Medicine & Science IN Sports & Exercise
The Official Journal of the American College of Sports Medicine
www.acsm-msse.org

. . . Published ahead of Print

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Accepted for Publication: 26 September 2017

Medicine & Science in Sports & Exercise, Publish Ahead of Print
DOI: 10.1249/MSS.0000000000001441

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This work was supported by a University of Kent 50th Anniversary Scholarship. No external funding was received for this work. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The authors report no competing interests for this work. The results of the present study do not constitute endorsement by ACSM.

Abstract

The temporal structure, or complexity, of muscle torque output decreases with neuromuscular fatigue. The role of central fatigue in this process is unclear. **Purpose:** We tested the hypothesis that caffeine administration would attenuate the fatigue-induced loss of torque complexity. **Methods:** Eleven healthy participants performed intermittent isometric contractions of the knee extensors to task failure at a target torque of 50% maximal voluntary contraction (MVC), with a 60% duty factor (6 s contraction, 4 s rest), 60 min after ingesting 6 $mg \cdot kg^{-1}$ caffeine or a placebo. Torque and surface EMG signals were sampled continuously. Complexity and fractal scaling of torque were quantified using approximate entropy (ApEn) and the detrended fluctuation analysis (DFA) α scaling exponent. Global, central and peripheral fatigue were quantified using MVCs with femoral nerve stimulation. **Results:** Caffeine ingestion increased endurance by 30 ± 16% (mean ± SD, P = 0.019). Complexity decreased in both trials (decreased ApEn, increased DFA α; both P < 0.01), as global, central and peripheral fatigue developed (all P < 0.01). Complexity decreased significantly more slowly following caffeine ingestion (ApEn, –0.04 ± 0.02 vs. –0.06 ± 0.01, P = 0.004; DFA α, 0.03 ± 0.02 vs. 0.04 ± 0.03, P = 0.024), as did the rates of global (–18.2 ± 14.1 vs. –23.0 ± 17.4 $N.m.min^{-1}$, P = 0.004) and central (–3.5 ± 3.4 vs. –5.7 ± 3.9 $\%\cdot min^{-1}$, P = 0.02) but not peripheral (–6.1 ± 4.1 vs. –7.9 ± 6.3 $N.m.min^{-1}$, P = 0.06) fatigue. **Conclusion:** Caffeine ingestion slowed the fatigue-induced loss of torque complexity and increased the time to task failure during intermittent isometric contractions, most likely through central mechanisms.

Keywords: knee extension; exercise; non-linear dynamics; electromyography.

Introduction

The outputs of healthy physiological systems continuously fluctuate over time. These fluctuations are not simply random noise; it is thought that they contain key information about the system's control processes (1, 2, 3). The fluctuations within a physiological time series can be quantified in terms of their amplitude (sing the standard deviation [SD] or coefficient of variation [CV]), their frequency content (using fast Fourier transform), and/or their "complexity". Complexity, in this context, refers to the temporal structure of the fluctuations in a time series: a complex time series is one which fluctuates in an irregular and unpredictable way. Physiological systems are complex principally because they are systems of interacting components. The resulting outputs of such systems produce fluctuations that are statistically irregular (unpredictable) and frequently possess long-range or "fractal" correlations (as seen in heart rate, respiratory rate and muscle torque output, 1, 2, 3, 4, 5). These properties cannot be quantified using amplitude or frequency metrics. Instead, complexity can be quantified using metrics derived from information theory (such as approximate entropy, ApEn, which quantifies the degree of signal regularity, 5) and/or fractal dynamics (such as detrended fluctuation analysis, DFA, which can identify noise color and the presence of long-range correlations, 6). Far from being unwanted noise, complexity in a physiological time series is thought to endow the underlying system with the ability to quickly adapt to changing environmental conditions (3, 7).

Lipsitz and Goldberger (8) demonstrated that a loss of physiological complexity characterizes many disease states as well as healthy aging. Further work has suggested that there is an optimal

level of complexity in physiological outputs, and systems whose output becomes either more regular or more random than this optimum are less adaptable to subsequent functional challenges (3). The neuromuscular system, for example, has been shown to be subject to an aging-induced decrease in muscle torque output complexity, independently of a loss of muscle strength (3, 9). This loss reduces the adaptability of motor control, thus increasing the risk of failing a motor task, resulting in dropping objects, tripping, or falling over. We have recently demonstrated that neuromuscular fatigue reduces the complexity of muscle torque output during maximal contractions and submaximal contractions (2). This effect of fatigue demonstrates that Lipsitz and Goldberger's (8) 'loss of complexity hypothesis' can also be applied to healthy systems, within which complexity can be lost in minutes as opposed to years or decades in the case of disease and aging, respectively. The mechanism underpinning this fatigue-induced loss of complexity is, however, unclear.

Neuromuscular fatigue is classically defined as an exercise-induced reduction in maximal voluntary contraction (MVC) torque, which we operationally define as "global fatigue". Fatigue can be further subdivided as central (within the CNS) or peripheral (with in the muscle) in nature, with the neuromuscular junction representing the anatomical division between the two. Importantly, we have demonstrated that the fatigue-induced loss of complexity occurred during contractions performed exclusively above the critical torque (7; i.e., above the asymptote of the hyperbolic torque-duration relationship, wherein a metabolic steady state is not attainable; 10), which suggests that metabolite-mediated peripheral fatigue plays a dominant role in this effect. Nevertheless, central fatigue also developed during contractions performed above the critical

torque, although whether this influences torque output complexity independently of peripheral alterations is unclear.

To address the potential contribution of central processes in the fatigue-induced loss of torque complexity, we administered caffeine (1,3,7-trimethylxanthine) prior to fatiguing knee extensor contractions. Caffeine has been shown to enhance performance during exercise requiring dynamic contractions of a large muscle mass (11, 12, 13, 14). It has also been shown to have direct effects on neuromuscular output during isometric tasks using isolated muscle groups (15). Evidence suggests that caffeine can potentiate twitch and tetanic tensions (16, 17), increase MVC torque (15, 18), and increase spinal excitability (19, 20). More pertinently, caffeine has been repeatedly demonstrated to increase muscular endurance (15). Studies conducted on the knee extensors alone have found single-leg isometric time to task failure to increase by in excess of 20% (18, 21). The enhancement of exercise performance following caffeine administration has been attributed to both peripheral and central mechanisms. Although a direct effect of caffeine on skeletal muscle calcium kinetics has been inferred from measurements of dorsiflexor torque in response to low frequency electrical stimulation (17), millimolar concentrations of caffeine, toxic to humans, seem to be required to demonstrate this effect in isolated muscle preparations (22). As a result, it is thought that the primary ergogenic effect of caffeine is to enhance central drive, through an antagonistic effect on adenosine receptors (23). Adenosine preferentially inhibits the release of excitatory neurotransmitters (23), and thus decreases the firing rate of cortical neurons (19). The resulting central effects of caffeine in exercising humans are diverse, including reduced pain sensation and perceived exertion (24, 25), and increased spinal and/or supraspinal excitability (18).

Caffeine-induced adenosine receptor inhibition may influence motor function by reducing the disfacilitation of α-motoneurons or by increasing spinal excitability (20). These should maintain central drive to the motoneurone pool during muscle contractions (i.e. reduce the rate of central fatigue development) and thus delay task failure (19). Under these conditions, if the loss of torque output complexity is driven, in part, by central mechanisms, we would expect caffeine to blunt the development of central fatigue and delay the fatigue-induced loss of torque complexity during intense intermittent contractions. We therefore hypothesized that caffeine ingestion would reduce the rate at which torque output complexity fell during fatiguing contractions. Specifically, the experimental hypotheses tested were that pre-exercise caffeine ingestion would increase time to task failure and attenuate the rate of the fatigue-induced reduction in torque complexity, quantified by a slower rate of decrease in approximate entropy (ApEn; 5) and a slower rate of increase in the detrended fluctuation analysis (DFA) α scaling exponent (6).

Methods

Subjects. Eleven healthy subjects (7 male, 4 female; mean ± SD: age 26.1 ± 6.0 years; height 1.75 ± 0.08 m; body mass 66.8 ± 9.3 kg) gave written informed consent to participate in the study, which was approved by the ethics committee of the University of Kent, and which adhered to the Declaration of Helsinki. All subjects were non-smokers as nicotine is known to alter the rate of caffeine degradation (26). Although we did not measure habitual caffeine intake in this study, the subjects were habitual caffeine consumers, typically consuming the equivalent of 1-3 medium-strength cups of coffee daily, in the form of tea, coffee, chocolate and cola. Subjects were instructed to arrive at the laboratory in a rested state (having performed no

strenuous exercise in the preceding 24 hours) and to have consumed neither any caffeine nor alcohol in the preceding 24 hours. Subjects attended the laboratory at the same time of day (± 2 hours) during each visit.

Experimental design. Subjects were required to visit the laboratory on three occasions, with a minimum of 72 hours between each visit. During their first visit, subjects were familiarised with all testing equipment and procedures, and the settings for the dynamometer and stimulator were recorded. During the next two visits, a double-blind, repeated measures, randomized design was used to assess the effect of caffeine on the complexity of torque fluctuations during fatiguing submaximal intermittent isometric knee extension contractions.

Dynamometry. During all visits, subjects were seated in the chair of a Cybex isokinetic dynamometer (HUMAC Norm; CSMi, Massachusetts, USA), initialized and calibrated according to the manufacturer's instructions. Their right leg was attached to the lever arm of the dynamometer, with the seating position adjusted to ensure that the lateral epicondyle of the femur was in line with the axis of rotation of the lever arm. Subjects sat with relative hip and knee angles of 85° and 90°, respectively, with full extension being 0°. The lower leg was securely attached to the lever arm above the malleoli with a padded Velcro strap, while straps secured firmly across both shoulders and the waist prevented any extraneous movement and the use of the hip extensors during the isometric contractions. The seating position was recorded during the first visit and replicated during each subsequent visit.

Femoral nerve stimulation. Electrical stimulation of the right femoral nerve was used to assess neuromuscular fatigue processes. The anode, a carbon rubber electrode with adhesive gel (100 x 50 mm; Phoenix Healthcare Products Ltd., Nottingham, UK), was placed lateral to the ischial tuberosity, on the posterior aspect of the leg. The position of the cathode was established using a motor point pen (Compex; DJO Global, Guildford, UK), and determined based on the location in the femoral triangle giving the largest twitch and greatest peak-to-peak amplitude of the compound muscle action potential (M-wave) following single stimulation at 100 mA, using a constant-current, variable voltage stimulator (Digitimer DS7AH, Welwyn Garden City, UK). Following establishment of the precise cathode location, an Ag/AgCl electrode (32 x 32 mm; Nessler Medizintechnik, Innsbruck, Austria) coated in conductive gel was placed over the femoral nerve.

The establishment of the appropriate stimulator current was then performed as described by Pethick et al. (2). Briefly, current was incrementally increased (in steps of 20 mA) until knee extensor torque and the M-wave response to single twitches had plateaued, and was verified with stimulation delivered during a contraction at 50% MVC to ensure a maximal M-wave during an isometric contraction was also evident. The stimulator current was then increased to 130% of the current producing a maximal M-wave. In all subsequent trials, doublet stimulation (two 200 µs pulses with 10 ms interpulse interval) was used.

Surface EMG. The EMG of the vastus lateralis was sampled using Ag/AgCl electrodes (32 x 32 mm; Nessler Medizintechnick, Innsbruck, Austria). Prior to attachment of the electrodes, the skin of the subjects was shaved, abraded and then cleaned with an alcohol swab over the belly of the

muscle, in order to reduce impedance. The electrodes were placed on the prepared skin over the belly of the muscle in a direction parallel to the approximate alignment of the muscle fibers. A reference electrode was placed on the prepared skin medial to the tibial tuberosity. Care was taken to ensure that the electrode locations were identical between sessions. The raw EMG signals were sampled at 1 kHz, amplified (gain 1000; Biopac MP150; Biopac Systems Inc., California, USA) and band-pass filtered (10-500 Hz; Biopac MP150; Biopac Systems Inc., California, USA).

Protocol. All visits followed a pattern of data acquisition similar to that which we have previously reported (2, 7); beginning with the instrumentation of the subjects and the establishment of the correct dynamometer seating position and supramaximal stimulation response. Subjects then performed a series of brief (3 second) MVCs to establish their maximum torque. These contractions were separated by at least 60 seconds rest, and continued until the peak torque in three consecutive contractions were within 5% of each other. Subjects were given a countdown, followed by very strong verbal encouragement to maximize torque. The first MVC was used to establish the fresh maximal EMG signal, against which the subsequent EMG signals were normalized (Data analysis; see below). The second and third MVCs were performed with femoral nerve stimulation; at 1.5 seconds into the contraction, during a plateau in torque, a doublet was delivered and a further doublet delivered at rest 2 seconds after the contraction. The pulses superimposed on the contraction tested the maximality of the contraction and provided the fresh voluntary activation, while the pulses after the contraction established the fresh potentiated doublet torque (Data analysis; see below). All subsequent contractions with femoral nerve stimulation were conducted in this manner.

Following the establishment of maximum torque, subjects ingested gelatin capsules containing either 6 $mg \cdot kg^{-1}$ caffeine (Myprotein, Cheshire, UK) or the same amount of all-purpose flour (placebo). A person not involved in the study prepared and arranged the order of the capsules, ensuring that both experimenter and participant were blinded to the experimental treatment condition. After ingestion of the capsules, subjects rested in the laboratory and repeated the process of establishing maximum torque after one hour, when plasma caffeine concentration has been shown to reach its peak (27). Subjects then rested for a further 10 minutes before performing the experimental trial (see below).

Experimental trials. Subjects performed intermittent isometric knee extension contractions until task failure. The target torque was 50% MVC, and was based on the highest instantaneous torque recorded during the pre-capsule ingestion MVCs in the first experimental session. The duty cycle for the contractions was 0.6; with contractions held for 6 seconds and being followed by 4 seconds rest. Subjects were instructed to match their instantaneous torque with a target bar superimposed on the display in front of them and were required to continue matching this torque for as much of the 6 second contraction as possible. At the end of each minute (i.e. every sixth contraction), subjects performed a 3 second MVC, accompanied by femoral nerve stimulation. Immediately following this MVC, subjects were asked to rate their perceived exertion, measured using the Borg Scale (28). The contractions were performed until task failure, the point at which the subjects failed to reach the target torque on three consecutive occasions, despite strong verbal encouragement. Subjects were not informed of the elapsed time during the trials, but were informed of each "missed" contraction. After the third missed contraction, subjects were

instructed to immediately produce an MVC, which was accompanied by femoral nerve stimulation.

Data acquisition and participant interface. Data acquisition was performed in the same manner as described in Pethick et al. (2). Briefly, all peripheral devices were connected via BNC cables to a Biopac MP150 (Biopac Systems Inc., California, USA) and a CED Micro 1401-3 (Cambridge Electronic Design, Cambridge, UK) interfaced with a personal computer. All signals were sampled at 1 kHz. The data were collected in Spike2 (Version 7; Cambridge Electronic Design, Cambridge, UK). A chart containing the instantaneous torque was projected onto a screen placed ~1 m in front of the participant. A scale consisting of a thin line (1 mm thick) was superimposed on the torque chart and acted as a target, so that subjects were able to match their instantaneous torque output to the target torque during each test.

Data analysis. All data were analyzed using code written in MATLAB R2013a (The MathWorks, Massachusetts, USA). The data analysis focused on three specific areas: 1) basic measures of torque and EMG; 2) measures of central and peripheral fatigue; and 3) the variability and complexity of torque output.

Torque and EMG: The mean and peak torque for each contraction in both trials were determined. The mean torque was calculated based on the steadiest five seconds of each contraction, with MATLAB code identifying the 5 seconds of each contraction with the lowest standard deviation. This criterion reliably extracts the contraction and rejects the torque rise and fall sections during contraction onset and termination. Moreover, other window lengths produce almost identical

results when calculating ApEn during muscular contractions (29). The point of task failure was determined as described in Pethick et al. (2): the mean torque produced during the first five contractions was calculated and task failure was deemed to occur when the mean torque recorded during three consecutive contractions was more than 5 N·m below the mean torque of the first five contractions, with the first of these contractions being considered the point of task failure.

The EMG output from the vastus lateralis for each contraction was full-wave rectified during each 5 second window. The average rectified EMG (arEMG) was then calculated and normalized by expressing the arEMG as a fraction of the arEMG obtained during an MVC from the fresh muscle performed at the beginning of the trial.

Central and peripheral fatigue: Measures of central and peripheral fatigue were calculated based on the stimuli delivered during and after the MVCs performed pre-test, at the end of each minute of the fatiguing contractions and at task failure. Peripheral fatigue was evidenced by a fall in the potentiated doublet torque. Central fatigue was evidenced by a decline in voluntary activation, quantified using the twitch interpolation technique (30):

$$Voluntary\ activation\ (\%) = (1 - superimposed\ doublet/resting\ doublet) \times 100 \quad [1]$$

where the superimposed doublet was that measured during the contraction of interest and the potentiated doublet was measured at rest 2 seconds after the contraction.

Variability and complexity: All measures of variability were calculated using the steadiest five seconds of each contraction, identified as the five seconds containing the lowest standard deviation (SD). The amount of variability in the torque output of each contraction was measured using the SD and CV. The SD provides a measure of the absolute amount of variability in a time series, while the CV provides a measure of the amount of variability in a time-series normalized to the mean of the time series.

The temporal structure, or complexity, of torque output was examined using multiple time domain analyses. The regularity of torque output was determined using approximate entropy (ApEn; 5) and the temporal fractal scaling of torque was estimated using detrended fluctuation analysis (DFA; 6). Sample entropy was also calculated, but as shown in Pethick et al. (2) this measure did not differ from ApEn, and was not included in the present analysis. As detailed in Pethick et al. (2), ApEn was calculated with the template length, m, set at 2 and the tolerance, r, set at 10% of the standard deviation of torque output, and DFA was calculated across time scales (57 boxes ranging from 1250 to 4 data points). The values returned by ApEn provide a measure of signal regularity. Values close to 0 represent regular signals (for example, a sinusoidal time series), whereas higher values (for torque output, typically in the range of 0.40-0.90) represent less regular and, thus, more complex time series (5). Whilst ApEn provides a measure of signal regularity, a signal with high values for ApEn, such as white noise, is not necessarily physiologically complex. To distinguish complexity from randomness, we used DFA analysis (6). In this analysis, a DFA α value of 0.5 represents uncorrelated white noise (which has a flat power spectrum). Pink noise [DFA α exponent = 1.0], in contrast, has a power spectral density of 1/f, where f is frequency. Brownian noise, or "red noise" has a power spectral density of $1/f^2$,

yielding a DFA α exponent of 1.5. Thus, a DFA α exponent shifting away from 1.0 towards 1.5 is a shift towards less complex "Brownian" noise.

Statistics. All data are presented as means ± SD. Two-way analysis of variance (ANOVAs) with repeated measures were used to test for differences between conditions and time points, and for a condition x time interaction for MVC torque, arEMG, potentiated doublet torque, voluntary activation, variability and complexity. The variability and complexity measures were analyzed using means from the first minute and final minute before task failure. When main effects were observed, Bonferroni-adjusted 95% paired-samples confidence intervals were used to identify specific differences. The rates of change in all parameters were analyzed using Student's paired-samples t-tests. If paired comparisons were not normally distributed (determined using the Shapiro-Wilk test) the Wilcoxon signed-rank test was used. Only the time to task failure comparison failed this normality test. Results were deemed statistically significant when $P < 0.05$.

Results

Preliminary measures. The contractile properties of the knee extensors and electrical activity of the vastus lateralis are shown in Table 1. These data were obtained immediately before and one hour after capsule ingestion and were intended to assess the effects of caffeine in a rested state. Caffeine ingestion resulted in an increase in MVC torque of 8.8 ± 13.1 N·m (or 4.0 ± 5.3%; 95% paired samples confidence intervals [95% CIs]: 0.1, 17.6 N·m); and an increase in maximal

absolute EMG activity (EMG_{max}; 95% CIs 0.006, 0.5 mV). Placebo ingestion resulted in no significant change in any of the variables.

Time to task failure, torque and EMG. Caffeine ingestion significantly increased time to task failure by 2.4 ± 2.6 min (95% CIs 0.7, 4.1 min) or 30 ± 16% (Table 2). Task failure occurred when subjects were no longer able to achieve the target torque (104.7 ± 26.2 N·m), despite a maximal effort. Both conditions resulted in significant decreases in MVC torque ($F_{1,10}$ = 87.04, P < 0.001; Figure 1; Table 2), with neither the peak nor the mean MVC torque at task failure being significantly different from the torque produced during the submaximal contractions. At task failure, there was no significant difference between the conditions for the peak MVC torque (placebo vs. caffeine: 106.6 ± 20.2 vs. 114.0 ± 23.8 N·m; 95% CIs –20.0, 5.1 N.m). However, at the time point in the caffeine condition equivalent to task failure in the placebo condition (henceforth referred to as isotime), MVC torque was significantly higher (caffeine vs. placebo: 136.0 ± 24.4 vs. 106.6 ± 20.2 N·m; 95% CIs 16.2, 42.8 N.m; Figure 1), indicating subjects still had a significant reserve of maximal torque. Furthermore, the rate of decrease in MVC torque was significantly attenuated in the caffeine condition (caffeine vs. placebo: –18.2 ± 14.1 vs. –23.0 ± 17.4 $N \cdot m \cdot min^{-1}$; 95% CIs –7.7, –1.9 $N \cdot m \cdot min^{-1}$; Table 2). The arEMG of the vastus lateralis increased over time in both conditions ($F_{1,10}$ = 17.0, P = 0.002), reaching 71.4 ± 16.4% in the placebo condition and 78.3 ± 22.5% in the caffeine condition at task failure.

Peripheral and central fatigue. Both conditions resulted in significant reductions in potentiated doublet torque ($F_{1,9}$ = 69.07, P < 0.001; Table 2), indicating the presence of peripheral fatigue. The values attained at task failure were not significantly different between the conditions

(placebo vs. caffeine: 62.2 ± 15.2 vs. 57.7 ± 17.1 N·m; 95% CIs –5.5, 14.5 N·m), nor was the value at task failure in the placebo condition different from the value at isotime in the caffeine condition (95% CIs –6.7, 11.4 N·m). The rate of decrease in potentiated doublet torque was not significantly different between conditions (95% CIs –2.9, 0.1 $N \cdot m \cdot min^{-1}$). Voluntary activation significantly declined in both conditions ($F_{1,9} = 54.4$, $P < 0.001$; Table 2), indicating the presence of central fatigue. The values attained at task failure were not significantly different between the conditions (placebo vs. caffeine: 64.0 ± 9.7 vs. 73.3 ± 19.5%; 95% CIs –21.2, 2.4%). The value attained at task failure in the placebo condition was, however, significantly different from the value at isotime in the caffeine condition (77.0 ± 11.6%; 95% CIs –25.7, –0.3%). The rate of decrease in voluntary activation was significantly attenuated in the caffeine condition (95% CIs –4.0, –0.4 $\%.min^{-1}$; Table 1).

Variability and complexity. Both conditions resulted in a significant increase in the amount of variability, as measured by the SD ($F_{1,10} = 39.30$, $P < 0.001$) and CV ($F_{1,10} = 86.62$, $P < 0.001$; Table 3). The values attained at task failure for the SD (95% CIs –1.6, 3.4 N·m) and CV (95% CIs –1.5, 3.4%) were not significantly different between conditions (Table 3). The SD (95% CIs –0.1, –6.0 N·m) and CV (95% CIs –0.7, –5.8%) were both significantly lower at isotime in the caffeine condition compared with task failure in the placebo condition (SD 4.5 ± 2.7 vs. 7.5 ± 2.7 N·m; CV 4.5 ± 2.3 vs. 7.8 ± 1.3%). Both the rates of increase in SD (95% CIs –0.7, –0.1 $N \cdot m \cdot min^{-1}$) and CV (95% CIs –0.7, –0.1 $\%.min^{-1}$) were significantly lower in the caffeine condition.

Example contractions from a representative participant are shown in Figure 2. Complexity decreased as fatigue developed in both conditions, as measured by ApEn ($F_{1,10}$ = 93.74, P < 0.001) and DFA α ($F_{1,10}$ = 53.62, P < 0.001; Table 3). ApEn significantly decreased as the trials progressed, with the values at task failure being not significantly different between the conditions (placebo vs. caffeine: 0.13 ± 0.05 vs. 0.15 ± 0.07; 95% CIs –0.09, 0.04, Table 3, Figure 2 and 3). At isotime in the caffeine condition, ApEn remained significantly higher than at task failure in the placebo condition (0.27 ± 0.12; 95% CIs 0.02, 0.26; Figure 2 and 3). The rate of decrease in ApEn was significantly lower in the caffeine condition (95% CIs –0.006, –0.03; Table 3). DFA α significantly increased, becoming more Brownian, as the trials progressed, with the values at task failure being not significantly different between the conditions (placebo vs. caffeine: 1.61 ± 0.05 vs. 1.60 ± 0.08; 95% CIs –0.07, 0.08). At isotime in the caffeine condition, DFA α was significantly lower than at task failure in the placebo condition (1.53 ± 0.06; 95% CIs –0.002, –0.1). The rate of increase in DFA α was significantly lower in the caffeine condition (95% CIs –0.02, –0.01).

Perceived exertion. Perceived exertion increased over time in both the placebo and caffeine conditions (Table 2). Perceived exertion was significantly lower at the end of the first minute of the caffeine condition (placebo vs. caffeine: 12.9 ± 1.2 vs. 11.8 ± 1.4; 95% CIs –1.8, –0.3), and also at isotime in the caffeine condition compared to task failure in the placebo condition (17.2 ± 1.5; 95% CIs –3.8, –1.2). There was no significant difference in perceived exertion between conditions at task failure (95% CIs –0.2, 0.5). The rate of increase in perceived exertion was significantly lower in the caffeine condition (95% CIs –0.3, –0.04; Table 2).

Discussion

The major novel finding of the present study was that caffeine ingestion slowed the loss of torque complexity, consequent to the slower development of neuromuscular fatigue. These responses were accompanied by increased time to task failure. Both the placebo and caffeine conditions were associated with a loss of MVC torque and the development of significant central and peripheral fatigue, which were accompanied by increasingly Brownian (DFA α = 1.50) fluctuations in torque output. Caffeine ingestion significantly attenuated the rate at which fatigue developed, such that at task failure common values were observed for torque complexity, MVC torque, and central and peripheral fatigue. These experiments reiterate that the loss of torque complexity is coupled to the neuromuscular fatigue process and, crucially, demonstrate that this coupling remains following a caffeine-induced slowing of fatigue development. This study is the first to show that a component of the loss of knee extensor torque complexity can be attributed to central processes, because MVC and voluntary activation where higher at isotime in the caffeine condition, whilst the degree of peripheral fatigue development was not different from placebo.

Effect of caffeine on torque complexity and fatigue. The present study demonstrated that the fatigue-induced loss of torque complexity we have previously reported (2, 7) can be slowed by the ingestion of caffeine. As fatigue developed, ApEn decreased (indicating increased signal regularity) and DFA α increased (indicating increasingly Brownian fluctuations), reaching common values at task failure in each condition. However, the rate at which ApEn decreased and the DFA α exponent increased were significantly attenuated following caffeine ingestion (Table 3). Moreover, at isotime in the caffeine condition ApEn was significantly higher, and DFA α

exponent was significantly lower, than at task failure in the placebo condition (Figure 3), both reflecting a lower complexity of muscle torque. This suggests that the adaptability of motor control (the ability to accurately adjust output to meet altered task demands), which measures of complexity are thought to reflect (1, 8), was maintained for longer in the caffeine trial (3, 7). This is supported by the smaller diminution of MVC torque at isotime in the caffeine condition (Figure 1, Table 2), and further suggests that changes in torque complexity are closely related to changes in the relative demands of the task.

The increase in time to task failure and slowing of the loss of complexity following caffeine ingestion were accompanied by a significant slowing in the rates of global and central fatigue development (Table 2). The values for MVC torque and potentiated doublet torque at task failure were not significantly different between the two conditions, indicating that subjects continued exercising to the same limiting values (i.e. the point at which task demands equalled maximal output) in each condition and that it simply took longer to reach these values following caffeine ingestion. Furthermore, at isotime in the caffeine condition both MVC torque and voluntary activation remained significantly higher than at task failure in the placebo condition, indicating that subjects still had a significant reserve of maximal torque, and thus of exercise capacity (Figure 1). In contrast, there was no difference in the decrease in the potentiated doublet torque at isotime between caffeine and placebo (Figure 1). Thus, the primary effect of caffeine in the present experiments appeared to be centrally mediated, which maintained voluntary activation and thus MVC torque beyond the task failure point in the placebo condition. This, in turn, extended time to task failure.

Physiological bases for changes in torque complexity with caffeine ingestion. The ability of caffeine to enhance muscular endurance has long been established, with this effect being manifest in a range of exercise tasks (11, 13, 18). The results of the present study also demonstrated that caffeine ingestion increased the time to task failure of the knee extensors during single leg intermittent isometric exercise by ~30% (Table 2). This performance enhancement is of similar magnitude to that previously observed for isometric contractions of the knee extensors (19, 21). Although the ability of caffeine to improve performance has long been recognised, the exact mechanism(s) behind this effect remains obscure. There is considerable evidence to suggest that the action of caffeine is on the central nervous system (19, 23, 31). However, many other mechanisms, such as a direct effect on skeletal muscle calcium kinetics (17) and an antinociceptive effect (25), have been proposed, and it has been suggested that the performance-enhancing effect of caffeine is likely to occur through multiple mechanisms (32, 33).

Caffeine acts as an adenosine antagonist (31), preventing adenosine from exerting an inhibitory effect on a variety of cortical and spinal neurons, including those related to motor command (23, 31). Indeed, caffeine has been demonstrated to increase spinal excitability (20) or offset its decline during fatiguing contractions (36). The results of the present study indicate that the rate of central fatigue development, as measured by a decrease in voluntary activation, is slowed following caffeine ingestion (Table 2). This could be indicative of a greater ability to excite the motor unit pool in the face of fatigue, be it through an increase in spinal excitability (20) or maintenance of optimal descending drive (35). It should be noted, however, that while caffeine ingestion has been demonstrated to offset a decline in spinal excitability, increased spinal

excitability did not offset the central activation failure seen with fatigue (34). MVC torque, voluntary activation, and ApEn were higher, and the DFA α exponent lower, at isotime in the absence of a difference in the level of peripheral fatigue. Thus, the difference in the fatigue-induced loss of torque complexity between placebo and caffeine is most likely associated with central mechanisms which maintain voluntary activation as exercise progresses. We are unable to identify the precise location of these central changes in the CNS and their effects on motor unit activation from the present data. However, given the apparent coherence between motor unit spike trains and force fluctuations (36, 37), the difference in torque output complexity between the caffeine and placebo trials most likely comes from centrally-induced differences in the ensemble activity of the motor unit pool. Direct measurement of individual motor units (e.g., 38), rather than analysis of the motor unit action potential trains recorded by bipolar EMG (as performed in the present study), will be required to confirm this.

We have previously demonstrated that only metabolically-mediated peripheral fatigue is capable of inducing the chain of events leading to a loss of torque complexity (7). A slowing of peripheral fatigue development with caffeine ingestion has previously been observed by Kalmar and Cafarelli (19), and could also account for caffeine's ergogenic effect. It has been speculated, based on observations of a slowing of peripheral fatigue (19) and the potentiation of contraction force during low frequency fatiguing stimuli (16, 17), that caffeine acts to decrease sarcoplasmic reticulum Ca^{2+} uptake, which would increase Ca^{2+} availability and serve to maintain submaximal force production in recruited muscle fibres (17, 19). It must be noted, though, that measurable effects on Ca^{2+} release or reuptake have generally only been observed during caffeine administration in the millimolar range in animal models (e.g., 22), which would be toxic to

humans (23). Furthermore, the complexity of torque output decreased late in the contractions in the caffeine trial without the further development of peripheral fatigue (Figure 1B vs. Figure 3). This seems to rule out a direct peripheral contribution to the difference in complexity between conditions in this study.

Limitations

This study's findings are subject to a number of limitations. Although we administered a dose of caffeine commonly used in the literature (6 $mg.kg^{-1}$ body mass) and provided an hour of passive rest for effect, we did not take measurements of plasma caffeine to confirm the kinetics and amplitude of systemic caffeine appearance. Nevertheless, the effects we observed in this study (increased MVC, maximal muscle activity, increased time to task failure) are consistent with the known effects of caffeine on muscle function. Thus, the effects on torque complexity between conditions are likely to be caffeine-mediated. We were also unable to identify the location of the central effects of caffeine, which could have been achieved with the use of transcranial and cervicomedullary stimulation during the MVCs. The present work was, however, intended to determine if there was any central effect of caffeine on torque complexity; voluntary activation derived from femoral nerve stimulation was therefore adequate to test the present hypothesis. Finally, as mentioned above, our electromyographic data were not able to separate and characterize individual motor unit recruitment thresholds and firing rate. High-density electrode arrays will be required to study the coherence between motor unit behaviour and torque complexity in a sufficiently large number of motor units in future studies.

Conclusion. The present study has demonstrated that caffeine ingestion slowed the fatigue-induced loss of torque complexity during isometric knee extensor exercise. Caffeine ingestion also slowed the rates of global and central fatigue development. The higher MVC torque and voluntary activation observed at isotime with caffeine ingestion compared to placebo, in the absence of differences in the degree of peripheral fatigue, suggests that the central effects of caffeine played a dominant role in the slowing of the fall in torque output complexity. The loss of motor output complexity thus appears to be tightly coupled to the neuromuscular fatigue process and remains so after caffeine administration. These results are the first to provide clear evidence of a central contribution to the loss of torque complexity with neuromuscular fatigue.

Acknowledgements:

Funding. This work was supported by a University of Kent 50th Anniversary Scholarship. No external funding was received for this work.

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Conflict of interest:

The authors report no competing interests for this work. The results of the present study do not constitute endorsement by ACSM.

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Figure legends

Figure 1. Influence of caffeine ingestion on neuromuscular fatigue responses to contractions at 50% MVC.

Panel A shows the torque produced during an MVC performed at the end of each minute in both conditions (placebo, black circles; caffeine, white circles). The final data point in each condition represents the MVC produced at task failure. In the caffeine condition, the penultimate data point represents the MVC produced at the same time point (to the nearest minute) as task failure in the placebo condition (isotime). Panels B and C present the potentiated doublet and voluntary activation responses, representing peripheral and central fatigue, respectively. Values are mean ± SD, n = 11. *significantly different from the placebo condition ($P < 0.05$).

Figure 2. Raw torque output during representative contractions in the placebo and caffeine trials in a single participant.

The placebo condition shows contractions in the first minute (contraction #2) and at task failure (contraction #22, representing the last successful contraction before failure). The caffeine condition shows contractions performed at identical time points to those above, with a third contraction representing task failure in the caffeine trial (contraction #33). ApEn, approximate entropy; DFA α, detrended fluctuation analysis α exponent. Note the similar complexity at the beginning and the end of each condition, but the more rapid loss of complexity in the placebo condition.

Figure 3. Influence of caffeine ingestion on torque output complexity during contractions performed at 50% MVC.

Panel A shows the effect of caffeine ingestion on approximate entropy (ApEn), panel B shows the detrended fluctuation analysis α scaling exponent (DFA α exponent). The black symbols represent the placebo condition, white symbols caffeine. Note the complexity at the start of the trials and at task failure are similar, but at isotime complexity is higher in the caffeine trial (shown but the higher ApEn and lower DFA α values respectively). Values are mean ± SD, n = 11. *significantly different from placebo ($P < 0.05$).

Figure 1

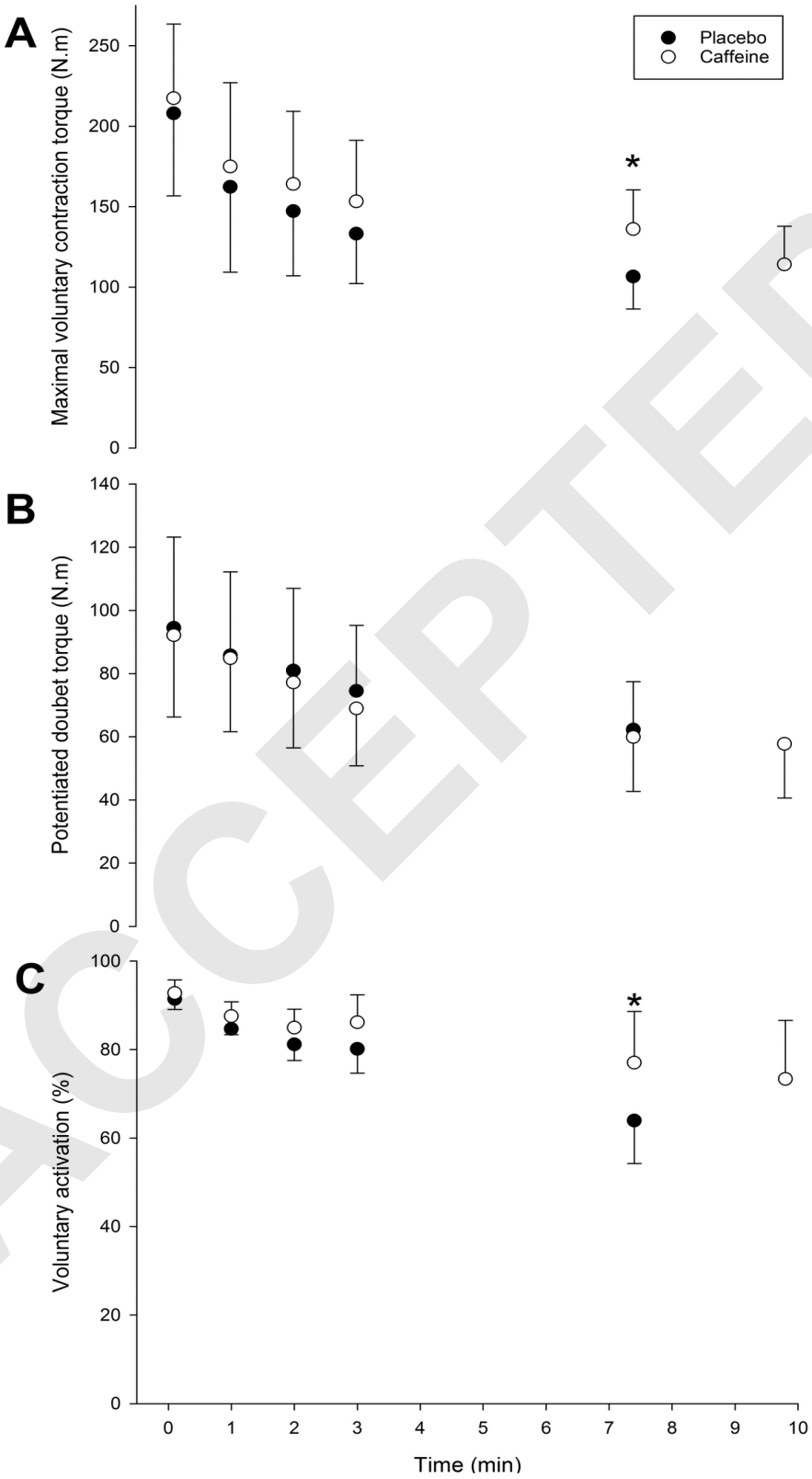

Figure 2

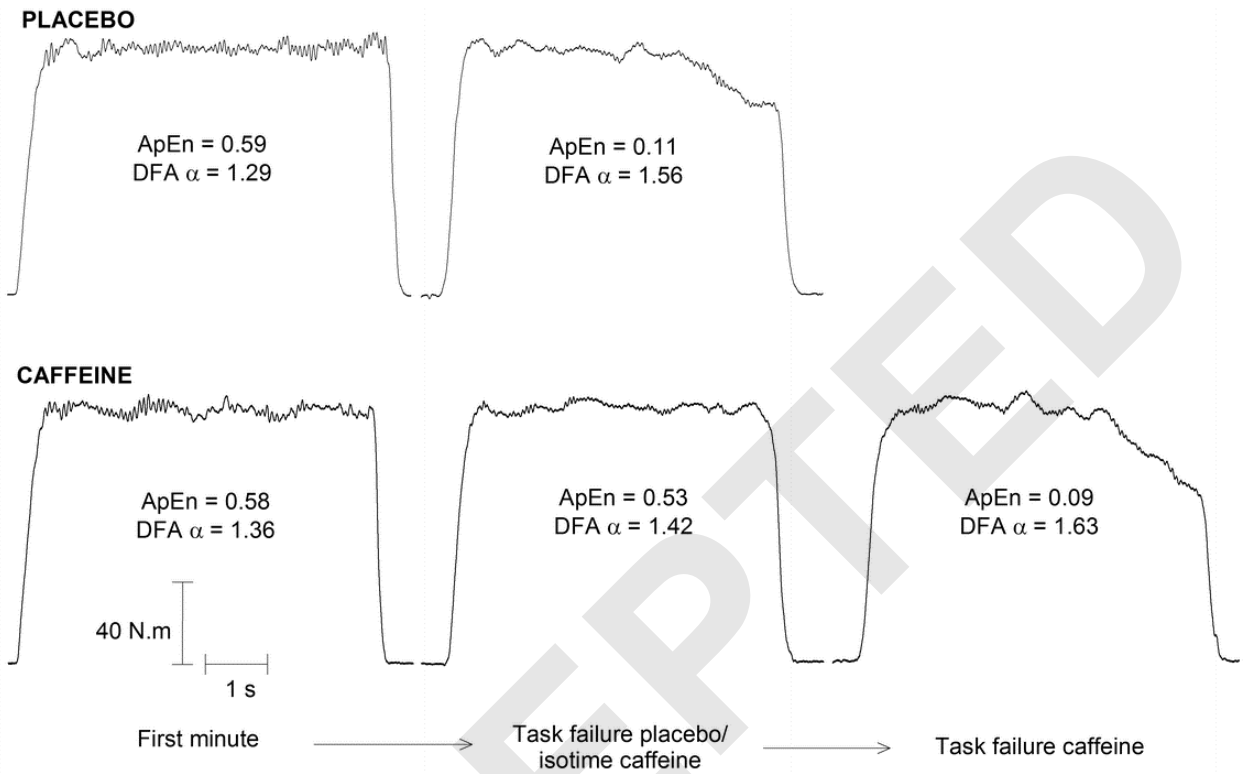

Figure 3

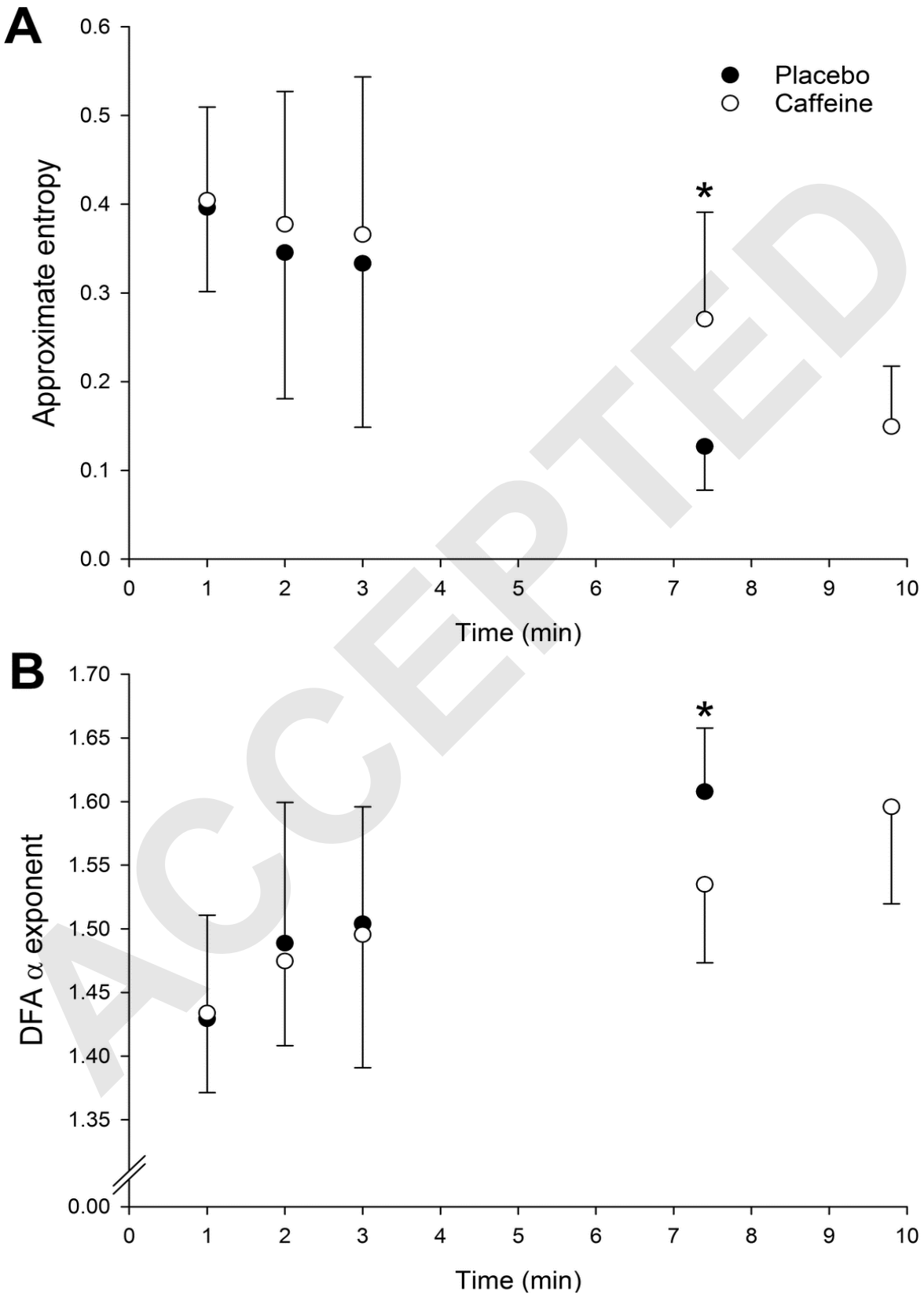

Table 1. Effects of caffeine and placebo ingestion on control measurements

	Placebo		Caffeine	
Parameter	Pre	Post	Pre	Post
MVC, N·m	210.5 ± 51.3	207.9 ± 53.0	209.3 ± 46.1	217.4 ± 52.1*
Doublet, N·m	98.4 ± 28.7	94.5 ± 26.5	94.7± 25.9	92.1 ± 23.3
VA, %	92.2 ± 2.4	91.4 ± 1.3	92.5 ± 3.0	92.8 ± 3.2
EMG_{max}, mV	0.27± 0.10	0.28 ± 0.10	0.28 ± 0.09	0.31 ± 0.09*

Values are means ± SD, n = 11. MVC, maximal voluntary contractions; VA, voluntary activation; EMG_{max}, maximal electrical activity of the vastus lateralis; mV, millivolts; * = significantly different from Pre ($P < 0.05$).

Table 2. Voluntary torque, potentiated doublet torque, voluntary activation, EMG and RPE responses during contractions in the placebo and caffeine trials.

Parameter	Placebo	Caffeine	CIs
Time to task failure, min	7.2 ± 5.6	9.5 ± 7.9[#]	0.7, 4.1
Global fatigue			
Pre-exercise MVC, N·m	207.9 ± 53.0	217.4 ± 52.1	–22.5, 3.7
MVC at isotime, N·m	–	136.0 ± 24.4[#]	16.2, 42.8
Peak MVC at task failure, N·m	106.6 ± 20.2[*]	114.0 ± 23.8[*]	–20.0, 5.1
Mean MVC at task failure, N·m	85.4 ± 13.8[*]	93.1 ± 17.3[*]	–14.4, 1.1
ΔMVC/Δt, N·m·min^{-1}	–23.0 ± 17.4	–18.2 ± 14.1[#]	–7.7, –1.9
Peripheral fatigue			
Pre-exercise doublet, N·m	94.5 ± 26.5	92.1 ± 23.3	–4.4, 8.3
Doublet at isotime, N·m	–	59.9 ± 17.2	–6.7, 11.4
Doublet at task failure, N·m	62.2 ± 15.2[*]	57.7 ± 17.1[*]	–5.5, 14.5
% Change at task failure	32.4 ± 7.1	36.2 ± 10.4	–11.3, 3.8
Δdoublet/Δt, N·m·min^{-1}	–7.9 ± 6.3	–6.1 ± 4.1	–2.9, 0.1
Central fatigue			
Pre-exercise VA, %	91.4 ± 1.3	92.8 ± 3.2	–5.4, 2.2
VA at isotime, %	–	77.0 ± 11.6[#]	–25.7, –0.3
VA at task failure, %	64.0 ± 9.7[*]	73.2 ± 19.5[*]	–21.2, 2.4
% Change at task failure	30.0 ± 10.9	21.1 ± 14.4	–0.4, 18.0
ΔVA/Δt, %/min	–5.7 ± 3.9	–3.5 ± 3.4[#]	–4.0, –0.4
Surface EMG			
arEMG at task beginning, % MVC	54.5 ± 9.4	56.3 ± 11.9	–13.4, 9.8
arEMG at isotime, % MVC	–	73.3 ± 5.9	–19.2, 15.6
arEMG at task failure, % MVC	71.4 ± 16.4[*]	78.3 ± 22.5[*]	–25.2, 11.4
ΔarEMG/Δt, % MVC/min	3.4 ± 3.7	3.4 ± 2.9	–1.5, 1.5
RPE			
RPE at task beginning	12.9 ± 1.2	11.8 ± 1.4[#]	–1.8, –0.3
RPE at isotime	–	17.2 ± 1.5[#]	–3.8, –1.2
RPE at task failure	19.7 ± 0.5[*]	19.6 ± 0.5[*]	–0.2, 0.5
ΔRPE/Δt	1.3 ± 0.6	1.2 ± 0.6[#]	–0.3, –0.04

Values are means ± SD, n = 11. MVC, maximal voluntary contraction; VA, voluntary activation; EMG, electromyogram; arEMG, average rectified EMG of the vastus lateralis; Δ, change; t, time. Symbols indicate a statistically significant difference compared to the following: [*]pre-exercise value/value at task beginning, [#]placebo. CIs are for comparisons between conditions. Isotime in the caffeine condition is compared with task failure in the placebo condition ($P < 0.05$).

Table 3. Variability, complexity and fractal scaling responses during contractions in the placebo and caffeine trials.

Parameter	Placebo	Caffeine	CIs
SD			
SD at task beginning, N·m	2.9 ± 0.9	2.8 ± 0.7	–0.5, 0.6
SD at isotime, N·m	–	4.5 ± 2.7$^{\#}$	–0.007, –6.0
SD at task failure, N·m	7.5 ± 2.7*	6.7 ± 3.1*	–1.6, 3.4
ΔSD/Δt, N·m·min^{-1}	1.1 ± 0.9	0.7 ± 0.8$^{\#}$	–0.7, –0.05
CV			
CV at task beginning, %	2.8 ± 0.6	2.7 ± 0.5	–0.5, 0.6
CV at isotime, %	–	4.5 ± 2.3$^{\#}$	–0.7, –5.8
CV at task failure, %	7.8 ± 1.3*	6.9 ± 2.3*	–1.5, 3.4
ΔCV/Δt, %/min	1.1 ± 0.7	0.7 ± 0.7$^{\#}$	–0.7, –0.07
ApEn			
ApEn at task beginning	0.40 ± 0.09	0.41 ± 0.1	–0.07, 0.06
ApEn at isotime	–	0.27 ± 0.12$^{\#}$	0.02, 0.26
ApEn at task failure	0.13 ± 0.04*	0.15 ± 0.07*	–0.09, 0.04
ΔApEn/Δt	–0.06 ± 0.03	–0.04 ± 0.02$^{\#}$	–0.006, –0.03
DFA α			
DFA α at task beginning	1.43 ± 0.07	1.43 ± 0.06	–0.04, 0.03
DFA α at isotime	–	1.53 ± 0.06$^{\#}$	0.002, 0.1
DFA α at task failure	1.61 ± 0.05*	1.60 ± 0.08*	–0.07, 0.08
ΔDFA α /Δt	–0.04 ± 0.03	–0.03 ± 0.02$^{\#}$	–0.02, –0.02

Values are means ± SD, n = 11. SD, standard deviation; CV, coefficient of variation; ApEn, approximate entropy; DFA α, detrended fluctuation analysis; Δ, change; t, time. Symbols indicate a statistically significant difference compared to the following: *pre-exercise value/value at task beginning, $^{\#}$placebo. CIs are for comparisons between conditions. Isotime in the caffeine condition is compared with task failure in the placebo condition ($P < 0.05$).