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Corticospinal excitability during fatiguing whole body exercise

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Abstract

The corticospinal pathway is considered the primary conduit for voluntary motor control in humans. The efficacy of the corticospinal pathway to relay neural signals from higher brain areas to the locomotor muscle, i.e., corticospinal excitability, is subject to alterations during exercise. While the integrity of this motor pathway has historically been examined during single-joint contractions, a small number of investigations have recently focused on whole body exercise, such as cycling or rowing. Although differences in methodologies employed between these studies complicate the interpretation of the existing literature, it appears that the net excitability of the corticospinal pathway remains unaltered during fatiguing whole body exercise. Importantly, this lack of an apparent effect does not designate the absence of change, but a counterbalance of excitatory and inhibitory influences on the two components of the corticospinal pathway, namely the motor cortex and the spinal motoneurons. Specific emphasis is put on group III/IV afferent feedback from locomotor muscle which has been suggested to play a significant role in mediating these changes. Overall, this review aims at summarizing our limited understanding of how fatiguing whole body exercise influences the corticospinal pathway.

Keywords

Corticospinal excitability; Exercise; Fatigue; Motor cortex; Motoneuron

1 INTRODUCTION

The transmission of descending drive from higher brain areas to evoke skeletal muscle contractions occurs predominately through the corticospinal motor pathway, consisting of the corticospinal tract (i.e., the motor cortex and descending axons) and spinal motoneurons (Brouwer and Ashby, 1990, 1992). While many studies have examined the corticospinal pathway during and following single-joint isometric and dynamic exercise (for review see Taylor and Gandevia, 2008), little is known about the influence of whole body exercise, such as cycling or running, on the excitability of this neuronal structure. A simple “translation” of findings from small to large muscle mass exercise is not acceptable since whole body

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exercise is characterized by a substantially different physiological challenge compared to single-joint exercise (Sidhu et al., 2013a). Specifically, the greater amount of muscular work associated with whole body exercise (Rossman et al., 2012) can, for example, change arterial blood gases (Hartley et al., 2016), hydration status (Bowtell et al., 2013), ventilatory responses (Hopkinson et al., 2004), and sympathetic nerve activity (Buharin et al., 2013), all of which have been suggested to influence the corticospinal pathway. This review summarizes the limited studies documenting the effect of whole body exercise on the excitability of the corticospinal pathway, including the motor cortex and the spinal motoneurons.

2 SIGNIFICANCE OF THE CORTICOSPINAL PATHWAY

The efficacy of the corticospinal pathway to relay neural signals from higher brain areas to the locomotor muscle, i.e., corticospinal excitability, is subject to alterations during fatiguing (i.e., causing a reduction in the force generating capacity of the locomotor muscle (Vollestad, 1997)) exercise. Decreases in the excitability of the corticospinal pathway can result from decreases in the excitability of the motor cortex and spinal motoneurons. A decreased excitability requires a greater synaptic input into the motor cortex and/or spinal motoneuron (i.e., greater central motor drive) in order to maintain muscle activation at the level needed to sustain a given task (Martin et al., 2006). This centrally-mediated increase in central motor drive would also increase perceived effort (Finn et al., 2018; McNeil et al., 2011). If an increase in neural drive into the cortex or motoneuron is not possible (e.g., during a maximal voluntary contraction, MVC) or insufficient to compensate for the diminished corticospinal excitability, the ability of the central nervous system to recruit motor units would be reduced and result in a lower muscle activation which is generally referred to as central fatigue (Klass et al., 2008; Martin et al., 2006; Petersen et al., 2003; Taylor et al., 2016). As central fatigue limits single-joint and whole body exercise performance (Hureau et al., 2018b; Taylor et al., 2006), it is important to understand how physical activity and associated fatigue influences the integrity of the corticospinal pathway.

3 EVALUATING THE EXCITABILITY OF THE CORTICOSPINAL PATHWAY

Exercise-induced alterations in corticospinal excitability can be quantified using non-invasive procedures. When transcranial magnetic stimulation (TMS) is applied to the contralateral hemisphere of the motor cortex, a short-latency electromyographic (EMG) response, termed motor-evoked potential (MEP), can be observed in a target muscle. The MEP, like the cervicomedullary-evoked potential and the M-wave (see below), is typically quantified as either a peak-to-peak amplitude or an area of the evoked response. Regardless of the method of analysis, increases in the magnitude of TMS-evoked MEP represents an increase in the excitability of the corticospinal pathway, whereas decreases in the MEP reflects a reduction. However, it is not possible to distinguish between changes in the excitability of the motor cortex vs spinal motoneurons with the use of TMS alone. In order to decipher between changes in the excitability of the distinct segments within the corticospinal pathway, electric or magnetic cervicomedullary stimulation (CMS), eliciting a cervicomedullary-evoked potential (CEMP), need to be employed in addition to TMS. CMS activates a similar portion of large corticospinal axons as TMS (Martin et al., 2008; Taylor et

al., 2002) and, as CMS bypasses the motor cortex, can be used as a direct measure of motoneuronal excitability. Again, increases in the amplitude or area of the CMS-evoked CMEP represents an increase in the excitability of the motoneuron pool, whereas decreases reflect a reduction. Because the section of the motor pathway stimulated by CMS lacks presynaptic inhibition (Jackson et al., 2006; Nielsen and Petersen, 1994) and has a mono-synaptic projection onto the spinal motoneuron (Brouwer and Ashby, 1992; Day et al., 1987), CMS provides an advantageous alternative to other assessments of spinal excitability, such as the H-reflex or V-wave (for review see McNeil et al., 2013). To account for possible changes in the excitability of the muscle, per se, the amplitude and/or area of MEP and CMEP is normalized to the amplitude and/or area of the maximal M-wave (M_{max}), a short-latency EMG response evoked by a supramaximal stimulation of the peripheral motor nerve (Gandevia et al., 1999; Todd et al., 2003). Moreover, indirect evidence of changes in motor cortical excitability can be acquired by normalizing MEPs to CMEPs (i.e., MEPs normalized for changes at the motoneuron level) (Martin et al., 2008; Taylor, 2006; Taylor and Gandevia, 2004). Furthermore, exercise-induced prolongations in the brief pause (typically <300ms) in voluntary EMG activity following a single TMS pulse, termed the silent period, have also been suggested to reflect a reduction in cortical excitability (Chen et al., 1999; Inghilleri et al., 1993). Importantly, however, the silent period is not only determined by cortical, but also by spinal mechanisms. Specifically, the early portion of the silent period (~50ms) has traditionally been related to spinal mechanisms, while the latter portion (>50ms) is thought to result from inhibition within the cortex (Chen et al., 1999; Inghilleri et al., 1993). More recent studies have now suggested that the spinal portion of the silent period may account for a longer segment than originally believed, up to 150ms or even more (Yacyshyn et al., 2016). Finally, several paired pulse paradigms have been used to quantify intracortical excitatory or inhibitory processes. Given the page limitation of this review, the reader is referred elsewhere for details on these techniques (Kujirai et al., 1993; Valls-Sole et al., 1992).

4 CHANGES IN CORTICOSPINAL EXCITABILITY FROM BEFORE TO AFTER FATIGUING WHOLE BODY EXERCISE

When tested in a relaxed muscle, a number of investigations suggest that corticospinal excitability is diminished (i.e., MEP amplitude decreased) after, compared to before, *fatiguing* whole body exercise, see Table 1. This depression appears to be independent of the exercise modality as it was observed following running (Ross et al., 2007; Verin et al., 2004), cycling (Ross et al., 2010), rowing (Fulton et al., 2002), and upper body press ups (Hollge et al., 1997). Importantly, this depression is not observed in healthy young participants following *non-exhaustive* running (Hollge et al., 1997) and leg cycling (Jonville et al., 2005) exercise, suggesting that fatigue compromises corticospinal excitability of a previously exercised, but otherwise relaxed muscle. However, this depression might be related to the timing of the post-exercise assessment of corticospinal excitability. Specifically, a previous study based on fatiguing rowing exercise found an initial facilitation of the MEP amplitude in the relaxed erector spinae muscle within the first 2min after completion, but a depression of MEPs from 6min to approximately 16min after the termination of exercise (Fulton et al., 2002). The site of corticospinal depression (or

facilitation) in the aforementioned studies remains unknown as spinal motoneuronal excitability was not assessed. Interestingly, however, based on a paired pulse paradigm, Verin et al. (2004) observed a diminished intracortical facilitation following an incremental maximal running test, suggesting that intracortical mechanisms (potentially GABA_A receptor mediated neurons (Ziemann et al., 1998)) contribute to the fatigue-induced depression, or lack of facilitation, in MEPs. It is important to emphasize that MEPs are influenced by a myriad of facilitatory and inhibitory processes during exercise, thus examining corticospinal excitability in a resting muscle may not be representative of the excitability present during exercise.

Unfortunately, the lack of a standardized methodology to assess corticospinal excitability during an isometric contraction before and again after whole body exercise makes it difficult to interpret the literature (Table 2). Specifically, corticospinal excitability has been assessed using three different types of contraction protocols: (1) brief submaximal constant force contractions, (2) brief constant EMG contractions, and/or (3) brief contractions of a given relative intensity (usually a percent of an immediately preceding MVC). Each method has its own merits and pitfalls. Briefly, although easy to perform, a submaximal constant force contraction is characterized by an increased central motor drive and a higher EMG when performed after, compared to before, fatiguing exercise (Bigland-Ritchie et al., 1986). Increases in central motor drive augment motor cortical (via increasing the amount of neural volleys to a given stimulus (Di Lazzaro et al., 1998b, Mazzocchio et al., 1994)) and motoneuronal (via bringing motoneurons closer to their firing threshold (Matthews, 1999)) excitability. Thus, the constant force protocol (which requires greater central motor drive after compared to before the exercise) may underestimate changes in corticospinal excitability.

In order to minimize differences in central motor drive during the brief contractions performed before and after the fatiguing exercise, contractions at a constant EMG have been employed. However, although EMG has been considered an index of central motor drive (Bigland-Ritchie et al., 1983; Place et al., 2007), it is important to recognize that fatigue alters motor cortical and motoneuronal responsiveness to synaptic input and/or the efficacy of the corticomotoneuronal synapse to relay neural signals. Therefore, matching EMG during brief muscle contractions performed post-exercise to that observed during pre-exercise contractions only assures similar motoneuronal activity, but does not necessarily ensure a comparable level of voluntary central motor drive during both contractions, i.e., despite similar levels of EMG, central motor drive could still be different after compared to before exercise.

Finally, a number of studies have used a contraction set at a relative proportion of the MVC (e.g., 100%, 75%, and 50%) to examine corticospinal excitability (Table 2). The reason for utilizing these contraction intensities is the fact that this contraction set is needed to estimate voluntary muscle activation when using TMS (Todd et al., 2003). Regardless, it is unclear how central motor drive may be affected by this protocol as the post-exercise contractions are now adjusted for the development of fatigue. Furthermore, the TMS intensity (i.e., high stimulator output) in this protocol needs to be high in order to evoke a large MEP and muscle twitch. This is a critical detail as it was previously suggested that high stimulation

intensities predominately recruit high threshold motor units, and low stimulator intensities predominately recruit low threshold motor units (McNeil et al., 2011). The type of motor units (e.g., low vs high) tested during the assessment of corticospinal excitability may be relevant as the low threshold motor units are likely to contribute more to locomotor exercise than the later recruited, and faster fatiguing, high threshold motor units (Stephens and Usherwood, 1977). Indeed, differences in exercise-induced changes in corticospinal excitability have been shown following fatiguing whole body exercise when using a low vs high stimulator output (Sidhu et al., 2014; Temesi et al., 2013, 2014). Thus, the interpretation of corticospinal excitability can be influenced by the methods used to assess corticospinal excitability (such as contraction protocol or stimulator intensity) independent of the influence of fatigue.

Corticospinal excitability has, compared to pre-exercise, been shown to be either unchanged or increased during an active isometric contraction performed after fatiguing whole body exercise (Table 2). This inconsistency might, at least in part, result from significant differences in the protocol utilized to assess corticospinal excitability. At first sight, this would appear to be different from the findings in a resting muscle which suggest that the corticospinal pathway is depressed following fatiguing whole body exercise. However, in the presence of unchanged MEPs, CMEPs (amplitude and area) appear to be increased following exhaustive cycling (Sidhu et al., 2017) and fatiguing arm cycling sprints (Pearcey et al., 2016). Thus, in the limited number of studies testing motoneuronal excitability, motor cortical excitability was decreased which agrees with the outcome of the studies using a resting muscle to assess corticospinal excitability (Ross et al., 2010; Verin et al., 2004). Furthermore, the silent period following fatiguing whole body exercise has been reported to increase (Temesi et al., 2014), decrease (Temesi et al., 2013), or remain unchanged (Girard et al., 2013; Goodall et al., 2012; Jubeau et al., 2014; Sidhu et al., 2017; Thomas et al., 2015). It is important to note that in an unfatigued muscle, the duration of the silent period may directly be influenced by the size of the MEP. This was suggested based on the positive correlation between the duration of the silent period and the size of the MEP (both amplitude and area) (Orth and Rothwell, 2004). However, in the presence of significant fatigue, the duration of the silent period and the size of the MEP can change independent from each other (Hilty et al., 2011; Sidhu et al., 2017; Temesi et al., 2014).

The mechanisms behind the decrease in motor cortical excitability following whole body exercise are unclear. Recent work has examined intracortical inhibition, specifically GABA_B receptor mediated intracortical inhibitory processes (Werhahn et al., 1999), as a potential mechanism contributing to motor cortical depression (Sidhu et al., 2018). Instead of an isometric contraction, the authors compared corticospinal excitability during low intensity cycling at a matched level of EMG before (~100W) and after (~90W) constant-load cycling performed to task failure (Sidhu et al., 2018). GABA_B-mediated changes on corticospinal excitability were examined using a paired pulse paradigm, in which a conditioned MEP or CMEP was evoked 100ms into the silent period of a conditioning TMS, thus testing long-interval inhibition (Valls-Sole et al., 1992; Wassermann et al., 1996). Following fatiguing cycling exercise, the area of conditioned MEPs decreased without any changes in the area of conditioned CMEPs, suggesting that whole body fatiguing exercise compromises cortical excitability independent of changes within the motoneuron (Sidhu et al., 2018). Similarly,

when the unconditioned response was examined (i.e., a TMS or CMS alone), the area of MEPs remained unchanged while CMEP area increased, thereby reducing the MEP/CMEP ratio and indicating a decreased motor cortical excitability compared to pre-exercise. Thus, despite both methods demonstrating a similar inhibitory effect of fatigue on motor cortical excitability, the manifestation of this change was different. This difference may be explained by a greater central motor drive during the post-exercise cycling (despite similar EMGs) which would facilitate the motor pathway (Weavil et al., 2015). Indeed, when central motor drive was removed, i.e., the conditioned response, the facilitation of the motoneuron was absent (Sidhu et al., 2018).

In summary, it appears that fatiguing whole body exercise decreases motor cortical excitability from pre- to post-exercise. However, this impact is only obvious when voluntary EMG is clamped during the pre- and post-exercise assessment and exercise-induced changes in both motor cortical and motoneuronal excitability are considered. Importantly, the pre- to post-exercise changes in corticospinal excitability may not reflect the status of the excitability of the corticospinal pathway during the fatiguing task. Specifically, rhythmic whole body exercise is, for example, characterized by substantial differences in central motor drive and motor unit recruitment as compared to the single-joint contractions performed before and after exercise. Additionally, background autonomic activity (e.g., sympathetic outflow), which is known to augment the corticospinal pathway (Buharin et al., 2013), is significantly larger during whole body compared to single-joint exercise (Esposito et al., 2010). Therefore, it is pertinent to examine how the corticospinal pathway changes *during* a fatiguing bout of whole body exercise.

5 CHANGES IN THE EXCITABILITY OF THE CORTICOSPINAL PATHWAY DURING FATIGUING WHOLE BODY EXERCISE

Recent studies have examined corticospinal excitability during fatiguing cycling exercise by eliciting neuromuscular stimulations at a given crank angle, and therefore muscle length, which is associated with the peak EMG signal during a pedal revolution (Table 3). In one of the first studies utilizing this technique *during* intense cycling exercise, corticospinal excitability of the knee extensors (i.e., MEPs and CMEPs) during non-fatiguing cycling (~1min at 110% peak power) was compared with the excitability of the knee extensors reached during intense constant-load cycling exercise (Sidhu et al., 2012a). It was reported that the excitability of the corticospinal pathway to the knee extensors during fatiguing cycling exercise was similar to that observed during the brief non-fatiguing cycling exercise (Sidhu et al., 2012a). Other studies have now corroborated these findings and further substantiate the hypothesis that the net excitability of the corticospinal pathway remains unchanged from the start of fatiguing whole body exercise to the point of exhaustion (Sidhu et al., 2017; Weavil et al., 2016). Specifically, when participants performed a constant-load cycling test at 80% peak power to task failure (e.g., a 10% fall in pedal frequency >5s), both the amplitude and area of the MEPs and CMEPs were equivalent during the first and final minute of exercise (Sidhu et al., 2017; Weavil et al., 2016).

This lack of change in corticospinal excitability during fatiguing cycling exercise (Table 3) was present despite an increase in background EMG in all three previously mentioned studies (Sidhu et al., 2012a, 2017; Weavil et al., 2016). This is of particular importance as increases in central motor drive, as estimated by EMG, have been shown to increase corticospinal excitability during whole body cycling exercise by facilitating the excitability of the motoneuron pool (Weavil et al., 2015). These data allude to a disfacilitating, or inhibitory influence of fatigue on corticospinal excitability during fatiguing cycling exercise.

In order to evaluate the impact of exercise-induced fatigue on the excitability of the corticospinal pathway during whole body exercise while considering the known facilitatory influence of EMG, a recent study compared alterations in corticospinal excitability during non-fatiguing and fatiguing cycling exercise (Weavil et al., 2016). Participants performed a fatiguing constant-load cycling exercise to task failure (~241W for ~8min), during which the amplitude and area of MEPs, and CMEPs, along with EMG, were quantified during the first and the final minute of exercise. During a second visit, short duration (~45s) non-fatiguing cycling was performed at a low (~244W) and a high workload (~331W), with the purpose of obtaining the same increase in EMG (~50%) observed during the fatiguing constant-load cycling test. Although the increase in EMG facilitated the corticospinal pathway during non-fatiguing cycling, the same increase in EMG did not alter corticospinal excitability during fatiguing cycling (Fig. 1). Specifically, both MEPs and CMEPs increased to a similar extent in amplitude and area (~40%) during non-fatiguing cycling, with no effect on the MEP/CMEP ratio. It was therefore concluded that fatiguing cycling exercise results in an inhibition, or disfacilitation, of the spinal motoneurons. Potential mechanisms for decreased excitability of the motoneuron pool resulting from fatiguing exercise include alterations in motoneuronal membrane potential (e.g., increased after-hyperpolarization (Matthews, 1999)), activation of extrasynaptic serotonin 1A receptors (D'Amico et al., 2017), and insufficient release, or depletion, of neurotransmitters (e.g., acetylcholine) resulting from repetitive activation.

Not only does fatiguing whole body exercise evoke changes at the motoneuronal level, it also causes alterations within the motor cortex (Sidhu et al., 2013b). Low threshold intracortical inhibitory pathways, which have projections to motor cortical cells, can be activated with a single low intensity TMS (just below resting motor threshold (Davey et al., 1994, Di Lazzaro et al., 1998a)). Although this stimulation intensity does not produce a descending neural volley when monitored by high cervical epidural electrodes (Di Lazzaro et al., 1998a), the activation of these inhibitory pathways has been shown to suppress voluntary EMG immediately after the stimulation during walking (Petersen et al., 2001) and low intensity cycling (Sidhu et al., 2012b). Furthermore, EMG suppression of the knee extensors and flexors is greater at the end of a fatiguing constant-load exercise (75% peak power for 30min) compared to the start of exercise (Sidhu et al., 2013b). These data suggest that fatigue-related processes facilitate intracortical inhibitory pathways which may lead to a diminished cortical excitability during whole body exercise. Importantly, although it has been proposed that changes in brain neurotransmitters during fatiguing whole body exercise may lead to a reduced corticospinal excitability, recent evidence indicates that this is not the case as pharmacological increases in extracellular concentrations of brain dopamine and noradrenaline do not alter corticospinal excitability following fatiguing cycling exercise

(Table 2) when compared to a placebo condition (Klass et al., 2012). However, more studies are needed as only TMS was used in the aforementioned study. Clearly, the reported unchanged corticospinal excitability may have been the result of a differential, and contrasting, response at the cortical vs the spinal level.

Interestingly, the corticospinal inhibition, or disfacilitation, associated with exhaustive cycling exercise has been documented to also affect a remote muscle not involved in the locomotor task. To this end, Sidhu et al. (2014) examined changes in corticospinal excitability of the elbow flexors throughout a fatiguing constant-load leg cycling test at 80% peak power output. Brief constant force contractions at 25% of the pre-exercise elbow flexion MVC were used to assess biceps brachii corticospinal excitability during the leg cycling exercise. Reflecting the broad influence of fatiguing exercise on the motor pathway, corticospinal excitability of the non-exercising upper limb was diminished during the final 25% of the cycling test when compared to the start of exercise (Sidhu et al., 2014). Since CMEPs were not evoked in this study, the results reflect the effect of fatiguing lower limb exercise on the net corticospinal excitability of the elbow flexors, but do not offer insights on motor cortical vs motoneuronal contributions to the overall decrease in MEPs.

6 THE ROLE OF GROUP III/IV MUSCLE AFFERENTS IN CORTICOSPINAL EXCITABILITY DURING FATIGUING WHOLE BODY EXERCISE

Projections of sensory neurons innervating skeletal muscle can modulate the corticospinal pathway during exercise; a simplified schematic is presented in Fig. 2. Although feedback from muscle spindles (group Ia/II) and Golgi tendon organs (group Ib) are an integral part of the control of locomotion (e.g., Capaday and Stein, 1986; Simonsen and Dyhre-Poulsen, 1999; Zehr et al., 2001), their role during fatiguing whole body exercise is unknown. In contrast, thinly myelinated mechanosensitive (group III) and metabosensitive (group IV) muscle afferents have recently been documented to influence the excitability of the corticospinal pathway during fatiguing whole body exercise. These muscle afferents project directly, or indirectly, to both cortical and spinal regions of the central nervous system (Brooks et al., 2005; Craig, 1995; Garland, 1991; Liu et al., 2003) and respond to skeletal muscle contractions (Adreani et al., 1997; Kaufman et al., 1984). Investigations attempting to decipher the role of group III/IV muscle afferents on corticospinal excitability during fatiguing whole body exercise have utilized a pharmacological approach to temporarily attenuate the activity of these muscle afferents. Lumbar intrathecal fentanyl, a μ -opioid receptor agonist, attenuates approximately 60% of group III and IV muscle afferent feedback from the legs (Amann et al., 2009; Hureau et al., 2018a) via the closing of N-type voltage-gated calcium channels (Estrada and Kaufman, 2018). While the attenuation of these afferents have implications on the regulation of cardiovascular, ventilatory, and fatigue responses to exercise (Amann et al., 2015), this section will focus on the role of group III/IV muscle afferent feedback as a mechanism influencing the excitability of the corticospinal pathway.

To address the influence of group III/IV muscle afferent feedback on the corticospinal pathway during leg cycling, Sidhu et al. (2017) have recently repeated the identical fatiguing

bout (80% of peak power output for ~8min) performed with and without muscle afferent blockade and compared exercise-induced alterations in motor cortical and motoneuronal excitability. As mentioned above, with intact afferent feedback, the net excitability of the corticospinal pathway remained unaltered from the start to the final minute of fatiguing constant-load cycling. However, when feedback from group III/IV muscle afferents was attenuated during the identical exercise, MEP amplitude and area increased during exercise (Sidhu et al., 2017). As CMEP amplitude and area remained unchanged throughout exercise, both with and without afferent feedback, these data suggest that group III/IV muscle afferents exert an inhibitory influence on the motor cortex during fatiguing whole body exercise (Sidhu et al., 2017). This conclusion was later confirmed in a similar cycling study during which the corticospinal pathway was assessed during brief cycling bouts which were matched for EMG when performed before and after the fatiguing constant-load trial (Sidhu et al., 2018). Furthermore, while the fatiguing cycling exercise with intact afferent feedback did not alter the duration of the TMS-evoked silent period, afferent blockade during the same exercise resulted in a significantly shorter silent period. These data suggest that the afferent-mediated motor cortical depression could be related to intracortical inhibitory mechanisms (Sidhu et al., 2017, 2018).

In order to further investigate the role of intracortical inhibition as a potential mechanism underlying the group III/IV-mediated inhibition of the motor cortex, a specific paired pulse paradigm was utilized (Sidhu et al., 2018). This paradigm, which is believed to primarily evaluate GABA_B-mediated inhibitory networks (Valls-Sole et al., 1992; Wassermann et al., 1996), was employed during low intensity cycling at a matched EMG pre- and post-fatiguing constant-load cycling. Compared to pre-exercise baseline responses, fatiguing cycling exercise with intact afferent feedback resulted in a post-exercise reduction of the conditioned MEP area with no change in the conditioned CMEP area (Sidhu et al., 2018). The greater reduction in the conditioned MEP area, without a change in the conditioned CMEP area, signifies an increase in the inhibitory pathways of the motor cortex, presumably related to the GABA_B-mediated inhibitory networks. Importantly, when afferent feedback was pharmacologically attenuated during the same exercise, the fatiguing cycling did not alter the MEP area nor CMEP area from pre-exercise baseline values (Sidhu et al., 2018). These findings suggest that the group III/IV-mediated inhibition of the motor cortex results, at least in part, from the facilitating effect of these sensory neurons on intracortical inhibitory networks, potentially mediated by GABA_B receptors.

Finally, it is important to mention that group III/IV muscle afferents also exert an influence on the corticospinal pathway during non-fatiguing whole body exercise. Specifically, during non-fatiguing brief cycling bouts (~45s at 80% peak power output), these sensory neurons disfacilitate spinal motoneurons while facilitating the motor cortex, resulting in a zero net change in corticospinal excitability (Sidhu et al., 2017). The disfacilitating effect of group III/IV muscle afferents on the excitability of the motoneuron pool during non-fatiguing cycling is possibly modulated through presynaptic inhibition of Ia afferents (Rossi et al., 1999) and the associated reduction in reflex facilitation of the motoneurons (Macefield et al., 1993).

7 THE INFLUENCE OF HYPOXIA ON CORTICOSPINAL EXCITABILITY DURING WHOLE BODY EXERCISE

The limited data available to date suggest that both acute ($>25\text{min}$, $\text{FiO}_2 \sim 0.12$, $\text{SpO}_2 \sim 75\%$, (Goodall et al., 2012; Rupp et al., 2012; Szubski et al., 2006)) and chronic (14 days at 5260m, $\text{PiO}_2 \sim 76\text{mmHg}$, $\text{SpO}_2 \sim 86\%$, (Goodall et al., 2014)) exposure to hypoxia can augment resting corticospinal excitability over that observed at sea level (i.e., in normoxic conditions). This heightened excitability may be related to the elevated sympathetic activity associated with acute and chronic hypoxia (Calbet, 2003; Xie et al., 2001) which, when experimentally increased with lower body negative pressure at sea level, has been shown to increase MEP amplitude (Buharin et al., 2013). However, the facilitating influence of acute hypoxia may critically depend on the exposure time (Rupp et al., 2012) as an increase in resting MEP amplitude and area is not apparent after approximately 10min of exposure (Goodall et al., 2014).

Despite the changes in corticospinal excitability at rest, hypoxia has been documented to have little, if any, effect on exercise-induced changes in corticospinal excitability. Specifically, pre- to post-exercise changes in MEP amplitude have been shown to be similar in normoxia (sea level), and acute (Goodall et al., 2014; Jubeau et al., 2017) and chronic (Goodall et al., 2014) hypoxia. Despite this similarity across conditions, it needs to be emphasized that the greater corticospinal excitability present at baseline in chronic hypoxia persists throughout the exercise (Goodall et al., 2014). Additionally, similar to sea level/normoxic conditions, the duration of the silent period remains unchanged from pre-to post-cycling exercise in both acute (Goodall et al., 2012, 2014; Jubeau et al., 2017) and chronic hypoxia (Goodall et al., 2014). It is important to note that one study, performed in acute hypoxia ($\text{FiO}_2 \sim 0.13$, $\text{SaO}_2 \sim 90\%$), has reported an increase in corticospinal excitability from pre- to post-exercise (Goodall et al., 2012). However this discrepancy may be related to the greater relative exercise intensity (78% vs 50% of peak power output in normoxia) and/or the shorter duration ($\sim 4\text{min}$ vs the more frequently utilized 10min) when compared to other studies (Goodall et al., 2014). Clearly, additional research is needed for a more definitive conclusion on the effect of hypoxia on corticospinal excitability during whole body exercise.

8 MODULATING MOTOR CORTICAL EXCITABILITY: IMPLICATIONS FOR WHOLE BODY EXERCISE PERFORMANCE

Transcranial direct current stimulation (tDCS) is a novel technique which can be employed to modulate cortical excitability. tDCS involves a weak but constant electrical current ($\sim 1\text{--}2\text{mA}$) delivered to the contralateral motor cortex which can acutely ($\sim 3\text{--}5\text{min}$) modulate motor cortical excitability with as little as 4s of stimulation (Nitsche and Paulus, 2000) or produce long-lasting changes in motor cortical excitability ($\sim 1\text{h}$) with tDCS of 5min or more (Bindman et al., 1962; Nitsche and Paulus, 2001). The effect of tDCS on cortical excitability is dependent on electrode polarity, such that an excitatory effect occurs under the anode and an inhibitory effect occurs under the cathode (Nitsche and Paulus, 2000). While the acute effects of short-term tDCS can be attributed to alterations in resting membrane potentials

(Purpura and McMurtry, 1965), the long-lasting effects of tDCS are dependent on changes to both resting membrane potentials and intracortical synaptic mechanisms (Nitsche et al., 2005).

Although not always present (Angius et al., 2015; Barwood et al., 2016), recent investigations employing ~10min of tDCS have demonstrated a significant 23% improvement in whole body cycling performance (Angius et al., 2018; Okano et al., 2015; Vitor-Costa et al., 2015). Of these studies, only one tested the effect of tDCS on corticospinal excitability and found an increased MEP area with no change in the TMS-evoked silent period following bilateral extra-cephalic tDCS over the motor cortex (Angius et al., 2018). The authors postulated that with an augmented motor cortical excitability, less excitatory input into the motor cortex would be necessary to recruit a similar level of locomotor muscle activity, resulting in the lower reported perceived exertion during submaximal stages of exercise and improved performance overall (Angius et al., 2018). Unfortunately, corticospinal excitability was not assessed during, nor post, cycling exercise so it is not known whether the presumed effect of tDCs persisted throughout exercise and contributed to the improved exercise performance. This would, however, be important to know as there is evidence suggesting that non-motor areas (e.g., the insular cortex) may also have been stimulated by tDCS which can potentially alter effort perception and influence exercise performance (Okano et al., 2015). Nevertheless, tDCS remains a promising tool to examine the role of motor cortical and corticospinal excitability in determining whole body exercise performance.

9 SUMMARY

Fatiguing whole body exercise is characterized by progressively changing processes simultaneously facilitating and inhibiting the corticospinal pathway. Based on the limited evidence available to date, the net effect of the complex integration of these processes appears to be an unchanged excitability of the corticospinal pathway throughout exercise. It is important to consider that this lack of an apparent effect does not designate an absence of change, but a counterbalance of excitatory and inhibitory processes. Specifically, whole body fatiguing exercise results in a depression of motor cortical and motoneuronal excitability, which may be offset by the facilitatory influence of the increases in central motor drive associated with the development of peripheral fatigue. Group III/IV afferent feedback from the locomotor muscles has been identified as a mechanism restricting corticospinal excitability by depressing the motor cortex during fatiguing whole body exercise.

REFERENCES

- Adreani CM, Hill JM, Kaufman MP, 1997 Responses of group III and IV muscle afferents to dynamic exercise. *J. Appl. Physiol* 82, 1811–1817. [PubMed: 9173945]
- Amann M, Proctor LT, Sebranek JJ, Pegelow DF, Dempsey JA, 2009 Opioid-mediated muscle afferents inhibit central motor drive and limit peripheral muscle fatigue development in humans. *J. Physiol* 587, 271–283. [PubMed: 19015193]
- Amann M, Sidhu SK, Weavil JC, Mangum TS, Venturelli M, 2015 Autonomic responses to exercise: group III/IV muscle afferents and fatigue. *Auton. Neurosci* 188, 19–23. [PubMed: 25458423]

- Angius L, Hopker JG, Marcora SM, Mauger AR, 2015 The effect of transcranial direct current stimulation of the motor cortex on exercise-induced pain. *Eur. J. Appl. Physiol* 115, 2311–2319.
- Angius L, Mauger AR, Hopker J, Pascual-Leone A, Santarnecchi E, Marcora SM, 2018 Bilateral extracephalic transcranial direct current stimulation improves endurance performance in healthy individuals. *Brain Stimul.* 11, 108–117. [PubMed: 29079458]
- Barwood MJ, Butterworth J, Goodall S, House JR, Laws R, Nowicky A, Corbett J, 2016 The effects of direct current stimulation on exercise performance, pacing and perception in temperate and hot environments. *Brain Stimul.* 9, 842–849. [PubMed: 27567471]
- Bigland-Ritchie B, Johansson R, Lippold OC, Woods JJ, 1983 Contractile speed and EMG changes during fatigue of sustained maximal voluntary contractions. *J. Neurophysiol* 50, 313–324. [PubMed: 6308182]
- Bigland-Ritchie B, Furbush F, Woods JJ, 1986 Fatigue of intermittent submaximal voluntary contractions: central and peripheral factors. *J. Appl. Physiol* 61, 421–429. [PubMed: 3745035]
- Bindman LJ, Lippold OC, Redfearn JW, 1962 Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. *Nature* 196, 584–585. [PubMed: 13968314]
- Bowtell JL, Avenell G, Hunter SP, Mileva KN, 2013 Effect of hypohydration on peripheral and corticospinal excitability and voluntary activation. *PLoS One* 8, e77004. [PubMed: 24098574]
- Brooks JC, Zambreanu L, Godinez A, Craig AD, Tracey I, 2005 Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. *Neuroimage* 27, 201–209. [PubMed: 15921935]
- Brouwer B, Ashby P, 1990 Corticospinal projections to upper and lower limb spinal motoneurons in man. *Electroencephalogr. Clin. Neurophysiol* 76, 509–519. [PubMed: 1701119]
- Brouwer B, Ashby P, 1992 Corticospinal projections to lower limb motoneurons in man. *Exp. Brain Res.* 89, 649–654. [PubMed: 1644127]
- Buharin VE, Butler AJ, Rajendra JK, Shinohara M, 2013 Enhanced corticospinal excitability with physiologically heightened sympathetic nerve activity. *J. Appl. Physiol* 114, 429–435. [PubMed: 23239871]
- Calbet JA, 2003 Chronic hypoxia increases blood pressure and noradrenaline spillover in healthy humans. *J. Physiol* 551, 379–386. [PubMed: 12844510]
- Capaday C, Stein RB, 1986 Amplitude modulation of the soleus H-reflex in the human during walking and standing. *J. Neurosci* 6, 1308–1313. [PubMed: 3711981]
- Chen R, Lozano AM, Ashby P, 1999 Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. *Exp. Brain Res.* 128, 539–542. [PubMed: 10541749]
- Craig AD, 1995 Distribution of brainstem projections from spinal lamina I neurons in the cat and the monkey. *J. Comp. Neurol* 361, 225–248. [PubMed: 8543660]
- D'Amico JM, Butler AA, Heroux ME, Cotel F, Perrier JM, Butler JE, Gandevia SC, Taylor JL, 2017 Human motoneurone excitability is depressed by activation of serotonin 1A receptors with buspirone. *J. Physiol* 595, 1763–1773. [PubMed: 27859267]
- Davey NJ, Romaiguere P, Maskill DW, Ellaway PH, 1994 Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. *J. Physiol* 477, 223–235. [PubMed: 7932215]
- Day BL, Rothwell JC, Thompson PD, Dick JP, Cowan JM, Berardelli A, Marsden CD, 1987 Motor cortex stimulation in intact man. 2. Multiple descending volleys. *Brain* 110 (Pt 5), 1191–1209. [PubMed: 3676698]
- Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, Mazzone P, Tonali P, Rothwell JC, 1998a Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. *Exp. Brain Res.* 119, 265–268. [PubMed: 9535577]
- Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, Mazzone P, Tonali P, Rothwell JC, 1998b Effects of voluntary contraction on descending volleys evoked by transcranial stimulation in conscious humans. *J. Physiol* 508 (Pt 2), 625–633. [PubMed: 9508823]

- Esposito F, Mathieu-Costello O, Shabetai R, Wagner PD, Richardson RS, 2010 Limited maximal exercise capacity in patients with chronic heart failure: partitioning the contributors. *J. Am. Coll. Cardiol* 55, 1945–1954. [PubMed: 20430267]
- Estrada JA, Kaufman MP, 2018 Micro-opioid receptors inhibit the exercise pressor reflex by closing N-type calcium channels but not by opening GIRK channels in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol* 314, R693–R699. [PubMed: 29341826]
- Fernandez-Del-Olmo M, Rodriguez FA, Marquez G, Iglesias X, Marina M, Benitez A, Vallejo L, Acero RM, 2013 Isometric knee extensor fatigue following a Wingate test: peripheral and central mechanisms. *Scand. J. Med. Sci. Sports* 23, 57–65. [PubMed: 21812824]
- Finn HT, Rouffet DM, Kennedy DS, Green S, Taylor JL, 2018 Motoneuron excitability of the quadriceps decreases during a fatiguing submaximal isometric contraction. *J. Appl. Physiol* 124, 970–979. [PubMed: 29357479]
- Fulton RC, Strutton PH, McGregor AH, Davey NJ, 2002 Fatigue-induced change in corticospinal drive to back muscles in elite rowers. *Exp. Physiol* 87, 593–600. [PubMed: 12481934]
- Gandevia SC, Petersen N, Butler JE, Taylor JL, 1999 Impaired response of human motoneurons to corticospinal stimulation after voluntary exercise. *J. Physiol* 521 (Pt 3), 749–759. [PubMed: 10601504]
- Garland SJ, 1991 Role of small diameter afferents in reflex inhibition during human muscle fatigue. *J. Physiol* 435, 547–558. [PubMed: 1770449]
- Girard O, Bishop DJ, Racinais S, 2013 Neuromuscular adjustments of the quadriceps muscle after repeated cycling sprints. *PLoS One* 8, e61793. [PubMed: 23650503]
- Goodall S, Gonzalez-Alonso J, Ali L, Ross EZ, Romer LM, 2012 Supraspinal fatigue after normoxic and hypoxic exercise in humans. *J. Physiol* 590, 2767–2782. [PubMed: 22473785]
- Goodall S, Twomey R, Amann M, Ross EZ, Lovering AT, Romer LM, Subudhi AW, Roach RC, 2014 AltitudeOmics: exercise-induced supraspinal fatigue is attenuated in healthy humans after acclimatization to high altitude. *Acta Physiol.* 210, 875–888.
- Goodall S, Charlton K, Howatson G, Thomas K, 2015 Neuromuscular fatigability during repeated-sprint exercise in male athletes. *Med. Sci. Sports Exerc.* 47, 528–536. [PubMed: 25010404]
- Hartley GL, Watson CL, Ainslie PN, Tokuno CD, Greenway MJ, Gabriel DA, O’leary DD, Cheung SS, 2016 Corticospinal excitability is associated with hypocapnia but not changes in cerebral blood flow. *J. Physiol* 594, 3423–3437. [PubMed: 26836470]
- Hilty L, Lutz K, Maurer K, Rodenkirch T, Spengler CM, Boutellier U, Jancke L, Amann M, 2011 Spinal opioid receptor-sensitive muscle afferents contribute to the fatigue-induced increase in intracortical inhibition in healthy humans. *Exp. Physiol* 96, 505–517. [PubMed: 21317218]
- Hollge J, Kunkel M, Ziemann U, Tergau F, Geese R, Reimers CD, 1997 Central fatigue in sports and daily exercises. A magnetic stimulation study. *Int. J. Sports Med.* 18, 614–617. [PubMed: 9443595]
- Hopkinson NS, Sharshar T, Ross ET, Nickol AH, Dayer MJ, Porcher R, Jonville S, Moxham J, Polkey MI, 2004 Corticospinal control of respiratory muscles in chronic obstructive pulmonary disease. *Respir. Physiol. Neurobiol* 141, 1–12. [PubMed: 15234671]
- Hopkinson NS, Dayer MJ, Antoine-Jonville S, Swallow EB, Porcher R, Vazir A, Poole-Wilson P, Polkey MI, 2013 Central and peripheral quadriceps fatigue in congestive heart failure. *Int. J. Cardiol* 167, 2594–2599. [PubMed: 22795722]
- Hureau TJ, Weavil JC, Thurston TS, Broxterman RM, Nelson AD, Bledsoe AD, Jessop JE, Richardson RS, Wray DW, Amann M, 2018a Identifying the role of group III/IV muscle afferents in the carotid baroreflex control of mean arterial pressure and heart rate during exercise. *J. Physiol* 596, 1373–1384. [PubMed: 29388218]
- Hureau TJ, Weavil JC, Thurston TS, Wan H, Gifford JR, Jessop JE, Buys MJ, Richardson RS, Amann M, 2018b Muscle afferent blockade improves endurance exercise performance when O₂ transport to locomotor muscles is preserved. *Med. Sci. Sports Exerc* 50, 849.
- Inghilleri M, Berardelli A, Cruccu G, Manfredi M, 1993 Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. *J. Physiol* 466, 521–534. [PubMed: 8410704]

- Jackson A, Baker SN, Fetz EE, 2006 Tests for presynaptic modulation of corticospinal terminals from peripheral afferents and pyramidal tract in the macaque. *J. Physiol* 573, 107–120. [PubMed: 16556658]
- Jonville S, Jutand L, Similowski T, Denjean A, Delpech N, 2005 Putative protective effect of inspiratory threshold loading against exercise-induced supraspinal diaphragm fatigue. *J. Appl. Physiol* 98, 991–998. [PubMed: 15489255]
- Jubeau M, Rupp T, Perrey S, Temesi J, Wuyam B, Levy P, Verges S, Millet GY, 2014 Changes in voluntary activation assessed by transcranial magnetic stimulation during prolonged cycling exercise. *PLoS One* 9, e89157. [PubMed: 24586559]
- Jubeau M, Rupp T, Temesi J, Perrey S, Wuyam B, Millet GY, Verges S, 2017 Neuromuscular fatigue during prolonged exercise in hypoxia. *Med. Sci. Sports Exerc.* 49, 430–439. [PubMed: 27753741]
- Kaufman MP, Waldrop TG, Rybicki KJ, Ordway GA, Mitchell JH, 1984 Effects of static and rhythmic twitch contractions on the discharge of group III and IV muscle afferents. *Cardiovasc. Res* 18, 663–668. [PubMed: 6498873]
- Klass M, Levenez M, Enoka RM, Duchateau J, 2008 Spinal mechanisms contribute to differences in the time to failure of submaximal fatiguing contractions performed with different loads. *J. Neurophysiol* 99, 1096–1104. [PubMed: 18184884]
- Klass M, Roelands B, Levenez M, Fontenelle V, Pattyn N, Meeusen R, Duchateau J, 2012 Effects of noradrenaline and dopamine on supraspinal fatigue in well-trained men. *Med. Sci. Sports Exerc.* 44, 2299–2308. [PubMed: 22776872]
- Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD, 1993 Corticocortical inhibition in human motor cortex. *J. Physiol* 471, 501–519. [PubMed: 8120818]
- Liu JZ, Shan ZY, Zhang LD, Sahgal V, Brown RW, Yue GH, 2003 Human brain activation during sustained and intermittent submaximal fatigue muscle contractions: an FMRI study. *J. Neurophysiol* 90, 300–312. [PubMed: 12634278]
- Macefield VG, Gandevia SC, Bigland-Ritchie B, Gorman RB, Burke D, 1993 The firing rates of human motoneurons voluntarily activated in the absence of muscle afferent feedback. *J. Physiol* 471, 429–443. [PubMed: 8120815]
- Martin PG, Smith JL, Butler JE, Gandevia SC, Taylor JL, 2006 Fatigue-sensitive afferents inhibit extensor but not flexor motoneurons in humans. *J. Neurosci* 26, 4796–4802. [PubMed: 16672652]
- Martin PG, Butler JE, Gandevia SC, Taylor JL, 2008 Noninvasive stimulation of human corticospinal axons innervating leg muscles. *J. Neurophysiol* 100, 1080–1086. [PubMed: 18509069]
- Matthews PB, 1999 The effect of firing on the excitability of a model motoneurone and its implications for cortical stimulation. *J. Physiol* 518 (Pt 3), 867–882. [PubMed: 10420021]
- Mazzocchio R, Rothwell JC, Day BL, Thompson PD, 1994 Effect of tonic voluntary activity on the excitability of human motor cortex. *J. Physiol* 474, 261–267. [PubMed: 8006812]
- McNeil CJ, Giesebrecht S, Gandevia SC, Taylor JL, 2011 Behaviour of the motoneurone pool in a fatiguing submaximal contraction. *J. Physiol* 589, 3533–3544. [PubMed: 21606110]
- McNeil CJ, Butler JE, Taylor JL, Gandevia SC, 2013 Testing the excitability of human motoneurons. *Front. Hum. Neurosci* 7, 152. [PubMed: 23630483]
- Nielsen J, Petersen N, 1994 Is presynaptic inhibition distributed to corticospinal fibres in man? *J. Physiol* 477, 47–58. [PubMed: 8071888]
- Nitsche MA, Paulus W, 2000 Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol* 527 (Pt 3), 633–639. [PubMed: 10990547]
- Nitsche MA, Paulus W, 2001 Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* 57, 1899–1901. [PubMed: 11723286]
- Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, Fricke K, Liebetanz D, Lang N, Antal A, Paulus W, Tergau F, 2005 Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J. Physiol* 568, 291–303. [PubMed: 16002441]
- Okano AH, Fontes EB, Montenegro RA, Farinatti Pde T, Cyrino ES, Li LM, Bikson M, Noakes TD, 2015 Brain stimulation modulates the autonomic nervous system, rating of perceived exertion and performance during maximal exercise. *Br. J. Sports Med* 49, 1213–1218. [PubMed: 23446641]

- Orth M, Rothwell JC, 2004 The cortical silent period: intrinsic variability and relation to the waveform of the transcranial magnetic stimulation pulse. *Clin. Neurophysiol* 115, 1076–1082. [PubMed: 15066533]
- Pearcey GE, Bradbury-Squires DJ, Monks M, Philpott D, Power KE, Button DC, 2016 Arm-cycling sprints induce neuromuscular fatigue of the elbow flexors and alter corticospinal excitability of the biceps brachii. *Appl. Physiol. Nutr. Metab* 41, 199–209. [PubMed: 26799694]
- Petersen NT, Butler JE, Marchand-Pauvert V, Fisher R, Ledebt A, Pyndt HS, Hansen NL, Nielsen JB, 2001 Suppression of EMG activity by transcranial magnetic stimulation in human subjects during walking. *J. Physiol* 537, 651–656. [PubMed: 11731595]
- Petersen NT, Taylor JL, Butler JE, Gandevia SC, 2003 Depression of activity in the corticospinal pathway during human motor behavior after strong voluntary contractions. *J. Neurosci* 23, 7974–7980. [PubMed: 12954858]
- Place N, Maffiuletti NA, Martin A, Lepers R, 2007 Assessment of the reliability of central and peripheral fatigue after sustained maximal voluntary contraction of the quadriceps muscle. *Muscle Nerve* 35, 486–495. [PubMed: 17221875]
- Purpura DP, Mcmurtry JG, 1965 Intracellular activities and evoked potential changes during polarization of motor cortex. *J. Neurophysiol* 28, 166–185. [PubMed: 14244793]
- Racinais S, Girard O, 2012 Neuromuscular failure is unlikely to explain the early exercise cessation in hot ambient conditions. *Psychophysiology* 49, 853–865. [PubMed: 22416901]
- Ross EZ, Middleton N, Shave R, George K, Nowicky A, 2007 Corticomotor excitability contributes to neuromuscular fatigue following marathon running in man. *Exp. Physiol* 92, 417–426. [PubMed: 17099060]
- Ross EZ, Gregson W, Williams K, Robertson C, George K, 2010 Muscle contractile function and neural control after repetitive endurance cycling. *Med. Sci. Sports Exerc.* 42, 206–212. [PubMed: 20010112]
- Rossi A, Decchi B, Ginanneschi F, 1999 Presynaptic excitability changes of group Ia fibres to muscle nociceptive stimulation in humans. *Brain Res.* 818, 12–22. [PubMed: 9914433]
- Rossman MJ, Venturelli M, McDaniel J, Amann M, Richardson RS, 2012 Muscle mass and peripheral fatigue: a potential role for afferent feedback? *Acta Physiol.* 206, 242–250.
- Rupp T, Jubeau M, Wuyam B, Perrey S, Levy P, Millet GY, Verges S, 2012 Time-dependent effect of acute hypoxia on corticospinal excitability in healthy humans. *J. Neurophysiol* 108, 1270–1277. [PubMed: 22696539]
- Sidhu SK, Bentley DJ, Carroll TJ, 2009 Cortical voluntary activation of the human knee extensors can be reliably estimated using transcranial magnetic stimulation. *Muscle Nerve* 39, 186–196. [PubMed: 19034956]
- Sidhu SK, Cresswell AG, Carroll TJ, 2012a Motor cortex excitability does not increase during sustained cycling exercise to volitional exhaustion. *J. Appl. Physiol* 113, 401–409. [PubMed: 22678968]
- Sidhu SK, Hoffman BW, Cresswell AG, Carroll TJ, 2012b Corticospinal contributions to lower limb muscle activity during cycling in humans. *J. Neurophysiol* 107, 306–314. [PubMed: 22013236]
- Sidhu SK, Cresswell AG, Carroll TJ, 2013a Corticospinal responses to sustained loco-motor exercises: moving beyond single-joint studies of central fatigue. *Sports Med.* 43, 437–449. [PubMed: 23456490]
- Sidhu SK, Lauber B, Cresswell AG, Carroll TJ, 2013b Sustained cycling exercise increases intracortical inhibition. *Med. Sci. Sports Exerc.* 45, 654–662. [PubMed: 23190593]
- Sidhu SK, Weavil JC, Venturelli M, Garten RS, Rossman MJ, Richardson RS, Gmelch BS, Morgan DE, Amann M, 2014 Spinal mu-opioid receptor-sensitive lower limb muscle afferents determine corticospinal responsiveness and promote central fatigue in upper limb muscle. *J. Physiol* 592, 5011–5024. [PubMed: 25172953]
- Sidhu SK, Weavil JC, Mangum TS, Jessop JE, Richardson RS, Morgan DE, Amann M, 2017 Group III/IV locomotor muscle afferents alter motor cortical and corticospinal excitability and promote central fatigue during cycling exercise. *Clin. Neurophysiol* 128, 44–55. [PubMed: 27866119]

- Sidhu SK, Weavil J, Thurston T, Wang E, Rosenberger D, Jessop J, Richardson R, Amann M, 2018 Fatigue modulates the effect of group III/IV muscle afferents on GABAB-mediated inhibition and corticospinal excitability. *J. Physiol* 10.1113/JP276460.
- Simonsen EB, Dyhre-Poulsen P, 1999 Amplitude of the human soleus H reflex during walking and running. *J. Physiol* 515 (Pt 3), 929–939. [PubMed: 10066917]
- Stephens JA, Usherwood TP, 1977 The mechanical properties of human motor units with special reference to their fatigability and recruitment threshold. *Brain Res.* 125, 91–97. [PubMed: 851876]
- Stuzski C, Burtcher M, Loscher WN, 2006 The effects of short-term hypoxia on motor cortex excitability and neuromuscular activation. *J. Appl. Physiol* 101, 1673–1677. [PubMed: 16902059]
- Taylor JL, 2006 Stimulation at the cervicomedullary junction in human subjects. *J. Electromyogr. Kinesiol* 16, 215–223. [PubMed: 16125974]
- Taylor JL, Gandevia SC, 2004 Noninvasive stimulation of the human corticospinal tract. *J. Appl. Physiol* 96, 1496–1503. [PubMed: 15016794]
- Taylor JL, Gandevia SC, 2008 A comparison of central aspects of fatigue in submaximal and maximal voluntary contractions. *J. Appl. Physiol* 104, 542–550. [PubMed: 18032577]
- Taylor JL, Petersen NT, Butler JE, Gandevia SC, 2002 Interaction of transcranial magnetic stimulation and electrical transmastoid stimulation in human subjects. *J. Physiol* 541, 949–958. [PubMed: 12068053]
- Taylor JL, Todd G, Gandevia SC, 2006 Evidence for a supraspinal contribution to human muscle fatigue. *Clin. Exp. Pharmacol. Physiol* 33, 400–405. [PubMed: 16620309]
- Taylor JL, Amann M, Duchateau J, Meeusen R, Rice CL, 2016 Neural contributions to muscle fatigue: from the brain to the muscle and back again. *Med. Sci. Sports Exerc.* 48, 2294–2306. [PubMed: 27003703]
- Temesi J, Arnal PJ, Davranche K, Bonnefoy R, Levy P, Verges S, Millet GY, 2013 Does central fatigue explain reduced cycling after complete sleep deprivation? *Med. Sci. Sports Exerc.* 45, 2243–2253. [PubMed: 23760468]
- Temesi J, Rupp T, Martin V, Arnal PJ, Feasson L, Verges S, Millet GY, 2014 Central fatigue assessed by transcranial magnetic stimulation in ultratrail running. *Med. Sci. Sports Exerc.* 46, 1166–1175. [PubMed: 24195865]
- Thomas K, Goodall S, Stone M, Howatson G, St Clair Gibson A, Ansley L, 2015 Central and peripheral fatigue in male cyclists after 4-, 20-, and 40-km time trials. *Med. Sci. Sports Exerc.* 47, 537–546. [PubMed: 25051388]
- Thomas K, Elmeua M, Howatson G, Goodall S, 2016 Intensity-dependent contribution of neuromuscular fatigue after constant-load cycling. *Med. Sci. Sports Exerc.* 48, 1751–1760. [PubMed: 27187101]
- Todd G, Taylor JL, Gandevia SC, 2003 Measurement of voluntary activation of fresh and fatigued human muscles using transcranial magnetic stimulation. *J. Physiol* 551, 661–671. [PubMed: 12909682]
- Valls-Sole J, Pascual-Leone A, Wassermann EM, Hallett M, 1992 Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalogr. Clin. Neurophysiol* 85, 355–364. [PubMed: 1282453]
- Verin E, Ross E, Demoule A, Hopkinson N, Nickol A, Fauroux B, Moxham J, Similowski T, Polkey MI, 2004 Effects of exhaustive incremental treadmill exercise on diaphragm and quadriceps motor potentials evoked by transcranial magnetic stimulation. *J. Appl. Physiol* 96, 253–259. [PubMed: 12959961]
- Vitor-Costa M, Okuno NM, Bortolotti H, Bertollo M, Boggio PS, Fregni F, Altimari LR, 2015 Improving cycling performance: transcranial direct current stimulation increases time to exhaustion in cycling. *PLoS One* 10, e0144916. [PubMed: 26674200]
- Vollestad NK, 1997 Measurement of human muscle fatigue. *J. Neurosci. Methods* 74, 219–227. [PubMed: 9219890]
- Wassermann EM, Samii A, Mercuri B, Ikoma K, Oddo D, Grill SE, Hallett M, 1996 Responses to paired transcranial magnetic stimuli in resting, active, and recently activated muscles. *Exp. Brain Res.* 109, 158–163. [PubMed: 8740220]

- Weavil JC, Sidhu SK, Mangum TS, Richardson RS, Amann M, 2015 Intensity-dependent alterations in the excitability of cortical and spinal projections to the knee extensors during isometric and locomotor exercise. *Am. J. Physiol. Regul. Integr. Comp. Physiol* 308, R998–1007. [PubMed: 25876651]
- Weavil JC, Sidhu SK, Mangum TS, Richardson RS, Amann M, 2016 Fatigue diminishes motoneuronal excitability during cycling exercise. *J. Neurophysiol* 116, 1743–1751. [PubMed: 27440242]
- Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J, 1999 Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J. Physiol* 517 (Pt 2), 591–597. [PubMed: 10332104]
- Xie A, Skatrud JB, Puleo DS, Morgan BJ, 2001 Exposure to hypoxia produces long-lasting sympathetic activation in humans. *J. Appl. Physiol* 91, 1555–1562. [PubMed: 11568136]
- Yacyshyn AF, Woo EJ, Price MC, McNeil CJ, 2016 Motoneuron responsiveness to corticospinal tract stimulation during the silent period induced by transcranial magnetic stimulation. *Exp. Brain Res.* 234, 3457–3463. [PubMed: 27481287]
- Zehr EP, Hesketh KL, Chua R, 2001 Differential regulation of cutaneous and H-reflexes during leg cycling in humans. *J. Neurophysiol* 85, 1178–1184. [PubMed: 11247987]
- Ziemann U, Tergau F, Wischer S, Hildebrandt J, Paulus W, 1998 Pharmacological control of facilitatory I-wave interaction in the human motor cortex. A paired transcranial magnetic stimulation study. *Electroencephalogr. Clin. Neurophysiol* 109, 321–330. [PubMed: 9751295]

FIG. 1.

Changes in the excitability of the motor pathway (area of MEP normalized to $M_{\max}$; A and D), the motoneuron pool (CMEP normalized to $M_{\max}$; B and E), and the motor cortex (MEP/CMEP ratio; C and F) associated with an ~50% increase in EMG occurring in the absence (non-fatiguing cycling) and presence (fatiguing cycling exercise) of significant central and peripheral fatigue. * $P < 0.05$, significant difference within trials.

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FIG. 2.

Steps involved in voluntary force production and factors acting at motoneuronal level. A: diagrammatic representation of the “chain” involved in voluntary contractions. A major source of feedback, that from the muscle, is shown acting at three levels in the central nervous system. Other sources of feedback that also act at these levels are not shown. B: summary of inputs to α - and γ -motoneurons for an agonist muscle. Cells with solid circles are inhibitory. Dotted curved region at premotoneuronal terminals denotes presynaptic inhibition acting selectively on the afferent paths to motoneurons.

Figure reproduced with permission from Gandevia, S.C., 2001. Spinal and supraspinal factors in human muscle fatigue. *Physiol. Rev.*, 81, 1725–1789.

Literature Quantifying Corticospinal Alterations to Fatiguing Whole Body Exercise Using Transcranial Magnetic Stimulation of the Target Muscle in a Relaxed State Pre- and Post-exercise

Table 1

Reference	Year	n	Exercise Modality	Protocol	Exercise Duration	Target Muscle	Remote Muscle	Time to Measure	Mode of Evaluation	TMS Stimulator Intensity	Qtw	VA	M _{max}	Motoneuron	MEP	Silent Period
Hollge et al.	1997	17	Aerobic jogging	50min	Range: 8–12 km	AH	N	NQ	NQ	NQ	NQ	NQ	NQ	NQ	↔ raw	NQ
				600 steps	Range: 6–9min	AH	N	NQ	NQ	NQ	NQ	NQ	NQ	NQ	↔ raw	NQ
		14	Anaerobic running	400 m sprint	Range: 50–79s	QF	N	NQ	NQ	NQ	NQ	NQ	NQ	NQ	↔ raw	NQ
	2002	23	Press ups	To exhaustion	Range: 10–35 repetitions	TB	N	NQ	NQ	NQ	NQ	NQ	NQ	NQ	↓ raw	NQ
				90° dumbbell hold	Range: 3–6min	BB	N	NQ	NQ	NQ	NQ	NQ	NQ	NQ	↓ raw	NQ
Fulton et al.	2002	11	Rowing	Submaximal and maximal rowing exercise	Submaximal: 10min Maximal: 1min	ES	N	<2min	Rest	120% resting motor threshold	NQ	NQ	NQ	NQ	↑ raw within 2min post, ↓ raw up to 16min post	NQ
		8	Walking	Slow walk	5min	RF/ Diaphragm	N	5min	Rest/FRC	Matched between muscles at ~90% stimulator output	↔	NQ	↔	NQ	↔ raw	NQ
Jonville et al.	2005	10	Leg cycling	Bruce protocol	18 ± 4min	RF/ Diaphragm	N	5min	Rest/FRC	~90% stimulator output	↔	NQ	↔	Q	↓ raw	NQ
				55% of maximal oxygen uptake	16min	Diaphragm	N	10min	Rest/FRC	Not reported	NQ	NQ	NQ	NQ	↓ raw, recovered by 20min post	NQ
Ross et al.	2007	9	Running	Treadmill marathon, ~5% lactate threshold start and could self select	208 ± 22 min	RF TA	N N	20min	Rest	120% resting motor threshold	NQ ↓	NQ ↓	NQ ↔	NQ NQ	↔ raw ↓ raw	NQ ↔
		8	Leg cycling	Simulated Tour de France (20 stages in	~522min/ day at 60% maximal heart rate	VL	N	On the two rest days (18 h after exercise)	Rest	60 ± 8%	↓ but not 2 days post	↓	↓ but not 2 days post	NQ	↓ raw	NQ

Reference	Year	n	Exercise Modality	Protocol 22 days)	Exercise Duration	Target Muscle	Remote Muscle	Time to Measure and 2 days post completion	Mode of Evaluation	TMS Stimulator Intensity	Q _{tw} completion	VA	M _{max} completion	Motoneuron	MEP	Silent Period
Hopkinson et al.	2013	20	Leg cycling	Incremental cycling: 20W/ min controls (53 years) 10W/min heart failure with preserved ejection fraction patients	~12min for both groups	RF	N	10min	Rest	140% resting motor threshold	↗	↔	↔	NQ	↗	NQ

AH, abductor hallucis; *BB*, biceps brachii; *ES*, erector spinae; *NQ*, not quantified; *Q_{tw}*, potentiated twitch; *QF*, quadriceps femoris; *RF*, rectus femoris; *TA*, tibialis anterior; *TB*, triceps brachii; *VA*, voluntary activation; *VL*, vastus lateralis;
↘, decrease;
↗, increase.

Literature Quantifying Corticospinal Alterations to Fatiguing Whole Body Exercise Using Transcranial Magnetic Stimulation of the Target Muscle During an Isometric Contraction Pre- and Post-exercise

Table 2

Reference	Year	n	Exercise Modality	Protocol	Exercise Duration	Target Muscle	Remote Muscle	Time to Measure	Mode of Evaluation	TMS Stimulator Intensity	Q _{tw}	VA	M _{max}	Motoneuron	MEP	Silent Period
Sidhu et al.	2009	10	Leg cycling	Eight 5min bouts of cycling at 80% peak power (60s recovery between bouts)	40min	RF	N	2.6min	Isometric knee extension (100% MVC)	range: 30–60%	✓	✓	↔	NQ	↔	↔
Goodall et al.	2012	9	Leg cycling	Constant-load cycling at ~292W in normoxia (N) and hypoxia (H) to task failure and time control in normoxia (ISO)	H— 4±1min N— 8±3min ISO— 4±4min	VL	N	2.5min	Isometric knee extension (50–75–100% MVC)	67 ±9%	✓ ✓ ✓, less than other two conditions	✓ ✓ ✓	↔ ↔ ↔	NQ NQ NQ	↑ raw at all contraction intensities ↔ ↔	↔ ↔ ↔
Klass et al.	2012	10	Leg cycling	60min constant-load at 55%W _{peak} followed by time trial equal to 30min at 75% W _{peak} with and without dopamine (DA) and noradrenaline (NE) reuptake inhibitors	CTRL— 31±2min DA— 30±1min NA— 34±4min	VM/RF	N	10min	Isometric knee extension (100% MVC)	range: 30–60%	✓ ✓ ✓	✓ ✓ ✓ larger than other conditions	↔ ↔ ↔	NQ NQ NQ	↔ ↔ ↔	NQ NQ NQ
Fernandez-del-Olom et al.	2013	10	Leg cycling	Wingate test × 2(30min recovery)	30 s	RF	N	~1min	Isometric knee extension (50–75–100% MVC)	~85%	✓	✓	↔	NQ	↑ during 50% and 75% MVC; ↔ at 100% MVC	NQ
Girard et al.	2013	12	Leg cycling	10 × 6s sprints with 30 s recovery followed 5min by 5 × 6s sprints (30 s recovery)	90s	VL	N	N/A	Isometric knee extension (50–75–100% MVC)	58 ± 13%	✓	↔	↔	NQ	↔	↔
Temesi et al.	2013	11	Leg cycling	35min at 65% peak power	Time to task failure	VL/RF/VM	N	2.5min	Isometric knee	Optimal intensity	✓	✓ post task	✓	NQ	Optimal intensity: ↑	Optimal

Reference	Year	n	Exercise Modality	Protocol	Exercise Duration ~1200s after submaximal stage	Target Muscle	Remote Muscle	Time to Measure	Mode of Evaluation extension (50–75–100% MVC)	TMS Stimulator Intensity (largest MEP): 65 ±8%; Suboptimal (intensity evoking half MEP): 35 ±7%	Q _{tw}	VA failure	M _{max}	Motoneuron	MEP in VL and VM, ↔, in RF Suboptimal: ↑ VL, ↔, RF or VM	Silent Period intensity: ↓ for all muscles at post 40 and task failure
Goodall et al.	2014	7	Leg cycling	followed by an increase of 5% every 5min until task failure	10±1min	VL	N	2.5min	Isometric knee extension (50–75–100% MVC)	N— 53 ±3% AcH— 54 ±5% CH— 51 ±6%	↔ ↓ ↓	↔ ↓ ↔	↔ ↔ ↔	NQ NQ NQ	↔↔ with exercise, ↑ with CH at 50% and MVC ↔ with exercise, ↓ with CH at 50% and 75% MVC ↔	↔↔ at any point ↔↔ at any point ↔↔ at any point
Jubeau	2014	10	Leg cycling	Constant-load cycling (45% W _{peak}) for three 80min bouts separated by 15min neuromuscular function assessments	240min	VL/RF/VM	N	~3min	Isometric knee extension (50–75–100% MVC)	58 ±9%	↓	↓	a general ↓	NQ	↔↔ in VM, ↑ post in VL and RF	↔↔ at any point
Sidhu et al.	2014	8	Leg cycling	Constant-load at 80% peak power to task failure with and without Fentanyl	10±1min	BB	Y	<1min	Isometric elbow flexion (25% MVC) post-exercise	44±1%	NQ	↓CTRL, ↔ Fent	↔	NQ	↓CTRL, ↔, Fent	↔↔ CTRL, ↓ Fent
Temesi et al.	2014	35	Running	Ultra trail running, pre measures were performed 1–3 days prior to running	20±3h	VL	N	~1 h post running	Isometric knee extension (50–75–100% MVC)	Optimal intensity (largest MEP): 66 ±9%; suboptimal (60% optimal): 40	↓	↓	↔	NQ	↑ at optimal intensity, ↔ at suboptimal intensity	↔↔ for optimal TMS, ↑ at suboptimal TMS
Goodall et al.	2015	12	Running	12 × 30m sprints (30 s recovery)	~54 s	VL	N	2.5min	Isometric knee extension (50–75–100% MVC)	73 ±9%	↓	↓	↔	NQ	↔	NQ
Pearcey et al.	2016	12	Arm cycling	10 × 10s sprints at 5%	100s	BB/TB	N	5s	Isometric elbow flexion	range 49–92%	↓	↓	↔	↑	↓	NQ

Reference	Year	n	Exercise Modality	Protocol	Exercise Duration	Target Muscle	Remote Muscle	Time to Measure	Mode of Evaluation (5% MVC)	TMS Stimulator Intensity	Qtw	VA	M _{max}	Motoneuron	MEP	Silent Period
Thomas et al.	2015	11	Leg cycling	of body weight (150 s recovery between sprints)	4 km: 6±1min 20km: 32±1min 40 km: 66±2min	VL	N	2.5min	Rest, during isometric knee extension (100% MVC)	49±12%	↓	↓	↔ after all distances	NQ	↓ after 20 and 40 km at rest, ↔ after all distances during MVC	↔ after all distances
				Time trial at 4km, 20km, and 40 km												
Thomas et al.	2016	12	Leg cycling	Constant-load cycling at severe, less severe, and steady state intensities	3±0.5min (severe domain) 11±2min (severe domain) 42±9min (heavy domain)	V1TRF	N	2.5min	Isometric knee extension (20% MVC)	48 ±7%	↓	↓	↔ following any intensity exercise	NQ	↔ following any intensity exercise	NQ
Jubeau et al.	2017	10	Leg cycling	Constant-load cycling in normoxia and hypoxia at 45% condition specific peak power	Measured after 80min, 160min, and 240min	VLA/M/ RF	N	3min after each stage	Isometric knee extension (50–75–100% MVC)	Not reported	↓	↓	↓ after all stages	NQ	↑ in VM and RF after all stages and contraction strengths, ↔ VL; same in hypoxia	↔ after all stages; same in hypoxia
Sidhu et al.	2017	14	Leg cycling	Constant-load at 80% peak power to task failure with and without Fentanyl	9±1min	VL	N	<1min	20% leg MVC post-exercise	45 ±4%	↓, larger in Fent	↓	↔	↑ in Ctrl ↔ in Fent	↔, ↑ in Fent	↔ in CTRL, ↓ in Fent

BB, biceps brachii; NQ, not quantified; Qtw, potentiated twitch; RF, rectus femoris; TB, triceps brachii; VA, voluntary activation; VL, vastus lateralis; VM, vastus medialis;

↓, decrease;

↑, increase.

Table 3

Literature Quantifying Corticospinal Alterations to Fatiguing Whole Body Exercise Using Transcranial Magnetic Stimulation of the Target Muscle During Cycling Exercise

Reference	Year	n	Exercise Modality	Protocol	Exercise Duration	Target Muscle	Remote Muscle	Time to Measure	Mode of Evaluation	TMS Stimulator Intensity	Q _{tw}	VA	M _{max}	Motoneuron	MEP	Silent period
Racinais and Girard	2012	12	Leg cycling	Incremental test to task failure	17±4	VL/RF	N	<1min	During cycling at 100W before and after protocol	68±7%	↓	↓	↔	NQ	↔ with exercise or hyperthermia	NQ
Sidhu et al.	2012a	9	Leg cycling	75% peak power for 30min then increased to 105% to task failure	31 ± 1	VL/RF	N	0min	During cycling, comparing the start to end of exercise	41 ± 1 %	NQ	NQ	↓	↔ in steady state or task failure	↔ in steady state or task failure	NQ
Sidhu et al.	2013b	13	Leg cycling	Control bouts at 75% at 37% peak power, sustained cycling at 75% for 30min followed by a 5min recovery at 37% peak power	Brief (~1min) of control cycling followed by 35min of sustained cycling	VL/BF/TA	N	0min	During cycling at 37% and 75% peak power	19±1%, used to activate low threshold inhibitory interneurons without a MEP	NQ	NQ	In all muscles, activation of inhibitory interneurons via subthreshold TMS was ↔ between 37% and 75% control and recovery exercise. Sustained cycling ↑ EMG inhibition compared to the start of exercise			
Sidhu et al.	2014	8	Leg cycling	Non-fatigue cycling, 80% peak power with and without Fentanyl	30 s	BB	Y	0min	Isometric elbow flexion (25% MVC) during cycling	44±1%	NQ	NQ	↔	NQ	↑ from rest to cycling, ↔ from rest to cycling with Fent	NQ
Weavil et al.	2016	8	Leg cycling	Constant-load at 80% peak power to task failure with and without Fentanyl	10±1min	BB	Y	0min	Isometric elbow flexion (25% MVC) during cycling	44±1%	NQ	↓ CTRL, ↔ Fent	↔	NQ	↓ CTRL, ↔ Fent	NQ
				Non-fatiguing cycling at ~244W and	~45 s	VL/RF	N	0min	During cycling, comparing low to high	39 ±4%	↔	↔	↔	↑	↑	NQ

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Reference	Year	n	Exercise Modality	Protocol	Exercise Duration	Target Muscle	Remote Muscle	Time to Measure	Mode of Evaluation	TMS Stimulator Intensity	Q _{rw}	VA	M _{max}	Motoneuron	MEP	Silent period
Sidhu et al.	2017	14	Leg cycling	331W Constant-load at 80% peak power to task failure	8±1min	VL/RF	N	0min	During cycling, comparing the start to end of exercise	39 ±4%	↓	↓	↔	↔	↔	NQ
				Non-fatigue cycling, 80% peak power with and without Fentanyl	~40s	VL	N	0min	During cycling	45 ±4%	NQ	NQ	↔	↑ with Fent	↔ with Fent	NQ
				Constant-load at 80% peak power to task failure with and without Fentanyl	9±1min	VL	N	0min	During cycling, comparing the start to end of exercise	45 ±4%	NQ	NQ	↔	↔ in either condition	↔, ↑ in Fent	NQ
Sidhu et al.	2018	11	Leg cycling	Constant-load at 80% peak power to task failure with and without Fentanyl. Also examined conditioned MEPs and CMEPs	~8min	VL	N	0min	Constant cycling EMG (~100W pre, ~90W Post)	Not reported	↓ larger ↓ in Fent	↓ CTRL, ↔ Fent	↔ in either condition	↑ CTRL, ↔ Fent; conditioned CMEP; ↔ in either condition	↔ in either condition; conditioned MEP; ↓ CTRL and ↔ in Fent	↔ CTRL, ↓ Fent

BB, biceps brachii; BF, biceps femoris; NQ, not quantified; Q_{rw}, potentiated twitch; RF, rectus femoris; VA, voluntary activation; VL, vastus lateralis; TA, tibialis anterior;

↓, decrease;

↑, increase.