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4	T	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

The study of exercise-induced fatigue has captivated academics within the field of sport and

53 Introduction

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 exercise¹. To this end, Enoka and Duchateau¹ 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 elicitthese 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 performance¹. 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.

134 The role of exercise intensity and duration on neuromuscular responses to fatiguing 135 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 VO₂ 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 ischaracterised by substantial mechanical demands.

155 Neuromuscular responses to 'all-out' exercise

156 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 function³³, such as interference with Ca²⁺ 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 Ptw 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 Ptw, 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

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2 3 4	202	the maximal muscle compound action potential (M_{max}) is progressively reduced throughout
5	203	repeated sprints, suggesting reduced $alpha(\alpha)$ -motoneuron output ^{39,46} . Accordingly, impaired
7 3	204	contractile function plays a particularly prominent role in reduced muscle force during the early
9 10 11	205	stages of repeated sprints, while reductions in VA become more apparent during the later
12 13	206	stages.
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	Author	Z	Exercise protocol	Exercise duration/distance	Muscle group	Time to post- exercise measure	Δ ΜΥС	ΔνΑ	ΔP_{tw}	A MEP	Δ СМЕР
	Leg cycling										
	Fernandez-del- Olmo <i>et al.</i> 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 <i>et al.</i> ³⁸	12	10 sprints (30 s recovery) followed by 5 sprints (6 min recovery)	6 s	KE	3 min	↓ 11%	\$	↓~43%	\$	ŊŊ
	Girard <i>et al.</i> ³⁷	12	10 sprints (30 s recovery) followed by 5 sprints (6 min recovery)	6 s	KE	3 min	↓~14%	\$	↓~44%	QN	NQ
	Racinais et al. 40	9	10 sprints (30 s recovery)	6 s	KE	5 min	↓17%	↓ 3%	%6↑	ŊŊ	ŊŊ
	Pearcey et al. 41	8	10 sprints (180 s recovery)	10 s	KE	< 20 s	↓ 24%	↓ 7%	↓ 30%	ŊŊ	NQ
	Tomazin <i>et al</i> . 47	11	5 sprints (24 s recovery) × 4 sets (3 min between set recovery)	6 s	KE	30 s	↓ 15%	¢	↓ 39%	NQ	ŊŊ
	Monks <i>et al</i> . ⁴²	10	10 sprints (30/180 s recovery)	10 s	KE	< 10 s	↓27%	1 6%	↓ 39%	ŊŊ	NQ
	Running										
	Tomazin <i>et al</i> . ⁴⁸	11	100 m sprint	15 s	KE	30 s	\$	\$	↓ 10%	ŊŊ	NQ
	Tomazin <i>et al</i> . 48	11	200 m sprint	31 s	KE	30 s	\$	¢	↓ 20%	NQ	NQ
	Tomazin <i>et al</i> . 48	11	400 m sprint	71 s	KE	30 s	↓ 14%	¢	↓35%	ŊŊ	NQ
	Tomazin <i>et al</i> . 47	Ξ	5 sprints (24 s recovery) × 4 sets (3 min between-set recovery)	6 s	KE	30 s	↓ 20%	↓ 7%	↓ 36%	ŊŊ	NQ

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																														EF: elbow flexors; K cervicomedullary mc	Pearcey et al. 45	Arm cycling	Perrey et al. 44	Goodall <i>et al</i> . ⁴³	
																														E: knee tor evok	12		16	12	
																														extensors; MEP: motor evoked ced potential; VA: voluntary act	10 sprints (150 s recovery)		12 sprints (30 s recovery)	12 sprints (30 s recovery)	
																														potential; MVC: maxi ivation	10 s		40 m (5.7-6.7 s)	30 m (4-5 s)	
				11																										mal voluntary c	EF		PF	KE	
																														ontraction; NQ: not qu	< 5 s		2 min	< 2.5 min	
																														antified; PF: p	%6↑		↓ 11%	↓12%	
																														antar flexors	1 6%		↓ 3%	18%	
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211 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

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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,

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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 $10 \times$ 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 Ptw 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 Ptw 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.

321 Neuromuscular responses to severe intensity, short-duration exercise

322 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 P₁²³. 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 Ptw 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

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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 Ptw 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 Ptw between studies (Table 2) if some

individuals reach critical impairments in contractile function while others reach the limit oftolerance 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 Ptw at task failure. For example, Thomas et al. ²¹ demonstrated a greater reduction in Ptw 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 Ptw, 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 Ptw, 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 Ptw) 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 postexercise 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 VO₂ 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 Ptw) 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-spurt⁸¹.

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 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".</th>

Author	Z	Exercise protocol	Exercise duration	Muscle group	Time to post- exercise measure		ΔνΑ	ΔP_{tw}	-
Leg cycling									
Thomas et al. ²¹	12	Power @ VO _{2max}	3 min	KE	2.5 min	↓~18%	↓ 3%	ڊن ڊن	3%
Schafer <i>et al.</i> 68	12	Power output predicted to deplete W' within 3 min based on power- time relationship	3 min	KE	60 s	J 20%	↓ 11%	↓ 35	%
Thomas et al. 22	13	4 km time-trial	6 min	KE	< 2.5 min	↓ 18%	↓ 7%	↓ 40	%
Temesi <i>et al</i> . 66	10	80% peak power output	6 min	KE	< 10 s	↓ 34%	18%	↓ 55	%
Ansdell et al. 84	10	4 km time trial	6 min	KE	< 1.5 min	↓ 21%	↓ 14%	↓ 34	%
Azevedo et al 81	11	4 km time trial	6 min	KE	1 min	↓ 13%	∜8 ↑	¢ 26	%
Amann <i>et al</i> . ⁸⁵	8	5 km time trial	7 min	KE	3 min	↓ 8%	NQ	↓ 32	%
Johnson <i>et al.</i> ⁷⁰	8	85% peak power output	7 min	KE	2 min	↓ 15%	↓ 5%	€~	%8
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%	1 8%	J 30	%
Goodall et al. 87	9	$\sim 80\%$ peak power output	8 min	KE	< 2.5 min	↓ 17%	1 6%	¢ 19	%
Amann <i>et al.</i> ⁸⁸	8	5 km time trial	8 min	KE	2.5 min	↓ 14%	NQ	€ 1	%
Hureau et al. ⁸⁹	8	5 km time trial	8 min	KE	30 s	↓ ~13%	↓ ~7%	↓ ~4	1%
Amann <i>et al.</i> ⁹⁰	7	80% peak power output	9 min	KE	3 min	↓ 10%	\$	↓ 34	%
Blain <i>et al.</i> ⁹¹	8	5 km time-trial	9 min	KE	1 min	$\downarrow \sim \! 10\%$	$\downarrow 6\%$	↓ 319	~
Sidhu <i>et al</i> . ¹⁶	10	80% peak power output	9 min	KE	49 s	↓ 11%	↓ 14%	¢380	<u>~</u>
V man at al 31	10	5% above second ventilatory	10 min	KE	10 s	1 38%	18%	↓ 44º	~

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voluntary activation	KE: knee extensors; N	Husmann <i>et al</i> . ⁹⁶	Rowing	Skof and Strojnik 95	Running	O'Leary et al. 94	O'Leary et al. 93	Schafer <i>et al.</i> ⁶⁸	Thomas <i>et al</i> . ²¹	Amann <i>et al</i> . ⁹²	
	MEP: mot	8		7		18	16	12	12	8	
	or evoked potential; MVC: maximal v	2000 m time trial		6 km time-trial		50% between lactate threshold and VO_{2max}	50% between lactate threshold and VO_{2max}	Power output predicted to deplete W' within 12 min based on power- time relationship	60% of differences between RCP and VO_{2max}	83% peak power output	threshold
	oluntary c	7 min		20 min		24 min	18 min	12 min	11 min	10 min	
	ontraction; N	KE		KE		KE	KE	KE	KE	KE	
22	VQ: not quantified; P _{tw} :	3 min		60 s		52 s	< 2 min	60 s	2.5 min	4 min	
n n n n n n n n n n n n n n n n n n n	peak twitch force; CN	↓ 20%		¢		↓ 21%	↓ 19%	↓ 15%	↓~16%	↓ 10%	
	MEP: cervic	↓ 18%		¢		↓ 7%	↓7%	↓ 12%	↓ 6%	\$	
	omedullary	¢		↓ 14%		J 37%	↓31%	↓ 31%	↓ 16%	↓36%	
	motor evo	NQ		NQ		\$		NQ	\$	NQ	
	ked potential; VA:	ŊŊ		NQ		ŊŊ		NQ	NQ	NQ	

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 GABAB 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

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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 GABAB 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.

⁸ 476 Using spinal stimulation at the cervicomedullary level, a number of recent studies have ⁹ assessed the effects of severe intensity exercise at the α -motoneuron excitability ^{16,86}. In these ¹ studies, which utilised constant-load exercise at 80% peak power until task failure, no change ⁴ in α -motoneuron excitability was demonstrated between the beginning and end of exercise. ⁵ While this implies no effect of severe intensity exercise at the α -motoneuron level, in non-⁸ 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.

⁴⁶ 500 The findings of Sidhu *et al.* ⁶⁰ appear contradictory to that of Weavil *et al.* ⁸⁶. That is, if α -⁴⁸ 501 motoneurons are disfacilitated during constant load severe intensity cycling exercise, but a ⁵⁰ 502 reduction in CMEP is not apparent due to the increased neural drive and EMG ⁸⁶, one might ⁵¹ 503 expect that CMEP would decrease when measured at the same EMG level. However, the ⁵⁴ 504 opposite was found by Sidhu *et al.* ⁶⁰, i.e. CMEPs increased. This result cannot be explained ⁵⁷ 505 by an increased descending drive at the same EMG level, since conditioned CMEPs exhibited ⁵⁹ 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

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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 Ptw ^{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

3 4 5 6 7 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

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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.

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609 Neuromuscular responses to sustained exercise below critical power

610 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 Ptw²². 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 Ptw following a constant load task in which task-failure

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3 4 5 6 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 Ptw of 9, 12 and 11%, respectively. Interestingly, this reduction in Ptw is lower than some studies assessing Ptw 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 Ca²⁺ release after 4 h of recovery when participants were given only water, while participants given carbohydrates concurrently demonstrated recovery of SR Ca²⁺ release. Inhibition of SR Ca²⁺ release is thought to occur below critical levels of muscle glycogen (250-300 mmol·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 Ca²⁺ 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, minat 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 or Review running and cycling task, respectively.

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

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	KE: knee extensors evoked potential; V	Millet <i>et al.</i> ¹³¹	Other	Millet et al. 130	Petersen et al. 129	Petersen et al. 129	Saldanha <i>et al</i> . ¹²⁸	Racinais et al. 114	Running	Lepers et al. 113	Sahlin & Seger ¹²⁷	Thomas et al. 22	Thomas <i>et al</i> . ²¹	Lepers et al. 112	Thomas et al. 22	Leg cycling	Author	were considered
	;; MEP: 7A: volu	11		12	8	8	8	11		8	7	13	12	10	13		Z	1 "heav
	motor evoked potential; MV(intary activation	42.2 km (ski skating)		30 km race	42.2 km (marathon)	42.2 km (marathon)	75% VO _{2peak}	First ventilatory threshold		65% PPO	$\sim 75\%$ VO _{2max}	40 km time trial	Power output @ RCP	75% PPO	20 km time trial		Exercise protocol	vy intensity".
	C: maximal voluntary	149 min		189 min	154 min	154 min	120 min	90 min		120 min	85 min	66 min	42 min	33 min	32 min		Exercise duration/distance	
33	/ contraction; NQ: not	KE		KE	PF	KE	PF	PF		KE	KE	KE	KE	KE	KE		Muscle group	
	quantified; PF: plantar	< 5 min		< 3 min	30 min	30 min	< 5 min	5 min		Immediately	NQ	< 2.5 min	2.5 min	~1 min	< 2.5 min		Time to post- exercise measure	
	flexors; P _{tw} :]	18%		↓ 25%	↓ 18%	↓ 23%	↓ 17%	↓ 11%		↓ 12%	↓ 44%	↓ 16%	↓~17%	↓ 7%	↓ 15%		ΔΜΥС	
	peak twitch f	¢		18%	NQ	NQ	↓ 19%	↓2%		NQ	↓ 26%	↓ 10%	%6 †	↓ 1%	↓ 11%		ΔνΑ	
	force; CME	<u>†</u> 7%		1∼6%	\$	\$	\$	↓11%		↓12%	NQ	↓ 29%	↓ 11%	%6↑	↓31%		ΔP_{tw}	
	P: cervicomedu	NQ		ŊŊ	ŊQ	NQ	NQ	NQ		NQ	NQ	↓restingMEP	\$	NQ	↓restingMEP		Δ MEP	
	llary motor	NQ		NQ	NQ	NQ	NQ	NQ		NQ	NQ	NQ	NQ	NQ	NQ		A CM	

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	Z	Exercise protocol	Exercise	Muscle group	Time to post-	Δ ΜΥС	ΔVA	$\Delta \ P_{tw}$	A MEP	A CMEP
			duration/distance		exercise measure					
Leg cycling										
Jubeau <i>et al</i> . ¹¹⁵	10	45% PPO	240 min	KE	< 3 min	↓ 25%	↓ 13%	↓28%	\rightarrow	NQ
Lepers et al. 116	9	55% PPO	300 min	KE	Immediately	↓ 18%	1 6%	↓ 16%	NQ	NQ
Running										
Ross et al. 132	9	42.2 km (marathon)	208 min	PF	< 20 min	↓ 18%	↓14%	↓71%	↓restingMEP	NQ
Millet et al. 130	11	140 km race	278 min	KE	15 min	%6↑	\$	\$	NQ	NQ
Place et al. 126	9	55% MAV	300 min	KE	Immediately	↓ 28%	$\downarrow 16\%$	† 18%	NQ	ŊŊ
Gauche et al. ¹³³	22	55 km trail run	413 min	KE	60 min	↓ 37%	$\downarrow 2\%^{CAR}$	NS	NQ	NQ
Millet et al. 134	9	65 km ultramarathon	511 min	KE	< 2 min	↓ 30%	↓ 20%	† 25%	NQ	NQ
Martin <i>et al</i> . ¹³⁵	12	Treadmill running	19 h (149km)	KE	ŊŊ	↓ 40%	↓ 33%	↓ 25%	NQ	NQ
Martin <i>et al.</i> ¹³⁵	12	Treadmill running	19 h (149 km)	PF	ŊŊ	↓ 30%	↓ 15%	↓ 23%	NQ	NQ
Giandolini <i>et al.</i> 136	23	110 km mountain ultra- marathon	20 h	KE	57 min	↓ 36%	↓ 18%	↓ 11%	NQ	NQ
Giandolini <i>et al.</i> 136	23	110 km mountain ultra- marathon	20 h	PF	57 min	↓ 28%	↓ 10%	↓ 17%	NQ	NQ
Temesi <i>et al.</i> ¹⁷	25	110 km mountain ultra- marathon	20 h	KE	61 min	↓ 34%	↓ 26%	↓ 10%	\rightarrow	ŊŊ
Temesi <i>et al.</i> ¹³⁷	20	110 km mountain ultra- marathon	20 h	KE	58 min	↓ 38%	↓24%	↓ 10%	\rightarrow	ŊŊ

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46	45	44	43	42	41	40	39	38	37	36	3	34	щ	32	31	30	29	28	27	25 26	24	23	22	19 20 21	18	16	14 15	11 12	9 9 10	7 6 7	ω4π	2 1
																	069		689	889	087	1	686	684 685								
																								CAR: central activ flexors; P _{tw} : peak t	Saugy et al. 140	Saugy et al. 140	Besson <i>et al.</i> ¹³⁹	Besson <i>et al.</i> ¹³⁹	Millet <i>et al.</i> ¹³⁸	Millet <i>et al.</i> ¹³⁸	Temesi <i>et al.</i> ¹³⁷	
																								ation rat witch fo	15	15	17	17	22	22	20	
																								io; KE: knee extensors; MA ^v rce; CMEP: cervicomedullar	330 trail run	330 trail run	169 km mountain ultra- marathon	169 km mountain ultra- marathon	166 km mountain ultra- marathon	166 km mountain ultra- marathon	110 km mountain ultra- marathon	
																								V: maximum aerob y motor evoked po	122 h	122 h	44 h	44 h	38 h	38 h	20 h	
																								ic velocity; MEP: motential; VA: voluntar	PF	KE	PF	KE	PF	KE	PF	
				35																				otor evoked potential;] y activation	$\sim 30 \min$	$\sim 30 \min$	23 min	24 min	20 min	20 min	80 min	
																								MVC: maximal vo	↓ 26%	↓ 24%	↓ 34%	↓ 32%	↓ 39%	↓ 35%	↓ 26%	
																								luntary cont	↓26%	↓ 20%	↓ 19%	↓23%	1 6%	↓ 19%	%6↑	
																								raction; NQ	↓ 19%	↓ 24%	↓ 23%	↓24%	J 20%	↓ 22%	↓ 16%	
																								: not quantifie	NQ	NQ	NQ	ŊŊ	NQ	NQ	NQ	
																								d; PF: plantar	NQ	NQ	NQ	NQ	NQ	NQ	NQ	
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 heavyexercise domains on the corticospinal pathway at both the supraspinal and spinal level.

718 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 highintensity 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 function¹⁴⁵. 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.

⁵¹ 735 Using a simulated soccer match protocol designed to replicate the physiological demands of
⁵² 736 soccer match-play, Goodall *et al.* ¹⁴⁵ investigated neuromuscular function before, at half-time
⁵⁵ 737 (i.e. 45 min), full-time (i.e. 90 min) and following a period of extra time (i.e. 120 min). An
⁵⁷ 738 interesting finding from this study was that while the simulated soccer match induced
⁵⁹ 739 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 Ca²⁺ 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 Ca²⁺ 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.

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771	Table 5. Studies asso	essing	neuromuscular resp	onses pre-to-post]	high-intensity	intermittent team	sport exer	cise.			
	Author	Z	Exercise protocol	Exercise duration/distance	Muscle group	Time to post- exercise measure	Δ ΜΥС	ΔνΑ	ΔP_{tw}	Δ ΜΕΡ	A CMEP
	Soccer										
	Brownstein et al. 15	16	Competitive match	90 min	KE	10-60 min	↓ 14%	↓ 7%	↓ 14%	\$	ŊŊ
	Rampinini <i>et al</i> . ¹⁴⁸	20	Competitive match	90 min	KE	40 min	↓ 11%	1 8%	18%	NQ	ŊŊ
	Thomas <i>et al.</i> ¹⁴⁷	15	Simulated match	90 min	KE	< 2.5 min	↓ 16%	∜6 ↑	↓ 14%	\$	ŊŊ
	Goodall <i>et al.</i> ¹⁴⁵	10	Simulated match	120 min	KE	< 2.5 min	↓ 27%	↓ 18%	↓ 23%	\$	ŊŊ
	Rugby league										
	Murphy et al. ¹⁵¹	9	Competitive match	80 min	KE	< 10 min	↓ 11%	\$	↓ 34%	ŊŊ	NQ
	Skein <i>et al.</i> ¹⁵²	11	Competitive match	80 min	KE	NQ	∜8 ↑	\$	NQ	ŊŊ	NQ
	Duffield et al. ¹⁵³	11	Competitive match	80 min	KE	NQ	∜8 ↑	\$	↓ 15%	ŊŊ	NQ
	Pointon & Duffield ¹⁵⁴	10	Simulated match	60 min	KE	< 10 min	↓~13%	↓~7%	↓21%	ŊŊ	ŊŊ
	Basketball										
	Ansdell et al. 155	10	Simulated match	60 min	KE	75 s	↓ 15%	NQ	↓ 13%	NQ	ŊŊ
	Intermittent sprint pr	otocol									
	Minett et al. ¹⁵⁶	9	Intermittent sprints	70 min	KE	< 10 min	↓~16%	↓~4%car	NQ	NQ	ŊŊ
	Pointon et al. 157	10	Intermittent sprints	60 min	KE	< 10 min	↓~25%	↓~11%	↓21%	NQ	NQ

773 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

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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 a-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

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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 \times 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

3 4 5 6 7 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, $\sim 60\%$ 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/h¹⁶⁶. 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 Ptw 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.

926	
927	Conclusions and future research
928	The present review provides a synopsis of literature, conducted primarily over the last two
929	decades, pertaining to alterations in neuromuscular function in response to fatiguing locomotor
930	exercise. The plethora of research which now exists in this area has clearly demonstrated the
931	integral importance of task-dependency on alterations within the neuromuscular system. It is
932	well established that neuromuscular function during exercise above critical intensity is
933	primarily limited by disturbances in metabolic homeostasis and consequent impairments in
934	contractile function. More prolonged exercise below critical intensity causes considerable
935	reductions in the capacity of the nervous system to activate muscle, though the precise
936	alterations within the central nervous system contributing to this reduction are still unclear.
937	During repeated sprint, constant load severe intensity, high-intensity intermittent, and
938	prolonged constant load moderate intensity exercise, impaired contractile function is
939	demonstrated during the first half of exercise, before impaired voluntary activation becomes
940	more evident during the latter half. Primarily, studies have utilised electrical nerve stimulation
941	at rest and during maximal voluntary contractions to determine the effects of locomotor
942	exercise at the peripheral and central level respectively. To further investigate alterations
943	within the nervous system many studies have additionally utilised transcranial magnetic
944	stimulation to assess the excitability of the corticospinal pathway electrical stimulation of
045	descending spinal tracts to assess a motoneuron excitability and perve stimulation to assess
945	uescending spinal fracts to assess u-motoneuron excitability, and herve stimulation to assess
946	spinal loop excitability at lest of during isometric contractions prior to and following locomotor
947	exercise. While these studies have provided valuable insight into how various types of
948	locomotor exercise impact the neuromuscular system, one limitation of this approach is that
949	measuring responses during isometric contractions deviates from the locomotor exercise task
950	itself, and thus hinders understanding of neuromuscular alterations that occur during the task.
	 926 927 928 929 930 931 932 933 934 935 940 941 942 943 944 945 946 947 948 949 950

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 exerciseinduced 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.

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2	075	
4	975	Table and Figure Legends
5		
0 7	976	Table 1. Literature quantifying neuromuscular alterations pre-to-post maximal intensity
8	077	locomotor avaraisa
9 10	577	locomotor exercise.
10		
12	978	Table 2. Literature quantifying neuromuscular alterations pre-to-post severe intensity
13	979	locomotor exercise. Studies utilising protocols which resulted in task-failure in < 30 min were
15	575	locomotor excreme. Studies utilising protocols which resulted in task fundre in 350 mill were
16	980	considered "severe intensity".
17 18		
19	981	Table 3. Literature assessing neuromuscular responses pre-to-post heavy intensity exercise.
20		
21 22	982	Studies in which exercise duration ranged from $> 30 - 189$ min were considered "heavy
23		
24	983	intensity".
25 26		
27	984	Table 4. Studies assessing neuromuscular responses pre-to-post moderate intensity exercise.
28	0.05	
29 30	985	Studies in which exercise duration was > 240 min were considered moderate intensity .
31		
32	986	Table 5. Studies assessing neuromuscular responses pre-to-post high-intensity intermittent
33 34	087	team sport exercise
35	507	
36 37	000	E' 1 Denne de la constructione in a construction de la construction de
38	988	Figure 1. Proposed alterations in neuromuscular function occurring during maximal intensity
39	989	exercise Adapted from Taylor <i>et al.</i> ⁶¹
40 41		
42	000	Figure 2 Palationship between time to post everyise assessment and reduction in knee
43	990	Figure 2. Relationship between time to post-exercise assessment and reduction in knee
44 45	991	extensor maximum voluntary contraction (MVC; A), voluntary activation (VA; B) and peak
46		
47	992	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
48 49	002	is deviced from the localithmic class ansauted on each manh
50	993	is derived from the logarithmic slope presented on each graph.
51 52		
53	994	Figure 3. Proposed alterations in neuromuscular function occurring during severe intensity
54	005	evercise. Adapted from Taylor at al^{-61}
55 56	555	exercise. Adapted from Taylor et al.
57	000	Figure 4. Deletionship between as butter in large entering in 1. 1. 1. (
58	996	rigure 4. Relationship between reduction in knee extensor maximal voluntary contraction
59 60	997	(MVC: A), voluntary activation (VA: B) and peak twitch force $(P_{twith} C)$ as a percentage of pre-

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2 3 4	998	exercise relative to the duration of exercise. Note that the figure pertains only to longer duration
5 6 7	999	with a minimum duration of 30 min $^{17,21,22,113-116,126-128,135-140}$. * outlier 127 .
, 8 9	1000	Figure 5. Maximum voluntary contraction (A), potentiated knee-extensor twitch force (B) and
10 11 12	1001	voluntary activation measured with motor nerve (VA), and motor cortical (VA $_{TMS}$) stimulation
13 14	1002	(c) at pre-exercise, half time (HT), full time (FT), and following extra time (ET) of a simulated
15 16	1003	soccer match. $P = < 0.05$ vs. the pre-exercise value, $\dagger = P < 0.05$ vs. HT, $\ddagger = P < 0.05$ vs. FT.
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20 21 22	1005	Conflict of Interest
23 24 25	1006	The authors have no conflicts of interest.
26 27 28	1007	
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2 3	1	Neuromuscular responses to fatiguing locomotor exercise
4	T	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

The study of exercise-induced fatigue has captivated academics within the field of sport and

53 Introduction

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 exercise¹. To this end, Enoka and Duchateau¹ 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 elicitthese 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 performance¹. 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.

134 The role of exercise intensity and duration on neuromuscular responses to fatiguing 135 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 VO₂ 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 ischaracterised by substantial mechanical demands.

155 Neuromuscular responses to 'all-out' exercise

156 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 function³³, such as interference with Ca²⁺ 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 Ptw 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 Ptw, 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.

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Author	Z	Exercise protocol	Exercise duration/distance	Muscle group	Time to post- exercise measure	Δ ΜVC	ΔVA	ΔP_{tw}	A MEP	ΔC
Leg cycling										
Fernandez-del- Olmo <i>et al.</i> 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 <i>et al</i> . ³⁹	12	10 sprints (30 s recovery)	10 s	KE	30 s	↓ 19%	↓~11%	↓~55%	NQ	NQ
Girard <i>et al.</i> ³⁸	12	10 sprints (30 s recovery) followed by 5 sprints (6 min recovery)	6 s	KE	3 min	↓ 11%	\$	↓~43%	¢	NQ
Girard <i>et al.</i> 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%	%6↑	ŊŊ	NQ
Pearcey et al. 41	8	10 sprints (180 s recovery)	10 s	KE	< 20 s	↓ 24%	↓ 7%	↓ 30%	ŊŊ	NQ
Tomazin <i>et al</i> . 47	11	5 sprints (24 s recovery) × 4 sets (3 min between set recovery)	6 s	KE	30 s	↓ 15%	¢	↓ 39%	NQ	NQ
Monks <i>et al</i> . ⁴²	10	10 sprints (30/180 s recovery)	10 s	KE	< 10 s	↓ 27%	↓ 6%	↓ 39%	NQ	NQ
Tomazin <i>et al</i> . ⁴⁸	11	100 m sprint	15 s	KE	30 s	\$	\$	↓10%	ŊŊ	NQ
Tomazin <i>et al.</i> 48	11	200 m sprint	31 s	KE	30 s	¢	\$	↓20%	NQ	NQ
Tomazin <i>et al</i> . ⁴⁸	11	400 m sprint	71 s	KE	30 s	↓ 14%	\$	↓35%	ŊŊ	NQ
Tomazin <i>et al</i> . 47	Ξ	5 sprints (24 s recovery) × 4 sets (3 min between-set recovery)	6 s	KE	30 s	↓ 20%	↓ 7%	↓ 36%	NQ	NQ

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																													210	208 209					
																														EF: elbow flexors; K cervicomedullary mc	Pearcey et al. 45	Arm cycling	Perrey et al. 44	Goodall <i>et al.</i> ⁴³	
																														E: knee tor evol	12		16	12	
																														extensors; MEP: motor evoked ced potential; VA: voluntary act	10 sprints (150 s recovery)		12 sprints (30 s recovery)	12 sprints (30 s recovery)	
																														potential; MVC: maxi ivation	10 s		40 m (5.7-6.7 s)	30 m (4-5 s)	
				11																										mal voluntary c	EF		PF	KE	
																														ontraction; NQ: not qu	< 5 s		2 min	< 2.5 min	
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																														; P _{tw} : peak t	J 27%		↓13%	↓ 24%	
																														witch force; CM	↓ 19%		NQ	\$	
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211 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

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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 $10 \times$ 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 Ptw 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 Ptw 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.

321 Neuromuscular responses to severe intensity, short-duration exercise

322 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 P₁²³. 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 Ptw 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

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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 Ptw 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 Ptw between studies (Table 2) if some

individuals reach critical impairments in contractile function while others reach the limit oftolerance 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 Ptw at task failure. For example, Thomas et al. ²¹ demonstrated a greater reduction in Ptw 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 Ptw, 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 Ptw, 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 Ptw) 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 postexercise 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 VO₂ 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 Ptw) 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-spurt⁸¹.

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 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".</th>

Author	Z	Exercise protocol	Exercise duration	Muscle group	Time to post- exercise measure	ΔΜΥϹ	ΔνΑ	ΔP_{tw}	A MEP
Leg cycling									
Thomas et al. 21	12	Power @ VO _{2max}	3 min	KE	2.5 min	↓ ~18%	↓ 3%	↓ 33%	\$
Schafer <i>et al.</i> 68	12	Power output predicted to deplete W' within 3 min based on power- time relationship	3 min	KE	60 s	↓ 20%	↓ 11%	↓ 35%	ŊŊ
Thomas et al. 22	13	4 km time-trial	6 min	KE	< 2.5 min	↓ 18%	↓ 7%	↓40%	\$
Temesi et al. 66	10	80% peak power output	6 min	KE	< 10 s	↓ 34%	18%	↓ 55%	NQ
Ansdell et al. 84	10	4 km time trial	6 min	KE	< 1.5 min	↓ 21%	↓ 14%	↓ 34%	NQ
Azevedo et al 81	11	4 km time trial	6 min	KE	1 min	↓ 13%	18%	↓26%	NQ
Amann et al. ⁸⁵	8	5 km time trial	7 min	KE	3 min	18%	NQ	↓ 32%	NQ
Johnson <i>et al.</i> ⁷⁰	8	85% peak power output	7 min	KE	2 min	↓ 15%	↓ 5%	↓~38%	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%	18%	↓ 30%	¢
Goodall et al. 87	9	~80% peak power output	8 min	KE	< 2.5 min	↓ 17%	1 6%	↓ 19%	¢
Amann et al. 88	8	5 km time trial	8 min	KE	2.5 min	↓ 14%	NQ	↓35%	NQ
Hureau <i>et al</i> . ⁸⁹	8	5 km time trial	8 min	KE	30 s	↓ ~13%	↓ ~7%	↓~41%	NQ
Amann <i>et al.</i> ⁹⁰	7	80% peak power output	9 min	KE	3 min	↓ 10%	€	↓ 34%	NQ
Blain et al. 91	8	5 km time-trial	9 min	KE	1 min	↓ ~10%	1 6%	↓31%	¢
Sidhu et al. ¹⁶	10	80% peak power output	9 min	KE	49 s	↓ 11%	↓ 14%	↓ 38%	¢
Kruger <i>et al.</i> ³¹	10	5% above second ventilatory	10 min	KE	10 s	↓ 38%	∜8 ↑	↓ 44%	NQ

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												431	430)	428 429										
														ţ	KE: knee extensors;] voluntary activation	Husmann <i>et al</i> . ⁹⁶	Rowing	Skof and Strojnik	Running	O'Leary <i>et al</i> . ⁹⁴	O'Leary et al. 93	Schafer <i>et al.</i> ⁶⁸	Thomas <i>et al.</i> ²¹	Amann <i>et al.</i> ⁹²	
															MEP: mo	8		7		18	16	12	12	8	
															tor evoked potential; MVC: maximal v	2000 m time trial		6 km time-trial		50% between lactate threshold and VO_{2max}	50% between lactate threshold and VO_{2max}	Power output predicted to deplete W' within 12 min based on power- time relationship	60% of differences between RCP and VO_{2max}	83% peak power output	threshold
															oluntary c	7 min		20 min		24 min	18 min	12 min	11 min	10 min	
															ontraction;	KE		KE		KE	KE	KE	KE	KE	
		22													NQ: not quantified; Ptw:	3 min		60 s		52 s	< 2 min	60 s	2.5 min	4 min	
															peak twitch force; CN	↓ 20%		¢		↓ 21%	J 19%	↓ 15%	↓~16%	↓ 10%	
															IEP: cervic	↓ 18%		\$		↓ 7%	J7%	↓ 12%	↓ 6%	\$	
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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 GABAB 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

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

⁸ 476 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 nonfatiguing 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.

⁴⁶ 500 The findings of Sidhu *et al.* ⁶⁰ appear contradictory to that of Weavil *et al.* ⁸⁶. That is, if α -⁴⁸ 501 motoneurons are disfacilitated during constant load severe intensity cycling exercise, but a ⁵⁰ 502 reduction in CMEP is not apparent due to the increased neural drive and EMG ⁸⁶, one might ⁵¹ 503 expect that CMEP would decrease when measured at the same EMG level. However, the ⁵⁴ 504 opposite was found by Sidhu *et al.* ⁶⁰, i.e. CMEPs increased. This result cannot be explained ⁵⁷ 505 by an increased descending drive at the same EMG level, since conditioned CMEPs exhibited ⁵⁹ 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

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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 Ptw ^{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

3 4 5 6 7 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

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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.

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609 Neuromuscular responses to sustained exercise below critical power

610 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 Ptw²². 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 Ptw following a constant load task in which task-failure

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3 4 5 6 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 Ptw of 9, 12 and 11%, respectively. Interestingly, this reduction in Ptw is lower than some studies assessing Ptw 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 Ca²⁺ release after 4 h of recovery when participants were given only water, while participants given carbohydrates concurrently demonstrated recovery of SR Ca²⁺ release. Inhibition of SR Ca²⁺ release is thought to occur below critical levels of muscle glycogen (250-300 mmol·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 Ca²⁺ 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 e perez cycling task, respectively.

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

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	KE: knee extensors evoked potential; V	Millet <i>et al.</i> ¹³¹	Other	Millet et al. 130	Petersen et al. 129	Petersen et al. 129	Saldanha <i>et al</i> . ¹²⁸	Racinais et al. 114	Running	Lepers et al. 113	Sahlin & Seger ¹²⁷	Thomas et al. 22	Thomas et al. ²¹	Lepers et al. 112	Thomas et al. 22	Leg cycling	Author	were considered
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	motor evoked potential; MV(intary activation	42.2 km (ski skating)		30 km race	42.2 km (marathon)	42.2 km (marathon)	75% VO _{2peak}	First ventilatory threshold		65% PPO	$\sim 75\%$ VO _{2max}	40 km time trial	Power output @ RCP	75% PPO	20 km time trial		Exercise protocol	vy intensity".
	C: maximal voluntary	149 min		189 min	154 min	154 min	120 min	90 min		120 min	85 min	66 min	42 min	33 min	32 min		Exercise duration/distance	
33	/ contraction; NQ: not	KE		KE	PF	KE	PF	PF		KE	KE	KE	KE	KE	KE		Muscle group	
	quantified; PF: plantar	< 5 min		< 3 min	30 min	30 min	< 5 min	5 min		Immediately	NQ	< 2.5 min	2.5 min	~1 min	< 2.5 min		Time to post- exercise measure	
	flexors; P _{tw} :]	18%		↓ 25%	↓ 18%	↓ 23%	↓ 17%	↓ 11%		↓ 12%	↓ 44%	↓ 16%	↓~17%	↓ 7%	↓ 15%		ΔΜΥС	
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	force; CME	<u>†</u> 7%		1∼6%	\$	\$	\$	↓ 11%		↓12%	NQ	↓ 29%	↓ 11%	%6↑	↓31%		ΔP_{tw}	
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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".

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Autnor	7	Exercise protocol	Exercise duration/distance	Muscie group	time to post- exercise measure		ΔΥΑ	ΔF_{tw}	A MEP	
Leg cycling										
Jubeau <i>et al</i> . ¹¹⁵	10	45% PPO	240 min	KE	< 3 min	↓ 25%	↓ 13%	↓ 28%	\rightarrow	NQ
Lepers et al. 116	9	55% PPO	300 min	KE	Immediately	↓ 18%	$\uparrow 6\%$	↓ 16%	NQ	NQ
Running										
Ross et al. 132	9	42.2 km (marathon)	208 min	PF	< 20 min	↓ 18%	↓ 14%	↓71%	↓restingMEP	NQ
Millet et al. 130	11	140 km race	278 min	KE	15 min	%6↑	¢	\$	NQ	NQ
Place et al. 126	9	55% MAV	300 min	KE	Immediately	↓ 28%	↓ 16%	$\uparrow 18\%$	NQ	NQ
Gauche et al. ¹³³	22	55 km trail run	413 min	KE	60 min	↓ 37%	$\downarrow 2\%^{CAR}$	NS	NQ	NQ
Millet et al. 134	9	65 km ultramarathon	511 min	KE	< 2 min	↓ 30%	↓ 20%	† 25%	NQ	NQ
Martin <i>et al.</i> ¹³⁵	12	Treadmill running	19 h (149km)	KE	ŊŊ	↓ 40%	↓ 33%	↓ 25%	NQ	NQ
Martin <i>et al.</i> ¹³⁵	12	Treadmill running	19 h (149 km)	PF	ŊŊ	↓ 30%	↓ 15%	↓ 23%	ŊŊ	NQ
Giandolini <i>et al.</i> 136	23	110 km mountain ultra- marathon	20 h	KE	57 min	↓ 36%	↓ 18%	↓ 11%	NQ	NQ
Giandolini <i>et al.</i> 136	23	110 km mountain ultra- marathon	20 h	PF	57 min	↓ 28%	↓ 10%	↓ 17%	NQ	NQ
Temesi <i>et al.</i> ¹⁷	25	110 km mountain ultra- marathon	20 h	KE	61 min	↓ 34%	↓ 26%	↓ 10%	\rightarrow	NQ
Temesi <i>et al.</i> ¹³⁷	20	110 km mountain ultra- marathon	20 h	KE	58 min	↓ 38%	↓24%	↓ 10%	\rightarrow	NQ

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																								CAR: central activ flexors; P _{tw} : peak t	Saugy et al. 140	Saugy et al. 140	Besson <i>et al.</i> ¹³⁹	Besson <i>et al.</i> ¹³⁹	Millet <i>et al.</i> ¹³⁸	Millet <i>et al.</i> ¹³⁸	Temesi <i>et al.</i> ¹³⁷	
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																								io; KE: knee extensors; MA ^v rce; CMEP: cervicomedullar	330 trail run	330 trail run	169 km mountain ultra- marathon	169 km mountain ultra- marathon	166 km mountain ultra- marathon	166 km mountain ultra- marathon	110 km mountain ultra- marathon	
																								V: maximum aerob y motor evoked pc	122 h	122 h	44 h	44 h	38 h	38 h	20 h	
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				35																				otor evoked potential;] y activation	$\sim 30 \min$	$\sim 30 \min$	23 min	24 min	20 min	20 min	80 min	
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691 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 heavyexercise domains on the corticospinal pathway at both the supraspinal and spinal level.

718 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 highintensity 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 function¹⁴⁵. 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.

⁵¹ 735 Using a simulated soccer match protocol designed to replicate the physiological demands of
⁵² 736 soccer match-play, Goodall *et al.* ¹⁴⁵ investigated neuromuscular function before, at half-time
⁵⁵ 737 (i.e. 45 min), full-time (i.e. 90 min) and following a period of extra time (i.e. 120 min). An
⁵⁷ 738 interesting finding from this study was that while the simulated soccer match induced
⁵⁹ 739 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 Ca²⁺ 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 Ca²⁺ 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.

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KE: knee extensors; MEP: m voluntary activation	Pointon <i>et al.</i> ¹⁵⁷	Minett et al. 156	Intermittent sprint pr	Ansdell <i>et al.</i> ¹⁵⁵	Basketball	Pointon & Duffield ¹⁵⁴	Duffield et al. ¹⁵³	Skein et al. ¹⁵²	Murphy et al. ¹⁵¹	Rugby league	Goodall <i>et al.</i> ¹⁴⁵	Thomas et al. 147	Rampinini <i>et al.</i> ¹⁴⁸	Brownstein et al. 15	Soccer	Author
otor evc	10	9	otocol	10		10	11	11	9		10	15	20	16		N
sked potential; MVC: n	Intermittent sprints	Intermittent sprints		Simulated match		Simulated match	Competitive match	Competitive match	Competitive match		Simulated match	Simulated match	Competitive match	Competitive match		Exercise protocol
naximal voluntary cont	60 min	70 min		60 min		60 min	80 min	80 min	80 min		120 min	90 min	90 min	90 min		Exercise duration/distance
traction; NQ: not 40	KE	KE		KE		KE	KE	KE	KE		KE	KE	KE	KE		Muscle group
quantified; P _{tw} : peak	< 10 min	< 10 min		75 s		< 10 min	NQ	NQ	< 10 min		< 2.5 min	< 2.5 min	40 min	10-60 min		Time to post- exercise measure
twitch force;	↓~25%	↓~16%		↓ 15%		↓~13%	18%	%8 †	↓ 11%		↓ 27%	↓ 16%	↓ 11%	↓ 14%		Δ ΜΥС
CMEP: cerv	↓~11%	↓~4%car		NQ		↓ ~7%	\$	\$	\$		↓ 18%	%6 †	1 8%	1 7%		ΔVA
/icomedull:	↓21%	NQ		↓ 13%		↓21%	↓ 15%	NQ	↓ 34%		↓ 23%	↓ 14%	18%	↓ 14%		ΔP_{tw}
try motor evo	NQ	NQ		NQ		ŊŊ	ŊŊ	ŊŊ	NQ		\$	\$	NQ	\$		A MEP
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exercise

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

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 a-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}.

851 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 \times 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

3 4 5 6 7 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, $\sim 60\%$ 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/h¹⁶⁶. 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 Ptw 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.

1 2		
3 4 5	926	
6 7	927	Conclusions and future research
8 9 10	928	The present review provides a synopsis of literature, conducted primarily over the last two
11 12	929	decades, pertaining to alterations in neuromuscular function in response to fatiguing locomotor
13 14 15	930	exercise. The plethora of research which now exists in this area has clearly demonstrated the
16 17	931	integral importance of task-dependency on alterations within the neuromuscular system. It is
18 19	932	well established that neuromuscular function during exercise above critical intensity is
20 21	933	primarily limited by disturbances in metabolic homeostasis and consequent impairments in
22 23 24	934	contractile function. More prolonged exercise below critical intensity causes considerable
25 26	935	reductions in the capacity of the nervous system to activate muscle, though the precise
27 28	936	alterations within the central nervous system contributing to this reduction are still unclear.
29 30 31	937	During repeated sprint, constant load severe intensity, high-intensity intermittent, and
32 33	938	prolonged constant load moderate intensity exercise, impaired contractile function is
34 35	939	demonstrated during the first half of exercise, before impaired voluntary activation becomes
36 37	940	more evident during the latter half. Primarily, studies have utilised electrical nerve stimulation
38 39 40	941	at rest and during maximal voluntary contractions to determine the effects of locomotor
41 42	942	exercise at the peripheral and central level, respectively. To further investigate alterations
43 44	943	within the nervous system, many studies have additionally utilised transcranial magnetic
45 46 47	944	stimulation to assess the excitability of the corticospinal pathway, electrical stimulation of
48 49	945	descending spinal tracts to assess α -motoneuron excitability, and nerve stimulation to assess
50 51	946	spinal loop excitability at rest or during isometric contractions prior to and following locomotor
52 53	947	exercise. While these studies have provided valuable insight into how various types of
54 55 56	948	locomotor exercise impact the neuromuscular system, one limitation of this approach is that
57 58	949	measuring responses during isometric contractions deviates from the locomotor exercise task
59 60	950	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 exerciseinduced 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.

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2 3 4 5	975	Table and Figure Legends
6 7	976	Table 1. Literature quantifying neuromuscular alterations pre-to-post maximal intensity
8 9 10 11 12 13 14 15	977	locomotor exercise.
	978	Table 2. Literature quantifying neuromuscular alterations pre-to-post severe intensity
	979	locomotor exercise. Studies utilising protocols which resulted in task-failure in < 30 min were
16 17 18	980	considered "severe intensity".
18 19 20	981	Table 3. Literature assessing neuromuscular responses pre-to-post heavy intensity exercise.
21 22	982	Studies in which exercise duration ranged from $> 30 - 189$ min were considered "heavy
23 24 25	983	intensity".
26 27	984	Table 4. Studies assessing neuromuscular responses pre-to-post moderate intensity exercise.
28 29 30	985	Studies in which exercise duration was > 240 min were considered "moderate intensity".
31 32 33	986	Table 5. Studies assessing neuromuscular responses pre-to-post high-intensity intermittent
34 35	987	team sport exercise.
36 37 38	988	Figure 1. Proposed alterations in neuromuscular function occurring during maximal intensity
39 40 41	989	exercise. Adapted from Taylor <i>et al.</i> ⁶¹ .
42 43	990	Figure 2. Relationship between time to post-exercise assessment and reduction in knee
44 45 46	991	extensor maximum voluntary contraction (MVC; A), voluntary activation (VA; B) and peak
47 48	992	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
49 50 51	993	is derived from the logarithmic slope presented on each graph.
52 53	994	Figure 3. Proposed alterations in neuromuscular function occurring during severe intensity
54 55 56	995	exercise. Adapted from Taylor et al. ⁶¹ .
57 58	996	Figure 4. Relationship between reduction in knee extensor maximal voluntary contraction
59 60	997	(MVC; A), voluntary activation (VA; B) and peak twitch force (P_{tw} ; C) as a percentage of pre-

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2 3 4	998	exercise relative to the duration of exercise. Note that the figure pertains only to longer duration
5 6 7	999	with a minimum duration of 30 min $^{17,21,22,113-116,126-128,135-140}$. * outlier 127 .
8 9	1000	Figure 5. Maximum voluntary contraction (A), potentiated knee-extensor twitch force (B) and
10 11 12	1001	voluntary activation measured with motor nerve (VA), and motor cortical (VA _{TMS}) stimulation
13 14	1002	(c) at pre-exercise, half time (HT), full time (FT), and following extra time (ET) of a simulated
15 16	1003	soccer match. $P = < 0.05$ vs. the pre-exercise value, $\dagger = P < 0.05$ vs. HT, $\ddagger = P < 0.05$ vs. FT.
17 18 19	1004	From Goodall <i>et al</i> . ¹⁴⁵ .
20 21 22	1005	Conflict of Interest
23 24 25	1006	The authors have no conflicts of interest.
26 27 28	1007	
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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)





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)

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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, $\dagger = P < 0.05$ vs. HT, $\ddagger = P < 0.05$ vs. FT. From Goodall et al. 145.

156x280mm (300 x 300 DPI)

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