The interaction between peripheral and central fatigue at different muscle temperatures during sustained isometric contractions

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Lloyd A, Hodder S, Havenith G. The interaction between peripheral and central fatigue at different muscle temperatures during sustained isometric contractions. Am J Physiol Regul Integr Comp Physiol 309: R410–R420, 2015. First published June 3, 2015; doi:10.1152/ajpregu.00061.2015.—Changes in central fatigue have been linked to active and passive changes in core temperature, as well as integration of sensory feedback from thermoreceptors in the skin. However, the effects of muscle temperature (Tm), and thereby metaboreceptor and local afferent nerve temperature, on central fatigue (measured using voluntary activation percentage) during sustained, high muscle fatigue exercise remain unexamined. In this study, we investigated Tm across the range of cold to hot, and its effect on voluntary activation percentage during sustained isometric contractions of the knee extensors. The results suggest that contrary to brief contractions, during a sustained fatiguing contraction Tm significantly (P < 0.001) influences force output (−0.7%/°C increase) and central fatigue (−0.5%/°C increase), showing a negative relationship across the Tm continuum in moderately trained individuals. The negative relationship between voluntary activation percentage and Tm indicates muscle temperature may influence central fatigue during sustained and high muscle fatigue exercise. On the basis of an integrative analysis between the present data and previous literature, the impact of core and muscle temperature on voluntary muscle activation is estimated to show a ratio of 5.5 to 1, respectively. Accordingly, Tm could assume a secondary or tertiary role in the reduction of voluntary muscle activation when body temperature leaves a thermoneutral range.

afferent feedback; limb discomfort; exercise regulation; sensory integration; central control

As defined by Gandevia (27), muscle fatigue is best described as any exercise-induced reduction in the muscles’ force [or power]-generating capacity. Fatigue arises as two segmented manifestations; “peripheral” fatigue, resulting from intramuscular factors (1, 25) distal to (or within) the neuromuscular junction, and “central” fatigue, resulting from a progressive reduction in voluntary muscle activation (VA) proximal to the neuromuscular junction (27). Thus, to understand central fatigue, it is necessary to define VA as well, which is the amount of voluntary (neural) drive used to activate skeletal muscle, including those efforts originating from a supraspinal (cortical) level (27, 58). Importantly, this means central fatigue combines both autonomic reflexes across the muscle-brain pathway, as well as perceptual and decision-making processes, since both present synonymously through reductions (or modulations) in VA during exercise (3, 9, 17, 27, 31, 58).

Recent studies have revealed that the effect of body temperature on performance during prolonged exercise might be, in part, attributable to central mechanisms, reflected in a progressive reduction in VA as core temperature (Tcore) increases (39, 42, 47, 60, 63). It has been suggested that this may be the result of a complex interplay between hypothalamic temperature, hyperventilation, arterial hypocapnia, and subsequent reductions in cerebral perfusion and/or oxygenation (40, 41). Moreover, during sustained isometric contractions, whole body hyperthermia (13) may have the inverse effect of hyperthermia on VA (63), indicating a potentially positive relationship between body temperature and central fatigue.

In addition to changes in Tcore (for reviews, see Refs. 40 and 41), other peripheral factors may contribute to modulations in VA during exercise at different body temperatures. For example, it has been proposed that ambient temperature (Ta) and relative humidity (rh) could influence central drive via changes in skin temperature (Tsk), through integration of anticipatory and/or sensory feedback mechanisms (2, 33, 34, 38, 54, 57). However, research examining the specific contribution of muscle temperature (Tm) to central fatigue has received relatively less attention. This may be because increasing muscle and efferent nerve temperatures are known to have beneficial Q10 effects (47), leading to improved performance when exercise tolerance is brief (i.e., instantaneous power activities) (e.g., 22, 23, 53).

Of the few studies that have examined the effect of local tissue (i.e., muscle) temperature on VA, all have utilized brief isometric contractions interspersed with adequate rest, introducing minimal or no peripheral fatigue (intramuscular metabolic disturbance). This may be limiting, as it has been shown that metabosensitive muscle afferents (which relay the status of peripheral fatigue in the muscles to the central nervous system), can highly influence VA (3, 4, 5, 14, 58) and respond strictly to situations in which both sustained neuromuscular drive (broken by little or no periods of rest) and high peripheral fatigue are present (5, 9, 16, 28, 35, 58). Thus, while short-duration contractions might adequately highlight the role of changes in Tm in central fatigue (39, 52, 60), brief contractions also negate the contribution of intramuscular and afferent factors that could worsen VA during a sustained, fatiguing effort.

Like efferent motor nerves (see above), metaboreceptive muscle afferents also appear to be significantly influenced by a Q10 effect of local temperature (50, 51). But whether a change in muscle temperature (i.e., metaboreceptor and local afferent nerve temperature) can alter autonomic responses (e.g., 3) and/or perceptual feedback (46), and thereby result in different modulations of voluntary drive (i.e., VA), is at present unknown. The latter mechanism is especially unclear in those who are only moderately trained, and perhaps more reliant on perceptual limits of exercise performance than elite athletes.
Thus, to investigate the effect of muscle temperature on central fatigue during sustained, high-fatigue isometric exercise, we examined the interaction between central and peripheral fatigue at different $T_m$. We hypothesized that during sustained contractions, 1) a negative relationship exists between $T_m$ and mean isometric force output; 2) a negative relationship exists between $T_m$ and mean voluntary activation (i.e., positive relationship between $T_m$ and central fatigue); 3) postexercise peripheral fatigue would be similar across muscle temperatures, supporting the role of a muscle afferent protective mechanism; and 4) the relative change in peripheral fatigue postexercise would be greater in hot muscle, supporting altered peripheral fatigue-development rates.

**MATERIALS AND METHODS**

**Subjects.** Eight physically active, healthy men were selected as participants for this study. Their (mean ± SD) age, height, weight, and maximal aerobic capacity ($\dot{V}O_2 \text{max}$) was 22.1 ± 2.5 yr, 176 ± 4 cm, 72.9 ± 8.8 kg, and 51.9 ± 5.8 ml·kg$^{-1}$·min$^{-1}$, respectively. All participants were right-leg dominant and had no history of muscular, neurological, or cardiovascular debility. It was requested that all participants abstain from stimulants, alcohol, and exhaustive exercise 24 h prior to each trial.

The experimental protocol was approved by the Loughborough University Ethical Advisory Committee, and all procedures were conducted in accordance with the World Medical Association’s Declaration of Helsinki. All participants were provided with an information sheet that outlined the procedure, risks, and requirements for the experiment. Participants completed a questionnaire-based health screening and provided written informed consent prior to the experiment.

*Study overview.* Participants attended the laboratory on eight separate occasions. During the first session, participants were familiarized with the experimental procedures and equipment (“familiarization sessions”). In the remaining sessions, participants completed an isometric, single-leg knee extension exercise protocol to quantify central and peripheral fatigue development at five different muscle temperatures. The incremental muscle temperatures were selected on the basis of pilot data and previous research (53, 60). Each condition was performed in a thermoneutral ($23^\circ\text{C}$, 50% rh) environment, whereas to assess the additional role of whole body changes in $T_{\text{_core}}$, the two most extreme muscle temperatures were also conducted in hot and cold ambient conditions, respectively. Thus, the seven main experimental conditions were COLDENV (Cold Environment) — $T_m$ of $22^\circ\text{C}$ with $−5^\circ\text{C}$ (50% rh) $T_\text{a}$; COLD-Tm of $22^\circ\text{C}$ with $23^\circ\text{C}$ (50% rh) $T_\text{a}$; WARM-Tm of $37^\circ\text{C}$ with $23^\circ\text{C}$ (50% rh) $T_\text{a}$; NEU-Tm of $34.9^\circ\text{C}$ with $23^\circ\text{C}$ (50% rh) $T_\text{a}$; HOT-Tm of $38.5^\circ\text{C}$ with $23^\circ\text{C}$ (50% rh) $T_\text{a}$; and HOTENV (Hot Environment) — $T_m$ of $38.5^\circ\text{C}$ with $38^\circ\text{C}$ (70% rh) $T_\text{a}$.

In each condition, participants performed a 120-s sustained isometric maximal voluntary contraction (ISO). Such contractions can be manipulated; $T_m$ and mean isometric force output; $T_{\text{_core}}$ and mean isometric force output; a negative relationship exists between $T_m$ and central fatigue; a negative relationship exists between $T_m$ and mean voluntary activation (i.e., positive relationship between $T_m$ and central fatigue); postexercise peripheral fatigue would be similar across muscle temperatures, supporting the role of a muscle afferent protective mechanism; and peripheral fatigue postexercise would be greater in hot muscle, supporting altered peripheral fatigue-development rates.

**Fig. 1.** A schematic of the general procedure. White boxes indicate the schematic overview of the experimental protocol. Gray boxes indicate the outcome measures. Dark gray areas provide a visual reference for muscle contraction and supramaximal twitches. $T_{\text{core}}$, rectal temperature; $T_{\text{muscle}}$, muscle temperature; $T_{\text{skin}}$, skin temperature; iMVC, maximal isometric voluntary contraction force of knee extensors; $Q_{\text{tw,pot}}$, resting potentiated twitch force; $Q_{\text{tw,sup}}$, superimposed twitch force. VA, voluntary activation percentage; PRE-WI, pre-water immersion; WI, water immersion; POST-WI, post-water immersion (temperature-manipulated); ISO, 120-s sustained isometric maximal exercise; POST-REC, 20-s post recovery maximal voluntary contraction.
Muscle temperature manipulation. To manipulate quadriceps femoris Tm, and confound the temperature shifts as much as possible to the exercising leg, participants sat in a temperature-controlled water-immersion bath. Seated immersion was used to minimize hydrostatic pressure to the lower limb. Each participant was immersed to the iliac crest, with their contralateral, nonexercising leg suspended by a support frame out of the water. The water immersion durations were based on Tm reaching the required temperature for each condition. Cooling and heating water temperature was maintained at 8° and 44°C, respectively. An immersion time limit of 50 min was applied for all conditions, although this was not exceeded by any participant in any condition. In thermoneutral conditions, participants were briefly (15 min) immersed to ensure a similar protocol was used in all trials. The water temperature was maintained at 33°C for thermoneutral conditions. Water was actively reheated/ cooled during immersion, circulated, and stirred via side-mounted jet connectors at a flow rate of 50 l/min. Tm was maintained at ~23°C and 50% rh during water immersion. To aid in maintaining core thermoneutrality, participants were permitted to add or remove any upper body clothing throughout the water immersion protocol, and variable intensity electric fans were also provided. During cold water immersion, a 3-N neoprene wetsuit sock (Ripcord, UK) was worn to protect the foot against extreme cold sensations. Water bath temperature was monitored and controlled using a calibrated thermistor and Squirrel Data Logger (1000 series; Grant Instruments, Cambridge, UK). Electrical isolation was achieved using isolation transformers.

Body temperature assessments. To measure intramuscular temperature (Tm;), a flexible thermocouple (Ellab, Denmark) was inserted into rectus femoris to an estimated depth of 2-cm subfascia through an 18 G single-use cannula. Using skinfold calipers (Harpenden International, Warwickshire, UK), we calculated adipose tissue thickness over the insertion site, and small adjustments to the insertion angle were made to achieve the correct depth. This technique was validated using ultrasound guidance (Logiq 700; GE, Fairfield, CT). The thermocouple and cannula remained in place during the temperature manipulation and was secured to the skin using a sterile, waterproof dressing (3M H-1013M) and were secured using 3 M medical tape. Identification of twitches was achieved by using a trigger mark system for the DataLog software (Biometrics). A constant current variable voltage nerve stimulator (DS7AH; Digitimer, Hertfordshire, UK) was used to deliver single percutaneous electrical impulses (0.2-ms, square wave) at 0.5 N when ambient and force conductivity, electrodes were applied with hypoallergenic conductivity gel (Lectron II, Newark, NJ) and were secured using 3 M medical grade tape. Identification of twitches was achieved by using a trigger marking system for the DataLog software (Biometrics).

Details of neuromuscular assessment. To examine central vs. peripheral fatigue, supramaximal femoral nerve stimulation (twitch interpolation) was used (37). Detailed descriptions of this procedure, with example traces and an exhaustive list of references, have been provided by Gandevia (27). In brief, twitch interpolation measures VA, and, thereby, central fatigue, by assessing the residual capacity of the muscle during contractions that are otherwise voluntarily controlled. By comparing an evoked force superimposed over a voluntary contraction (superimposed twitch) with that of an evoked contraction after muscle relaxation (resting twitch), the VA percentage can be calculated (see below). In addition, the resting evoked contraction allows assessment of the mechanical response to fixed supramaximal intensity stimuli, thereby removing the influence of the central nervous system, thus solely evaluating peripheral fatigue (e.g., 4).

In this experiment, two superimposed twitches (Qtw,super) were evoked over the force plateau of all 3-s iMVCs (PRE-WI, POST-WI, POST-REC). Each contraction was also followed by two resting potentiated twitches (Qtw,pot) 1-s after full relaxation from the contraction. Each set of Qtw,super and each set of Qtw,pot were averaged for each iMVC. For the sustained contractions (ISO), a total of five Qtw,super were evoked; one at initial peak force (manually delivered 1 s after the start of the contraction) followed by a single twitch at 30, 60, 90, and 120 s into the contraction. On completion of each sustained contraction, a further two resting Qtw,pot were delivered upon relaxation of the muscle (Fig. 1). The mean rate of force development (MRFD) and half relaxation time (RT50) for all Qtw,pot were also calculated for all resting twitches (4).

For all iMVCs (sustained or brief), participants sat with a hip joint angle of 90° and knee joint angle at 100°. Participants were secured using a waist and ankle belt system. Single leg knee extension force (N) was quantified using an s-shaped aluminum force transducer (Teledyne-Huntleigh, model 615; Vishay Precision Group, Rancho Cucamonga, CA) with a linear response up to 2000 N. The force transducer was mounted to an adjustable frame and harness proximal of the ankle malleolus. Force data were PC interfaced (DataLog software; Biometrics, Newport, UK) using a Bluetooth wireless, 8-channel data logger (Miniature DataLog MXW8; Biometrics). Live force feedback was displayed to participants to maximize iMVC performance. Data were sampled at 1,000 Hz and rounded to the nearest 0.5 N. Baseline noise was <0.5 N when ambient and force transducer baseline had stabilized (e.g., during COLENV and HOTENV conditions). All quadriceps femoris twitches were evoked using a constant current variable voltage nerve stimulator (D57AH; Digitimer, Hertfordshire, UK), delivered manually by the experimenter. Single percutaneous electrical impulses (0.2-ms, square wave) were delivered to the femoral nerve via a metal-tipped pen cathode and 140 cm² carbon rubber anode (Electro-Medical Supplies, Greenwich, UK). The cathode was placed at the femoral triangle, and the anode was placed over the greater trochanter (62). Consistent placement was achieved using indelible pen marking. Full supramaximal stimulation was confirmed using incremental increases in current (25 mA) until a plateau in knee extension force (234 ± 55 N) was observed (4, 45, 62). A further 25% was added to ensure the stimulus was supramaximal (mean current: 157 ± 15 mA). To ensure effective conductivity, electrodes were applied with hypoallergenic conductivity gel (Lectron II, Newark, NJ) and were secured using 3 M medical grade tape. Identification of twitches was achieved by using a trigger marking system for the DataLog software (Biometrics).
Equations for voluntary activation percentage. Two different equations can be found in the literature to calculate VA:

\[
VA_1 = \left(1 - \frac{Q_{tw,\text{sup}}}{Q_{tw,\text{pot}}}\right) \cdot 100 \text{ (%) (1)}
\]

and

\[
VA_2 = \frac{iMVC}{iMVC + Q_{tw,\text{pot}}} \text{ (%) (2)}
\]

where iMVC is the isometric maximal contraction immediately prior to stimulation; \(Q_{tw,\text{sup}}\) is the evoked force amplitude of the superimposed contraction; and \(Q_{tw,\text{pot}}\) is the evoked force amplitude of the resting contraction.

VA1 is traditionally used for the estimation of VA (26, 37), although in some cases VA2 has been used (27). However, VA2 omits any independent and direct thermal or temporal (e.g., fatiguing) influence on evoked force amplitude. Thus when time, temperature, or fatigue influence iMVC and evoked force disproportionately, estimates of \(\Delta VA_2\) are limited (27). Even in the absence of fatigue or thermal stress, linearity between voluntary force and evoked force is not well supported (26, 27). VA2 is also proportionally overestimated if the evoked contraction is less than the true maximum force of a tested muscle group. VA1, however, uses both VA1 and VA2 are reported in this study. Additionally, the decline in VA during a sustained iMVC does not occur uniformly; therefore, an average VA over the duration of a given contraction was calculated (27, 47).

Statistics. To test for significance, dependent variables were analyzed for the effect of condition (\(T_m\)) using a one-way repeated-measures ANOVA. Significance was tested at a 95% confidence level (\(P < 0.05\)). If a significant \(F\) ratio was observed, then relevant pairwise comparisons were quantified using paired \(t\) tests. Given the high number of possible comparisons (\(n = 21\)), insufficient power is available (threshold Bonferroni corrected \(P = 0.05/21 = 0.0023\)) to avoid type II (false negative) error when using a full (Holm)-Bonferroni correction for multiple comparisons (56). Instead, to illustrate the likelihood of type I error (false positive) due to the multiple comparisons, the chance of achieving and/or exceeding the observed number of significant comparisons (out of 21 possible) as a result of a type I error was calculated using Eq. 3.

\[
p = \sum_{i=1}^{n} \frac{X^i \cdot (1 - X)^{(n-i)}}{i! \cdot (n-i)!} (3)
\]

where \(p\) is the total probability of \(\geq r\) pairwise false positives, \(X\) is the tested \(p\) value (i.e., 0.05), \(n\) is the number of pairwise comparisons, and \(r\) is the number of observed significant results out of \(n\).

For example, in this study, 21 comparisons were tested to 95% confidence per dependent variable; finding either 21, 14 (or more), or 7 (or more) significant type I errors has extremely low probability level (\(P = 4.8 \times 10^{-2} \times 5 \times 1.10^{-11} \times 4.9 \times 10^{-11}\)). In fact, reaching or exceeding the lowest number of significant pairwise findings observed in this study (\(\geq 5\)) has a less than 0.33% (\(P < 0.005\)) chance of false-negative occurrence. In contrast, any analyses yielding 4 or less significant comparisons has an exponentially higher chance of false positive (\(P = 0.02, 0.08, 0.28, \text{and} 0.65\) for equal to or greater than 4, 3, 2, and 1 significant comparisons, respectively). As this study aimed to infer the relationship between \(T_m\) and voluntary activation, Pearson correlations were determined for \(T_m\) against dependent variables (both individual and group mean data) after all significant ANOVAs.

PRE-WI values for iMVC force max (\(P = 0.891\)), iMVC 1-s force plateau (\(P = 0.855\)), VA1 (\(P = 0.890\)), VA2 (\(P = 0.915\)) \(Q_{tw,\text{pot}}\) (\(P = 0.759\)), \(Q_{tw,\text{sup}}\) (\(P = 0.915\)), MRFD (\(P = 0.890\)), \(RT_{0.5}\) (\(P = 0.967\)), \(T_m\) (\(P = 0.514\)), \(T_{tw,\text{sup}}\) (\(P = 0.180\)), and \(T_{sk}\) (\(P = 0.181\)) were not significantly different between conditions. Thus, for contextual purposes, all twitch and force data are referred to as a percentage of pre-water immersion (% of PRE-WI) for all conditions. All results are displayed as means ± SE.

RESULTS

Thermal responses. Table 1 summarizes the \(T_m\), \(T_{core}\), and local \(T_{sk}\) by condition at the start of the experiments, immediately after water immersion, and immediately postrecovery contraction. The required \(T_m\) manipulation for each condition (\(T_m = 22/28/35.1/37.8/35.5^\circ C\)) was achieved in all individual sessions (\(T_m\) at time POST-WI, \(P < 0.001\)). \(T_m\) increased postexercise (measured only in part of the group) by up to 5.0 ± 0.8°C (strongest in COLD) but the final temperatures remained significantly different in the order of the conditions and showed no overlap between them (\(T_m\) at time POST-REC \(P < 0.001\); Table 1). Single-leg water immersion induced variations in \(T_{core}\) (at time \(POST\) \(P < 0.001\)); however, the total variation from PRE-WI was not greater than a mean of −0.6°C (\(\Delta T_{core}\)) in COLD and +0.5 (\(\Delta T_{core}\)) in HOT, with small changes (≤0.4°C \(\Delta T_{core}\)) during COOL, NEU, and WARM (see Table 1 for statistical comparisons from PRE-WI and from NEU). Post-water immersion \(T_{sk}\) over the thigh was reduced by −20°C to similar levels in all cooling trials. In response to heating, post-water immersion thigh \(T_{sk}\) was increased to −41°C in all heating trials. The mean water immersion times by condition are also reported in Table 1.

Brief contractions and muscle temperature. Force traces for the merged heated (WARM, HOT, and HOTENV) and cooled (COOL, COLD, and COLDENV) conditions compared with NEU are displayed in Fig. 2A.

Post-water immersion, iMVC force (Fig. 2, A and B), as well as \(VA_1\) and \(VA_2\) (Figs. 2B and 3B) remained nonsignificant (\(P = 0.659, 0.389, \text{and} 0.080\), respectively) across \(T_m\) conditions during the brief 3-s isometric contractions post-water immersion (POST-WI). However, \(T_m\) did significantly influence postimmersion \(Q_{tw,\text{pot}}\) (\(P < 0.001\)) and, thereby, \(Q_{tw,\text{sup}}\) (\(P = 0.026\)) augmenting or attenuating resting twitch amplitude by 1.9%/°C rise or fall in \(T_m\) respectively (\(P = 0.001;\) Fig. 3A). Postimmersion \(Q_{tw,\text{pot}}\) also developed force and relaxed at a faster rate as \(T_{tw,\text{sup}}\) increased; augmenting MRFD by 0.8 N·ms⁻¹·°C⁻¹ and decreasing \(RT_{0.5}\) time by 1.6 ms·°C⁻¹ rise in \(T_m\) (\(P < 0.001;\) Fig. 3C). To summarize, despite a clear effect of \(T_m\) on twitch characteristics, the data suggest voluntary muscle contractility (iMVC force) remained largely unaffected, and \(T_{tw,\text{sup}}\) had little influence on central drive (\(VA_1\) and \(VA_2\)) at time point POST-WI.

Sustained contractions and muscle temperature. Contrary to brief contractions, during the sustained efforts (ISO), mean iMVC force, as well as mean \(VA_1\) and \(VA_2\), were each significantly affected by \(T_m\) (Figs. 2B and 3B) showing significant (\(P < 0.001\)) and negative correlations with \(T_m\) (individual \(r = −0.65, −0.56, \text{and} −0.65\), respectively; group mean \(r = −0.95, −0.94, \text{and} −0.94, \text{respectively}\), reducing values by −0.7, −0.5, and −0.4%/°C increase in \(T_m\)). Mean force was also correlated to mean \(VA_1\) and \(VA_2\) (individual \(r = 0.57 \text{and} 0.69, \text{respectively};\) group mean \(r = 0.97 \text{and} 0.97, \text{respectively}\)). During the final seconds of the sustained contraction (119 s), a similar relationship between \(T_m\),
force, and VA was observed; although only force and VA2 maintained significance and correlation with \( T_m \) (Figs. 2B and 3B). Together, the results point to an increase in central fatigue as \( T_m \) increases, as shown by the simultaneous reduction in voluntary force and VA percentage (using both equations).

\( Q_{tw, pot} \) (peripheral fatigue; Fig. 3A) had an average reduction of 44 ± 4% (\( P < 0.001 \)) across conditions in response to fatigue (ISO). Interestingly, however, on completion of the ISO contraction, \( Q_{tw, pot} \) had an attenuated relationship with \( T_m \) (Fig. 3A), reaching a relatively temperature-independent level across COLDENV, COLD, COOL, NEU, WARM, and HOTENV. Where significant pairwise comparisons were observed (5 of 21), they occurred in relation to the HOT condition only. \( RT_{0.5} \) trended (\( P = 0.08 \)) and MRFD was significantly (\( P < 0.001 \)) influenced by ISO; however, contrary to \( Q_{tw, pot} \) force, both MRFD and \( RT_{0.5} \) maintained their previous relationship with \( T_m \) (\( P < 0.001 \) and \( P = 0.02 \)). Furthermore, despite the decline in \( Q_{tw, pot} \) during ISO, \( Q_{tw, sup} \) was actually increased (compared to POST-WI) in response to both fatigue and \( T_m \) (14 ± 6% and 0.5%/°C), signifying the rising failure in VA (Fig. 3, A and B). In summary, the results show the relative change in \( Q_{tw, pot} \) from POST-WI to the end of ISO is increased with rising \( T_m \), suggesting peripheral fatigue rates may be influenced by \( T_m \). Furthermore, the nonproportional increase in \( Q_{tw, sup} \) (compared to \( Q_{tw, pot} \)) highlights the increased failure in VA (i.e., greater central fatigue) over time and between conditions.

### Neuromuscular recovery and muscle temperature

After 20 s of recovery (POST-REC), iMVC force returned to 68 ± 3% (of PRE-WI), compared with the final seconds of the ISO contraction, where the average force was 22 ± 3% (of PRE-WI). Likewise, VA1 and VA2 also recovered significantly (\( P < 0.001 \)) from 57 ± 8 and 81 ± 5% during ISO to 90 ± 3 and 98 ± 1% at POST-REC, respectively. As such, the effect of \( T_m \) on muscle recovery and central fatigue was not evident as \( T_m \) increased.
across conditions for iMVC force, VA1, and VA2 were no longer significant (P = 0.498, 0.256, 0.095) at POST-REC and the short break in neural drive between ISO and POST-REC appeared to sufficiently stabilize VA, resulting in a largely temperature-independent effect (Fig. 2B).

Interestingly, while the recovery in $Q_{tw,pot}$, MRFD, and $RT_{0.5}$ at POST-REC did not return fully to POST-WI levels, $Q_{tw,sup}$ returned to the value close to that observed at time point POST-WI (15.9% POST-WI vs. 25.0% ISO vs. 13.4% POST-REC) (Fig. 3, A and C). Thus, it appears the changes in VA and force are not simply the result of changes in the twitch rate characteristics per se. Together, the fast recovery in VA, force and $Q_{tw,sup}$ suggests central fatigue was largely reliant on duration of the contraction, and/or influenced by the brief period of rest experienced between contractions.

**Ambient and muscle temperature comparisons.** Mean iMVC force during ISO significantly ($P < 0.01$) increased in HOTENV compared with HOT trials (Fig. 2B); however, no other significant effects of extreme T_a over and above the effect of T_m were observed.

**DISCUSSION**

The focus of this study was to quantify the relationship between muscle temperature and voluntary muscle activation (central fatigue) across a wide range of temperatures [i.e., 38.5 (moderate intensity whole body exercise) to 22°C (very cold tissue temperatures)], during both brief (3-s) and sustained (120-s) isometric exercises. Our primary finding was that different quadriceps muscle temperatures can induce significant changes in voluntary activation—and thereby total force production—when neural drive to the muscle was sustained, voluntary activation varied significantly and inversely with T_m, suggesting increases in T_m may accelerate central fatigue via afferent feedback, at least in individuals who are only moderately trained as the present test population. These findings show that local cooling has the inverse effect of local heating on VA, indicating a negative relationship across the T_m continuum from heating to cooling, for muscle temperatures in the range of 38.5 to 22°C.

**The interaction between peripheral and central fatigue.** In recent years, research has attributed the exercise-induced reduction in voluntary activation or “central fatigue”, to sensory feedback via metaboreceptive group III and IV muscle afferents (3, 4, 5, 58, 59). To prevent excessive peripheral fatigue development, muscle afferents are thought to aid regulation of exercise intensity, and exhaustion, by adding sensory contributions to exercise tolerance (5, 27). Within this paradigm, the
observed negative relationship between $T_m$ and VA could be attributable to two modes of action. The first includes regulated response to protect muscle homeostasis from faster peripheral fatigue development as $T_m$ increases. Previous research has shown that higher $T_m$ is associated with optimized muscle energetics (49) and improved short-duration performance (e.g., 22, 23, 53), but also with increases in metabolite production and peripheral fatigue during prolonged exercise, with the inverse effect observable during cooling (1, 6, 20, 25, 53). In fresh muscle, we observed a positive correlation between $T_m$ and $Q_{tw,pot}$ post-water immersion; however, $Q_{tw,pot}$ postexercise declined to a similar level, independent of starting and postexercise $T_m$ (Fig. 3A). This may support faster peripheral fatigue development rates at higher $T_m$. As such, the decline in VA could be mediated by increases in metabolite production (e.g., 1, 20) due to faster $Q_{10}$ effects and/or less efficient (faster) twitch fusion frequencies (13, 55, 63), along with the presence of a protective mechanism to avert excessive, unsustainable or intolerable peripheral fatigue development (3, 4, 5, 59). Accordingly, the attenuation of VA with increasing $T_m$ may occur as a regulatory response to protect muscle metabolic homeostasis from faster rates of metabolite production, a factor that would certainly be exacerbated by higher cardiovascular strain with rising $T_{sk}$ and $T_{core}$ (21, 29, 44).

The second possible mode of action comprises alterations in the relay of fatigue via group III/IV afferents at different $T_m$. The observed negative relationship between $T_m$ and VA could be attributable to two modes of action. The first includes regulated response to protect muscle homeostasis from faster peripheral fatigue development as $T_m$ increases. Previous research has shown that higher $T_m$ is associated with optimized muscle energetics (49) and improved short-duration performance (e.g., 22, 23, 53), but also with increases in metabolite production and peripheral fatigue during prolonged exercise, with the inverse effect observable during cooling (1, 6, 20, 25, 53). In fresh muscle, we observed a positive correlation between $T_m$ and $Q_{tw,pot}$ post-water immersion; however, $Q_{tw,pot}$ postexercise declined to a similar level, independent of starting and postexercise $T_m$ (Fig. 3A). This may support faster peripheral fatigue development rates at higher $T_m$. As such, the decline in VA could be mediated by increases in metabolite production (e.g., 1, 20) due to faster $Q_{10}$ effects and/or less efficient (faster) twitch fusion frequencies (13, 55, 63), along with the presence of a protective mechanism to avert excessive, unsustainable or intolerable peripheral fatigue development (3, 4, 5, 59). Accordingly, the attenuation of VA with increasing $T_m$ may occur as a regulatory response to protect muscle metabolic homeostasis from faster rates of metabolite production, a factor that would certainly be exacerbated by higher cardiovascular strain with rising $T_{sk}$ and $T_{core}$ (21, 29, 44).

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The second possible mode of action comprises alterations in the relay of fatigue via group III/IV afferents at different $T_m$.
Muscle temperature and central fatigue

thereby either modifying the sensation of peripheral fatigue (15, 46) or altering autonomic responses associated with group III/IV afferents (3). Opposing the first mode of action (faster peripheral fatigue rates), this second mechanism suggests a given level of peripheral fatigue could be perceived (cognitive) or tolerated (autonomic) differently with changes in muscle, local afferent nerve, and/or metaboreceptor temperature. Consequently, any alterations in afferent feedback, including perceptions of pain, fatigue, and discomfort may influence individuals’ limits of “sensory tolerance,” resulting in the observed variations in voluntary drive (VA; Figs. 2B and 3B) (5, 15, 46). In fact, previous research has shown that local tissue temperature is positively correlated with the firing rate of metabo-

ceptive muscle afferents (50, 51), signifying that afferent feedback of muscle fatigue to spinal or supraspinal centers (58) could be subject to analgesia at lower temperatures, with “sensed” fatigue accentuated as the local temperature increases. As such, VA (central fatigue) may be influenced by a change in the body’s sensitivity to peripheral fatigue signals at different local tissue temperatures. This mechanism may be testable using a post-fatigue limb blood flow occlusion combined with sustained exercise of the contralateral leg (e.g., 5, 8, 28).

Previous research considerations. In previous research, Tm independent of Tcore has been suggested as inconsequential to central fatigue onset (19, 40, 60). However, it has been shown that the magnitude of muscle afferent feedback is a combined function of 1) the level of peripheral fatigue and 2) the duration and magnitude of neural drive (5, 59). This confines interactions between peripheral state and central fatigue to exercise that requires a sustained neural drive, to overcome high metabolic disturbance, for extended periods of time (5, 46). This is contrary to conventional core factors (e.g., cerebral temperature and oxygenation), which could influence VA during brief contractions (39, 52, 60). Accordingly, previous literature reports relatively greater effects on VA observed during sustained (36, 42, 47, 63) or repeated high-intensity efforts (19). As such, it seems possible that the presence of sensed metabolic and thermal afferent feedback may explain the apparent contrast between the present findings and previous suggestions (60). That is, muscle temperature can influence VA, but during sustained, high-fatigue exercise only (19, 48) and in the moderately trained population that may rely more greatly on perceptual inference to regulate exercise.

In other research, it has been suggested that during isometric exercise, energy efficiency may increase with fatigue and cooling due to a lower neural stimulation and slower twitch fusion frequencies for a given force (7, 11, 49, 55). Although such changes in twitch durations are supported by this study (Fig. 3C), during the 20-s recovery, only modest returns to POST-WI were observed (see also Ref. 8). Despite this, the short break in neural drive appeared to adequately stabilize VA and force output at time point POST-REC. This suggests the changes in VA were not a solitary effect of altered tetanic fusion frequencies (8, 10, 61) and more likely dependent on the cessation in metabo receptive feedback from the exercising muscle (see also 28, 43, 48, 58).

Body temperature. The main approach underpinning this study was isolated quadriceps muscle temperature manipulation across a wide physiological range. Using single-leg water immersion, we successfully manipulated Tm (range of 16.5°C) to the required level for each condition, in all sessions. Importantly, postexercise Tm increased in all conditions, but the muscle temperature in each condition remained significantly lower than the next corresponding warmer condition. However, Tcore did also vary significantly with water temperature after water immersion. Even so, the changes in Tcore were modest and almost certainly exacerbated by local variations in tissue temperature around the rectum (12). On the basis of this, the large changes (outside a reasonable thermoneutral range) in superior central or cerebral temperatures (Tcore) were likely small, suggesting a mainly localized influence of temperature.

In support, during 120-s sustained contractions, studies spanning both cooling and heating report approximate increases in Q̇w,sup of 1.4% iMVC/°C rise in Tcore (13, 63). This would explain less than half of the change observed in the present study, suggesting a role for additional factors. Similarly, the mean estimated effects of Tcore in other comparable studies (passive core heating; 120-s sustained contractions; single twitches) equates ~6.3% reduction in VA per °C rise in Tcore (47), assuming all of the change in VA is due to Tcore. With the same methods of VA calculation applied to the present study (see Ref. 47) and attributing the observed change completely to Tm, VA reduces by 1.16%/°C of Tm change. Taken together, these data suggest the ratio of the impact of Tcore and Tm is 5.4 to 1. However, a better estimate of this ratio can be obtained using the observed Tcore and Tm changes in both studies [for Ref. 47, ΔTcore = 1.7°C, ΔTm = 3.5°C (estimated), ∆VA = 10.8%, and for the current study, ΔTcore = 1.2°C, ΔTm = 16.5°C, ∆VA = 19.2%] and then solve the two equations to obtain the coefficients for the respective Tcore and Tm contributions. This produces the equation: ∆%VA = 4.6 ΔTcore + 0.83 ΔTm, i.e., a ratio of 5.5 to 1 for core and muscle temperature contributions, respectively.

Limitations. It should be acknowledged that sustained isometric contractions may not reflect central fatigue at exhaustion, or during dynamic, whole body exercise. Certainly, before definitive conclusions can be drawn, research is needed to substantiate a role of body temperature (Tm, Tsk, and Tcore) on afferent feedback mechanisms during more complex exercise modalities. Furthermore, isometric exercise removes the contribution of muscle blood flow and mechanical efficiency to peripheral fatigue in the cold, a factor that would limit dynamic exercise performance with cooled muscles (35, 49).

In addition, local Tsk cannot be ruled out as a contributing factor to the reduction in VA in this study, and while the effect appears linear between VA and Tm (Table 2), the relevance of the present findings to body temperatures experienced during hyperthermia (42) remains to be confirmed.

Perspectives and significance

In recent research, divisions between the internal sense of effort (18) and the sensation of limb discomfort (3, 4, 5) have been reported (e.g., 17). While the sensory disconnection between effort and discomfort is logical (17, 18), the exclusion of either from the regulation and cessation of VA is harder to reconcile. Without both internal and external points of reference, the physical response to a given internal sense of effort is arbitrary; thus, to accurately regulate exercise (VA), there must be reliance on at least one, but most likely a large number, of sensory modalities. As such a noncritical multisensory estima-

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### Table 2. Statistical overview

<table>
<thead>
<tr>
<th>Figure Reference</th>
<th>POST-WI (Post-Heating/Cooling)</th>
<th>ISO-Mean (Mean of 120-s Contraction)</th>
<th>ISO-End (Last 1 s of 120-s Contraction)</th>
<th>POST-REC (After 20-s of Recovery)</th>
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<tr>
<td><strong>Force</strong></td>
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<tr>
<td>Figure 2B Main effect</td>
<td>$P = 0.659$</td>
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<td>$P = 0.016$</td>
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<td>Figure 2B and 3M Main effect</td>
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<td>Group mean correlation (VA vs. $T_m$)</td>
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<td>Figure 3A Main effect</td>
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<td>Figure 3B Main effect</td>
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<td>Figure 3C Main effect</td>
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Statistical analysis of Figs. 2B and 3A–C, including each outcome variable at each time point analyzed for the effect of muscle temperature. All statistics are displayed in the order of analysis, starting with the ANOVA ($P < 0.05$) followed by the number of significant pairwise comparisons ($P < 0.05$), the number of pairwise trends ($P < 0.1$), and the Pearson’s correlation coefficients ($P < 0.05$). Dashes indicate that no further action was taken when the main effect of an ANOVA was not significant.
tion based on internal, metabolic, mechanical, thermal, visual, proprioceptive sensations perhaps describes the perception and regulation of VA more appropriately. Existing models such as Bayesian Decision Theory (32) utilize multimodal sensory integration (31) to make inferences about internal perceptions (24), assuming there is no cardinal factor in the regulation of central drive (VA) (17), but instead a complex series of interactions between internal and peripheral sensory pathways (57) referenced against past experience (30). It is perhaps within this model that a role for muscle discomfort (metabo-reception, thermoreception, and mechanoreception) in the regulation of VA is most appropriate (Figs. 2B and 3B).

**Conclusion**

The present study examined the relationship between voluntary muscle activation (central fatigue) and muscle temperature during both brief (3-s) and sustained (120-s) isometric exercises. Our primary finding was that different quadriceps muscle temperatures can induce significant changes in voluntary activation—and thereby total force production—when neural drive is sustained for a prolonged effort; however, this effect is not exhibited during brief fresh or brief fatigued efforts. The observed reduction in voluntary drive likely arises out of the response to altered peripheral fatigue rates and/or an individual’s sensitivity to peripheral fatigue. Although this does not supersede the force-velocity improvements of high $T_m$ during short-duration dynamic exercise (e.g., 22, 23, 53), the effect of changes to “sensed” muscle feedback may still contribute significantly to limit peripheral fatigue tolerance within the integration of sensory factors associated with hyperthermic exercise (41). Accordingly, $T_m$ could assume a secondary or tertiary role in the reduction of VA during hyperthermia (42, 47) (5.5 to 1 core-to-muscle temperature ratio), particularly in the moderately trained populations that perhaps rely more heavily on perceptual inference to regulate effort. Although a possible explanation is presented here, more research is required before extensive conclusions can be drawn.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

Author contributions: A.B.L., S.H., and G.H. conception and design of research; A.B.L., performed experiments; A.B.L., analyzed data; A.B.L., S.H., and G.H. interpreted results of experiments; A.B.L., prepared figures; A.B.L., drafted manuscript; A.B.L., S.H., and G.H. edited and revised manuscript; A.B.L., S.H., and G.H. approved final version of manuscript.

**REFERENCES**