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Title: Effects of ipsilateral and contralateral fatigue and muscle blood flow occlusion on the complexity of knee extensor torque output in humans

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Author Conflict: No competing interests declared

Running Title: Fatigue-induced loss of torque complexity

Abstract: Neuromuscular fatigue reduces the temporal structure, or complexity, of torque output during muscular contractions. To determine whether the fatigue-induced loss of torque complexity could be accounted for by central or peripheral factors, nine healthy participants performed four experimental trials involving intermittent isometric contractions of the knee extensors at 50% of the maximal voluntary contraction (MVC) torque. These trials involved: 1) two bouts of contractions to failure using the right leg separated by 3 min recovery (IPS); 2) the same protocol but with cuff occlusion during the 3-min recovery (IPS-OCC); 3) contractions of the left leg to failure, followed 1 min later by contractions of the right leg to failure (CONT); and 4) the same protocol but with cuff occlusion applied to the left leg throughout both the recovery period and right leg contractions (CONT-OCC). Supramaximal electrical stimulation during MVCs was used to determine the degree of central and peripheral fatigue, whilst complexity was determined using Approximate Entropy (ApEn) and Detrended Fluctuation Analysis α

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exponent (DFA α). Neuromuscular fatigue was consistently associated with a loss of torque complexity in all conditions (e.g., IPS bout 1 ApEn from [mean {plus minus} SD]: 0.46 {plus minus} 0.14 to 0.12 {plus minus} 0.06 [P < 0.001]). In IPS-OCC, occlusion abolished the recovery from fatigue and torque complexity remained at the values observed at task failure in the preceding bout (IPS-OCC bout 2, first minute: 0.14 {plus minus} 0.03, P < 0.001). Prior contralateral contractions, with or without blood flow occlusion, had no effect on torque complexity.

New Findings: • In this study we show that the fatigue-induced loss of isometric torque complexity does not recover if the fatigued muscle's blood flow is occluded during recovery, suggesting a pivotal role for peripheral mechanisms in this effect. • When the contralateral limb is fatigued, the complexity of isometric torque output is unaffected even if the contralateral limb's blood flow is occluded, which suggests neither central fatigue nor afferent feedback from ischaemic muscle influence the complexity of torque output in an otherwise fresh muscle.

Dual Publication: No

1 **Effects of ipsilateral and contralateral fatigue and muscle blood flow occlusion on the**

2 **complexity of knee extensor torque output in humans.**

3

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New findings

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67   **Abstract**

68

69   Neuromuscular fatigue reduces the temporal structure, or complexity, of torque output during

70   muscular contractions. To determine whether the fatigue-induced loss of torque complexity

71   could be accounted for by central or peripheral factors, nine healthy participants performed

72   four experimental trials involving intermittent isometric contractions of the knee extensors at

73   50% of the maximal voluntary contraction (MVC) torque. These trials involved: 1) two bouts

74   of contractions to failure using the right leg separated by 3 min recovery (IPS); 2) the same

75   protocol but with cuff occlusion during the 3-min recovery (IPS-OCC); 3) contractions of the

76   left leg to failure, followed 1 min later by contractions of the right leg to failure (CONT); and

77   4) the same protocol but with cuff occlusion applied to the left leg throughout both the

78   recovery period and right leg contractions (CONT-OCC). Supramaximal electrical

79   stimulation during MVCs was used to determine the degree of central and peripheral fatigue,

80   whilst complexity was determined using Approximate Entropy (ApEn) and Detrended

81   Fluctuation Analysis α exponent (DFA α). Neuromuscular fatigue was consistently

82   associated with a loss of torque complexity in all conditions (e.g., IPS bout 1 ApEn from

83   [mean $\pm$ SD]: 0.46 ± 0.14 to 0.12 ± 0.06 [$P < 0.001$]). In IPS-OCC, occlusion abolished the

84   recovery from fatigue and torque complexity remained at the values observed at task failure

85   in the preceding bout (IPS-OCC bout 2, first minute: 0.14 ± 0.03, $P < 0.001$). Prior

86   contralateral contractions, with or without blood flow occlusion, had no effect on torque

87   complexity.

88

3

Introduction

Physiological systems produce outputs that inherently fluctuate over time (Goldberger et al., 2002). Such fluctuations are typically quantified according to their amplitude, using the standard deviation (SD) or coefficient of variation (CV), or their frequency content, using the fast Fourier transform. It is now recognised that these fluctuations can also be quantified according to their temporal structure or "complexity". Complex outputs are characterised by temporal irregularity, time irreversibility and long-range (fractal) correlations (Lipsitz and Goldberger, 1992; (Pincus, 1994; Goldberger et al., 2002), properties which amplitude and frequency metrics cannot quantify. Measures of complexity can be divided into those that quantify the regularity of the output (e.g. Approximate Entropy [ApEn]; Pincus, 1991) and those that quantify temporal fractal scaling and noise colour (e.g. Detrended Fluctuation Analysis [DFA]; Peng et al., 1994). The presence of complex outputs in physiological systems are thought to be a signature of good health (Peng et al., 2009). Consequently, a loss of complexity is indicative of system dysfunction, as frequently observed in ageing (as seen, inter alia, in heart rate dynamics, gait and muscle torque output; Goldberger et al., 2002; Manor and Lipsitz, 2012).

We have extended the loss of complexity observed in ageing to neuromuscular fatigue, demonstrating a reduction in torque complexity during intermittent isometric contractions of the knee extensors (Pethick et al., 2015). These experiments have demonstrated that as fatigue develops during high-intensity contractions (at 40-50% of the maximal voluntary contraction [MVC]), ApEn declines and the DFA α scaling exponent increases to values approximating 'Brownian' noise (DFA $\alpha = 1.50$), indicating a torque output that has become more regular and in which its previously fractal nature has broken down. However, because both central and peripheral fatigue developed during these contractions (i.e., mechanisms of force loss residing in the central nervous system or the muscle itself, respectively), the precise mechanistic origin of the fatigue-induced loss of torque complexity is not clear. As a first step towards resolving the mechanistic basis of the fatigue-induced loss of torque complexity, we have designed a series of experiments intended to accentuate either central or peripheral fatigue.

121 The fatigue-induced loss of torque complexity has been observed only during contractions

122 performed above the critical torque (Pethick et al., 2016), a threshold above which

123 metabolite-mediated peripheral fatigue (assessed using the potentiated doublet torque)

124 appears to be the dominant mechanism of force/torque loss (Burnley, 2009; Burnley et al.,

125 2012). This suggests that metabolite-mediated peripheral fatigue could be a major contributor

126 to the loss of torque complexity during high-intensity contractions (Pethick et al., 2016). If

127 so, we would expect to observe no recovery of torque complexity when a fatigued muscle is

128 subject to blood flow occlusion, which arrests arterial inflow and prevents recovery from

129 peripheral fatigue (Bigland-Ritchie et al., 1986; Quistorff et al., 1993; Gandevia et al., 1996;

130 Lanza et al., 2006).

131

132 We have recently observed that caffeine ingestion attenuates the development of central

133 fatigue (assessed using the twitch interpolation technique) and the fatigue-induced loss of

134 torque complexity, independently of the development of peripheral fatigue (Pethick et al.,

135 2018). This suggests the central processes make a small, but significant, contribution to the

136 fatigue-induced loss of torque. If the loss of torque complexity is mechanistically linked to

137 the myriad of central nervous system adjustments responsible for central fatigue, we would

138 expect that increased central fatigue at the start of an exercise bout, induced by prior exercise

139 of the homologous muscles of the contralateral limb (Zijdewind et al,. 1998; Todd et al.,

140 2003; Rattey et al., 2006), would result in reduced torque complexity.

141

142 It has also been proposed that central and peripheral fatigue mechanisms interact (Amann and

143 Dempsey, 2008); with metabosensitive group III and IV muscle afferents within working

144 muscle detecting exercise-induced metabolic perturbations associated with peripheral fatigue

145 (Kaufman et al., 2002). This results in a feedback loop, proposed to limit voluntary drive (i.e.

146 increases central fatigue) and restrict the development of further peripheral fatigue (Amann et

147 al., 2006; Amann et al., 2013). If such a feedback loop is involved in the fatigue-induced loss

148 of torque complexity, we would expect contractions performed whilst fatigued contralateral

149 muscle blood flow is occluded would result in a reduction in torque complexity.

150

151 The purpose of the present study was, therefore, to attempt to separate the effects of central

152 fatigue, peripheral fatigue and afferent feedback. The experimental hypotheses tested were:

153 1) that pre-existing peripheral fatigue, induced by circulatory occlusion, would decrease time

154 to task failure and reduce torque complexity; 2) that pre-existing central fatigue, induced by

155 prior exercise of the contralateral limb, would decrease time to task failure and reduce torque

156 complexity at the start of an exercise bout; and 3) that enhanced afferent feedback, induced

157 by prior exercise and occlusion of the contralateral limb, would decrease time to task failure

158 and reduce torque complexity at the start of an exercise bout.

159

160 **Materials and Methods**

161

162 Ethical approval

163 Nine healthy participants (5 male, 4 female; mean ± SD: age 23.9 ± 5.7 years; height 1.74 ±

164 0.09 m; body mass 66.0 ± 12.4 kg) provided written informed consent to participate in the

165 study, which was approved by the ethics committee of the University of Kent

166 (Prop_54_2014_2015), and which adhered to the Declaration of Helsinki, except for

167 registration in a database. Participants were instructed to arrive at the laboratory rested

168 (having performed no heavy exercise in the preceding 24 hours) and not to have consumed

169 any food or caffeinated beverages in the three hours before arrival. Participants attended the

170 laboratory at the same time of day (± 2 hours) during each visit.

171

172 Experimental design

173 Participants were required to visit the laboratory on five occasions, with a minimum of 48

174 hours between visits. During their first visit, participants were familiarised with all testing

175 equipment and procedures, and the settings for the dynamometer and stimulator were

176 recorded. During visits two to five, participants performed a series of intermittent isometric

177 contractions to task failure, during which we attempted to manipulate the type and degree of

178 neuromuscular fatigue that the participants experienced ("Experimental trials"; see below).

179 These trials were presented in a randomised order.

180

181 Dynamometry

182 Participants sat in the chair of a Cybex isokinetic dynamometer (HUMAC Norm; CSMi,

183 Stoughton, Massachusetts, USA), initialised and calibrated according to the manufacturer's

184 instructions. Participants sat with relative hip and knee angles of 85° and 90°, respectively

185 with full extension being 0°. The leg to be tested was attached to the lever arm of the

186 dynamometer, with the seating position adjusted to ensure that the lateral epicondyle of the

187 femur was in line with the axis of rotation of the lever arm. The lower leg was securely

188 attached to the lever arm above the malleoli with a padded Velcro strap. Straps secured firmly

189 across the waist and shoulder prevented any extraneous movement and the use of the hip

190 extensors during the isometric contractions. The seating position was recorded during the

191 familiarisation and replicated during each subsequent visit.

192

193 Femoral nerve stimulation

194 The anode, a carbon rubber electrode with adhesive gel (100 mm x 50 mm; Phoenix

195 Healthcare Products Ltd., Nottingham, UK), was placed lateral to the ischial tuberosity, on

196 the posterior aspect of the leg. The position of the cathode was located using a motor point

197 pen (Compex; DJO Global, Guildford, UK), and an Ag/AgCl electrode (32 x 32 mm; Nessler

198 Medizintechnick, Innsbruck, Austria) was placed over that point. Establishment of the

199 appropriate stimulator current was performed as described by Pethick et al. (2015), using a

200 constant-current, variable voltage stimulator (Digitimer. DS7AH, Welwyn Garden City, UK).

201 Briefly, current was incrementally increased until knee extensor twitch torque and the

202 compound motor unit action potential (M-wave) response to single twitches had plateaued

203 and was verified with stimulation delivered during a contraction at 50% MVC to ensure a

204 maximal M-wave was also evident during an isometric contraction. The stimulator current

205 was then increased to 130% of the current producing a maximal M-wave. In all trials, doublet

206 stimulation (two 200 µs pulses with 10 ms interpulse interval) was then used.

207

208 Electromyography

209 On arrival at the laboratory participants had the leg(s) to be tested shaved and cleaned using

210 an alcohol swab over the belly of the vastus lateralis and on the medial aspect of the tibia at

211 the level of the tibial tuberosity. Two Ag/AgCl electrodes (32 x 32 mm; Nessler

212 Medizintechnik, Innsbruck, Austria) were placed on the vastus lateralis in line with the

213 muscle fibres and a single electrode placed on the tibial tuberosity for EMG acquisition.

214

215 Protocol

216 All visits followed a similar pattern of data acquisition, beginning with the instrumentation of

217 the participants and the (re-)establishment of the correct dynamometer seating position and

218 supramaximal stimulation response. Participants then performed a series of brief (3 s) MVCs

219 to establish their maximum torque. These contractions were separated by 60 s rest, and

220 continued until three consecutive peak torques were within 5% of each other. Participants

221 were given a countdown, followed by very strong verbal encouragement to maximise torque.

222 The first MVC was used to establish the fresh maximal EMG signal, against which the

223 subsequent EMG signals were normalised ("Data analysis"; see below). The second and third

224 MVCs were performed with peripheral nerve stimulation. In all instances, where MVCs were

225 performed with stimuli, the stimuli were manually delivered ~1.5 s into the contraction to

226 coincide with maximal torque, in order to test the maximality of the contraction and provide

227 the voluntary activation; and 2 s after the contraction, to provide a resting potentiated doublet.

228

229 In the visits involving contractions performed on both legs, after ten minutes rest participants

230 repeated this process for the left leg. Following the establishment of maximal torque,

231 participants rested for a further ten minutes and then performed one of the experimental trials

232 (see below).

233

234 Experimental trials

235 The four experimental trials were termed: 1) Ipsilateral trial (IPS); 2) Contralateral trial

236 (CONT; 3) Ipsilateral trial with occlusion (IPS-OCC); and 4) Contralateral trial with

237 occlusion (CONT-OCC). All four trials consisted of two bouts of exercise. IPS involved

238 exercising the right leg to task failure, followed by three minutes rest, and then exercising the

239 right leg to task failure again. CONT involved exercising the left leg to task failure, then

240 switching to the right leg and exercising to task failure. The switch from the left to right leg

241 in the CONT and CONT-OCC conditions took approximately 50 seconds, and the second

242 exercise bout was commenced 60 seconds after completion of the first bout. IPS-OCC

243 involved exercising the right leg to task failure, then resting for three minutes with the blood

244 flow to the right leg occluded, and then exercising the right leg to task failure again (with the

245 occlusion released). CONT-OCC involved exercising the left leg to task failure, then

246 occluding blood flow to the left leg and immediately switching to the right leg and exercising

247 to task failure. During this trial, the occlusion of the left leg was released after six minutes of

248 contractions or at task failure, whichever occurred sooner. Blood flow occlusion in the IPS-

249 OCC and CONT-OCC trials was accomplished using a standard, double-bladder, adult thigh

250 cuff, rapidly inflated to a pressure of 200 mmHg using compressed air (AG101, D.E.

251 Hokanson Inc., Washington, USA). The trials are presented schematically in Figure 1.

252

253 During visit two (the first of the experimental trials), the highest instantaneous pre-test

254 measure of voluntary torque was recorded as the peak MVC torque, and 50% of this value

255 was used as the target torque for the subsequent trials. As in our previous work (Pethick et

256 al., 2015; Pethick et al., 2016), the submaximal contractions were performed using a duty

cycle of 0.6; with contractions held for 6 s, followed by 4 s rest. Participants 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 s contraction as possible. At the end of each minute (i.e. every sixth contraction), participants performed an MVC, accompanied by peripheral nerve stimulation. Each exercise bout was conducted until task failure, the point at which the participant failed to reach the target torque on three consecutive occasions, despite strong verbal encouragement. Participants were not informed of the elapsed time during the test, but were informed of each "missed" contraction. After the third consecutive missed contraction, participants were instructed to immediately produce an MVC, which was accompanied by peripheral nerve stimulation.

Following the MVC at the end of the first exercise bout, participants rested for three minutes and exercised the same leg again (IPS and IPS -OCC) or switched (over the course of 60 s, see above) to exercising their other leg (CONT and CONT-OCC). Immediately prior to the commencement of the second exercise bout, participants performed an MVC of the leg to be exercised in the second bout, accompanied by peripheral nerve stimulation. The second exercise bout was then performed in an identical manner to the first.

Data acquisition and participant interface

Data acquisition was performed in the same manner as described in Pethick et al. (2015). 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 participants were able to match their instantaneous torque output to the target torque during each test.

Data analysis

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

291

Torque and EMG. The mean and peak torque for every contraction in each exercise bout conducted on the right leg were determined. The mean torque was calculated based on the steadiest five seconds of each contraction. Task failure was determined as in Pethick et al. (2015). The mean contraction torque produced during the first five contractions was calculated, and task failure was deemed to have occurred when participants' mean torque output failed to achieve that of the first five contractions by more than 5 N·m for three consecutive contractions, with the first of these contractions being the point of task failure.

The EMG output from the vastus lateralis was filtered (10-500 Hz) and full-wave rectified with a gain of 1000. The average rectified EMG (arEMG) for each contraction was then calculated and normalised by expressing the arEMG as a fraction of the arEMG obtained during an MVC from the fresh muscle performed at the beginning of each 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, during the exercise bouts and at task failure. Peripheral fatigue was assessed by a fall in the peak potentiated doublet torque; and central fatigue was assessed by the decline in voluntary activation, quantified using the twitch interpolation technique (Behm et al., 1996):

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

where the superimposed doublet was 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 and complexity were calculated using the steadiest five seconds of each contraction; that is, the five seconds containing the lowest standard deviation (SD; Forrest et al., 2014). The amount of variability in the torque output of each contraction was measured using the SD, which provides a measure of the absolute amount of variability in a time-series, and the coefficient of variation (CV), which provides a measure of the amount of variability in a time-series normalised to the mean of the time-series.

323

10

The temporal structure, or complexity, of torque output was examined using multiple time domain analyses. As in our previous work (Pethick et al., 2015; Pethick et al., 2016), the complexity of the torque output was determined using Approximate Entropy (ApEn; Pincus, 1991), and temporal fractal scaling was estimated using Detrended Fluctuation Analysis (DFA; Peng et al., 1994). Sample Entropy was also calculated (Richman and Moorman, 2000), though as shown in Pethick et al. (2015) this measure did not differ from ApEn and was not included in the present analysis. As detailed in Pethick et al. (2015), 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).

Statistics

All data are presented as means ± SD. The first exercise bout of the IPS trial (IPS1) acted as a control, against which the second exercise bouts of the experimental trials (IPS2, CONT2, IPS-OCC2 and CONT-OCC2) were compared. The first exercise bouts of the CONT, IPS-OCC and CONT-OCC trials were used to induce pre-existing fatigue in the right leg and were not considered for analysis. Two-way 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 analysed using means from the first minute and final minute before task failure. The rates of change in all parameters were analysed using one-way ANOVAs with repeated measures. Main effects were considered significant when $P < 0.05$. When main effects were observed, Bonferroni-adjusted 95% confidence intervals were then used to determine specific differences.

Results

Time to task failure and MVC torque

Time to task failure in IPS1 (the control trial, with no pre-existing fatigue) was 4.7 ± 2.7 min. There was a significant effect of condition on time to task failure (F = 17.52, P < 0.001). Time to task failure was significantly shorter in IPS2 and IPS-OCC2 compared to IPS1 (paired samples confidence intervals (CIs): IPS1 vs. IPS2, –5.0, –0.4 mins; IPS vs. IPS-OCC2, –6.8, –1.4 mins; Table 1). Time to task failure was not significantly different in

357 CONT2 or CONT-OCC2 compared to IPS1 (CIs: IPS1 vs. CONT2, –1.1, 2.8 mins; IPS1 vs.

358 CONT-OCC2, –0.4, 2.0 mins; Table 1).

359

360 Task failure occurred when participants were no longer able to achieve the target torque

361 (106.6 ± 31.6 N·m), despite a maximal effort. All trials resulted in significant decreases in

362 MVC torque (F = 25.66, P = 0.001), except for IPS-OCC2 (CIs: –26.6, 28.6 N·m), in which

363 neither the pre- nor post-test MVC torques were significantly different from the target torque.

364 At task failure neither the peak, nor the mean, MVC torques in any trial were significantly

365 different from the torque produced during the submaximal contractions (Table 1). MVC

366 torque was significantly lower at the start of the second exercise bout compared to IPS1 for

367 all conditions (F = 21.99, P < 0.001), except for CONT2 (CIs: –8.3, 65.3 N·m). Significant

368 recovery of the right leg was observed at the start of IPS2 (CIs: 8.0, 75.5 N·m), but not IPS-

369 OCC2 (CIs: –8.4, 38.4 N·m).

370

371 Peripheral and central fatigue

372 There was a condition x time interaction for potentiated doublet torque (F = 8.92, P = 0.004),

373 and all trials resulted in significant reductions in potentiated doublet torque (F = 47.22, P <

374 0.001; Table 1), indicating the presence of peripheral fatigue. Potentiated doublet torque was

375 significantly lower at the start of the second bout of exercise compared to IPS1 for all

376 conditions, except for CONT-OCC2 (CIs: –12.3, 26.7 N·m; Table 1). The values attained at

377 task failure were not significantly different between the trials (Table 1). Significant recovery

378 was observed at the start of IPS2 (CIs: 9.1, 39.9 N·m), but not IPS-OCC2 (CIs: –30.9, 5.1

379 N·m).

380

381 Voluntary activation demonstrated a condition x time interaction (F = 4.45, P = 0.022), with

382 VA declining across IPS2 (CIs: –2.4, –22.2%) and CONT2 (CIs: –35.0, –9.2%), indicating

383 the presence of central fatigue. Voluntary activation was significantly lower at the start of the

384 second bout of exercise compared to IPS1 for IPS2 (CIs: –23.0, –2.9%) and IPS-OCC2 (CIs:

385 –28.4, –8.5%). The values attained at task failure were not significantly different between the

386 conditions (Table 1). No recovery was observed at the start of either IPS2 (CIs: –20.4, 6.7%)

387 or IPS-OCC2 (CIs: –23.0, 20.2%).

388

389 Variability and complexity

390   The variability and complexity data are presented in Table 2. There were significant
391   condition x time interactions for both the SD (F = 5.62, P = 0.002) and CV (F = 7.74, P =
392   0.004). The SD significantly increased over time in IPS1 (CIs: 2.8, 8.3 N·m) and CONT-
393   OCC2 (CIs: 1.6, 3.9 N·m). The CV significantly increased in all conditions, except for IPS-
394   OCC2 (CIs: –0.02, 0.01 %). The amount of variability was significantly greater at the start of
395   IPS-OCC2 compared to IPS1 (CIs: SD, 0.3, 5.3 N·m; CV, 0.007, 0.06 %). The values
396   attained at task failure were not significantly different for either the SD or CV (Table 2).

397

398   The torque profiles of contractions in a representative participant in all conditions is shown in
399   Figure 2. The mean time course of complexity in the ipsilateral and contralateral conditions is
400   shown in Figures 3 and 4, respectively. Complexity, as measured by ApEn, demonstrated a
401   condition x time interaction (F = 14.97, P < 0.001). The ApEn decreased as a function of
402   time in all conditions except for IPS-OCC2 (CIs: –0.02, 0.05). The ApEn was significantly
403   lower at the start of IPS-OCC2 compared to IPS1 (CIs: –0.5, –0.2). There were no significant
404   differences between conditions at task failure (Table 2). Significant recovery was observed at
405   the start of IPS2 (CIs: 0.04, 0.4), but not IPS-OCC2 (CIs: –0.1, 0.07).

406

407   There was a significant condition x time interaction for the DFA α exponent (F = 18.45, P <
408   0.001). The DFA α exponent increased with time in all conditions, except for IPS-OCC2
409   (CIs: –0.03, 0.03). DFA α was significantly greater at the start of IPS-OCC2 compared to
410   IPS1 (CIs: 0.03, 0.3). There were no significant differences between the values attained at
411   task failure between the different conditions (Table 2). Significant recovery was observed at
412   the start of IPS2 (CIs: 0.03, 0.2), but not IPS-OCC2 (CIs: –0.08, 0.2).

413

414   **Discussion**

415

416   The major novel findings of the present study were as follows: 1) that fatigue in the ipsilateral
417   limb, followed by 3 minutes of passive recovery (the IPS trial), resulted in the recovery of
418   torque output complexity to values close to that in fresh muscle at the onset of subsequent
419   isometric contractions. 2) The recovery from fatigue, and of torque complexity, was
420   abolished when muscle blood flow was occluded (the IPS-OCC trial), and participants were
421   unable to complete a full minute of contractions. 3) Contractions of the contralateral limb
422   performed to task failure, followed by contractions of the unexercised limb (the CONT trial)

423 resulted in no crossover of central fatigue and no significant effect on torque output
424 complexity. 4) Performing contractions of the contralateral limb and occluding blood flow at
425 task failure in order to accentuate afferent feedback (the CONT-OCC trial) did not result in
426 increased central fatigue or significant reductions in torque output complexity. These findings
427 suggest that the fatigue-induced loss of torque complexity can be attributed primarily to
428 events occurring in the periphery. Ultimately, however, the torque output (and its complexity)
429 represents the integration of central and peripheral processes, as reflected in the lack of
430 recovery of central fatigue in the IPS-OCC condition.

431

432 Complexity and neuromuscular fatigue in pre-fatigued muscle
433 At the start of the second bout of the IPS trial (IPS2), which was designed to provide
434 incomplete recovery from neuromuscular fatigue, significant decrements in MVC torque,
435 potentiated doublet torque and voluntary activation were evident compared with fresh muscle
436 (Table 1: IPS1). These observations indicate that neuromuscular function remained
437 compromised for the subsequent exercise bout, a fact confirmed by the significantly shorter
438 time to task failure in IPS2 (Table 1). Nevertheless, the complexity values at the start of IPS2
439 were not significantly different from fresh muscle, though were, nonetheless, blunted (Table
440 2; Figure 2). That there was evidence of neuromuscular fatigue at the onset of exercise
441 suggests that the recovery kinetics of neuromuscular complexity is somewhat faster than that
442 of neuromuscular fatigue. One interesting observation is that in IPS2 the initial EMG
443 amplitude was higher as a fraction of the normalised maximum than IPS1 (~70% vs. ~55%)
444 suggesting that a larger recruitment and/or firing frequency was required throughout IPS2.
445 The complexity of torque output in this bout rapidly declined to values similar at task failure
446 to IPS1. We have previously demonstrated that torque complexity can be systematically
447 reduced by both increasing the absolute demand of a task (i.e. by increasing torque
448 requirements) or by increasing the relative demand of a task (i.e. by fatiguing the muscle;
449 Pethick et al., 2015; Pethick et al., 2016). In this case, it appears that the carry-over effects of
450 fatigue in IPS2 more rapidly increased the relative demand of the task, resulting in a
451 precipitous fall in complexity alongside the mechanical measures of central and peripheral
452 fatigue.

453

454 The IPS-OCC condition was designed to prevent the recovery from peripheral fatigue by
455 occluding the leg for 3 min after contractions performed to task failure. The results showed
456 that occlusion completely abolished the recovery from fatigue of all types (Table 1; Figure 2),

457   a finding consistent with previous research (Bigland-Ritchie et al., 1986; Woods et al., 1987;

458   Quistorff et al., 1993). As a result, the time to task failure during subsequent contractions was

459   significantly shorter than when fresh, with participants unable to complete a full minute of

460   exercise (Table 1). Knee extensor torque complexity at the start of IPS-OCC2 was also no

461   different than at task failure in IPS1 (Table 2), indicating that circulatory occlusion prevented

462   its recovery. Given that circulatory occlusion holds the muscle ischaemic, preventing the

463   recovery of the muscle metabolic milieu (Yoshida and Watari, 1997; Lanza et al., 2006), it is

464   likely that the failure of ApEn and DFA α to demonstrate any recovery was mediated, at least

465   partially, by this maintained peripheral fatigue. However, the loss of torque complexity does

466   not simply appear to be caused by a peripheral fatigue-induced failure to transduce central

467   drive into mechanical output, since a depression in voluntary activation was also present at

468   the onset of contractions. The mechanism of this maintained central fatigue following

469   occlusion is not as obvious as its peripheral counterpart, but the previous observation of the

470   rapid recovery in the EMG response to motor cortex stimulation during cuff occlusion of the

471   arm suggests the effects occur upstream of the motor cortex (Gandevia et al., 1996).

472   Specifically, the perturbed muscle metabolic milieu may have been detected by group III and

473   IV afferents, resulting in inhibitory feedback acting to limit motor cortical drive (Gandevia et

474   al., 1996; Amann and Dempsey, 2008; Amann et al., 2011). Such a response would seem to

475   suggest that peripheral and central fatigue are inextricably linked under these experimental

476   conditions, with changes in torque output complexity reflecting the integrated response to

477   neuromuscular fatigue.

478

479   We performed two trials which initially exercised the left knee extensors to task failure

480   followed by 1 min rest and then contractions of the right knee extensors to failure (CONT), or

481   the same protocol with cuff occlusion from task failure of the left knee extensors maintained

482   until task failure of the right knee extensors occurred (CONT-OCC). Both were performed in

483   an attempt to isolate the effects of central fatigue on subsequent exercise. CONT-OCC was

484   itself performed in an attempt to further diminish central drive consequent to afferent

485   feedback. In contrast to our hypotheses, neither condition influenced the extent or

486   progression of central fatigue nor the loss of knee extensor torque complexity (Table 1, Table

487   2, Figure 3 and Figure 4). Therefore, fatiguing contralateral exercise, with or without cuff

488   occlusion, did not reduce voluntary activation. Although the potentiated doublet was

489   significantly reduced following the CONT trial, this reduction was relatively small and does

490   not appear to have had any functional impact, since surface EMG, as well as measures of

491   variability and complexity did not change compared to IPS1. These results suggest that

492   contralateral exercise had no meaningful effect on central or peripheral function in the

493   unexercised leg, and thus no effect on torque complexity. Our failure to disentangle the

494   effects of central and peripheral fatigue experimentally is most likely an indication that the

495   fatigue-induced loss of torque complexity has both central and peripheral components which

496   cannot be effectively separated.

497

498   Physiological basis for changes in neuromuscular system behaviour

499   The sustained loss of torque complexity only following ipsilateral exercise and femoral

500   occlusion adds weight to our previous suggestion that peripheral fatigue is a major

501   contributor to the loss of neuromuscular complexity (Pethick et al., 2016). This loss of torque

502   complexity was associated with both peripheral and central fatigue at the onset of

503   contractions in IPS-OCC2. The reduced mechanical output of the motor units, reflected in the

504   decreased potentiated doublet torque, cannot on its own explain the reduced torque

505   complexity, since this would only serve to reduce the amplitude of torque fluctuations. Such a

506   reduction would have no effect on the complexity metrics used in the present study, and in

507   any case the amplitude of torque fluctuations actually increased with muscle fatigue (SD and

508   CV data in Table 2). To alter torque complexity, the pattern of motor unit firing must also

509   have changed in some way. It may be, therefore, that metabolite-mediated peripheral fatigue

510   is simply a pre-requisite for central adjustments which act on the motor unit pool and are

511   themselves responsible for the loss of torque complexity (see below).

512

513   We have previously speculated that increased common synaptic input to motoneurons could

514   be responsible for the fatigue-induced loss of torque complexity (Pethick et al., 2016). It has

515   recently been demonstrated that common synaptic input to motoneurons is increased with the

516   development of neuromuscular fatigue (Castronovo et al., 2015). As common synaptic input

517   has been proposed as the main determinant of torque variability (Diderkisen et al., 2012;

518   Farina et al., 2014), any increase in this common synaptic input could be reflected in a

519   change in torque complexity. Motor unit synchronisation, the correlated discharge of action

520   potentials (Semmler, 2002), is a necessary consequence of common synaptic input and

521   should, therefore, also increase as common synaptic input increases. Increased motor unit

522   synchronisation has been associated with reduced force steadiness during simulated

523   contractions (Yao et al., 2000), decreased complexity of postural tremor with ageing

524   (Sturman et al., 2005), and increased regularity in the surface EMG as fatigue develops

525   (Mesin et al., 2009; Beretta-Piccoli et al., 2015). Fatigue at the start of the IPS-OCC2 bout

526   may, therefore, have been accompanied by increased common synaptic input and motor unit

527   synchronisation, with this being responsible for the reduced complexity observed. However,

528   direct measurements of motor unit behaviour will be required to confirm this.

529

530   As observed previously (Pethick et al., 2016), the values of each of ApEn, the DFA α

531   exponent, and the potentiated doublet torque reached consistently low values at task failure

532   across experimental conditions, despite each commencing with different levels of fatigue and

533   complexity. It has been suggested that consistent levels of peripheral fatigue at the

534   termination of exercise might reflect the achievement of a 'sensory tolerance limit' (see

535   Hureau et al., 2016 for review). The sensory tolerance limit proposes that metabolic

536   perturbations (i.e. those contributing to peripheral fatigue) are detected by group III and IV

537   afferents, which provide inhibitory feedback to the central nervous system at various levels.

538   This, in turn, reduces central motor drive in order to restrict the development of peripheral

539   fatigue beyond a certain limit (Amann et al., 2006). Evidence is accumulating to suggest an

540   important role for the aforementioned afferents in CNS adjustments during various types of

541   physical exercise (Blain et al., 2016). It is therefore tempting to link the consistency of torque

542   complexity to the sensory tolerance limit hypothesis. However, present data show only that

543   torque complexity is one of a number of parameters which reach similarly low (or high)

544   values at task failure. The functional significance of these findings is unclear, but consistently

545   low complexity at task failure could be viewed in the following way: neuromuscular fatigue

546   results in maximal or near maximal effort being required to attain the desired target torque,

547   and maximal efforts are associated with low torque complexity (Pethick et al., 2015). In

548   addition, the increased variability in torque output results in targeting error which, by virtue

549   of low physiological complexity, the neuromuscular system can no longer correct with

550   sufficient haste (i.e., the system has lost its adaptability; Pethick et al., 2016). Task failure,

551   from this perspective, is a fatigue-induced loss of motor control and adaptability. To what

552   extent the processes purported to account for the sensory tolerance limit might contribute to

553   the loss of motor control at this point (by limiting further increases in central drive) requires

554   further experimentation.

555

556   Limitations

557 In the present experiments, it was not possible to perform the switch between measures of the
558 left (contralateral) leg and the right leg instantaneously, due to the design of the
559 dynamometer. The delay between measurements (1 minute) may, therefore, have reduced the
560 degree of central fatigue measured in CONT and CONT-OCC. Voluntary activation has been
561 shown to recover within 2 min following fatiguing contractions (for review, see Carroll et al.,
562 2016). However, as occlusion has been shown to prevent the recovery of voluntary activation
563 (Gandevia et al., 1996) any reduction would have been preserved in the CONT-OCC
564 condition. This was not the case, and we therefore concluded that central fatigue did not
565 influence either of the CONT conditions. We were also unable to measure muscle metabolite
566 concentration or muscle oxygenation to establish the effect of occlusion on these parameters.
567 However, we are confident that occlusion was effective due to the lack of recovery in both
568 fatigue and complexity in the IPS-OCC trial. Finally, direct measurements of motor unit
569 behaviour during fatiguing contractions will be necessary in future work to establish the
570 precise neurophysiological basis for the loss in torque output complexity.

571

572 Conclusion

573 In summary, this study has demonstrated that pre-existing fatigue influences the complexity
574 of knee extensor torque at the start of an exercise bout. Specifically, when recovery from
575 fatigue was prevented by occluding the previously exercised leg for 3 minutes, the recovery
576 of complexity was also abolished, in contrast to the same protocol performed without
577 occlusion. Contralateral contractions performed to failure, with or without subsequent
578 occlusion, did not significantly diminish torque complexity during subsequent contractions of
579 the opposite leg. These results support the notion that peripheral fatigue is a primary
580 contributor to the loss of torque complexity. However, since torque output complexity is
581 ultimately the expression of both central and peripheral processes, the loss of torque
582 complexity is most likely to be an integrated response of both to this peripheral fatigue.

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Additional information:

Table 1. Voluntary torque, potentiated doublet, voluntary activation, and EMG responses during contractions in the first exercise bout of IPS and the second exercise bouts of IPS, CONT, IPS-OCC and CONT-OCC.

Parameter	IPS1	IPS2	CONT2	IPS-OCC2	CONT-OCC2
Mean test torque, N·m	106.6 ± 31.6				
Time to task failure, min	4.7 ± 2.7	2.0 ± 0.9^b	3.8 ± 2.3	0.6 ± 0.4^b	3.9 ± 1.4
Global fatigue					
Pre-exercise MVC, N·m	218.9 ± 72.0	$157.2 \pm 37.3^{b,c}$	190.4 ± 68.8	100.4 ± 15.0^b	180.6 ± 57.5^b
Peak MVC at task failure, N·m	115.4 ± 19.1^a	112.4 ± 31.6^a	108.1 ± 14.4^a	99.4 ± 24.5	119.6 ± 16.7^a
Mean MVC at task failure, N·m	97.9 ± 23.2^a	93.2 ± 25.2^a	97.3 ± 19.1^a	85.1 ± 23.1	100.3 ± 13.1^a
Peripheral fatigue					
Pre-exercise doublet, N·m	95.7 ± 23.6	$77.3 \pm 17.7^{b,c}$	86.4 ± 22.0^b	65.7 ± 15.5^b	88.5 ± 29.0
Doublet at task failure, N·m	52.8 ± 9.7^a	$53.7 \pm 13.4^{a,b}$	$55.7 \pm 12.6^{a,b}$	$55.9 \pm 15.0^{a,b}$	$58.8 \pm 14.0^{a,b}$
% Change at task failure	43.4 ± 11.7	30.7 ± 7.2	34.6 ± 11.4	15.2 ± 12.3	31.3 ± 15.6
Central fatigue					
Pre-exercise VA, %	92.5 ± 2.6	79.5 ± 9.8^b	88.9 ± 8.9	74.1 ± 6.7^b	89.6 ± 5.5
VA at task failure, %	72.7 ± 18.0	$67.2 \pm 14.7^{a,b}$	$66.8 \pm 9.2^{a,b}$	73.9 ± 7.3^b	75.2 ± 13.4^b
% Change at task failure	21.6 ± 20.1	16.2 ± 12.9	24.5 ± 10.8	0.2 ± 10.5	15.5 ± 18.0
Surface EMG					
arEMG at task beginning, % MVC	55.6 ± 6.9	70.1 ± 14.9	56.3 ± 10.3	68.7 ± 13.8	61.0 ± 9.1
arEMG at task failure, % MVC	75.7 ± 20.5^a	74.1 ± 16.7	71.5 ± 26.5	69.1 ± 14.1	77.2 ± 23.8

Values are means ± SD, n = 9. IPS1 is the first exercise bout in the global fatigue condition; IPS2, CONT2, IPS-OCC2 and CONT-OCC2 are the second exercise bouts in these respective conditions; MVC, maximal voluntary contraction; VA, voluntary activation; arEMG, average rectified EMG of the vastus lateralis. Letters indicate a statistically significant difference compared to the following: [a]pre-exercise/task beginning value, [b]IPS1, [c]IPS1 at task failure.

Table 2. Variability, complexity and fractal scaling responses during contractions in the first exercise bout of IPS and the second exercise bouts of IPS, CONT, IPS-OCC and CONT-OCC.

Parameter	IPS1	IPS2	CONT2	IPS-OCC2	CONT-OCC2
SD					
SD at task beginning, N·m	3.1 ± 1.0	3.6 ± 1.6	3.6 ± 1.6	5.9 ± 3.0[b]	4.4 ± 2.7
SD at task failure, N·m	8.6 ± 1.1[a]	7.6 ± 1.6	8.4 ± 2.0	6.3 ± 0.9	7.2 ± 1.0[a]
CV					
CV at task beginning, %	2.9 ± 0.4	3.4 ± 1.1	3.6 ± 1.3	6.1 ± 2.1[b]	4.1 ± 2.0
CV at task failure, %	8.8 ± 1.6[a]	7.7 ± 3.1[a]	8.4 ± 3.6[a]	6.8 ± 2.4	7.3 ± 2.4[a]
ApEn					
ApEn at task beginning	0.46 ± 0.14	0.35 ± 0.17[c]	0.38 ± 0.16	0.14 ± 0.08[b]	0.34 ± 0.16
ApEn at task failure	0.12 ± 0.06[a]	0.15 ± 0.06[a]	0.14 ± 0.09[a]	0.12 ± 0.07	0.14 ± 0.05[a]
DFA α					
DFA α at task beginning	1.39 ± 0.10	1.49 ± 0.08[c]	1.44 ± 0.10	1.56 ± 0.10[b]	1.48 ± 0.11
DFA α at task failure	1.60 ± 0.05[a]	1.58 ± 0.05[a]	1.62 ± 0.06[a]	1.56 ± 0.10	1.62 ± 0.06[a]

Values are means ± SD, n = 9. IPS1 is the first exercise bout in the neuromuscular fatigue condition; IPS2, CONT2, IPS-OCC2 and CONT-OCC2 are the second exercise bouts in these respective conditions; SD, standard deviation; CV, coefficient of variation; ApEn, approximate entropy; DFA α, detrended fluctuation analysis. Letters indicate a statistically significant different compared to the following: [a]pre-exercise value/value at task beginning, [b]IPS1, [c]IPS1 at task failure.

Figure legends

Figure 1: Schematic of the experimental trials

IPS, ipsilateral trial; IPS-OCC, ipsilateral occlusion trial; CONT, contralateral trial; CONT-OCC, contralateral occlusion trial. Black bars represent intermittent contractions of the leg in question, grey bars represent periods of occlusion.

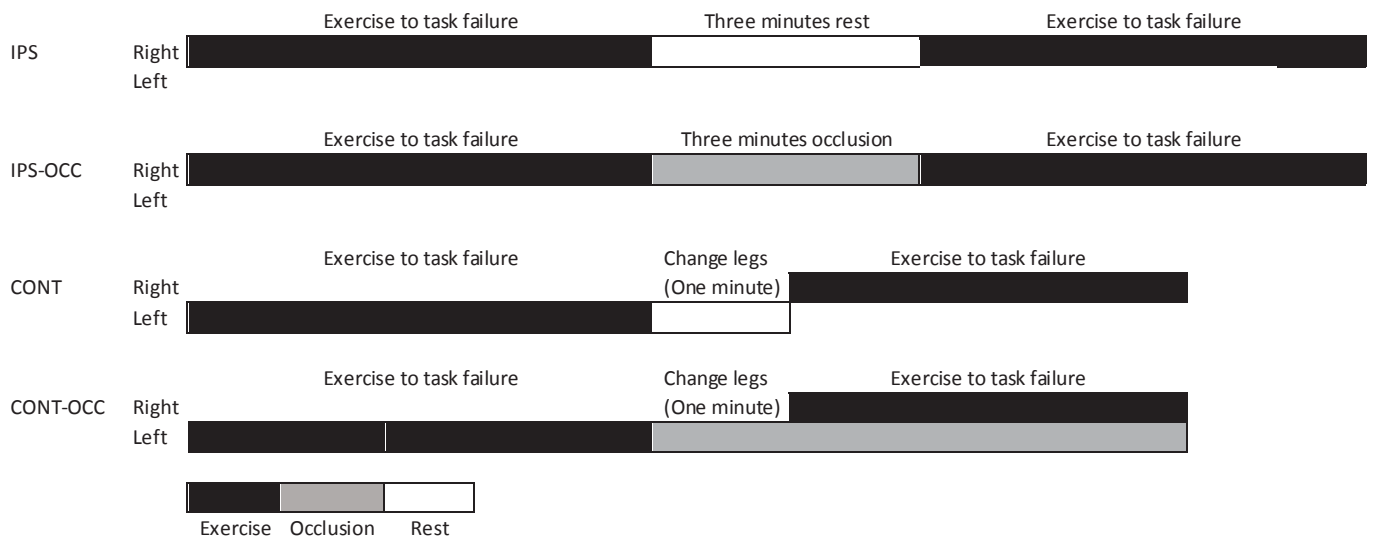**Figure 2: Raw torque output during contractions in a representative participant**

Contractions are all drawn from the first minute of exercise to illustrate the effect of each trial on torque complexity. The ipsilateral trial's first bout is presented as the 'fresh muscle' condition (panel A). Note that complexity is substantially reduced in the first minute of the Ipsilateral Occlusion trial only (panel C).
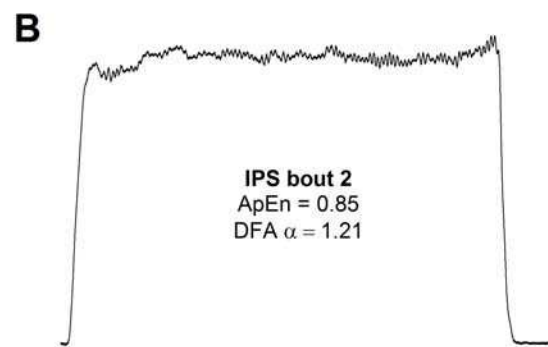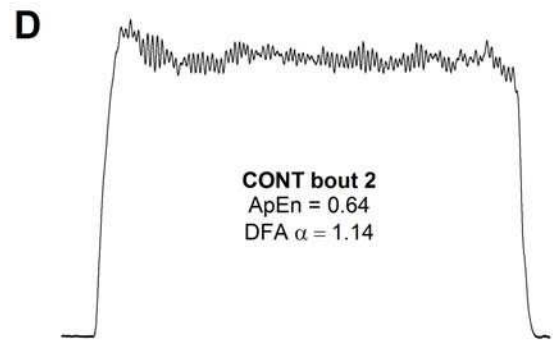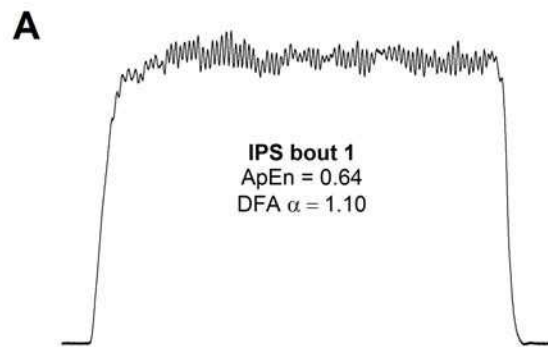
Figure 3 Torque output complexity during the ipsilateral trials (IPS, IPS-OCC)

The top panels (A and C) show the Approximate Entropy (ApEn) values during each trial. Black symbols represent the first bout of contractions in the ISP condition, whilst the white symbols represent the second bout of IPS (Panels A and B) and IPS-OCC (Panels C and D). Bottom panels (B and D) show the detrended fluctuation analysis α exponent (DFA α). Note the reduction in ApEn and increase in DFA α as the contractions progress, as well as the lack of recovery at the start of the second Ipsilateral Occlusion trial. Values are mean $\pm$ SD, n = 9.

Figure 4: Torque output complexity during the contralateral trials (CONT, CONT-OCC)

The top panels (A and C) show the Approximate Entropy (ApEn) values during each trial. Black symbols represent the first bout of contractions in the ISP condition, whilst the white symbols represent the second bouts in CONT (Panels A and B) and CONT-OCC (Panels C and D). Bottom panels (B and D) show the detrended fluctuation analysis α exponent (DFA α). Note the lack of significant alterations in ApEn and in DFA α during the second contraction buts in each condition. Values are mean $\pm$ SD, n = 9.

		Exercise to task failure	Three minutes rest	Exercise to task failure

IPS   Right
       Left

		Exercise to task failure	Three minutes occlusion	Exercise to task failure

IPS-OCC   Right
          Left

		Exercise to task failure	Change legs (One minute)	Exercise to task failure

CONT   Right
       Left

		Exercise to task failure	Change legs (One minute)	Exercise to task failure

CONT-OCC   Right
           Left

Exercise   Occlusion   Rest

A

IPS bout 1
ApEn = 0.64
DFA α = 1.10

B

IPS bout 2
ApEn = 0.85
DFA α = 1.21

C

IPS-OCC bout 2
ApEn = 0.07
DFA α = 1.65

D

CONT bout 2
ApEn = 0.64
DFA α = 1.14

E

CONT-OCC bout 2
ApEn = 0.50
DFA α = 1.30

20 N.m

1 s

IPSILATERAL TRIAL

IPSILATERAL OCCLUSION TRIAL

CONTRALATERAL TRIAL

A

CONTRALATERAL OCCLUSION TRIAL

C

B

D