The Role of the Nervous System in Neuromuscular Fatigue Induced by Ultra-Endurance Exercise

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Abstract

Ultra-endurance events are not a recent development but they have only become very popular in the last two decades, particularly ultramarathons run on trails. The present paper reviews the role of the central nervous system (CNS) in neuromuscular fatigue induced by ultra-endurance exercise. Large decreases in voluntary activation are systematically found in ultra-endurance running but are attenuated in ultra-endurance cycling for comparable intensity and duration. This indirectly suggests that afferent feedback, rather than neurobiological changes within the CNS, is determinant in the amount of central fatigue produced. Whether this is due to inhibition from type III and IV afferent fibres induced by inflammation, disfacilitation of Ia afferent fibers due to repeated muscle stretching or other mechanisms still needs to be determined. Sleep deprivation *per se* does not seem to play a significant role in central fatigue although it still affects performance by elevating ratings of perceived exertion. The kinetics of central fatigue and recovery, the influence of muscle group (knee extensors vs plantar flexors) on central deficit as well as the limitations related to studies on central fatigue in ultra-endurance exercise are also discussed in the present article. To date, no study has quantified the contribution of spinal modulations to central fatigue in ultra-endurance events. Future investigations utilizing spinal stimulation (i.e. thoracic stimulation) must be conducted to assess the role of changes in motoneuronal excitability on the observed central fatigue. Recovery after ultra-endurance events and the effect of sex on neuromuscular fatigue must also be studied further.

Key words: aerobic exercise; central nervous system; cycling; fatigue; running; ultra-marathon.

Résumé

Les épreuves d'ultra-endurance existent depuis longtemps mais sont réellement devenues populaires depuis deux décennies seulement, en particulier en raison de l'essor des épreuves d'ultra-trails. Cet article examine le rôle du système nerveux central (SNC) dans la fatigue neuromusculaire induite par les épreuves d'ultra-endurance. De grandes diminutions du niveau maximal d'activation volontaire sont systématiquement observées en ultramarathon, ce qui est moins le cas pour des épreuves de cyclisme de durée et d'intensité comparables. Cela suggère indirectement que les afférences périphériques, plutôt que les modifications neurobiologiques dans le SNC, sont clés dans le haut niveau de fatigue centrale mesuré. Il reste à déterminer si cela est dû à une inhibition des fibres de type III et IV en réponse à l'inflammation, une défacilitation des fibres afférentes Ia liée à la répétition d'étirements musculaires ou bien à d'autres mécanismes. En revanche, la privation de sommeil *per se* ne semble pas jouer un rôle significatif dans la fatigue centrale bien que cela puisse altérer la performance en raison de son effet sur la perception de l'effort. Dans ce papier, nous discutons aussi des cinétiques d'apparition de la fatigue et de la récupération ou de l'influence du groupe musculaire (extenseurs du genou vs fléchisseurs plantaires) sur le déficit nerveux. De futures investigations utilisant la stimulation thoracique devront être conduites pour évaluer le rôle potentiel d'une baisse d'excitabilité motoneuronale sur le haut niveau de fatigue centrale observé après les épreuves d'ultra-endurance. Enfin, la récupération et l'influence du sexe sur la fonction neuromusculaire en ultra-endurance devront aussi être davantage étudiées.

Mots clés: course à pied; cyclisme; exercice aérobie; fatigue; système nerveux central; ultra-marathon.

Introduction

Although the roots of endurance running may be as ancient as the origin of the human genus (Bramble and Lieberman 2004), endurance and ultra-endurance running is now primarily a form of recreation. One simple definition of ultramarathons is any sporting event involving running longer than the traditional marathon length of 42.195 km (26.2 miles). However, there is no consensus about the definition of ultramarathons as for some authors, it is any event that exceeds 4 or 6 h in duration (Millet 2011). Contrary to popular belief, ultramarathon is not a recent sport. For instance, 6-day professional pedestrian races were already organized in London and New York by the 1880s (Noakes 2006), with some runners already at that time able to run more than 1000 km. In 1928 and 1929, a running race equivalent to the famous cycling Race Across America was organized. The Bunion Derby was a 4,960-km multi-stage race from Los Angeles to New York. In 1921, the first edition was held of what is certainly the world's largest and most popular ultramarathon in the world: the Comrades Marathon (South Africa). While all the aforementioned races are on roads or tracks, the vast majority of ultramarathons in the world are now performed on trails (Hoffman et al. 2010), and very often in mountainous regions. What is considered by many specialists as the root of ultra-trail running race took place in California in 1974 when one runner joined the horses of the 100-mile Western States Trail Ride to see if he could complete the course on foot. In 1977, 14 men participated in the first official Western States Endurance Run (WS100). Many ultra-trail races are now organized in various regions in the world, particularly in USA, Japan and Europe. Without being as popular as major marathons (> 40,000 runners), some ultra-trail running races are very popular, with the best example being Ultra-Trail du Mont-Blanc® (UTMB) with over 10,000 runners participating across several race distances.

Even if the ultramarathon is not a recent development, it is fair to say that they have only become very popular in the last two decades. Although running is by far the most popular ultra-

endurance activity, other sports such as cycling (Race Across America) or swimming (open water races) are also performed. Scientists are increasingly being attracted to this type of ultra-endurance exercise that is considered as an outstanding model for the study of adaptive responses to extreme load and stress (Millet and Millet 2012). One of the characteristics of the research related to ultra-endurance is that many studies have used races, for instance UTMB (e.g. Millet et al. 2011; Morin et al. 2011; Temesi et al. 2014; Temesi et al. 2015; Wuthrich et al. 2015), WS100 (e.g. Bruso et al. 2010; Hoffman and Fogard 2011; Hoffman et al. 2012), Tor des Geants (TdG) (e.g. Saugy et al. 2013; Vernillo et al. 2014; Andonian et al. 2016; Degache et al. 2016) and TransEurope FootRace (e.g. Schutz et al. 2012; Schutz et al. 2013), to conduct their experimental protocols. The reason is quite obvious: it is very difficult, but not impossible (e.g. Martin et al. 2010), to simulate an ultra-endurance event in laboratory settings.

Among the studies that address both performance- and health-related issues, a significant number have been conducted on fatigue. Although there is no accepted definition of fatigue, exercise physiologists often define fatigue as a reduction in the force-generating capacity of the neuromuscular system that occurs during sustained activity (Bigland-Ritchie et al. 1983), sometimes associated with an increase in the perceived effort necessary to exert a desired force (Enoka and Stuart 1992). In this paper, we will focus on neuromuscular fatigue (NMF) defined as the progressive change that occurs in the central nervous system and/or muscles from exercise, resulting in a force output that is less than anticipated for a given voluntary contraction or stimulation (MacIntosh and Rassier 2002). More specifically, we will focus on the central aspect of NMF, defined as a reduction in voluntary activation leading to an inability to recruit all motor units and/or discharge them at the rates necessary to maximize force or power. Although this paper deals with central fatigue induced by ultra-endurance exercise bouts, most research has investigated running so we will mostly cite papers on ultramarathon running, and to a lesser extent, prolonged cycling. The principal studies that have investigated central fatigue development during ultra-endurance exercise are summarized in Table 1.

Central fatigue: a major contributor of fatigue in ultramarathons

Central vs peripheral fatigue in ultramarathons

Neuromuscular function is negatively affected by ultra-endurance running exercise. This has been extensively demonstrated in running for the knee extensors (KE) and plantar flexors (PF), in addition to cycling. This fatigue manifests primarily as a large decrease in isometric maximal voluntary strength in leg muscles that increases with exercise duration and manifests in large part due to central factors. Recently, respiratory-muscle fatigue has also been demonstrated in ultra-endurance running (Vernillo et al. 2015; Wuthrich et al. 2015).

The first investigation of neuromuscular function in ultra-endurance running was performed by Davies and Thompson (1986). After a simulated race on a treadmill (the highest intensity the subjects could sustain for 4 h), they observed decreased KE voluntary muscle strength without concomitant changes in evoked responses, leading the authors to propose that performance decrements were due to involuntary inhibition causing decreased central drive. Subsequent studies have led to unanimous agreement that decreased voluntary activation following an ultra-endurance running bout occurs in both KE (Place et al. 2004; Martin et al. 2010; Millet et al. 2002; Millet et al. 2011; Saugy et al. 2013; Temesi et al. 2014; Temesi et al. 2015) and PF (Martin et al. 2010; Millet et al. 2011; Saugy et al. 2013; Temesi et al. 2015) as assessed by a number of methods that include voluntary activation assessed by twitch interpolation (VA_{NS}) and normalized EMG. The decrease in voluntary activation that develops over the course of a 110-km trail-running bout also includes an important supraspinal component (Temesi et al. 2014) as determined by voluntary activation assessed using transcranial magnetic stimulation (VA_{TMS}). Conversely, voluntary activation of the inspiratory respiratory muscles was not impaired after a 110-km trail-running race (Wuthrich et al. 2015), suggesting that voluntary activation of the respiratory muscles

may be preferentially preserved because of the importance of respiration although any deficits may have been masked due to the > 1 h delay to post-exercise assessment. Reductions in voluntary activation were also observed after repeated endurance cycling bouts during a simulation of the 2007 Tour de France after stages 8, 15 and 20 despite a minimum of an 18-h delay to neuromuscular assessments (Ross et al. 2010) (see below). Handgrip strength was also assessed by Place et al. (2004) and no change in maximal handgrip strength was observed over 5 h of running suggesting that the development of central fatigue may be limited to the primary locomotor muscles during ultra-endurance exercise. There are limits to the ability to measure neuromuscular fatigue within the brain and central nervous system, including the gold standard of the interpolated twitch technique. The limits of the interpolated twitch technique have previously been raised (Contessa et al. 2016) and debated (de Haan et al. 2009). However, much of the focus of debate concerning this technique has centred on studies that have performed short-duration exercise bouts and/or isometric contractions. Given the magnitude of the decrease in voluntary activation generally observed following ultra-endurance exercise bouts and the unique characteristics of ultra-endurance events (e.g. extremely long durations, environmental conditions, etc.), there is a strong likelihood that central factors are an important contributor to fatigue development despite limitations in the ability to accurately measure them. Furthermore, the rapid recovery of many central factors, in comparison to peripheral factors, likely underestimates their importance.

While substantial decrements to measures of central functioning have been observed following bouts of ultra-endurance, this cannot explain all of the observed decrease in maximal force. Therefore, peripheral (i.e. within the muscle) changes such as excitation-contraction coupling failure and reduced neuromuscular propagation, must contribute to reduced maximal force production. Evoked twitch and doublet responses in KE (Martin et al. 2010; Millet et al. 2011; Saugy et al. 2013; Temesi et al. 2014) and PF (Martin et al. 2010; Millet et al. 2011; Saugy et al. 2013; Temesi et al. 2015) in running studies have

been observed to decrease. Decreased evoked twitch and tetanic forces have not always been observed (Davies and Thompson 1986; Place et al. 2004), perhaps because of inconsistent potentiation of the former during the protocols. A reduction in KE potentiated twitch was also observed with multi-stage ultra-endurance cycling (Ross et al. 2010). Decreases in evoked twitch and doublet forces predominantly indicate decrements in excitation-contraction coupling. Additionally, during longer duration running bouts, cross-bridge force production may become impaired as demonstrated by decreased tetanic force production in Martin et al. (2010) whereas shorter exercise bouts (Davies and Thompson 1986; Place et al. 2004) did not demonstrate impaired evoked tetanic force production. Decreased evoked twitch force was also observed in non-locomotor inspiratory respiratory muscles in addition to decreases in maximal voluntary expiratory and inspiratory pressures (Wuthrich et al. 2015). Peripheral respiratory muscle fatigue also presents as impaired inspiratory and expiratory pulmonary function and reduced endurance of the respiratory muscles following an ultra-endurance exercise bout (Vernillo et al. 2015).

Conversely, effects of ultra-endurance exercise on sarcolemmal propagation, as inferred from M waves, are equivocal. Studies have reported unchanged M-wave amplitude and duration in KE (Martin et al. 2010; Saugy et al. 2013; Temesi et al. 2014) and PF (Saugy et al. 2013; Temesi et al. 2015) following ultra-trail running races. However, Martin et al. (2010) reported a decrease in M-wave amplitude in the soleus from 4 h during a 24-h treadmill run and Place et al. (2004) a decrease in vastus lateralis M-wave amplitude after 5 h of treadmill running. These collective results may indicate differential effects of trail and level treadmill running on M-wave characteristics. Meanwhile, Ross et al. (2010) also observed decreased M-wave amplitude following stages 8 and 15 of a simulated Tour de France cycling event.

Kinetics of central fatigue and recovery

As previously stated, it is difficult to simulate an ultra-endurance event in laboratory settings where repeated measurements can be conducted. As a consequence, there are only a limited number of studies that have addressed the time-course of fatigue. Place et al. (2004) investigated the effects of a 5-h level run on a treadmill at 55% of maximal aerobic velocity (Figure 1A). As often reported in the literature for central and peripheral fatigue kinetics (Decorte et al. 2012; Froyd et al. 2013), it was found that central fatigue occurred only toward the end of the exercise bout. Indeed, the reduction of VA_{NS} was only found to be significant after 4 h.

Of note is the fact that a similar cycling study (5 h at 55% of maximal aerobic power) was also conducted by our group (see comparison in the *cycling vs running* section below). Again, it was found that VA_{NS} reduction was only significant near the end, in this case after 5 h of exercise (Lepers et al. 2002). Although slightly shorter and less intense (4 h of cycling at 45% of maximal aerobic power), Jubeau et al. (2014) confirmed that central fatigue appears near the end of exercise as VA_{NS} only decreased after 2 h 40 min of cycling and VA_{TMS} decreased at exercise termination. Martin et al. (2010) is the only study that has examined the time course of NMF for an extreme-duration exercise. These authors measured NMF and blood parameters every 4 h during a self-paced 24-h level run on a treadmill. The results are presented in Figure 1B. Unlike the previously-reported studies, central fatigue decreased linearly with increasing duration, although the reasons for this are unclear.

In the field, Saugy et al. (2013) measured central fatigue mid-race in TdG (distance = 330 km; positive elevation change = 24000 m, considered as the world's most challenging mountain ultramarathon). One interesting aspect of this measurement is that the exercise completed at the midpoint of TdG was comparable in terms of distance and elevation change to a previous study

conducted at UTMB (distance = 165 km; positive elevation change = 9500 m) (Millet et al. 2011). Since the average speed was ~15% slower than at UTMB, it allowed for the investigation of pacing. The decrease in MVC was two times greater (-31% vs -13%) for KE and four times greater (-40% vs -10%) for PF in UTMB than at the midpoint of TdG. Even more interesting is the fact that central fatigue was not detected at the midpoint of TdG for either KE or PF (Saugy et al. 2013). Conversely, central fatigue was significant for both muscle groups after UTMB and in fact represented the largest component contributing to total fatigue for KE (Millet et al. 2011) as VA_{NS} decreased by ~30% and tetanic force decreased by ~10%.

To the best of our knowledge, only one study (Millet et al. 2011) has evaluated NMF recovery after an ultra-endurance exercise. Neuromuscular function was measured before and after UTMB as well as 2, 5, 9 and 16 days after the race. MVC of KE and PF decreased by ~35-40% and remained 10-15% below pre-race values 2 days after the race before gradually returning to pre-race values 16 days after the race (-2-3%, NS). Interestingly, while VA_{NS} was ~20% lower for KE immediately after the race, central fatigue was no longer detected as early as 2 days after the race despite the persistence of a significant amount of inflammation since C-Reactive Protein was still 30 $mg \cdot L^{-1}$ (Millet et al. 2011). This suggests that type III and IV afferent fibres probably play a minor role in the high level of central fatigue generally observed after ultramarathon running events (see next section).

Origin of central fatigue in ultramarathons

Most of the studies that have been conducted on neuromuscular fatigue induced by ultra-endurance events have investigated central factors by VA_{NS} and EMG measurements, such that it was impossible to identify the origin of the reduced voluntary activation. Nevertheless, recent studies have provided insights into the origin of the reduced voluntary activation. KE VA_{TMS} was shown to decrease after a 110-km trail-running bout, suggesting that voluntary output from the motor cortex became suboptimal (Temesi et al. 2014). Similarly, Jubeau et al. (2014), observed a decrease of KE VA_{TMS} after a 4-h cycling bout. In both studies, motor-evoked potentials, elicited at optimal intensity, increased without any change in the cortical silent period, indicating that corticospinal excitability increased while intracortical inhibition remained unchanged. However, Temesi et al. (2014) also showed that the cortical silent period duration increased while motor-evoked potentials remained unchanged when elicited at suboptimal TMS intensities. The relevance of these results still remains to be elucidated but they suggest that intracortical inhibition may play a significant role in the performance deficits when exercising at low intensities for prolonged durations. Although the studies of Temesi et al. (2014) and Jubeau et al. (2014) demonstrated the involvement of supraspinal factors, the contribution of spinal factors to the reduced voluntary activation is currently unknown. To date, no study has quantified the contribution of spinal modulations to the neuromuscular fatigue in ultra-endurance events.

Afferent feedback from the exercising muscles has been frequently advocated as a potential inhibitory mechanism. Specifically, group III and IV nociceptive afferent fibres that respond to mechanical (i.e. pressure) and chemical (i.e. pro-inflammatory mediators) stimuli have the potential to inhibit neural drive at the spinal and supraspinal levels (via direct or pre-synaptic inhibition of motoneurons). Ultra-endurance sport participation is associated with significant muscle damage and inflammation (Martin et al. 2010), as well as considerable pain within the exercising muscles and joints, especially during ultramarathons. It is therefore possible that nociceptive afferents play a significant role in the generation of central fatigue during ultramarathons, although direct evidence is still lacking in the literature. However, the fact that central fatigue could no longer be detected as early as 2 days after an ultramarathon race despite the presence of inflammation (Millet et al. 2011) rules out the possibility of a major contribution of group III and IV afferent fibres to central fatigue in ultramarathons. Other modulations may therefore occur via Ib afferent fibers, or the disfacilitation of Ia afferents, as previously suggested for various fatigue paradigms (for a review, see Gandevia 2001). Interestingly, Avela et al. (1999) demonstrated that the repetitive stretching of skeletal muscle, as occurs during prolonged running, leads to an alteration of reflex sensitivity, related to a reduction in the activity of Ia afferents, resulting from reduced sensitivity of the muscle spindles to repeated stretching. Whether this occurs in the context of ultra-endurance events needs to be experimentally verified.

Other factors may nevertheless contribute to the reduction of the voluntary activation, especially at the supraspinal level. Specifically, hypoglycemia (Davis and Bailey 1997), decreased cerebral catecholamine concentrations (Hasegawa et al. 2008), increased core temperature (Nybo and Nielsen 2001), cerebral ammonia accumulation (Nybo et al. 2005) and altered brain neurotransmitter concentrations (Meeusen et al. 2006) could reduce the voluntary activation during ultra-endurance events. Ohta et al. (2005) observed increases in serum serotonin, free tryptophan and free fatty acid concentrations following 24 h of continuous running. It is believed that the accumulation of the neurotransmitter serotonin contributes to the development of central fatigue (Davis and Bailey 1997) by concomitant increases in both the serotonin precursor, free tryptophan, and free fatty acids that dissociate tryptophan from albumin. However, several studies attempted and failed to alter exercise capacity through pharmacological manipulation of serotonergic neurotransmission in humans, indicating that the role of serotonin in neuromuscular fatigue may be exaggerated (Roelands and Meeusen 2010). Recent studies suggest that neuromuscular fatigue is determined by the interplay of different neurotransmitter systems especially those of catecholamines in warm environments (Meeusen and Roelands 2018). Ultra-endurance events may thus constitute a fantastic paradigm to study the involvement of neurochemistry in the generation of neuromuscular fatigue. Since Ohta et al. (2005) is the only study that has investigated brain neurochemistry changes induced by ultra-endurance exercise, further studies must confirm these results.

Sleep deprivation

Sleep deprivation is most frequently a condition of insufficient sleep duration. In ultra-endurance exercise bouts, this may present as either complete (i.e. no sleep) or partial (some sleep) sleep deprivation, depending on the duration of the ultra-endurance event or experience or sleep strategy of

the athlete (Poussel et al. 2015). Individuals experiencing sleep deprivation often report subjective feelings of tiredness, clumsiness and fatigue. Numerous studies of locomotor activities have observed reduced exercise performance with sleep deprivation ranging from one night to 50 h of sleep deprivation (Martin 1981; Martin and Chen 1984; Oliver et al. 2009; Temesi et al. 2013). However, taking the time to sleep during an ultra-endurance race may increase finishing time (Poussel et al. 2015), and therefore, result in a worse performance. Ratings of perceived exertion (RPE), while not directly a measure of neuromuscular function or central fatigue may play an important role in ultra-endurance exercise performance, especially in ultra-endurance exercise bouts that occur in conjunction with sleep deprivation. Increased RPE at constant exercise workloads have been found after sleep deprivation [e.g. (Martin et al. 1986; Temesi et al. 2013)]. Similarly, Oliver et al. (2009) asked their subjects to run on a treadmill at 60% VO_2max for 30 min followed immediately by a 30-min time trial. They found that RPE was not different during the 30-min time trial despite the speed being lower in the sleep deprivation condition. These results suggest that when individuals are sleep deprived, such as during an ultra-endurance exercise event, the level of physical effort may be adjusted in order to maintain a manageable RPE. Whether increased RPE coupled with the known performance impairments from sleep deprivation is related to reductions in voluntary activation had been a source of debate until recently.

Three studies have examined the effects of sleep deprivation and exercise on central fatigue (Skein et al. 2011; Temesi et al. 2013; Arnal et al. 2016), including one that also investigated the effects of prior sleep extension (Arnal et al. 2016). Skein, Duffield et al. (2011) observed reductions in MVC and voluntary activation assessed by electrical muscle stimulation following approximately 30 h of sleep deprivation. In an investigation on the effects of 30 h of sleep deprivation, Temesi et al. (2013) observed no influence of sleep deprivation on maximal voluntary force nor voluntary activation assessed by peripheral nerve stimulation in KE either prior to, during, or immediately following cycling exercise. The opposite of sleep deprivation is sleep extension, or storing sleep. Arnal et al. (2016) investigated the

effects of 6 nights of spending 1.5-2 h longer in bed each night prior to a 34-37 h period of sleep deprivation. Despite increased isometric exercise performance and lower RPE with sleep extension vs normal sleep, neuromuscular parameters were not different between the two conditions. The positive effect of greater sleep time on exercise performance is supported by findings from UTMB where runners that slept longer the night before the race had faster finishing times than the runners that did not (Poussel et al. 2015). Another relevant study occurred in conjunction with TdG. Investigators involved in a study at the 330-km trail running race, who were also sleep deprived, were compared to race participants (Saugy et al. 2013). The investigators slept a total of 12 ± 5 h during the event that took their subjects 122 ± 17 h to complete. No change in MVC or central activation ratio was observed for either KE or PF. This contrasts with the large decreases in both MVC and central activation ratio in the athletes who slept a similar duration (9 ± 5 h) during the race.

Only two studies have employed transcranial magnetic stimulation to evaluate supraspinal changes with sleep deprivation and exercise. Temesi et al. (2013) did not observe any difference in supraspinal fatigue development between a control condition and a 30-h sleep-deprived condition either before or after exercise. Similarly, Arnal et al. (2016) observed no difference in supraspinal fatigue with sleep deprivation of 34-37 h following six days of normal or extended sleep. This suggests that during ultra-endurance exercise bouts of up to 37 h, supraspinal fatigue is unaffected by sleep deprivation. The current evidence suggests that sleep deprivation likely has a limited role on the development of central fatigue (i.e voluntary activation) during ultra-endurance exercise bouts although it increases ratings of perceived exertion.

Factors influencing central fatigue in ultramarathons

Knee extensors vs plantar flexors

Some single-joint isometric investigations showed that central fatigue induced by sustained MVCs (Neyroud et al. 2013) is more pronounced in the PF than KE, whereas peripheral fatigue is higher in the KE than PF. Whether this applies to central fatigue induced by ultra-endurance events remains unclear. To date, four studies (Martin et al. 2010; Millet et al. 2011; Saugy et al. 2013; Temesi et al. 2015) have compared voluntary activation reductions in the KE and PF induced by ultramarathons. Three of these studies (Martin et al. 2010; Millet et al. 2011; Temesi et al. 2015) reported a ~2-3-fold greater decrease in KE than PF VA_{NS}, suggesting that the KE may be more prone to central fatigue. Conversely, Saugy et al. (2013) reported a slightly greater decrement in central activation ratio in PF than KE after the TdG. Whether the greater voluntary activation reduction observed in PF is related to the extreme positive elevation change (+ 24 000 m) and/or the extreme duration (mean study participant race time = 122 h) of the race is unknown. Interestingly, changes to the foot strike pattern and running mechanics have been observed after a 110-km trail-running bout (Giandolini et al. 2016) and the magnitude of these changes were related to the amount of peripheral fatigue. This suggests that in a fatigued state, ultra-trail runners use compensatory and/or protective adjustments in a fatigue dose-dependent manner, to reduce the overall load applied to the musculoskeletal system (i.e. impact shock and muscle stretch). The link between these changes in running mechanics and the relative amount of voluntary activation reduction in the lower-limb extensors has not been established, but a potential relationship cannot be excluded. The increased contribution of the hip extensors while walking uphill (Lay et al. 2006), and the use of poles (Foissac et al. 2008) may also modify the relative contribution of the different muscle groups, and therefore may modulate the amount of central fatigue in PF and KE muscles.

Cycling vs running

Only one study examined cycling alterations in neuromuscular function for longer than 5 h, and this was during endurance cycling that replicated the 2007 Tour de France route and schedule (Ross et al. 2010). More specifically, 8 well-trained male cyclists completed 20 prolonged cycling bouts interspersed by two rest days (after stages 8 and 15) where fatigue measurements were performed. Fatigue was also assessed 2 days after the simulated race. The main findings regarding central changes were that (i) VA_{NS} was reduced by 6-10% during and after the race and (ii) peak-to-peak motor-evoked potential amplitude (expressed in μV) was depressed by 44% after stage 8 and remained depressed both after stage 15 and 2 days after completion of the race. Unfortunately, motor-evoked potential amplitude was not normalized to M-wave amplitude, limiting the ability to interpret corticospinal changes. In addition, although the exercise was undoubtedly very strenuous, simulating the Tour de France is very different than single-stage races that represent the majority of ultramarathon events.

Without studies on fatigue in extreme duration cycling without rest (e.g. Race Across America), comparisons between cycling and running are limited. Yet two studies (Lepers et al. 2002; Place et al. 2004) directly compared level running and cycling using a similar methodology (5 h at 55% of maximal aerobic velocity or power in laboratory settings, i.e. treadmill and ergocycle) although the subjects were not the same in both experiments. It was found that the MVC reduction was greater in running than in cycling and, importantly, that the decrease in VA_{NS} was twice as large in running compared to cycling (Table 1). This suggests that muscle damage and/or the type of contraction play a significant role in central fatigue. Although not ultra-endurance exercise, we also found that for ~3-h races, central fatigue was significant in running (VA_{NS} decreased by 8%) (Millet et al. 2003a) while no change in VA_{NS} was detected in ski skating (Millet et al. 2003b). While cross-country skiing is not cycling, both activities,

unlike running, are characterized by minimal muscle damage as the intensity of the eccentric phase in cross-country skiing is much lower than in running.

Males vs females

The participation of women in ultra-endurance sports is increasing. Despite the increasing participation, very little is known about sex differences on neuromuscular function during ultra-endurance exercise bouts. To date, only one study (Temesi et al. 2015) has compared ultra-endurance neuromuscular responses between men and women. In a 110-km trail-running race participants were matched by percentage of the winning time by sex. No sex differences in central fatigue were observed in either PF or KE following the race. Similarly, no difference in KE supraspinal fatigue was observed between men and women. While no sex differences were observed, the mean delay of almost 1 h to post-race assessments may have masked any differences. Sex differences in the development and magnitude of fatigue is dependent on a number of factors including the type of exercise (e.g. isometric vs isokinetic, sustained vs intermittent) and exercise intensity. In general, women are less fatigable than men during concentric (i.e. shortening) contractions, although this difference disappears when investigating individuals of comparable strength and as exercise intensity increases to maximum (Hunter 2014). Thus, at submaximal intensities comparable to those during ultra-endurance exercise, women experience less fatigue. There has been a lack of investigation into sex differences with eccentric (i.e. lengthening) exercise. One of the few studies investigating eccentric exercise observed similar strength loss between men and women while post-exercise range-of-motion was more impaired in women (Rinard et al. 2000). However, it is unclear how these results transfer to ultra-endurance exercise as this study was performed as repeated maximal eccentric contractions.

Limitations

The scientific research described above suffers from several limitations. One of the main limitations is the delay that exists between the end of the race/exercise bout and the subsequent fatigue measurements. Even though the delay is probably less critical after an ultra-endurance event than after a shorter and more intense exercise bout, it is known that peripheral (Froyd et al. 2013) and, more importantly, central (Mira et al. 2017) fatigue recover quickly so the amount of central fatigue was probably underestimated and fatigue etiology misinterpreted. However, this is not specific to fatigue induced by ultra-endurance exercise (Doyle-Baker et al. 2018). Reductions in voluntary activation must also not be confounded with central drive during exercise. The Flush Model (Millet 2011) was proposed to explain the regulation of neural drive during ultra-endurance events that is only partially determined by central (i.e. reduction in voluntary activation) and peripheral fatigue. Briefly, we propose that afferent feedback from the exercising muscles and other peripheral organs as well as peripheral fatigue are integrated within the central nervous system to regulate neural drive, and consequently running/cycling intensity. The amount of afferent feedback and feedforward mechanisms related to muscle fatigue are regulated within the limits of a security reserve that aim to prevent physiological damage. Other factors not related to neuromuscular fatigue such as environmental conditions, mental fatigue, sleep deprivation, race conditions, pain and nutrition also play a role in the determination of pace and performance.

Conclusion and future directions

The present paper emphasizes the role of the central component in neuromuscular fatigue due to ultra-endurance exercise. This is particularly true in running, which suggests that afferent feedback is determinant in the amount of central fatigue. Yet whether this is due to type III and IV afferent fibres, disfacilitation of Ia afferent fibers or other mechanisms still needs to be determined. Future investigations utilizing spinal stimulation (i.e. thoracic stimulation) must also be conducted to assess the role of changes in motoneuronal excitability in the observed central fatigue. Because the number of studies that have examined recovery after an ultra-endurance event and sex differences in ultra-endurance exercise are limited and have been performed by only a few research groups worldwide, more research is needed on these topics. Finally, we suggest that future studies should combine electrophysiological studies with other methods such as magnetic resonance imaging (e.g. Freund et al. 2012) to better understand the impact of ultra-endurance exercise on the central nervous system.

The authors have no conflicts of interest to report

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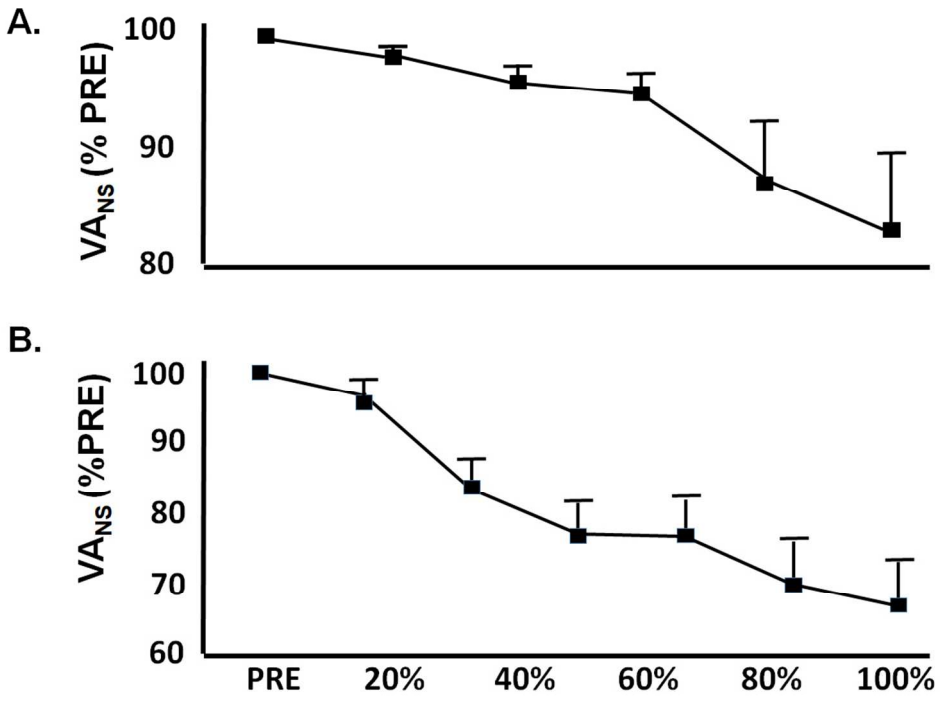
Figure legends

Figure 1. Changes in voluntary activation assessed by twitch interpolation (VA_{NS}) during 5-h (panel A) and 24-h (panel B) level treadmill runs. Data are expressed in percentage total duration (x axis) and are normalized to VA_{NS} measured before the run (y axis). Values are means ± SD.



Changes in voluntary activation assessed by twitch interpolation (VANS) during 5-h (panel A) and 24-h (panel B) level treadmill runs. Data are expressed in percentage total duration (x axis) and are normalized to VANS measured before the run (y axis). Values are means ± SD.

104x83mm (300 x 300 DPI)

Table 1. Reduction in voluntary activation measured with peripheral nerve stimulation (VA_{NS}) or transcranial magnetic stimulation (VA_{TMS}) for either the knee extensors (KE) or the planter flexors (PF) for various cycling and running exercises of a duration ≥ 4 hours. The percentage reduction in MVC is also indicated in parentheses for comparison purpose.

Reference	Activity	Intensity	Duration	Muscle	Parameter	Reduction in VA (MVC)*
(Lepers et al. 2002)	Cycling	55% MAP	5 h	KE	VA_{NS}	8% (18%)
(Millet et al. 2003c)	Cycling	Race	4 h 38 min	KE	VA_{NS}	2% (~9%)
(Jubeau et al. 2014)	Cycling	45% MAP	4 h	KE	VA_{TMS}	~7% (25%)
(Jubeau et al. 2014)	Cycling	45% MAP	4 h	KE	VA_{NS}	~13% (25%)
(Place et al. 2004)	Running	55% MAV (treadmill)	5 h	KE	VA_{NS}	16% (28%)
(Millet et al. 2002).	Running	Race (trail)	8 h 31 min	KE	VA_{NS}	23% (~31%)
(Martin et al. 2010)	Running	Race condition (treadmill)	18 h 39 min	KE	VA_{NS}	29% (41%)

(Martin et al. 2010)	Running	Race condition (treadmill)	18 h 39 min	PF	VA_{NS}	16% (32%)
(Temesi et al. 2014)	Running	Race (trail)	20 h 17 min	KE**	VA_{TMS}	16% (34%)
(Temesi et al. 2014)	Running	Race (trail)	20 h 17 min	KE**	VA_{NS}	26% (34%)
(Temesi et al. 2015)	Running	Race (trail)	18 h 22 min	KE	VA_{TMS}	14% (38%)
(Temesi et al. 2015)	Running	Race (trail)	18 h 22 min	KE	VA_{NS}	24% (38%)
(Temesi et al. 2015)	Running	Race (trail)	21 h 53 min	KE (females)	VA_{TMS}	12% (29%)
(Temesi et al. 2015)	Running	Race (trail)	21 h 53 min	KE (females)	VA_{NS}	19% (29%)
(Temesi et al. 2015)	Running	Race (trail)	18 h 22 min	PF	VA_{NS}	9% (26%)
(Temesi et al. 2015)	Running	Race (trail)	21 h 53 min	PF (females)	VA_{NS}	18% (31%)
(Millet et al. 2011)	Running	Race (trail)	37 h 37 min	KE	VA_{NS}	19% (35%)
(Millet et al. 2011)	Running	Race (trail)	37 h 37 min	PF	VA_{NS}	6% (39%)
(Saugy et al. 2013)	Running	Race (trail)	122 h 26 min	KE	VA_{NS}	20% (24%)
(Saugy et al. 2013)	Running	Race (trail)	122 h 26 min	PF	VA_{NS}	26% (26%)

All data is exclusively from males unless stated; MAP: maximal aerobic power; MAP: maximal aerobic velocity; * percentages indicate the difference for VA and variation for MVC from PRE; **: 11 females and 14 males – data were pooled.