 30 s test, and athletic events such as 400 m track running. Moreover, repeated sprint exercise, characterised by short maximal efforts (3-7 s) separated by brief recovery periods (< 60 s), is a common and effective training modality [29], and is implicated in team sports such as basketball [30]. Despite the relatively brief nature of this mode of exercise, there is a substantial and progressive decrease in the force generating capacity of the muscle. Following a 30 s all out cycle sprint, Kruger *et al.* [31] found a 19% reduction in knee extensor maximum voluntary contraction (MVC). Similar results have been observed following running or cycling repeated sprint protocols, with reductions in MVC when measured within 30 s post-exercise ranging from 15-24% (Table 1). It is well-established that the decrease in performance during all-out exercise is due primarily to alterations occurring within the muscle. Indeed, following 30 s all-out cycling, Kruger *et al.* [31] and Fernandez-del Olmo *et al.* [32] reported a 50% and 41% reduction in peak twitch force (P_{tw}), respectively, indicating the presence of considerable impairments within the contractile machinery [32]. The reduction in the ability of the muscle to produce force in response to neural input during all-out exercise is likely due to the reliance on anaerobic metabolism, the by-products of which are deleterious to contractile function. Specific mechanisms proposed to contribute to impaired contractile function include the accumulation

of inorganic phosphate (P_i) derived from the creatine kinase reaction, which has multiple roles in impaired contractile function[33], such as interference with Ca^{2+} release and sensitivity, reductions in specific force per cross-bridge and the rate of cross-bridge formation [34,35]. Accumulation of H^+ ions occurring due to anaerobic glycolysis, and subsequent interference with the excitation-contraction coupling process is also a commonly cited mechanism[26,36].

Discrepancies exist in the literature regarding the effect of maximal intensity exercise on voluntary activation (VA). For example, following two 30 s all-out cycling tasks separated by 30 min, Fernandez-del-Olma *et al.* [32] found a 34% reduction in VA, whereas Kruger *et al.* [31] found no reduction in VA following a similar exercise task. Following repeated sprint exercise, some studies have reported no change in VA [37,38], while many others reported significant decreases ranging between 3 and 11% [39-45] (Table 1). While these discrepancies could be related to differences in the exercise protocols (e.g. number or duration of sprint, exercise mode, between-sprint recovery duration), time to post-exercise neuromuscular assessment, and/or characteristics of the participants studied (sex, age, physical condition), the body of evidence would suggest short-duration, all-out exercise could inhibit the capacity of the CNS to activate muscle (Table 1).

In regards to the kinetics of change in neuromuscular function during repeated sprints, impairments in MVC, VA and P_{tw} have been shown to occur following just two sprints of a repeated sprint protocol [43]. Both Goodall *et al.* [43] and Hureau *et al.* [39] showed that most of the reduction in P_{tw} occurred during the first half of a repeat-sprint protocol, and reached a nadir around the mid stage. In contrast, impairments in VA were shown to be more pronounced during the later stages of the protocol [39]. These kinetics could be explained by the early utilisation of higher threshold fatigable motor units during the initial sprints causing the rapid reduction in P_{tw}, while the reduction in VA during the later stages could be due to a number of mechanisms (discussed below). In addition, root mean square EMG (EMG_{RMS}) normalised to

the maximal muscle compound action potential (M_{max}) is progressively reduced throughout repeated sprints, suggesting reduced alpha(α)-motoneuron output [39,46]. Accordingly, impaired contractile function plays a particularly prominent role in reduced muscle force during the early stages of repeated sprints, while reductions in VA become more apparent during the later stages.

Table 1. Literature quantifying neuromuscular alterations pre-to-post maximal intensity locomotor exercise.

Author	N	Exercise protocol	Exercise duration/distance	Muscle group	Time to post-exercise measure	Δ MVC	Δ VA	Δ P_{tw}	Δ MEP	Δ CMEP
Leg cycling										
Fernandez-del-Olmo *et al.* [32]	10	Wingate × 2 (30 min recovery)	30 s	KE	~1 min	↓ 17%	↓ 34%	↓ 41%	↑ @ 50 and 75% abs MVC	NQ
Kruger *et al.* [31]	10	Wingate	30 s	KE	10 s	↓ 19%	↔	↓ 50%	NQ	NQ
Hureau *et al.* [39]	12	10 sprints (30 s recovery)	10 s	KE	30 s	↓ 19%	↓ ~11%	↓ ~55%	NQ	NQ
Girard *et al.* [38]	12	10 sprints (30 s recovery) followed by 5 sprints (6 min recovery)	6 s	KE	3 min	↓ 11%	↔	↓ ~43%	↔	NQ
Girard *et al.* [37]	12	10 sprints (30 s recovery) followed by 5 sprints (6 min recovery)	6 s	KE	3 min	↓ ~14%	↔	↓ ~44%	NQ	NQ
Racinais *et al.* [40]	9	10 sprints (30 s recovery)	6 s	KE	5 min	↓ 17%	↓ 3%	↓ 9%	NQ	NQ
Pearcey *et al.* [41]	8	10 sprints (180 s recovery)	10 s	KE	< 20 s	↓ 24%	↓ 7%	↓ 30%	NQ	NQ
Tomazin *et al.* [47]	11	5 sprints (24 s recovery) × 4 sets (3 min between set recovery)	6 s	KE	30 s	↓ 15%	↔	↓ 39%	NQ	NQ
Monks *et al.* [42]	10	10 sprints (30/180 s recovery)	10 s	KE	< 10 s	↓ 27%	↓ 6%	↓ 39%	NQ	NQ
Running										
Tomazin *et al.* [48]	11	100 m sprint	15 s	KE	30 s	↔	↔	↓ 10%	NQ	NQ
Tomazin *et al.* [48]	11	200 m sprint	31 s	KE	30 s	↔	↔	↓ 20%	NQ	NQ
Tomazin *et al.* [48]	11	400 m sprint	71 s	KE	30 s	↓ 14%	↔	↓ 35%	NQ	NQ
Tomazin *et al.* [47]	11	5 sprints (24 s recovery) × 4 sets (3 min between-set recovery)	6 s	KE	30 s	↓ 20%	↓ 7%	↓ 36%	NQ	NQ

Goodall *et al.* [43]	12	12 sprints (30 s recovery)	30 m (4-5 s)	KE	< 2.5 min	↓ 12%	↓ 8%	↓ 24%	↔	NQ
Perrey *et al.* [44]	16	12 sprints (30 s recovery)	40 m (5.7-6.7 s)	PF	2 min	↓ 11%	↓ 3%	↓ 13%	NQ	NQ
Arm cycling										
Pearcey *et al.* [45]	12	10 sprints (150 s recovery)	10 s	EF	< 5 s	↓ 9%	↓ 6%	↓ 27%	↓ 19%	↔

EF: elbow flexors; KE: knee extensors; MEP: motor evoked potential; MVC: maximal voluntary contraction; NQ: not quantified; PF: plantar flexors; P_{tw}: peak twitch force; CMEP: cervicomedullary motor evoked potential; VA: voluntary activation

Central nervous system alterations during 'all-out' exercise

While the peripheral changes which contribute to impaired neuromuscular function during all-out exercise are well-established, the mechanisms which contribute to reductions in VA are less clear. A number of functional changes can occur within the CNS and contribute to impairments in VA and muscle force, including impairments in motor cortical output [49], changes in the intrinsic properties of α-motoneurons [50], altered reflex responses at the spinal cord [51], increases in group III/IV afferent firing ascending to supraspinal and spinal centres [46], and alterations in descending neuromodulatory systems [52]. While the invasive nature associated with directly assessing the activity of some these systems preclude their measurement in humans, indirect measures can provide insights into adjustments in the neuromuscular pathway that occur during maximal intensity exercise. Figure 1 depicts the neuromuscular pathway and the potential alterations within this pathway that contribute to or occur with reduced performance during maximal intensity exercise based on current evidence primarily derived from maximal cycling exercise.

Regarding cortical output, this is commonly estimated via the delivery of TMS over the motor cortex to estimate VA (VA_{TMS}). This technique involves delivering single-pulse TMS during a MVC, with an increase in the evoked superimposed force relative to an estimated resting twitch thought to be indicative of a decrease in cortical output. It should be noted that while VA_{TMS} is the most common method of estimating changes in maximal cortical output, it is associated with various limitations, such as activation of antagonist muscles, submaximal activation of the motoneuron pool, and accuracy of the estimated resting twitch [53], and spinal influences on VA_{TMS} cannot be ruled out. Studies using this technique in response to maximal intensity exercise have provided mixed evidence, with some reporting a decrease [32,43] in VA_{TMS} while others report no change [38,54]. Thus, while there is some evidence that output from the motor cortex could be impaired during all-out exercise, the limitations in VA_{TMS} as well as the

conflicting findings in the literature preclude a definitive conclusion on the matter. The mechanism(s) which could reduce motor cortical output are unclear, but could relate to alterations in the properties of cortical neurons, or synaptic inputs acting at or upstream of the motor cortex [45,49,55]. While evidence regarding the activity of these neurons in response to maximal intensity exercise is scarce, Pearcey *et al.* [45] demonstrated a reduction in the motor evoked potential to cervicomedullary evoked potential (MEP/CMEP) ratio measured post-exercise and between bouts of repeated arm sprint cycling, indicative of a decrease in the excitability of motor cortical neurons. Although the relationship between MEP and voluntary activation is not entirely clear, a decrease in the excitability of motor cortical neurons responsible for producing descending drive would require a compensatory increase in neural drive into the cortex, and if such an increase is not possible (e.g. due to the maximal nature of all-out exercise), recruitment of α-motoneurons would be diminished and VA reduced. More studies utilising VA_{TMS} and cortical combined with spinal stimulation are required to elucidate the effects of all-out exercise on motor cortical output and excitability.

Alterations in α-motoneuron excitability can be assessed by measure the CMEP in response to all-out exercise. This measure is advantageous given that cortical projections to α-motoneurons lack conventional presynaptic inhibition, which can influence responses such as the H-reflex independently of altered motoneuron excitability [56]. Motoneuron excitability is influenced by the level of descending synaptic input, sensory input, monoaminergic input, and alterations in the intrinsic properties of α-motoneurons, all of which could be altered during fatiguing exercise [5]. Only one study has assessed the CMEP in response to all-out exercise, with Pearcey *et al.* [45] demonstrating a 29% increase in CMEP amplitude when measuring responses during an isometric contraction following repeated arm-cycle sprinting. This increase in α-motoneuron excitability could be considered surprising given that studies have observed a decrease in spinal excitability during fatiguing isometric tasks (e.g. [50,57]), highlighting the

importance of task-dependency and contraction mode on the neuromuscular adjustments to fatiguing exercise. The authors posited that the increased excitability could be due to a decrease in voltage threshold for action potential, activation of persistent inward currents and the monoaminergic system during exercise, and/or the facilitatory effects of firing of group III/IV afferents on the biceps brachii [58,45]. It should be noted that when measured during ongoing voluntary contractions, CMEPs can be influenced by alterations in descending drive from the motor cortex, and thereby confound estimations of α-motoneuron excitability. Thus, further studies measuring CMEPs (or other methods of estimating α-motoneuron excitability such as measuring thoracic or lumbar evoked potentials) in the absence of ongoing descending drive (e.g. during the TMS evoked silent period [59,60]), and during more traditional forms of maximal intensity exercise (e.g. cycle sprints), are warranted to further understanding on the effect of maximal intensity locomotor exercise on α-motoneuron excitability.

Changes in motor cortical output and α-motoneuron excitability can occur in addition to, and/or secondary to alterations in input from sensory neurons. For example, projections from sensory neurons innervating skeletal muscle, including muscle spindles (group Ia/II), Golgi tendon organs (group Ib) and group III/IV afferents, can modulate the corticospinal pathway during exercise. The role of Golgi tendon organs during locomotor exercise is unknown, but are suggested to play a limited role in exercise-induced impairments in neuromuscular function [5,61]. During locomotor activity, group Ia afferents provide facilitatory feedback to α-motoneurons, and exercise-induced disfacilitation of these afferents has been suggested as a potential mechanism of impaired α-motoneuron firing rate and thereby VA [5,62]. The excitability of the spinal loop between muscle spindle afferents projecting to α-motoneurons can be assessed through the H-reflex, involving exogenous stimulation of the motor nerve to activate Ia afferents. The H-reflex can be influenced by numerous pre- and post-synaptic mechanisms, with exercise-induced reductions in H-reflex largely attributed to reduced Ia afferent discharge,

increased presynaptic inhibition onto Ia afferents, and decreased α-motoneuron excitability. Only one study has used this technique in response to maximal intensity repeated sprint cycling, consisting of 7 × 10 s sprints [51]. The study assessed the effects of repeated sprints on pre-synaptic inhibition of the spinal reflex pathway by utilising stimulation of cutaneous afferents of the foot, which is known to reduce presynaptic inhibition of Ia afferents [63]. Concurrently, the study measured H-reflex amplitude with and without cutaneous stimulation to assess the effect of exercise-induced changes in pre-synaptic inhibition on spinal loop excitability. The results showed that delivering cutaneous stimulation attenuated the sprint induced reduction in H-reflex, possibly through reduced presynaptic inhibition of Ia afferents, whilst also attenuating the decline in power output throughout the sprints. These results suggest that disfacilitation from group Ia afferents, possibly owing to increased presynaptic inhibition, could be implicated in impaired α-motoneuron output during maximal intensity exercise.

Furthermore, the firing rate of group III and IV muscle afferents, which are mechano- and metabosensitive sensitive sensory receptors that project inhibitory and/or facilitatory feedback to cortical and spinal regions of the motor pathway, likely increases substantially during all-out exercise [64]. However, the role of these afferents on neuromuscular function during maximal intensity exercise is not entirely clear. Torres-Peralta *et al.* [65] had participants perform isokinetic sprints before an incremental exercise test to exhaustion. After the incremental test, the quadriceps were occluded for 10 or 60 s, and a second isokinetic sprint was performed immediately after the occlusion periods. Despite the presumably augmented build-up of metabolites and increased group III/IV afferent feedback elicited by 60 s of occlusion, peak power recovered and was higher than that after 10 s of occlusion. Thus, the authors suggested that the role if group III/IV afferent feedback on maximal sprint performance is negligible, and can be overcome by a strong central command. Hureau *et al.* [46] had participants perform 10 × 10 s cycle sprints, which were preceded by neuromuscular electrical stimulation (NMES) to

elicit metabolic disturbances in the quadriceps. Power output during the sprints, EMG activity, and post-exercise changes in P_{tw} where compared between the NMES and a control condition without NMES. It was shown that both power output and EMG activity were reduced in the NMES condition relative to control, while the post-exercise reduction in P_{tw} was consistent between conditions. Thus, the authors suggested that the metabolic disturbances caused increased group III/IV feedback, thereby reducing neural drive estimated through EMG in order to prevent peripheral homeostasis from deviating beyond tolerable limits. Thus, different interpretations exist on the role of group III/IV afferent feedback during maximal intensity exercise, precluding firm conclusions on the matter [16].

Neuromuscular responses to severe intensity, short-duration exercise

Muscle force generating capacity, voluntary activation and contractile function

Many sporting activities are characterised by short-duration, high-intensity locomotor exercise, such as middle-distance running (i.e. 800-5000 m) or track cycling events lasting ~2-20 min. The exercise intensity associated with these events falls within the 'severe' domain, i.e. above the maximum sustainable exercise intensity, or 'critical intensity'. Due to the rapid energy requirements associated with severe intensity exercise and the consequent generation of ATP from anaerobic pathways, exercise within this domain is associated with a progressive loss of muscle homeostasis, such as a reduction in pH and glycogen and an increase in P_i [23]. These disturbances occurring at the peripheral level impair the capacity of the muscle to produce force in response to neural stimulation. Evidence suggests that disturbances within the muscle are the primary contributor to impairments in muscle force during severe-intensity exercise [21,22,66]. Reductions in P_{tw} range from 16-55% when measured post-exercise (Table 2). This large variability in the magnitude of P_{tw} decrease could be due to a number of factors. Namely, the time to post-exercise neuromuscular assessment ranges from < 10 s to 4 min, with longer

durations often being required to manoeuvre participants to the neuromuscular testing apparatus. Kruger *et al.* [31] recently showed that P_{tw} recovered from −44% immediately post-exercise to −34% following 2 minutes of recovery after severe intensity exercise, likely due to the rapid recovery of metabolic factors thought to interfere with the excitation-contraction coupling [36]. Given that many studies take > 2 min to assess neuromuscular function, there is likely considerable underestimation of the effects of severe intensity exercise on P_{tw}, and Figure 2 highlights that studies with a shorter time to post-exercise neuromuscular assessment demonstrate higher reductions in P_{tw}.

Two other factors could contribute to the discrepancy in the level of reduced P_{tw} observed throughout the literature. Firstly, it is thought that the mechanisms contributing to the limit of tolerance, or the degree of fatigue which can be tolerated, could differ between individuals. Hodgson *et al*. [67] dichotomised a group of apparently homogenous individuals based on those who reached the limit of tolerance during ramp-incremental cycling with a knee-extension power reserve which exceeded the power produced at the limit of tolerance, and those without a power reserve. Those without a power reserve demonstrated exacerbated reductions in P_{tw} relative to those with a power reserve. Thus, it was suggested that task failure in individuals without a power reserve could be due to inhibitions in contractile function rendering them unable to achieve the required power output. In individuals with a power reserve, factors other than impaired contractile function might contribute to the limit of tolerance, or the willingness to tolerate a stronger symptom of fatigue might be lower than those without a power reserve. If disparate inter-individual mechanisms contributing to the limit of tolerance do exist, this could conceivably contribute to the variable reductions in P_{tw} between studies (Table 2) if some

individuals reach critical impairments in contractile function while others reach the limit of tolerance before these occur.

Secondly, the variable reductions in P_{tw} could be due to the considerable variance in the exercise intensity above critical power/speed between studies, with Table 2 displaying that task failure/completion occurred between 3 and 24 min. Conflicting evidence exists on whether the level of intensity above critical intensity influences the magnitude of reduction in P_{tw} at task failure. For example, Thomas *et al.* [21] demonstrated a greater reduction in P_{tw} at task failure when exercise was performed at a higher intensity (task failure at ~3 min) compared with a lower intensity (task failure at ~11 min) within the severe domain (33% vs 16% reduction in P_{tw}, respectively). In contrast, Schafer *et al.* [68] found no difference in end exercise reduction in P_{tw} when the power output was set to deplete the W' within either 3 or 12 min (35% vs 31% reduction in P_{tw}, respectively), though it should be noted in this study participants didn't necessarily exercise to volitional exhaustion. Furthermore, Black *et al.* [23] measured changes in a range of metabolic variables including PCr, lactate, K^+, ATP, pH and glycogen (variables which are linked with the reduction in P_{tw} [36]), and found no difference in the change in any variable when exercise was performed at three different intensities within the severe domain (65, 75 and 85% of work-rate difference between gas exchange threshold and VO_{2max}, in which task failure occurred from 2.2 to 13.9 min), although peak twitch was not measured in the study. It has been proposed that a consistent magnitude of end-exercise alterations in metabolic variables (and thus P_{tw}) could exist due to a task specific 'individual critical threshold' of peripheral alterations in response to severe intensity locomotor exercise, beyond which the degree of associated sensory perceptions would not be tolerable [69]. Proponents of this theory suggested that the individual critical limit of altered metabolic homeostasis is mediated by group III/IV muscle afferents, which could reduce drive from the motor cortex through inhibitory feedback in response to metabolic stimuli. [70-72]. Whether or not alterations within

the muscle are regulated to an unvarying "critical threshold" during locomotor exercise is debated [73-75], and numerous theories exist on exercise tolerance and the degree to which metabosensitive afferent feedback plays a role [76-78]. Nevertheless, when considering the alterations within the neuromuscular system which occur during severe intensity exercise, it is clear that these primarily reside in the muscle.

Impairments in VA are evident in response to severe intensity exercise, with reductions in post-exercise voluntary activation range from 3-14% (Table 2). One study assessed the kinetics of change in neuromuscular function throughout constant load severe intensity exercise. Decorte *et al.* [79] had participants perform intermittent bouts of 6 min cycling at ~80% peak power output, with 4 min recovery between cycling bouts during which neuromuscular function was assessed, and the task completed to exhaustion (occurring on average after 3 bouts of cycling). Their study demonstrated a curvilinear relationship between exercise duration and the decline in P_{tw}, such that most of the decline occurred in the first half of exercise. Concurrently, EMG_{RMS} increased considerably during the first half of exercise, indicative of a higher descending drive required to sustain force due to impairments within the muscle, an interpretation further supported by the positive association between the change in *rectus femoris* EMG_{RMS} and reduction in Q_{tw}. This progressive impairment in contractile function and requirement to activate a greater volume of muscle to maintain a given power output is also thought to be the primary contributor to the VO_2 slow component during severe intensity exercise [80]. Towards the latter stages of exercise (80% and 100% of total cycling duration), there was a plateau in EMG_{RMS}, concurrent with a significant decrease in voluntary activation. These results suggest that once either a certain level of impairment in contractile function or a level of increase in motor drive are reached, no additional increase in motor drive occurs. Whether this plateau in motor drive serves as a protective mechanism to prevent further, potentially harmful, alterations within the muscle, or if further increases in motor drive are

prevented by intrinsic changes along the motor pathway, is unclear [79]. Nevertheless, the results indicate that, during constant-load severe intensity exercise, the impairment in VA widely observed throughout the literature (Table 2) occur primarily during the latter stages of severe intensity exercise, and could thus be implicated in task failure during constant load tasks [79].

It should be noted that the kinetics of altered neuromuscular function likely differ between self-paced versus constant load exercise. For example, Azevedo *et al*. [81] recently characterised neuromuscular responses to a 4 km cycling time-trial, in which the pacing strategy was characterised by a fast-start, even paced, and end-spurt phase. Across three separate visits, neuromuscular function (MVC, VA and P_{tw}) was measured following these three phases. The results demonstrated that all three variables were reduced by 12%, 8% and 23%, respectively, following the fast-start phase, with no further reduction thereafter. The lack of further reduction in MVC, VA or P_{tw} could have been the result of the lower selected intensity during the middle phase, which likely fell below the critical intensity and thereby permitted repletion of work capacity and recovery of neuromuscular function [82,83]. It should be noted, however, that the delay between exercise cessation and neuromuscular testing might have limited the ability to capture further decrements in neuromuscular function following the end-spurt [81].

Table 2. Literature quantifying neuromuscular alterations pre-to-post severe intensity locomotor exercise. Studies utilising protocols which resulted in task-failure in < 30 min were considered "severe intensity".

Author	N	Exercise protocol	Exercise duration	Muscle group	Time to post-exercise measure	Δ MVC	Δ VA	Δ P_{tw}	Δ MEP	Δ CMEP
Leg cycling										
Thomas *et al.* [21]	12	Power @ VO_{2max}	3 min	KE	2.5 min	↓ ~18%	↓ 3%	↓ 33%	↔	NQ
Schafer *et al.* [68]	12	Power output predicted to deplete W' within 3 min based on power-time relationship	3 min	KE	60 s	↓ 20%	↓ 11%	↓ 35%	NQ	NQ
Thomas *et al.* [22]	13	4 km time-trial	6 min	KE	< 2.5 min	↓ 18%	↓ 7%	↓ 40%	↔	NQ
Temesi *et al.* [66]	10	80% peak power output	6 min	KE	< 10 s	↓ 34%	↓ 8%	↓ 55%	NQ	NQ
Ansdell *et al.* [84]	10	4 km time trial	6 min	KE	< 1.5 min	↓ 21%	↓ 14%	↓ 34%	NQ	NQ
Azevedo *et al* [81]	11	4 km time trial	6 min	KE	1 min	↓ 13%	↓ 8%	↓ 26%	NQ	NQ
Amann *et al.* [85]	8	5 km time trial	7 min	KE	3 min	↓ 8%	NQ	↓ 32%	NQ	NQ
Johnson *et al.* [70]	8	85% peak power output	7 min	KE	2 min	↓ 15%	↓ 5%	↓ ~38%	NQ	NQ
Weavil *et al.* [86]	8	80% peak power output	8 min	KE	36 s	↓ 14%	↓ 4%	↓ 43%	↔	↔
Sidhu *et al.* [60]	11	80% peak power output	8 min	KE	10 s - 3 min	↓ 11%	↓ 8%	↓ 30%	↔	↑
Goodall *et al.* [87]	9	~80% peak power output	8 min	KE	< 2.5 min	↓ 17%	↓ 6%	↓ 19%	↔	NQ
Amann *et al.* [88]	8	5 km time trial	8 min	KE	2.5 min	↓ 14%	NQ	↓ 35%	NQ	NQ
Hureau *et al.* [89]	8	5 km time trial	8 min	KE	30 s	↓ ~13%	↓ ~7%	↓ ~41%	NQ	NQ
Amann *et al.* [90]	7	80% peak power output	9 min	KE	3 min	↓ 10%	↔	↓ 34%	NQ	NQ
Blain *et al.* [91]	8	5 km time-trial	9 min	KE	1 min	↓ ~10%	↓ 6%	↓ 31%	↔	↔
Sidhu *et al.* [16]	10	80% peak power output	9 min	KE	49 s	↓ 11%	↓ 14%	↓ 38%	↔	↑
Kruger *et al.* [31]	10	5% above second ventilatory	10 min	KE	10 s	↓ 38%	↓ 8%	↓ 44%	NQ	NQ

		threshold								
Amann *et al.* [92]	8	83% peak power output	10 min	KE	4 min	↓ 10%	↔	↓ 36%	NQ	NQ
Thomas *et al.* [21]	12	60% of differences between RCP and VO_{2max}	11 min	KE	2.5 min	↓ ~16%	↓ 6%	↓ 16%	↔	NQ
Schafer *et al.* [68]	12	Power output predicted to deplete W' within 12 min based on power-time relationship	12 min	KE	60 s	↓ 15%	↓ 12%	↓ 31%	NQ	NQ
O'Leary *et al.* [93]	16	50% between lactate threshold and VO_{2max}	18 min	KE	< 2 min	↓ 19%	↓7%	↓ 31%		
O'Leary *et al.* [94]	18	50% between lactate threshold and VO_{2max}	24 min	KE	52 s	↓ 21%	↓ 7%	↓ 37%	↔	NQ
Running										
Skof and Strojnik [95]	7	6 km time-trial	20 min	KE	60 s	↔	↔	↓ 14%	NQ	NQ
Rowing										
Husmann *et al.* [96]	8	2000 m time trial	7 min	KE	3 min	↓ 20%	↓ 18%	↔	NQ	NQ

KE: knee extensors; MEP: motor evoked potential; MVC: maximal voluntary contraction; NQ: not quantified; P_{tw}: peak twitch force; CMEP: cervicomedullary motor evoked potential; VA: voluntary activation

Central nervous system alterations during severe intensity exercise

Central nervous system alterations during severe intensity exercise have been studied extensively. Figure 3 depicts alterations which occur throughout the neuromuscular pathway in response to severe intensity exercise based on current evidence. To assess specific alterations within the CNS occurring with severe intensity exercise, studies have implemented VA_{TMS} [21,22] and the MEP/CMEP ratio [16,60,86] to assess motor cortical output and excitability, respectively, CMEP to assess α-motoneuron excitability [16,60,86], and afferent blockade through intrathecal fentanyl to assess the effects of group III/IV afferent feedback on neuromuscular function [16,60,69,71,91]. Using VA_{TMS}, a number of studies have demonstrated reductions in the region of 5-8% [21,22,87,93,97]. This could indicate a modest impairment in motor cortical output in response to severe intensity exercise. An impairment in motor cortical output is plausible given the plateau in EMG_{RMS} throughout exercise in this domain as previously discussed [79], i.e. the motor cortex could be unable to 'drive' the α-motoneurons to cause further increases in EMG_{RMS}, although it should be noted that VA_{TMS} provides only surrogate measures of cortical output. Impaired cortical output could be due, at least in part, to inhibition of motor cortical cells due to feedback from group III/IV afferents [16,98]. During exhaustive cycling exercise at 80% peak power output, Sidhu *et al.* [16] demonstrated that the MEP/CMEP amplitude ratio was increased by 25% when group III/IV afferent feedback was reduced with fentanyl-blockade, but was unchanged in the presence of continued afferent feedback in control conditions, thus indicating the inhibitory influence on the motor cortex during severe intensity exercise. Concurrently, the study showed no reduction in VA with reduced afferent feedback, with a 14% reduction in control conditions.

To further explore the mechanisms by which group III/IV afferent feedback inhibits cortical excitability, Sidhu *et al.* [60] assessed the effect of afferent blockade on $GABA_B$ inhibitory intracortical interneurons. Both $GABA_A$ and $GABA_B$ inhibitory interneurons play an integral role in generating and shaping voluntary output from the motor cortex. These intracortical

neurons have indirect projections onto corticospinal neurons, and can influence the excitability of the motor cortex through hyperpolarisation of corticospinal neurons elicited by inhibitory post-synaptic potentials (IPSPs) [99]. By applying a paired-pulse TMS stimulus paradigm known as long-interval inhibition (LII) coupled with conditioned CMEPs during severe intensity cycling, Sidhu *et al.* [60] showed an increase in $GABA_B$ mediated inhibition which was abolished when group III/IV afferents were blocked. Thus, a potential mechanism by which severe intensity exercise inhibits the excitability of the motor cortex is through an increase in $GABA_B$ mediated inhibition as a result of group III/IV afferent feedback. Other severe-intensity exercise induced changes in intracortical inhibition, such as increases in $GABA_A$ mediated short-interval intracortical inhibition (SICI), have been demonstrated [93], though conflicting evidence exists [94]. However, the study of Sidhu *et al.* [60] improved on previous study designs by measuring during post-exercise cycling at an EMG level matched to pre-exercise, as opposed to post-exercise measures taken during isometric contractions. To improve understanding of the effects of severe intensity exercise at the motor cortical level, more research is required assessing motor cortical output and excitability, intracortical inhibitory and facilitatory activity, with measures taken during or immediately following exercise given that these measures can recover rapidly after exercise cessation [100]. The assessment of other possible mechanisms which could contribute to altered cortical output in response to severe intensity exercise, such as alterations in brain neurotransmitters, is also warranted [101].

Using spinal stimulation at the cervicomedullary level, a number of recent studies have assessed the effects of severe intensity exercise at the α-motoneuron excitability [16,86]. In these studies, which utilised constant-load exercise at 80% peak power until task failure, no change in α-motoneuron excitability was demonstrated between the beginning and end of exercise. While this implies no effect of severe intensity exercise at the α-motoneuron level, in non-fatiguing circumstances, the same increase in EMG activity which occurs throughout severe

intensity exercise would cause an increase in spinal excitability [86]. This was aptly shown by Weavil *et al.* [86], who found no change in MEP or CMEP during fatiguing cycling, but a ~40% increase in MEP and CMEP during a subsequent non-fatiguing trial when the EMG was set to increase by the same magnitude. Thus, while the net corticospinal excitability remains unchanged, these results indicated a disfacilitation of the corticospinal tract mediated at the spinal level.

If α-motoneurons are disfacilitation during severe intensity exercise, this does not appear to be related to increased group III/IV afferent feedback. In fact, Sidhu *et al.* [60] found that CMEP amplitude was increased during post-exercise cycling at a matched level of EMG relative to pre-exercise which did not occur when afferent feedback was reduced, suggesting that group III/IV afferents facilitate, rather than inhibit spinal α-motoneurons projecting to the knee extensors. Indeed, previous work has suggested that group III/IV afferent feedback can inhibit or facilitate α-motoneuron depending on the muscle group studied [58]. Furthermore, Sidhu *et al.* [60] also measured CMEP during the silent period to mitigate the potential influence of changes in on-going descending drive on α-motoneuron excitability, but found no change in conditioned CMEPs during control conditions or when afferent feedback was reduced. The authors speculated that the facilitatory effects of group III/IV feedback on α-motoneuron excitability might only occur in the presence of descending drive.

The findings of Sidhu *et al*. [60] appear contradictory to that of Weavil *et al*. [86]. That is, if α-motoneurons are disfacilitated during constant load severe intensity cycling exercise, but a reduction in CMEP is not apparent due to the increased neural drive and EMG [86], one might expect that CMEP would decrease when measured at the same EMG level. However, the opposite was found by Sidhu *et al*. [60], i.e. CMEPs increased. This result cannot be explained by an increased descending drive at the same EMG level, since conditioned CMEPs exhibited no change [60]. One possible explanation is that Weavil *et al*. [86] measured responses during

constant load cycling, while Sidhu *et al*. [60] had participants reduce their power output at post-exercise in order to achieve the same EMG level as pre-exercise. It is possible that processes which disfacilitate α-motoneuron excitability (such as changes in intrinsic properties, activation of serotonin 1A receptors, of neurotransmitter depletion[16,86]) exhibited some recovery due to the decrease in intensity. This, coupled with the elevated facilitatory afferent feedback in the control trial, might have resulted in the increase α-motoneuron excitability at the same EMG level. Further studies measuring α-motoneuron excitability during severe intensity exercise, with both on-going descending drive and during the TMS evoked silent period, are warranted to provide further insight into the effects of severe intensity exercise on α-motoneuron excitability.

Alterations in spinal-loop excitability could also contribute to impaired neuromuscular function during severe intensity exercise, with reductions in H-reflex found to occur in an intensity-dependent manner [102,103]. Bulbulian and Darabos [102] found a 22% reduction in H-reflex amplitude relative to M_{max} measured in the gastrocnemius following 20 minutes of non-exhaustive treadmill running at 75% VO_{2max}, compared to a 13% reduction at 40% VO_{2max}. Similar reductions in H-reflex have been demonstrated following non-exhaustive high-intensity cycling exercise [103]. While the H-reflex alone cannot decipher between altered excitatory input from Ia afferents and a decrease in α-motoneuron excitability, evidence from fatiguing isometric contractions using microneurography show that muscle spindle afferent discharge is progressively reduced during sustained contractions [104], and that the efficacy of Ia input to facilitate the α-motoneuron is impaired due to increased presynaptic inhibition [105]. During severe intensity exercise, presynaptic mechanisms, such as group III and IV afferent induced increases in presynaptic inhibition of Ia terminals, are likely given the metabolic disturbances and the proposed inputs of group III/IV afferents onto Ia afferent terminals [106]. However, challenges associated with measurement techniques preclude definitive conclusions

on the role of Ia feedback in disfacilitating α-motoneurons and thereby contributing to impaired neuromuscular function.

In addition to measuring the specific effects on group III/IV afferent feedback on motor cortical and α-motoneuronal excitability discussed above, a plethora of studies have assessed the effects of group III/IV afferent feedback on neuromuscular function through more global responses such as EMG and P_{tw} [16,60,71,89,91]. These studies have demonstrated that group III/IV afferents constrain motoneuronal output (estimated through EMG) to active skeletal muscle, thereby limiting exercise-induced intramuscular alterations. For example, Blain *et al.* [91] had participants perform a 5 km cycling time trial under control conditions and with fentanyl induced impairment in afferent feedback. With reduced afferent feedback, it was demonstrated that motoneuron output (estimated through *vastus lateralis* EMG) was 21% higher when afferent feedback was reduced compared to control conditions. Due to the greater activation levels throughout cycling, intramuscular alterations such as P_i, H^+ and ADP, concentrations, which are correlated reductions in P_{tw} [107], were all significantly higher compared with control conditions when measured through muscle biopsies following exercise. Consequently, the reduction in P_{tw} was substantially greater when feedback was reduced (52 vs 31% reduction compared with control condition). The increased motoneuron output and end-exercise level of reduced P_{tw} with afferent blockade are consistent findings throughout the literature [85,89,90,108]. Thus, it is suggested that, through metabosensitive firing of group III/IV afferent feedback, the level of metabolic disturbance is sensed within the CNS, and the drive to the muscle is subsequently regulated to prevent abnormal or interoperable deviations in muscle homeostasis [78].

What is not entirely clear is how group III/IV constrains motoneuron output. It is unlikely to be a result of altered α-motoneuron excitability, given that reduced afferent feedback facilitates [61] or has no effect [17] on CMEP amplitude. However, given the inhibitory effects of group III/IV afferent feedback within [16,60] and potentially upstream of the motor cortex [98], as well as their proposed inputs to Ia terminals [106], motoneuron output could be constrained through the neurophysiological adjustments that group III/IV afferents elicit within the CNS. However, as well as having proposed non-nociceptive effects through alterations in CNS function and induction of the pressor reflex [85], group III/IV afferents also elicit nociceptive effects, which could also have implications for perception of effort during exercise. The increased level of effort associated with discomfort and increased cardiopulmonary response as a result of group III/IV feedback could impact how hard participants are willing to 'push' during exercise, and thereby influence motoneuron output. During exercise at a constant load of 80% peak power output, Amann *et al*. [90] demonstrated the rate of perceived exertion (RPE) was lower following the initial 3 minutes of the task when afferent feedback was reduced relative to control conditions. During self-paced exercise, the RPE remains similar between reduced afferent feedback and control conditions throughout exercise, but the power output is enhanced during the early stages of exercise with reduced afferent feedback [91]. Thus, early during severe intensity exercise, nociceptive and cardiopulmonary feedback likely contributes to an increased sense of effort associated with the same power output [90], or causes participants to choose a lower power output during self-paced tasks [91]. Towards the latter stages of exercise, however, RPE is similar with and without reduced afferent feedback [90]. This is likely the result of the increased drive to the muscle occurring throughout exercise due to the lack of nociceptive feedback, thereby 'allowing' greater activation of muscle, and in turn causing greater disturbances within the muscle. As the muscle becomes less responsive, a greater level of drive is required to compensate for contractile impairment and sustain the same power output [90], with

this increase in efferent command emitting parallel messages (corollary discharge) to brain regions associated with perceptions of exertion, thereby increasing RPE [109]. Accordingly, in addition to the alterations along the neuromuscular pathway induced by group III/IV feedback, the nociceptive and cardiopulmonary signals evoked by these afferents likely influences the regulation of voluntary drive and perceptions of effort throughout exercise.

Neuromuscular responses to sustained exercise below critical power

Muscle force generating capacity, voluntary activation and contractile function

Exercise between lactate threshold and critical intensity is classified as heavy intensity exercise, while exercise below lactate threshold is termed moderate intensity [23,24]. Heavy intensity exercise can be sustained for prolonged periods, with time to task failure ranging between ~40 min to 3 hours [23,110]. Moderate intensity exercise can be performed for durations well above 3-5 hours, and constitute the intensity at which ultra-endurance events are performed [20,77]. The neuromuscular responses measured in studies in which exercise lasted from > 30 min to 3 hours (likely falling predominantly within the heavy domain) and > 3 hours (predominantly within the moderate domain) are displayed in Tables 3 and 4, respectively. While variation exists in the literature, a comparison between the results from the studies in these tables suggests that the loss in muscle strength is greater with increasing exercise duration before reaching an eventual plateau above exercise lasting ~1000 min (Figure 4), a phenomenon previously highlighted by Millet when examining running-based exercise [77].

Within the heavy and moderate domains, energy supply is achieved through oxidative metabolism, rather than anaerobic pathways [25,111]. Consequently, alterations in muscle metabolism are much more limited than with exercise in the severe domain, with steady-state values of PCr, pH and P_i achieved within the first few minutes of exercise [23,25]. Nevertheless, impairments in contractile function have been widely observed following both moderate and severe intensity exercise (Tables 3 and 4). Following self-paced tasks, some of the reductions in P_{tw} could be a result of a "sprint-finish", in which intensity increases towards the latter stages of a race and thus fall within the severe domain, with associated metabolic changes which contribute to reduced P_{tw} [22]. For example, following a self-paced 20 km time trial lasting on average 32 min, Thomas *et al.* [22] showed a 31% reduction in P_{tw}, while in a separate study by the same group, the reduction in P_{tw} following a constant load task in which task-failure

occurred at 42 min was just 11% [21]. Thus, the self-paced versus constant pace exercise challenges used across studies is another potential source of heterogeneity in results regarding neuromuscular responses to moderate and heavy intensity exercise (Tables 3 and 4). However, the magnitude of reduced P_{tw} observed by Thomas *et al.* [21] following constant load exercise is consistent with other studies within the heavy domain, with Lepers *et al.* [112,113] and Racinais *et al.* [114] demonstrating reductions in P_{tw} of 9, 12 and 11%, respectively. Interestingly, this reduction in P_{tw} is lower than some studies assessing P_{tw} following more prolonged constant load moderate intensity exercise [115,116] (Figure 4C), suggesting a possible greater extent of impaired contractile function following more prolonged locomotor exercise, though heterogenous results exist throughout the literature (Table 4).

It is thought that glycogen depletion is the primary contributor towards impaired contractile function following prolonged heavy and moderate intensity exercise [111,117]. Glycogen depletion could interfere with the excitation-contraction coupling through localised depletion of muscle glycogen at the t-tubular-sarcoplasmic reticulum (SR) junction [118]. Indeed, following 4 h of glycogen depleting exercise, Gejl *et al.* [119] showed a persistent reduction in SR Ca^{2+} release after 4 h of recovery when participants were given only water, while participants given carbohydrates concurrently demonstrated recovery of SR Ca^{2+} release. Inhibition of SR Ca^{2+} release is thought to occur below critical levels of muscle glycogen (250-300 $mmol \cdot kg^{-1}$) [120], and values below these concentrations have been demonstrated following heavy and moderate intensity exercise [23,110], including ultramarathon running [121]. Another mechanism likely contributing to impaired contractile function include increased production of reactive oxygen and nitrogen species [122], which increase following prolonged exercise [123] and interfere with Ca^{2+} release through redox modifications of ryanodine receptors [124]. Furthermore, following running based exercise involving repeated stretch shortening cycles, muscle damage induced myofibrillar disintegrity and disorganisation of sarcomeres likely occurs, leading to a reduced

ability of the contractile machinery to produce force [125]. Thus, while the magnitude of impaired contractile function is not as prominent following moderate and heavy intensity exercise compared to severe intensity, the consistently reduced P_{tw} across studies (Tables 3 and 4) suggests that alterations within the muscle contribute to reduced neuromuscular function within these domains.

Reductions in VA are substantial following moderate and heavy intensity exercise, and these appear to be exacerbated as exercise duration increases (Figure 4). This likely explains, ~~min~~at least in part, the increased strength loss associated with longer duration exercise (Figure 4). Studies examining the kinetics of altered neuromuscular function during prolonged moderate duration exercise have shown that reduced VA occurs in the latter stages, with Place *et al.* [126] and Lepers *et al.* [116] demonstrating that VA was reduced only following 4 and 5 h of a 5 h running and cycling task, respectively.

Table 3. Literature assessing neuromuscular responses pre-to-post heavy intensity exercise. Studies in which exercise duration ranged from > 30 – 189 min were considered "heavy intensity".

Author	N	Exercise protocol	Exercise duration/distance	Muscle group	Time to post-exercise measure	Δ MVC	Δ VA	Δ P_{tw}	Δ MEP	Δ CMEP
Leg cycling										
Thomas *et al.* [22]	13	20 km time trial	32 min	KE	< 2.5 min	↓ 15%	↓ 11%	↓ 31%	$\downarrow_{restingMEP}$	NQ
Lepers *et al.* [112]	10	75% PPO	33 min	KE	~1 min	↓ 7%	↓ 1%	↓ 9%	NQ	NQ
Thomas *et al.* [21]	12	Power output @ RCP	42 min	KE	2.5 min	↓ ~17%	↓ 9%	↓ 11%	↔	NQ
Thomas *et al.* [22]	13	40 km time trial	66 min	KE	< 2.5 min	↓ 16%	↓ 10%	↓ 29%	$\downarrow_{restingMEP}$	NQ
Sahlin & Seger [127]	7	~75% VO_{2max}	85 min	KE	NQ	↓ 44%	↓ 26%	NQ	NQ	NQ
Lepers *et al.* [113]	8	65% PPO	120 min	KE	Immediately	↓ 12%	NQ	↓ 12%	NQ	NQ
Running										
Racinais *et al.* [114]	11	First ventilatory threshold	90 min	PF	5 min	↓ 11%	↓ 2%	↓ 11%	NQ	NQ
Saldanha *et al.* [128]	8	75% VO_{2peak}	120 min	PF	< 5 min	↓ 17%	↓ 19%	↔	NQ	NQ
Petersen *et al.* [129]	8	42.2 km (marathon)	154 min	KE	30 min	↓ 23%	NQ	↔	NQ	NQ
Petersen *et al.* [129]	8	42.2 km (marathon)	154 min	PF	30 min	↓ 18%	NQ	↔	NQ	NQ
Millet *et al.* [130]	12	30 km race	189 min	KE	< 3 min	↓ 25%	↓ 8%	↓ ~6%	NQ	NQ
Other										
Millet *et al.* [131]	11	42.2 km (ski skating)	149 min	KE	< 5 min	↓ 8%	↔	↑ 7%	NQ	NQ

KE: knee extensors; MEP: motor evoked potential; MVC: maximal voluntary contraction; NQ: not quantified; PF: plantar flexors; P_{tw}: peak twitch force; CMEP: cervicomedullary motor evoked potential; VA: voluntary activation

682 **Table 4.** Studies assessing neuromuscular responses pre-to-post moderate intensity exercise. Studies in which exercise duration was > 240 min were
683 considered "moderate intensity".

Author	N	Exercise protocol	Exercise duration/distance	Muscle group	Time to post-exercise measure	Δ MVC	Δ VA	Δ P_{tw}	Δ MEP	Δ CMEP
Leg cycling										
Jubeau *et al.* [115]	10	45% PPO	240 min	KE	< 3 min	↓ 25%	↓ 13%	↓ 28%	↑	NQ
Lepers *et al.* [116]	9	55% PPO	300 min	KE	Immediately	↓ 18%	↓ 6%	↓ 16%	NQ	NQ
Running										
Ross *et al.* [132]	9	42.2 km (marathon)	208 min	PF	< 20 min	↓ 18%	↓ 14%	↓ 71%	$\downarrow_{restingMEP}$	NQ
Millet *et al.* [130]	11	140 km race	278 min	KE	15 min	↓ 9%	↔	↔	NQ	NQ
Place *et al.* [126]	9	55% MAV	300 min	KE	Immediately	↓ 28%	↓ 16%	↑ 18%	NQ	NQ
Gauche *et al.*[133]	22	55 km trail run	413 min	KE	60 min	↓ 37%	↓ 2%^{CAR}	NS	NQ	NQ
Millet *et al.* [134]	9	65 km ultramarathon	511 min	KE	< 2 min	↓ 30%	↓ 20%	↑ 25%	NQ	NQ
Martin *et al.* [135]	12	Treadmill running	19 h (149km)	KE	NQ	↓ 40%	↓ 33%	↓ 25%	NQ	NQ
Martin *et al.* [135]	12	Treadmill running	19 h (149 km)	PF	NQ	↓ 30%	↓ 15%	↓ 23%	NQ	NQ
Giandolini *et al.* [136]	23	110 km mountain ultra-marathon	20 h	KE	57 min	↓ 36%	↓ 18%	↓ 11%	NQ	NQ
Giandolini *et al.* [136]	23	110 km mountain ultra-marathon	20 h	PF	57 min	↓ 28%	↓ 10%	↓ 17%	NQ	NQ
Temesi *et al.* [17]	25	110 km mountain ultra-marathon	20 h	KE	61 min	↓ 34%	↓ 26%	↓ 10%	↑	NQ
Temesi *et al.* [137]	20	110 km mountain ultra-marathon	20 h	KE	58 min	↓ 38%	↓ 24%	↓ 10%	↑	NQ

Temesi *et al.* [137]	20	110 km mountain ultra-marathon	20 h	PF	80 min	↓ 26%	↓ 9%	↓ 16%	NQ	NQ
Millet *et al.* [138]	22	166 km mountain ultra-marathon	38 h	KE	20 min	↓ 35%	↓ 19%	↓ 22%	NQ	NQ
Millet *et al.* [138]	22	166 km mountain ultra-marathon	38 h	PF	20 min	↓ 39%	↓ 6%	↓ 20%	NQ	NQ
Besson *et al.* [139]	17	169 km mountain ultra-marathon	44 h	KE	24 min	↓ 32%	↓ 23%	↓ 24%	NQ	NQ
Besson *et al.* [139]	17	169 km mountain ultra-marathon	44 h	PF	23 min	↓ 34%	↓ 19%	↓ 23%	NQ	NQ
Saugy *et al.* [140]	15	330 trail run	122 h	KE	~30 min	↓ 24%	↓ 20%	↓ 24%	NQ	NQ
Saugy *et al.* [140]	15	330 trail run	122 h	PF	~30 min	↓ 26%	↓ 26%	↓ 19%	NQ	NQ

CAR: central activation ratio; KE: knee extensors; MAV: maximum aerobic velocity; MEP: motor evoked potential; MVC: maximal voluntary contraction; NQ: not quantified; PF: plantar flexors; P_{tw}: peak twitch force; CMEP: cervicomedullary motor evoked potential; VA: voluntary activation

Central nervous system alterations during moderate and heavy intensity exercise

Overall, little research exists examining specific alterations within the CNS in response to moderate or heavy intensity exercise. Studies have demonstrated reductions in VA_{TMS} within both domains [17,21,115], possibly indicating impaired motor cortical output. The impact of prolonged exercise on the excitability of the motor pathway is unclear. When measured with the muscle at rest, studies have demonstrated reductions in MEP amplitude following prolonged exercise ranging from 20 km cycling [22], marathon running [132], and a simulated Tour de France [141]. However, changes in MEP amplitude at rest might not reflect alterations in corticospinal excitability that occur during contractions. When corticospinal excitability has been assessed pre- and post-prolonged exercise during isometric contractions, conflicting findings exist, with studies reporting an increase [17], decrease [132,141], or no change in MEP amplitude [21,22,142]. Similarly conflicting results have been shown for the silent period, with no change [115] or an increase [17] being reported. The conflicting findings could be the result of the substantial heterogeneity in the exercise challenges, such as the modalities and the duration of the task, as well as methodological differences such as stimulation intensities and the contraction intensities at which corticospinal excitability is measured, both of which can influence the change in MEP in response to exercise [17,143]. No research to date has utilised spinal stimulation to assess the effect of prolonged exercise on α-motoneuron excitability, and this represents an area for future research. Racinais *et al.* [114] demonstrated a 61% reduction in H-reflex amplitude following 90 min of non-exhaustive running exercise. Avela *et al.* [62] observed similar reductions in H-reflex amplitude following marathon running, whilst also displaying reductions in the EMG response and passive stretch-resisting force following a natural stretch reflex evoked through sudden changes in muscle length. However, whether this was due to altered Ia excitatory input or impaired α-motoneuron excitability is unclear. Further

work is required to elucidate the effects of prolonged exercise within the moderate and heavy exercise domains on the corticospinal pathway at both the supraspinal and spinal level.

Neuromuscular responses to high-intensity intermittent exercise

While an increasing number of studies have assessed neuromuscular responses to continuous locomotor exercise during tasks such as cycling and running, many team sports, such as association football (soccer), rugby league, and hockey, are characterised by bouts of high-intensity exercise interspersed with prolonged periods of low-to-moderate intensity activity. In addition, team sport players also complete numerous dynamic actions throughout competitive matches, such as jumping, changing direction, tackling and/or kicking, which are often performed with incomplete recovery [144]. Consequently, high-intensity intermittent team sports are associated with a high physiological and neuromuscular demand, resulting in substantial fatigue and impairments in neuromuscular function [145]. During team sports such as soccer and hockey, fatigue manifests through transient reductions in work-rate following the most demanding periods of a match, and cumulative reductions in work-rate towards the end of a match [144]. In addition, fatigue is thought to increase the risk of sustaining an injury during match-play, as players are more susceptible to sustaining injuries towards the latter stages of a match [6]. In order to better understand the physiology underpinning fatigue experienced during match-play, studies have examined the neuromuscular responses to simulated and competitive high-intensity intermittent team sport activity.

Using a simulated soccer match protocol designed to replicate the physiological demands of soccer match-play, Goodall *et al.* [145] investigated neuromuscular function before, at half-time (i.e. 45 min), full-time (i.e. 90 min) and following a period of extra time (i.e. 120 min). An interesting finding from this study was that while the simulated soccer match induced reductions in MVC and impairments in both contractile function and VA, the reduction in

contractile function demonstrated a plateau after half-time (Figure 5). It was hypothesised that this plateau was due to the early fatigue of higher threshold motor units, which are more susceptible to fatigue, within the first half. In the second half, the lower reduction in contractile function was suggested to be a result of the recruitment of more fatigue-resistant motor units, which exert a smaller reduction in the size of evoked twitch responses. In contrast to the nadir in contractile function, impairments in VA increased progressively, with a VA lower at half-time compared with pre-match, and lower at the end of extra-time compared with half-time. These impairments in neuromuscular function were concurrent with increases in perceptions of effort and impairments in voluntary physical performance (sprint speed and jump height) measured in a companion study [146].

Numerous other studies have assessed neuromuscular function following a range of competitive and simulated high intensity intermittent team sport protocols (Table 5). Following simulated [147] and competitive soccer match-play [15,148], studies have demonstrated impairments in P_{tw} and VA of around 14% and 8%, respectively [15,148], resulting in a 11-14% reduction in knee extensor MVC. These impairments occurred concurrently with decreases in jump height, reactive strength and sprint speed [15,147]. The mechanisms of impaired contractile function following match-play likely relate to the considerable muscle damage elicited by the numerous eccentric actions associated with match-play [149], glycogen depletion, with glycogen levels reported to fall below concentrations at which Ca^{2+} handling is impaired [119,150], and increases in reactive oxygen and nitrogen species, with measures of oxidative stress increased following a single match [149], possibly inhibiting Ca^{2+} handling [122]. The mechanisms of impaired VA are less clear, with the limited number of studies examining corticospinal and intracortical responses following simulated [145,147] and competitive match-play [15] showing no changes post-exercise, though further research is required to assess the effect of high-intensity intermittent exercise on spinal reflex pathways and α-motoneuronal excitability. Thus, during prolonged

high-intensity intermittent exercise such as soccer match-play, neuromuscular function is impaired both at the peripheral and central level, with peripheral disturbances more prevalent in the earlier stages of exercise, and impairments in VA more apparent as exercise progresses. These disruptions in neuromuscular function likely contribute to the decline in physical performance known to occur following the most demanding periods of match-play and towards the end of a match.

Table 5. Studies assessing neuromuscular responses pre-to-post high-intensity intermittent team sport exercise.

Author	N	Exercise protocol	Exercise duration/distance	Muscle group	Time to post-exercise measure	Δ MVC	Δ VA	Δ P_{tw}	Δ MEP	Δ CMEP
Soccer										
Brownstein *et al.* [15]	16	Competitive match	90 min	KE	10-60 min	↓ 14%	↓ 7%	↓ 14%	↔	NQ
Rampinini *et al.* [148]	20	Competitive match	90 min	KE	40 min	↓ 11%	↓ 8%	↓ 8%	NQ	NQ
Thomas *et al.* [147]	15	Simulated match	90 min	KE	< 2.5 min	↓ 16%	↓ 9%	↓ 14%	↔	NQ
Goodall *et al.* [145]	10	Simulated match	120 min	KE	< 2.5 min	↓ 27%	↓ 18%	↓ 23%	↔	NQ
Rugby league										
Murphy *et al.* [151]	9	Competitive match	80 min	KE	< 10 min	↓ 11%	↔	↓ 34%	NQ	NQ
Skein *et al.* [152]	11	Competitive match	80 min	KE	NQ	↓ 8%	↔	NQ	NQ	NQ
Duffield *et al.*[153]	11	Competitive match	80 min	KE	NQ	↓ 8%	↔	↓ 15%	NQ	NQ
Pointon & Duffield [154]	10	Simulated match	60 min	KE	< 10 min	↓ ~13%	↓ ~7%	↓ 21%	NQ	NQ
Basketball										
Ansdell *et al.* [155]	10	Simulated match	60 min	KE	75 s	↓ 15%	NQ	↓ 13%	NQ	NQ
Intermittent sprint protocol										
Minett *et al.* [156]	9	Intermittent sprints	70 min	KE	< 10 min	↓ ~16%	↓ ~4%^{CAR}	NQ	NQ	NQ
Pointon *et al.* [157]	10	Intermittent sprints	60 min	KE	< 10 min	↓ ~25%	↓ ~11%	↓ 21%	NQ	NQ

KE: knee extensors; MEP: motor evoked potential; MVC: maximal voluntary contraction; NQ: not quantified; P_{tw}: peak twitch force; CMEP: cervicomedullary motor evoked potential; VA: voluntary activation

Conclusions on the role of exercise intensity on neuromuscular responses to locomotor exercise

The above synopsis of the current literature pertaining to neuromuscular responses to maximal, severe, heavy, moderate and high-intensity intermittent intensity locomotor exercise, provides insight into the challenge imposed on the neuromuscular system during fatiguing locomotor activity. Across the exercise domains, there are both commonalities and differences in neuromuscular responses which warrant discussion.

Overall, the reduction in muscle force generating capacity is similarly reduced following exhaustive maximal, severe and heavy intensity exercise [21,31]. Reductions in MVC are more pronounced following long-duration moderate intensity exercise, which appears to be related to exercise duration (Figure 3). However, different neuromuscular mechanisms are likely to contribute to declines in MVC between domains. While VA has been shown to be reduced following exercise across all domains, possibly due in part to impaired motor cortical output, these reductions are more substantial following prolonged moderate and heavy intensity exercise. For example, Thomas *et al*. [21] demonstrated a 9% reduction in VA following 42 min of cycling at the power output associated at the respiratory compensation point, compared to a 3% reduction at the power output associated with $VO_{2max,}$ with a similarly greater magnitude of reduced VA following prolonged compared with short-duration self-paced cycling [22]. As indicated in previous sections, reductions in VA appear to occur in a dose-response manner based on the duration of exercise. What is unclear at present is which mechanisms contribute to the exacerbated reduction in VA following prolonged exercise. While increases in group III/IV afferent feedback have been suggested to contribute to impaired VA in response to severe intensity exercise [16], the firing rate of these afferents are less likely to increase below critical intensities given that there is a lower build-up of metabolites or, in the case of cycling, markers of muscle damage to which these afferents are sensitive [158]. The greater reduction in

VA_{TMS} following prolonged heavy intensity exercise compared with short-duration severe intensity exercise [21,22] would suggest that impaired cortical output could be an important contributor. However, the mechanisms contributing to impaired VA_{TMS} are not well understood. Exacerbated increases in core temperature [159] and alterations in neurotransmitter concentrations [101] have both been suggested, however comparisons between these potential contributors across domains has not been made.

Similarly, no evidence exists comparing the effects of exercise within different domains on α-motoneuron responses to exercise. Following maximal intensity arm cycling exercise, one study observed an increase in α-motoneuron excitability [45]. During severe intensity exercise, it is suggested that α-motoneurons are disfacilitated [86], while another study suggests a fatigue-induced facilitation of α-motoneurons [60]. No evidence exists on the effect of prolonged moderate or heavy intensity exercise on α-motoneuron excitability. Thus, the precise effects of different intensities of locomotor exercise on α-motoneuron excitability is unclear, and more research is required to better understand these responses.

Contractile function is also impaired following exercise within all domains. The magnitude and the mechanisms of this reduction, however, differ. Impairments in contractile function are greater following maximal and severe intensity exercise compared with moderate and heavy intensity exercise [21,22,31]. For example, Kruger *et al*. [31] found a 50% reduction in P_{tw} following a 30 s of all-out cycling, a 44% reduction following 10 min of severe intensity exercise, and a 14% reduction following 90 min of moderate intensity exercise. The mechanisms contributing to impairments in contractile function following maximal and severe intensity exercise are likely relate to a build-up of metabolites associated with high anaerobic energy turnover. In contrast, the reduction in P_{tw} following prolonged exercise is thought to be related to glycogen depletion [119], increased production of reactive oxygen and nitrogen species [122], and, following running-based exercise, muscle damage [125]. Accordingly, the distinct metabolic responses

between exercise domains causes impaired contractile function through different mechanisms and to different degrees.

Finally, there are similarities across all domains with respect to the kinetics of altered neuromuscular function. For example, during repeated sprint [43], constant load severe intensity [79], high-intensity intermittent [145], and prolonged constant load moderate intensity exercise [116], impaired contractile function is demonstrated during the first half of exercise, before impaired VA becomes more evident during the latter half. During repeated sprint exercise, motoneuron output estimated through EMG is progressively reduced [39], while EMG is increased before plateauing during severe intensity exercise [79]. Thus, the nadir in reduction P_{tw} commonly observed during exercise within these domains could be due to the reduced or plateaued recruitment of muscle during the later stages of exercise, causing no further decrements in contractile function.

To better understand the effects of different intensities of locomotor exercise on neuromuscular function, more research is required, similar to that of Thomas *et al*. [21,22], to compare neuromuscular responses at a segmented level between different exercise domains. Furthermore, although challenging, studies should attempt to deliver stimulations to probe the excitability of the corticospinal tract, both at the cortical and spinal level, during the task itself [16,60,86]. Finally, due to the rapid recovery of contractile and CNS following exercise [31,160], studies should attempt to rapidly deliver stimulations upon exercise cessation in situations where neuromuscular function is being assessed post-exercise. This can be achieved using custom-built exercise ergometers which permit immediate neuromuscular assessments without the requirement to manoeuvre between exercise and testing apparatus [31,66,161].

The effect of exercise modality on neuromuscular responses to locomotor exercise

One of the central themes surrounding research into the neuromuscular responses to fatiguing exercise is task-dependency. In addition to the influence of exercise intensity and duration discussed earlier, exercise modality, or the type of locomotor exercise being performed, can have a profound influence on the demands placed on the neuromuscular system [130]. Exercise modality can influence the contraction type in the prime movers involved in locomotor exercise, as well as contraction duration or time under tension, the active skeletal muscle mass, mechanical efficiency and muscle recruitment strategy. All of these factors can in turn influence the metabolic and mechanical stress imposed on the muscle, and the mechanisms underpinning decrements in neuromuscular function during exercise.

While several different modes of locomotor exercise exist (e.g. running, cycling, rowing, skiing), systematic comparisons delineating the neuromuscular responses to different exercise modes are scarce. However, studies by Lepers *et al.* [116] and Place *et al.* [126] assessed the neuromuscular responses to cycling and running exercise, respectively, at the same relative intensity (55% maximal aerobic power or velocity) and duration (5 h). Comparisons between the results of those studies show that, despite the similar exercise intensity and duration, the reduction in knee extensor strength was greater following running (28%) compared with cycling exercise (18%). The greater reduction in MVC was likely due to the greater reduction in VA following running (16%) compared with cycling (8%). In a study directly comparing cycling and running exercise, Tomazin *et al.* [47] had participants perform three sets of five × six second repeated sprints on both a treadmill and a cycle ergometer, on separate occasions. The study found that the reduction in MVC was greater during and following running sprints compared with cycling. In addition, the reduction in MVC was accompanied by a reduction in VA throughout the running protocol which was not seen during cycling. Following ~3 h of running [130] and skiing exercise [131], a significant reduction in VA (8%) was only observed

following running based exercise. Thus, it appears that alterations to CNS function and consequent impairments in muscle strength are greater following running-based exercise compared with other locomotor exercise modes. This is likely a result of the muscle damage associated with running based exercise, and the lower mechanical demands imposed during exercise such as cycling and skiing. Specifically, running involves multiple stretch shortening cycles and associated eccentric contractions, likely to elicit considerable muscle damage, whereas cycling and skiing impose a high metabolic stress but a substantially lower mechanical stress. In turn, muscle damage could elicit reductions in VA through reduced sensitivity of muscle spindles and disfacilitation of α-motoneurons from Ia afferents [62], and/or increased inhibitory feedback from group III/IV afferents which are sensitive to various markers of muscle damage [162]. Furthermore, muscle damage elicited by eccentric exercise protocols have been shown to elicit substantial impairments in VA when measured immediately post-exercise [158], further suggesting that muscle damage sustained during running contributes to the greater reduction in VA compared with cycling.

At the peripheral level, studies have reported a greater reduction in contractile function during and following cycling compared with running [116,126,163]. For example, following 5 × 6 s cycling and running sprints, Rampinini *et al.* [163] demonstrated a significantly greater reduction in knee extensor peak twitch force following cycling (~55% reduction) compared with running (~35%). Similarly, Lepers *et al.* [116] found a significant reduction in knee extensor peak twitch during every hour throughout 5 h of cycling, whereas Place *et al.* [126] showed a potentiation of quadriceps contractile properties throughout 5 h of running exercise. The higher disturbances at the peripheral level in response to cycling could be a consequence of the differences in the involved muscle mass. For example, during weight supported sports such as cycling, the overall active muscle mass involved is lower than during running, with force primarily generated from the quadriceps. It has been demonstrated throughout the literature that during tasks involving

lower active muscle mass, the reduction in twitch force is higher [164,165]. This is likely because during tasks involving a higher muscle mass, there is a greater sensory input (e.g. from group III/IV afferents) from the involved muscle mass, as well as a greater disruption to homeostasis in other physiological systems (e.g. cardiovascular, respiratory) [73]. Consequently, there is a greater contribution to fatigue and the limit of tolerance from multiple physiological systems, whereas during cycling the more local, less diffuse signal from the lower muscle mass permits greater disturbances within the muscle to be tolerated [73]. Moreover, running and cycling comprise different types of muscle contraction, with implications for the metabolic cost of exercise and thereby the neuromuscular responses. For example, during running, ~60% of the time taken to complete one stride is spent in the support phase (i.e. foot contact with the ground) for speeds between 12 and 23 km/h [166]. In turn, around 34% of the support phase comprised eccentric muscle action, which has implications for the metabolic demand of running both due to the lower metabolic cost of eccentric contractions, and the higher efficiency of subsequent concentric contractions due to the "preloading" of muscle during the eccentric phase (i.e. through the stretch-shortening cycle) [167]. Furthermore, the greater central deficit during running exercise possibly related to Ia disfacilitation (see above) could also limit alterations in contractile function. During cycling exercise, there is a high intramuscular tension throughout the majority of the pedal revolution, requiring high force generating of the quadriceps, and consequently greater recruitment of type II motor units. The high intramuscular pressure could also lead to partial occlusion of femoral artery blood flow, thereby reducing oxygen delivery and leading to greater metabolic disturbances [168]. Thus, there are several potential explanations to the greater impairment in P_{tw} found after cycling versus running based exercise. Overall, there remains limited evidence comparing neuromuscular responses to different modes of locomotor exercise, and research in this area could provide useful information for athletes and practitioners when devising training programmes.

Conclusions and future research

The present review provides a synopsis of literature, conducted primarily over the last two decades, pertaining to alterations in neuromuscular function in response to fatiguing locomotor exercise. The plethora of research which now exists in this area has clearly demonstrated the integral importance of task-dependency on alterations within the neuromuscular system. It is well established that neuromuscular function during exercise above critical intensity is primarily limited by disturbances in metabolic homeostasis and consequent impairments in contractile function. More prolonged exercise below critical intensity causes considerable reductions in the capacity of the nervous system to activate muscle, though the precise alterations within the central nervous system contributing to this reduction are still unclear. During repeated sprint, constant load severe intensity, high-intensity intermittent, and prolonged constant load moderate intensity exercise, impaired contractile function is demonstrated during the first half of exercise, before impaired voluntary activation becomes more evident during the latter half. Primarily, studies have utilised electrical nerve stimulation at rest and during maximal voluntary contractions to determine the effects of locomotor exercise at the peripheral and central level, respectively. To further investigate alterations within the nervous system, many studies have additionally utilised transcranial magnetic stimulation to assess the excitability of the corticospinal pathway, electrical stimulation of descending spinal tracts to assess α-motoneuron excitability, and nerve stimulation to assess spinal loop excitability at rest or during isometric contractions prior to and following locomotor exercise. While these studies have provided valuable insight into how various types of locomotor exercise impact the neuromuscular system, one limitation of this approach is that measuring responses during isometric contractions deviates from the locomotor exercise task itself, and thus hinders understanding of neuromuscular alterations that occur during the task.

For example, while prolonged exercise elicits substantial reductions in voluntary activation of muscle during a maximal voluntary contraction, the relevance of this reduction to exercise performance during submaximal intensity tasks is unclear, and has been questioned [74]. Measuring the force generating capacity of muscle during isometric contractions also deviates from the types of contractions performed during dynamic locomotor exercise, and indeed measures of neuromuscular function during isometric contractions are not interchangeable with those measured during dynamic assessments [169]. Moreover, the delay between exercise cessation and commencing neuromuscular assessments represents a significant general limitation when studying neuromuscular responses to locomotor exercise. To overcome these limitations, studies over the last decade have developed methodologies allowing them to deliver transcranial magnetic and electrical spinal stimulation during the locomotor exercise task itself [60,86]. This represents an important advancement in the field, and future research should seek to employ similar techniques to better understand how various locomotor exercise challenges influence the nervous system during exercise. New and emerging methodologies, such as high-density surface EMG, have the potential to provide further insight into exercise-induced alterations in nervous system function, though incorporating these techniques in response to locomotor exercise is a challenging prospect. Overall, while considerable advancements have been made in the last two decades, more work is required to provide further insight into locomotor exercise induced alterations in neuromuscular function, particularly within the central nervous system.

Table and Figure Legends

Table 1. Literature quantifying neuromuscular alterations pre-to-post maximal intensity locomotor exercise.

Table 2. Literature quantifying neuromuscular alterations pre-to-post severe intensity locomotor exercise. Studies utilising protocols which resulted in task-failure in < 30 min were considered "severe intensity".

Table 3. Literature assessing neuromuscular responses pre-to-post heavy intensity exercise. Studies in which exercise duration ranged from > 30 – 189 min were considered "heavy intensity".

Table 4. Studies assessing neuromuscular responses pre-to-post moderate intensity exercise. Studies in which exercise duration was > 240 min were considered "moderate intensity".

Table 5. Studies assessing neuromuscular responses pre-to-post high-intensity intermittent team sport exercise.

Figure 1. Proposed alterations in neuromuscular function occurring during maximal intensity exercise. Adapted from Taylor *et al.* [61].

Figure 2. Relationship between time to post-exercise assessment and reduction in knee extensor maximum voluntary contraction (MVC; A), voluntary activation (VA; B) and peak twitch force (P_{tw}; C) as a percentage of pre-exercise [16,21,22,31,60,66,68,70,84,86,87,89,91,93,94,96]. The R^2 is derived from the logarithmic slope presented on each graph.

Figure 3. Proposed alterations in neuromuscular function occurring during severe intensity exercise. Adapted from Taylor *et al.* [61].

Figure 4. Relationship between reduction in knee extensor maximal voluntary contraction (MVC; A), voluntary activation (VA; B) and peak twitch force (P_{tw}; C) as a percentage of pre-

exercise relative to the duration of exercise. Note that the figure pertains only to longer duration with a minimum duration of 30 min [17,21,22,113-116,126-128,135-140]. * outlier [127].

Figure 5. Maximum voluntary contraction (A), potentiated knee-extensor twitch force (B) and voluntary activation measured with motor nerve (VA), and motor cortical (VA_{TMS}) stimulation (c) at pre-exercise, half time (HT), full time (FT), and following extra time (ET) of a simulated soccer match. $P = < 0.05$ vs. the pre-exercise value, † = $P < 0.05$ vs. HT, ‡ = $P < 0.05$ vs. FT. From Goodall *et al*. [145].

Conflict of Interest

The authors have no conflicts of interest.

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Neuromuscular responses to fatiguing locomotor exercise

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Abstract

Over the last two decades, an abundance of research has explored the impact of fatiguing locomotor exercise on the neuromuscular system. Neurostimulation techniques have been implemented prior to and following locomotor exercise tasks of a wide variety of intensities, durations, and modes. These techniques have allowed for the assessment of alterations occurring within the central nervous system and the muscle, while techniques such as transcranial magnetic stimulation and spinal electrical stimulation have permitted further segmentalisation of locomotor exercise-induced changes along the motor pathway. To this end, the present review provides a comprehensive synopsis of the literature pertaining to neuromuscular responses to locomotor exercise. Sections of the review were divided to discuss neuromuscular responses to maximal, severe, heavy and moderate intensity, high-intensity intermittent exercise, and differences in neuromuscular responses between exercise modalities. During maximal and severe intensity exercise, alterations in neuromuscular function reside primarily within the muscle. Although post-exercise reductions in voluntary activation following maximal and severe intensity exercise are generally modest, several studies have observed alterations occurring at the cortical and/or spinal level. During prolonged heavy and moderate intensity exercise, impairments in contractile function are attenuated with respect to severe intensity exercise, but are still widely observed. While reductions in voluntary activation are greater during heavy and moderate intensity exercise, the specific alterations occurring within the central nervous system remain unclear. Further work utilising stimulation techniques during exercise and integrating new and emerging techniques such as high-density electromyography is warranted to provide further insight into neuromuscular responses to locomotor exercise.

Key words: Cycling, fatigue, neurostimulation, neuromuscular physiology, running

Introduction

The study of exercise-induced fatigue has captivated academics within the field of sport and exercise for centuries, with research into the topic dating back as far as the 18th century through the pioneering work of Alessandro Mosso, documented in his book *La fatica*. Today, fatigue remains the subject of considerable research attention, with over 3000 scientific publications on this topic in the last 20 years. Despite this interest, a strict definition of fatigue remains elusive, likely due to the numerous divisions within sport and exercise science providing definitions which best suit their individual discipline. Recent efforts have been made to provide a universal definition of fatigue, applicable to both athletic and clinical populations, which encompasses the interdependent physical and cognitive processes that occur with numerous chronic health conditions, and during and following strenuous exercise [1]. To this end, Enoka and Duchateau [1] define fatigue as a debilitating symptom of tiredness and weakness, dictated by interactions between performance fatigability, which involves an acute exercise-induced reduction in force or power output of the involved muscles, and perceived fatigability, involving changes in sensations that accompany fatigue. The definition of fatigue as a sensation of tiredness and weakness, underpinned and/or modulated by a myriad of physiological and psychological processes, is used for the purposes of this review.

In sport and exercise science, considerable research has focused on the effect of fatiguing exercise on objective measures of performance, such as alterations in the force and/or power generating capacity of muscle (i.e. the 'performance fatigability' aspects) [2-4]. Such endeavours are logical given that the ability of the muscle to exert force is imperative to successful sporting performance. During high-intensity or prolonged exercise, the force generating capacity of the muscle is reduced [5]. This reduction in muscle force during exercise, and the neurophysiological changes which accompany it, are integral contributors to fatigue and impaired exercise performance, and also possibly increase injury risk [6,7]. Consequently, understanding exercise-

induced impairments in muscle force generating capacity, and the mechanisms which elicit these impairments, is a pertinent area of research.

Voluntary force is produced through a complex chain of events which occur throughout the neuromuscular pathway, from brain to muscle. As every step along this pathway is susceptible to change during fatiguing exercise, determining the alterations within the neuromuscular pathway that occur during exercise can facilitate understanding of the causes of reduced muscle force, and in turn exercise performance [1]. Using peripheral nerve stimulation, it is possible to differentiate between the contribution of alterations within the muscle and central nervous system (CNS) to impaired neuromuscular function and force generating capacity during exercise. Peripheral contributors to reductions in muscle force involve disturbances at sites at or distal to the neuromuscular junction and can be assessed by measuring involuntary evoked responses to electrical stimulation on relaxed muscle. This technique offers a method to assess the manifestation of biochemical and histological changes occurring within muscle fibers through changes in the resting twitch force. Other methods, such as muscle biopsies and Ultrasound, can be used to provide further insight into biochemical and histological alterations occurring during locomotor exercise [8,24]. Central contributors to fatigue involve processes occurring proximal to the neuromuscular junction, resulting in an impairment in the capacity of the CNS to voluntarily activate the muscle, and can be examined through evoked responses to electrical or magnetic stimulation during submaximal and maximal voluntary contractions (MVCs) [5]. Moreover, exercise-induced alterations in the corticospinal tract, which represents the primary motor pathway for control of human movement, can be further segmented through the use of transcranial magnetic stimulation (TMS), with concurrent spinal stimulation enabling the differentiation between cortical and spinal components of the motor pathway [8,9]. Other techniques, such as the assessment of stretch-reflex responses following physical perturbations, can also be used to monitor natural reflex responses [10], though the application of

these methods in response to fatiguing locomotor exercise is limited. While many of these techniques permit the assessment of neuromuscular function at a segmented level, it should be noted that the peripheral and central contributors to impairments in neuromuscular function are not mutually exclusive. For example, changes occurring within the muscle influence the activation signal discharged by motor neurons during voluntary contractions, while sensory feedback transmitted from the muscle travels to various sites within the CNS, and can influence the behaviour of cortical and spinal neurons [1,11,12].

A common approach when studying neuromuscular responses to fatiguing exercise is to deliver electrical and magnetic stimuli during fatiguing single-limb, isometric exercise protocols. While this approach is convenient because participants are not required to manoeuvre to the designated apparatus for the fatiguing task (i.e. the equipment used to measure isometric force), the 'real-world' applicability of the findings from these studies is questionable due to a lack of ecological validity. That is, the type of exercise being performed differs substantially from that performed in a sport and exercise environment, where dynamic, locomotor exercise is performed with multiple limbs, and the systemic and local responses are considerably different to that of isometric exercise. Given the well-established importance of task dependency in determining the aetiology of exercise-induced fatigue [13], extrapolations from findings using isometric exercise models in the context of locomotor activity should be made with caution [14], and there is a requirement to assess neuromuscular function in response to locomotor exercise itself. As such, a plethora of research over the last two decades have documented neuromuscular responses to locomotor exercise of varying intensities, durations and modes, both during and in the recovery period following exercise [15-17]. While a number of reviews exist in the literature on corticospinal excitability during locomotor exercise [8,18], neuromuscular function responses to repeated sprints [19] and extreme endurance exercise [20], a comprehensive review of the literature describing neuromuscular responses to locomotor exercise is lacking.

An understanding of how locomotor exercise impacts the neuromuscular system has implications for those working with both athletic and clinical populations. Accordingly, the aim of this review is to summarise literature examining neuromuscular responses during and following fatiguing locomotor exercise, with a focus on the role of locomotor exercise intensity, duration, and mode on the modulation of neuromuscular function.

The role of exercise intensity and duration on neuromuscular responses to fatiguing exercise

Research has demonstrated that the intensity and duration of locomotor exercise has a profound influence on the aetiology of impairments in neuromuscular function [21-23]. Exercise intensity during locomotor exercise can be categorised into distinct domains demarcated by physiological thresholds. Specifically, four intensity domains have so far been established; moderate (power output below lactate threshold), heavy (power output between lactate threshold and critical intensity, defined as the asymptote of the relationship between intensity and time, and the maximum sustainable exercise intensity), severe (power output above critical intensity that can be sustained until VO_{2max} is reached) and extreme (supra-severe intensity in which exercise intensity is so great that VO_{2max} cannot be reached before exhaustion) [24]. Each intensity domain is characterised by differences in VO_2 kinetics, muscle metabolic, and blood acid-base responses [25]. In turn, the exercise intensity domain and the distinct physiological responses within these domains are proposed to influence the mechanisms responsible for impairments in neuromuscular function. In addition, many sporting activities are characterised by intermittent bouts of maximal or severe intensity exercise interspersed with periods of recovery or moderate and heavy intensity exercise, such as in team sports. Thus, this form of activity imposes a unique challenge to all physiological systems, including the neuromuscular

system, in that it is of prolonged duration, spans the four exercise intensity domains, and is characterised by substantial mechanical demands.

Neuromuscular responses to 'all-out' exercise

Muscle force generating capacity, voluntary activation and contractile function

Short-duration, maximum intensity exercise (30-60 s), in which there is maximum effort and a considerable decrease in performance, is referred to as 'all-out' exercise [26]. This form of exercise is commonplace during sprint interval training, which is regularly implemented as a means of improving health [27] and sports performance [28], as well as the Wingate 30 s test, and athletic events such as 400 m track running. Moreover, repeated sprint exercise, characterised by short maximal efforts (3-7 s) separated by brief recovery periods (< 60 s), is a common and effective training modality [29], and is implicated in team sports such as basketball [30]. Despite the relatively brief nature of this mode of exercise, there is a substantial and progressive decrease in the force generating capacity of the muscle. Following a 30 s all out cycle sprint, Kruger *et al.* [31] found a 19% reduction in knee extensor maximum voluntary contraction (MVC). Similar results have been observed following running or cycling repeated sprint protocols, with reductions in MVC when measured within 30 s post-exercise ranging from 15-24% (Table 1). It is well-established that the decrease in performance during all-out exercise is due primarily to alterations occurring within the muscle. Indeed, following 30 s all-out cycling, Kruger *et al.* [31] and Fernandez-del Olmo *et al.* [32] reported a 50% and 41% reduction in peak twitch force (P_{tw}), respectively, indicating the presence of considerable impairments within the contractile machinery [32]. The reduction in the ability of the muscle to produce force in response to neural input during all-out exercise is likely due to the reliance on anaerobic metabolism, the by-products of which are deleterious to contractile function. Specific mechanisms proposed to contribute to impaired contractile function include the accumulation

of inorganic phosphate (P_i) derived from the creatine kinase reaction, which has multiple roles in impaired contractile function[33], such as interference with Ca^{2+} release and sensitivity, reductions in specific force per cross-bridge and the rate of cross-bridge formation [34,35]. Accumulation of H^+ ions occurring due to anaerobic glycolysis, and subsequent interference with the excitation-contraction coupling process is also a commonly cited mechanism[26,36].

Discrepancies exist in the literature regarding the effect of maximal intensity exercise on voluntary activation (VA). For example, following two 30 s all-out cycling tasks separated by 30 min, Fernandez-del-Olma *et al.* [32] found a 34% reduction in VA, whereas Kruger *et al.* [31] found no reduction in VA following a similar exercise task. Following repeated sprint exercise, some studies have reported no change in VA [37,38], while many others reported significant decreases ranging between 3 and 11% [39-45] (Table 1). While these discrepancies could be related to differences in the exercise protocols (e.g. number or duration of sprint, exercise mode, between-sprint recovery duration), time to post-exercise neuromuscular assessment, and/or characteristics of the participants studied (sex, age, physical condition), the body of evidence would suggest short-duration, all-out exercise could inhibit the capacity of the CNS to activate muscle (Table 1).

In regards to the kinetics of change in neuromuscular function during repeated sprints, impairments in MVC, VA and P_{tw} have been shown to occur following just two sprints of a repeated sprint protocol [43]. Both Goodall *et al.* [43] and Hureau *et al.* [39] showed that most of the reduction in P_{tw} occurred during the first half of a repeat-sprint protocol, and reached a nadir around the mid stage. In contrast, impairments in VA were shown to be more pronounced during the later stages of the protocol [39]. These kinetics could be explained by the early utilisation of higher threshold fatigable motor units during the initial sprints causing the rapid reduction in P_{tw}, while the reduction in VA during the later stages could be due to a number of mechanisms (discussed below). In addition, root mean square EMG (EMG_{RMS}) normalised to

the maximal muscle compound action potential (M_{max}) is progressively reduced throughout repeated sprints, suggesting reduced alpha(α)-motoneuron output [39,46]. Accordingly, impaired contractile function plays a particularly prominent role in reduced muscle force during the early stages of repeated sprints, while reductions in VA become more apparent during the later stages.

207 **Table 1.** Literature quantifying neuromuscular alterations pre-to-post maximal intensity locomotor exercise.

Author	N	Exercise protocol	Exercise duration/distance	Muscle group	Time to post-exercise measure	Δ MVC	Δ VA	Δ P_{tw}	Δ MEP	Δ CMEP
Leg cycling										
Fernandez-del-Olmo *et al.* [32]	10	Wingate × 2 (30 min recovery)	30 s	KE	~1 min	↓ 17%	↓ 34%	↓ 41%	↑ @ 50 and 75% abs MVC	NQ
Kruger *et al.* [31]	10	Wingate	30 s	KE	10 s	↓ 19%	↔	↓ 50%	NQ	NQ
Hureau *et al.* [39]	12	10 sprints (30 s recovery)	10 s	KE	30 s	↓ 19%	↓ ~11%	↓ ~55%	NQ	NQ
Girard *et al.* [38]	12	10 sprints (30 s recovery) followed by 5 sprints (6 min recovery)	6 s	KE	3 min	↓ 11%	↔	↓ ~43%	↔	NQ
Girard *et al.* [37]	12	10 sprints (30 s recovery) followed by 5 sprints (6 min recovery)	6 s	KE	3 min	↓ ~14%	↔	↓ ~44%	NQ	NQ
Racinais *et al.* [40]	9	10 sprints (30 s recovery)	6 s	KE	5 min	↓ 17%	↓ 3%	↓ 9%	NQ	NQ
Pearcey *et al.* [41]	8	10 sprints (180 s recovery)	10 s	KE	< 20 s	↓ 24%	↓ 7%	↓ 30%	NQ	NQ
Tomazin *et al.* [47]	11	5 sprints (24 s recovery) × 4 sets (3 min between set recovery)	6 s	KE	30 s	↓ 15%	↔	↓ 39%	NQ	NQ
Monks *et al.* [42]	10	10 sprints (30/180 s recovery)	10 s	KE	< 10 s	↓ 27%	↓ 6%	↓ 39%	NQ	NQ
Running										
Tomazin *et al.* [48]	11	100 m sprint	15 s	KE	30 s	↔	↔	↓ 10%	NQ	NQ
Tomazin *et al.* [48]	11	200 m sprint	31 s	KE	30 s	↔	↔	↓ 20%	NQ	NQ
Tomazin *et al.* [48]	11	400 m sprint	71 s	KE	30 s	↓ 14%	↔	↓ 35%	NQ	NQ
Tomazin *et al.* [47]	11	5 sprints (24 s recovery) × 4 sets (3 min between-set recovery)	6 s	KE	30 s	↓ 20%	↓ 7%	↓ 36%	NQ	NQ

Goodall *et al.* [43]	12	12 sprints (30 s recovery)	30 m (4-5 s)	KE	< 2.5 min	↓ 12%	↓ 8%	↓ 24%	↔	NQ
Perrey *et al.* [44]	16	12 sprints (30 s recovery)	40 m (5.7-6.7 s)	PF	2 min	↓ 11%	↓ 3%	↓ 13%	NQ	NQ
Arm cycling										
Pearcey *et al.* [45]	12	10 sprints (150 s recovery)	10 s	EF	< 5 s	↓ 9%	↓ 6%	↓ 27%	↓ 19%	↔

EF: elbow flexors; KE: knee extensors; MEP: motor evoked potential; MVC: maximal voluntary contraction; NQ: not quantified; PF: plantar flexors; P_{tw}: peak twitch force; CMEP: cervicomedullary motor evoked potential; VA: voluntary activation

Central nervous system alterations during 'all-out' exercise

While the peripheral changes which contribute to impaired neuromuscular function during all-out exercise are well-established, the mechanisms which contribute to reductions in VA are less clear. A number of functional changes can occur within the CNS and contribute to impairments in VA and muscle force, including impairments in motor cortical output [49], changes in the intrinsic properties of α-motoneurons [50], altered reflex responses at the spinal cord [51], increases in group III/IV afferent firing ascending to supraspinal and spinal centres [46], and alterations in descending neuromodulatory systems [52]. While the invasive nature associated with directly assessing the activity of some these systems preclude their measurement in humans, indirect measures can provide insights into adjustments in the neuromuscular pathway that occur during maximal intensity exercise. Figure 1 depicts the neuromuscular pathway and the potential alterations within this pathway that contribute to or occur with reduced performance during maximal intensity exercise based on current evidence primarily derived from maximal cycling exercise.

Regarding cortical output, this is commonly estimated via the delivery of TMS over the motor cortex to estimate VA (VA_{TMS}). This technique involves delivering single-pulse TMS during a MVC, with an increase in the evoked superimposed force relative to an estimated resting twitch thought to be indicative of a decrease in cortical output. It should be noted that while VA_{TMS} is the most common method of estimating changes in maximal cortical output, it is associated with various limitations, such as activation of antagonist muscles, submaximal activation of the motoneuron pool, and accuracy of the estimated resting twitch [53], and spinal influences on VA_{TMS} cannot be ruled out. Studies using this technique in response to maximal intensity exercise have provided mixed evidence, with some reporting a decrease [32,43] in VA_{TMS} while others report no change [38,54]. Thus, while there is some evidence that output from the motor cortex could be impaired during all-out exercise, the limitations in VA_{TMS} as well as the

conflicting findings in the literature preclude a definitive conclusion on the matter. The mechanism(s) which could reduce motor cortical output are unclear, but could relate to alterations in the properties of cortical neurons, or synaptic inputs acting at or upstream of the motor cortex [45,49,55]. While evidence regarding the activity of these neurons in response to maximal intensity exercise is scarce, Pearcey *et al.* [45] demonstrated a reduction in the motor evoked potential to cervicomedullary evoked potential (MEP/CMEP) ratio measured post-exercise and between bouts of repeated arm sprint cycling, indicative of a decrease in the excitability of motor cortical neurons. Although the relationship between MEP and voluntary activation is not entirely clear, a decrease in the excitability of motor cortical neurons responsible for producing descending drive would require a compensatory increase in neural drive into the cortex, and if such an increase is not possible (e.g. due to the maximal nature of all-out exercise), recruitment of α-motoneurons would be diminished and VA reduced. More studies utilising VA_{TMS} and cortical combined with spinal stimulation are required to elucidate the effects of all-out exercise on motor cortical output and excitability.

Alterations in α-motoneuron excitability can be assessed by measure the CMEP in response to all-out exercise. This measure is advantageous given that cortical projections to α-motoneurons lack conventional presynaptic inhibition, which can influence responses such as the H-reflex independently of altered motoneuron excitability [56]. Motoneuron excitability is influenced by the level of descending synaptic input, sensory input, monoaminergic input, and alterations in the intrinsic properties of α-motoneurons, all of which could be altered during fatiguing exercise [5]. Only one study has assessed the CMEP in response to all-out exercise, with Pearcey *et al.* [45] demonstrating a 29% increase in CMEP amplitude when measuring responses during an isometric contraction following repeated arm-cycle sprinting. This increase in α-motoneuron excitability could be considered surprising given that studies have observed a decrease in spinal excitability during fatiguing isometric tasks (e.g. [50,57]), highlighting the

importance of task-dependency and contraction mode on the neuromuscular adjustments to fatiguing exercise. The authors posited that the increased excitability could be due to a decrease in voltage threshold for action potential, activation of persistent inward currents and the monoaminergic system during exercise, and/or the facilitatory effects of firing of group III/IV afferents on the biceps brachii [58,45]. It should be noted that when measured during ongoing voluntary contractions, CMEPs can be influenced by alterations in descending drive from the motor cortex, and thereby confound estimations of α-motoneuron excitability. Thus, further studies measuring CMEPs (or other methods of estimating α-motoneuron excitability such as measuring thoracic or lumbar evoked potentials) in the absence of ongoing descending drive (e.g. during the TMS evoked silent period [59,60]), and during more traditional forms of maximal intensity exercise (e.g. cycle sprints), are warranted to further understanding on the effect of maximal intensity locomotor exercise on α-motoneuron excitability.

Changes in motor cortical output and α-motoneuron excitability can occur in addition to, and/or secondary to alterations in input from sensory neurons. For example, projections from sensory neurons innervating skeletal muscle, including muscle spindles (group Ia/II), Golgi tendon organs (group Ib) and group III/IV afferents, can modulate the corticospinal pathway during exercise. The role of Golgi tendon organs during locomotor exercise is unknown, but are suggested to play a limited role in exercise-induced impairments in neuromuscular function [5,61]. During locomotor activity, group Ia afferents provide facilitatory feedback to α-motoneurons, and exercise-induced disfacilitation of these afferents has been suggested as a potential mechanism of impaired α-motoneuron firing rate and thereby VA [5,62]. The excitability of the spinal loop between muscle spindle afferents projecting to α-motoneurons can be assessed through the H-reflex, involving exogenous stimulation of the motor nerve to activate Ia afferents. The H-reflex can be influenced by numerous pre- and post-synaptic mechanisms, with exercise-induced reductions in H-reflex largely attributed to reduced Ia afferent discharge,

increased presynaptic inhibition onto Ia afferents, and decreased α-motoneuron excitability. Only one study has used this technique in response to maximal intensity repeated sprint cycling, consisting of 7 × 10 s sprints [51]. The study assessed the effects of repeated sprints on pre-synaptic inhibition of the spinal reflex pathway by utilising stimulation of cutaneous afferents of the foot, which is known to reduce presynaptic inhibition of Ia afferents [63]. Concurrently, the study measured H-reflex amplitude with and without cutaneous stimulation to assess the effect of exercise-induced changes in pre-synaptic inhibition on spinal loop excitability. The results showed that delivering cutaneous stimulation attenuated the sprint induced reduction in H-reflex, possibly through reduced presynaptic inhibition of Ia afferents, whilst also attenuating the decline in power output throughout the sprints. These results suggest that disfacilitation from group Ia afferents, possibly owing to increased presynaptic inhibition, could be implicated in impaired α-motoneuron output during maximal intensity exercise.

Furthermore, the firing rate of group III and IV muscle afferents, which are mechano- and metabosensitive sensitive sensory receptors that project inhibitory and/or facilitatory feedback to cortical and spinal regions of the motor pathway, likely increases substantially during all-out exercise [64]. However, the role of these afferents on neuromuscular function during maximal intensity exercise is not entirely clear. Torres-Peralta *et al.* [65] had participants perform isokinetic sprints before an incremental exercise test to exhaustion. After the incremental test, the quadriceps were occluded for 10 or 60 s, and a second isokinetic sprint was performed immediately after the occlusion periods. Despite the presumably augmented build-up of metabolites and increased group III/IV afferent feedback elicited by 60 s of occlusion, peak power recovered and was higher than that after 10 s of occlusion. Thus, the authors suggested that the role if group III/IV afferent feedback on maximal sprint performance is negligible, and can be overcome by a strong central command. Hureau *et al.* [46] had participants perform 10 × 10 s cycle sprints, which were preceded by neuromuscular electrical stimulation (NMES) to

elicit metabolic disturbances in the quadriceps. Power output during the sprints, EMG activity, and post-exercise changes in P_{tw} where compared between the NMES and a control condition without NMES. It was shown that both power output and EMG activity were reduced in the NMES condition relative to control, while the post-exercise reduction in P_{tw} was consistent between conditions. Thus, the authors suggested that the metabolic disturbances caused increased group III/IV feedback, thereby reducing neural drive estimated through EMG in order to prevent peripheral homeostasis from deviating beyond tolerable limits. Thus, different interpretations exist on the role of group III/IV afferent feedback during maximal intensity exercise, precluding firm conclusions on the matter [16].

Neuromuscular responses to severe intensity, short-duration exercise

Muscle force generating capacity, voluntary activation and contractile function

Many sporting activities are characterised by short-duration, high-intensity locomotor exercise, such as middle-distance running (i.e. 800-5000 m) or track cycling events lasting ~2-20 min. The exercise intensity associated with these events falls within the 'severe' domain, i.e. above the maximum sustainable exercise intensity, or 'critical intensity'. Due to the rapid energy requirements associated with severe intensity exercise and the consequent generation of ATP from anaerobic pathways, exercise within this domain is associated with a progressive loss of muscle homeostasis, such as a reduction in pH and glycogen and an increase in P_i [23]. These disturbances occurring at the peripheral level impair the capacity of the muscle to produce force in response to neural stimulation. Evidence suggests that disturbances within the muscle are the primary contributor to impairments in muscle force during severe-intensity exercise [21,22,66]. Reductions in P_{tw} range from 16-55% when measured post-exercise (Table 2). This large variability in the magnitude of P_{tw} decrease could be due to a number of factors. Namely, the time to post-exercise neuromuscular assessment ranges from < 10 s to 4 min, with longer

durations often being required to manoeuvre participants to the neuromuscular testing apparatus. Kruger *et al.* [31] recently showed that P_{tw} recovered from −44% immediately post-exercise to −34% following 2 minutes of recovery after severe intensity exercise, likely due to the rapid recovery of metabolic factors thought to interfere with the excitation-contraction coupling [36]. Given that many studies take > 2 min to assess neuromuscular function, there is likely considerable underestimation of the effects of severe intensity exercise on P_{tw}, and Figure 2 highlights that studies with a shorter time to post-exercise neuromuscular assessment demonstrate higher reductions in P_{tw}.

Two other factors could contribute to the discrepancy in the level of reduced P_{tw} observed throughout the literature. Firstly, it is thought that the mechanisms contributing to the limit of tolerance, or the degree of fatigue which can be tolerated, could differ between individuals. Hodgson *et al*. [67] dichotomised a group of apparently homogenous individuals based on those who reached the limit of tolerance during ramp-incremental cycling with a knee-extension power reserve which exceeded the power produced at the limit of tolerance, and those without a power reserve. Those without a power reserve demonstrated exacerbated reductions in P_{tw} relative to those with a power reserve. Thus, it was suggested that task failure in individuals without a power reserve could be due to inhibitions in contractile function rendering them unable to achieve the required power output. In individuals with a power reserve, factors other than impaired contractile function might contribute to the limit of tolerance, or the willingness to tolerate a stronger symptom of fatigue might be lower than those without a power reserve. If disparate inter-individual mechanisms contributing to the limit of tolerance do exist, this could conceivably contribute to the variable reductions in P_{tw} between studies (Table 2) if some

individuals reach critical impairments in contractile function while others reach the limit of tolerance before these occur.

Secondly, the variable reductions in P_{tw} could be due to the considerable variance in the exercise intensity above critical power/speed between studies, with Table 2 displaying that task failure/completion occurred between 3 and 24 min. Conflicting evidence exists on whether the level of intensity above critical intensity influences the magnitude of reduction in P_{tw} at task failure. For example, Thomas *et al.* [21] demonstrated a greater reduction in P_{tw} at task failure when exercise was performed at a higher intensity (task failure at ~3 min) compared with a lower intensity (task failure at ~11 min) within the severe domain (33% vs 16% reduction in P_{tw}, respectively). In contrast, Schafer *et al.* [68] found no difference in end exercise reduction in P_{tw} when the power output was set to deplete the W' within either 3 or 12 min (35% vs 31% reduction in P_{tw}, respectively), though it should be noted in this study participants didn't necessarily exercise to volitional exhaustion. Furthermore, Black *et al.* [23] measured changes in a range of metabolic variables including PCr, lactate, K^+, ATP, pH and glycogen (variables which are linked with the reduction in P_{tw} [36]), and found no difference in the change in any variable when exercise was performed at three different intensities within the severe domain (65, 75 and 85% of work-rate difference between gas exchange threshold and VO_{2max}, in which task failure occurred from 2.2 to 13.9 min), although peak twitch was not measured in the study. It has been proposed that a consistent magnitude of end-exercise alterations in metabolic variables (and thus P_{tw}) could exist due to a task specific 'individual critical threshold' of peripheral alterations in response to severe intensity locomotor exercise, beyond which the degree of associated sensory perceptions would not be tolerable [69]. Proponents of this theory suggested that the individual critical limit of altered metabolic homeostasis is mediated by group III/IV muscle afferents, which could reduce drive from the motor cortex through inhibitory feedback in response to metabolic stimuli. [70-72]. Whether or not alterations within

the muscle are regulated to an unvarying "critical threshold" during locomotor exercise is debated [73-75], and numerous theories exist on exercise tolerance and the degree to which metabosensitive afferent feedback plays a role [76-78]. Nevertheless, when considering the alterations within the neuromuscular system which occur during severe intensity exercise, it is clear that these primarily reside in the muscle.

Impairments in VA are evident in response to severe intensity exercise, with reductions in post-exercise voluntary activation range from 3-14% (Table 2). One study assessed the kinetics of change in neuromuscular function throughout constant load severe intensity exercise. Decorte *et al.* [79] had participants perform intermittent bouts of 6 min cycling at ~80% peak power output, with 4 min recovery between cycling bouts during which neuromuscular function was assessed, and the task completed to exhaustion (occurring on average after 3 bouts of cycling). Their study demonstrated a curvilinear relationship between exercise duration and the decline in P_{tw}, such that most of the decline occurred in the first half of exercise. Concurrently, EMG_{RMS} increased considerably during the first half of exercise, indicative of a higher descending drive required to sustain force due to impairments within the muscle, an interpretation further supported by the positive association between the change in *rectus femoris* EMG_{RMS} and reduction in Q_{tw}. This progressive impairment in contractile function and requirement to activate a greater volume of muscle to maintain a given power output is also thought to be the primary contributor to the VO_2 slow component during severe intensity exercise [80]. Towards the latter stages of exercise (80% and 100% of total cycling duration), there was a plateau in EMG_{RMS}, concurrent with a significant decrease in voluntary activation. These results suggest that once either a certain level of impairment in contractile function or a level of increase in motor drive are reached, no additional increase in motor drive occurs. Whether this plateau in motor drive serves as a protective mechanism to prevent further, potentially harmful, alterations within the muscle, or if further increases in motor drive are

prevented by intrinsic changes along the motor pathway, is unclear [79]. Nevertheless, the results indicate that, during constant-load severe intensity exercise, the impairment in VA widely observed throughout the literature (Table 2) occur primarily during the latter stages of severe intensity exercise, and could thus be implicated in task failure during constant load tasks [79].

It should be noted that the kinetics of altered neuromuscular function likely differ between self-paced versus constant load exercise. For example, Azevedo *et al*. [81] recently characterised neuromuscular responses to a 4 km cycling time-trial, in which the pacing strategy was characterised by a fast-start, even paced, and end-spurt phase. Across three separate visits, neuromuscular function (MVC, VA and P_{tw}) was measured following these three phases. The results demonstrated that all three variables were reduced by 12%, 8% and 23%, respectively, following the fast-start phase, with no further reduction thereafter. The lack of further reduction in MVC, VA or P_{tw} could have been the result of the lower selected intensity during the middle phase, which likely fell below the critical intensity and thereby permitted repletion of work capacity and recovery of neuromuscular function [82,83]. It should be noted, however, that the delay between exercise cessation and neuromuscular testing might have limited the ability to capture further decrements in neuromuscular function following the end-spurt [81].

Table 2. Literature quantifying neuromuscular alterations pre-to-post severe intensity locomotor exercise. Studies utilising protocols which resulted in task-failure in < 30 min were considered "severe intensity".

Author	N	Exercise protocol	Exercise duration	Muscle group	Time to post-exercise measure	Δ MVC	Δ VA	Δ P_{tw}	Δ MEP	Δ CMEP
Leg cycling										
Thomas *et al.* [21]	12	Power @ VO_{2max}	3 min	KE	2.5 min	↓ ~18%	↓ 3%	↓ 33%	↔	NQ
Schafer *et al.* [68]	12	Power output predicted to deplete W' within 3 min based on power-time relationship	3 min	KE	60 s	↓ 20%	↓ 11%	↓ 35%	NQ	NQ
Thomas *et al.* [22]	13	4 km time-trial	6 min	KE	< 2.5 min	↓ 18%	↓ 7%	↓ 40%	↔	NQ
Temesi *et al.* [66]	10	80% peak power output	6 min	KE	< 10 s	↓ 34%	↓ 8%	↓ 55%	NQ	NQ
Ansdell *et al.* [84]	10	4 km time trial	6 min	KE	< 1.5 min	↓ 21%	↓ 14%	↓ 34%	NQ	NQ
Azevedo *et al* [81]	11	4 km time trial	6 min	KE	1 min	↓ 13%	↓ 8%	↓ 26%	NQ	NQ
Amann *et al.* [85]	8	5 km time trial	7 min	KE	3 min	↓ 8%	NQ	↓ 32%	NQ	NQ
Johnson *et al.* [70]	8	85% peak power output	7 min	KE	2 min	↓ 15%	↓ 5%	↓ ~38%	NQ	NQ
Weavil *et al.* [86]	8	80% peak power output	8 min	KE	36 s	↓ 14%	↓ 4%	↓ 43%	↔	↔
Sidhu *et al.* [60]	11	80% peak power output	8 min	KE	10 s - 3 min	↓ 11%	↓ 8%	↓ 30%	↔	↑
Goodall *et al.* [87]	9	~80% peak power output	8 min	KE	< 2.5 min	↓ 17%	↓ 6%	↓ 19%	↔	NQ
Amann *et al.* [88]	8	5 km time trial	8 min	KE	2.5 min	↓ 14%	NQ	↓ 35%	NQ	NQ
Hureau *et al.* [89]	8	5 km time trial	8 min	KE	30 s	↓ ~13%	↓ ~7%	↓ ~41%	NQ	NQ
Amann *et al.* [90]	7	80% peak power output	9 min	KE	3 min	↓ 10%	↔	↓ 34%	NQ	NQ
Blain *et al.* [91]	8	5 km time-trial	9 min	KE	1 min	↓ ~10%	↓ 6%	↓ 31%	↔	↔
Sidhu *et al.* [16]	10	80% peak power output	9 min	KE	49 s	↓ 11%	↓ 14%	↓ 38%	↔	↑
Kruger *et al.* [31]	10	5% above second ventilatory	10 min	KE	10 s	↓ 38%	↓ 8%	↓ 44%	NQ	NQ

		threshold								
Amann *et al.* [92]	8	83% peak power output	10 min	KE	4 min	↓ 10%	↔	↓ 36%	NQ	NQ
Thomas *et al.* [21]	12	60% of differences between RCP and VO_{2max}	11 min	KE	2.5 min	↓ ~16%	↓ 6%	↓ 16%	↔	NQ
Schafer *et al.* [68]	12	Power output predicted to deplete W' within 12 min based on power-time relationship	12 min	KE	60 s	↓ 15%	↓ 12%	↓ 31%	NQ	NQ
O'Leary *et al.* [93]	16	50% between lactate threshold and VO_{2max}	18 min	KE	< 2 min	↓ 19%	↓7%	↓ 31%		
O'Leary *et al.* [94]	18	50% between lactate threshold and VO_{2max}	24 min	KE	52 s	↓ 21%	↓ 7%	↓ 37%	↔	NQ
Running										
Skof and Strojnik [95]	7	6 km time-trial	20 min	KE	60 s	↔	↔	↓ 14%	NQ	NQ
Rowing										
Husmann *et al.* [96]	8	2000 m time trial	7 min	KE	3 min	↓ 20%	↓ 18%	↔	NQ	NQ

KE: knee extensors; MEP: motor evoked potential; MVC: maximal voluntary contraction; NQ: not quantified; P_{tw}: peak twitch force; CMEP: cervicomedullary motor evoked potential; VA: voluntary activation

Central nervous system alterations during severe intensity exercise

Central nervous system alterations during severe intensity exercise have been studied extensively. Figure 3 depicts alterations which occur throughout the neuromuscular pathway in response to severe intensity exercise based on current evidence. To assess specific alterations within the CNS occurring with severe intensity exercise, studies have implemented VA_{TMS} [21,22] and the MEP/CMEP ratio [16,60,86] to assess motor cortical output and excitability, respectively, CMEP to assess α-motoneuron excitability [16,60,86], and afferent blockade through intrathecal fentanyl to assess the effects of group III/IV afferent feedback on neuromuscular function [16,60,69,71,91]. Using VA_{TMS}, a number of studies have demonstrated reductions in the region of 5-8% [21,22,87,93,97]. This could indicate a modest impairment in motor cortical output in response to severe intensity exercise. An impairment in motor cortical output is plausible given the plateau in EMG_{RMS} throughout exercise in this domain as previously discussed [79], i.e. the motor cortex could be unable to 'drive' the α-motoneurons to cause further increases in EMG_{RMS}, although it should be noted that VA_{TMS} provides only surrogate measures of cortical output. Impaired cortical output could be due, at least in part, to inhibition of motor cortical cells due to feedback from group III/IV afferents [16,98]. During exhaustive cycling exercise at 80% peak power output, Sidhu *et al.* [16] demonstrated that the MEP/CMEP amplitude ratio was increased by 25% when group III/IV afferent feedback was reduced with fentanyl-blockade, but was unchanged in the presence of continued afferent feedback in control conditions, thus indicating the inhibitory influence on the motor cortex during severe intensity exercise. Concurrently, the study showed no reduction in VA with reduced afferent feedback, with a 14% reduction in control conditions.

To further explore the mechanisms by which group III/IV afferent feedback inhibits cortical excitability, Sidhu *et al.* [60] assessed the effect of afferent blockade on $GABA_B$ inhibitory intracortical interneurons. Both $GABA_A$ and $GABA_B$ inhibitory interneurons play an integral role in generating and shaping voluntary output from the motor cortex. These intracortical

neurons have indirect projections onto corticospinal neurons, and can influence the excitability of the motor cortex through hyperpolarisation of corticospinal neurons elicited by inhibitory post-synaptic potentials (IPSPs) [99]. By applying a paired-pulse TMS stimulus paradigm known as long-interval inhibition (LII) coupled with conditioned CMEPs during severe intensity cycling, Sidhu *et al.* [60] showed an increase in $GABA_B$ mediated inhibition which was abolished when group III/IV afferents were blocked. Thus, a potential mechanism by which severe intensity exercise inhibits the excitability of the motor cortex is through an increase in $GABA_B$ mediated inhibition as a result of group III/IV afferent feedback. Other severe-intensity exercise induced changes in intracortical inhibition, such as increases in $GABA_A$ mediated short-interval intracortical inhibition (SICI), have been demonstrated [93], though conflicting evidence exists [94]. However, the study of Sidhu *et al.* [60] improved on previous study designs by measuring during post-exercise cycling at an EMG level matched to pre-exercise, as opposed to post-exercise measures taken during isometric contractions. To improve understanding of the effects of severe intensity exercise at the motor cortical level, more research is required assessing motor cortical output and excitability, intracortical inhibitory and facilitatory activity, with measures taken during or immediately following exercise given that these measures can recover rapidly after exercise cessation [100]. The assessment of other possible mechanisms which could contribute to altered cortical output in response to severe intensity exercise, such as alterations in brain neurotransmitters, is also warranted [101].

Using spinal stimulation at the cervicomedullary level, a number of recent studies have assessed the effects of severe intensity exercise at the α-motoneuron excitability [16,86]. In these studies, which utilised constant-load exercise at 80% peak power until task failure, no change in α-motoneuron excitability was demonstrated between the beginning and end of exercise. While this implies no effect of severe intensity exercise at the α-motoneuron level, in non-fatiguing circumstances, the same increase in EMG activity which occurs throughout severe

intensity exercise would cause an increase in spinal excitability [86]. This was aptly shown by Weavil *et al.* [86], who found no change in MEP or CMEP during fatiguing cycling, but a ~40% increase in MEP and CMEP during a subsequent non-fatiguing trial when the EMG was set to increase by the same magnitude. Thus, while the net corticospinal excitability remains unchanged, these results indicated a disfacilitation of the corticospinal tract mediated at the spinal level.

If α-motoneurons are disfacilitation during severe intensity exercise, this does not appear to be related to increased group III/IV afferent feedback. In fact, Sidhu *et al.* [60] found that CMEP amplitude was increased during post-exercise cycling at a matched level of EMG relative to pre-exercise which did not occur when afferent feedback was reduced, suggesting that group III/IV afferents facilitate, rather than inhibit spinal α-motoneurons projecting to the knee extensors. Indeed, previous work has suggested that group III/IV afferent feedback can inhibit or facilitate α-motoneuron depending on the muscle group studied [58]. Furthermore, Sidhu *et al.* [60] also measured CMEP during the silent period to mitigate the potential influence of changes in on-going descending drive on α-motoneuron excitability, but found no change in conditioned CMEPs during control conditions or when afferent feedback was reduced. The authors speculated that the facilitatory effects of group III/IV feedback on α-motoneuron excitability might only occur in the presence of descending drive.

The findings of Sidhu *et al*. [60] appear contradictory to that of Weavil *et al*. [86]. That is, if α-motoneurons are disfacilitated during constant load severe intensity cycling exercise, but a reduction in CMEP is not apparent due to the increased neural drive and EMG [86], one might expect that CMEP would decrease when measured at the same EMG level. However, the opposite was found by Sidhu *et al*. [60], i.e. CMEPs increased. This result cannot be explained by an increased descending drive at the same EMG level, since conditioned CMEPs exhibited no change [60]. One possible explanation is that Weavil *et al*. [86] measured responses during

constant load cycling, while Sidhu *et al*. [60] had participants reduce their power output at post-exercise in order to achieve the same EMG level as pre-exercise. It is possible that processes which disfacilitate α-motoneuron excitability (such as changes in intrinsic properties, activation of serotonin 1A receptors, of neurotransmitter depletion[16,86]) exhibited some recovery due to the decrease in intensity. This, coupled with the elevated facilitatory afferent feedback in the control trial, might have resulted in the increase α-motoneuron excitability at the same EMG level. Further studies measuring α-motoneuron excitability during severe intensity exercise, with both on-going descending drive and during the TMS evoked silent period, are warranted to provide further insight into the effects of severe intensity exercise on α-motoneuron excitability.

Alterations in spinal-loop excitability could also contribute to impaired neuromuscular function during severe intensity exercise, with reductions in H-reflex found to occur in an intensity-dependent manner [102,103]. Bulbulian and Darabos [102] found a 22% reduction in H-reflex amplitude relative to M_{max} measured in the gastrocnemius following 20 minutes of non-exhaustive treadmill running at 75% VO_{2max}, compared to a 13% reduction at 40% VO_{2max}. Similar reductions in H-reflex have been demonstrated following non-exhaustive high-intensity cycling exercise [103]. While the H-reflex alone cannot decipher between altered excitatory input from Ia afferents and a decrease in α-motoneuron excitability, evidence from fatiguing isometric contractions using microneurography show that muscle spindle afferent discharge is progressively reduced during sustained contractions [104], and that the efficacy of Ia input to facilitate the α-motoneuron is impaired due to increased presynaptic inhibition [105]. During severe intensity exercise, presynaptic mechanisms, such as group III and IV afferent induced increases in presynaptic inhibition of Ia terminals, are likely given the metabolic disturbances and the proposed inputs of group III/IV afferents onto Ia afferent terminals [106]. However, challenges associated with measurement techniques preclude definitive conclusions

on the role of Ia feedback in disfacilitating α-motoneurons and thereby contributing to impaired neuromuscular function.

In addition to measuring the specific effects on group III/IV afferent feedback on motor cortical and α-motoneuronal excitability discussed above, a plethora of studies have assessed the effects of group III/IV afferent feedback on neuromuscular function through more global responses such as EMG and P_{tw} [16,60,71,89,91]. These studies have demonstrated that group III/IV afferents constrain motoneuronal output (estimated through EMG) to active skeletal muscle, thereby limiting exercise-induced intramuscular alterations. For example, Blain *et al.* [91] had participants perform a 5 km cycling time trial under control conditions and with fentanyl induced impairment in afferent feedback. With reduced afferent feedback, it was demonstrated that motoneuron output (estimated through *vastus lateralis* EMG) was 21% higher when afferent feedback was reduced compared to control conditions. Due to the greater activation levels throughout cycling, intramuscular alterations such as P_i, H^+ and ADP, concentrations, which are correlated reductions in P_{tw} [107], were all significantly higher compared with control conditions when measured through muscle biopsies following exercise. Consequently, the reduction in P_{tw} was substantially greater when feedback was reduced (52 vs 31% reduction compared with control condition). The increased motoneuron output and end-exercise level of reduced P_{tw} with afferent blockade are consistent findings throughout the literature [85,89,90,108]. Thus, it is suggested that, through metabosensitive firing of group III/IV afferent feedback, the level of metabolic disturbance is sensed within the CNS, and the drive to the muscle is subsequently regulated to prevent abnormal or interoperable deviations in muscle homeostasis [78].

What is not entirely clear is how group III/IV constrains motoneuron output. It is unlikely to be a result of altered α-motoneuron excitability, given that reduced afferent feedback facilitates [61] or has no effect [17] on CMEP amplitude. However, given the inhibitory effects of group III/IV afferent feedback within [16,60] and potentially upstream of the motor cortex [98], as well as their proposed inputs to Ia terminals [106], motoneuron output could be constrained through the neurophysiological adjustments that group III/IV afferents elicit within the CNS. However, as well as having proposed non-nociceptive effects through alterations in CNS function and induction of the pressor reflex [85], group III/IV afferents also elicit nociceptive effects, which could also have implications for perception of effort during exercise. The increased level of effort associated with discomfort and increased cardiopulmonary response as a result of group III/IV feedback could impact how hard participants are willing to 'push' during exercise, and thereby influence motoneuron output. During exercise at a constant load of 80% peak power output, Amann *et al*. [90] demonstrated the rate of perceived exertion (RPE) was lower following the initial 3 minutes of the task when afferent feedback was reduced relative to control conditions. During self-paced exercise, the RPE remains similar between reduced afferent feedback and control conditions throughout exercise, but the power output is enhanced during the early stages of exercise with reduced afferent feedback [91]. Thus, early during severe intensity exercise, nociceptive and cardiopulmonary feedback likely contributes to an increased sense of effort associated with the same power output [90], or causes participants to choose a lower power output during self-paced tasks [91]. Towards the latter stages of exercise, however, RPE is similar with and without reduced afferent feedback [90]. This is likely the result of the increased drive to the muscle occurring throughout exercise due to the lack of nociceptive feedback, thereby 'allowing' greater activation of muscle, and in turn causing greater disturbances within the muscle. As the muscle becomes less responsive, a greater level of drive is required to compensate for contractile impairment and sustain the same power output [90], with

this increase in efferent command emitting parallel messages (corollary discharge) to brain regions associated with perceptions of exertion, thereby increasing RPE [109]. Accordingly, in addition to the alterations along the neuromuscular pathway induced by group III/IV feedback, the nociceptive and cardiopulmonary signals evoked by these afferents likely influences the regulation of voluntary drive and perceptions of effort throughout exercise.

Neuromuscular responses to sustained exercise below critical power

Muscle force generating capacity, voluntary activation and contractile function

Exercise between lactate threshold and critical intensity is classified as heavy intensity exercise, while exercise below lactate threshold is termed moderate intensity [23,24]. Heavy intensity exercise can be sustained for prolonged periods, with time to task failure ranging between ~40 min to 3 hours [23,110]. Moderate intensity exercise can be performed for durations well above 3-5 hours, and constitute the intensity at which ultra-endurance events are performed [20,77]. The neuromuscular responses measured in studies in which exercise lasted from > 30 min to 3 hours (likely falling predominantly within the heavy domain) and > 3 hours (predominantly within the moderate domain) are displayed in Tables 3 and 4, respectively. While variation exists in the literature, a comparison between the results from the studies in these tables suggests that the loss in muscle strength is greater with increasing exercise duration before reaching an eventual plateau above exercise lasting ~1000 min (Figure 4), a phenomenon previously highlighted by Millet when examining running-based exercise [77].

Within the heavy and moderate domains, energy supply is achieved through oxidative metabolism, rather than anaerobic pathways [25,111]. Consequently, alterations in muscle metabolism are much more limited than with exercise in the severe domain, with steady-state values of PCr, pH and P_i achieved within the first few minutes of exercise [23,25]. Nevertheless, impairments in contractile function have been widely observed following both moderate and severe intensity exercise (Tables 3 and 4). Following self-paced tasks, some of the reductions in P_{tw} could be a result of a "sprint-finish", in which intensity increases towards the latter stages of a race and thus fall within the severe domain, with associated metabolic changes which contribute to reduced P_{tw} [22]. For example, following a self-paced 20 km time trial lasting on average 32 min, Thomas *et al.* [22] showed a 31% reduction in P_{tw}, while in a separate study by the same group, the reduction in P_{tw} following a constant load task in which task-failure

occurred at 42 min was just 11% [21]. Thus, the self-paced versus constant pace exercise challenges used across studies is another potential source of heterogeneity in results regarding neuromuscular responses to moderate and heavy intensity exercise (Tables 3 and 4). However, the magnitude of reduced P_{tw} observed by Thomas *et al.* [21] following constant load exercise is consistent with other studies within the heavy domain, with Lepers *et al.* [112,113] and Racinais *et al.* [114] demonstrating reductions in P_{tw} of 9, 12 and 11%, respectively. Interestingly, this reduction in P_{tw} is lower than some studies assessing P_{tw} following more prolonged constant load moderate intensity exercise [115,116] (Figure 4C), suggesting a possible greater extent of impaired contractile function following more prolonged locomotor exercise, though heterogenous results exist throughout the literature (Table 4).

It is thought that glycogen depletion is the primary contributor towards impaired contractile function following prolonged heavy and moderate intensity exercise [111,117]. Glycogen depletion could interfere with the excitation-contraction coupling through localised depletion of muscle glycogen at the t-tubular-sarcoplasmic reticulum (SR) junction [118]. Indeed, following 4 h of glycogen depleting exercise, Gejl *et al.* [119] showed a persistent reduction in SR Ca^{2+} release after 4 h of recovery when participants were given only water, while participants given carbohydrates concurrently demonstrated recovery of SR Ca^{2+} release. Inhibition of SR Ca^{2+} release is thought to occur below critical levels of muscle glycogen (250-300 $mmol \cdot kg^{-1}$) [120], and values below these concentrations have been demonstrated following heavy and moderate intensity exercise [23,110], including ultramarathon running [121]. Another mechanism likely contributing to impaired contractile function include increased production of reactive oxygen and nitrogen species [122], which increase following prolonged exercise [123] and interfere with Ca^{2+} release through redox modifications of ryanodine receptors [124]. Furthermore, following running based exercise involving repeated stretch shortening cycles, muscle damage induced myofibrillar disintegrity and disorganisation of sarcomeres likely occurs, leading to a reduced

ability of the contractile machinery to produce force [125]. Thus, while the magnitude of impaired contractile function is not as prominent following moderate and heavy intensity exercise compared to severe intensity, the consistently reduced P_{tw} across studies (Tables 3 and 4) suggests that alterations within the muscle contribute to reduced neuromuscular function within these domains.

Reductions in VA are substantial following moderate and heavy intensity exercise, and these appear to be exacerbated as exercise duration increases (Figure 4). This likely explains, at least in part, the increased strength loss associated with longer duration exercise (Figure 4). Studies examining the kinetics of altered neuromuscular function during prolonged moderate duration exercise have shown that reduced VA occurs in the latter stages, with Place *et al.* [126] and Lepers *et al.* [116] demonstrating that VA was reduced only following 4 and 5 h of a 5 h running and cycling task, respectively.

Table 3. Literature assessing neuromuscular responses pre-to-post heavy intensity exercise. Studies in which exercise duration ranged from > 30 – 189 min were considered "heavy intensity".

Author	N	Exercise protocol	Exercise duration/distance	Muscle group	Time to post-exercise measure	Δ MVC	Δ VA	Δ P_{tw}	Δ MEP	Δ CMEP
Leg cycling										
Thomas *et al.* [22]	13	20 km time trial	32 min	KE	< 2.5 min	↓ 15%	↓ 11%	↓ 31%	$\downarrow_{restingMEP}$	NQ
Lepers *et al.* [112]	10	75% PPO	33 min	KE	~1 min	↓ 7%	↓ 1%	↓ 9%	NQ	NQ
Thomas *et al.* [21]	12	Power output @ RCP	42 min	KE	2.5 min	↓ ~17%	↓ 9%	↓ 11%	↔	NQ
Thomas *et al.* [22]	13	40 km time trial	66 min	KE	< 2.5 min	↓ 16%	↓ 10%	↓ 29%	$\downarrow_{restingMEP}$	NQ
Sahlin & Seger [127]	7	~75% VO_{2max}	85 min	KE	NQ	↓ 44%	↓ 26%	NQ	NQ	NQ
Lepers *et al.* [113]	8	65% PPO	120 min	KE	Immediately	↓ 12%	NQ	↓ 12%	NQ	NQ
Running										
Racinais *et al.* [114]	11	First ventilatory threshold	90 min	PF	5 min	↓ 11%	↓ 2%	↓ 11%	NQ	NQ
Saldanha *et al.* [128]	8	75% VO_{2peak}	120 min	PF	< 5 min	↓ 17%	↓ 19%	↔	NQ	NQ
Petersen *et al.* [129]	8	42.2 km (marathon)	154 min	KE	30 min	↓ 23%	NQ	↔	NQ	NQ
Petersen *et al.* [129]	8	42.2 km (marathon)	154 min	PF	30 min	↓ 18%	NQ	↔	NQ	NQ
Millet *et al.* [130]	12	30 km race	189 min	KE	< 3 min	↓ 25%	↓ 8%	↓ ~6%	NQ	NQ
Other										
Millet *et al.* [131]	11	42.2 km (ski skating)	149 min	KE	< 5 min	↓ 8%	↔	↑ 7%	NQ	NQ

KE: knee extensors; MEP: motor evoked potential; MVC: maximal voluntary contraction; NQ: not quantified; PF: plantar flexors; P_{tw}: peak twitch force; CMEP: cervicomedullary motor evoked potential; VA: voluntary activation

682 **Table 4.** Studies assessing neuromuscular responses pre-to-post moderate intensity exercise. Studies in which exercise duration was > 240 min were
683 considered "moderate intensity".

Author	N	Exercise protocol	Exercise duration/distance	Muscle group	Time to post-exercise measure	Δ MVC	Δ VA	Δ P_{tw}	Δ MEP	Δ CMEP
Leg cycling										
Jubeau *et al.* [115]	10	45% PPO	240 min	KE	< 3 min	↓ 25%	↓ 13%	↓ 28%	↑	NQ
Lepers *et al.* [116]	9	55% PPO	300 min	KE	Immediately	↓ 18%	↓ 6%	↓ 16%	NQ	NQ
Running										
Ross *et al.* [132]	9	42.2 km (marathon)	208 min	PF	< 20 min	↓ 18%	↓ 14%	↓ 71%	$\downarrow_{restingMEP}$	NQ
Millet *et al.* [130]	11	140 km race	278 min	KE	15 min	↓ 9%	↔	↔	NQ	NQ
Place *et al.* [126]	9	55% MAV	300 min	KE	Immediately	↓ 28%	↓ 16%	↑ 18%	NQ	NQ
Gauche *et al.*[133]	22	55 km trail run	413 min	KE	60 min	↓ 37%	↓ 2%^{CAR}	NS	NQ	NQ
Millet *et al.* [134]	9	65 km ultramarathon	511 min	KE	< 2 min	↓ 30%	↓ 20%	↑ 25%	NQ	NQ
Martin *et al.* [135]	12	Treadmill running	19 h (149km)	KE	NQ	↓ 40%	↓ 33%	↓ 25%	NQ	NQ
Martin *et al.* [135]	12	Treadmill running	19 h (149 km)	PF	NQ	↓ 30%	↓ 15%	↓ 23%	NQ	NQ
Giandolini *et al.* [136]	23	110 km mountain ultra-marathon	20 h	KE	57 min	↓ 36%	↓ 18%	↓ 11%	NQ	NQ
Giandolini *et al.* [136]	23	110 km mountain ultra-marathon	20 h	PF	57 min	↓ 28%	↓ 10%	↓ 17%	NQ	NQ
Temesi *et al.* [17]	25	110 km mountain ultra-marathon	20 h	KE	61 min	↓ 34%	↓ 26%	↓ 10%	↑	NQ
Temesi *et al.* [137]	20	110 km mountain ultra-marathon	20 h	KE	58 min	↓ 38%	↓ 24%	↓ 10%	↑	NQ

Temesi *et al.* [137]	20	110 km mountain ultra-marathon	20 h	PF	80 min	↓ 26%	↓ 9%	↓ 16%	NQ	NQ
Millet *et al.* [138]	22	166 km mountain ultra-marathon	38 h	KE	20 min	↓ 35%	↓ 19%	↓ 22%	NQ	NQ
Millet *et al.* [138]	22	166 km mountain ultra-marathon	38 h	PF	20 min	↓ 39%	↓ 6%	↓ 20%	NQ	NQ
Besson *et al.* [139]	17	169 km mountain ultra-marathon	44 h	KE	24 min	↓ 32%	↓ 23%	↓ 24%	NQ	NQ
Besson *et al.* [139]	17	169 km mountain ultra-marathon	44 h	PF	23 min	↓ 34%	↓ 19%	↓ 23%	NQ	NQ
Saugy *et al.* [140]	15	330 trail run	122 h	KE	~30 min	↓ 24%	↓ 20%	↓ 24%	NQ	NQ
Saugy *et al.* [140]	15	330 trail run	122 h	PF	~30 min	↓ 26%	↓ 26%	↓ 19%	NQ	NQ

CAR: central activation ratio; KE: knee extensors; MAV: maximum aerobic velocity; MEP: motor evoked potential; MVC: maximal voluntary contraction; NQ: not quantified; PF: plantar flexors; P_{tw}: peak twitch force; CMEP: cervicomedullary motor evoked potential; VA: voluntary activation

Central nervous system alterations during moderate and heavy intensity exercise

Overall, little research exists examining specific alterations within the CNS in response to moderate or heavy intensity exercise. Studies have demonstrated reductions in VA_{TMS} within both domains [17,21,115], possibly indicating impaired motor cortical output. The impact of prolonged exercise on the excitability of the motor pathway is unclear. When measured with the muscle at rest, studies have demonstrated reductions in MEP amplitude following prolonged exercise ranging from 20 km cycling [22], marathon running [132], and a simulated Tour de France [141]. However, changes in MEP amplitude at rest might not reflect alterations in corticospinal excitability that occur during contractions. When corticospinal excitability has been assessed pre- and post-prolonged exercise during isometric contractions, conflicting findings exist, with studies reporting an increase [17], decrease [132,141], or no change in MEP amplitude [21,22,142]. Similarly conflicting results have been shown for the silent period, with no change [115] or an increase [17] being reported. The conflicting findings could be the result of the substantial heterogeneity in the exercise challenges, such as the modalities and the duration of the task, as well as methodological differences such as stimulation intensities and the contraction intensities at which corticospinal excitability is measured, both of which can influence the change in MEP in response to exercise [17,143]. No research to date has utilised spinal stimulation to assess the effect of prolonged exercise on α-motoneuron excitability, and this represents an area for future research. Racinais *et al.* [114] demonstrated a 61% reduction in H-reflex amplitude following 90 min of non-exhaustive running exercise. Avela *et al.* [62] observed similar reductions in H-reflex amplitude following marathon running, whilst also displaying reductions in the EMG response and passive stretch-resisting force following a natural stretch reflex evoked through sudden changes in muscle length. However, whether this was due to altered Ia excitatory input or impaired α-motoneuron excitability is unclear. Further

work is required to elucidate the effects of prolonged exercise within the moderate and heavy exercise domains on the corticospinal pathway at both the supraspinal and spinal level.

Neuromuscular responses to high-intensity intermittent exercise

While an increasing number of studies have assessed neuromuscular responses to continuous locomotor exercise during tasks such as cycling and running, many team sports, such as association football (soccer), rugby league, and hockey, are characterised by bouts of high-intensity exercise interspersed with prolonged periods of low-to-moderate intensity activity. In addition, team sport players also complete numerous dynamic actions throughout competitive matches, such as jumping, changing direction, tackling and/or kicking, which are often performed with incomplete recovery [144]. Consequently, high-intensity intermittent team sports are associated with a high physiological and neuromuscular demand, resulting in substantial fatigue and impairments in neuromuscular function [145]. During team sports such as soccer and hockey, fatigue manifests through transient reductions in work-rate following the most demanding periods of a match, and cumulative reductions in work-rate towards the end of a match [144]. In addition, fatigue is thought to increase the risk of sustaining an injury during match-play, as players are more susceptible to sustaining injuries towards the latter stages of a match [6]. In order to better understand the physiology underpinning fatigue experienced during match-play, studies have examined the neuromuscular responses to simulated and competitive high-intensity intermittent team sport activity.

Using a simulated soccer match protocol designed to replicate the physiological demands of soccer match-play, Goodall *et al.* [145] investigated neuromuscular function before, at half-time (i.e. 45 min), full-time (i.e. 90 min) and following a period of extra time (i.e. 120 min). An interesting finding from this study was that while the simulated soccer match induced reductions in MVC and impairments in both contractile function and VA, the reduction in

contractile function demonstrated a plateau after half-time (Figure 5). It was hypothesised that this plateau was due to the early fatigue of higher threshold motor units, which are more susceptible to fatigue, within the first half. In the second half, the lower reduction in contractile function was suggested to be a result of the recruitment of more fatigue-resistant motor units, which exert a smaller reduction in the size of evoked twitch responses. In contrast to the nadir in contractile function, impairments in VA increased progressively, with a VA lower at half-time compared with pre-match, and lower at the end of extra-time compared with half-time. These impairments in neuromuscular function were concurrent with increases in perceptions of effort and impairments in voluntary physical performance (sprint speed and jump height) measured in a companion study [146].

Numerous other studies have assessed neuromuscular function following a range of competitive and simulated high intensity intermittent team sport protocols (Table 5). Following simulated [147] and competitive soccer match-play [15,148], studies have demonstrated impairments in P_{tw} and VA of around 14% and 8%, respectively [15,148], resulting in a 11-14% reduction in knee extensor MVC. These impairments occurred concurrently with decreases in jump height, reactive strength and sprint speed [15,147]. The mechanisms of impaired contractile function following match-play likely relate to the considerable muscle damage elicited by the numerous eccentric actions associated with match-play [149], glycogen depletion, with glycogen levels reported to fall below concentrations at which Ca^{2+} handling is impaired [119,150], and increases in reactive oxygen and nitrogen species, with measures of oxidative stress increased following a single match [149], possibly inhibiting Ca^{2+} handling [122]. The mechanisms of impaired VA are less clear, with the limited number of studies examining corticospinal and intracortical responses following simulated [145,147] and competitive match-play [15] showing no changes post-exercise, though further research is required to assess the effect of high-intensity intermittent exercise on spinal reflex pathways and α-motoneuronal excitability. Thus, during prolonged

high-intensity intermittent exercise such as soccer match-play, neuromuscular function is impaired both at the peripheral and central level, with peripheral disturbances more prevalent in the earlier stages of exercise, and impairments in VA more apparent as exercise progresses. These disruptions in neuromuscular function likely contribute to the decline in physical performance known to occur following the most demanding periods of match-play and towards the end of a match.

Table 5. Studies assessing neuromuscular responses pre-to-post high-intensity intermittent team sport exercise.

Author	N	Exercise protocol	Exercise duration/distance	Muscle group	Time to post-exercise measure	Δ MVC	Δ VA	Δ P_{tw}	Δ MEP	Δ CMEP
Soccer										
Brownstein *et al.* [15]	16	Competitive match	90 min	KE	10-60 min	↓ 14%	↓ 7%	↓ 14%	↔	NQ
Rampinini *et al.* [148]	20	Competitive match	90 min	KE	40 min	↓ 11%	↓ 8%	↓ 8%	NQ	NQ
Thomas *et al.* [147]	15	Simulated match	90 min	KE	< 2.5 min	↓ 16%	↓ 9%	↓ 14%	↔	NQ
Goodall *et al.* [145]	10	Simulated match	120 min	KE	< 2.5 min	↓ 27%	↓ 18%	↓ 23%	↔	NQ
Rugby league										
Murphy *et al.* [151]	9	Competitive match	80 min	KE	< 10 min	↓ 11%	↔	↓ 34%	NQ	NQ
Skein *et al.* [152]	11	Competitive match	80 min	KE	NQ	↓ 8%	↔	NQ	NQ	NQ
Duffield *et al.*[153]	11	Competitive match	80 min	KE	NQ	↓ 8%	↔	↓ 15%	NQ	NQ
Pointon & Duffield [154]	10	Simulated match	60 min	KE	< 10 min	↓ ~13%	↓ ~7%	↓ 21%	NQ	NQ
Basketball										
Ansdell *et al.* [155]	10	Simulated match	60 min	KE	75 s	↓ 15%	NQ	↓ 13%	NQ	NQ
Intermittent sprint protocol										
Minett *et al.* [156]	9	Intermittent sprints	70 min	KE	< 10 min	↓ ~16%	↓ ~4%^{CAR}	NQ	NQ	NQ
Pointon *et al.* [157]	10	Intermittent sprints	60 min	KE	< 10 min	↓ ~25%	↓ ~11%	↓ 21%	NQ	NQ

KE: knee extensors; MEP: motor evoked potential; MVC: maximal voluntary contraction; NQ: not quantified; P_{tw}: peak twitch force; CMEP: cervicomedullary motor evoked potential; VA: voluntary activation

Conclusions on the role of exercise intensity on neuromuscular responses to locomotor exercise

The above synopsis of the current literature pertaining to neuromuscular responses to maximal, severe, heavy, moderate and high-intensity intermittent intensity locomotor exercise, provides insight into the challenge imposed on the neuromuscular system during fatiguing locomotor activity. Across the exercise domains, there are both commonalities and differences in neuromuscular responses which warrant discussion.

Overall, the reduction in muscle force generating capacity is similarly reduced following exhaustive maximal, severe and heavy intensity exercise [21,31]. Reductions in MVC are more pronounced following long-duration moderate intensity exercise, which appears to be related to exercise duration (Figure 3). However, different neuromuscular mechanisms are likely to contribute to declines in MVC between domains. While VA has been shown to be reduced following exercise across all domains, possibly due in part to impaired motor cortical output, these reductions are more substantial following prolonged moderate and heavy intensity exercise. For example, Thomas *et al*. [21] demonstrated a 9% reduction in VA following 42 min of cycling at the power output associated at the respiratory compensation point, compared to a 3% reduction at the power output associated with $VO_{2max,}$ with a similarly greater magnitude of reduced VA following prolonged compared with short-duration self-paced cycling [22]. As indicated in previous sections, reductions in VA appear to occur in a dose-response manner based on the duration of exercise. What is unclear at present is which mechanisms contribute to the exacerbated reduction in VA following prolonged exercise. While increases in group III/IV afferent feedback have been suggested to contribute to impaired VA in response to severe intensity exercise [16], the firing rate of these afferents are less likely to increase below critical intensities given that there is a lower build-up of metabolites or, in the case of cycling, markers of muscle damage to which these afferents are sensitive [158]. The greater reduction in

VA_{TMS} following prolonged heavy intensity exercise compared with short-duration severe intensity exercise [21,22] would suggest that impaired cortical output could be an important contributor. However, the mechanisms contributing to impaired VA_{TMS} are not well understood. Exacerbated increases in core temperature [159] and alterations in neurotransmitter concentrations [101] have both been suggested, however comparisons between these potential contributors across domains has not been made.

Similarly, no evidence exists comparing the effects of exercise within different domains on α-motoneuron responses to exercise. Following maximal intensity arm cycling exercise, one study observed an increase in α-motoneuron excitability [45]. During severe intensity exercise, it is suggested that α-motoneurons are disfacilitated [86], while another study suggests a fatigue-induced facilitation of α-motoneurons [60]. No evidence exists on the effect of prolonged moderate or heavy intensity exercise on α-motoneuron excitability. Thus, the precise effects of different intensities of locomotor exercise on α-motoneuron excitability is unclear, and more research is required to better understand these responses.

Contractile function is also impaired following exercise within all domains. The magnitude and the mechanisms of this reduction, however, differ. Impairments in contractile function are greater following maximal and severe intensity exercise compared with moderate and heavy intensity exercise [21,22,31]. For example, Kruger *et al*. [31] found a 50% reduction in P_{tw} following a 30 s of all-out cycling, a 44% reduction following 10 min of severe intensity exercise, and a 14% reduction following 90 min of moderate intensity exercise. The mechanisms contributing to impairments in contractile function following maximal and severe intensity exercise are likely relate to a build-up of metabolites associated with high anaerobic energy turnover. In contrast, the reduction in P_{tw} following prolonged exercise is thought to be related to glycogen depletion [119], increased production of reactive oxygen and nitrogen species [122], and, following running-based exercise, muscle damage [125]. Accordingly, the distinct metabolic responses

between exercise domains causes impaired contractile function through different mechanisms and to different degrees.

Finally, there are similarities across all domains with respect to the kinetics of altered neuromuscular function. For example, during repeated sprint [43], constant load severe intensity [79], high-intensity intermittent [145], and prolonged constant load moderate intensity exercise [116], impaired contractile function is demonstrated during the first half of exercise, before impaired VA becomes more evident during the latter half. During repeated sprint exercise, motoneuron output estimated through EMG is progressively reduced [39], while EMG is increased before plateauing during severe intensity exercise [79]. Thus, the nadir in reduction P_{tw} commonly observed during exercise within these domains could be due to the reduced or plateaued recruitment of muscle during the later stages of exercise, causing no further decrements in contractile function.

To better understand the effects of different intensities of locomotor exercise on neuromuscular function, more research is required, similar to that of Thomas *et al*. [21,22], to compare neuromuscular responses at a segmented level between different exercise domains. Furthermore, although challenging, studies should attempt to deliver stimulations to probe the excitability of the corticospinal tract, both at the cortical and spinal level, during the task itself [16,60,86]. Finally, due to the rapid recovery of contractile and CNS following exercise [31,160], studies should attempt to rapidly deliver stimulations upon exercise cessation in situations where neuromuscular function is being assessed post-exercise. This can be achieved using custom-built exercise ergometers which permit immediate neuromuscular assessments without the requirement to manoeuvre between exercise and testing apparatus [31,66,161].

The effect of exercise modality on neuromuscular responses to locomotor exercise

One of the central themes surrounding research into the neuromuscular responses to fatiguing exercise is task-dependency. In addition to the influence of exercise intensity and duration discussed earlier, exercise modality, or the type of locomotor exercise being performed, can have a profound influence on the demands placed on the neuromuscular system [130]. Exercise modality can influence the contraction type in the prime movers involved in locomotor exercise, as well as contraction duration or time under tension, the active skeletal muscle mass, mechanical efficiency and muscle recruitment strategy. All of these factors can in turn influence the metabolic and mechanical stress imposed on the muscle, and the mechanisms underpinning decrements in neuromuscular function during exercise.

While several different modes of locomotor exercise exist (e.g. running, cycling, rowing, skiing), systematic comparisons delineating the neuromuscular responses to different exercise modes are scarce. However, studies by Lepers *et al.* [116] and Place *et al.* [126] assessed the neuromuscular responses to cycling and running exercise, respectively, at the same relative intensity (55% maximal aerobic power or velocity) and duration (5 h). Comparisons between the results of those studies show that, despite the similar exercise intensity and duration, the reduction in knee extensor strength was greater following running (28%) compared with cycling exercise (18%). The greater reduction in MVC was likely due to the greater reduction in VA following running (16%) compared with cycling (8%). In a study directly comparing cycling and running exercise, Tomazin *et al.* [47] had participants perform three sets of five × six second repeated sprints on both a treadmill and a cycle ergometer, on separate occasions. The study found that the reduction in MVC was greater during and following running sprints compared with cycling. In addition, the reduction in MVC was accompanied by a reduction in VA throughout the running protocol which was not seen during cycling. Following ~3 h of running [130] and skiing exercise [131], a significant reduction in VA (8%) was only observed

following running based exercise. Thus, it appears that alterations to CNS function and consequent impairments in muscle strength are greater following running-based exercise compared with other locomotor exercise modes. This is likely a result of the muscle damage associated with running based exercise, and the lower mechanical demands imposed during exercise such as cycling and skiing. Specifically, running involves multiple stretch shortening cycles and associated eccentric contractions, likely to elicit considerable muscle damage, whereas cycling and skiing impose a high metabolic stress but a substantially lower mechanical stress. In turn, muscle damage could elicit reductions in VA through reduced sensitivity of muscle spindles and disfacilitation of α-motoneurons from Ia afferents [62], and/or increased inhibitory feedback from group III/IV afferents which are sensitive to various markers of muscle damage [162]. Furthermore, muscle damage elicited by eccentric exercise protocols have been shown to elicit substantial impairments in VA when measured immediately post-exercise [158], further suggesting that muscle damage sustained during running contributes to the greater reduction in VA compared with cycling.

At the peripheral level, studies have reported a greater reduction in contractile function during and following cycling compared with running [116,126,163]. For example, following 5 × 6 s cycling and running sprints, Rampinini *et al.* [163] demonstrated a significantly greater reduction in knee extensor peak twitch force following cycling (~55% reduction) compared with running (~35%). Similarly, Lepers *et al.* [116] found a significant reduction in knee extensor peak twitch during every hour throughout 5 h of cycling, whereas Place *et al.* [126] showed a potentiation of quadriceps contractile properties throughout 5 h of running exercise. The higher disturbances at the peripheral level in response to cycling could be a consequence of the differences in the involved muscle mass. For example, during weight supported sports such as cycling, the overall active muscle mass involved is lower than during running, with force primarily generated from the quadriceps. It has been demonstrated throughout the literature that during tasks involving

lower active muscle mass, the reduction in twitch force is higher [164,165]. This is likely because during tasks involving a higher muscle mass, there is a greater sensory input (e.g. from group III/IV afferents) from the involved muscle mass, as well as a greater disruption to homeostasis in other physiological systems (e.g. cardiovascular, respiratory) [73]. Consequently, there is a greater contribution to fatigue and the limit of tolerance from multiple physiological systems, whereas during cycling the more local, less diffuse signal from the lower muscle mass permits greater disturbances within the muscle to be tolerated [73]. Moreover, running and cycling comprise different types of muscle contraction, with implications for the metabolic cost of exercise and thereby the neuromuscular responses. For example, during running, ~60% of the time taken to complete one stride is spent in the support phase (i.e. foot contact with the ground) for speeds between 12 and 23 km/h [166]. In turn, around 34% of the support phase comprised eccentric muscle action, which has implications for the metabolic demand of running both due to the lower metabolic cost of eccentric contractions, and the higher efficiency of subsequent concentric contractions due to the "preloading" of muscle during the eccentric phase (i.e. through the stretch-shortening cycle) [167]. Furthermore, the greater central deficit during running exercise possibly related to Ia disfacilitation (see above) could also limit alterations in contractile function. During cycling exercise, there is a high intramuscular tension throughout the majority of the pedal revolution, requiring high force generating of the quadriceps, and consequently greater recruitment of type II motor units. The high intramuscular pressure could also lead to partial occlusion of femoral artery blood flow, thereby reducing oxygen delivery and leading to greater metabolic disturbances [168]. Thus, there are several potential explanations to the greater impairment in P_{tw} found after cycling versus running based exercise. Overall, there remains limited evidence comparing neuromuscular responses to different modes of locomotor exercise, and research in this area could provide useful information for athletes and practitioners when devising training programmes.

Conclusions and future research

The present review provides a synopsis of literature, conducted primarily over the last two decades, pertaining to alterations in neuromuscular function in response to fatiguing locomotor exercise. The plethora of research which now exists in this area has clearly demonstrated the integral importance of task-dependency on alterations within the neuromuscular system. It is well established that neuromuscular function during exercise above critical intensity is primarily limited by disturbances in metabolic homeostasis and consequent impairments in contractile function. More prolonged exercise below critical intensity causes considerable reductions in the capacity of the nervous system to activate muscle, though the precise alterations within the central nervous system contributing to this reduction are still unclear. During repeated sprint, constant load severe intensity, high-intensity intermittent, and prolonged constant load moderate intensity exercise, impaired contractile function is demonstrated during the first half of exercise, before impaired voluntary activation becomes more evident during the latter half. Primarily, studies have utilised electrical nerve stimulation at rest and during maximal voluntary contractions to determine the effects of locomotor exercise at the peripheral and central level, respectively. To further investigate alterations within the nervous system, many studies have additionally utilised transcranial magnetic stimulation to assess the excitability of the corticospinal pathway, electrical stimulation of descending spinal tracts to assess α-motoneuron excitability, and nerve stimulation to assess spinal loop excitability at rest or during isometric contractions prior to and following locomotor exercise. While these studies have provided valuable insight into how various types of locomotor exercise impact the neuromuscular system, one limitation of this approach is that measuring responses during isometric contractions deviates from the locomotor exercise task itself, and thus hinders understanding of neuromuscular alterations that occur during the task.

For example, while prolonged exercise elicits substantial reductions in voluntary activation of muscle during a maximal voluntary contraction, the relevance of this reduction to exercise performance during submaximal intensity tasks is unclear, and has been questioned [74]. Measuring the force generating capacity of muscle during isometric contractions also deviates from the types of contractions performed during dynamic locomotor exercise, and indeed measures of neuromuscular function during isometric contractions are not interchangeable with those measured during dynamic assessments [169]. Moreover, the delay between exercise cessation and commencing neuromuscular assessments represents a significant general limitation when studying neuromuscular responses to locomotor exercise. To overcome these limitations, studies over the last decade have developed methodologies allowing them to deliver transcranial magnetic and electrical spinal stimulation during the locomotor exercise task itself [60,86]. This represents an important advancement in the field, and future research should seek to employ similar techniques to better understand how various locomotor exercise challenges influence the nervous system during exercise. New and emerging methodologies, such as high-density surface EMG, have the potential to provide further insight into exercise-induced alterations in nervous system function, though incorporating these techniques in response to locomotor exercise is a challenging prospect. Overall, while considerable advancements have been made in the last two decades, more work is required to provide further insight into locomotor exercise induced alterations in neuromuscular function, particularly within the central nervous system.

Table and Figure Legends

Table 1. Literature quantifying neuromuscular alterations pre-to-post maximal intensity locomotor exercise.

Table 2. Literature quantifying neuromuscular alterations pre-to-post severe intensity locomotor exercise. Studies utilising protocols which resulted in task-failure in < 30 min were considered "severe intensity".

Table 3. Literature assessing neuromuscular responses pre-to-post heavy intensity exercise. Studies in which exercise duration ranged from > 30 – 189 min were considered "heavy intensity".

Table 4. Studies assessing neuromuscular responses pre-to-post moderate intensity exercise. Studies in which exercise duration was > 240 min were considered "moderate intensity".

Table 5. Studies assessing neuromuscular responses pre-to-post high-intensity intermittent team sport exercise.

Figure 1. Proposed alterations in neuromuscular function occurring during maximal intensity exercise. Adapted from Taylor *et al.* [61].

Figure 2. Relationship between time to post-exercise assessment and reduction in knee extensor maximum voluntary contraction (MVC; A), voluntary activation (VA; B) and peak twitch force (P_{tw}; C) as a percentage of pre-exercise [16,21,22,31,60,66,68,70,84,86,87,89,91,93,94,96]. The R^2 is derived from the logarithmic slope presented on each graph.

Figure 3. Proposed alterations in neuromuscular function occurring during severe intensity exercise. Adapted from Taylor *et al*. [61].

Figure 4. Relationship between reduction in knee extensor maximal voluntary contraction (MVC; A), voluntary activation (VA; B) and peak twitch force (P_{tw}; C) as a percentage of pre-

exercise relative to the duration of exercise. Note that the figure pertains only to longer duration with a minimum duration of 30 min [17,21,22,113-116,126-128,135-140]. * outlier [127].

Figure 5. Maximum voluntary contraction (A), potentiated knee-extensor twitch force (B) and voluntary activation measured with motor nerve (VA), and motor cortical (VA_{TMS}) stimulation (c) at pre-exercise, half time (HT), full time (FT), and following extra time (ET) of a simulated soccer match. $P = < 0.05$ vs. the pre-exercise value, † = $P < 0.05$ vs. HT, ‡ = $P < 0.05$ vs. FT. From Goodall *et al*. [145].

Conflict of Interest

The authors have no conflicts of interest.

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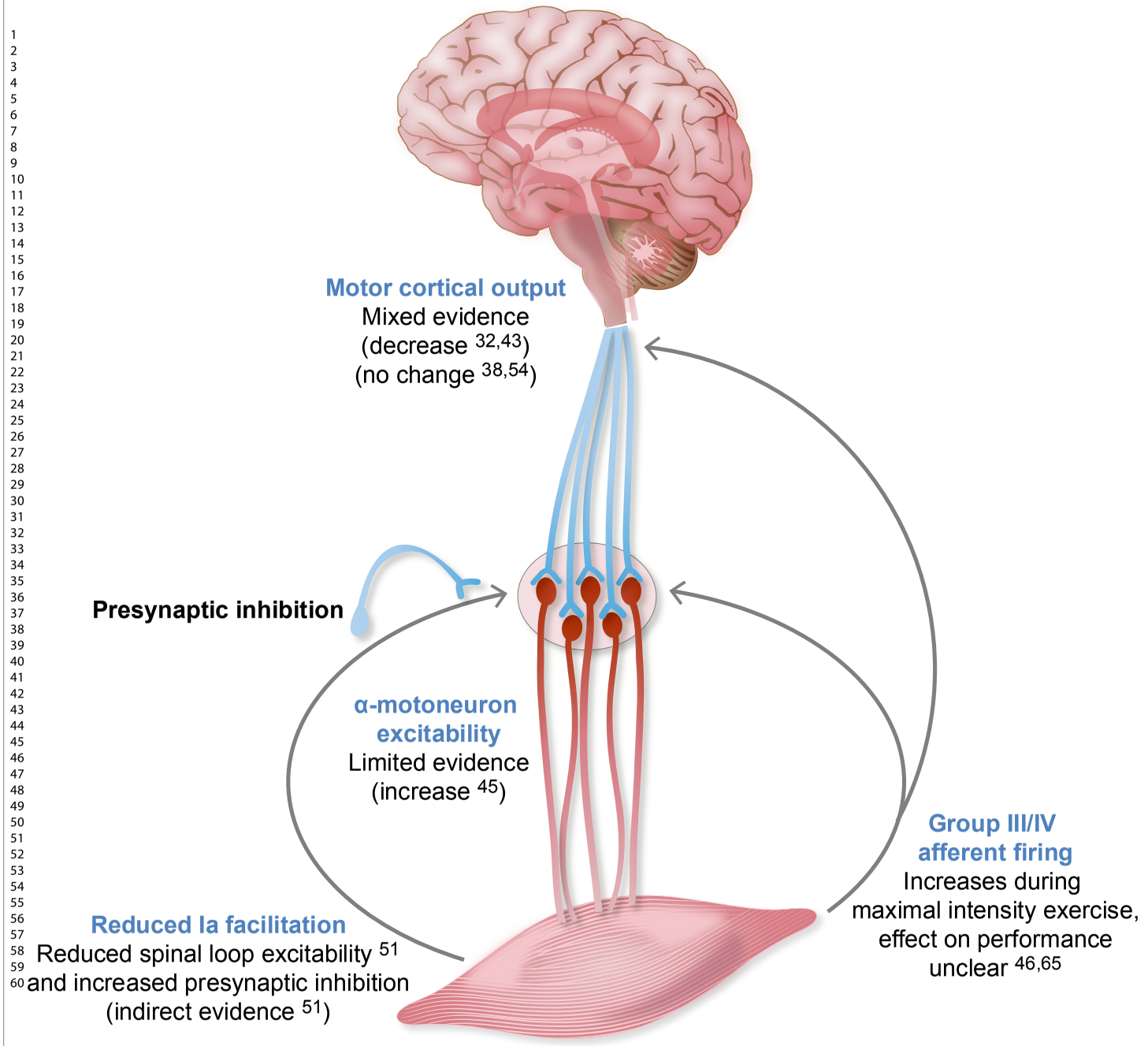

Motor cortical output
Mixed evidence
(decrease 32,43)
(no change 38,54)
Presynaptic inhibition
α-motoneuron excitability
Limited evidence
(increase 45)
Group III/IV afferent firing
Increases during maximal intensity exercise, effect on performance unclear 46,65
Reduced Ia facilitation
Reduced spinal loop excitability 51
and increased presynaptic inhibition
(indirect evidence 51)

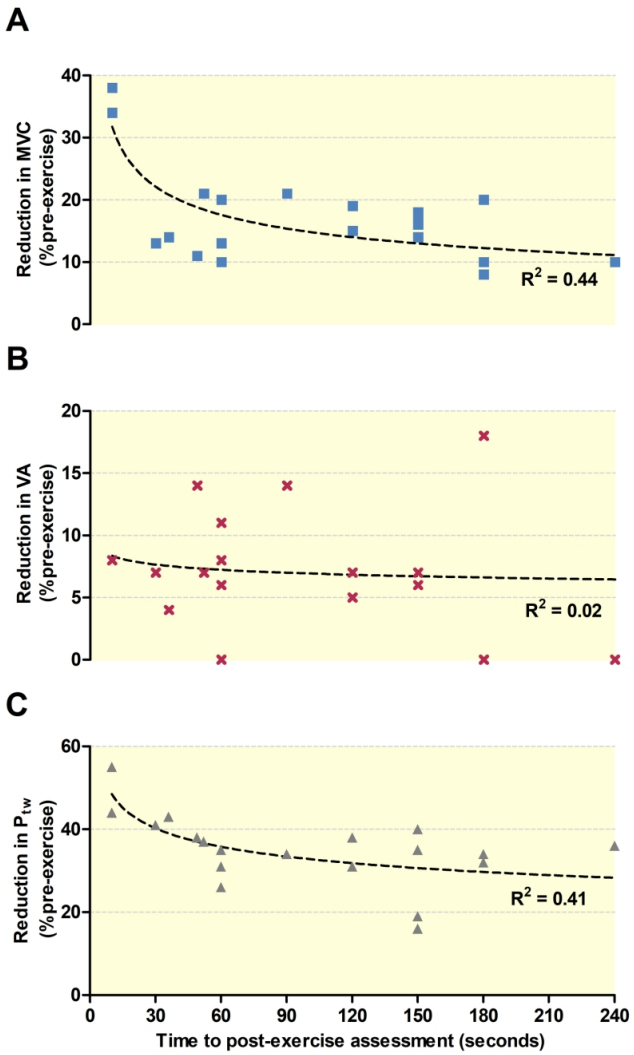
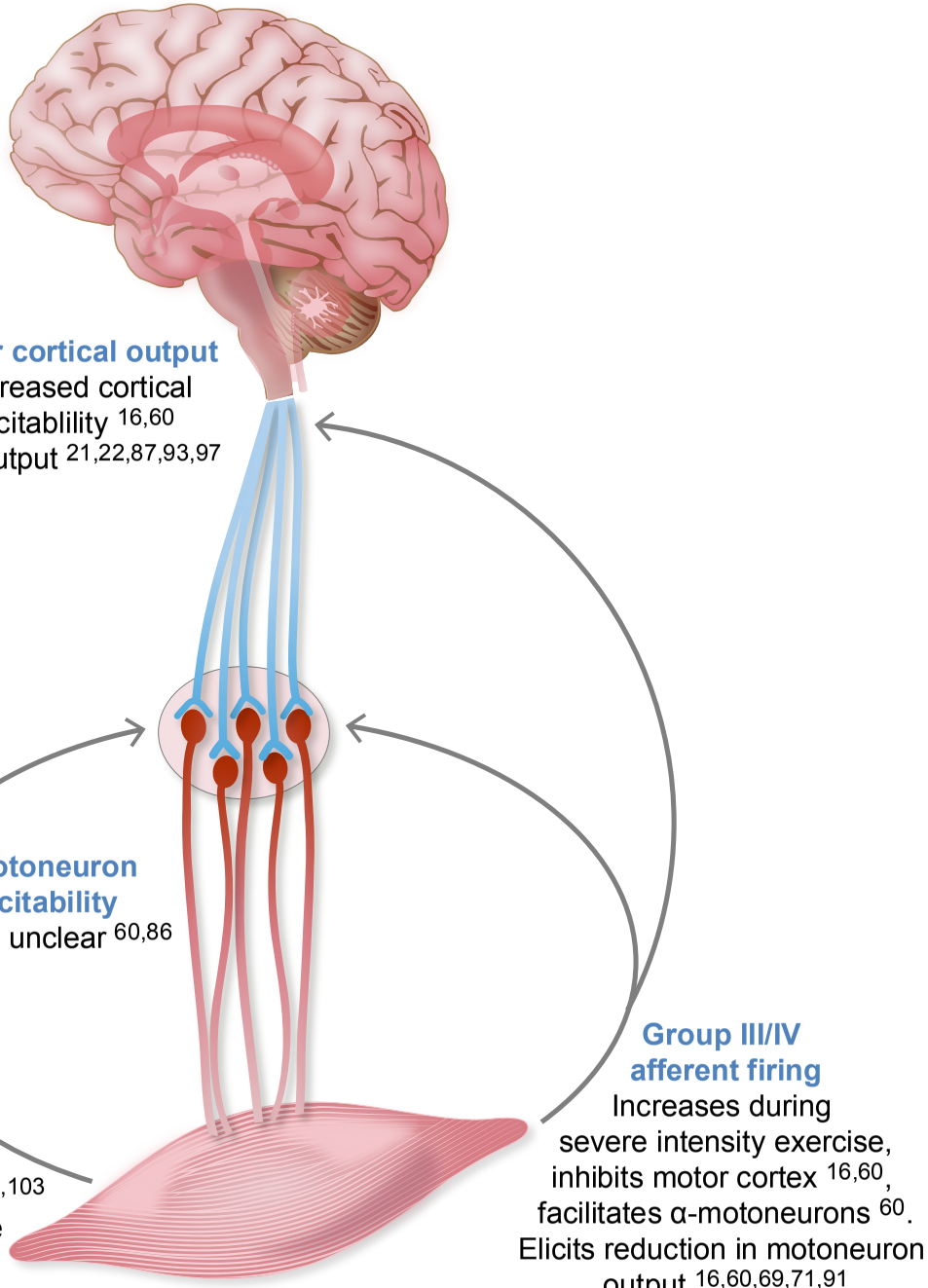


Figure 2. Relationship between time to post-exercise assessment and reduction in knee extensor maximum voluntary contraction (MVC; A), voluntary activation (VA; B) and peak twitch force (P¬tw; C) as a percentage of pre-exercise 16,21,22,31,60,66,68,70,84,86,87,89,91,93,94,96. The R2 is derived from the logarithmic slope presented on each graph.

152x237mm (300 x 300 DPI)


Motor cortical output
Decreased cortical excitablility 16,60 and output 21,22,87,93,97
α-motoneuron excitability
Effects unclear 60,86
Ia facilitation
Reduced spinal loop excitability 102,103 but no direct evidence on severe intensity exercise effects on Ia facilitation.
Group III/IV afferent firing
Increases during severe intensity exercise, inhibits motor cortex 16,60, facilitates α-motoneurons 60. Elicits reduction in motoneuron output 16,60,69,71,91

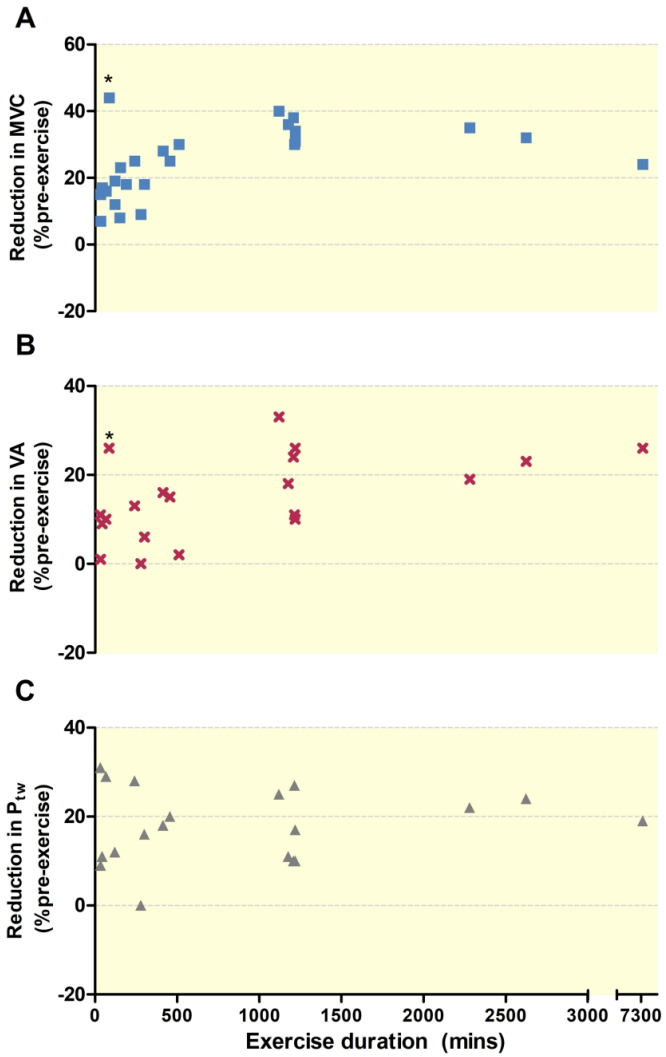


Figure 4. Relationship between reduction in knee extensor maximal voluntary contraction (MVC; A), voluntary activation (VA; B) and peak twitch force (Ptw; C) as a percentage of pre-exercise relative to the duration of exercise. Note that the figure pertains only to longer duration with a minimum duration of 30 min 17,21,22,113-116,126-128,135-140. * outlier 127.

184x267mm (300 x 300 DPI)

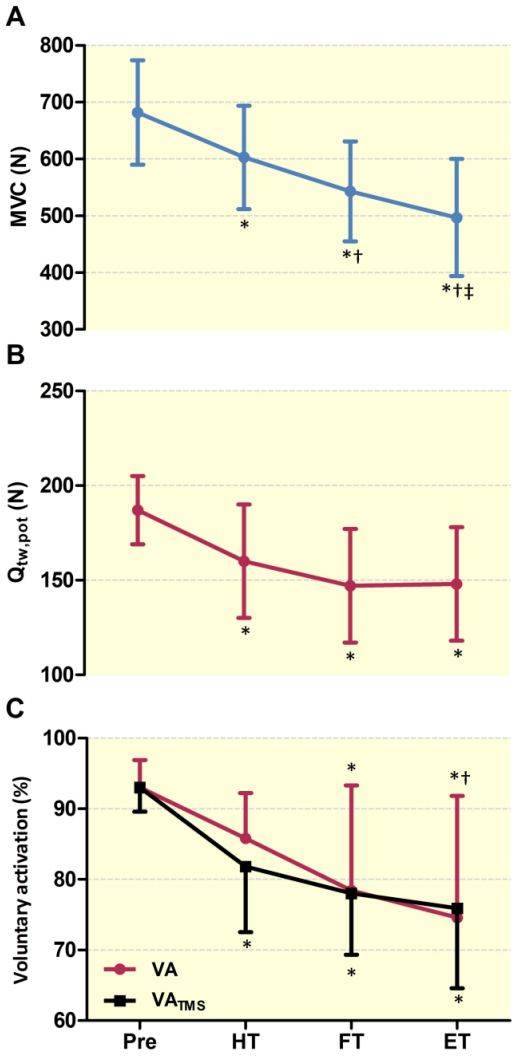


Figure 5. Maximum voluntary contraction (A), potentiated knee-extensor twitch force (B) and voluntary activation measured with motor nerve (VA), and motor cortical (VATMS) stimulation (c) at pre-exercise, half time (HT), full time (FT), and following extra time (ET) of a simulated soccer match. P = < 0.05 vs. the pre-exercise value, † = P < 0.05 vs. HT, ‡ = P < 0.05 vs. FT. From Goodall et al. 145.

156x280mm (300 x 300 DPI)