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Experimental Physiology

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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

Authors: Jamie Pethick
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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 a

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.

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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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8

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35 **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

89 **Introduction**

90

91 Physiological systems produce outputs that inherently fluctuate over time (Goldberger et al.,
92 2002). Such fluctuations are typically quantified according to their amplitude, using the
93 standard deviation (SD) or coefficient of variation (CV), or their frequency content, using the
94 fast Fourier transform. It is now recognised that these fluctuations can also be quantified
95 according to their temporal structure or “complexity”. Complex outputs are characterised by
96 temporal irregularity, time irreversibility and long-range (fractal) correlations (Lipsitz and
97 Goldberger, 1992; Pincus, 1994; Goldberger et al., 2002), properties which amplitude and
98 frequency metrics cannot quantify. Measures of complexity can be divided into those that
99 quantify the regularity of the output (e.g. Approximate Entropy [ApEn]; Pincus, 1991) and
100 those that quantify temporal fractal scaling and noise colour (e.g. Detrended Fluctuation
101 Analysis [DFA]; Peng et al., 1994). The presence of complex outputs in physiological
102 systems are thought to be a signature of good health (Peng et al., 2009). Consequently, a loss
103 of complexity is indicative of system dysfunction, as frequently observed in ageing (as seen,
104 *inter alia*, in heart rate dynamics, gait and muscle torque output; Goldberger et al., 2002;
105 Manor and Lipsitz, 2012).

106

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

120

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 \pm SD: age 23.9 ± 5.7 years; height $1.74 \pm$
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 Medizintechnik, 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 μ s 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

257 cycle of 0.6; with contractions held for 6 s, followed by 4 s rest. Participants were instructed
258 to match their instantaneous torque with a target bar superimposed on the display in front of
259 them and were required to continue matching this torque for as much of the 6 s contraction as
260 possible. At the end of each minute (i.e. every sixth contraction), participants performed an
261 MVC, accompanied by peripheral nerve stimulation. Each exercise bout was conducted until
262 task failure, the point at which the participant failed to reach the target torque on three
263 consecutive occasions, despite strong verbal encouragement. Participants were not informed
264 of the elapsed time during the test, but were informed of each “missed” contraction. After the
265 third consecutive missed contraction, participants were instructed to immediately produce an
266 MVC, which was accompanied by peripheral nerve stimulation.

267

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

274

275 Data acquisition and participant interface

276 Data acquisition was performed in the same manner as described in Pethick et al. (2015).
277 Briefly, all peripheral devices were connected via BNC cables to a Biopac MP150 (Biopac
278 Systems Inc., California, USA) and a CED Micro 1401-3 (Cambridge Electronic Design,
279 Cambridge, UK) interfaced with a personal computer. All signals were sampled at 1 kHz.
280 The data were collected in Spike2 (Version 7; Cambridge Electronic Design, Cambridge,
281 UK). A chart containing the instantaneous torque was projected onto a screen placed ~1 m in
282 front of the participant. A scale consisting of a thin line (1 mm thick) was superimposed on
283 the torque chart and acted as a target, so that participants were able to match their
284 instantaneous torque output to the target torque during each test.

285

286 Data analysis

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

291

292 Torque and EMG. The mean and peak torque for every contraction in each exercise bout
293 conducted on the right leg were determined. The mean torque was calculated based on the
294 steadiest five seconds of each contraction. Task failure was determined as in Pethick et al.
295 (2015). The mean contraction torque produced during the first five contractions was
296 calculated, and task failure was deemed to have occurred when participants' mean torque
297 output failed to achieve that of the first five contractions by more than 5 N·m for three
298 consecutive contractions, with the first of these contractions being the point of task failure.

299

300 The EMG output from the vastus lateralis was filtered (10-500 Hz) and full-wave rectified
301 with a gain of 1000. The average rectified EMG (arEMG) for each contraction was then
302 calculated and normalised by expressing the arEMG as a fraction of the arEMG obtained
303 during an MVC from the fresh muscle performed at the beginning of each trial.

304

305 Central and peripheral fatigue. Measures of central and peripheral fatigue were calculated
306 based on the stimuli delivered during and after the MVCs performed pre-test, during the
307 exercise bouts and at task failure. Peripheral fatigue was assessed by a fall in the peak
308 potentiated doublet torque; and central fatigue was assessed by the decline in voluntary
309 activation, quantified using the twitch interpolation technique (Behm et al., 1996):

310

311 $Voluntary\ activation\ (\%) = (1 - superimposed\ doublet / resting\ doublet) \times 100$ [1]

312

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

315

316 Variability and complexity. All measures of variability and complexity were calculated using
317 the steadiest five seconds of each contraction; that is, the five seconds containing the lowest
318 standard deviation (SD; Forrest et al., 2014). The amount of variability in the torque output of
319 each contraction was measured using the SD, which provides a measure of the absolute
320 amount of variability in a time-series, and the coefficient of variation (CV), which provides a
321 measure of the amount of variability in a time-series normalised to the mean of the time-
322 series.

323

324 The temporal structure, or complexity, of torque output was examined using multiple time
325 domain analyses. As in our previous work (Pethick et al., 2015; Pethick et al., 2016), the
326 complexity of the torque output was determined using Approximate Entropy (ApEn; Pincus,
327 1991), and temporal fractal scaling was estimated using Detrended Fluctuation Analysis
328 (DFA; Peng et al., 1994). Sample Entropy was also calculated (Richman and Moorman,
329 2000), though as shown in Pethick et al. (2015) this measure did not differ from ApEn and
330 was not included in the present analysis. As detailed in Pethick et al. (2015), ApEn was
331 calculated with the template length, m , set at 2, and the tolerance, r , set at 10% of the
332 standard deviation of torque output; and DFA was calculated across time scales (57 boxes
333 ranging from 1250 to 4 data points).

334

335 Statistics

336 All data are presented as means \pm SD. The first exercise bout of the IPS trial (IPS1) acted as a
337 control, against which the second exercise bouts of the experimental trials (IPS2, CONT2,
338 IPS-OCC2 and CONT-OCC2) were compared. The first exercise bouts of the CONT, IPS-
339 OCC and CONT-OCC trials were used to induce pre-existing fatigue in the right leg and
340 were not considered for analysis. Two-way ANOVAs with repeated measures were used to
341 test for differences between conditions and time points, and for a condition \times time interaction
342 for MVC torque, arEMG, potentiated doublet torque, voluntary activation, variability and
343 complexity. The variability and complexity measures were analysed using means from the
344 first minute and final minute before task failure. The rates of change in all parameters were
345 analysed using one-way ANOVAs with repeated measures. Main effects were considered
346 significant when $P < 0.05$. When main effects were observed, Bonferroni-adjusted 95%
347 confidence intervals were then used to determine specific differences.

348

349 Results

350

351 Time to task failure and MVC torque

352 Time to task failure in IPS1 (the control trial, with no pre-existing fatigue) was 4.7 ± 2.7 min.
353 There was a significant effect of condition on time to task failure ($F = 17.52$, $P < 0.001$).
354 Time to task failure was significantly shorter in IPS2 and IPS-OCC2 compared to IPS1
355 (paired samples confidence intervals (CIs): IPS1 vs. IPS2, -5.0 , -0.4 mins; IPS vs. IPS-
356 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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This work was completed at the University of Kent. Pethick, Winter and Burnley were each involved in the conception and design of the study and contributed to the writing and critical revisions of the manuscript. Pethick collected the data; Winter wrote the MATLAB code to process the data. All authors were involved in the analysis and interpretation of the data. All authors approved the final version of the manuscript.

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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 ± 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 ± 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 ± 13.4 ^{a,b}	55.7 ± 12.6 ^{a,b}	55.9 ± 15.0 ^{a,b}	58.8 ± 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 ± 14.7 ^{a,b}	66.8 ± 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: ^apre-exercise/task beginning value, ^bIPS1, ^cIPS1 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: ^apre-exercise value/value at task beginning, ^bIPS1, ^cIPS1 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

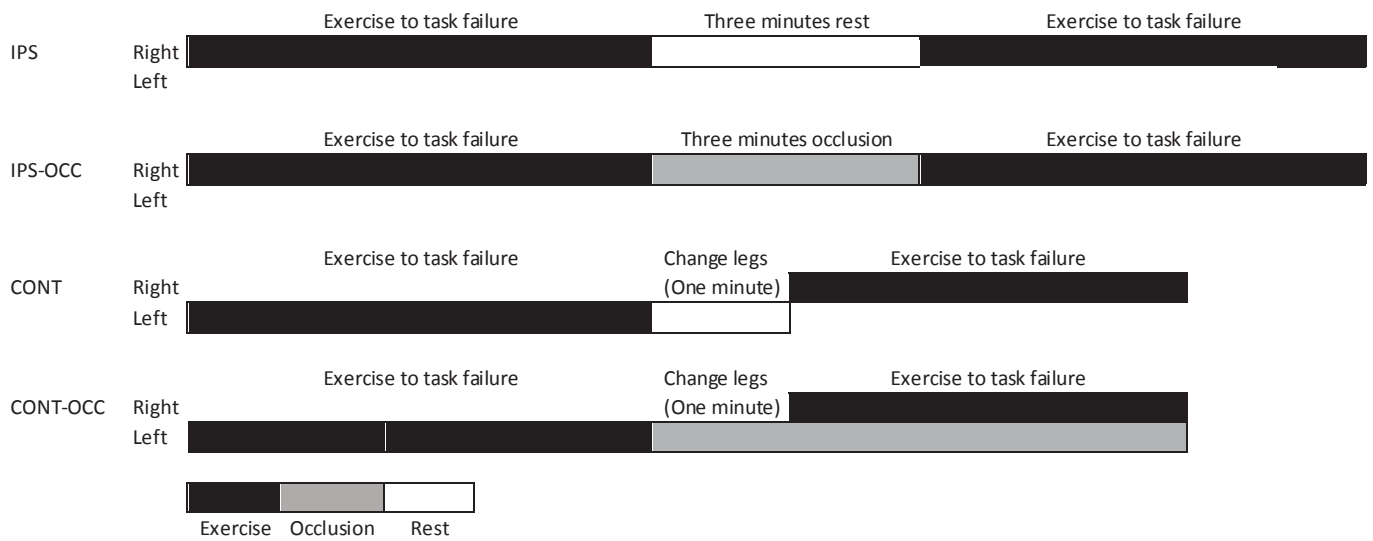
Contractions are all drawn from the first minute of exercise to illustrate the effect of each trial on torque complexity. The ipsilateral trial's first bout is presented as the 'fresh muscle' condition (panel A). Note that complexity is substantially reduced in the first minute of the Ipsilateral Occlusion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

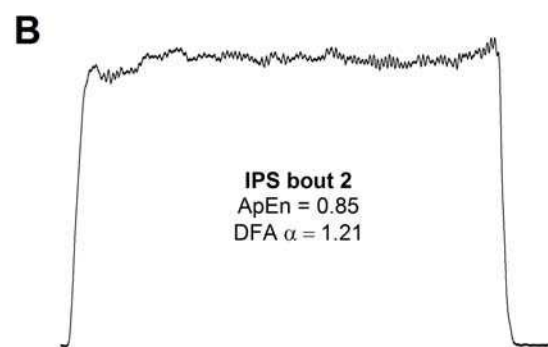
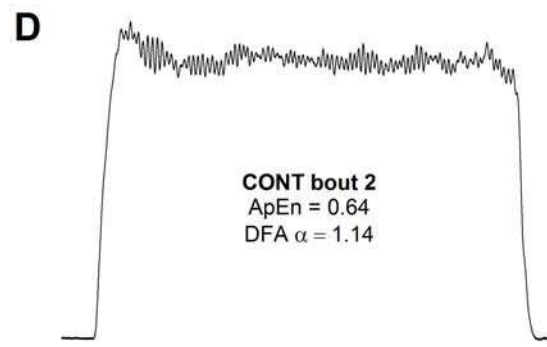
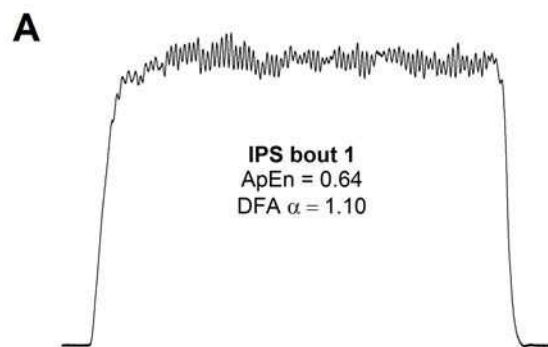
Figure 3 Torque output complexity during the ipsilateral trials (IPS, IPS-OCC)

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 but in each condition. Values are mean \pm SD, n = 9.





20 N.m
1 s

