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Mista, Christian Ariel; Bergin, M.; Hirata, Rogerio Pessoto; Christensen, Steffan Wittrup; Tucker, K.; Hodges, P.; Graven-Nielsen, Thomas

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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.

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

CA Mista[1], M Bergin[2], R Hirata[1], S Christensen[1], K Tucker[2,3], P Hodges[2], T Graven-Nielsen[1]

[1] Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, DENMARK

[2] University of Queensland, NHMRC Centre of Clinical Research Excellence in Spinal Pain, Injury and Health, School of Health and Rehabilitation Sciences, Australia

[3] University of Queensland, School of Biomedical Sciences, Australia

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Corresponding author:
Professor Thomas Graven-Nielsen, DMSc, Ph.D.
Center for Neuroplasticity and Pain (CNAP)
SMI, Department of Health Science and Technology
Faculty of Medicine
Aalborg University
Fredrik Bajers Vej 7D-3
9220 Aalborg E, Denmark
Phone: +45 9940 9832
Fax: +45 9815 4008
E-mail: tgn@hst.aau.dk

ABSTRACT

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

Perspectives

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

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

INTRODUCTION

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

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

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

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

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

METHODS

Participants

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

Experimental protocol

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

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

Motor task

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

Force and torque recordings

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

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

Pain intensity assessment

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

Data analysis

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

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

Statistical analysis

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

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

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

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

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

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

RESULTS

Pain

Participants injected with NGF reported greater NRS pain scores when performing "repeated arm movements" on day-2 (2.6/10) and day-4 (1.6/10) than those injected with isotonic saline (Table 1, $Z=3.3$, $P<0.001$). The NGF group also reported greater "maximum pain experienced over the 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

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

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

Effect of saline-induced pain (control group)

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

Pain during hypertonic saline and NGF injection

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

Changes in isometric wrist extension force with pain

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

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

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

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

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

Factors involved in the consolidation of motor adaptations over time

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

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

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

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

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

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

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

CONCLUSION

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

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

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557

FIGURE LEGENDS

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

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

Fig. 3. Distribution of centroid position difference (CPD) of the tangential forces (Fx and Fy). Data are shown for the Control group in the absence of pain (contrast between baseline day-0 and baseline day-2; far left, upper panel) and for the NGF group after 2 days of pain (contrast between measures before NGF injection on day-0 and before saline injection day 2; far left, 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 (±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 (±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±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 ± 0	0 ± 0	0 ± 0
	Day-2	0.31 ± 0.24	2.69 ± 0.36*#	3.31 ± 0.40*#
	Day-4	0.15 ± 0.10	1.61 ± 0.33*#	2.38 ± 0.50*#
Control group	Day-0	0 ± 0	0 ± 0	0 ± 0
	Day-2	0 ± 0	0.08 ± 0.08	0.61 ± 0.21
	Day-4	0 ± 0	0 ± 0	0.23 ± 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#	7.27 ± 0.43*	0.58 ± 0.3#
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

	Centroid position difference			
		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#	0.39 ± 0.08	0.45 ± 0.06*
Control group	0.18 ± 0.05	0.45 ± 0.08#	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 (±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 (#, P<0.001).

Figures

Figure 1

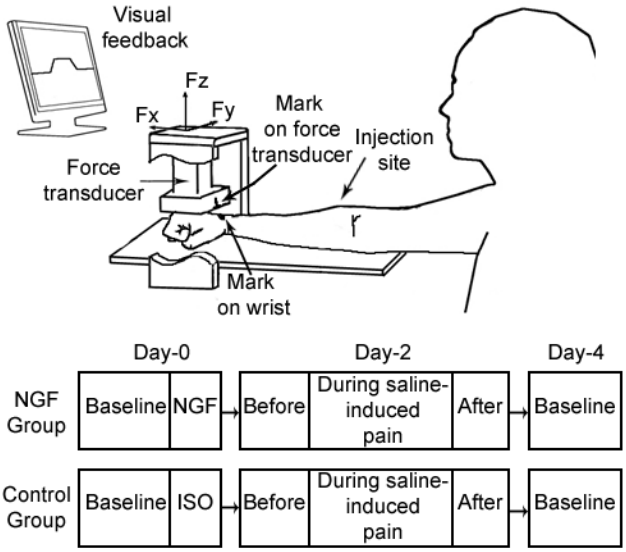


Figure 2

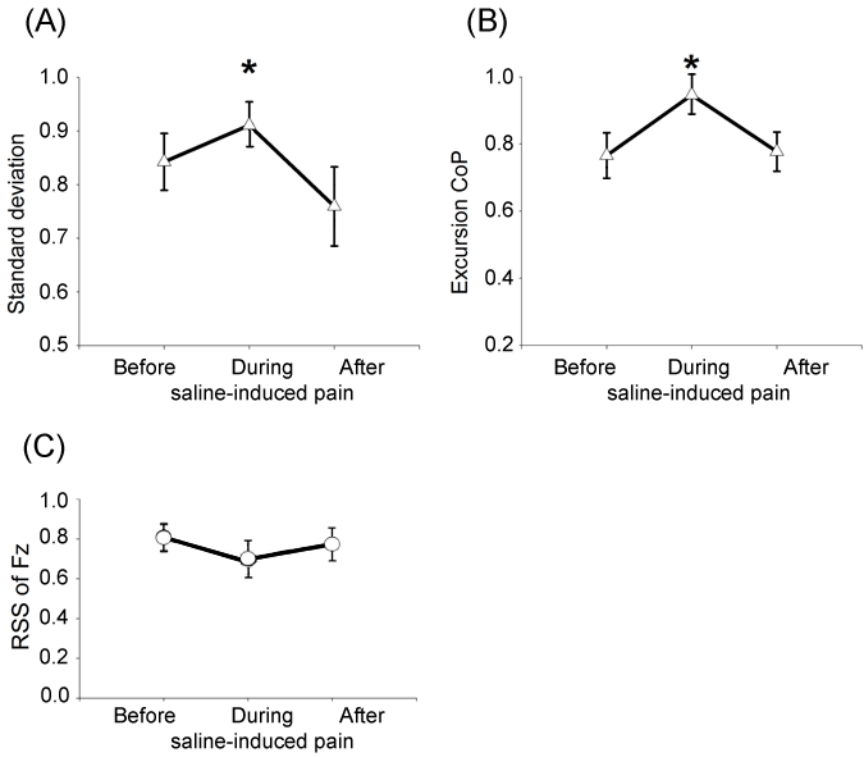
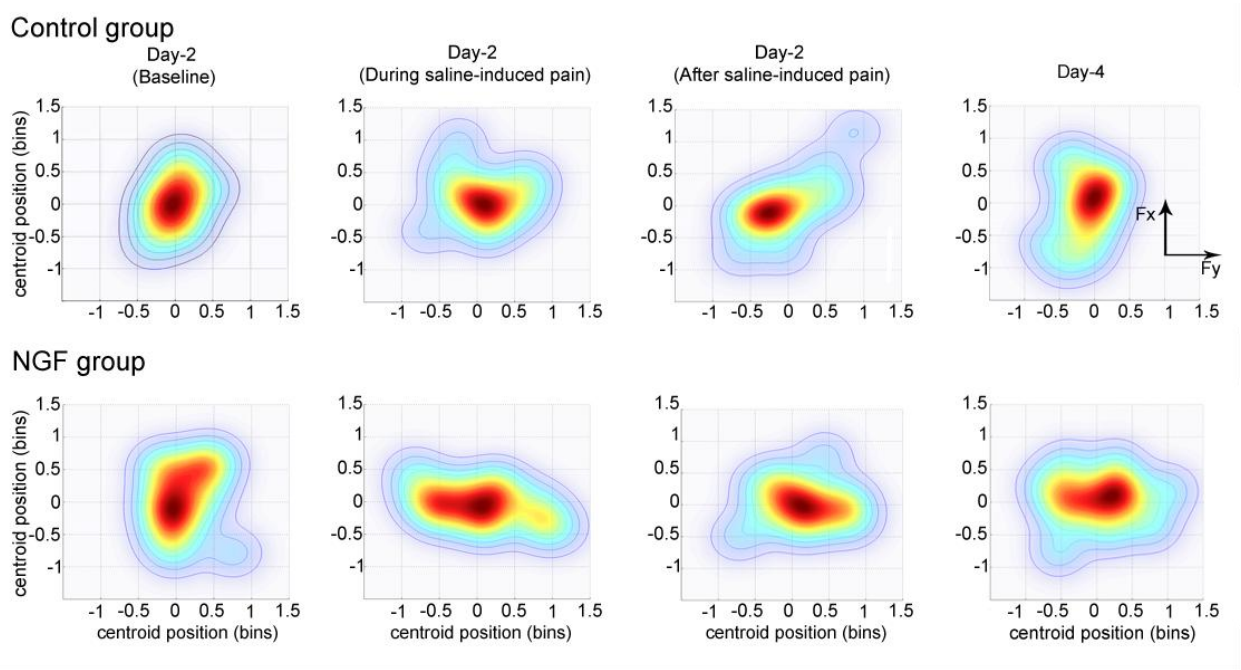

(A)
Standard deviation
1.0
0.9
0.8
0.7
0.6
0.5
*
Before
During
After
saline-induced pain
(B)
Excursion CoP
1.0
0.8
0.6
0.4
0.2
*
Before
During
After
saline-induced pain
(C)
RSS of Fz
1.0
0.8
0.6
0.4
0.2
0.0
Before
During
After
saline-induced pain

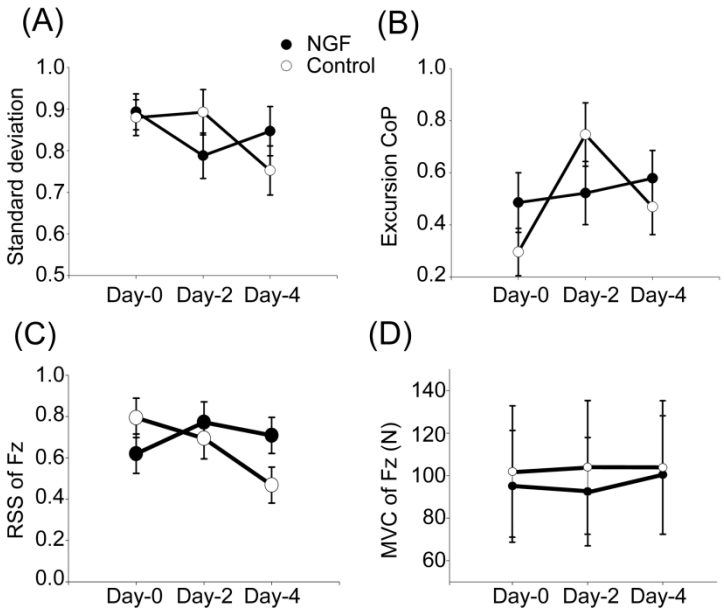
Figure 3


Control group
Day-2
(Baseline)
Day-2
(During saline-induced pain)
Day-2
(After saline-induced pain)
Day-4
NGF group
centroid position (bins)
Fx
Fy

5

6

Figure 4


(A)
NGF
Control
Standard deviation
1.0
0.9
0.8
0.7
0.6
0.5
Day-0 Day-2 Day-4
(B)
Excursion CoP
1.0
0.8
0.6
0.4
0.2
Day-0 Day-2 Day-4
(C)
RSS of Fz
1.0
0.8
0.6
0.4
0.2
0.0
Day-0 Day-2 Day-4
(D)
MVC of Fz (N)
140
120
100
80
60
Day-0 Day-2 Day-4

*Manuscript (revised, marked copy)

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

CA Mista[1], M Bergin[2], R Hirata[1], S Christensen[1], K Tucker[2,3], P Hodges[2], T Graven-Nielsen[1]

[1] Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, DENMARK

[2] University of Queensland, NHMRC Centre of Clinical Research Excellence in Spinal Pain, Injury and Health, School of Health and Rehabilitation Sciences, Australia

[3] University of Queensland, School of Biomedical Sciences, Australia

Target journal: Journal of Pain

Corresponding author:

Professor Thomas Graven-Nielsen, DMSc, Ph.D.

Center for Neuroplasticity and Pain (CNAP)

SMI, Department of Health Science and Technology

Faculty of Medicine

Aalborg University

Fredrik Bajers Vej 7D-3

9220 Aalborg E, Denmark

Phone: +45 9940 9832

Fax: +45 9815 4008

E-mail: tgn@hst.aau.dk

ABSTRACT

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

Perspectives

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

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

INTRODUCTION

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

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

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

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

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

METHODS

Participants

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

Experimental protocol

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

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

Motor task

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

Force and torque recordings

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

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

Pain intensity assessment

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

Data analysis

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

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

Statistical analysis

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

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

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

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

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

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

RESULTS

Pain

Participants injected with NGF reported greater NRS pain scores when performing "repeated arm movements" on day-2 (2.6/10) and day-4 (1.6/10) than those injected with isotonic saline (Table 1, $Z=3.3$, $P<0.001$). The NGF group also reported greater "maximum pain experienced over the 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

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

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

Effect of saline-induced pain (control group)

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

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

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

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

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

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

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

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

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

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

When saline-induced pain was added to the ~~persistent~~ movement-evoked ~~related~~ pain induced by NGF injection, the CPD in the Fy direction calculated using the contrast of measures made on day-2 *during* and day-2 *before* saline-induced pain (i.e. effect of saline induced pain) 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.[28,34]
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

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

Changes in isometric wrist extension force with pain

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

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

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

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

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

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

Factors involved in the consolidation of motor adaptations over time

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

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

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

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

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

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

CONCLUSION

Acute pain increases force variation and changes the force direction, but when pain is sustained 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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FIGURE LEGENDS

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

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

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

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

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

supplementary_figure_CONSORT_FlowDiagram