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27 **Purpose.** We tested the hypothesis that central and peripheral fatigue after constant-load  
28 cycling exercise would vary with exercise intensity and duration. **Methods.** Twelve, well-  
29 trained male cyclists ( $\dot{V}O_{2\max}$ ,  $4.49\pm 0.35$  L·min<sup>-1</sup>) completed three constant-load cycling  
30 trials to the limit of tolerance in a randomized, crossover design. Exercise intensities were set  
31 according to the respiratory responses to a preliminary ramp test to elicit cardiorespiratory  
32 and metabolic responses consistent with exercise in the severe and heavy exercise domains;  
33 1) at power at  $\dot{V}O_{2\max}$  (S+,  $379\pm 31$  W), 2) at 60% of the difference between gas exchange  
34 threshold and  $\dot{V}O_{2\max}$  (S-,  $305\pm 23$  W) and 3) at the respiratory compensation point (RCP,  
35  $254\pm 26$  W). Pre- and post-exercise twitch responses from the quadriceps to electrical  
36 stimulation of the femoral nerve and magnetic stimulation of the motor cortex were recorded  
37 to assess neuromuscular and corticospinal function, respectively. **Results.** Exercise time was  
38  $3.14\pm 0.59$  min,  $11.11\pm 1.86$  min and  $42.14\pm 9.09$  min for S+, S- and RCP respectively. All  
39 trials resulted in similar reductions in maximum voluntary force ( $P=0.61$ ). However, the  
40 degree of peripheral fatigue varied in an intensity-dependent manner, with greater reductions  
41 in potentiated twitch force after S+ ( $-33\pm 9\%$ ) compared to both S- ( $-16\pm 9\%$ ,  $P<0.001$ ) and  
42 RCP trials ( $-11\pm 9\%$ ,  $P<0.001$ ) and greater after S- compared to RCP ( $P<0.05$ ). For central  
43 fatigue this trend was reversed, with smaller reductions in voluntary activation after S+  
44 compared to RCP ( $-2.7\pm 2.2\%$  vs.  $-9.0\pm 4.7\%$ ,  $P<0.01$ ). **Conclusion.** These data suggest the  
45 magnitude of peripheral and central fatigue after locomotor cycling exercise is exacerbated  
46 with exercise intensity and duration, respectively.

47

48 **Key words:** Central, locomotor exercise, muscle, peripheral, voluntary activation,  
49 transcranial magnetic stimulation.

50

## Introduction

51 Fatigue is an exercise-induced impairment in the ability to produce muscular force (19) in the  
52 presence of an increased perception of effort (16). The neuromuscular mechanisms  
53 contributing to fatigue can be broadly attributed to processes along the motor pathway that  
54 are deemed central or peripheral in origin. For high-intensity locomotor cycling exercise, a  
55 consistent magnitude of peripheral fatigue (~35% reduction in potentiated quadriceps twitch  
56 force) has been documented at exercise termination under various experimental conditions  
57 (2-6). This observation has been proposed to represent a centrally mediated “individual  
58 critical threshold” regulated by inhibitory afferent feedback to protect against excessive  
59 disruption to homeostasis (1). Although the consistency of end-exercise peripheral fatigue in  
60 these studies is striking, whether this plays a determining role in exercise tolerance is  
61 controversial, and recent evidence suggests any individual critical threshold is likely to be  
62 task-dependent. For example, subsequent work from the same group has demonstrated  
63 greater end-exercise peripheral fatigue after dynamic single compared to double-limb  
64 exercise (32, 33), and Johnson *et al.* (25) recently reported end-exercise peripheral fatigue  
65 after high-intensity cycling is attenuated, central fatigue is exacerbated, and exercise  
66 tolerance is reduced if exercise is preceded by high-intensity arm-cranking.

67

68 For self-paced cycling time-trial exercise, the magnitude of end-exercise peripheral fatigue  
69 also varies with the intensity and duration of the task. We recently demonstrated greater  
70 peripheral fatigue after short-duration, high-intensity 4 km self-paced time-trials in  
71 comparison to longer, lower-intensity 20 and 40 km time-trials, where central fatigue was  
72 exacerbated (38). It was hypothesized that the task-dependent nature of the fatigue observed  
73 after self-paced cycling time-trials could be explained by differences in the exercise intensity  
74 domain in which the trials were predominantly completed. The exercise intensity domain

75 concept describes the distinct physiological responses that occur during exercise above and  
76 below an individual's maximum sustainable intensity, or critical power (10, 26, 31). The  
77 shorter, high-intensity 4 km trial, where peripheral fatigue was higher, was characterized by  
78 non-linear physiological responses consistent with exercise in the severe-intensity domain  
79 (38). In contrast the longer time-trials, where peripheral fatigue was lower but central fatigue  
80 was exacerbated, were characterized by steady-state physiological responses for the majority  
81 of the trial, consistent with sustainable exercise below critical power in the heavy exercise  
82 intensity domain (38). The distinct physiological responses associated with non-steady state,  
83 severe-intensity exercise compared to steady-state, heavy-intensity exercise might therefore  
84 be associated with a distinct profile of neuromuscular fatigue. However the varying nature of  
85 self-selected power output in these trials meant participants were traversing between exercise  
86 intensity domains, particularly at the start and end of the trial, limiting the validity of this  
87 conclusion.

88

89 These limitations notwithstanding, a similar intensity and duration-dependent pattern of  
90 central and peripheral processes to fatigue has been observed for exhaustive, intermittent,  
91 single-limb exercise above and below critical torque (10). Interestingly, this study reported  
92 that at varying intensities above critical torque, central fatigue was exacerbated in a duration-  
93 dependent manner, but the decline in potentiated twitch force was consistent between trials  
94 (10). This similar decline in potentiated twitch force suggests that peripheral fatigue is a  
95 primary determinant of exercise tolerance during single-limb contractions at intensities above  
96 critical torque. Whether this posit can be extended to locomotor exercise above critical power  
97 in the severe-intensity domain is not known. Recently, de Souza *et al.* (13) demonstrated no  
98 difference in the magnitude of end-exercise fatigue after exercise in the severe-intensity  
99 domain of 3 min vs. 10 min duration, but the contribution of central and peripheral processes

100 was not assessed. Given 1) the accelerated development of fatigue and associated metabolic  
101 perturbations at severe exercise intensities (10, 26, 31), 2) the consistency of end-exercise  
102 peripheral fatigue after high-intensity cycling exercise (2-6) and 3) the consistency of  
103 exercise-induced fatigue after severe-intensity cycling of varying durations (13) it makes the  
104 expectation tenable that exercise termination during short duration, high-intensity exercise  
105 above critical power in the severe-intensity domain would be concurrent with a consistent  
106 magnitude of peripheral fatigue. Conversely, longer duration, steady-state exercise in the  
107 heavy domain likely terminates with a smaller magnitude of peripheral fatigue, but a greater  
108 contribution from central fatigue mechanisms (10, 38). Accordingly, the aims of this study  
109 were to test whether central and peripheral fatigue would differ after short-duration, severe-  
110 intensity constant-load locomotor exercise compared to longer-duration, heavy-intensity  
111 exercise, and to assess whether exercise at intensities in the severe domain would terminate  
112 with a similar degree of peripheral fatigue. We hypothesized that 1) central fatigue would be  
113 exacerbated in a duration-dependent manner, 2) that peripheral fatigue would be lower after  
114 long-duration constant-load cycling exercise compared to short-duration, severe-intensity  
115 cycling exercise, and 3) that exercise in the severe-intensity domain would terminate with a  
116 similar degree of peripheral fatigue.

117

118



119

## Methods

### 120 *Participants*

121 Twelve well-trained male cyclists (mean  $\pm$  SD age,  $28 \pm 8$  years; stature,  $1.80 \pm 0.05$  m, body  
122 mass,  $76 \pm 8$  kg; maximum oxygen uptake ( $\dot{V}O_{2\max}$ ),  $4.49 \pm 0.35$  L $\cdot$ min $^{-1}$ ; power at  
123  $\dot{V}O_{2\max}$ ,  $399 \pm 31$  W) gave written informed consent to volunteer. Ethical approval was  
124 obtained from the Northumbria University Faculty of Health & Life Sciences Ethics  
125 Committee. All participants were in regular cycling training and competition in road and/or  
126 time-trial disciplines.

127

### 128 *Design*

129 Participants visited the lab on four separate occasions to complete a preliminary ramp test,  
130 followed by three experimental constant-load cycling trials to the limit of tolerance in a  
131 randomized, crossover design. Exercise intensities were set relative to the cardiorespiratory  
132 responses measured during the preliminary ramp test. Two of the trials were set at intensities  
133 predicted to elicit times to the limit of tolerance of 2-4 min, and 8-15 min, and physiological  
134 responses consistent with exercise above critical power in the severe-intensity domain. One  
135 trial was set at an intensity predicted to elicit a time to task failure of  $>30$  min, and steady-  
136 state physiological responses consistent with sustainable exercise in the heavy-intensity  
137 domain. Trials were conducted at the same time of day ( $\pm 1$  h), separated by a minimum of  
138 two and a maximum of seven days. Prior to each experimental trial participants were  
139 instructed to refrain from caffeine (for at least 12 h), strenuous exercise (for at least 24 h) and  
140 to arrive at the lab two hours post-prandial in a fully rested, hydrated state. Participants  
141 completed a 48 h food and activity diary prior to their first experimental trial and were  
142 required to replicate their exercise and nutrition as closely as possible before each subsequent  
143 trial. Cardiorespiratory, blood lactate concentration and rating of perceived exertion (RPE)

144 were recorded during each trial and measures of neuromuscular function were assessed pre-  
145 and within 2.5 min post-trial.

146

## 147 **Procedures**

### 148 *Preliminary visit*

149 Participants attended the laboratory to complete an incremental ramp test to measure  $\dot{V}O_{2\max}$   
150 and respiratory thresholds, and habituate to the measurement tools of the study; specifically,  
151 electrical stimulation of the femoral nerve and magnetic stimulation of the motor cortex pre-  
152 and post-exhaustive cycling exercise. The incremental ramp test was performed on an  
153 electromagnetically braked cycle ergometer (Excalibur Sport, Lode, Groningen,  
154 Netherlands), and consisted of cycling at 100 W followed by a continuous ramped increase in  
155 power of  $30 \text{ W} \cdot \text{min}^{-1}$  to the limit of tolerance. The test was terminated when participants  
156 cadence reduced by  $>20$  rpm from their self-selected cadence for the test. Expired air was  
157 analysed breath-by-breath using an online system (Oxycon Pro, Care Fusion, Hoechberg,  
158 Germany). Oxygen ( $O_2$ ) and carbon dioxide ( $CO_2$ ) concentrations were analysed via a  
159 paramagnetic chemical fuel cell and non-dispersive infrared cell respectively. Before each  
160 test the analyzers were calibrated using ambient air and a gas of known  $O_2$  (14.00%) and  $CO_2$   
161 (6.00%) concentrations. Ventilatory volumes were inferred from measurement of gas flow  
162 using a digital turbine transducer (volume 0 to 10 L, resolution 3 mL, flow 0 to  $15 \text{ L} \cdot \text{s}^{-1}$ ),  
163 calibrated prior to each test using a 3 L syringe (Hans Rudolph Inc. Kansas City, USA), and  
164 attached to a face mask via a transducer holder (dead space of 30 mL). The gas-exchange  
165 threshold (GET) was determined using multiple parallel methods as follows: 1) the first  
166 disproportionate increase in carbon dioxide output ( $\dot{V}CO_2$ ) relative to  $\dot{V}O_2$ , 2) an increase in  
167 the ventilatory equivalent for oxygen ( $\dot{V}_E/\dot{V}O_2$ ) with no increase in the ventilatory equivalent  
168 for carbon dioxide ( $\dot{V}_E/\dot{V}CO_2$ ) and 3) an increase in end-tidal  $O_2$  tension with no fall in end-

169 tidal CO<sub>2</sub> tension (8, 40). Respiratory compensation point (RCP) was determined from plots  
170 of minute ventilation ( $\dot{V}_E$ ) vs  $\dot{V}CO_2$  (8). Maximum oxygen uptake was calculated as the  
171 highest 30 s mean value attained prior to test termination, and the end test power was  
172 recorded as power at  $\dot{V}O_{2max}$  ( $P_{max}$ ).

173

#### 174 *Experimental trials*

175 Participants completed three constant-load cycling trials to the limit of tolerance. The  
176 exercise intensities were determined from the respiratory indices and associated intensities  
177 measured during the preliminary ramp test. Two trials were set to elicit non-steady state  
178 physiological responses consistent with exercise in the severe-intensity domain with  
179 predicted exercise durations of 2-4 min (hereafter referred to as S+) and 8-15 min (hereafter  
180 referred to as S-). The third trial was set at a sustainable intensity (hereafter referred to as  
181 RCP), with a predicted exercise duration of >30 min. The S+ trial was set at  $P_{max}$ , which  
182 approximates the upper limit of the severe-intensity domain. The S- trial was set at an  
183 exercise intensity equivalent to 60% of the difference between GET and  $\dot{V}O_{2max}$ , which  
184 would also elicit responses consistent with exercise above critical power in the severe  
185 domain, but for a greater duration than S+ (20). The RCP trial was set at the power output  
186 associated with RCP, as this intensity approximates an upper limit for sustainable exercise  
187 (15). When determining constant-load exercise intensities from a ramp protocol, it is  
188 recommended the intensity be adjusted to accommodate the mean rise time of  $\dot{V}O_2$  during  
189 ramp exercise, which approximates two-thirds of the ramp rate (i.e. 20 W; 41). For all trials  
190 this recommendation was adhered to, and 20 W was subtracted from the calculated exercise  
191 intensity. Each experimental trial was preceded by a 5 min warm up at 150 W before a “step”  
192 increase in exercise intensity. Participants remained seated throughout exercise, and the test  
193 was terminated when participants could not maintain a cadence within 10 rpm of their self-

194 selected cadence for the test. Expired air was measured breath-by-breath throughout.  
195 Fingertip capillary blood was sampled post-warm-up, at 5 min intervals during constant-load  
196 exercise and 3 min post-trial, and immediately analysed for [lactate] using an automated  
197 instrument (Biosen C\_Line, EFK Diagnostic, Germany). At the same time points during  
198 exercise, participants were asked to provide a rating of perceived exertion (RPE) taking into  
199 account all sensations of physical stress, effort and fatigue (9).

200

### 201 *Neuromuscular function*

202 Measures of neuromuscular function were assessed pre- and post-exercise using electrical  
203 stimulation of the femoral nerve and transcranial magnetic stimulation (TMS) of the motor  
204 cortex, with evoked force and electromyographic (EMG) responses recorded from the knee  
205 extensors of the dominant leg at rest and during voluntary contraction. Following two  
206 practice attempts to ensure adequate potentiation, participants completed three isometric  
207 maximum voluntary contractions (MVC) of the knee extensors separated by 60 s rest, with  
208 femoral nerve stimulation delivered during and  $\sim 2$  s post to measure voluntary activation  
209 (VA) and potentiated quadriceps twitch force ( $Q_{tw,pot}$ ). Subsequently, TMS was delivered  
210 during brief (3-5 s) contractions at 100%, 75% and 50% MVC, separated by 5 s rest, for  
211 determination of corticospinal voluntary activation. This procedure was repeated 3 times with  
212 30 s rest between each set. Finally TMS ( $\times 8$  stimulations) and electrical nerve stimulation ( $\times$   
213 5 stimulations) were delivered during submaximal contraction at 20% MVC for  
214 determination of corticospinal excitability. Immediately post-exercise these measures were  
215 repeated. In accordance with other similar investigations of exercise-induced fatigue of the  
216 knee extensors, the assessment of voluntary activation measured with motor nerve and motor  
217 cortical stimulation was completed within 2.5 min of exercise cessation (20, 32, 34, 38). The  
218 rapid nature of this procedure is necessary to capture the extent of fatigue elicited by the

219 exercise before it dissipates (18) and the duration (2 to 2.5 min) was consistent between trials.  
220 Further details on these procedures are presented in subsequent sections.

221

### 222 *Force and EMG recordings*

223 During stimulations participants sat upright in a custom-built chair with hips and knees at 90°  
224 of flexion. A calibrated load cell (MuscleLab force sensor 300, Ergotest technology, Norway)  
225 was attached via a non-compliant cuff positioned on the participant's right leg, superior to the  
226 malleoli, to measure knee extensor force (N). Surface Ag/AgCl electrodes (Kendall  
227 H87PG/F, Covidien, Mansfield, MA, USA) were placed 2 cm apart over the rectus femoris  
228 (RF), vastus lateralis (VL) and biceps femoris (BF) to record the compound muscle action  
229 potential (M-wave) elicited by electrical stimulation of the femoral nerve, the motor evoked  
230 potential (MEP) elicited by TMS and root-mean-square amplitude during isometric and  
231 dynamic (cycling) exercise. The position of the electrodes was consistent with SENIAM  
232 (Surface EMG for the Non-Invasive Assessment of Muscles) guidelines, and a reference  
233 electrode was placed over the patella. Electrode placement was marked with permanent ink to  
234 ensure a consistent placement between trials. Signals were amplified; gain  $\times 1000$  for EMG  
235 and  $\times 300$  for force (CED 1902, Cambridge Electronic Design, UK), band-pass filtered (EMG  
236 only: 20-2000 Hz), digitised (4 kHz; CED 1401, Cambridge Electronic Design, UK) and  
237 analysed off line (Spike2 v7.12, Cambridge Electronic Design, UK).

238

### 239 *Motor nerve stimulation*

240 Single electrical stimuli (200  $\mu$ s duration) were applied to the right femoral nerve using a  
241 constant-current stimulator (DS7AH Digitimer Ltd., Welwyn Garden City, UK) via adhesive  
242 surface electrodes (CF3200, Nidd Valley Medical Ltd., Harrogate, UK) at rest and during  
243 voluntary contraction. The cathode was positioned over the nerve in the femoral triangle in

244 the location that elicited the maximum quadriceps twitch amplitude ( $Q_{tw}$ ) and M-wave ( $M_{max}$ )  
245 at rest. The anode was positioned midway between the greater trochanter and iliac crest. The  
246 optimal stimulation intensity was determined as the minimum current that elicited maximum  
247 values of  $Q_{tw}$  and  $M_{max}$  at rest. To ensure a supramaximal stimulus and account for fatigue-  
248 dependent changes in axonal excitability, the intensity was increased by 30%, and was not  
249 different between trials ( $211 \pm 71$  mA,  $215 \pm 76$  mA,  $219 \pm 74$  mA,  $P = 0.13$ ).

250

### 251 *Transcranial magnetic stimulation*

252 Single pulse magnetic stimuli (1 ms duration) were delivered to the left motor cortex via a  
253 concave double cone coil (110 mm diameter, maximum output 1.4 T) powered by a  
254 monopulse magnetic stimulator (Magstim 200, The Magstim Company Ltd., Whitland, UK).  
255 The coil position was tilted and held lateral to the vertex over the area relating to Brodmann  
256 Area 4 of the primary motor cortex, generating a posterior-anterior intracranial current flow  
257 within the left hemisphere. The exact “hot-spot” (marked in semi-permanent ink for  
258 reproducible placement between trials) was determined as the coil position that elicited the  
259 largest MEP in the rectus femoris during a submaximal (20% MVC) contraction, and a  
260 concurrent small MEP in the antagonist muscle. For measures of corticospinal excitability,  
261 active motor threshold (AMT) was determined as the stimulator output that elicited a  
262 consistent MEP of approximately 0.2 mV in at least 3 of 5 stimulations during 20% MVC  
263 (37). The stimulator output was increased by 20% and was not different between trials ( $48 \pm$   
264  $7\%$ ,  $48 \pm 7\%$  and  $47 \pm 6\%$  of mean stimulator output,  $P = 0.58$ ). Setting the stimulator  
265 intensity relative to AMT in this manner ensures the resulting MEP is not close to saturation  
266 on the stimulus-response curve (39) permitting a suitable window for exercise-induced  
267 changes. The use of a sub-maximal contraction allows for the monitoring of the status of  
268 smaller motoneurons (29). For measurement of corticospinal voluntary activation, the

269 stimulator output was set to produce the largest superimposed twitch force during a  
270 contraction at 50% MVC (37), which averaged  $67 \pm 17$  N, or  $12 \pm 5\%$  of MVC. The  
271 stimulation intensity, which was not different between trials ( $63 \pm 5\%$ ,  $63 \pm 4\%$  and  $62 \pm 4\%$   
272 of mean stimulator output,  $P = 0.68$ ), elicited a large MEP in the RF (approximately 70% of  
273  $M_{\max}$  during contractions  $\geq 50\%$  MVC) indicating the TMS stimulus activated a high  
274 proportion of knee extensor motor units, while causing only a small MEP in the antagonist  
275 (0.40 mV on average, or  $<10\%$  of RF  $M_{\max}$  during knee-extensor contractions). Participants  
276 were given specific instructions to achieve a plateau in the target force when contracting at  
277 varying force levels whilst receiving TMS (22).

278

#### 279 *Data analysis*

280 Voluntary activation measured via motor nerve stimulation was quantified using the twitch  
281 interpolation method:  $VA (\%) = (1 - [SIT/Q_{tw,pot}] \times 100)$ , where SIT is the amplitude of the  
282 superimposed twitch force measured during MVC, and  $Q_{tw,pot}$  is the amplitude of the resting  
283 potentiated twitch force assessed 2 s post-MVC. For motor cortical stimulation, voluntary  
284 activation was assessed by measurement of the superimposed twitch responses to TMS at  
285 100%, 75% and 50% MVC. As corticospinal excitability increases during voluntary  
286 contraction, it is necessary to estimate the amplitude of the resting twitch in response to  
287 motor cortex stimulation (21, 39). The amplitude of the estimated resting twitch (ERT) was  
288 calculated as the  $y$ -intercept of the linear regression between the mean amplitude of the  
289 superimposed twitches evoked by TMS at 100%, 75% and 50% MVC and voluntary force;  
290 regression analyses confirmed the existence of a linear relationship both pre- and post-  
291 exercise ( $r^2 = 0.90 \pm 0.05$  and  $0.86 \pm 0.11$ , respectively). Voluntary activation (%) measured  
292 with TMS was subsequently calculated as  $(1 - [SIT/ERT] \times 100)$ . The reproducibility and  
293 validity of this procedure for the knee extensors has been previously established (21). The

294 peak-to-peak amplitude and area of the evoked  $M_{\max}$  and MEP responses were quantified  
295 offline. Corticospinal excitability was determined as the ratio between the MEP and M-wave  
296 responses measured during a 20% MVC from eight cortical and five motor nerve  
297 stimulations. Contraction strength was adjusted post-trial to equate to 20% of the fatigued  
298 MVC force. Electromyography of the vastus lateralis and rectus femoris during the cycling  
299 bout was band-pass filtered in both directions between 20-450 Hz using a 4<sup>th</sup> order zero lag  
300 Butterworth filter. The root mean square of the EMG amplitude was measured over ten  
301 consecutive pedal revolutions from the middle of minute 4 of the warm-up, and the first and  
302 final minutes of cycling exercise, to quantify changes in neuromuscular activation. Onsets  
303 and offsets of EMG bursts were determined visually by the same investigator (11, 25). The  
304 warm-up and first minute EMG data were normalized to the  $M_{\max}$  measured pre-trial, and the  
305 final minute EMG data was normalized to the post-trial  $M_{\max}$  (average of three electrical  
306 stimulations at rest for both).

307

### 308 *Reproducibility coefficients*

309 Typical error as a coefficient of variation (CV, %) and intra-class correlation coefficients  
310 (ICC, 23) between the pre-trial scores were calculated to quantify reproducibility of  
311 neuromuscular function measures. Reproducibility was high for MVC (ICC = 0.96, CV =  
312 4.4%),  $Q_{\text{tw,pot}}$  (ICC = 0.90, CV = 4.8%), motor nerve VA (ICC = 0.89, CV = 3.1%),  
313 corticospinal VA (ICC = 0.90, CV = 2.6%) and moderate for ERT (ICC = 0.85, CV =  
314 10.0%),  $M_{\max}$  (RF; ICC = 0.70, CV = 24.7%, VL; ICC = 0.79, CV = 25.2%) and MEP/ $M_{\max}$   
315 ratio (RF; ICC = 0.74, CV = 13.6%, VL; ICC = 0.79, CV = 26.3%). The reproducibility of  
316 the cardiorespiratory responses ( $\dot{V}_E$ ,  $\dot{V}O_2$ ,  $\dot{V}CO_2$ , respiratory exchange ratio, RER and HR)  
317 was determined from responses to the standardized 5 min warm-up and was considered high  
318 for all measures (ICC range = 0.87 to 0.93, CV range = 4.0% to 5.3%).



319

320 *Statistical analysis*

321 All analyses were planned *a priori*. For all neuromuscular measures the expected impact of  
322 exhaustive exercise on measures of fatigue were assessed using Student's paired-sample t-  
323 tests. One-way repeat measures ANOVA analyses of the pre- to post-exercise change scores  
324 were used to assess the effect of exercise intensity (S+ vs. S- vs. RCP) on measures of  
325 fatigue and neuromuscular function. Differences between trials for exercise time, power  
326 output, and cardiorespiratory and metabolic responses were assessed using the same  
327 procedure. Trial (S+ vs. S- vs. RCP) by time (warm-up vs. first min vs. final minute)  
328 factorial repeat measures ANOVA were used to assess EMG responses; significant main  
329 effects were followed up using one-way repeat measures ANOVA. For all ANOVA analyses,  
330 pairwise comparisons were made using Tukey's test. Friedman's ANOVA with *post-hoc*  
331 Wilcoxon signed-ranks test were employed for non-parametric data (RPE). The assumptions  
332 underpinning these statistical procedures were verified and all data were considered normal.  
333 Descriptive data are presented as means  $\pm$  SD in text, tables and figures. Statistical analysis  
334 was conducted using Graphpad (GraphPad Prism 5, Version 5.03, La Jolla, CA, USA).  
335 Statistical significance was assumed at  $P < 0.05$ .

336

337

338

## Results

339 **Exercise responses.** Power output for S+ ( $379 \pm 31$  W) S- ( $305 \pm 23$  W) and RCP ( $254 \pm 26$   
340 W) equated to relative intensities of  $100\% P_{\max}$ ,  $76 \pm 3\% P_{\max}$  and  $64 \pm 5\%$  of  $P_{\max}$ . The  
341 resulting exercise times to the limit of tolerance for each trial were  $3.14 \pm 0.59$  min,  $11.11 \pm$   
342  $1.86$  min and  $42.14 \pm 9.09$  min for S+, S- and RCP respectively.

343

344 The mean cardiorespiratory (Figure 1) and blood [lactate] (Figure 2, panel A) responses to S+  
345 and S- were consistent with exercise above critical power in the severe-intensity domain, and  
346 for RCP consistent with exercise in the heavy domain. For S+ exercise, oxygen uptake rose  
347 rapidly (Figure 1, panel B), reaching peak values of  $98 \pm 8\%$  of maximum, and peak RER  
348 and  $\dot{V}CO_2$  were higher compared to S- and RCP exercise ( $P < 0.05$ ). For S- exercise,  
349 oxygen uptake also rose rapidly, followed by a gradual increase to task failure where peak  
350 values averaged  $98 \pm 6\%$  of maximum oxygen uptake. For RCP, an oxygen uptake slow  
351 component was observed, with peak values averaging  $91 \pm 6\%$  of  $\dot{V}O_{2\max}$  (Figure 1, panel  
352 B). Blood [lactate] post-exercise was highest after S+ ( $12.3 \pm 1.8$   $\text{mMol}\cdot\text{L}^{-1}$ ) compared to  
353 both S- ( $10.6 \pm 2.1$   $\text{mmol}\cdot\text{L}^{-1}$ ,  $P < 0.05$ ) and RCP ( $5.9 \pm 1.8$   $\text{mMol}\cdot\text{L}^{-1}$ ,  $P < 0.001$ ) exercise,  
354 and higher after S- compared to RCP ( $P < 0.001$ ) (Figure 2, panel A).

355

356 Surface EMG data was successfully sampled for all three trials in nine participants. Estimated  
357 muscle activation ( $\text{RMS}/M_{\max}$ ) was different across time ( $P < 0.001$ ), between trials ( $P =$   
358  $0.001$ ) and responded differently to S+, S- and RCP (time  $\times$  trial  $P = 0.001$ , Figure 3). There  
359 were no differences observed in muscle activation during the warm-up between trials. During  
360 the 1<sup>st</sup> minute of exercise, EMG  $\text{RMS}/M_{\max}$  was higher in S+ compared to RCP ( $P = 0.01$ ),  
361 and in the final minute was higher in S+ compared to both S- ( $P = 0.04$ ) and RCP ( $P =$   
362  $0.001$ ). The increase in EMG  $\text{RMS}/M_{\max}$  during S+ exercise was higher than RCP between

363 warm-up and the first minute of exercise ( $P = 0.001$ ), and higher than both S<sup>-</sup> ( $P = 0.04$ ) and  
364 RCP ( $P = 0.001$ ) between the first and final minute of exercise (Figure 3).

365

366 For RPE, participants reported higher peak scores for S<sup>+</sup> compared to RCP exercise ( $P <$   
367  $0.05$ ), with no difference between S<sup>+</sup> and S<sup>-</sup>, or between S<sup>-</sup> and RCP exercise (Figure 2,  
368 panel B). When expressed relative to exercise time, the RPE response was similar between  
369 trials (Figure 2, panel C).

370

371 **Neuromuscular responses pre- and post-exercise.** One participant exhibited small  
372 responses to TMS (MEP:M<sub>max</sub> ratio in RF  $< 60\%$ , superimposed twitch force during 50%  
373 MVC  $< 5\%$  MVC force). Low MEP:M<sub>max</sub> ratios and a small SIT are indicative of an  
374 incomplete activation of the available motoneuron pool by the magnetic stimulus, which  
375 could invalidate the measurement of voluntary activation. This participant was subsequently  
376 excluded from analysis of data elicited by TMS.

377

378 Exercise resulted in a similar level of global fatigue after all trials, as evidenced by  
379 substantial reductions in MVC force ( $P < 0.05$ ) that were not different between trials ( $-111 \pm$   
380  $54$  N,  $-93 \pm 48$  N and  $-98 \pm 59$  N for S<sup>+</sup>, S<sup>-</sup> and RCP exercise, respectively,  $P = 0.61$ )  
381 (Figure 4, panel A). The loss in voluntary force was accompanied by significant peripheral  
382 and central fatigue in all trials (all  $P < 0.05$ , Figure 4); however there were differences in the  
383 magnitude of central and peripheral fatigue between trials. Peripheral fatigue ( $\Delta Q_{tw,pot}$   
384 amplitude) was greater after S<sup>+</sup> exercise ( $-33 \pm 9\%$ ) compared to both S<sup>-</sup> ( $-16 \pm 9\%$ ,  $P <$   
385  $0.001$ ) and RCP exercise ( $-11 \pm 9\%$ ,  $P < 0.001$ ), and greater after S<sup>-</sup> compared to RCP  
386 exercise ( $P < 0.05$ ) (Figure 4, panel B). For central fatigue this pattern was reversed. For  
387 motor nerve estimates of VA, central fatigue was less after S<sup>+</sup> ( $-2.7 \pm 2.2\%$ ) compared to

388 RCP ( $-9.0 \pm 4.7\%$ ,  $P < 0.01$ ) but not after S+ compared to S- ( $-6.3 \pm 5.5\%$ ,  $P = 0.056$ ) or  
389 after S- compared to RCP ( $P = 0.084$ ) (Figure 4, panel C). For motor cortical estimates of  
390 VA no statistical differences were observed after S+ ( $-2.7 \pm 3.5\%$ ) compared to RCP ( $-9.2 \pm$   
391  $8.0\%$ ,  $P = 0.06$ ) or S- ( $-7.9 \pm 7.4\%$ ,  $P = 0.07$ ), or after S- compared to RCP ( $P = 0.46$ )  
392 (Figure 4, panel D). Changes in voluntary activation were not accompanied by any changes in  
393 MEP or M-wave properties measured during a 20% MVC (Table 1) or during higher force  
394 contractions (Table, supplementary digital content 1, neuromuscular function and surface  
395 EMG responses to motor nerve and motor cortical stimulation).

396

397

## Discussion

398 This study shows that the magnitude of central and peripheral fatigue observed after constant-  
399 load locomotor cycling varies with exercise intensity and duration. Specifically, the data  
400 suggest a task-dependent contribution of peripheral and central fatigue; peripheral fatigue is  
401 exacerbated with increases in exercise intensity, whereas central fatigue tends to increase as  
402 exercise intensity decreases and duration increases. For non-steady-state exercise in the  
403 severe domain, the degree of end-exercise peripheral fatigue was exacerbated at higher  
404 intensities, a finding incongruent with the proposal of an individual critical threshold for  
405 muscle fatigue after high-intensity locomotor exercise above critical power.

406

407 Contrary to our hypothesis, the degree of end-exercise peripheral fatigue was not consistent  
408 between exercise intensities in the severe domain, a finding that does not support the proposal  
409 that muscle fatigue after high-intensity locomotor exercise is regulated to an individual  
410 critical threshold. The concept of an individual critical threshold, or sensory tolerance limit,  
411 was originally proposed by Amann and colleagues (1-7) who completed a series of studies  
412 demonstrating that the magnitude of exercise-induced peripheral fatigue was remarkably  
413 similar after locomotor exercise under conditions of pre-fatiguing exercise (3), altered arterial  
414 oxygen saturation (4) and, perhaps most convincingly, was exacerbated only under conditions  
415 of impaired afferent feedback (2, 5). Similar support has also been provided for “all-out”  
416 repeat-sprint exercise with and without pre-fatiguing exercise (24). These studies proposed a  
417 feedback loop whereby inhibitory input from group III/IV afferents in the active musculature  
418 act on the central nervous system to compel a reduction in exercise intensity in order to  
419 prevent excessive homeostatic disruption, and restrain the development of muscle fatigue to a  
420 consistent limit that would not be exceeded in normal conditions. Although conceptually  
421 attractive, our previous work comparing different durations of cycling time-trial exercise

422 (38), and evidence from the work of others comparing single vs. double leg exercise (32),  
423 have demonstrated that any peripheral limit is task-dependent, a point which the authors of  
424 this proposal were careful to emphasise (7). Nonetheless, in the current study we  
425 hypothesised that an individual, consistent limit for peripheral fatigue might exist for non-  
426 steady-state exercise in the severe-intensity domain. This posit was based on the distinct,  
427 non-linear responses to severe-intensity exercise (26), the observation of a consistent  
428 reduction in potentiated twitch force of ~35% after high-intensity cycling exercise (2, 3, 5, 6),  
429 and the finding that peripheral fatigue is similar after single-limb, intermittent, isometric knee  
430 extensor contractions at varying intensities above critical torque (10). Contrary to our original  
431 hypothesis, the greater reduction in potentiated twitch force observed after the highest  
432 intensity trial suggests the degree of peripheral fatigue incurred after exhaustive locomotor  
433 exercise above critical power is intensity- and duration-dependent, and not regulated to a  
434 critical limit.

435

436 An alternative explanation for the differing magnitude of end-exercise peripheral fatigue  
437 observed in this, and other studies (2, 5, 24, 32, 33), could simply be related to the force and  
438 motoneuron recruitment strategy required to complete the task. In the current study, the force  
439 demands of the task and subsequent activation of muscle were highest in the S+ trial, where  
440 peripheral fatigue was also highest; the higher peripheral fatigue could simply be explained  
441 by the recruitment and subsequent fatigue of a greater portion of the available motoneuron  
442 pool. This proposal would also explain a number of previous observations relating to the  
443 critical threshold concept. For example, observations of a greater end-exercise peripheral  
444 fatigue after single vs. double-limb exercise (32, 33), and after locomotor cycling exercise  
445 with afferent blockade (2, 5), could both be explained by a greater activation of muscle, as  
446 evidenced by the higher EMG that was concurrent with greater end-exercise peripheral

447 fatigue in these experimental trials. Additionally, the highest absolute reductions in  
448 potentiated twitch force (measured with single electrical stimuli) have been reported after  
449 repeat sprint cycling exercise; -51% (24) compared to a range of -33 to -40% after high-  
450 intensity time-trial (5, 38) and constant-load cycling exercise (2). Repeat sprint exercise  
451 would theoretically require repeated maximum activation of the locomotor musculature, with  
452 compromised recovery, and as such the high force demands of the task would elicit a greater  
453 recruitment and fatigue of larger, faster motor units, and a consequent higher level of muscle  
454 fatigue. In support of this proposal, Decorte *et al.* (14) demonstrated the increase in  
455 quadriceps EMG during exhaustive constant-load cycling was significantly correlated with  
456 the reduction in quadriceps potentiated twitch force. A limitation to this explanation is an  
457 acknowledgement that estimates of muscle activation via surface EMG are subject to a  
458 number of valid critiques (17, 27), not least the insensitivity of measures of muscle activation  
459 to small differences in exercise intensities. These limitations notwithstanding, the higher  
460 EMG that accompanied the higher power output in the S+ trial gives credence to the  
461 interpretation that this is indicative of a higher degree of muscle activation. Thus, the  
462 proposal that peripheral fatigue after locomotor exercise can be explained by the force and/or  
463 motor unit recruitment strategy required for the task remains plausible, and provides a better  
464 fit with the available data than a model which emphasises regulation to an individual critical  
465 threshold.

466

467 While these data question the concept of an individual critical threshold for peripheral  
468 fatigue, the proposal that group III/IV muscle afferent feedback acts in an inhibitory manner  
469 to contribute to the regulation of exercise intensity remains a logical proposition. Without  
470 such feedback regulation is almost certainly compromised, at least for high-intensity  
471 locomotor exercise lasting < 10 min (5). Indeed, Amann *et al.* (2, 5) clearly demonstrate that

472 when such feedback is blocked with administration of an intrathecal opioid analgesic,  
473 participants self-select exercise intensities and/or adopt inappropriate recruitment strategies  
474 that result in significant additional peripheral fatigue in comparison to a control, with no  
475 improvement in performance. These data clearly support the idea that group III/IV afferent  
476 feedback is important for the regulation of high-intensity, locomotor exercise. However, the  
477 findings of the present study, previous work comparing different durations of self-paced  
478 cycling exercise (38), and the observation that prior fatiguing arm exercise can modulate end-  
479 exercise peripheral fatigue in high-intensity cycling (25), indicate that peripheral muscle  
480 fatigue contributes to, rather than determines, the decision to terminate or modulate  
481 locomotor exercise intensity.

482

483 In accordance with our hypothesis, longer duration, heavy-intensity exercise terminated with  
484 more central fatigue and less peripheral fatigue compared to severe-intensity exercise. This  
485 duration-dependent contribution of central fatigue is similar to that previously observed in  
486 self-paced (38) and constant-load cycling (14), and single-limb intermittent contractions (10),  
487 and indicates that exercise tolerance in longer duration tasks is mediated to a greater extent  
488 by mechanisms of central fatigue. Despite differences in the etiology of neuromuscular  
489 fatigue, the sensory perception of exertion rose similarly over time independent of exercise  
490 duration/intensity (Figure 2, panel C). This is a consistent response to various exercise tasks  
491 under varying conditions, which has prompted the development of holistic models that  
492 emphasise a mediating role for sensory perception in the etiology of fatigue (28, 30).  
493 Interestingly, the highest RPE at exercise termination was reported in the highest intensity  
494 trial, where peripheral fatigue was also highest; a finding concurrent with our previous work  
495 in self-paced exercise (38). This could support the idea that afferent feedback contributes to  
496 the sensory perception of fatigue and the decision to terminate exercise (30), or it could be



497 argued that the shorter duration of the trial and the lower degree of central fatigue permitted a  
498 higher potential motivation for the task and a consequent higher tolerance to a high  
499 perception of effort (28). Although a definitive explanation is elusive, it is clear that the  
500 decision to terminate exercise was influenced differently depending on the intensity of the  
501 trial, and understanding how the mediating inputs to this decision vary across exercise tasks  
502 remains an important endeavour to advance our understanding of the factors that limit or  
503 modulate exercise performance.

504

505 The task-dependent, intensity-domain specificity of peripheral fatigue observed in the present  
506 study after constant-load cycling exercise supports our previous work in different durations of  
507 self-paced cycling exercise (38), with one caveat. In this previous study we observed a  
508 similar degree of peripheral fatigue after 20 and 40 km time-trial exercise ( $-31\%$  and  $-29\%$   
509 on average, respectively) despite significant differences in the duration (32 min vs. 66 min)  
510 and average intensity (279 W vs. 255 W) of the bouts (38). We hypothesised that this lack of  
511 difference could reflect a similarity in the exercise domain in which the trials were  
512 completed, predominantly in the heavy domain and below critical power. However, in the  
513 present study using the same femoral nerve stimulation methods, and a similar population of  
514 well-trained cyclists, the absolute decline in potentiated twitch force after 45 min of constant-  
515 load cycling in the heavy exercise intensity domain was only 11%. Based on this new  
516 information and the proposal that peripheral fatigue is determined in a task-dependent manner  
517 based on the force and/or motoneuron recruitment strategies required for the task, we now  
518 consider it likely that the higher, and similar degree of peripheral fatigue observed after 20  
519 and 40 km self-paced exercise was determined primarily by the finishing sprint, which was  
520 similar between trials (38). Such a sprint at the end of the trial is common in self-paced  
521 exercise and requires higher force and therefore recruitment of higher threshold motor units.

522 Collectively, this reasoning could explain the greater degree of peripheral fatigue observed  
523 after self-paced exercise compared to the relatively modest degree of peripheral fatigue  
524 observed in the present study after a similar duration and intensity constant-load bout. These  
525 data therefore suggest that the magnitude of peripheral fatigue observed at the end of a self-  
526 paced bout of exercise likely reflects the recent contractile history of the muscle, and  
527 emphasises the importance and challenge of developing methods to ascertain the time-course  
528 development of fatigue *during* as well as post-exercise.

529

530 Corticospinal excitability was unchanged in response to locomotor exercise, when measured  
531 >2 minutes post-exercise. This response is common in studies employing locomotor exercise  
532 where corticospinal excitability is measured pre- and post-exercise (34, 38). However, the  
533 lack of change from pre- to post-exercise might not fully reflect modulations in corticospinal  
534 excitability that could occur during exercise. Indeed, when responses are elicited during  
535 locomotor exercise using a bespoke experimental set-up, there is evidence to suggest  
536 corticospinal excitability is reduced (35) and intracortical inhibition is increased (36), which  
537 might therefore contribute to the aetiology of fatigue. The lack of change in measures of  
538 excitability commonly observed post-exercise might be explained by a rapid recovery, and  
539 the lack of specificity of the task in which it is measured. A limitation of the present study is  
540 the measurement of corticospinal excitability took place > 2 min post-exercise during  
541 isometric contraction, and as such any change in response to exercise might not be elucidated.

542

543 The estimate of exercise intensities in the present study was based on the ventilatory and  
544 performance responses to a ramp exercise protocol. Two of these intensities (S+, S-) were set  
545 to elicit physiological responses consistent with exercise above critical power in the severe-  
546 intensity domain, for exercise durations of between 2-4 min and 8-15 min respectively. In

547 both of these trials, oxygen uptake progressively rose to values that were within 2% of  
548 maximum oxygen uptake at exercise termination (Figure 1), and blood [lactate] was not  
549 stabilised (Figure 2, panel A), indicative of exercise in the severe domain. The third trial  
550 (RCP) was set at the respiratory compensation point, which approximates the critical power  
551 (15), and was designed to elicit exercise durations >30 min and physiological responses  
552 consistent with sustainable exercise. Though it is acknowledged that the weight of evidence  
553 suggests the RCP and critical power are distinct thresholds (12, 31), the exercise duration in  
554 RCP exceeded 30 min for all participants, and the cardiorespiratory (Figure 1) and blood  
555 [lactate] (Figure 2, panel A) responses were submaximal and stable for the duration of the  
556 RCP trial on a group level, indicative of exercise below critical power in the heavy-intensity  
557 domain. However, the range in exercise durations (31 to 59 min) suggests a less precise  
558 estimate of this intensity, which was likely in the heavy domain for most, but not all,  
559 participants. This limitation notwithstanding, the contribution of central and peripheral  
560 processes to fatigue after this longer duration bout were distinctive from the shorter, higher-  
561 intensity bouts. A more precise estimate of the critical power would allow future research to  
562 better assess any differences in the etiology of neuromuscular fatigue at exercise intensities  
563 below critical power.

564

565 To conclude, the contribution of central and peripheral processes to fatigue after constant-  
566 load cycling exercise differs in a task-dependent manner. Central fatigue is exacerbated as  
567 exercise duration increases and intensity decreases, whereas peripheral fatigue is greater at  
568 higher intensities and shorter durations of exercise. These data suggest that the extent of end-  
569 exercise peripheral fatigue is not regulated to an individual critical threshold, but is  
570 determined by the force and/or motor unit recruitment strategies required for the task. These

571 data have implications for the concept of a critical limit for peripheral fatigue and our  
572 understanding of the etiology of fatigue under different locomotor exercise conditions.

573

574

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### Figure Legends

724 **Figure 1.** Minute ventilation ( $\dot{V}_E$ , A), respiratory exchange ratio (B), oxygen uptake ( $\dot{V}O_2$ ,  
725 C) and carbon dioxide output ( $\dot{V}CO_2$ , D) during severe- (S+ ○ and S- ▲) and heavy-  
726 intensity (RCP ■) constant-load cycling exercise. Values are mean  $\pm$  SD (n = 12). The  
727 vertical dashed line on the x axis marks the end of the 5 min warm-up and the start of the  
728 constant-load trial. The horizontal error bars on the final data point show the variability in  
729 time to the limit of tolerance for each trial. Symbols indicate a statistically significant  
730 difference ( $P < 0.05$ ) in the peak scores compared to the following: \*different from S-,  
731 †different from RCP.

732

733 **Figure 2.** Blood lactate (A), rating of perceived exertion (B) and rating of perceived exertion  
734 relative to trial duration (C) responses to severe- (S+ ○ and S- ▲) and heavy-intensity (RCP  
735 ■) constant-load cycling exercise. The vertical dashed line on the x axis marks the end of the  
736 5 min warm-up and the start of the constant-load trial. The horizontal error bars on the final  
737 data point in (A) and (B) show the variability in time to the limit of tolerance for each trial.  
738 Values are mean  $\pm$  SD (n = 12). Symbols indicate a statistically significant difference ( $P <$   
739  $0.05$ ) in the peak trial scores compared to the following: \*different from S-, †different from  
740 RCP.

741

742 **Figure 3.** Muscle activation estimated from electromyography of the vastus lateralis and  
743 rectus femoris during a standardized warm-up and the first and final minute of severe- (S+ ○  
744 and S- ▲) and heavy-intensity (RCP ■) constant-load cycling exercise. Values are mean  $\pm$   
745 SD (n = 9) Symbols above error bars indicate a statistically significant difference between  
746 trials for the measured time point. Symbols on horizontal lines indicate a statistically



747 significant interaction between time points (all  $P < 0.05$ ). \* different from S-, † different from  
748 RCP.

749

750 **Figure 4.** Pre- to post-trial percentage change in maximum voluntary contraction (A),  
751 potentiated twitch force (B), voluntary activation measured with motor nerve stimulation (C)  
752 (n = 12) and voluntary activation measured with cortical stimulation (VA<sub>TMS</sub>) (n = 11) (D)  
753 after severe- (S+ and S-) and heavy-intensity (RCP) constant-load cycling exercise. Values  
754 are mean ± SD. Symbols indicate a statistically significant difference ( $P < 0.05$ ) compared to  
755 the following: \* different from S-, † different from RCP.

756

757

#### Tables

758

759 **Table 1.** Motor evoked potentials (MEP), muscle compound action potentials (M-waves) and  
760 MEP/M-wave measured in vastus lateralis (VL) and rectus femoris (RF) during a sub-  
761 maximal contraction (20% MVC) pre- and post- constant-load cycling exercise. Values are  
762 mean ± SD (n = 11).

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### Supplemental Digital Content

765 Table, Supplementary Digital Content 1. Neuromuscular function and surface EMG  
766 responses (in *rectus femoris*) to motor nerve (n = 12) and motor cortical (n = 11) stimulation  
767 during contraction and at rest, pre- and post- severe- (S+ and S-) and heavy-intensity (RCP)  
768 constant-load cycling exercise. Values are mean  $\pm$ SD.

769

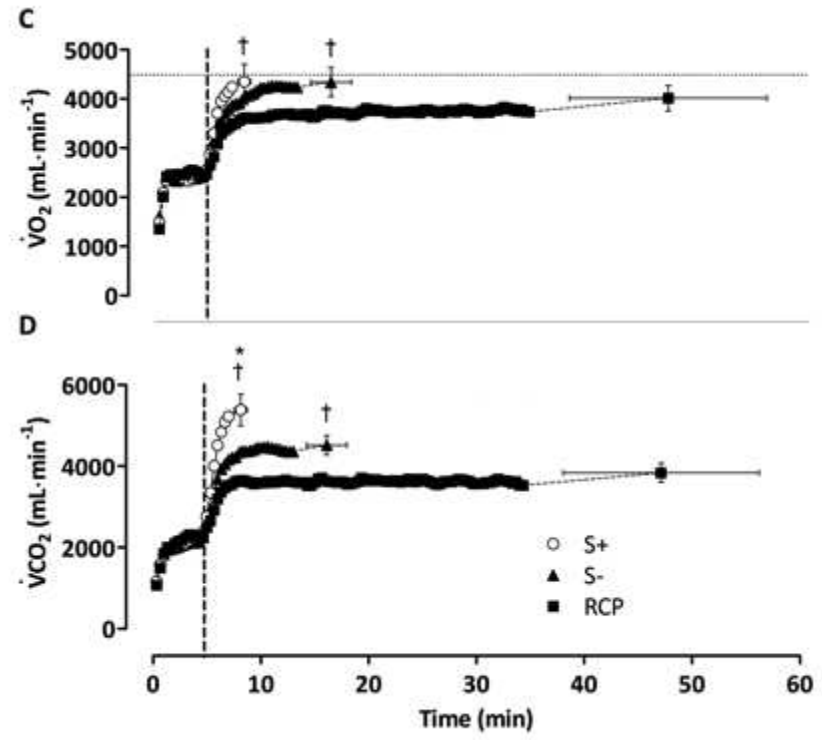
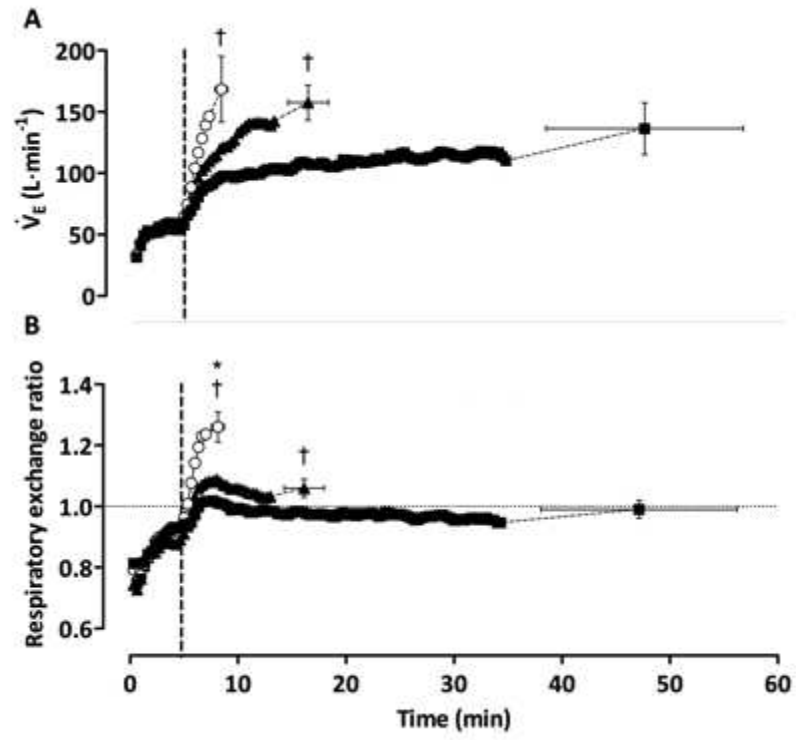
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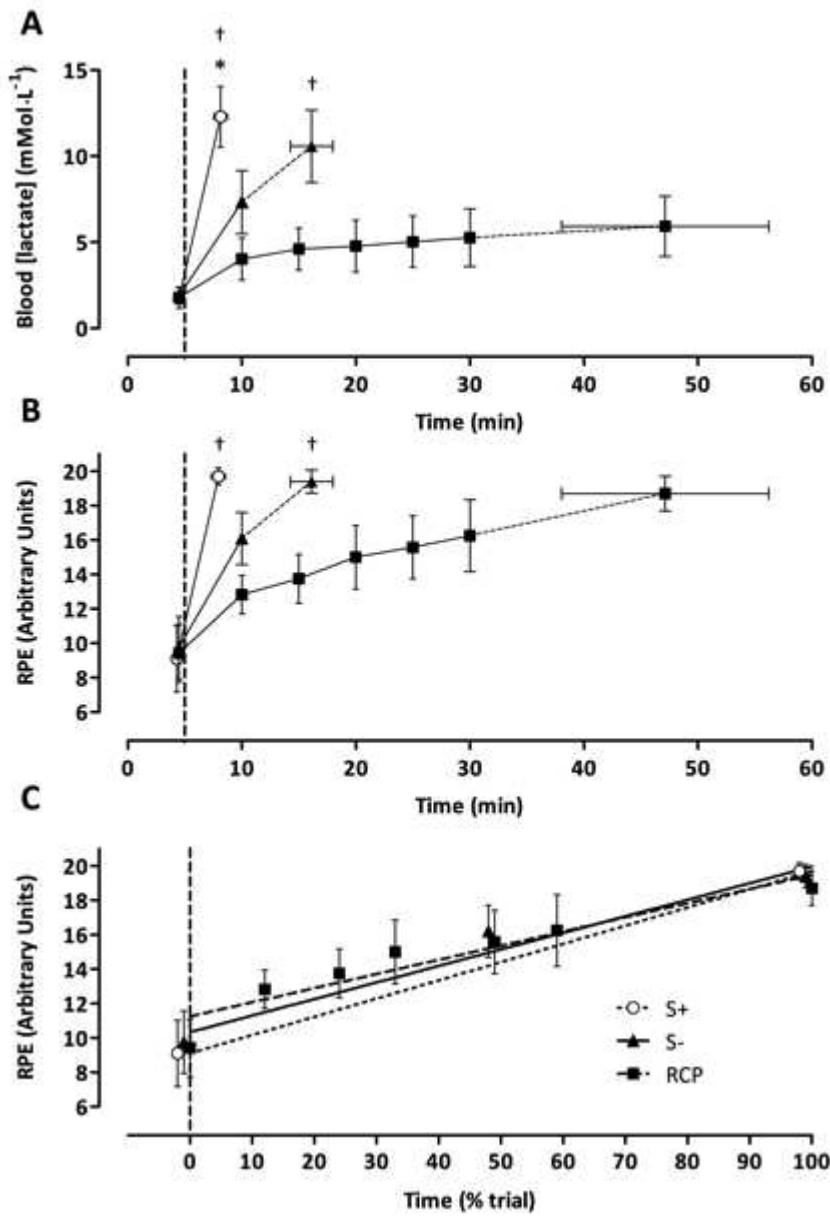
771 **Table 1.** Motor evoked potentials (MEP), muscle compound action potentials (M-waves) and  
 772 corticospinal excitability (MEP:M-wave) measured in vastus lateralis (VL) and rectus  
 773 femoris (RF) during a sub-maximal contraction (20% MVC) pre- and post- severe- (S+ and  
 774 S-) and heavy-intensity (RCP) constant-load cycling exercise. Values are mean  $\pm$  SD (n =  
 775 11).

776

		S+	S-	RCP
<i>Rectus Femoris</i>				
MEP	Pre	2.95 $\pm$ 2.20	3.11 $\pm$ 1.95	2.43 $\pm$ 1.46
amplitude (mV)	Post	2.64 $\pm$ 1.28	2.42 $\pm$ 1.58	2.34 $\pm$ 1.84
M-wave	Pre	5.36 $\pm$ 2.95	5.58 $\pm$ 2.60	5.51 $\pm$ 2.34
amplitude (mV)	Post	5.10 $\pm$ 3.04	5.77 $\pm$ 3.14	4.76 $\pm$ 3.61
MEP / M-wave	Pre	52 $\pm$ 16	54 $\pm$ 18	44 $\pm$ 18
(%)	Post	50 $\pm$ 20	43 $\pm$ 14	40 $\pm$ 14
<i>Vastus Lateralis</i>				
MEP	Pre	3.46 $\pm$ 2.15	2.26 $\pm$ 1.35	2.88 $\pm$ 2.29
amplitude (mV)	Post	2.94 $\pm$ 1.33	1.89 $\pm$ 0.76	1.74 $\pm$ 0.83
M-wave	Pre	9.19 $\pm$ 3.14	7.28 $\pm$ 2.70	8.92 $\pm$ 4.24
amplitude (mV)	Post	8.58 $\pm$ 3.36	7.03 $\pm$ 2.95	7.62 $\pm$ 3.72
MEP / M-wave	Pre	36 $\pm$ 16	31 $\pm$ 11	33 $\pm$ 17
(%)	Post	37 $\pm$ 19	28 $\pm$ 8	28 $\pm$ 13

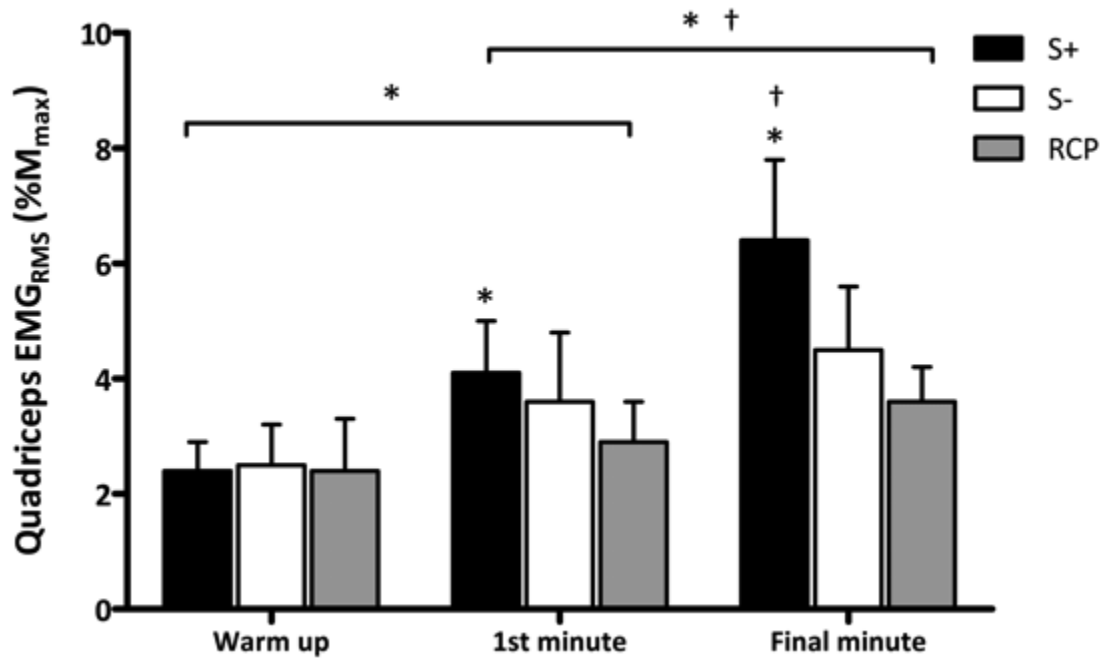
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