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## **Effects of prolonged and acute muscle pain on the force control strategy during isometric contractions**

CA Mista, M Bergin, R Hirata, S Christensen, K Tucker, P Hodges, T Graven-Nielsen

### Highlights

- Participants were injected with NGF (day 0) and hypertonic saline (day 2).
- Saline-induced pain increases the variation and changes the direction of the force.
- Persistent pain changes force direction from the pain-free direction.
- Supporting the search and consolidation of new motor strategies during pain.



22

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35

## 36 **ABSTRACT**

37 Musculoskeletal pain is associated with multiple adaptations in movement control. This study  
38 aimed to determine whether changes in movement control acquired during acute pain are  
39 maintained over days of pain exposure. On day-0, the extensor carpi radialis brevis (ECRB)  
40 muscle of healthy participants was injected with nerve growth factor (NGF) to induce persistent  
41 movement-evoked pain (N=13) or isotonic saline as a control (N=13). On day-2, short-lasting  
42 pain was induced by injection of hypertonic saline into ECRB muscles of all participants. Three-  
43 dimensional force components were recorded during submaximal isometric wrist extensions on  
44 day-0, day-4, and before, during, and after saline-induced pain on day-2. Standard deviation  
45 (variation of task-related force) and total excursion of center of pressure (variation of force  
46 direction) were assessed. Maximal movement-evoked pain was  $3.3 \pm 0.4$  (0-10 numeric scale) in  
47 the NGF-group on day-2 whereas maximum saline-induced pain was  $6.8 \pm 0.3$  cm (10-cm visual  
48 analogue scale). The difference in centroid position of force direction relative to day-0 was  
49 greater in the NGF-group than controls ( $P < 0.05$ ) on day-2 (before saline-induced pain) and day-  
50 4, reflecting changes in tangential force direction used to achieve the task. During saline-induced  
51 pain in both groups, tangential and task-related force variation was greater than before and after  
52 saline-induced pain ( $P < 0.05$ ).

## 53 **Perspectives**

54 Persistent movement-evoked pain changes force direction from the pain-free direction. Acute  
55 pain leads to increase variation in force direction irrespective of persistent movement-evoked  
56 pain preceding the acutely painful event. These differences provide novel insight into the search  
57 and consolidation of new motor strategies in the presence of pain.

58 **Key words:** Force, NGF, muscle pain, persistent pain.

59

## 60 INTRODUCTION

61 Transient muscle pain is accompanied by changes in movement patterns<sup>2,17,32</sup> and is thought to  
62 serve a protective function to reduce threat to the painful/injured region. Resolution of pain is not  
63 necessarily associated with a return to the original motor pattern.<sup>17,43</sup> One hypothesis is that  
64 movement changes during pain are achieved by an initial increase in variation to search for a  
65 new strategy, and once a beneficial strategy is found, variation is reduced to maintain the new  
66 strategy.<sup>27</sup> Motor adaptations may be maintained for the duration of pain, or continue to undergo  
67 change if pain persists.

68 Transient muscle pain induced by hypertonic saline injection changes coordination  
69 between muscles<sup>12,16</sup> and the spatial distribution of activation within a muscle.<sup>18,23</sup> The principal  
70 interpretation of altered muscle activity is to reduce the potential for further pain and tissue  
71 damage.<sup>17,22</sup> Noxious input also increases variability in force during submaximal isometric  
72 contractions in both the primary direction of task-related force<sup>2</sup> and in directions tangential to the  
73 primary task force.<sup>25,32</sup> Increased variation in different directions could have different  
74 interpretations. Variation in the tangential force could represent a search for less  
75 painful/threatening directions that redistribute load across painful structures.<sup>17</sup> In the primary  
76 task-related force direction increased variation is unlikely to represent a search for a new strategy  
77 as this would compromise the goal to maintain a target force, instead it might be the result of to  
78 the purposeful variation in tangential force or result from interference by pain secondary to  
79 distraction,<sup>8</sup> impaired proprioception,<sup>7</sup> or altered synchronization/recruitment of different  
80 populations of motor units.<sup>24,41,46</sup> Although these interpretations appear logical when a person is  
81 first exposed to noxious input, features of the motor adaptation may differ over longer periods. If  
82 pain is sustained it might be expected that the new motor solution would become consolidated,

83 and variation would reduce around a new motor solution. How motor adaptations in pain change  
84 over time has received little attention, primarily as a consequence of the lack of suitable  
85 experimental methods that induce suitably prolonged noxious stimulus.

86 One possibility to induce persistent pain is intramuscular injection of nerve growth factor  
87 (NGF), which induces muscle soreness and movement-evoked pain for several days.<sup>1,4,38,39</sup>  
88 Administration of NGF does not elicit immediate muscle pain<sup>1,30,38,39</sup> but induces localised  
89 hyperalgesia after several hours that is provoked during function.<sup>1,4,14</sup> This presents a possible  
90 method to study the time-course of motor adaptation.

91 This study aimed to compare changes of direction and variation of multidirectional (task-  
92 related and tangential) forces: (1) in the presence of acute experimental pain; (2) after  
93 experimental movement-evoked pain had been sustained for several days; and (3) with the  
94 combined effect of additional acute pain on a background of persistent movement-evoked pain. It  
95 was hypothesised that: (1) acute experimental muscle pain would increase variation in the  
96 primary force direction consistent with pain interference, and variation in the force direction  
97 consistent with a search for a less threatening motor pattern, and alter the direction of the  
98 tangential force, but without compromising their ability to maintain the task goal; (2) *direction* of  
99 tangential force would differ by a greater amount between baseline and follow-up after several  
100 days of persistent movement-evoked pain (maintenance of a new solution), than it would  
101 between days in the absence of pain (3) *variation* in force direction would not be greater than  
102 baseline after several days of persistent pain as a “search” for a new movement solution would  
103 be expected to have occurred when pain was first experienced, but variation in the task-related  
104 force may continue if interference by pain persisted; and (4) addition of acute pain on persistent  
105 pain would lead to a new search (increased variation) and additional change in direction.

## 106 **METHODS**

### 107 *Participants*

108 Twenty-six healthy volunteers (7 females, age:  $26 \pm 5$  years, mean  $\pm$  standard deviation)  
109 participated in the study. Participants were free of upper limb pain, and had no history of pain or  
110 neuromuscular disorders affecting the upper limb region. All participants received written and  
111 verbal description of the procedures and gave written informed consent. The experimental  
112 procedures were approved by the local ethics committee (N-201200640) and the Declaration of  
113 Helsinki was respected.

114

### 115 *Experimental protocol*

116 Participants sat upright in a height-adjustable chair with their back resting against backrest. The  
117 forearm of the dominant arm was in a pronated position, and the hand formed a fist. The distal  
118 portion of the hand was in slight contact with a force transducer, which recorded the force output  
119 during wrist extension (Fig. 1). The experiment was performed as a randomised, double-blinded,  
120 placebo-controlled design, across 3 sessions (day-0, day-2, and day-4). During the first session  
121 (day-0), participants from the NGF group (N=13; five females) received a single dose of 5  $\mu$ g  
122 human  $\beta$ -Nerve Growth Factor (0.2 ml, 25  $\mu$ g/ml, prepared by the pharmacy at Aalborg  
123 University, Hospital), and participants from the Control group received a single dose of sterile  
124 isotonic saline (0.2 ml, 0.9%; N=13; two females), injected into the extensor carpi radialis brevis  
125 (ECRB) muscle. The number of participants included in each group was based on previous  
126 studies using a similar design to evaluate the effects of intramuscular NGF injections.<sup>14,38,39</sup> All  
127 injections were performed on the dominant side, and injection site and depth was determined by  
128 guidance of ultrasound imaging. The injection site was marked with indelible ink. Participant's  
129 wrist was also marked in order to ensure consistent alignment of the arm position with the force



130 transducer between sessions. Participants performed a series of force-matched wrist extensions  
131 before and after the injection. During the second session (day-2), acute muscle pain was induced  
132 by injection of hypertonic saline (0.5 ml, 5.8%) in the ECRB muscle (same location as NGF/iso  
133 injection) of participants in both groups. Participants performed the motor task before, during,  
134 and after the acute pain experienced by injection of hypertonic saline. Note that at this time point  
135 it was expected that the NGF group would have experienced movement-evoked pain induced by  
136 the NGF injection for multiple days. In the third session (day-4), participants performed one trial  
137 of the motor task without any injection (Fig. 1).

138

### 139 *Motor task*

140 In each session, the maximal voluntary contraction (MVC) was recorded by performing three  
141 consecutive maximal isometric wrist extension trials for 10 s with an interval of 30 s in-between.  
142 The maximum force (calculated in the Fz direction) among the three wrist extension repetitions  
143 was used as the MVC force for the remaining trials and sessions. After a 60-s rest, a set of  
144 submaximal isometric wrist extensions was performed, consisting of 3 consecutive trials at 10%  
145 MVC with a 5-s ascending ramp, 10 s of steady phase, and a 5-s descending ramp. The target  
146 force level and the participant's actual force in the task-related direction (i.e. in Fz direction)  
147 were presented as lines on a computer screen. Participants matched the target force as precisely  
148 as possible. Tangential forces were recorded during each trial.

149

### 150 *Force and torque recordings*

151 Three-dimensional force components and torques were measured using a six-axis load cell  
152 transducer (MC3A 250, AMTI, USA) with high sensitivity (0.054, 0.054, 0.0134 V/N for Fx, Fy,

153 Fz; and 2.744, 2.744, 2.124 V/Nm for Mx, My, Mz). The analogue outputs of the transducer  
154 were amplified and low-pass filtered at 1 kHz (MSA-6, AMTI, USA). The force and torque  
155 signals were sampled at 2 kHz and stored after 12-bit A/D conversion.

156

#### 157 *Pain intensity assessment*

158 Participants completed a pain questionnaire in the evening of each session day. The  
159 questionnaire consisted of three questions relating to their pain quantified used an 11-point  
160 numerical rating scale (NRS) where 0 = ‘no pain’ and 10 = ‘worst pain imaginable’. Pain  
161 intensity was reported: “at rest”, while performing a task involving “repeated wrist  
162 extension/flexion and elbow flexion/extension movements in daily life activities” in the previous 48  
163 hours, and the “maximum pain that had been experienced in the previous 48 hours”. Following  
164 the hypertonic saline injection, pain intensity was scored continuously until pain resolution, on a  
165 10-cm electronic visual analogue scale (VAS) where 0 cm indicated ‘no pain’ and 10 cm ‘worst  
166 pain imaginable’. The peak VAS score following the injection was extracted for further analysis.

167

#### 168 *Data analysis*

169 Force and torque signals were digitally low-pass filtered at 20 Hz using a second order  
170 Butterworth filter. In order to avoid regions within the force trace that may be associated with  
171 slow force development and anticipation to the decreasing force phase of the task, 8 s in the  
172 middle of the steady period of force maintenance was selected for data analysis. Standard  
173 deviation (SD) was used to quantify force variability in the task-related direction. Force error  
174 was calculated using the residual sum of squares error (RSS) of the force trace from the target  
175 line, reflecting the force accuracy in the Fz direction. The total excursion of the centre of

176 pressure (CoP) was used to quantify lateral shifts of the quasi-static net force (i.e. changes in  
177 force direction). This index reflects the total length of the CoP path in a given time period<sup>29</sup> and  
178 represents an indirect measure of the tangential force variation.<sup>26,32,33</sup> A two-dimensional  
179 histogram of tangential force components was developed using a 5-by-5 equally spaced grid to  
180 represent the range of the force in the Fy (wrist radial-ulnar deviation) and Fx (longitudinal  
181 movement of the wrist) direction. Coordinates of the centroid were extracted from the force  
182 histogram. For the analysis of the effect of persistent pain, the centroid position at day-2 and at  
183 day-4 was subtracted from the position of the centroid obtained during baseline day-0 for both  
184 groups. For saline-induced muscle pain, centroid position *during* and *after* saline-induced pain  
185 was subtracted from the *baseline* (before saline-induced pain trial) at the same day (day-2). To  
186 provide a “no-pain” measure of the change in centroid position against which the hypertonic  
187 saline conditions could be compared, we subtracted the centroid position prior to saline induced  
188 pain on day-2 from the centroid position prior to isotonic saline injection on day-0, for the  
189 Control group. The absolute difference in Fy and Fx directions were extracted (Fy and Fx,  
190 respectively). A centroid position difference (Fx-CPD and Fy-CPD) value deviating from zero  
191 indicates that new combinations of tangential forces were used in that condition reflecting  
192 changes the direction of the net force.<sup>15,25</sup> Thus, CoP quantifies variability of the force direction,  
193 whereas CPD represents magnitude of change in the direction of the force between two trials.

194

### 195 *Statistical analysis*

196 SD of the force (Fz) and excursion of the CoP were normalised for each injection type. To  
197 reduce the between-subject variability of the samples,<sup>37</sup> normalisation was implemented by  
198 dividing parameters of each participant with their peak value across trials (Baseline day-0,

199 Baseline day-2 [before saline-induced pain], and Baseline day-4 for NGF/isotonic saline  
200 injection; and before, during, and after saline-induced pain for hypertonic saline injection).

201 *Effects of saline-induced pain:* To test the first hypothesis whether force variation in the  
202 tangential direction (excursion of CoP), and/or variation (SD of Fz) and error (Fz RSS) in the  
203 primary task direction were altered by saline-induced muscle pain on day-2, a repeated measures  
204 analysis of variance (ANOVA) was applied using *Time* (before, during, and after saline-induced  
205 muscle pain) as a within-subject factor for the Control group. This analysis did not include the  
206 NGF group who received saline injection in addition to NGF. To test whether force direction is  
207 altered by saline-induced pain on day-2, CPD were analysed using a repeated measures ANOVA  
208 with *Time* (Baseline [pre-injection day-0 minus pre-injection day-2], during saline-induced pain  
209 [pre-pain minus pain], and after [post-pain minus pain]) as a within-subject factor.

210 *Effects of injection of NGF and isotonic saline:* To test hypotheses 2 and 3, whether force  
211 direction variation (excursion of CoP), and/or variation (SD of Fz) and error (Fz RSS) in the  
212 primary task direction were modified after several days of sustained pain following NGF  
213 injections; these data were analysed using a mixed-model design ANOVA with *Group* (NGF and  
214 isotonic saline) as a between-subject factor, and *Session* (day-0, day-2 before-saline injection,  
215 and day-4) as a within-subject factor. To test whether tangential force direction is altered by  
216 persistent pain, CPD were analysed using a mixed-model ANOVA with *Group* (NGF and  
217 isotonic saline) as a between-subject factor and *Session* (day-2 before-saline injection minus pre-  
218 injection day-0 and day-4 minus pre-injection day-0) as a within-subject factor. Newman-Keuls  
219 (NK) post-hoc tests were applied in case of significant effects from main factors or interactions.  
220 We also compared maximum force between sessions to investigate whether this was constant  
221 across days.

222 *Effects of saline-induced pain during persistent movement-evoked pain:* To test hypothesis  
223 4, whether variation in the force direction (excursion of CoP), and/or variation (SD of Fz) and  
224 error (Fz RSS) in the primary task direction were altered by saline-induced muscle pain during  
225 movement-evoked pain on day-2, a repeated measures analysis of variance (ANOVA) was  
226 applied using *Time* (before, during, and after saline-induced muscle pain) as a within-subject  
227 factor for the NGF group. CPD were analysed using a repeated measures ANOVA with *Time*  
228 (Baseline [pre-injection day-0 minus pre-injection day-2], during saline-induced pain [pre-pain  
229 minus pain], and after [post-pain minus pain]) as a within-subject factor.

230 As peak VAS scores and data from the pain questionnaire were not normally distributed,  
231 Mann-Whitney U tests were used to assess differences between groups (before, during, and after  
232 saline-induced pain for peak VAS scores, and day-0, day-2, and day-4 for pain questionnaire  
233 measures, respectively). The Wilcoxon Signed Rank test was used to analyse for differences  
234 between sessions within a group across time trials (VAS scores) and days (pain questionnaire,  
235 measures were analysed individually), and Bonferroni corrections were used to adjust P-values  
236 for multiple comparisons. Data are presented as magnitude of relevant difference in the results  
237 section, and mean and standard error of the mean (SEM) throughout the tables and figures. P-  
238 values less than 0.05 were regarded as significant.

239

## 240 **RESULTS**

### 241 *Pain*

242 Participants injected with NGF reported greater NRS pain scores when performing “repeated arm  
243 movements” on day-2 (2.6/10) and day-4 (1.6/10) than those injected with isotonic saline (Table  
244 1,  $Z=3.3$ ,  $P<0.001$ ). The NGF group also reported greater “maximum pain experienced over the  
245 past 48 hours” on day-2 (2.7/10) and day-4 (2.1/10) than day-0 ( $Z=3.05$ ,  $P<0.002$ ), and the

246 highest “maximum pain experienced over the past 48 hours” was reported on day-2 (0.9/10)  
247 (Z=3.17, P<0.001). There was no significant difference in NRS pain scores “at rest” between  
248 groups.

249 The NGF group reported higher VAS scores before (1.04/10) and after (0.58/10) saline-  
250 induced pain than the control group (Z=4.46, P<0.001), although these difference in the levels of  
251 pain might not be considered as clinically relevant. Both groups reported higher VAS scores  
252 during saline-induced pain than before and after saline-induced pain (6.23/10) (Table 2, Z=4.45,  
253 P<0.001). VAS scores did not differ between groups during saline-induced pain (Z=1.64,  
254 P=0.09).

255

#### 256 *Effect of saline-induced pain (control group)*

257 Comparison of force between trials performed *before*, *during*, and *after* saline-induced pain on  
258 day-2 for the control group showed that variation was increased in the primary task-direction  
259 *during* acute pain (0.11/1) (SD of Fz; ANOVA:  $F_{(2,24)}=3.52$ ; P<0.05; NK: P<0.05) consistent  
260 with a decrease in motor performance during pain (Fig. 2A). Variation of the force direction was  
261 also greater (0.18/1) (CoP excursion; ANOVA:  $F_{(2,21)}=4.44$ , P=0.023; NK: P<0.005) *during*  
262 acute pain compared with before and after trials (Fig. 2A). This shows that increased variation of  
263 force in directions other than the task-direction, which is consistent with a search for a new  
264 solution. There was no significant difference in force error (Fz RSS) *during* saline-induced pain  
265 (ANOVA:  $F_{(2,22)}=1.29$ ; P>0.15; Fig. 2B) indicating that despite the increase in variation they  
266 could maintain the level of force.

267 In the Control group, CPD in the Fy direction (wrist radial-ulnar deviation) during saline-  
268 induced pain (contrast between measures made on day-2 *during* and *before* saline-induced pain)  
269 was greater than the contrast between measures made *before* injections on day-2 and day-0 (as an

270 estimate of CPD expected between sessions in the absence of pain) and after saline-induced pain  
271 (contrast between measures made on day-2 *after* and *before* saline-induced pain) (0.28/5)  
272 (ANOVA:  $F_{(2,22)}=9.35$ ;  $P<0.001$ ; NK:  $P<0.02$ ; Fig. 3 and Table 3). This shows a greater change  
273 in force direction when challenged by saline-induced muscle pain than would be expected  
274 between sessions without pain.

275

276 *Effect of prolonged movement-evoked pain on the direction of the force*

277 CPD (contrast of measures made on day-2 *before* saline-induced pain and day-0, and the contrast  
278 between measures made on day-4 and day-0) in the Fy direction (wrist radial-ulnar deviation)  
279 was greater in the NGF than control group (0.12/5) (ANOVA:  $F_{(1,22)}=4.26$ ;  $P<0.05$ ; NK:  $P<0.05$ ;  
280 Fig. 3). This shows that persistent pain involves a new task “solution” as indicated by the  
281 modification of the combination of forces used to achieve the task goal.

282

283 *Effect of prolonged movement-evoked pain on the variation of the force*

284 Comparison of contraction force between trials performed *before* injection of NGF, day-2  
285 (*before* saline-induced pain), and day-4 showed no difference in variation in the primary task-  
286 direction (SD of Fz;  $F_{2,42}=1.87$ ,  $P=0.15$ ) and variation of the direction (CoP excursion;  
287  $F_{1,42}=1.11$ ,  $P=0.30$ ; Fig. 4A). This finding shows that there is no on-going increase in force  
288 variation (i.e. no on-going “search”) in the presence of persistent pain. The force error (Fz RSS)  
289 (ANOVA:  $F_{(1,22)}=2.20$ ;  $P=0.15$ ; Fig. 4C) and the MVC in the task-related direction (ANOVA:  
290  $F_{(2,22)}=2.31$ ;  $P=0.10$ ; Fig. 4D) were not affected significantly by persistent movement-evoked  
291 pain, indicating that they could maintain the level of force despite the modified force direction.

292

293 *Effect of saline-induced acute pain during prolonged movement-evoked pain*

294 Comparison of contraction force for wrist extension performed *before*, *during* and *after* saline-  
295 induced pain on day-2 for the NGF group showed greater variation in the task-related direction  
296 (0.15/1) (SD of Fz; ANOVA:  $F_{(2,22)}=4.42$ ;  $P<0.05$ ) and in the variation of the force direction  
297 (0.19/1) (CoP excursion; ANOVA:  $F_{(2,10)}=11.10$ ,  $P<0.005$ ; NK:  $P<0.005$ ) *during* acute pain.

298 When saline-induced pain was added to the movement-evoked pain induced by NGF  
299 injection, the CPD in the Fy direction calculated using the contrast of measures made on day-2  
300 *during* and day-2 *before* saline-induced pain (i.e. effect of saline induced pain) was greater than  
301 the contrast of day-2 *before* saline-induced pain and day-0 (i.e. effect of persistent pain) (0.25/5)  
302 (ANOVA:  $F_{(1,24)}=13.55$ ;  $P=0.001$ ; NK:  $P=0.001$ ). In the presence of persistent pain, participants  
303 retained the capacity to adapt in the same manner (increase variation in the force direction and  
304 change force direction) as participants who had no persistent pain.

305

## 306 **DISCUSSION**

307 These results show that saline-induced acute muscle pain increases variation in the task-related  
308 force and changes the variation and direction of the forces, but without affecting the ability to  
309 achieve the task goal. When people are assessed after a period of persistent pain the force  
310 direction differs from baseline, but with no difference in variation. These findings can be  
311 interpreted according to contemporary theories of motor adaptation and are likely to represent  
312 different elements of the *search* and then *consolidation* of a new, potentially more protective  
313 solution, while maintain the capacity to achieve the task goal.

314

315 *Pain during hypertonic saline and NGF injection*



316 The two pain models used in this study induced pain with different intensities, qualities and pain  
317 duration profiles. These were selected to study the impact of short-term acute pain and persistent  
318 movement-evoked pain on motor control strategies. Participants receiving NGF injections  
319 reported soreness and pain evoked by arm movement in the days following the injection, but not  
320 immediately after injection and minimal or no pain at rest (no spontaneous pain). Although the  
321 mechanism underlying the pain response following NGF injection remains unclear, it has been  
322 suggested to involve sensitization of nociceptors without inducing spontaneous discharge.<sup>28,34</sup>  
323 The intensity and duration of movement-evoked pain by administration of NGF provides a useful  
324 model to study effects of prolonged pain. Intramuscular injection of hypertonic saline induced  
325 spontaneous and transient muscle pain in both groups that lasted a few minutes. Saline-induced  
326 pain has been associated with robust excitation of the nociceptive afferent fibres<sup>13,20</sup> but is not  
327 clearly related to movement/muscle activation.<sup>40</sup> The lack of difference in the intensity of pain  
328 induced by hypertonic saline injection between groups has several interpretations. First,  
329 sensitisation of nociceptive neurons by NGF may not enhance their responsiveness to hypertonic  
330 saline. Second, that the hypertonic saline may not have excited the same population of  
331 nociceptive neurons that were sensitised by NGF (injection in a slightly different location).  
332 Comparable pain intensity has been reported during saline-induced pain between muscles with  
333 and without sensitisation by eccentric exercise.<sup>11,36,45</sup> Similar results have been observed in  
334 glutamate-evoked pain in participants with and without injection of NGF in the masseter  
335 muscle.<sup>39</sup>

336

337 *Changes in isometric wrist extension force with pain*

338 Variation of the task-related and tangential force direction was increased during saline-induced  
339 muscle pain for both groups (i.e. irrespective of whether there was an underlying persistent pain).  
340 This concurs with previous findings of the effect of acute muscle pain on the force variation for  
341 isometric shoulder-abduction,<sup>2</sup> elbow flexion,<sup>25,32</sup> knee extension<sup>31</sup>, and dorsiflexion.<sup>32</sup>

342 Increased variation in the task-related direction may represent a detrimental effect of pain  
343 mediated by several possible mechanisms. Experimental muscle pain decreases the ability of  
344 central nervous system to process proprioceptive information,<sup>7</sup> and alters the population of  
345 recruited motor units,<sup>9,41</sup> each of which may impact the capacity of the muscle to maintain  
346 constant force. It is important to note that although the quality of the motor tasks was  
347 compromise, they could still achieve the task goal (no change in task error). Although the  
348 increase in variation of the tangential direction may also represent a similar mechanism, it may  
349 also serve a purpose; to aid the search for a new less provocative solution (see below).

350 NGF-induced muscle soreness (without the addition of hypertonic saline injection) was not  
351 associated with more force variation than baseline (day-0) when tested after pain had been  
352 experienced for 2 and 4 days. This implies that in this model of slowly increasing movement-  
353 evoked pain there is either no change in variation or that there is an initial increased in variation,  
354 that resolves when pain is maintained. This latter possibility is consistent with previous findings  
355 demonstrating that force variability is only affected for a few hours after the onset of muscle  
356 soreness induced by eccentric exercise although maximal force is reduced for several days in that  
357 model.<sup>21,35</sup>

358 Immediate motor adaptations to acute nociceptive input are task dependent,<sup>5,17,25</sup> whereas  
359 the effects of persistent pain remain unclear. From our study it is not possible to determine  
360 whether soreness and movement-evoked pain induced by NGF was associated with greater

361 variation of the forces in the primary task direction or tangential directions at the onset of pain  
362 provocation as participants were not tested until 2 days after the injection. Despite this, the data  
363 show convincing evidence of isometric wrist extension with different direction of tangential  
364 forces, but with unchanged variation in force in any direction, after several days with pain. This  
365 corroborates the hypothesis that motor adaptations are consolidated over time, that is, although  
366 an initial increase in variation may have facilitated a search for a new solution, when pain is  
367 persistent and a new solution is identified, variation returns to baseline levels. Changes in the  
368 force direction during experimental pain has been found in previous studies<sup>32,42</sup> and it has been  
369 suggested that this strategy aims to reduce pain further and potential tissue damage.<sup>17,42</sup> Even  
370 slight altered direction of the force represents a great impact on the efficiency of the mechanical  
371 system during pain.<sup>42</sup>

372

### 373 *Factors involved in the consolidation of motor adaptations over time*

374 The motor system enables people to perform daily activities using pre-learned motor strategies,  
375 acquired by repetition, failure and success in previous experiences.<sup>3</sup> Using fMRI, it has been  
376 shown that the extent of cortical activation increases in healthy subjects when learning an  
377 untrained motor skill for 2 weeks<sup>44</sup> and then decreases with further training. This adaptation is  
378 thought to relate to the initial exploration and heightened attention to perform the new task  
379 during training, followed by the consolidation of a new strategy. Thus, the motor system need to  
380 explore for a strategy that satisfies the new requirements, and increasing the tangential force  
381 variation may facilitate the searching in acute pain.<sup>27</sup>

382 High precision force-matching tasks are an unfamiliar motor activity, and most likely  
383 require participants to focus their attention during performance. Results from chronic pain

384 patients have shown that those who report high pain intensities have reduced attention when  
385 performing complex motor tasks than those with low pain and controls.<sup>8</sup> Distraction due to high-  
386 pain intensity could account for the increased variation in the force during saline-induced pain.

387 Motor adaptations induced by soreness and movement-evoked pain lasted for several days.  
388 The adaptations caused by persistent pain are observed as reorganisation of the tangential force  
389 to perform the motor task sustained across days. There was a non-significant tendency for greater  
390 changes in the tangential force combination at day 4 than day 2, even though peak soreness and  
391 pain were reported at day 2. This means that participants who received NGF injection continued  
392 to display protective behaviours even when persistent pain had begun to resolve. It has been  
393 suggested that the anticipation to experience pain, rather than pain itself, might account for the  
394 sustained pain adaptations in chronic pain patients.<sup>10</sup> Moreover, pain has been described as a  
395 “motivator” for motor adaptation, but pain cessation does not necessarily motivate a return to the  
396 pre-pain pattern.<sup>17</sup> Whether the force recovered after the resolution of the sustained pain was not  
397 studied in this experiment, but should be considered in future work.

398 There is debate whether pain interferes with learning a motor skill. Although some data  
399 show reduced adaptation of cortical excitability during learning in the presence of pain,<sup>6</sup> when  
400 the quality of practice of the task is controlled, there is no interference.<sup>19</sup> Thus, pain may not  
401 compromise learning, but appears to lead to the learning of a different task such as an adaptation  
402 to alter the motor strategy used to achieve the goal of the motor task during pain.<sup>17</sup> The present  
403 results showed that participants with persistent pain retained the new strategy (potentially a  
404 protective behaviour) across sessions.

405 Interpretation of the present findings requires consideration of several limitations. First, the  
406 current findings are limited to steady force control during low level of isometric wrist extensions,

407 and do not necessarily generalize to other types of contractions relevant to functional activities,  
408 such as, for example, dynamic force control during concentric/eccentric contractions or higher  
409 level of contractions. Second, the data was collected in confined time intervals and the motor  
410 adaptations were not constantly monitored following NGF injection, so learning and  
411 consolidation of a new motor strategy is assumed from the results. However, because of the  
412 specificity of the assessed motor task and for practical reasons, it was not possible to perform a  
413 continuous assessment of the motor task. Therefore, changes in the movement pattern for daily  
414 activities at times between the data collection sessions, including isometric wrist extensions,  
415 remain unknown. Third, changes in the arm position between trials might affect the CoP,  
416 although SD Fz and CPD indexes are not affected by the reposition of the arm. To reduce this  
417 error, participants' wrist was marked facilitating the same position between trials. Fourth, the  
418 number of female participants was not balanced between groups. A previous study showed no  
419 gender difference in NGF evoked sensitization, although hypertonic saline superimposed to NGF  
420 elicited higher pain in males than females.<sup>1</sup> Gender comparison between groups during  
421 hypertonic saline was not performed and it was beyond the scope of this study because of the  
422 sample size.

## 423 **CONCLUSION**

424 Acute pain increases force variation and changes the force direction, but when pain is sustained  
425 only the force direction differs from that in a pain-free state. These differences imply different  
426 elements of learning a new motor strategy in the presence of pain; an initial “search” for a  
427 beneficial solution mediated by increased variation, and a later “consolidation” to the new  
428 alternative. In a clinical context if pain is sustained, treatments that target pain relief might

429 require additional intervention that targets changes in motor performance to restore the pain-free  
430 optimal control of the task.

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436

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- 556
- 557

558 **FIGURE LEGENDS**

559

560 **Fig. 1.** Experimental setup and protocol. *Upper panel:* Wrist extension force was recorded in the  
561 task-related (Z) and the tangential (X and Y) directions using a three-dimensional force  
562 transducer. Marks on the wrist and on the force transducer were used to replace the arm in the  
563 same position at each session. *Lower panel:* Time-course of the experimental protocol. On day-0,  
564 the extensor carpi radialis brevis muscle (dominant arm) of twenty-six healthy volunteers was  
565 injected with nerve growth factor (NGF, N=13) or isotonic saline (ISO, N=13). On day-2, acute  
566 experimental muscle pain was induced by injection of hypertonic saline into the extensor carpi  
567 radialis brevis muscle (same side as the first injection) of all participants.

568

569 **Fig. 2.** Normalised mean ( $\pm$ SEM, N=13) (A) standard deviation (SD) of task-related force and  
570 (B) excursion of the centre of pressure for tangential forces (CoP) during the steady contraction  
571 period (wrist extension at 10% maximal voluntary contraction force) for saline-induced pain.  
572 Significantly increased during saline-induced pain compared with before and after saline-induced  
573 pain sessions (\*,  $P < 0.05$ ). (C) Normalised mean ( $\pm$ SEM, N=13) residual sum of squares error  
574 (RSS) in the task-related (Fz) direction before, during, and after saline-induced pain.

575

576 **Fig. 3.** Distribution of centroid position difference (CPD) of the tangential forces (Fx and Fy).  
577 Data are shown for the Control group in the absence of pain (contrast between baseline day-0  
578 and baseline day-2; far left, upper panel) and for the NGF group after 2 days of pain (contrast  
579 between measures before NGF injection on day-0 and before saline injection day 2; far left,  
580 lower panel). Subsequent panels show CPD for both groups during and after saline-induced pain

581 (contrasted to before saline-induced pain) on day-2, and on day-4 (contrast between baseline  
582 day-0 and day-4; far right panel). Both groups showed greater CPD (spread of the colours) in the  
583 Fy direction ( $P < 0.001$ ) when challenged with saline-induced pain compared with the baseline  
584 condition. This reflects greater changes in the direction of tangential force used to achieve the  
585 motor task. The NGF group showed greater CPD than the control group across days in the Fy  
586 direction ( $P < 0.05$ ), i.e. NGF group deviate from the baseline direction of tangential force across  
587 days.

588

589 **Fig. 4.** Normalised mean ( $\pm$ SEM, N=13) (A) standard deviation (SD) of task-related force and  
590 (B) excursion of the centre of pressure for tangential forces (CoP) during the steady contraction  
591 period (wrist extension at 10% MVC force) across days (day-0, baseline day-2, day-4) for  
592 persistent movement-evoked pain (NGF) and controls. (C) Normalised mean ( $\pm$ SEM, N=13)  
593 residual sum of squares error (RSS) in the task-related (Fz) direction. (D) Maximal voluntary  
594 contraction (MVC) force in the task-related direction (Fz) across days.

595

## TABLES

**Table 1** Pain intensity (mean $\pm$ SEM) reported on numerical rating scale related to nerve growth factor injection

		Pain at rest	Pain during repeated arm movement	Worst pain in past 48 hours
NGF group	Day-0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
	Day-2	0.31 $\pm$ 0.24	2.69 $\pm$ 0.36* <sup>#</sup>	3.31 $\pm$ 0.40* <sup>#</sup>
	Day-4	0.15 $\pm$ 0.10	1.61 $\pm$ 0.33* <sup>#</sup>	2.38 $\pm$ 0.50* <sup>#</sup>
Control group	Day-0	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
	Day-2	0 $\pm$ 0	0.08 $\pm$ 0.08	0.61 $\pm$ 0.21
	Day-4	0 $\pm$ 0	0 $\pm$ 0	0.23 $\pm$ 0.17

\* - NGF group reported higher pain on the NRS on day-2 and day-4 than the control group (P<0.001).

# - NGF group reported higher pain on the NRS on day-2 and day-4 than Day-0 (P<0.01).

**Table 2** Pain intensity (mean±SEM) reported on visual analogue scale related to hypertonic saline injection

	Before	During saline-induced pain	After
NGF group	1.04 ± 0.38 <sup>#</sup>	7.27 ± 0.43*	0.58 ± 0.3 <sup>#</sup>
Control group	0 ± 0	6.23 ± 0.33*	0 ± 0

\* - Higher VAS scores during the saline-induced pain than before and after saline-induced pain trials (P<0.001).

# - NGF group reporter higher VAS scores than the Control group (P<0.05).

**Table 3**

---

<b>Centroid position difference</b>				
		Fy direction		
		Day-2		Day-4
	Baseline	During saline- induced pain	After saline- induced pain	
NGF group	0.25 ± 0.05*	0.62 ± 0.09 <sup>#</sup>	0.39 ± 0.08	0.45 ± 0.06*
Control group	0.18 ± 0.05	0.45 ± 0.08 <sup>#</sup>	0.31 ± 0.08	0.24 ± 0.06
Fx direction				
NGF group	0.41 ± 0.07	0.21 ± 0.06	0.26 ± 0.08	0.28 ± 0.07
Control group	0.31 ± 0.07	0.30 ± 0.06	0.35 ± 0.08	0.41 ± 0.07

---

Mean ( $\pm$ SEM, N=13) of the absolute centroid position difference (CPD) of the Fx-Fy plane at baseline (contrast before saline-induced pain day-2 with day-0), during and after saline-induced pain (contrasting each trial with before saline-induced pain day-2), and day-4 (contrast day-4 with day-0). The NGF group showed greater (CDP) compared with the control group (\*, NK: P=0.048). Significantly increased during saline-induced pain compared with baseline and after saline-induced pain sessions (<sup>#</sup>, P<0.001).

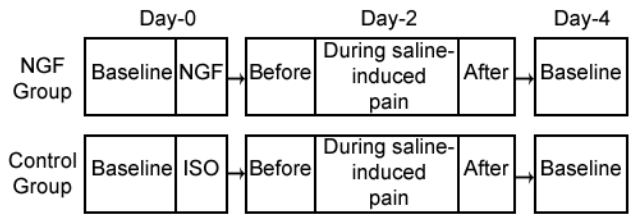
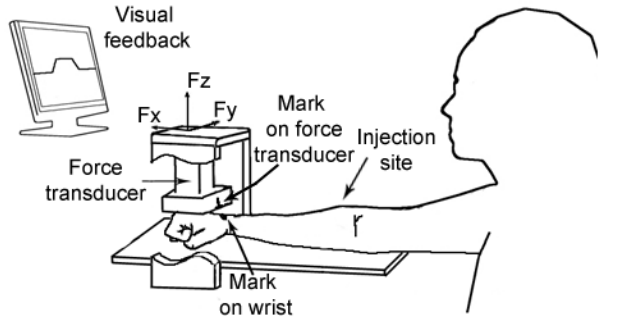


1 **Figures**

2

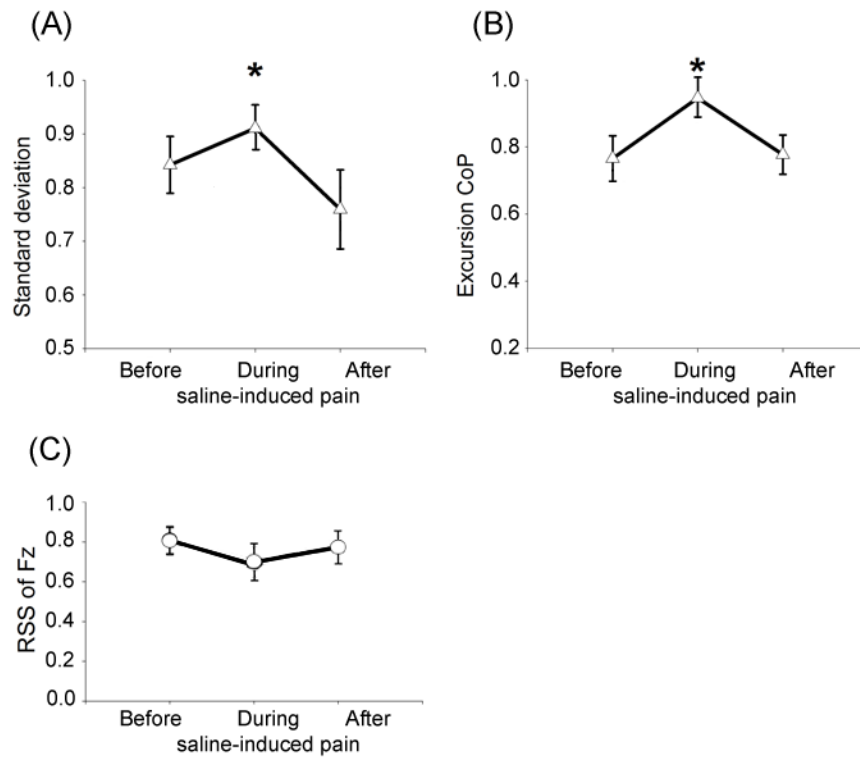
3 **Figure 1**

4



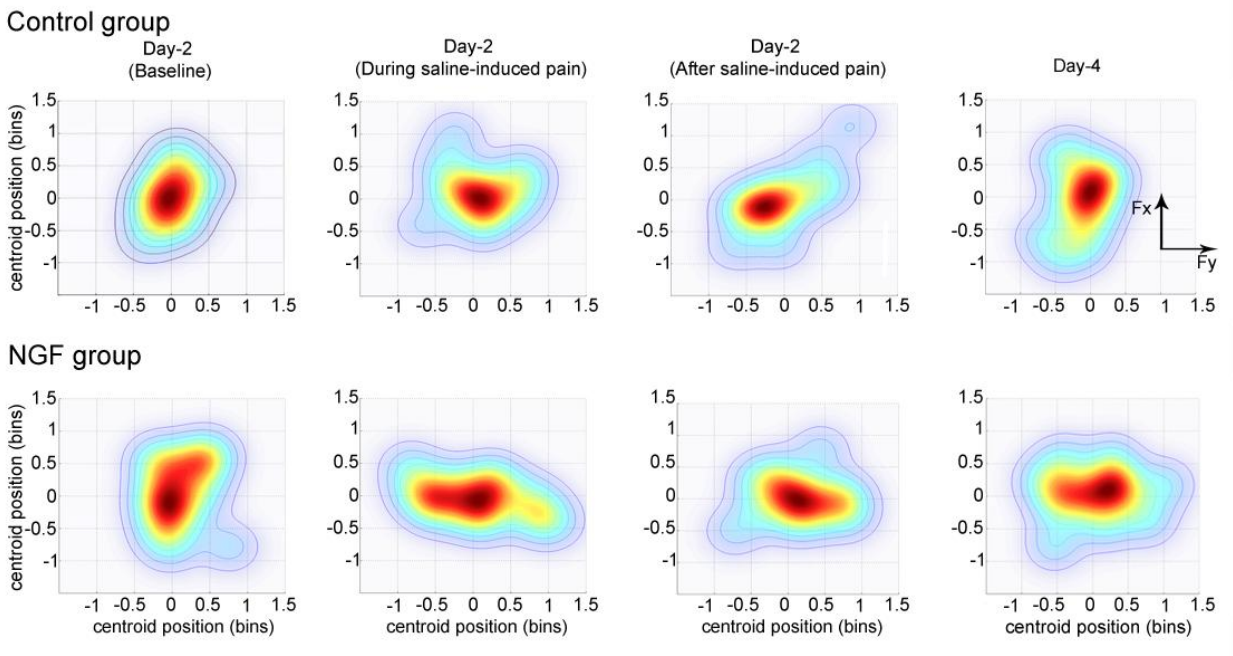
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Figure 2



1 **Figure 3**

2



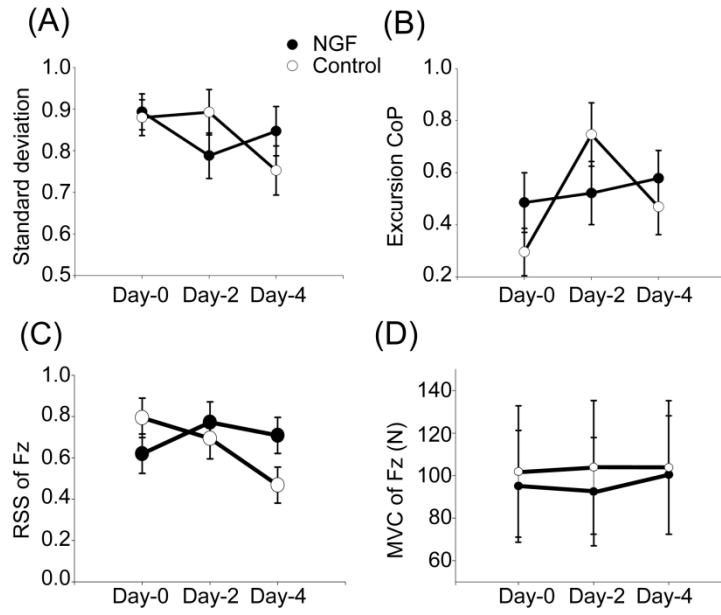
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Figure 4



1 | **E**ffects of prolonged and acute muscle pain on the force control strategy  
2 | **during isometric contractions**

3 |  
4 | CA Mista<sup>1</sup>, M Bergin<sup>2</sup>, R Hirata<sup>1</sup>, S Christensen<sup>1</sup>, K Tucker<sup>2,3</sup>, P Hodges<sup>2</sup>, T Graven-Nielsen<sup>1</sup>

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15 | **Target journal:** Journal of Pain

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30 |

31 **ABSTRACT**

32 Musculoskeletal pain is associated with multiple adaptations in movement control. This study  
33 aimed to determine whether changes in movement control acquired during acute pain are  
34 maintained over days of pain exposure. On day-0, the extensor carpi radialis brevis (ECRB)  
35 muscle of healthy participants was injected with nerve growth factor (NGF) to induce persistent  
36 movement-evoked pain (N=13) or isotonic saline as a control (N=13). On day-2, short-lasting  
37 pain was induced by injection of hypertonic saline into ECRB muscles of all participants. Three-  
38 dimensional force components were recorded during submaximal isometric wrist extensions on  
39 day-0, day-4, and before, during, and after saline-induced pain on day-2. Standard deviation  
40 (variation of task-related force) and total excursion of center of pressure (variation of force  
41 direction) were assessed. Maximal movement-evoked pain was  $3.3 \pm 0.4$  (0-10 numeric scale) in  
42 the NGF-group on day-2 whereas maximum saline-induced pain was  $6.8 \pm 0.3$  cm (10-cm visual  
43 analogue scale). The difference in centroid position of force direction relative to day-0 was  
44 greater in the NGF-group than controls ( $P < 0.05$ ) on day-2 (before saline-induced pain) and day-  
45 4, reflecting changes in tangential force direction used to achieve the task. During saline-induced  
46 pain in both groups, tangential and task-related force variation was greater than before and after  
47 saline-induced pain ( $P < 0.05$ ).

48 **Perspectives**

49 Persistent movement-evoked pain changes force direction from the pain-free direction. Acute  
50 pain leads to increase variation in force direction irrespective of persistent movement-evoked  
51 pain preceding the acutely painful event. These differences provide novel insight into the search  
52 and consolidation of new motor strategies in the presence of pain.

53 **Key words:** Force, NGF, muscle pain, persistent pain.

54

## 55 INTRODUCTION

56 Transient muscle pain is accompanied by changes in movement patterns<sup>2,17,32</sup> and is thought to  
57 serve a protective function to reduce threat to the painful/injured region. Resolution of pain is not  
58 necessarily associated with a return to the original motor pattern.<sup>17,43</sup> One hypothesis is that  
59 movement changes during pain are achieved by an initial increase in variation to search for a  
60 new strategy, and once a beneficial strategy is found, variation is reduced to maintain the new  
61 strategy.<sup>27</sup> Motor adaptations may be maintained for the duration of pain, or continue to undergo  
62 change if pain persists.

63 Transient muscle pain induced by hypertonic saline injection changes coordination  
64 between muscles<sup>12,16</sup> and the spatial distribution of activation within a muscle.<sup>18,23</sup> The principal  
65 interpretation of altered muscle activity is to reduce the potential for further pain and tissue  
66 damage.<sup>17,22</sup> Noxious input also increases variability in force during submaximal isometric  
67 contractions in both the primary direction of task-related force<sup>2</sup> and in directions tangential to the  
68 primary task force.<sup>25,32</sup> Increased variation in different directions could have different  
69 interpretations. Variation in the tangential force could represent a search for less  
70 painful/threatening directions that redistribute load across painful structures.<sup>17</sup> In the primary  
71 task-related force direction increased variation is unlikely to represent a search for a new strategy  
72 as this would compromise the goal to maintain a target force, instead it might be the result of to  
73 the purposeful variation in tangential force or result from interference by pain secondary to  
74 distraction,<sup>8</sup> impaired proprioception,<sup>7</sup> or altered synchronization/recruitment of different  
75 populations of motor units.<sup>24,41,46</sup> Although these interpretations appear logical when a person is  
76 first exposed to noxious input, features of the motor adaptation may differ over longer periods. If  
77 pain is sustained it might be expected that the new motor solution would become consolidated,



78 and variation would reduce around a new motor solution. How motor adaptations in pain change  
79 over time has received little attention, primarily as a consequence of the lack of suitable  
80 experimental methods that induce suitably prolonged noxious stimulus.

81 One possibility to induce persistent pain is intramuscular injection of nerve growth factor  
82 (NGF), which induces muscle soreness and movement-evoked pain for several days.<sup>1,4,38,39</sup>  
83 Administration of NGF does not elicit immediate muscle pain<sup>1,30,38,39</sup> but induces localised  
84 hyperalgesia after several hours that is provoked during function.<sup>1,4,14</sup> This presents a possible  
85 method to study the time-course of motor adaptation.

86 This study aimed to compare changes of direction and variation of multidirectional (task-  
87 related and tangential) forces: (1) in the presence of acute experimental pain; (2) after  
88 experimental movement-evoked pain had been sustained for several days; and (3) with the  
89 combined effect of additional acute pain on a background of persistent movement-evoked pain. It  
90 was hypothesised that: (1) acute experimental muscle pain would increase variation in the  
91 primary force direction consistent with pain interference, and variation in the force direction  
92 consistent with a search for a less threatening motor pattern, and alter the direction of the  
93 tangential force, but without compromising their ability to maintain the task goal; (2) *direction* of  
94 tangential force would differ by a greater amount between baseline and follow-up after several  
95 days of persistent movement-evoked pain (maintenance of a new solution), than it would  
96 between days in the absence of pain (3) *variation* in force direction would not be greater than  
97 baseline after several days of persistent pain as a “search” for a new movement solution would  
98 be expected to have occurred when pain was first experienced, but variation in the task-related  
99 force may continue if interference by pain persisted; and (4) addition of acute pain on persistent  
100 pain would lead to a new search (increased variation) and additional change in direction.

## 101 **METHODS**

### 102 *Participants*

103 Twenty-six healthy volunteers (7 females, age:  $26 \pm 5$  years, mean  $\pm$  standard deviation)  
104 participated in the study. Participants were free of upper limb pain, and had no history of pain or  
105 neuromuscular disorders affecting the upper limb region. All participants received written and  
106 verbal description of the procedures and gave written informed consent. The experimental  
107 procedures were approved by the local ethics committee (N-201200640) and the Declaration of  
108 Helsinki was respected.

109

### 110 *Experimental protocol*

111 Participants sat upright in a height-adjustable chair with their back resting against backrest. The  
112 forearm of the dominant arm was in a pronated position, and the hand formed a fist. The distal  
113 portion of the hand was in slight contact with a force transducer, which recorded the force output  
114 during wrist extension (Fig. 1). The experiment was performed as a randomised, double-blinded,  
115 placebo-controlled design, across 3 sessions (day-0, day-2, and day-4). During the first session  
116 (day-0), participants from the NGF group (N=13; five females) received a single dose of 5  $\mu$ g  
117 human  $\beta$ -Nerve Growth Factor (0.2 ml, 25  $\mu$ g/ml, prepared by the pharmacy at Aalborg  
118 University, Hospital), and participants from the Control group received a single dose of sterile  
119 isotonic saline (0.2 ml, 0.9%; N=13; two females), injected into the extensor carpi radialis brevis  
120 (ECRB) muscle. The number of participants included in each group was based on previous  
121 studies using a similar design to evaluate the effects of intramuscular NGF injections.<sup>14,38,39</sup> All  
122 injections were performed on the dominant side, and injection site and depth was determined by  
123 guidance of ultrasound imaging. The injection site was marked with indelible ink. Participant's  
124 wrist was also marked in order to ensure consistent alignment of the arm position with the force

125 transducer between sessions. Participants performed a series of force-matched wrist extensions  
126 before and after the injection. During the second session (day-2), acute muscle pain was induced  
127 by injection of hypertonic saline (0.5 ml, 5.8%) in the ECRB muscle (same location as NGF/iso  
128 injection) of participants in both groups. Participants performed the motor task before, during,  
129 and after the acute pain experienced by injection of hypertonic saline. Note that at this time point  
130 it was expected that the NGF group would have experienced movement-evoked pain induced by  
131 the NGF injection for multiple days. In the third session (day-4), participants performed one trial  
132 of the motor task without any injection (Fig. 1).

133

#### 134 *Motor task*

135 In each session, the maximal voluntary contraction (MVC) was recorded by performing three  
136 consecutive maximal isometric wrist extension trials for 10 s with an interval of 30 s in-between.  
137 The maximum force (calculated in the Fz direction) among the three wrist extension repetitions  
138 was used as the MVC force for the remaining trials and sessions. After a 60-s rest, a set of  
139 submaximal isometric wrist extensions was performed, consisting of 3 consecutive trials at 10%  
140 MVC with a 5-s ascending ramp, 10 s of steady phase, and a 5-s descending ramp. The target  
141 force level and the participant's actual force in the task-related direction (i.e. in Fz direction)  
142 were presented as lines on a computer screen. Participants matched the target force as precisely  
143 as possible. Tangential forces were recorded during each trial.

144

#### 145 *Force and torque recordings*

146 Three-dimensional force components and torques were measured using a six-axis load cell  
147 transducer (MC3A 250, AMTI, USA) with high sensitivity (0.054, 0.054, 0.0134 V/N for Fx, Fy,

148 Fz; and 2.744, 2.744, 2.124 V/Nm for Mx, My, Mz). The analogue outputs of the transducer  
149 were amplified and low-pass filtered at 1 kHz (MSA-6, AMTI, USA). The force and torque  
150 signals were sampled at 2 kHz and stored after 12-bit A/D conversion.

151

### 152 *Pain intensity assessment*

153 Participants completed a pain questionnaire in the evening of each session day. The  
154 questionnaire consisted of three questions relating to their pain quantified used an 11-point  
155 numerical rating scale (NRS) where 0 = ‘no pain’ and 10 = ‘worst pain imaginable’. Pain  
156 intensity was reported: “at rest”, while performing a task involving “repeated wrist  
157 extension/flexion and elbow flexion/extension movements in daily life activities” in the previous 48  
158 hours, and the “maximum pain that had been experienced in the previous 48 hours”. Following  
159 the hypertonic saline injection, pain intensity was scored continuously until pain resolution, on a  
160 10-cm electronic visual analogue scale (VAS) where 0 cm indicated ‘no pain’ and 10 cm ‘worst  
161 pain imaginable’. The peak VAS score following the injection was extracted for further analysis.

162

### 163 *Data analysis*

164 Force and torque signals were digitally low-pass filtered at 20 Hz using a second order  
165 Butterworth filter. In order to avoid regions within the force trace that may be associated with  
166 slow force development and anticipation to the decreasing force phase of the task, 8 s in the  
167 middle of the steady period of force maintenance was selected for data analysis. Standard  
168 deviation (SD) was used to quantify force variability in the task-related direction. Force error  
169 was calculated using the residual sum of squares error (RSS) of the force trace from the target  
170 line, reflecting the force accuracy in the Fz direction. The total excursion of the centre of

171 pressure (CoP) was used to quantify lateral shifts of the quasi-static net force (i.e. changes in  
172 force direction). This index reflects the total length of the CoP path in a given time period<sup>29</sup> and  
173 represents an indirect measure of the tangential force variation.<sup>26,32,33</sup> A two-dimensional  
174 histogram of tangential force components was developed using a 5-by-5 equally spaced grid to  
175 represent the range of the force in the Fy (wrist radial-ulnar deviation) and Fx (longitudinal  
176 movement of the wrist) direction. Coordinates of the centroid were extracted from the force  
177 histogram. For the analysis of the effect of persistent pain, the centroid position at day-2 and at  
178 day-4 was subtracted from the position of the centroid obtained during baseline day-0 for both  
179 groups. For saline-induced muscle pain, centroid position *during* and *after* saline-induced pain  
180 was subtracted from the *baseline* (before saline-induced pain trial) at the same day (day-2). To  
181 provide a “no-pain” measure of the change in centroid position against which the hypertonic  
182 saline conditions could be compared, we subtracted the centroid position prior to saline induced  
183 pain on day-2 from the centroid position prior to isotonic saline injection on day-0, for the  
184 Control group. The absolute difference in Fy and Fx directions were extracted (Fy and Fx,  
185 respectively). A centroid position difference (Fx-CPD and Fy-CPD) value deviating from zero  
186 indicates that new combinations of tangential forces were used in that condition reflecting  
187 changes the direction of the net force.<sup>15,25</sup>

Thus, CoP quantifies variability of the force direction,

whereas CPD represents magnitude of change in the direction of the force between two trials.

189

### 190 *Statistical analysis*

191 SD of the force (Fz) and excursion of the CoP were normalised for each injection type. To  
192 reduce the between-subject variability of the samples,<sup>37</sup> normalisation was implemented by  
193 dividing parameters of each participant with their peak value across trials (Baseline day-0,

194 Baseline day-2 [before saline-induced pain], and Baseline day-4 for NGF/isotonic saline  
195 injection; and before, during, and after saline-induced pain for hypertonic saline injection).

196 *Effects of saline-induced pain:* To test the first hypothesis whether force variation in the  
197 tangential direction (excursion of CoP), and/or variation (SD of Fz) and error (Fz RSS) in the  
198 primary task direction were altered by saline-induced muscle pain on day-2, a repeated measures  
199 analysis of variance (ANOVA) was applied using *Time* (before, during, and after saline-induced  
200 muscle pain) as a within-subject factor for the Control group. This analysis did not include the  
201 NGF group who received saline injection in addition to NGF. To test whether force direction is  
202 altered by saline-induced pain on day-2, CPD were analysed using a repeated measures ANOVA  
203 with ~~and~~-*Time* (Baseline [pre-injection day-0 minus pre-injection day-2], during saline-induced  
204 pain [pre-pain minus pain], and after [post-pain minus pain]) as a within-subject factor.

205 *Effects of injection of NGF and isotonic saline:* To test hypotheses 2 and 3, whether force  
206 direction variation (excursion of CoP), and/or variation (SD of Fz) and error (Fz RSS) in the  
207 primary task direction were modified after several days of sustained pain following NGF  
208 injections; these data were analysed using a mixed-model design ANOVA with *Group* (NGF and  
209 isotonic saline) as a between-subject factor, and *Session* (day-0, day-2 before-saline injection,  
210 and day-4) as a within-subject factor. To test whether tangential force direction is altered by  
211 persistent pain, CPD were analysed using a mixed-model ANOVA with *Group* (NGF and  
212 isotonic saline) as a between-subject factor and *Session* (day-2 before-saline injection minus pre-  
213 injection day-0 and day-4 minus pre-injection day-0) as a within-subject factor. Newman-Keuls  
214 (NK) post-hoc tests were applied in case of significant effects from main factors or interactions.  
215 We also compared maximum force between sessions to investigate whether this was constant  
216 across days.

217 *Effects of saline-induced pain during persistent movement-evoked pain:* To test hypothesis  
218 4, whether **force** variation in the force direction (excursion of CoP), and/or variation (SD of Fz)  
219 and error (Fz RSS) in the primary task direction were altered by saline-induced muscle pain  
220 during movement-evoked pain on day-2, a repeated measures analysis of variance (ANOVA)  
221 was applied using *Time* (before, during, and after saline-induced muscle pain) as a within-subject  
222 factor for the NGF group. CPD were analysed using a repeated measures ANOVA with *Time*  
223 (Baseline [pre-injection day-0 minus pre-injection day-2], during saline-induced pain [pre-pain  
224 minus pain], and after [post-pain minus pain]) as a within-subject factor.

225 As peak VAS scores and data from the pain questionnaire were not normally distributed,  
226 Mann-Whitney U tests were used to assess differences between groups (before, during, and after  
227 saline-induced pain for peak VAS scores, and day-0, day-2, and day-4 for pain questionnaire  
228 measures, respectively). The Wilcoxon Signed Rank test was used to analyse for differences  
229 between sessions within a group across time trials (VAS scores) and days (pain questionnaire,  
230 measures were analysed individually), and Bonferroni corrections were used to adjust P-values  
231 for multiple comparisons. Data are presented as magnitude of relevant difference in the results  
232 section, and mean and standard error of the mean (SEM) throughout the text-tables and figures.  
233 P-values less than 0.05 were regarded as significant.

234

## 235 **RESULTS**

### 236 *Pain*

237 Participants injected with NGF reported greater NRS pain scores when performing “repeated arm  
238 movements” on day-2 (2.6/10) and day-4 (1.6/10) than those injected with isotonic saline (Table  
239 1, Z=3.3, P<0.001). The NGF group also reported greater “maximum pain experienced over the  
240 past 48 hours” on day-2 (2.7/10) and day-4 (2.1/10) than day-0 (Z=3.05, P<0.002), and the

241 highest “maximum pain experienced over the past 48 hours” was reported on day-2 (0.9/10)  
242 (Z=3.17, P<0.001). There was no significant difference in NRS pain scores “at rest” between  
243 groups.

244 The NGF group reported higher VAS scores before (1.04/10) and after (0.58/10) saline-  
245 induced pain than the control group (Z=4.46, P<0.001), although these difference in the levels of  
246 pain might not be considered as clinically relevant. Both groups reported higher VAS scores  
247 during saline-induced pain than before and after saline-induced pain (6.23/10) (Table 2, Z=4.45,  
248 P<0.001). VAS scores did not differ between groups during saline-induced pain (Z=1.64,  
249 P=0.09).

250

251 *Effect of saline-induced pain (control group)*

252 Comparison of force between trials performed before, during, and after saline-induced pain on  
253 day-2 for the control group showed that variation was increased in the primary task-direction  
254 during acute pain (0.11/1) (SD of Fz; ANOVA:  $F_{(2,24)}=3.52$ ; P<0.05; NK: P<0.05) consistent  
255 with a decrease in motor performance during pain (Fig. 2A). Variation of the force direction was  
256 also ~~Comparison of force between trials performed before, during, and after saline induced pain~~  
257 ~~on day-2 for the control group showed greater (0.18/1) variation in the force direction (CoP~~  
258 ~~excursion; ANOVA:  $F_{(2,21)}=4.44$ , P=0.023; NK: P<0.005) during acute pain compared with~~  
259 ~~before and after trials (Fig. 2A). This shows that increased variation of force in directions other~~  
260 ~~than the task-direction, which is consistent with a search for a new solution. Variation was also~~  
261 ~~increased during acute pain in the primary task direction (SD of Fz; ANOVA:  $F_{(2,24)}=3.52$ ;~~  
262 ~~P<0.05; NK: P<0.05) consistent with pain (Fig. 2A).~~ There was no significant difference in force  
263 error (Fz RSS) during saline-induced pain (ANOVA:  $F_{(2,22)}=1.29$ ; P>0.15; Fig. 2B) indicating  
264 that despite the increase in variation they could maintain the level of force.



265 In the Control group, CPD in the Fy direction (wrist radial-ulnar deviation) during saline-  
266 induced pain (contrast between measures made on day-2 *during* and *before* saline-induced pain)  
267 was greater than the contrast between measures made *before* injections on day-2 and day-0 (as an  
268 estimate of CPD expected between sessions in the absence of pain) and after saline-induced pain  
269 (contrast between measures made on day-2 *after* and *before* saline-induced pain) (0.28/5)  
270 (ANOVA:  $F_{(2,22)}=9.35$ ;  $P<0.001$ ; NK:  $P<0.02$ ; Fig. 3 and Table 3). This shows a greater change  
271 in force direction when challenged by saline-induced muscle pain than would be expected  
272 between sessions without pain.

273

274 Effect of prolonged movement-evoked pain on the direction of the force  
275 CPD (contrast of measures made on day-2 before saline-induced pain and day-0, and the contrast  
276 between measures made on day-4 and day-0) in the Fy direction (wrist radial-ulnar deviation)  
277 was greater in the NGF than control group (0.12/5) (ANOVA:  $F_{(1,22)}=4.26$ ;  $P<0.05$ ; NK:  $P<0.05$ ;  
278 Fig. 3). This shows that persistent pain involves a new task “solution” as indicated by the  
279 modification of the combination of forces used to achieve the task goal.

280

281 Effect of prolonged movement-evoked pain on the variation of the force

282 Comparison of contraction force between trials performed *before* injection of NGF, day-2  
283 (*before* saline-induced pain), and day-4 showed no difference in variation in the primary task-  
284 direction (SD of Fz;  $F_{2,42}=1.87$ ,  $P=0.15$ ) and variation of the direction (CoP excursion;  
285  $F_{1,42}=1.11$ ,  $P=0.30$ ; Fig. 4A). This finding shows that there is no on-going increase in force  
286 variation (i.e. no on-going “search”) in the presence of persistent pain. The force error (Fz RSS)  
287 (ANOVA:  $F_{(1,22)}=2.20$ ;  $P=0.15$ ; Fig. 4C) and the MVC in the task-related direction (ANOVA:

288  $F_{(2,22)}=2.31$ ;  $P=0.10$ ; Fig. 4D) were not affected significantly by persistent movement-evoked  
289 pain, indicating that they could maintain the level of force despite the modified force direction.

290  
291 ~~CPD (contrast of measures made on day-2 before saline-induced pain and day-0, and the~~  
292 ~~contrast between measures made on day-4 and day-0) in the Fy direction (wrist radial ulnar~~  
293 ~~deviation) was greater in the NGF than control group (ANOVA:  $F_{(1,22)}=4.26$ ;  $P<0.05$ ; NK:~~  
294  ~~$P<0.05$ ; Fig. 3). This shows that persistent pain involves a new task “solution” as indicated by~~  
295 ~~the modification of the combination of forces used to achieve the task goal. The force error (Fz~~  
296 ~~RSS) (ANOVA:  $F_{(1,22)}=2.20$ ;  $P=0.15$ ; Fig. 4C) and the MVC in the task-related direction~~  
297 ~~(ANOVA:  $F_{(2,22)}=2.31$ ;  $P=0.10$ ; Fig. 4D) were not affected significantly by persistent movement-~~  
298 ~~evoked pain, indicating that they could maintain the level of force despite the modified force~~  
299 ~~direction.~~

300

301 *Effect of saline-induced acute pain during prolonged movement-evoked pain*

302 ~~Similar to the control group, e~~Comparison of contraction force for wrist extension performed  
303 *before, during and after* saline-induced pain on day-2 for the NGF group showed greater  
304 variation in the task-related direction (0.15/1) (SD of Fz; ANOVA:  $F_{(2,22)}=4.42$ ;  $P<0.05$ ) and in  
305 the variation of the force direction (0.19/1) (CoP excursion; ANOVA:  $F_{(2,10)}=11.10$ ,  $P<0.005$ ;  
306 NK:  $P<0.005$ ) *during* acute pain.

307 When saline-induced pain was added to the ~~persistent~~ movement-evoked ~~related~~ pain  
308 induced by NGF injection, the CPD in the Fy direction calculated using the contrast of measures  
309 made on day-2 *during* and day-2 *before* saline-induced pain (i.e. effect of saline induced pain)  
310 was greater than the contrast of day-2 *before* saline-induced pain and day-0 (i.e. effect of

311 | persistent pain) (0.25/5) (ANOVA:  $F_{(1,24)}=13.55$ ;  $P=0.001$ ; NK:  $P=0.001$ ). In the presence of  
312 | persistent pain, participants retained the capacity to adapt in the same manner (increase variation  
313 | in the force direction and change force direction) as participants who had no persistent pain.

314

## 315 | **DISCUSSION**

316 | These results show that saline-induced acute muscle pain increases variation in the task-related  
317 | force and changes the variation and direction of the forces, but without affecting the ability to  
318 | achieve the task goal. When people are assessed after a period of persistent pain the force  
319 | direction differs from baseline, but with no difference in variation. These findings can be  
320 | interpreted according to contemporary theories of motor adaptation and are likely to represent  
321 | different elements of the *search* and then *consolidation* of a new, potentially more protective  
322 | solution, while maintain the capacity to achieve the task goal.

323

### 324 | *Pain during hypertonic saline and NGF injection*

325 | The two pain models used in this study induced pain with different intensities, qualities and pain  
326 | duration profiles. These were selected to study the impact of short-term acute pain and persistent  
327 | movement-evoked pain on motor control strategies. Participants receiving NGF injections  
328 | reported soreness and pain evoked by arm movement in the days following the injection, but not  
329 | immediately after injection and minimal or no pain at rest (no spontaneous pain). Although the  
330 | mechanism underlying the pain response following NGF injection remains unclear, it has been  
331 | suggested to involve sensitization of nociceptors without inducing spontaneous discharge.<sup>28,34</sup>  
332 | The intensity and duration of movement-evoked pain by administration of NGF provides a useful  
333 | model to study effects of prolonged pain. Intramuscular injection of hypertonic saline induced

334 spontaneous and transient muscle pain in both groups that lasted a few minutes. Saline-induced  
335 pain has been associated with robust excitation of the nociceptive afferent fibres<sup>13,20</sup> but is not  
336 clearly related to movement/muscle activation.<sup>40</sup> The lack of difference in the intensity of pain  
337 induced by hypertonic saline injection between groups has several interpretations. First,  
338 sensitisation of nociceptive neurons by NGF may not enhance their responsiveness to hypertonic  
339 saline. Second, that the hypertonic saline may not have excited the same population of  
340 nociceptive neurons that were sensitised by NGF (injection in a slightly different location).  
341 Comparable pain intensity has been reported during saline-induced pain between muscles with  
342 and without sensitisation by eccentric exercise.<sup>11,36,45</sup> Similar results have been observed in  
343 glutamate-evoked pain in participants with and without injection of NGF in the masseter  
344 muscle.<sup>39</sup>

345

#### 346 *Changes in isometric wrist extension force with pain*

347 Variation of the task-related and tangential force direction was increased during saline-induced  
348 muscle pain for both groups (i.e. irrespective of whether there was an underlying persistent pain).  
349 This concurs with previous findings of the effect of acute muscle pain on the force variation for  
350 isometric shoulder-abduction,<sup>2</sup> elbow flexion,<sup>25,32</sup> knee extension<sup>31</sup>, and dorsiflexion.<sup>32</sup>

351 Increased variation in the task-related direction may represent a detrimental effect of pain  
352 mediated by several possible mechanisms. Experimental muscle pain decreases the ability of  
353 central nervous system to process proprioceptive information,<sup>7</sup> and alters the population of  
354 recruited motor units,<sup>9,41</sup> each of which may impact the capacity of the muscle to maintain  
355 constant force. It is important to note that although the quality of the motor tasks was  
356 compromise, they could still achieve the task goal (no change in task error). Although the

357 increase in variation of the tangential direction may also represent a similar mechanism, it may  
358 also serve a purpose; to aid the search for a new less provocative solution (see below).

359 NGF-induced muscle soreness (without the addition of hypertonic saline injection) was not  
360 associated with more force variation than baseline (day-0) when tested after pain had been  
361 experienced for 2 and 4 days. This implies that in this model of slowly increasing movement-  
362 evoked pain there is either no change in variation or that there is an initial increased in variation,  
363 that resolves when pain is maintained. This latter possibility is consistent with previous findings  
364 demonstrating that force variability is only affected for a few hours after the onset of muscle  
365 soreness induced by eccentric exercise although maximal force is reduced for several days in that  
366 model.<sup>21,35</sup> ~~In such case the decrease in maximal force beyond 24 hours after eccentric exercise is  
367 most likely mediated by muscle fibre damage.<sup>38</sup> Although it could be argued that soreness and  
368 movement-related pain following eccentric exercise might also be involved via effects of pain on  
369 motor output,<sup>47</sup> the absence of decrement in MVC across days in the present study does not  
370 support this proposal. Taken together these findings support the hypothesis that muscle damage,  
371 but not soreness and movement-evoked pain, explain the diminished force after eccentric  
372 exercise.<sup>29,38</sup>~~

373 Immediate motor adaptations to acute nociceptive input are task dependent,<sup>5,17,25</sup> whereas  
374 the effects of persistent pain remain unclear. From our study it is not possible to determine  
375 whether soreness and movement-evoked pain induced by NGF was associated with greater  
376 variation of the forces in the primary task direction or tangential directions at the onset of pain  
377 provocation as participants were not tested until 2 days after the injection. Despite this, the data  
378 show convincing evidence of isometric wrist extension with different direction of tangential  
379 forces, but with unchanged variation in force in any direction, after several days with pain. This

380 corroborates the hypothesis that motor adaptations are consolidated over time, that is, although  
381 an initial increase in variation may have facilitated a search for a new solution, when pain is  
382 persistent and a new solution is identified, variation returns to baseline levels. Changes in the  
383 force direction during experimental pain has been found in previous studies<sup>32,42</sup> and it has been  
384 suggested that this strategy aims to reduce pain further and potential tissue damage.<sup>17,42</sup> Even  
385 slight altered direction of the force represents a great impact on the efficiency of the mechanical  
386 system during pain.<sup>42</sup>

387

### 388 *Factors involved in the consolidation of motor adaptations over time*

389 The motor system enables people to perform daily activities using pre-learned motor strategies,  
390 acquired by repetition, failure and success in previous experiences.<sup>3</sup> Using fMRI, it has been  
391 shown that the extent of cortical activation increases in healthy subjects when learning an  
392 untrained motor skill for 2 weeks<sup>44</sup> and then decreases with further training. This adaptation is  
393 thought to relate to the initial exploration and heightened attention to perform the new task  
394 during training, followed by the consolidation of a new strategy. Thus, the motor system need to  
395 explore for a strategy that satisfies the new requirements, and increasing the tangential force  
396 variation may facilitate the searching in acute pain.<sup>27</sup>

397 High precision force-matching tasks are an unfamiliar motor activity, and most likely  
398 require participants to focus their attention during performance. Results from chronic pain  
399 patients have shown that those who report high pain intensities have reduced attention when  
400 performing complex motor tasks than those with low pain and controls.<sup>8</sup> Distraction due to high-  
401 pain intensity could account for the increased variation in the force during saline-induced pain.

402 Motor adaptations induced by soreness and movement-evoked pain lasted for several days.  
403 The adaptations caused by persistent pain are observed as reorganisation of the tangential force  
404 to perform the motor task sustained across days. There was a non-significant tendency for greater  
405 changes in the tangential force combination at day 4 than day 2, even though peak soreness and  
406 pain were reported at day 2. This means that participants who received NGF injection continued  
407 to display protective behaviours even when persistent pain had begun to resolve. It has been  
408 suggested that the anticipation to experience pain, rather than pain itself, might account for the  
409 sustained pain adaptations in chronic pain patients.<sup>10</sup> Moreover, pain has been described as a  
410 “motivator” for motor adaptation, but pain cessation does not necessarily motivate a return to the  
411 pre-pain pattern.<sup>17</sup> Whether the force recovered after the resolution of the sustained pain was not  
412 studied in this experiment, but should be considered in future work.

413 There is debate whether pain interferes with learning a motor skill. Although some data  
414 show reduced adaptation of cortical excitability during learning in the presence of pain,<sup>6</sup> when  
415 the quality of practice of the task is controlled, there is no interference.<sup>19</sup> Thus, pain may not  
416 compromise learning, but appears to lead to the learning of a different task such as an adaptation  
417 to alter the motor strategy used to achieve the goal of the motor task during pain.<sup>17</sup> The present  
418 results showed that participants with persistent pain retained the new strategy (potentially a  
419 protective behaviour) across sessions. ~~It has been shown that supplementary motor areas are  
420 associated with the programming of the motor sequence, whereas the primary motor cortex is  
421 involved with the execution of the motor tasks.<sup>31</sup> This could clarify why subjects reported pain  
422 and reduced function of the NGF injected ECRB muscle 2 days before significant primary motor  
423 cortex reorganisation was found.<sup>37</sup> Taken together this implies that early changes induced by~~

424 ~~hypertonic saline injection and the retention of adapted motor strategies after NGF induced pain~~  
425 ~~may involve different brain regions.~~

426 Interpretation of the present findings requires consideration of several limitations. First, the  
427 current findings are limited to steady force control during low level of isometric wrist extensions,  
428 and do not necessarily generalize to other types of contractions relevant to functional activities,  
429 such as, for example, dynamic force control during concentric/eccentric contractions or higher  
430 level of contractions. Second, the data was collected in confined time intervals and the motor  
431 adaptations were not constantly monitored following NGF injection, so learning and  
432 consolidation of a new motor strategy is assumed from the results. However, because of the  
433 specificity of the assessed motor task and for practical reasons, it was not possible to perform a  
434 continuous assessment of the motor task. Therefore, changes in the movement pattern for daily  
435 activities at times between the data collection sessions, including isometric wrist extensions,  
436 remain unknown. Third, changes in the arm position between trials might affect the CoP,  
437 although SD Fz and CPD indexes are not affected by the reposition of the arm. To reduce this  
438 error, participants' wrist was marked facilitating the same position between trials. Fourth, the  
439 number of female participants was not balanced between groups. A previous study showed no  
440 gender difference in NGF evoked sensitization, although hypertonic saline superimposed to NGF  
441 elicited higher pain in males than females.<sup>1</sup> Gender comparison between groups during  
442 hypertonic saline was not performed and it was beyond the scope of this study because of the  
443 sample size.

#### 444 **CONCLUSION**

445 Acute pain increases force variation and changes the force direction, but when pain is sustained  
446 only the force direction differs from that in a pain-free state. These differences imply different



447 elements of learning a new motor strategy in the presence of pain; an initial “search” for a  
448 beneficial solution mediated by increased variation, and a later “consolidation” to the new  
449 alternative. In a clinical context if pain is sustained, treatments that target pain relief might  
450 | require additional intervention that targets changes in motor performance to restore the pain-free  
451 optimal control of the task.

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578 **FIGURE LEGENDS**

579

580 **Fig. 1.** Experimental setup and protocol. *Upper panel:* Wrist extension force was recorded in the  
581 task-related (Z) and the tangential (X and Y) directions using a three-dimensional force  
582 transducer. Marks on the wrist and on the force transducer were used to replace the arm in the  
583 same position at each session. *Lower panel:* Time-course of the experimental protocol. On day-0,  
584 the extensor carpi radialis brevis muscle (dominant arm) of twenty-six healthy volunteers was  
585 injected with nerve growth factor (NGF, N=13) or isotonic saline (ISO, N=13). On day-2, acute  
586 experimental muscle pain was induced by injection of hypertonic saline into the extensor carpi  
587 radialis brevis muscle (same side as the first injection) of all participants.

588

589 **Fig. 2.** Normalised mean ( $\pm$ SEM, N=13) (A) standard deviation (SD) of task-related force and  
590 (B) excursion of the centre of pressure for tangential forces (CoP) during the steady contraction  
591 period (wrist extension at 10% maximal voluntary contraction force) for saline-induced pain.  
592 Significantly increased during saline-induced pain compared with before and after saline-induced  
593 pain sessions (\*,  $P < 0.05$ ). (C) Normalised mean ( $\pm$ SEM, N=13) residual sum of squares error  
594 (RSS) in the task-related (Fz) direction before, during, and after saline-induced pain.

595

596 **Fig. 3.** Distribution of centroid position difference (CPD) of the tangential forces (Fx and Fy).  
597 Data are shown for the Control group in the absence of pain (contrast between baseline day-0  
598 and baseline day-2; far left, upper panel) and for the NGF group after 2 days of pain (contrast  
599 between measures before NGF injection on day-0 and before saline injection day 2; far left,  
600 lower panel). Subsequent panels show CPD for both groups during and after saline-induced pain

601 (contrasted to before saline-induced pain) on day-2, and on day-4 (contrast between baseline  
602 day-0 and day-4; far right panel). Both groups showed greater CPD (spread of the colours) in the  
603 Fy direction ( $P < 0.001$ ) when challenged with saline-induced pain compared with the baseline  
604 condition. This reflects greater changes in the direction of tangential force used to achieve the  
605 motor task. The NGF group showed greater CPD than the control group across days in the Fy  
606 direction ( $P < 0.05$ ), i.e. NGF group deviate from the baseline direction of tangential force across  
607 days.

608

609 **Fig. 4.** Normalised mean ( $\pm$ SEM, N=13) (A) standard deviation (SD) of task-related force and  
610 (B) excursion of the centre of pressure for tangential forces (CoP) during the steady contraction  
611 period (wrist extension at 10% MVC force) across days (day-0, baseline day-2, day-4) for  
612 persistent movement-evoked pain (NGF) and controls. (C) Normalised mean ( $\pm$ SEM, N=13)  
613 residual sum of squares error (RSS) in the task-related (Fz) direction. (D) Maximal voluntary  
614 contraction (MVC) force in the task-related direction (Fz) across days.

615





# CONSORT

TRANSPARENT REPORTING of TRIALS

