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1 **MUSCLE PAIN FROM AN INTRAMUSCULAR INJECTION OF HYPERTONIC**
2 **SALINE INCREASES VARIABILITY IN KNEE EXTENSOR TORQUE**
3 **REPRODUCTION**

4
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13
14 **Author Contributions**

15 SAS and ARM were responsible for the conception and design of the study, and data
16 acquisition. SAS, DM, SLW, and ARM were responsible for data analysis and interpretation.
17 SAS was responsible for drafting the manuscript. SAS, DM, SLW and ARM were
18 responsible for critically revising and editing intellectual content.

19
20 **Running head:** Muscle pain increases variability in torque reproduction

21
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26 **ABSTRACT**

27 **Purpose:** The intensity of exercise-induced pain (EIP) reflects the metabolic environment in
28 the exercising muscle, so during endurance exercise this may inform the intelligent regulation
29 of work rate. Conversely, the acute debilitating effects of EIP on motor unit recruitment could
30 impair the estimation of force produced by the muscle and impair judgement of current
31 exercise intensity. This study investigated whether muscle pain that feels like EIP,
32 administered via intramuscular injection of hypertonic saline, interferes with the ability to
33 accurately reproduce torque in a muscle group relevant to locomotive exercise. **Methods:** On
34 separate days, fourteen participants completed an isometric torque reproduction task of the
35 knee extensors. Participants were required to produce torque at 15 and 20% maximal
36 voluntary torque (MVIT), without visual feedback before (Baseline), during (Pain/No Pain),
37 and after (Recovery) an injection of 0.9% isotonic saline (Control) or 5.8% hypertonic saline
38 (Experimental) into the vastus lateralis of the right leg. **Results:** An elevated reported
39 intensity of pain, and a significantly increased variance in mean contraction torque at both
40 15% ($P=0.049$) and 20% ($P=0.002$) MVIT was observed in the Experimental compared to the
41 Control condition. Both 15 and 20% target torques were performed at a similar pain intensity
42 in the Experimental condition (15% MVIT, 4.2 ± 1.9 ; 20% MVIT, 4.5 ± 2.2 ; $P>0.05$).
43 **Conclusion:** These findings demonstrate that the increased muscle pain from the injection of
44 hypertonic saline impeded accurate reproduction of knee extensor torque. These findings
45 have implications for the detrimental impact of EIP on exercise regulation and endurance
46 performance.

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51 **New & Noteworthy**

52 We provide novel data demonstrating that the presence of muscle pain interferes with
53 estimations of torque produced by the knee extensors, which could impair judgement of
54 work-rate during endurance exercise. The novelty of our study is in the application of the
55 hypertonic saline experimental model into a quadriceps muscle during short, submaximal
56 isometric contractions at an intensity that provides a more translatable assessment of the
57 impact of exercise-induced pain on work-rate regulation during whole-body exercise.

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59 **Key words:** Nociception, Exercise Regulation, Proprioception, Effort perception, Pain

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76 **INTRODUCTION**

77 Exercise-induced pain (EIP) increases linearly with exercise intensity and duration (9), and
78 has been suggested to provide useful sensory feedback about the relative strain of exercising
79 muscles (7, 27, 31). During intense and fatiguing muscle contractions, nociceptors of Group
80 III and IV muscle afferents become sensitised and activated by an accumulation of
81 metabolites which induce the perception of EIP, but are also implicated in peripheral fatigue
82 and the description of its perception (31, 38). Resultantly, EIP is often associated with other
83 physiological and psychological factors of fatigue, and has been suggested to independently
84 exacerbate or contribute to the development of fatigue (27). A change in muscle torque
85 complexity, which is suggested to reflect the adaptability of the neuromuscular system and is
86 reduced during fatiguing maximal and submaximal isometric contractions (34), could provide
87 a non-invasive method to evaluate the fatiguing effect of EIP.

88

89 During whole-body exercise, sensations of EIP may facilitate conscious control of
90 homeostatic disturbance during exercise by enabling the intelligent regulation of available
91 energetic resources (i.e. pacing) (12, 27, 54). However, the relationship between EIP and
92 fatigue is likely more complex since it also causes various acute debilitating effects
93 associated with motor unit recruitment (17) and, as a protective mechanism, restricts
94 movement to reduce pain. Consequentially, whilst EIP may provide insight about the
95 metabolic environment in the exercising muscle, these potentially detrimental adaptations
96 may reduce the accuracy of estimations of work done and/or force applied by the muscle,
97 which could impair pacing decisions during whole-body exercise.

98

99 Suppressing the unpleasant sensations associated with intense exercise may allow a higher
100 exercise-intensity to be tolerated and sustained (28), however near complete removal of this

101 information via spinal afferent blockade appears to impair the exerciser's ability to select and
102 maintain a physiologically optimal work rate (3). Spinal blockade studies show the
103 importance of Group III and IV afferents to the performance of whole-body exercise (2, 3)
104 but reveal less about the parallel effects of nociception and perceived pain on other systems
105 such as cardiovascular control.

106

107 Intramuscular hypertonic saline injection produces a muscle pain that feels like the naturally
108 occurring EIP experienced during intense exercise (16, 50), and is therefore a useful method
109 to investigate how EIP affects self-regulation of exercise intensity. This technique has
110 previously been used in contralateral limb-matching tasks to assess the impact of tonic
111 muscle pain on the judgement of torque in small muscle groups (40, 41, 57). In these studies,
112 increased pain impeded the ability to accurately match torque, with pain intensity and degree
113 of error correlating such that participants consistently overestimated the force generated by
114 the painful muscle.

115

116 This experimental approach could, however, be confounded by potential differences between
117 the contralateral limbs (1, 36). To provide a more translatable assessment of the impact of
118 EIP on whole-body exercise, the relationship between muscle pain and the reproduction of
119 isometric torque production should be evaluated in the larger muscle groups of the lower limb
120 such as the knee extensors, which have an important and fundamental role in the generation
121 of force during locomotion and exercise.

122

123 As such, the aim of the present study was to ascertain whether experimentally induced
124 muscle pain in the vastus lateralis (VL) using an intramuscular injection of hypertonic saline
125 would affect the ability to accurately gauge the torque produced by the knee extensor muscles

126 in a single-limb isometric torque reproduction task. We tested the hypothesis that
127 experimental muscle pain in the VL reduces torque reproduction accuracy (as quantified by
128 the variance in mismatch between target and actual torque) of low intensity isometric
129 contractions when compared to a placebo control condition.

130

131 **METHODS**

132 *Ethical Approval*

133 All procedures and protocols were approved by the School of Sport and Exercises (University
134 of Kent) Research Ethics Advisory Group (Prop 140_2016_17) in conformity with the
135 Declaration of Helsinki, and its later amendments or comparable ethical standards. All
136 participants were informed of the study experimental procedures, and written informed
137 consent was obtained to confirm participation.

138

139 *Participants*

140 Fourteen healthy and recreationally active participants (13 male, 1 female; mean \pm SD: age,
141 25.3 ± 4.5 years; height 1.78 ± 0.1 m; body mass 73.9 ± 12.3 kg; physical activity 5.6 ± 2.2
142 hours per week) volunteered to participate in the present study. Assuming a statistical power
143 of 0.8 at an alpha level of 0.05, the sample size was estimated using G*Power software (13)
144 based on the effect size reported in a similar study in our laboratory using hypertonic saline
145 injections (50). All participants attended each visit in a similar psychological state as assessed
146 by the Positive and Negative Affect Schedule (PANAS) (56), which was completed at the
147 start of each visit.

148

149 Before each visit, participants were instructed to refrain from vigorous exercise (24 h) and
150 abstain from the consumption of alcohol (48 h), analgesics (6 h) and caffeine (8 h).

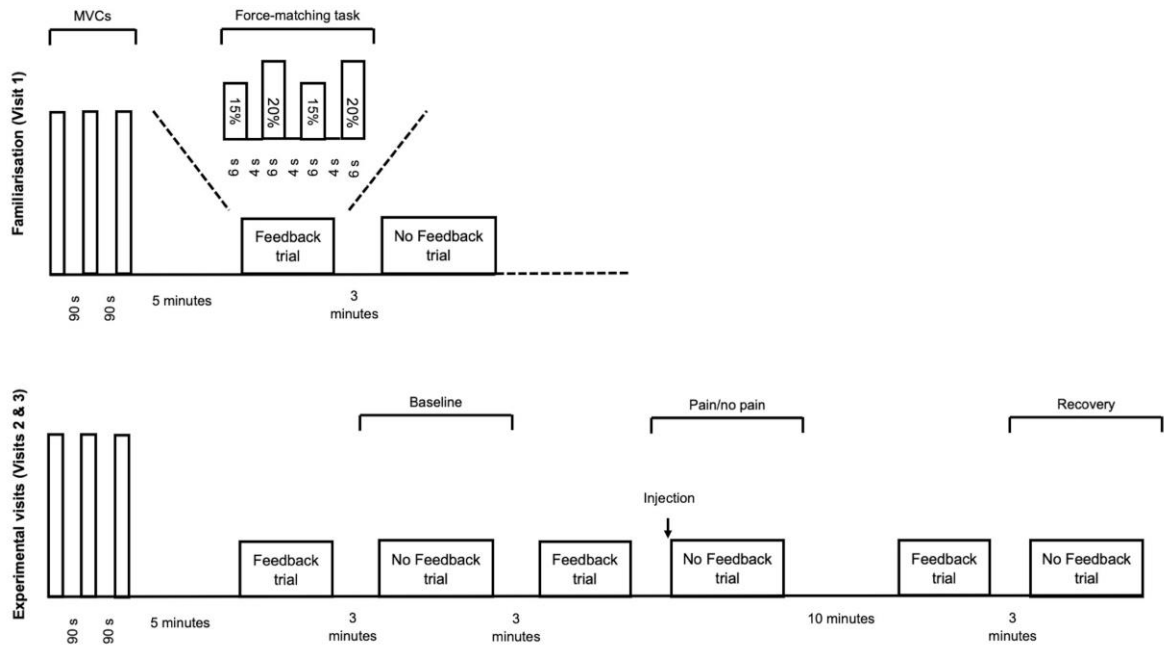
151 Participants with existing knee pain, cardiorespiratory disease, neurological disorders, blood
152 borne viruses, sore deep tissues, phobia to needles and any allergy were excluded from the
153 study.

154

155 *Experimental design*

156 In a two-way repeated-measures experimental design, participants performed an isometric
157 torque matching and reproduction task with either pain (a single intramuscular injection of
158 hypertonic saline) or a placebo control (a single intramuscular injection of isotonic saline)
159 (condition factor). Participants attended a familiarisation session, and then completed the
160 experimental conditions in a randomised and counterbalanced order, with each visit separated
161 by a minimum of seven days. During the task participants attempted to produce torque at two
162 set targets without the aid of real-time visual feedback before (Baseline), during (Pain/No
163 Pain), and after (Recovery) the induction of pain and no pain (time factor). Measures of
164 torque, rating of perceived effort (RPE), surface electromyography (sEMG) and heart rate
165 (HR) were taken during each contraction. Pain intensity was recorded continuously using an
166 electronic visual analogue scale (VAS) and pain quality through the completion of a McGill
167 Pain Questionnaire (MPQ). A schematic of the experimental design and protocol is outlined
168 in Figure 1.

169



170

171 **Fig 1.** Schematic overview of the experimental design and procedures. MVICs: maximal
 172 voluntary contractions

173

174

175 ***Experimental Procedures***

176 ***Torque matching and reproduction task***

177 All visits were performed seated on an isokinetic dynamometer (Cybex HUMAC Norm
 178 isokinetic dynamometer; CSMi, Soughton, MA, USA) set up for the right leg, with the knee
 179 set at an angle of 75° of flexion (0° = full extension of the knee), and a hip angle of 90°.
 180 Torque matching and reproduction for knee extension were determined at isometric
 181 contractions of 15% and 20% maximal voluntary isometric torque (MVIT). These values
 182 were selected based on the percentage of MVIT utilised during maximal (100% maximal
 183 oxygen uptake; VO_{2MAX}) and submaximal (70% VO_{2MAX}) cycling exercise performed at a
 184 pedal rate between 60-80 revolutions per minute (24). At the start of each visit, participants
 185 completed 3×3 s maximum voluntary isometric contractions (MVICs) separated by 90 s rest,
 186 with the greatest instantaneous value taken as MVIT. If the MVIT of consecutive MVICs

187 were not within 5% of each other, additional MVICs were performed until this criteria was
188 achieved.

189

190 Participants attempted the target torques in a trial with real-time torque-production visual
191 feedback ('Feedback Trial') and a trial without visual feedback ('No Feedback Trial').

192 During the Feedback Trials, target torques (15% and 20% MVIT) were presented with actual
193 torque produced via a computer display. Participants were instructed to remember muscular
194 sensations experienced during each target torque and use these to reproduce the same torque
195 in the subsequent No Feedback Trial (7). All Feedback and No Feedback trials were
196 separated by a 3-minute period of rest.

197

198 For each trial, participants performed four 6 s contractions separated by 4 s of rest in a
199 randomised counter-balanced order, which provided two attempts at both target torques (i.e.
200 2×15% MVIT, 2×20% MVIT). During each contraction, participants were instructed to try
201 and match the target torque within the first 2 s, and then maintain it for a further 4 s.

202

203 *Intramuscular injection procedure*

204 A single bolus of 1.0 mL hypertonic saline (5.8%) was manually injected into the middle
205 third of the VL of the right leg over a 20 s window (10 s infusion period). The injection was
206 performed using a 3 mL Luer-Lok syringe connected to a 25 G × 38 mm SurGuard2
207 disposable stainless needle (Terumo, Japan). In the control condition, a single bolus of 1.0
208 mL isotonic saline (0.9%) was injected.

209

210

211

212 *Visit 1 – Familiarisation*

213 Participant anthropometric and descriptive measures of age, height, body mass, and hours of
214 physical activity engaged in per week were recorded. Participants were then familiarised with
215 the RPE and pain scales (8), as well as the performance of MVICs, and the Feedback/No
216 Feedback Trials. Five minutes after the completion of the final MVIC, participants performed
217 an initial Feedback Trial followed by a No Feedback Trial. Verbal confirmation of the actual
218 torque produced in each contraction was given after the completion of the trial. All four
219 contractions in the No Feedback Trial were required to be within 10% of target torque, with
220 further No Feedback Trials completed until this was satisfied. The visit concluded upon the
221 successful completion of a No Feedback Trial or following ten unsuccessful trials.

222

223 *Visits 2 & 3 – Experimental visits*

224 All participants completed a Control (isotonic saline) and an Experimental (hypertonic saline)
225 condition in a randomised and counterbalanced order. In each condition, five-minutes after
226 the completion of the MVICs, participants completed six trials (Feedback, No Feedback,
227 Feedback, No Feedback, Feedback, No Feedback). Prior to the second No Feedback Trial,
228 participants received an intramuscular injection of either isotonic (Control) or hypertonic
229 saline (Experimental), with the No Feedback Trial beginning 20 s after the removal of the
230 needle. This ensured that the 15% and 20% MVIT contractions in this No Feedback Trial
231 were performed with a “moderate” to “strong” muscle pain intensity elicited from the painful
232 hypertonic saline infusion. Ten minutes after the completion of this second No Feedback
233 Trial, the final Feedback and No Feedback (Recovery) Trials were performed.

234

235

236

237 ***Perceptual and psychological measurements***

238 At the start of each visit participants rated the expected pain (0 = “no pain” to 10 = “worst
239 possible pain”) and their confidence to cope with it (0 = “not confident at all” to 10 =
240 “completely confident”). Muscle pain was evaluated by intensity and quality. Participants
241 rated pain intensity on a moment-to-moment basis using an electronic VAS ranging from 0
242 (“no pain”) to 10 (“extremely intense pain”). Participants were instructed to anchor the scale
243 to previous experiences of EIP (4). The device recorded the reported pain value every 5 s,
244 providing measures of pain for each individual contraction. In addition, onset pain intensity
245 (VAS onset), maximal pain intensity (VAS peak), time to maximal intensity (VAS time to
246 peak; from the commencement of sampling), mean pain intensity (VAS mean) and duration
247 of pain (VAS duration; from VAS onset until the state of “no pain”) were also calculated
248 using data from the electronic VAS.

249

250 After the second No Feedback Trial, when pain had subsided, Total Pain Rating Index and
251 Subclass Rating Index was calculated using a 78 item MPQ (29), with overall quality of pain
252 described by descriptors (sensory, affective, evaluative and miscellaneous) chosen by more
253 than one-third of participants. Upon the completion of each trial, participants provided a RPE,
254 defined as the effort to drive the limb (32), of both target torques using the 15-point Borg (6-
255 20) scale (6).

256

257 ***Physiological measurements***

258 Heart rate (HR) was recorded upon the completion of each individual contraction, and muscle
259 electrical activity was continuously recorded using surface electromyography (sEMG). sEMG
260 was attained through square surface electrodes (Ag/AgCl, 32 × 32 mm; Nessler
261 Medizintechnik, Innsbruck, Austria) mounted in a bipolar set-up, and placed on the muscle

262 belly of the VL, vastus medialis (VM) and rectus femoris (RF). For each muscle a reference
263 electrode was placed on the patella. Prior to application of the electrodes, the skin was shaven
264 and cleansed with an alcohol swab. The electrical signal was sampled at 1000 Hz (Biopac
265 MP150, Biopac Systems Inc., California, USA).

266

267 *Data analysis*

268 The sEMG and torque data (for analysis of torque output complexity) were analysed using
269 custom code written in MATLAB 2018a (The MathWorks, Massachusetts, USA).

270

271 *Torque and error*

272 Torque was recorded through Spike2 software (Cambridge Electronics Design (CED),
273 Cambridge, UK). For each 6 s contraction, the torque produced over the last 4 s was
274 averaged. The average of the actual torque produced for each 15% and 20% target was used
275 to define the error in participant torque reproduction. Error was defined as the unidirectional
276 difference between the required target torque and the actual torque produced, and expressed
277 as a percentage of MVIT (i.e. actual torque of 17.5% MVIT for the 15% MVIT target would
278 be equal to an error of 2.5% MVIT). All values of error are presented as positive integers
279 regardless of whether the participant over- or undershot the target torque. The pain on the
280 VAS reported for the corresponding contractions were also averaged for the two attempts at
281 each target torque to provide a mean VAS value for each target torque.

282

283 *Surface electromyography (sEMG)*

284 To create a linear envelope representation of the data, rectified absolute values of the raw
285 sEMG signals were two-pass zero-lag filtered using a fourth-order low-pass Butterworth
286 filter, with a cut-off frequency of 5 Hz. The amplitude for the VL, RF and VM were averaged

287 over the final 4 s period of each 6 s contraction. These values were normalised to the
288 maximum amplitude of the prior MVICs (% MVIC). For each trial, the sEMG activity was
289 averaged for the two contractions performed at each target torque.

290

291 *Torque complexity*

292 The complexity and regularity of the torque output was estimated through the use of
293 approximate entropy (ApEn) and sample entropy (SampEn) (37, 43). When applied to
294 physiological time-series data, ApEn is an index that quantifies the predictability or
295 probability of the subsequent values based on prior values, whilst SampEn provides the same
296 output but excludes self-matches (37, 43). Both ApEn and SampEn are defined by a value
297 between 0 ('high regularity, low complexity') and 2 ('low regularity, high complexity'). A
298 detailed guide to the algorithms for the calculation of ApEn are evidenced in the appendix of
299 Slifkin and Newell (48), whilst SampEn was calculated using the parameters outlined by
300 Pethick and colleagues (34).

301

302 *Statistical analysis*

303 To compare reproduction error between the Control and Experimental conditions at the three
304 time-points (Baseline, Pain/No Pain, and Recovery), a Levene's test was used to determine
305 equality of variance for each normalised target torque (15% and 20% MVIT). Changes in
306 HR, RPE, sEMG activity and complexity were evaluated using two-way Analysis of variance
307 (ANOVA) with treatment factor with two fixed levels (Control, Experimental) and a repeated
308 measures Time factor with two time-points (Baseline, Pain/No Pain). A two-way ANOVA
309 with a treatment factor with two fixed levels (No Feedback, Feedback) and a repeated
310 measures Time factor with two time-points (Baseline, Pain/No Pain) was also implemented to
311 evaluate changes in complexity. When an interaction effect was observed, follow-up paired

312 samples t-tests were used to assess differences between conditions. Paired samples t-tests
313 were also implemented to evaluate the differences between conditions for pain expectation
314 and confidence, VAS scores, pre-test PANAS, and the change in torque produced in Baseline
315 compared to the Pain/No Pain time-point. A Pearson Bivariate correlation was used to
316 evaluate the correlation between torque error and VAS score reported during the Pain/No
317 Pain contractions. Cohen's guidelines of 0.1 (small), 0.3 (medium) and greater than or equal
318 to 0.5 (large) were used to indicate the strength of correlation.

319

320 All data was checked for the standard assumptions associated with the performance of the
321 above statistical tests prior to analysis. Data that did not satisfy the Shapiro-Wilk test of
322 normality ($P < 0.05$) were logarithmically transformed. Results are presented as mean \pm
323 standard deviation (SD). Cohen's d and partial eta square (η_p^2) values are reported as
324 measures of effect size. Statistical significance was accepted at an alpha level of $P < 0.05$. All
325 statistical analysis were completed using SPSS Statistics v25.0 (SPSS, IBM, New York,
326 USA).

327

328 **RESULTS**

329 *Experimental muscle pain*

330 As shown in Table 1, paired samples t-tests revealed a significant difference in VAS pain
331 data between the Control and Experimental conditions. The pain experienced in Experimental
332 was significantly greater in terms of the onset VAS pain reported, with a significantly longer
333 time to peak, yet greater peak VAS pain compared to Control. The reported VAS pain in
334 Experimental was also longer in duration, inducing a significantly greater mean VAS pain,
335 equivalent to a "moderate" to "somewhat strong" muscle pain, and therefore producing a
336 greater overall VAS pain area than Control.

337

338 The pain experienced in Experimental was predominantly described in the sensory and
339 evaluative dimensions of pain as “aching” (50% of participants), “throbbing” (43% of
340 participants), “shooting” (36% of participants), “cramping” (36% of participants), “annoying”
341 (36% of participants). This produced a mean Total Pain Index of 14 ± 8 , with an overall
342 Present Pain Intensity of 2.1 ± 0.7 (“discomforting”).

343

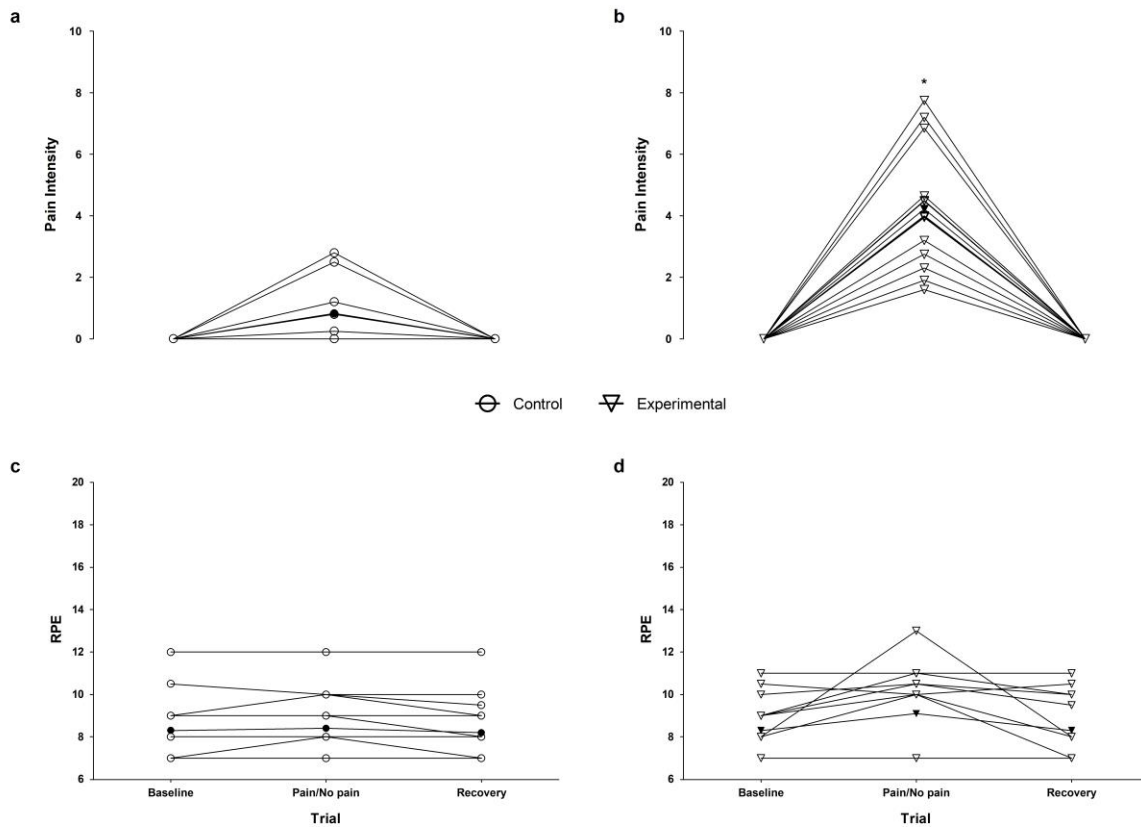
344 During the Pain/No Pain trial, a paired samples t-test revealed no significant difference ($t_{13}=-$
345 $0.9, P=0.366, CI_{95} -0.9, 0.3, d=0.1$) in mean VAS between contractions performed at 15%
346 MVIT (4.2 ± 1.9) and 20% MVIT (4.5 ± 2.2) in the Experimental condition. Each of the two
347 target torques in the Pain/No Pain trial was therefore completed at a similar intensity of pain
348 (Fig 2b. and Fig 3b.).

349

350 **Table 1.** Summary VAS pain data across the entire duration of the Control and Experimental
351 conditions

	Control	Experimental	<i>P</i>
VAS mean	0.8 ± 1.0	$3.1 \pm 1.0^{**}$	<0.001
VAS peak	1.6 ± 2.2	$5.7 \pm 1.7^{**}$	<0.001
VAS onset	0.5 ± 0.8	$1.7 \pm 1.3^*$	0.012
VAS time to peak (s)	41 ± 29	$71 \pm 24^*$	0.020
VAS duration (s)	55 ± 56	$233 \pm 60^{**}$	<0.001
VAS area	86.3 ± 115.4	$759.8 \pm 325.6^{**}$	<0.001

352 Values are means \pm SD. ******Significant difference between Control and Experimental ($P <$
353 0.001). *****Significant difference between Control and Experimental ($P < 0.05$). VAS scale 0
354 (no pain) to 10 (extremely intense pain)



356

357 **Fig 2.** Individual (*open symbol*) and group mean (*filled symbol*) perceptual differences
 358 between conditions (Control and Experimental) at Baseline, Pain/No Pain and Recovery
 359 time-points at a target torque of 15% MVIT. Differences in pain intensity after injection of
 360 isotonic saline (Control, *a*) and hypertonic saline (Experimental, *b*). Differences in RPE in
 361 Control (*c*) and Experimental (*d*) conditions. *Significantly greater where hypertonic saline
 362 was injected.

363

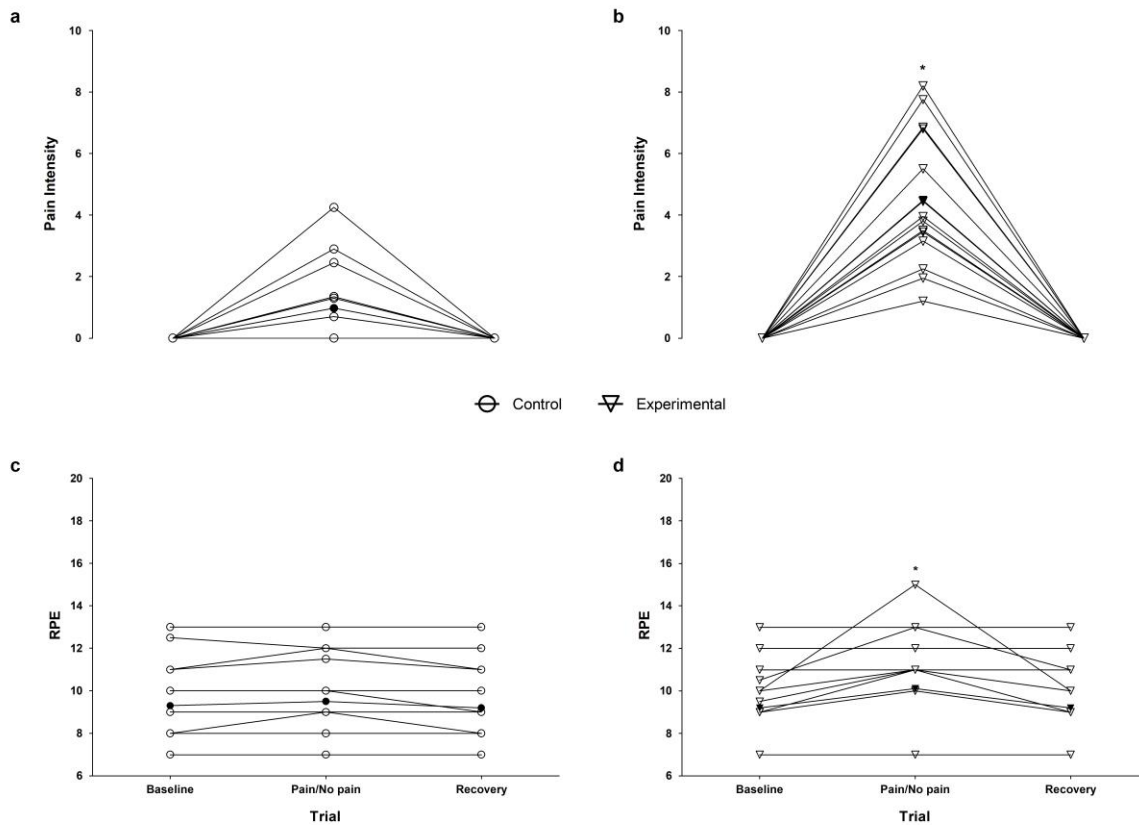
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370

371 **Fig 3.** Individual (*open symbol*) and group mean (*filled symbol*) perceptual differences
 372 between conditions (Control and Experimental) at Baseline, Pain/No Pain and Recovery
 373 time-points at a target torque of 20% MVIT. Differences in pain intensity after injection of
 374 isotonic saline (Control, *a*) and hypertonic saline (Experimental, *b*). Differences in RPE in
 375 Control (*c*) and Experimental (*d*) conditions. *Significantly greater where hypertonic saline
 376 was injected

377

378

379 Paired samples *t* tests revealed no significant difference ($t_{13}=-1.8$, $P=0.096$, $CI_{95} -2.08, 0.19$,
 380 $d=0.5$) in expectations of pain between the Control (4.5 ± 2.1) and Experimental (5.4 ± 1.8)
 381 conditions, with no significant differences in the confidence to cope with the expected pain

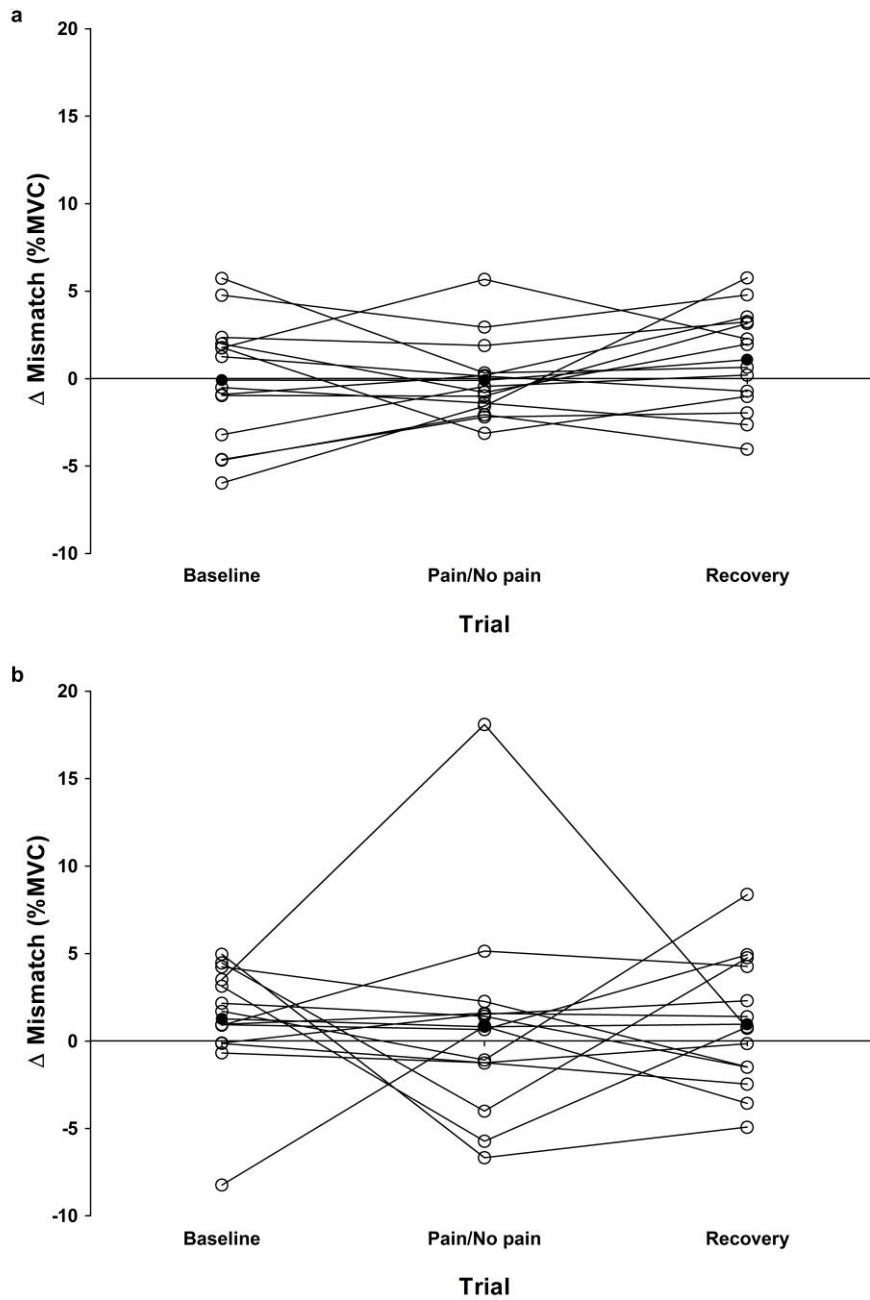
382 ($t_{13}=0.2$, $P=0.818$, CI_{95} -0.29, 0.37, $d=0.1$) between Control (9.5 ± 1.0) and Experimental (9.4
383 ± 1.0).

384

385 *Comparisons of torque production accuracy*

386 In the presence of greater levels of pain, participants demonstrated an increased variability in
387 their ability to reproduce target torque without visual feedback. However, once the pain had
388 subsided, participants were able to produce the target torque with the same accuracy as
389 Baseline. This is demonstrated by the Levene test for equality of variance, which revealed a
390 significant difference in the variance of mean contraction torque in the Pain/No Pain trial
391 between the Experimental and Control conditions at both 15% MVIT ($F_{1,26}=4.3$, $P=0.049$,
392 $d=0.6$) and 20% MVIT ($F_{1,26}=12.0$, $P=0.002$, $d=1.0$), as shown in Figures 4 and 5. There was
393 no correlation between Pain/No Pain error and the pain intensity reported during the
394 contractions (15% MVIT; $r= -0.053$, $P=0.858$, 20% MVIT; $r=0.172$, $P=0.557$). In addition,
395 there was no significant difference in variance between conditions at the Baseline (15%
396 MVIT; $F_{1,26}=0.2$, $P=0.612$, $d=0.1$, 20% MVIT; $F_{1,26}=2.1$, $P=0.161$, $d=0.2$) and Recovery
397 (15% MVIT; $F_{1,26}=1.8$, $P=0.195$, $d=0.2$, 20% MVIT; $F_{1,26}=3.9$, $P=0.058$, $d=0.4$) time-points.

398



399

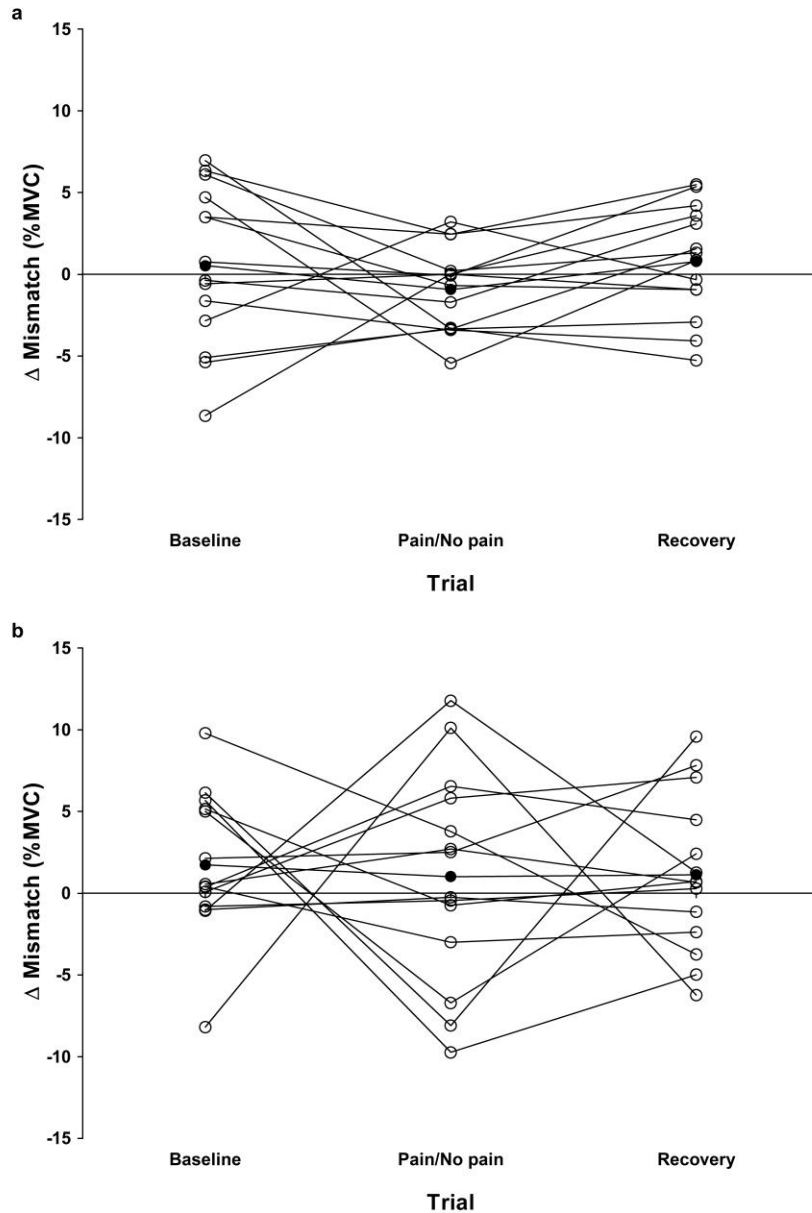
400 **Fig 4.** Individual (*open circle*) and group mean (*filled circle*) torque reproduction error at a
 401 target torque of 15% MVIT before (Baseline), during (Pain/No Pain) and after (Recovery)
 402 injection of isotonic saline (Control, *a*) or hypertonic saline (Experimental, *b*).

403

404

405

406



407

408 **Fig 5.** Individual (*open circle*) and group mean (*filled circle*) torque reproduction error at a
 409 target torque of 20% MVIT before (Baseline), during (Pain/No Pain) and after (Recovery)
 410 injection of isotonic saline (Control, *a*) or hypertonic saline (Experimental, *b*).

411

412

413 A paired samples t-test found no significant difference in the change in torque mismatch
 414 between Baseline and Pain/No Pain trials at 15% MVIT ($t_{13}=-1.5$, $P=0.169$, $CI_{95} -1.1, 0.2$,
 415 $d=0.5$) when comparing the Control (2.5 ± 1.7 %MVIT) and Experimental (4.8 ± 4.8

416 %MVIT) conditions. Furthermore, the paired samples t-test highlighted no significant
417 difference in the same change in torque mismatch between Control (4.2 ± 3.5 %MVIT) and
418 Experimental (7.4 ± 6.0 %MVIT) when contractions were performed at 20% MVIT ($t_{13}=-1.3$,
419 $P=0.235$, CI_{95} -1.6, 0.4, $d=0.4$). This suggests that the target torque absolute error in the
420 ‘Pain/No Pain’ was similar to the error made at Baseline despite the change in pain
421 experienced.

422

423 *Rating of perceived effort*

424 It was apparent that the effort experienced during the contraction was greater in the presence
425 of increased pain, when performed at 20% MVIT. The 2 x 2 (condition x trial) repeated
426 measures ANOVA demonstrated a significant interaction effect at 20% MVIT for RPE over
427 trials between conditions ($F_{1,13}=6.0$, $P=0.030$, $\eta_p^2=0.314$). Follow-up paired samples t-tests
428 revealed a significantly greater RPE ($t_{13}=-2.3$, $P=0.038$, CI_{95} -1.31, -0.04, $d=0.3$) in the
429 Pain/No Pain trial in Experimental compared to Control. A significantly greater ($t_{13}=-2.4$,
430 $P=0.033$, CI_{95} 0.1, 1.8, $d=0.4$) RPE was also reported in the Experimental condition at the
431 Pain/No Pain trial compared to the Baseline trial. No significant main effect of condition was
432 observed at either 15 or 20% MVIT ($P>0.05$). A significant effect of trial was reported at
433 20% MVIT ($F_{1,13}=5.2$, $P=0.041$, $\eta_p^2=0.284$), but not at 15% MVIT ($P>0.05$) (Figs. 2c., 2d.,
434 3c. and 3d.). There was no interaction effect observed at 15% MVIT ($P>0.05$).

435

436 *Surface electromyography (sEMG)*

437 Due to excessive noise in sEMG signal, two participants were removed from the dataset and
438 analysis was performed on the remaining participants ($n=12$). Despite a greater variance in
439 mean contraction torque in the presence of muscle pain, there were no discernible alterations
440 in activation of the agonist and synergist muscles. At 15 and 20% MVIT, the performance of

441 a 2 x 2 (condition x trial) repeated measures ANOVA demonstrated no significant main effect
442 of condition or trial in either the VL, VM or RF ($P>0.05$). The VL, VM or RF also
443 demonstrated no significant interaction effect for sEMG activity over trial between conditions
444 at both target torques ($P>0.05$).

445

446 *Torque complexity*

447 As shown in Table 2, the presence of visual feedback resulted in a more complex (less
448 regular) torque signal (assessed by both ApEn and SampEn) than when torque was being
449 reproduced (No Feedback Trials) ($P<0.001$). No condition ($P>0.05$) and no interaction
450 effect was observed for either ApEn or SampEn ($P>0.05$) at both target torques. At 15 and
451 20% MVIT, the performance of a 2 x 2 (condition x trial) repeated measures ANOVA
452 demonstrated no significant main effect of condition for either ApEn or SampEn, as well as
453 no significant main effect of trial for either complexity statistic ($P>0.05$). There was no
454 interaction effect observed for either ApEn or SampEn ($P>0.05$) at both target torques.

455

456 *Heart rate (HR)*

457 The 2 x 2 (condition x trial) repeated measures ANOVA revealed no significant main effect
458 of condition at 15 or 20% MVIT ($P>0.05$). At 15% MVIT there was no significant main
459 effect of trial ($P>0.05$), however there was at 20% MVIT ($F_{1,13}=5.2$, $P=0.041$, $\eta_p^2=0.284$). No
460 significant interaction effect for HR and trial between conditions was observed at 15 or 20%
461 MVIT ($P>0.05$).

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466 **Table 2.** Torque complexity (ApEn) during Feedback and No Feedback trials at the Baseline
 467 and Pain/No Pain time-points

Condition	Time-point	Trial	Target Torque				
			15% MVIT		20% MVIT		
			ApEn	SampEn	ApEn	SampEn	
Control	Baseline	Feedback	0.71 ± 0.25*	0.71 ± 0.29*	0.57 ± 0.22*	0.56 ± 0.27*	
		No Feedback	0.35 ± 0.17 *	0.32 ± 0.17*	0.31 ± 0.21*	0.29 ± 0.22*	
	Pain/No Pain	Feedback	0.73 ± 0.21*	0.72 ± 0.24*	0.60 ± 0.26*	0.61 ± 0.30*	
		No Feedback	0.35 ± 0.21*	0.32 ± 0.22*	0.28 ± 0.17*	0.26 ± 0.17*	
	Experimental	Baseline	Feedback	0.78 ± 0.24*	0.79 ± 0.30*	0.64 ± 0.21*	0.64 ± 0.25*
			No Feedback	0.29 ± 0.13*	0.26 ± 0.13*	0.27 ± 0.12*	0.24 ± 0.12*
Pain/No Pain		Feedback	0.74 ± 0.27*	0.75 ± 0.31*	0.68 ± 0.23*	0.68 ± 0.28*	
		No Feedback	0.32 ± 0.19*	0.29 ± 0.19*	0.22 ± 0.11*	0.20 ± 0.10*	

468 Values are means ± SD. * Significant difference between Feedback and No Feedback trial
 469 within condition and time-point (P < 0.001).

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 473

474 **DISCUSSION**

475 The present study demonstrates for the first time that the experience of muscle pain,
476 administered by the intramuscular injection of hypertonic saline into the VL, resulted in a
477 greater variance in the mean contraction torque at both 15 and 20% MVIT when compared to
478 the injection of isotonic saline (a placebo control). The increased variance was paralleled by
479 an elevated experience of pain at both contraction intensities, and a greater perceived effort
480 when performed at 20% MVIT. Once the pain had subsided, accuracy of torque production
481 returned to baseline levels. This study for the first time demonstrates that the presence of
482 muscle pain (that feels like EIP) impedes the ability to accurately reproduce torque in the
483 knee extensors. This important finding provides key experimental evidence for the
484 deleterious implications of EIP on the ability to self-regulate exercise intensity.

485

486 *Effect of pain on isometric torque reproduction*

487

488 The purpose of the present study was to establish whether the presence of pain in a muscle
489 with a major contributing role to force generation during both dynamic contractions and
490 whole-body exercise (i.e. the VL) has a debilitating effect on producing a given torque using
491 the ipsilateral knee extensor muscle group. The primary finding from this study is that the
492 mismatch between the actual torque produced and the target torque (when required to
493 reproduce both 15 and 20% MVIT) was significantly more variable with pain, with no
494 discernible direction of error (i.e. participants both under- and overshoot the target torque).
495 Resultantly, this study is the first to demonstrate that the experimental induction of pain in a
496 large locomotor muscle group impairs the judgement of torque during an isometric
497 reproduction task performed at an intensity of relevance to endurance exercise performance.

498

499 The compromised ability to accurately reproduce torque during pain is in line with previous
500 research that has implemented the hypertonic saline model in the elbow flexors to investigate
501 the impact of pain on estimation error in a contralateral torque estimation task (40, 41, 57).
502 However, this prior literature has consistently reported that participants specifically
503 *overestimated* the torque that is produced in the painful muscle, and therefore produced less
504 torque than required. In contrast with lack of direction in error reported in the present study,
505 this observed disparity could be due to potential differences in the limb evaluated (e.g.
506 contralateral or ipsilateral). Alternatively, as the knee extensor muscles respond differently to
507 exercise-induced fatigue (55), the muscle group tested (elbow flexor vs. knee extensors)
508 should also be considered.

509

510 *Proposed mechanisms*

511 The presence of the hypertonic saline solution in addition to the short-duration muscle
512 contraction creates a noxious environment within the skeletal musculature (31), which results
513 in an alteration in activity of both ascending metaboreceptive and nociceptive group III and IV
514 afferent fibers (18). In this noxious environment, there are several neuromuscular
515 mechanisms that, when acting in singularity or in combination, may provide an explanation
516 for the impaired reproduction of torque in the present study.

517

518 Convergent projection from group III and IV afferents on common interneurons from group
519 Ib proprioceptive afferents (45) provide information on muscle force (15). As discussed by
520 Salomoni and Graven-Nielsen (44), the large variance in the mean contraction torque in the
521 Experimental condition could be a result of the spatial facilitation between these afferents
522 interfering in the central interpretation of proprioceptive information essential for the
523 accurate control of torque. A discrepancy between the centrally mediated judgement of

524 torque and the actual afferent feedback from the periphery could therefore have resulted in
525 the torque reproduction error.

526

527 In addition, the projection of the group III and IV afferents have inhibitory effects on the
528 central nervous system. The increased afferent feedback from the hypertonic saline may have
529 limited motor cortical excitability, and reduced central motor drive and voluntary activation
530 of the knee extensors (14, 19). In order to compensate for the hypertonic saline-induced
531 impairment of motor cortex excitability, a greater effort is required to drive the limb to meet
532 the required torque (30, 39). As an outcome reflected in the present study, this could provide
533 a possible explanation for some of the differences in actual and perceived torque produced.
534 The findings from Proske and colleagues (40) where the matching of torque through effort
535 resulted in an overshoot of the target torque, are in support of this explanation.

536

537 Despite the observed impairment in torque-reproduction performance during pain, there was
538 no change in the torque complexity of the knee extensors, or the level of muscle activity
539 assessed by sEMG. The absence of alterations in sEMG is comparable with findings from the
540 established literature into the implications of EIP on muscle activity during submaximal
541 isometric contractions, where a lack of marked changes in sEMG signal are also observed
542 (16, 44, 46). Combined, these observations contradict the underpinning theory of the ‘Pain
543 Adaptation Model’ (25) where it is predicted that the presence of pain has a reliable
544 inhibitory influence on agonist muscles, whilst simultaneously activating the antagonists.
545 Instead, the observations of the present study could, with caution, be in-line with the “moving
546 differently in pain” model proposed by Hodges and Tucker (17). This theory postulates that
547 pain initiates a non-uniform effect across the motor neurone pool, causing a redistribution of
548 activity between and within muscles to provide a key adaptive and protective function. Whilst

549 this alteration has the immediate benefit of minimising the pain experienced and preventing
550 further injury or damage to the area in pain during muscular contraction, this change to a
551 “sub-optimal” movement strategy could have consequences for the efficiency of task
552 performance (17, 53). Detection of these adaptations would however require the use of fine-
553 wire electrodes (52) or high density sEMG, as a combination of changes in order of motor
554 unit activation or synchronisation can occur without alteration in amplitude of gross sEMG
555 (51).

556

557 A loss of knee-extensor torque complexity during both prolonged maximal and submaximal
558 contractions has been closely associated with fatigue (34, 35), and is suggested to have a
559 detrimental impact on the performance of motor tasks in the lower limb (10). In the present
560 study, the lack of change in torque complexity suggests that the acute pain from the
561 hypertonic saline was unlikely to have independently caused neuromuscular fatigue. The
562 increased variance in mean contraction torque is therefore unable to be explained by pain-
563 induced mechanisms of fatigue during the short-duration and submaximal isometric
564 contractions.

565

566 This finding is consistent with prior literature, where differences in torque complexity are not
567 observed in the first few seconds of isometric muscle contraction despite the presence of pain
568 (from an eccentric contraction muscle damage protocol) and the consequential impaired
569 ability to perform a maximal voluntary contraction (33). As torque complexity progressively
570 decreases over time during submaximal contractions until the point of task failure (34), if the
571 torque reproduction task in the present study was performed over a longer duration, a pain-
572 induced *acceleration* of exercise-induced fatigue (and therefore loss of torque complexity)
573 would likely be observed in addition to the impaired the ability to accurately reproduce

574 torque. As such the findings of the present study reinforce the notion that acute, moderate
575 muscle pain alone is not necessarily fatiguing, but may accelerate the development of fatigue
576 during prolonged or exhaustive exercise (27, 50), or impair maximal voluntary contraction.

577

578 A further point of consideration is that in the absence of visual feedback, and sole reliance on
579 afferent/efferent information and task memory, the ability to accurately reproduce torque
580 depreciates (22) and that this is characteristically coupled with a lower complexity of the
581 torque signal (indicative of a reduced adaptability in force control) (21, 49). This observation
582 is replicated in the present study, and it is noteworthy that the values for ApEn and SampEn
583 in the No Feedback conditions are similar to those shown at task failure in exhaustive
584 exercise (34). Therefore, it is possible that the induction of muscle pain in the present study
585 was not able to reduce the complexity of the torque signal beyond that already caused by the
586 removal of visual feedback.

587

588 Alternatively, the compromised ability to accurately reproduce torque (despite no change in
589 loss of torque complexity) could be due to the experience of pain preventing some attentional
590 focus on the task (23), making the task more challenging. It is plausible that the elevated
591 intensity of pain (induced by the injection of hypertonic saline), which was rated as
592 “moderate” to “somewhat strong” in both target torques, provided a stimulus which was
593 perceived as threatening. With some attentional resources focused on coping with the ‘threat’
594 of the noxious stimuli, attention may have been directed away from the task, which could
595 have resulted in a compromised accuracy of torque reproduction (11); a notion supported by
596 evidence from previous experimental work (5, 26). However, in the current study, there was
597 no relationship between pain intensity and error, which indicates that the sensation of pain
598 alone was unlikely to have had a direct influence on task performance.

599

600 Overall, it is evident that the presence of pain interferes with proprioception during
601 submaximal isometric contractions in the lower-limb. The design and findings of the present
602 study therefore provide a key indication of the potential mechanism underpinning the
603 detrimental effect of EIP on exercise intensity regulation and endurance performance. Some
604 caution should however be taken when extrapolating these findings to whole-body exercise.
605 In order to improve task relevance to whole-body locomotor exercise and further apply the
606 findings of the present study, there is the need for the impact of this experimental model to be
607 evaluated during isokinetic or dynamic muscular contractions performed at a varying or
608 higher work rate.

609

610 *Methodological considerations*

611 Whilst there is inconsistent evidence for sex-related differences in the pain intensity response
612 to the hypertonic saline model (20, 42), the fluctuations in hormone concentration across the
613 different menstrual cycle phases may cause differences in pain perception to experimental
614 pain (47). It is acknowledged that the present study did not account for menstrual cycle
615 phases of the female participant, and this is a limitation. It is also important to note that the
616 short-duration and submaximal isometric contractions used in the current study were not
617 fatiguing, and this limits the ability to examine the notion that pain accelerates the
618 development of exercise-induced fatigue in addition to the impairment in accurate torque
619 reproduction. To explore this in combination, future investigations should attempt to employ
620 a similar study design examining torque reproduction ability in the presence of muscle pain
621 during contractions performed at a greater exercise intensity, or over a longer duration.

622

623 *Conclusion*

624 In conclusion, the injection of hypertonic saline into the VL during a torque reproduction task
625 created muscle pain that resulted in an impaired ability to accurately produce a given
626 submaximal target torque during a short, submaximal isometric contractions. The presence of
627 pain was linked with a greater effort to drive the limb and meet the given target torque when
628 attempting to contract at 20% MVIT, but not at 15% MVIT. The compromised ability to
629 reproduce torque returned to baseline levels once pain had subsided. These findings have
630 implications for the impact of EIP on self-selected work rate regulation during endurance
631 exercise performance.

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