Central Fatigue Assessed by Transcranial Magnetic Stimulation in Ultratrail Running

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ABSTRACT

TEMESI, J., T. RUPP, V. MARTIN, P. J. ARNAL, L. FÉASSON, S. VERGES, and G. Y. MILLET. Central Fatigue Assessed by Transcranial Magnetic Stimulation in Ultratrail Running. *Med. Sci. Sports Exerc.*, Vol. 46, No. 6, pp. 1166–1175, 2014. **Purpose**: The well-established central deficit in ultraendurance running races is not understood. The use of transcranial magnetic stimulation (TMS) in parallel with peripheral nerve stimulation provides insight into the source of these central changes. The aims of this study were to determine the presence and magnitude of voluntary activation deficits, especially supraspinal deficits, after a mountain trail-running race and to determine whether this can be explained by simultaneous changes in corticospinal excitability and intracortical inhibition. **Methods**: Neuromuscular function (TMS and femoral nerve electrical stimulation) of the knee extensors was evaluated before and after a 110-km ultratrail in 25 experienced ultraendurance trail runners during maximal and submaximal voluntary contractions and in relaxed muscle. **Results**: Voluntary activation assessed by both femoral nerve electrical stimulation (−26%) and TMS (−16%) decreased and were correlated ($P < 0.01$). Decreases in potentiated twitch and doublet amplitudes were correlated with decreased voluntary activation assessed by TMS ($P < 0.05$). There was increased motor-evoked potential (MEP) amplitude ($P < 0.05$) without change in cortical silent period (CSP) elicited by TMS at optimal stimulus intensity. Conversely, CSP at suboptimal TMS intensity increased ($P < 0.05$) without concurrent change in MEP amplitude. **Conclusions**: The present results demonstrate the development of a large central activation deficit assessed by TMS, indicating that cortical motoneurons are severely impaired in their ability to fire at optimal frequency or be fully recruited after an ultraendurance running race. MEP and CSP responses suggest a shift in the sigmoidal MEP–stimulus intensity relationship toward larger MEP at higher TMS intensity without change in inflection point of the curve and a left shift in the CSP–stimulus intensity relationship. **Key Words:** CORTICAL VOLUNTARY ACTIVATION, CORTICOSPINAL EXCITABILITY, INTRACORTICAL INHIBITION, NEUROMUSCULAR FATIGUE

Probably because of the explosion of ultraendurance running participation, a large amount of research on the physiological consequences of ultramarathons has been conducted recently (7,25,31,33). This type of event permits the investigation and greater understanding of the limits of human performance (28). The origins of fatigue are dependent on numerous factors, including the type of exercise, making the ultratrail running subgroup of endurance-running a unique field of study. With substantial elevation change and long duration, ultratrails combine a range of exercise intensities and use various muscle groups, activation patterns, and types of muscle contraction (i.e., combining concentric and severe eccentric loads).

Neuromuscular fatigue is an exercise-related decrease in the maximal voluntary torque of a muscle or muscle group, regardless of whether or not a task can be sustained (2). This may involve processes at all levels of the motor pathway from the brain to the skeletal muscle. Large central fatigue (i.e., reduced maximal voluntary activation) has been observed in running bouts longer than 5 h (25,31,33,37). The presence of central fatigue does not mean an absence of

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peripheral fatigue, although compared with the central component, peripheral fatigue appears to be only of moderate importance in extremely long-duration exercise. Only a few studies have investigated central fatigue in running exercise longer than 12 h in duration (25,33,40), and only two have combined elevation change and extreme duration (33,40). All these studies used the classic peripheral electrical stimulation techniques of twitch interpolation and central activation ratio to assess voluntary activation (27). The major issue with these techniques is that they do not permit the differentiation between spinal and supraspinal components of central fatigue.

Using transcranial magnetic stimulation (TMS) in parallel with peripheral nerve stimulation during voluntary isometric contractions, Gandevia et al. (9) observed that as exercise duration increases, the role of supraspinal factors in fatigue increases and that supraspinal deficits and failure are not necessarily paralleled by impairment of motor cortical excitability. Furthermore, the presence of central fatigue does not mean that both spinal and supraspinal fatigue are certainties.

Dynamic whole-body exercise has only recently been investigated with TMS, predominantly in cycling studies (e.g., 11,44,50). Only one published study has used TMS with running (39), observing decreased cortical voluntary activation of the dorsiflexors after a treadmill marathon. This study also observed decreased motor-evoked potential (MEP) amplitude of the tibialis anterior in relaxed muscle immediately after marathon; however, MEP amplitude assessed in relaxed muscle limits interpretation because of both the greater MEP variability and lower corticospinal excitability in the relaxed muscle state (14). All other whole-body investigations of voluntary activation assessed by TMS (VA_{TMS}) have been conducted with cycling and generally showed decreased VA_{TMS} when evaluated 2–4 min after exercise (11,43,50), although not 10 min after ~1.5 h of cycling (21). The inconsistent changes in VA_{TMS} after exercise may be due to the variable delay to postexercise measures and/or differences in exercise intensity and/or duration.

At similar exercise intensities, there is less central fatigue in cycling than running (24,37), and this has been proposed to be related to increased influence of group III/IV afferents because of increased muscle damage in running (30). Unlike the dorsiflexors, which do not limit running performance (8), and plantar flexors, which display only moderate central deficits, the knee extensors demonstrate large central deficits after prolonged exercise (25,33). Whether this manifests at the supraspinal level in trail running, particularly given the muscle damage associated with the eccentric nature of downhill running, remains to be determined. The use of TMS in parallel with peripheral nerve stimulation can provide greater insight into the source of these central changes. These two techniques used to investigate central deficits provide different mechanistic insights. An increase in the evoked response to peripheral nerve stimulation indicates derecruitment or decreased motoneuron firing. Meanwhile, an increase in the mechanical response to TMS demonstrates that the limiting factor is not due to an inability of the upper motoneurons to respond to increased motor input.

Despite large central consequences, the effects of long running bouts on supraspinal activity and any subsequent effect on knee extensor function are unknown. Specifically, whether a supraspinal deficit occurs with an ultraendurance trail-running race and whether or not any such deficit is associated with changes in corticospinal excitability and/or intracortical inhibition remain to be determined. The aim of this study was thus to test the hypotheses that (i) an ultratrail decreases VA_{TMS} and (ii) corticospinal fatigue occurs despite no change or increased MEP amplitude and unchanged cortical silent period (CSP).

METHODS

Subjects

Thirty-five healthy experienced ultraendurance trail runners (15 females and 20 males) were recruited to participate in this study. Six subjects (three females and three males) did not complete the ultratrail, and three others (one female and two males) did not perform postrace testing due to time constraints. One other subject was only physically capable of completing a small portion of the post-ultratrail evaluations and was subsequently eliminated from analyses. Thus, 25 subjects (11 females and 14 males) participated in all aspects of this study (mean ± SD; age = 43 ± 9 yr, height = 172 ± 8 cm, body mass = 65.4 ± 9.5 kg, maximal oxygen consumption [$\dot{V}O_{2max}$] = 56.3 ± 6.5 $mL \cdot kg^{-1} \cdot min^{-1}$). Subjects were informed of the experimental protocol and all associated risks before giving written informed consent as part of a medical inclusion. All procedures conformed to the Declaration of Helsinki and were approved by the local ethics committee. All subjects were experienced ultraendurance trail runners because participation in the partner ultratrail (the North Face® Ultra-Trail du Mont-Blanc® 2012) required completion of a minimum of two demanding trail-running races with significant elevation change in the 2 yr preceding the race.

Experimental Design

Each subject completed one preliminary session and two experimental sessions. During the preliminary session, subjects completed a maximal incremental running test. They were also introduced to all experimental procedures and repeated trials until they were able to perform all tests consistently and as directed. The first experimental session (PRE) occurred on 1 of the 3 d before the North Face® Ultra-Trail du Mont-Blanc® 2012 and the second (POST) 1:01:30 ± 0:22:37 after completing the ultratrail. Because of exceptional inclement weather, the 2012 edition of the North Face® Ultra-Trail du Mont Blanc® involved running/walking 110 km with total positive elevation change of 5862 m (see Figure, Supplemental Digital Content 1, http://links.lww.com/MSS/A392). Under conditions of a mixture of rain, snow and clouds, the

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temperature reached a maximum of 12°C in Chamonix and decreased lower than 0°C at altitudes higher than 1800 m.

Preliminary Session

After a medical examination, subjects performed a maximal incremental running test to exhaustion on a treadmill (EF1800; HEF Tecmachine, Andrezieux-Boutheon, France). The subjects began the test at 10% grade and a speed of 4–6 $km \cdot h^{-1}$, with starting speed corresponding to running ability. The speed was then increased by 1 $km \cdot h^{-1}$ until volitional exhaustion. Subjects ran 2 min 30 s at each speed and then stopped for 30 s for a blood sample for lactate measurement. Respiratory measures were assessed breath by breath by an online system (Ergocard, Medisoft, Sorinnes, Belgium) and averaged every 30 s. $\dot{V}O_{2max}$ was considered as the oxygen consumption during the last 30 s before exhaustion.

The familiarization portion of the preliminary visit included maximal and submaximal contractions of the knee extensors with and without femoral nerve electrical stimulation (FNES) and TMS (see Neuromuscular Testing Protocol section). For TMS, this included training subjects to return to the prestimulus torque as soon as possible after the stimulus to permit accurate measurement of the CSP.

Neuromuscular Testing Protocol

Neuromuscular measures (Fig. 1) were assessed PRE and POST with real-time visual feedback. Maximal torque was determined from 3 maximal voluntary contractions (MVC) separated by 30 s with FNES (100-Hz paired pulses and single pulses) delivered at peak torque and immediately after in the relaxed state (100-Hz paired pulses and single pulses). Then, three series of four contractions were performed with TMS delivered at the desired torque level (100%, 75%, and 50% MVC at optimal TMS intensity (51) and 50% MVC at suboptimal TMS intensity; for further details, see the following sections). Contractions were separated by 15 s and series by 30 s.

Force and EMG Recordings

Knee extensor force was measured during voluntary and evoked contractions by a calibrated force transducer (Meiri F2732 200 daN; Celians, Montauban, France) with amplifier attached by a noncompliant strap to the right leg just proximal to the malleoli of the ankle joint. Subjects were seated upright in a custom-built chair with both right knee and hips at 90° of flexion. The load cell was fixed to the chair such that force was measured in direct line to the applied force. Torque was calculated as force measured by the force transducer multiplied by the length of the lever arm (i.e., distance from the tibial condyles to where the force transducer was attached to the leg).

EMG activity of the right knee extensors (vastus lateralis [VL]) was recorded with a pair of self-adhesive surface electrodes (Meditrace 100; Covidien, Mansfield, MA) in bipolar configuration with a 30-mm interelectrode distance and the reference on the patella. Low impedance (<5 kΩ) between electrodes was obtained by shaving, gently abrading the skin and then cleaning it with isopropyl alcohol. Signals were converted from analog to digital at a sampling rate of 2000 Hz using PowerLab system (16/30-ML880/P; ADInstruments,

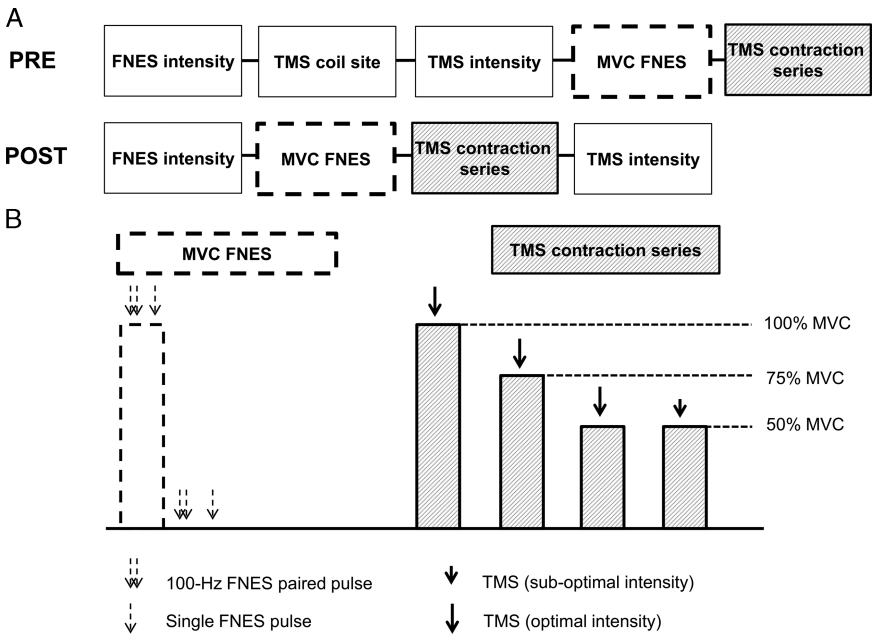

FIGURE 1—A, Neuromuscular testing order PRE and POST ultratrail for FNES and TMS. B, Neuromuscular testing protocol for FNES MVC and TMS contraction series.

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Bella Vista, Australia) and octal bio-amplifier (ML138, ADInstruments; common mode rejection ratio = 85 dB, gain = 500) with band-pass filter (5–500 Hz) and analyzed offline using Labchart 7 software (ADInstruments).

FNES

Single electrical stimuli of 1-ms duration were delivered via constant-current stimulator (DS7A; Digitimer, Welwyn Garden City, Hertfordshire, UK) to the right femoral nerve via a 30-mm-diameter surface cathode manually pressed into the femoral triangle (Meditrace 100; Covidien) and 50 × 90 mm rectangular anode (Durastick Plus; DJO Global, Vista, CA) in the gluteal fold. Single stimuli were delivered incrementally until maximal *M*-wave (M_{max}) and twitch amplitudes plateaued. Stimulus intensity of 130% of the intensity to produce M_{max} and maximal twitch responses was used to confirm supramaximality. Stimulus intensity was determined at the start of each session. Supramaximal FNES intensity increased from PRE (58 ± 16 mA) to POST (65 ± 19 mA) ($P = 0.025$).

Transcranial Magnetic Stimulation

Single TMS pulses of 1-ms duration were manually delivered to elicit MEP and superimposed twitches (SIT) during voluntary isometric knee extension. The contralateral motor cortex was stimulated by a magnetic stimulator (Magstim 200^2, The Magstim Company Ltd., Whitland, UK) with a 110-mm double-cone coil (maximum output of 1.4 T) to induce a posteroanterior current. The coil was manually controlled by an experienced investigator throughout the protocol. Subjects wore a cervical collar during all TMS measures to stabilize the head and neck. Subjects also wore a latex swim cap on which lines were drawn between the preauricular points and from nasion to inion to identify the vertex. Every centimeter was demarcated from the vertex to 2 cm posterior to the vertex along the nasal-inion line and also to 1 cm over the left motor cortex. At each point, a stimulus was delivered at 50% maximal stimulator output during brief voluntary contractions of the knee extensors at 10% MVC torque to determine the optimal stimulus site. The coil was positioned at the site evoking the largest MEP amplitude and SIT throughout the protocol. Stimulus intensity was determined from a stimulus–response curve determined from MEP responses evoked during brief (~2–3 s) voluntary contractions at 20% MVC. TMS was delivered during two consecutive contractions at each of the randomly ordered stimulus intensities of 40%, 50%, 60%, and 70% maximal stimulator output. Stimuli were delivered at 15-s intervals. Optimal TMS intensity was defined as the lowest stimulus intensity eliciting maximal MEP amplitudes (13). If a plateau was not confirmed from these intensities, higher TMS intensities were investigated. A suboptimal TMS intensity equivalent to 60% of the optimal intensity (i.e., corresponding to the rising part of the MEP stimulus–response curve) was also selected to identify any shift in the stimulus–response curve. Mean TMS intensities PRE were 66% ± 9% and 40% ± 5% maximal stimulator output for optimal and suboptimal TMS intensities, respectively. Coil position in relation to the vertex was noted because identical coil position and TMS intensities were used PRE and POST. Immediately after POST evaluation, optimal TMS intensity was redetermined in subjects still physically capable of sustaining the target torque level (20% MVC POST) ($n = 21$). Optimal TMS intensity in these subjects was similar PRE and POST (66% ± 9% vs 67% ± 6% maximal stimulator output, respectively; $P = 0.54$). During voluntary contractions, TMS was always delivered once the subject had contracted to the appropriate torque level and the torque had stabilized. Subjects were also instructed to recontract to the prestimulus torque level immediately after TMS delivery.

Data Analysis

EMG and FNES. *M*-wave peak-to-peak amplitude and duration were calculated from FNES in both relaxed (M_{max}) and contracted (M_{sup} at 100% MVC) muscles. Maximal torque was calculated as the mean peak torque from three MVC. EMG root mean square (RMS) was calculated as the mean from three MVC for a 200-ms period after the torque had reached a plateau and before FNES was delivered (RMS_{MVC}). Then, RMS_{MVC} was normalized to both M_{max} and M_{sup}. The amplitudes of the potentiated peak twitch (TwPot) and doublet (100-Hz paired pulse, Db100) torques were also determined.

Voluntary activation (VA_{FNES}) was also assessed by twitch interpolation using the superimposed and potentiated doublet amplitudes elicited by 100-Hz FNES paired pulses during and after MVC and calculated from the equation: $[1 - (\text{FNES 100-Hz superimposed doublet amplitude}) \cdot Db100^{-1}] \times 100$. Raw traces of the superimposed doublet are presented in Supplemental Digital Content 2 (http://links.lww.com/MSS/A393).

Transcranial magnetic stimulation. The peak-to-peak amplitudes of MEP were measured and normalized to M_{sup} measured at the same time point. VA_{TMS} during maximal effort was measured with TMS by modified twitch interpolation. For each series of contractions, estimated resting twitch (ERT) was determined by the linear regression of the relation between SIT amplitude evoked when optimal-intensity TMS was delivered at 100%, 75%, and 50% MVC (see Figure, Supplemental Digital Content 2, http://links.lww.com/MSS/A393) and voluntary torque (12,42,51). This relation was extrapolated, and the *y*-intercept was interpreted as the ERT amplitude. In cases where the linear regression was not linear ($r < 0.9$), ERT was excluded and VA_{TMS} was not calculated for the series (17). ERT was linear for all subjects for at least one series at both PRE and POST, thus permitting VA_{TMS} to be determined in all subjects. VA_{TMS} was assessed with the following equation: $[1 - (SIT \cdot ERT^{-1})] \times 100$. The reliability of this method has recently been validated in the knee extensors (12,42). The duration of the CSP was determined visually and defined as

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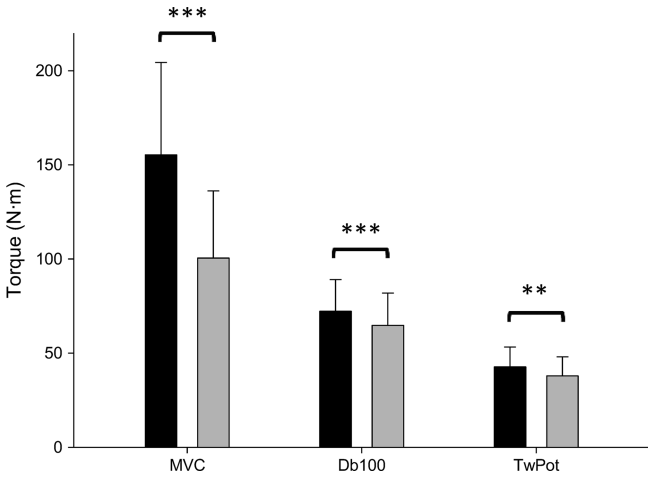

FIGURE 2—MVC and electrically evoked mechanical responses PRE and POST ultratrail. Values are presented as mean ± SD. Significant difference PRE–POST, **$P < 0.01$ and ***$P < 0.001$.

the duration from the stimulus to the return of continuous voluntary EMG (43). Subjects were excluded from CSP analyses if they did not recontract to the prestimulus torque level immediately after delivery of single TMS pulses.

Statistics

Statistical analyses were performed with Statistica (version 8; StatSoft, Tulsa, OK). The Shapiro–Wilk test was used to verify data normality. Two-way repeated-measures ANOVA were used to evaluate PRE–POST and contraction intensity changes for MEP and CSP elicited by optimal-intensity TMS. When the ANOVA revealed significant interactions, the Newman–Keuls *post hoc* test was used to identify differences. Paired *t*-tests were used to evaluate differences between PRE and POST for all other variables. The relationships between percentage change (Δ) PRE–POST in selected central and peripheral parameters were determined by Pearson product correlation. Statistical significance was set at $P < 0.05$. All data are presented as mean ± SD.

RESULTS

Performance. Subjects completed the 110-km ultratrail in a mean time of 20:17:04 ± 3:25:41 (range = 13:49:31–25:49:23), equivalent to 192% ± 33% of the overall winning time (range = 131%–245%).

Maximal voluntary torque and evoked responses. One subject with very large central deficit was an outlier and excluded from MVC and VA analyses only. There was a significant 34% decrease in MVC postrace ($T_{23} = 7.58$, $P < 0.001$; Fig. 2). Peripheral potentiated twitch and doublet amplitudes decreased significantly by 11% and 10%, respectively (TwPot: $T_{24} = 3.14$, $P = 0.004$; Db100: $T_{24} = 4.45$, $P < 0.001$; Fig. 2).

***M*-waves and RMS.** *M*-wave amplitudes were unchanged, although there was a tendency for both M_{max} and M_{sup} to be smaller POST (Table 1). Peak-to-peak *M*-wave duration was also unchanged (Table 1). RMS_{MVC}, both raw and normalized, significantly decreased from PRE to POST (Table 1).

Voluntary activation. There was a mean decrease of 16% for VA_{TMS} (93% ± 7% to 80% ± 11%, $T_{23} = 6.91$, $P < 0.001$) and 26% for VA_{FNES} (91% ± 8% to 72% ± 14%, $T_{23} = 7.64$, $P < 0.001$). There was a correlation between ΔVA_{FNES} and ΔVA_{TMS} ($r = 0.54$, $P = 0.007$; Fig. 3). ΔVA_{TMS} and ΔVA_{FNES} were correlated with ΔMVC ($r = 0.61$, $P = 0.002$ and $r = 0.79$, $P < 0.001$, respectively). ΔVA_{TMS} was also correlated with ΔTwPot ($r = 0.53$, $P = 0.008$), and there was a trend for ΔVA_{TMS} to be correlated with ΔDb100 ($r = 0.37$, $P = 0.074$; see Figure, Supplemental Digital Content 3, http://links.lww.com/MSS/A394). There were no significant correlations between ΔVA_{FNES} and peripheral changes.

MEP. There was an increase in $MEP \cdot M_{sup}^{-1}$ elicited by optimal TMS intensity from PRE to POST ($F_{1,24} = 11.2$, $P = 0.003$). There was also an intensity effect ($F_{2,48} = 32.1$, $P < 0.001$) and time–intensity interaction ($F_{2,48} = 6.85$, $P = 0.002$). *Post hoc* analyses identified that $MEP \cdot M_{sup}^{-1}$ was greater at 50% and 75% MVC than at 100% MVC and that at all contraction intensities $MEP \cdot M_{sup}^{-1}$ increased from PRE to POST ($P < 0.05$; Fig. 4A; see Figure, Supplemental Digital Content 2, http://links.lww.com/MSS/A393). Conversely, the amplitude of MEP elicited at suboptimal TMS intensity was unchanged ($T_{23} = 0.548$, $P = 0.59$; Fig. 4A).

CSP. There were no changes in CSP during contractions at 50%, 75%, or 100% MVC elicited by optimal TMS intensity from PRE to POST ($F_{1,21} = 0.0024$, $P = 0.96$) or time–intensity interaction ($F_{2,42} = 2.20$, $P = 0.12$) (Fig. 4B; see Figure, Supplemental Digital Content 2, http://links.lww.com/MSS/A393). A contraction intensity effect presented ($F_{2,42} = 16.37$, $P < 0.001$) and the *post hoc* analyses indicate that CSP at 100% MVC were longer than CSP at 50% and 75% MVC. Conversely, CSP elicited by

TABLE 1. Vastus lateralis *M*-wave amplitude and duration and RMS.

	PRE	POST	*T* and *P* Values
M_{max} amplitude (mV)	13.2 ± 3.9	12.3 ± 4.1	$T_{24} = 1.86$, $P = 0.07$
M_{sup} amplitude (mV)	12.9 ± 3.7	12.0 ± 4.4	$T_{24} = 1.69$, $P = 0.10$
M_{max} peak-to-peak duration (ms)	9.7 ± 2.2	9.6 ± 2.4	$T_{24} = 0.803$, $P = 0.43$
M_{sup} peak-to-peak duration (ms)	6.8 ± 1.5	7.2 ± 1.4	$T_{24} = 1.66$, $P = 0.11$
RMS_{MVC} (mV)	0.63 ± 0.32	0.37 ± 0.15	$T_{24} = 4.64$, $P < 0.001$
$RMS_{MVC} \cdot M_{max}^{-1}$	0.047 ± 0.015	0.030 ± 0.008	$T_{24} = 5.50$, $P < 0.001$
$RMS_{MVC} \cdot M_{sup}^{-1}$	0.048 ± 0.016	0.035 ± 0.021	$T_{24} = 2.60$, $P = 0.016$

Values are presented as mean ± SD.

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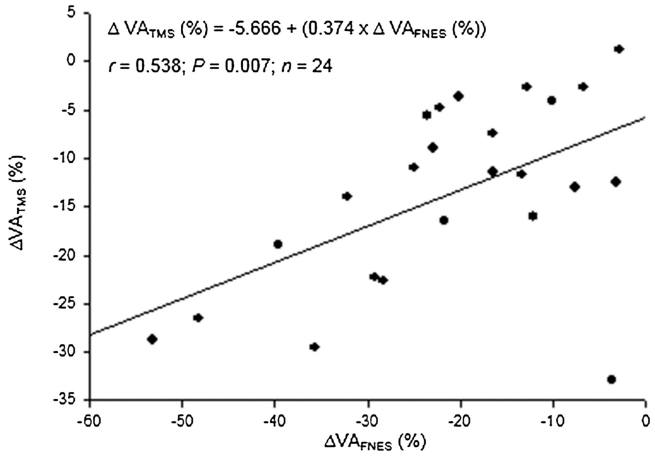

FIGURE 3—Correlation between ΔVA_{TMS} and ΔVA_{FNES}.

suboptimal stimulus intensity at 50% MVC increased in duration from PRE to POST ($T_{20} = 2.61$, $P = 0.017$; Fig. 4B). At suboptimal TMS intensity, no CSP was elicited in at least one contraction in five subjects PRE and in one subject POST due to the stimulus intensity being insufficient.

DISCUSSION

Central fatigue has been reported to be the main cause of knee extensor strength loss after prolonged running (25,29,31). The primary aim of the present study was to determine whether at least part of this central fatigue was supraspinal. The main results are that after a 110-km ultratrail, (i) there were significant and correlated decreases in VA_{TMS} and VA_{FNES}; (ii) there were correlations between peripheral changes and decreases in VA_{TMS}, suggesting that the large central deficits consistently observed after extreme duration running exercise have both central and peripheral origins; and (iii) there was increased corticospinal excitability (as indicated by greater VL MEP amplitude) and no change in intracortical inhibition (as indicated by unchanged VL CSP) at optimal TMS intensity. There was also increased CSP duration and unchanged MEP amplitude at suboptimal TMS intensity. These suggest that during contractions at 50% MVC, there is a shift in the VL MEP–stimulus intensity relationship toward larger MEP amplitudes only at higher TMS intensities and that there is also a left shift in the VL CSP–stimulus intensity relationship.

Maximal torque and FNES measures: comparison with the literature. Only a couple studies (25,33,40) have examined long-distance running comparable with that of the ultratrail in the present study. Despite being of shorter duration than these studies, the mean MVC decrease was similar (25,33) or greater (40) after a similar delay to post-exercise evaluation (40–60 min) (33,40), a finding compatible with the existence of a plateau in the strength loss–exercise duration relationship (29). In this study, ΔVA_{FNES} was comparable with that reported after a 24-h treadmill run (25), a 330-km ultratrail (mean time ~122.5 h) with 24 000 m of elevation change (40), and a 166-km ultratrail (mean time ~37.5 h) with 9500 m of elevation change (33). The latter study reported decreased VL *M*-wave amplitude and increased VL *M*-wave duration. A similar tendency for M_{max} and M_{sup} amplitude and M_{sup} duration was observed in the present study. Finally, as with longer treadmill and ultratrail runs (25,33,40), potentiated twitch amplitude in the present study decreased, although to a lesser extent than that in previous studies. With shorter trail (mean time < 9 h) and treadmill runs (mean time < 3.5 h), a change in twitch amplitude PRE to POST was not observed (7,31,32,38,39), suggesting an effect of distance and/or duration on twitch amplitude. The present results confirm previously published consequences of extreme running exercise on both central and peripheral fatigue.

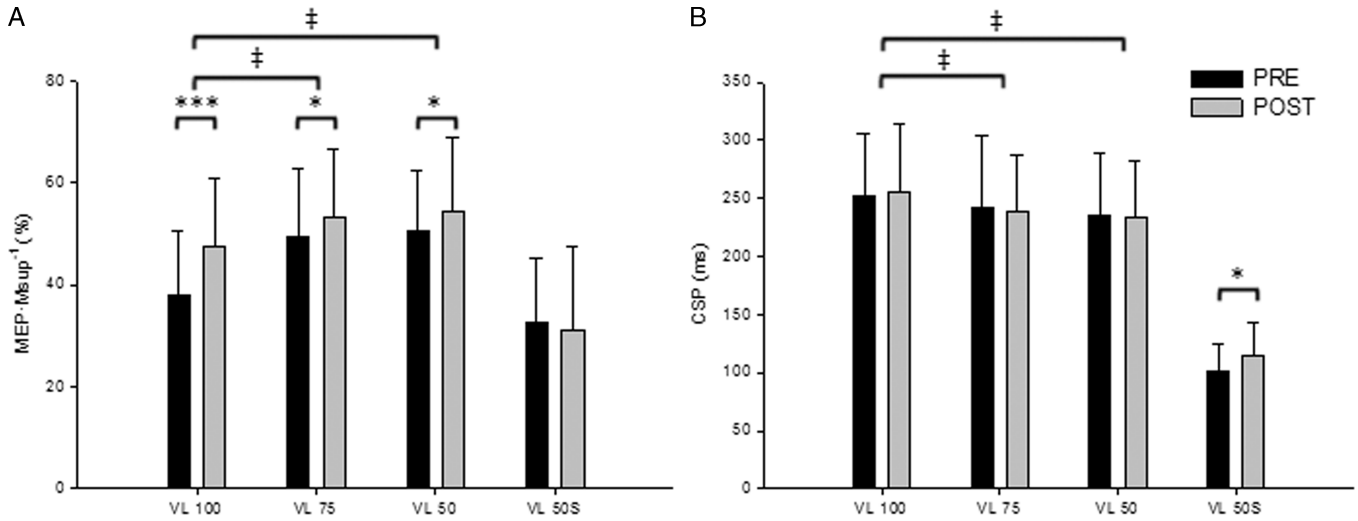

FIGURE 4—Vastus lateralis (A) MEP amplitude normalized to M_{sup} and (B) CSP elicited by optimal-intensity TMS during contractions at 50%, 75%, and 100% MVC and by suboptimal TMS intensity at 50% MVC (50S) PRE and POST ultratrail. Values are presented as mean ± SD. Significant difference PRE–POST, *$P < 0.05$ and ***$P < 0.001$. Significant difference by voluntary contraction intensity (% MVC), ‡$P < 0.001$.

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Voluntary activation assessed by TMS and FNES. This study was the first to measure VA_{TMS} of the knee extensors with fatigue induced by long-distance running. Previously, Ross et al. (39) observed decreased dorsiflexor VA_{TMS} after a 42.2-km treadmill marathon, but dorsiflexors are not considered limiting to trail running performance (8). All other investigations of knee extensor VA_{TMS} have been conducted with cycling, and all showed decreased VA_{TMS} after exercise (11,43,50), except the study of Klass et al. (21), where no decrease in VA_{TMS} was observed 10 min after ~1.5 h of cycling.

In the present study, despite greater ΔVA_{FNES} than ΔVA_{TMS} (−26% vs −16%), these changes were well correlated, indicating that supraspinal fatigue plays an important role in the decrease of VA_{FNES}. The greater decrease in central fatigue assessed by FNES than TMS has been previously observed by our group (50) and suggests that VA_{FNES} comprises both fatigue manifesting at the cortical and spinal levels while VA_{TMS} is representative of central fatigue only at the supraspinal level. This finding is however in contrast to previous cycling studies that have observed greater maximal force loss linked to VA_{TMS} (43) or no difference between methods of VA determination (21). Caution must also be taken when comparing these methods due to differences in torque–SIT relationships (i.e., linear at contraction intensities ≥50% MVC for VA_{TMS} [12,42] and nonlinear at near-maximal contraction intensities [22]) and the precise mechanisms evaluated by each method (for an explanation of differences between VA_{TMS} and VA_{FNES}, see Introduction). The correlation between ΔVA_{FNES} in knee extensors and plantar flexors previously observed in an ultratrail (33) suggests there is one or more common regulatory components independent of peripheral factors that contribute to decreased VA. Candidates include hypoglycemia (3), cerebral catecholamine concentrations (15), core temperature (36), cerebral ammonia accumulation (35), and brain neurotransmitters (26), all of which are involved in brain signaling or have a demonstrated link to the development of fatigue.

Conversely, there are significant correlations between ΔVA_{TMS}, but not ΔVA_{FNES}, and peripheral factors (ΔTwPot and ΔDb) in the present study. Fatigue is multifactorial, and despite the significant correlations between VA_{TMS} and peripheral changes, some are weak (see Figure, Supplemental Digital Content 3, http://links.lww.com/MSS/A394). Collectively, these correlations cannot explain an important portion of the observed fatigue, indicating that factors not investigated in the present study play an important role in the development of fatigue. The observed correlations also suggest that afferent feedback from the muscle is involved in central fatigue observed after an ultratrail and that information communicated from the evaluated muscles via type III and IV afferents is integrated at the supraspinal level. This idea has previously been proposed for shorter endurance cycling exercise (1). Recently, elbow extensor fatigue was observed to induce central deficits in the elbow flexor due to afferent feedback (19), suggesting that knee flexor fatigue may have also contributed to the decreased VA observed after an ultratrail in the present study. Previous research also suggests that neither acidosis nor potassium are major factors in ultraendurance activities (33), indicating that group III and group IV afferents likely respond to mechanical stimuli (i.e., stress and pressure) (10,23) and inflammatory processes (16,41) in this type of event. After extreme endurance activities, inflammatory markers remain elevated up to 5 d after the cessation of the exercise bout (33,34), well beyond the 1-h delay to POST testing in the present study. Meanwhile, the lack of correlation between ΔVA_{FNES} and peripheral factors suggests that other factors, perhaps reduced spinal excitation/increased spinal inhibition by Ia and Ib afferents, are integrated to cause fatigue at the spinal level. The specific role of peripheral muscle afferents and direct spinal and supraspinal mechanisms remains to be determined.

MEP and CSP. The TMS contraction series required maximal (100% MVC) and submaximal (50% and 75% MVC) isometric contractions. Increased MEP amplitude and unchanged CSP at optimal TMS intensity in the VL after the ultratrail could indicate a transient increase in corticospinal excitability without change in intracortical inhibition that translates into a more effective corticospinal response to a given stimulus.

Previous studies from other laboratories have not shown any change in MEP amplitude/area or CSP duration after cycling (intensity = 55%–80% maximal power output, mean duration = 4–94 min) (11,21,43) when investigated in a similar manner. These results contrast those observed in the present study. Two factors, exercise duration and TMS intensity, may contribute to these differences. Another study from our group observed MEP amplitude in the VL and vastus medialis to increase during 40 min of cycling at 65% maximal aerobic power output followed by an incremental cycling test to task failure (50). MEP amplitude also increased at optimal TMS intensity in the present study, after a more extreme activity in terms of duration. Together, these studies suggest that the duration of effort and the associated consequences (e.g., hydration, glycemia, pain, and also sleep deprivation for extreme-duration exercise) play an important role in transient changes toward higher corticospinal excitability when tested at optimal TMS intensity (66% ± 9% maximal stimulator output). The concurrent use of optimal and suboptimal TMS intensities to evaluate MEP and CSP changes is novel, and our results suggest that selection of an appropriate TMS intensity is essential. Both Klass et al. (21) and Sidhu et al. (43) performed TMS at intensities comparable with suboptimal TMS intensities in the present study (i.e., 30%–60% maximal stimulator output vs 40% ± 5% maximal stimulator output in the present study). At suboptimal TMS intensity, the unchanged MEP amplitudes in the present study mirrored the aforementioned findings of these studies (21,43). Furthermore, Sidhu et al. (44) found no change in MEP amplitude normalized to M_{sup} at similar TMS intensities (i.e., 41.4% ± 0.9% maximal stimulator output) during a cycling bout in the only truly sport-specific TMS investigation. Unlike the observed

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increase in CSP at suboptimal TMS intensity in the present study, other studies of total duration from ~45 to 90 min (21,43) did not observe a change in CSP despite similar mean CSP durations and TMS intensities. This supports the proposal that corticospinal changes are related to exercise duration. The finding that increased corticospinal inhibition occurs during exercise at suboptimal TMS intensity has previously been observed during cycling using a different method of evaluation (45).

Although the contraction mode is different from the stretch–shortening cycle observed during running, among the isometric voluntary contractions evaluated in the present study, those at 50% MVC with suboptimal-intensity TMS would probably be the contractions most similar to conditions during an ultratrail because maximal physical efforts are rare and there are many diverse mental demands during this type of effort (29). Unlike the unchanged CSP and increased MEP amplitude at optimal TMS intensity, CSP induced by TMS at suboptimal intensity increased in duration while MEP amplitude remained unchanged. These results can be placed within the framework of the previously demonstrated sigmoidal MEP–stimulus intensity (4,6) and CSP–stimulus intensity (6,20) relationships. In the present study, optimal TMS intensity was determined as the lowest stimulus intensity eliciting a maximal MEP response (i.e., the intensity at the start of the plateau in an MEP–stimulus intensity curve) at 20% MVC. The observed changes in MEP amplitude and CSP duration suggest that if both MEP and CSP stimulus–response curves had been performed at 50% MVC, they would have undergone transformations and/or shifts but that these changes would have been different (Fig. 5). It is proposed that after ultraendurance running exercise, there would be a shift of the MEP stimulus–response curve toward greater MEP amplitudes at higher TMS intensities without change in the lower inflection point (Fig. 5A). Concurrently, it is proposed that there would be a left shift of the CSP stimulus–response curve (Fig. 5B). This suggests that an ultratrail may cause a decrease in the threshold to induce CSP during contractions at 50% MVC at a suboptimal TMS intensity. The functional relevance of these shifts remain to be elucidated; however, they suggest that the delivery of TMS at an intensity to elicit a maximal response is supraphysiological and perhaps less relevant to the normal functioning of the human body than a stimulus intensity that corresponds to the rising part of a stimulus–response curve. These shifts also suggest that the role of intracortical inhibition may increase with increasing exercise duration and may have a role in the performance deficits exhibited after prolonged exercise.

Limitations. Subjects were tested as soon as possible after they completed the ultratrail competition. Despite efforts to conduct POST measures in a timely manner, there was a large delay (1:01:30 ± 0:22:37) and some variability in the time between race completion and the start of testing because of the distance from the finish to the testing site and the necessity of ensuring the safety of the subjects. The same coil position and TMS stimulus intensity were used at PRE and POST. This was performed for several reasons: (i) given the physical state of the subjects at POST, including several that were unable to complete the three series of contractions with TMS, the reassessment of TMS intensity before POST assessment would probably have reduced the number of subjects and affected data analysis; and (ii) to be able to compare CSP and MEP because changes to stimulus intensity influence both these parameters. Optimal stimulus intensity was similar PRE and POST. Because of the delay in conducting POST, the magnitude of voluntary activation decreases may be underestimated, and MEP and CSP changes may be underestimated or masked. Previous studies have shown MEP and CSP to recover rapidly after isometric single-joint exercise (e.g., 48,49). Because of the nature of the ultratrail, it was impossible to test subjects at the same

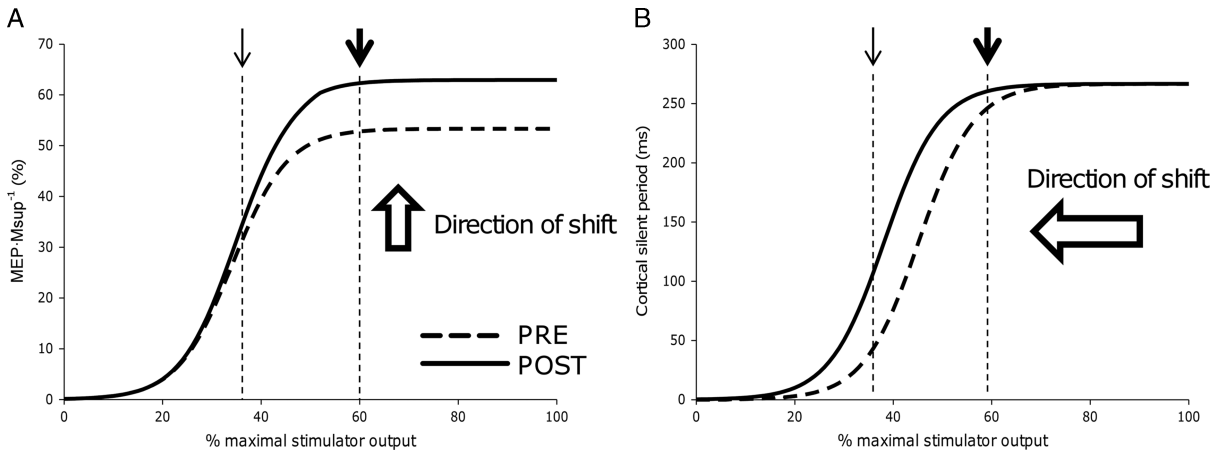

FIGURE 5—Proposed theoretical changes to the sigmoidal MEP and CSP stimulus–response curves from PRE to POST ultratrail. Optimal and suboptimal TMS intensities of 60 (thick arrow and dotted line) and 36% (thin arrow and dotted line) maximal stimulator output, respectively, are used as examples. Optimal and suboptimal stimulus intensities are based on PRE evaluation for both PRE and POST. A, The large vertical arrow indicates the proposed shift at moderate to high TMS intensities in the MEP–stimulus intensity relationship. There is also no change in inflection point of the relationship. B, The large horizontal arrow illustrates the proposed left shift in CSP–stimulus intensity relationship.

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time of day. Nevertheless, this was unlikely to influence results as corticospinal and intracortical excitability have been shown to be unaffected by time of day (5). Because this study was conducted in conjunction with an existing ultratrail, there was no control over the part of the menstrual cycle of the female subjects. Although hormonal changes during the menstrual cycle may have influenced the results (46,47), the random distribution of women across their cycles would probably have nullified any effects. Furthermore, in isometric contraction protocols, neither the time to task failure (18) nor the decrease in maximal voluntary force (17) were influenced by the timing of the menstrual cycle, and supraspinal deficits with exercise were observed to be similar between men and women (17,18). Finally, antagonist (e.g., biceps femoris) EMG was not measured because of time constraints. Changes in the relative contribution of agonists and antagonists may affect measures such as VA.

CONCLUSIONS

This study was the first to combine TMS and extreme endurance to investigate the physiological consequences of an extreme duration exercise on central changes at the supraspinal level. The hypotheses that an ultratrail decreases VA_{TMS} and that corticospinal fatigue occurs with a concomitant increase in MEP amplitude and unchanged CSP duration were confirmed. However, CSP induced by suboptimal TMS intensity increased without concurrent change in MEP amplitude at this intensity. This suggests a left shift in the CSP–stimulus intensity relationship and a shift in the MEP–stimulus intensity relationship toward larger MEP at higher TMS intensities without change in the inflection point of the curve.

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