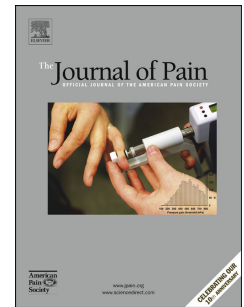


# Accepted Manuscript

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PII: S1526-5900(16)30002-5

DOI: [10.1016/j.jpain.2016.03.005](https://doi.org/10.1016/j.jpain.2016.03.005)

Reference: YJPAI 3240

To appear in: *Journal of Pain*

Received Date: 22 November 2015

Revised Date: 19 February 2016

Accepted Date: 9 March 2016

Please cite this article as: Tsay . AJ, Giummarra MJ, Position sense in chronic pain: Separating peripheral and central mechanisms in proprioception in unilateral limb pain, *Journal of Pain* (2016), doi: 10.1016/j.jpain.2016.03.005.

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# Position sense in chronic pain: Separating peripheral and central mechanisms in proprioception in unilateral limb pain

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Running Title: Position sense in chronic pain

Disclosure: Melita Giummarra was supported by a National Health and Medical Research Council (NHMRC, Australia) early career fellowship [APP1036124]. The authors have no conflicts of interest to declare.

## Abstract

Awareness of limb position is derived primarily from muscle spindles and higher-order body representations. Although chronic pain appears to be associated with motor and proprioceptive disturbances, it is not clear if this is due to disturbances to position sense, muscle spindle function or central representations of the body. This study examined position sense errors, as an indicator of spindle function, in participants with unilateral chronic limb pain. The sample included 15 individuals with upper-limb pain, 15 with lower-limb pain, and 15 sex- and age-matched pain-free controls. A two-limb forearm matching task in blindfolded participants, and a single-limb pointer task, with the reference limb hidden from view, assessed forearm position sense. Position sense was determined after muscle contraction or stretch, intended to induce a high or low spindle activity in the painful and non-painful limbs, respectively. Both unilateral upper- and lower-limb chronic pain groups produced position errors comparable to healthy controls for position matching and pointer tasks. The results indicate that both the painful and non-painful limb are involved in limb matching. Lateralised pain, whether in the arm or leg, does not influence forearm position sense.

## Perspectives

Both the painful and non-painful limbs are involved in bilateral limb matching. Muscle spindle function appears to be preserved in the presence of chronic pain.

## Keywords

Position sense, chronic pain, muscle spindles, proprioception, thixotropy

## Introduction

The sense of limb position allows us to determine where our limbs are in space when we are not looking at them. This information is primarily derived from muscle spindles, which are stretch receptors that signal length changes imposed on the muscle. Spindles also play a role in motor control, reflexively regulating muscle tension and providing input to body representations in the brain, especially body schemata [52]. These factors, collectively, appear to be disturbed in chronic pain patients [2; 21; 34; for a review, see 59]. However, the role of muscle spindles in proprioceptive disturbances associated with chronic pain remains unclear.

While there is evidence of reduced position sense acuity in persons with chronic pain [4; 7; 13; 18; 26; 31; 45; 46; 49; 50; 56], others have reported no such differences between healthy controls and chronic pain groups [1; 8; 9; 28; 29; 39; 44]. The aforementioned studies employed a repositioning task, in which participants reproduce a previously remembered postural position. In contrast, the present study examined the role of simultaneous afferent information to make positional judgements by manipulating the thixotropic properties of the muscle [53; 54; 59].

The background firing rate in spindles is dependent on the preceding contraction and length changes of the muscle fibre [53]. Thixotropic behaviour occurs with the formation of stable cross-bridges between actin and myosin when the muscle relaxes after a contraction. Shortening the muscle introduces slack into the sensory ending of spindles, lowering the spindle discharge. Because the length of the muscle is signalled by muscle spindle activity, manipulating its sensitivity to stretch can lead to reproducible errors in perceived limb position [54]. Previous studies have not controlled for the thixotropic properties of muscles. Therefore, it is unclear whether disturbances to position sense in persons with chronic pain occur at the level of the muscle spindles [2; 25], or in higher-order brain regions involved in motor control or body representation [19; 40].

Our group has developed a simple, non-invasive method of conditioning a muscle, based on recordings of spindle discharges [15] and on measurements of position sense [52-54; 61]. In the present study, we assessed position sense after thixotropic muscle conditioning, to determine whether this led to position errors consistent with an alteration in spindle function in the presence of chronic unilateral limb pain. If proprioceptive disturbance in chronic pain is due to altered activity in, or processing of, spindle discharge, participants with unilateral upper-limb pain would be expected to show forearm matching errors that could not be explained by spindle discharge. As spindles seem to play less of a role in pointing tasks [60], differences in pointing errors between pain and control groups would suggest altered reference maps from body schemata or exteroceptive cues in position sense [51]. Finally, disruptions to body schemata seem to generalise to the affected

side of the body [57], reflecting higher-order neuroplastic changes across the body midline [41-43]. Therefore, we expected participants with lower-limb pain would show deficits in pointing to the forearm on the affected side of the body, however the role of spindle signals would remain unaffected. These findings may shed light on the source of motor dysfunctions observed in chronic pain disorders.

## Methods

### *Participants*

Forty-five volunteers participated in the study, including 15 with unilateral upper-limb pain, 15 with unilateral lower-limb pain and 15 pain-free controls. Participants were recruited from Caulfield Pain Management and Research Centre, and the general community. Inclusion criteria for the patient groups included: 18 to 65 years of age, having experienced pain more days than not for at least 3 months, experiencing pain that was localised to one arm or leg, and having no history of diabetes. While a wide range of chronic pain aetiologies were accepted, we excluded those with pain caused by inflammation, such as arthritis, or fibromyalgia, which is generally experienced as a diffuse pain affecting multiple body regions. Table 1 lists the demographic and clinical characteristics for each group. The pain groups were matched for sex, age, duration of pain, average pain intensity, pain interference (PBI), and kinesiophobia (TSK) scores. However, the upper-limb pain group reported higher pain severity (BPI) on average than the lower-limb pain group. All DASS measures were significantly higher in the pain groups compared to healthy controls, as confirmed by Bonferroni post-hoc test ( $p < 0.01$ ). The study was approved by the Alfred Hospital Ethics Committee. All participants gave written informed consent and were financially reimbursed for their time.

### *Materials and Procedure*

Forearm position sense was assessed in the vertical plane using two tasks, which have been described in detail elsewhere [60]. For the matching task, the blindfolded participant sat at a table with the upper arms on horizontal supports (allowing shoulder muscles to be relaxed), and both forearms placed on lightweight paddles in a custom-built apparatus. Velcro straps (5 cm in width) were wrapped just below the crease of the wrist with the palms supinated. Participants were asked if the tension in the two wrist straps felt the same, and adjusted as instructed by the participant in order to minimize potential differences in skin sensations between the two arms. One arm was designated the *reference arm* (the arm placed at the test angle by the experimenter) and the other was the *indicator arm* (the arm moved by the participant to match the position of the reference arm). The reference arm was passively moved by the experimenter to the test angle, which ranged

from 40° to 50° to the horizon. In all conditions, unless stated otherwise, the painful limb or side was assigned as the reference arm. For the control group, the reference arm was randomly assigned to minimise biases arising from arm dominance [14].

For the pointer task, only the reference arm remained strapped to the paddle, which was hidden from view by a screen. Unlike the matching task, participants had full view of the contralateral paddle, designated the *indicator*. Participants could manoeuvre the indicator paddle to the perceived angle of the reference arm by pushing a lever downwards, which was attached to the indicator paddle. They were given the instruction to “show me where your arm is with the paddle.”

Potentiometers (25 kΩ; Spectra Symbol Corp., Salt Lake City, UT, USA) located at the hinges of each paddle were used to measure the angle at the elbow joint. The potentiometers provided a continuous voltage output proportional to the angle of each paddle, a reading of 0° indicated the forearm lay horizontal, while 90° referred to a forearm in the vertical position. Correct calibration of the potentiometers was checked prior to each experiment.

Position error was calculated between the two paddles using the formula:

$$\text{position error (}^\circ\text{)} = \text{reference angle (}^\circ\text{)} - \text{indicator angle (}^\circ\text{)}$$

Hence, a positive value meant that the indicator was placed in a more extended position than the reference arm. Conversely, where the indicator was placed in a more flexed position, relative to the reference arm, a negative value was assigned.

### *Muscle Conditioning*

Prior to each trial, the elbow muscles were conditioned to place them into a defined thixotropic state, using either a muscle contraction with or without a subsequent stretch. The thixotropic properties arise in a muscle when stable cross-bridges form between actin and myosin filaments in a passive muscle [54]. This produces tension in the muscle fibres, when contracted at a short muscle length. When the fibre is stretched to a longer length, this raises passive tension further leading to a rise in the background activity. Spindle discharge rates can also be lowered by allowing cross-bridges to be formed when the muscle is held at a long length and later the muscle is brought to a shorter length introducing slack in the muscle fibres [15; 16].

Two muscle conditioning techniques were performed in this study. The first, *flexion conditioning*, involved a contraction of the elbow flexors with both arms locked in the vertical position (90°). Participants were instructed to contract with half of their maximal strength. This procedure altered

the mechanical state of the elbow flexors in the arms, leaving them taut while slackening the elbow extensors during the matching task [54; 58]. This increases the resting spindle discharge of the elbow flexors.

The second type of muscle conditioning, *flexion conditioning and stretch*, similarly, involved flexion conditioning of both arms in the vertical position. However, the indicator arm was then passively moved, by the experimenter, to the horizontal position (approximately 0°), thereby stretching the elbow flexors in that arm only to induce asymmetrical spindle signals in each arm. The participant was instructed to rest in that position for six seconds, allowing for sufficient time for the formation of stable cross-bridges [38]. The reference arm was then moved, by the experimenter, to the test angle, before participants were asked to match the position of the arms. Because the cross-bridges in the indicator arm had formed at a long length, the movement to the test angle by the subject slackened the muscles in the elbow flexors, producing a low resting discharge rate in the muscle spindles. For the single-limb pointer task, only the reference arm was conditioned. Participants performed three trials under each condition, to limit the number of conditioning contractions performed by the painful limb.

To prevent inadvertent muscular contractions, muscle activity of the reference arm was continuously measured and monitored by the experimenter using surface electromyogram (EMG). A pair of Ag-AgCl electrodes with an adhesive base and solid gel contact points (AD Instruments, Castle Hill, NSW, Australia) were placed approximately 2.5 cm apart over the surface of the biceps brachii and triceps brachii. A grounding electrode was placed on the collar bone. EMG output was connected to an audio amplifier for biofeedback, producing noise during a muscular contraction. The conditioning contraction was repeated where inadvertent muscle contractions were performed. Position, force and EMG signals were acquired at 40 Hz using MacLab 4/s data acquisition module running Chart software (AD Instruments, Castle Hill, NSW, Australia) on a Macintosh computer.

#### *Characterising Pain*

Pain was evaluated using the short-form Brief Pain Inventory (BPI) [5], which profiles a measure of pain severity and interference of pain on daily functions (Table 1). Beliefs, attitudes and fear of exacerbating pain through movement were measured using the Tampa Scale of Kinesiophobia (TSK)[37]. The short-form, 21 item Depression, Anxiety and Stress Scale (DASS-21) was used to assess mood profiles [35].

#### *Statistical Analysis*

Statistical tests were performed using SPSS 23 (SPSS, Chicago, IL, USA) with significance at  $\alpha = 0.05$ . One-way ANOVAs were used to compare group characteristics, including age, gender and DASS scores. For the primary outcome of position error, differences between pain groups (upper-limb pain/lower-limb pain) were examined with mixed model repeated measures ANOVAs with the within subjects factor of limb-side (i.e., reference limb: painful side/pain-free side), with a separate ANOVA testing each conditioning method (flexion/flexion and stretch). Given that position error did not differ with respect to limb-side, separate univariate ANOVAs then tested differences between groups (upper-limb pain/lower-limb pain/ pain-free control) for position errors in each conditioning method, with the dependent variable collapsed across limb side. One-sample t-tests were used to confirm that position errors for each conditioning method differed significantly from zero. The same analytic approach was applied to the pointing task. Finally, a comparison of position errors between the pointing and matching tasks (flexion condition task only) was done using an ANOVA between groups (upper-limb pain/lower-limb pain) and across limbs (i.e., reference limb: painful side/pain-free side). For all ANOVAs the assumption of sphericity was not violated and no corrections were applied to the degrees of freedom. Bonferroni test was used for post-hoc analyses.

## Results

### *Matching Trials After Bilateral Flexion Conditioning*

Participants performed a flexion contraction in both arms prior to matching the position of their forearms. Typically, when conditioned in this way, the indicator arm is matched in a slightly more flexed posture relative to the reference arm [54; 61]. That is, errors fall below the zero line (Figure 1). A mixed model ANOVA comprising the pain group (upper-limb pain/lower-limb pain) and limb side, i.e. when the painful limb or side acted as the reference or indicator arm, did not show a main effect for limb side on matching errors,  $F(1, 28) = .81$ ,  $p = .38$ ,  $\eta_p^2 = .03$ , nor was there a difference between those with upper-limb pain or lower-limb pain,  $F(1, 28) = .29$ ,  $p = .59$ ,  $\eta_p^2 = .01$ , Table 2. The univariate ANOVA showed that there was also no difference in matching errors between participants with upper-limb pain ( $0.43^\circ \pm 0.84^\circ$ ), lower-limb pain ( $2.22^\circ \pm 1.33^\circ$ ) or pain-free controls ( $-0.95^\circ \pm 1.39^\circ$ ) when indicating perceived forearm location,  $F(2, 42) = 1.73$ ,  $p = .19$ ,  $\eta_p^2 = .08$ . Thus, participants with chronic unilateral pain did not show significant differences in position error, compared with pain-free controls, when both arms were flexion conditioned.

### *Matching Trials After Asymmetrical Muscle Conditioning*

Conditioning the indicator arm with a flexion contraction followed by a stretch was then conducted with the intention of *lowering* the resting spindle discharge in elbow flexors in one of the arms. In these experiments, the reference arm was always the painful limb or side in the pain group.

Analysis with mixed model ANOVA found no interaction between muscle conditioning (reference limb: flexion conditioned/flexion and stretch conditioned) between groups (upper-limb pain/lower-limb pain/pain-free control),  $F(2, 42) = .23$ ,  $p = .80$ ,  $\eta_p^2 = .80$ , suggesting the effect of conditioning was not significantly different between control and pain groups. However, there was a significant main effect of muscle conditioning on position error,  $F(1, 42) = 57.03$ ,  $p < .01$ ,  $\eta_p^2 = .58$ . That is, flexion conditioning without stretch brought about matching errors in the direction of extension for each group—i.e., upper-limb pain group ( $8.7^\circ \pm 2.0^\circ$ ), lower-limb pain group ( $8.0^\circ \pm 1.8^\circ$ ) or pain-free controls ( $10.8^\circ \pm 1.8^\circ$ ), Figure 2, filled circles—which differed significantly from zero,  $t(44) = 8.48$ ,  $p < .01$ . Reversing the conditioning sequence (i.e. when the reference arm was flexion conditioned and stretched, while the indicator arm was flexion conditioned only) caused a shift of about  $13^\circ$  in the direction of flexion in all groups (control group:  $-3.7^\circ \pm 1.7^\circ$ ; upper-limb pain:  $-4.5^\circ \pm 1.8^\circ$ ; lower-limb pain:  $-4.0^\circ \pm 1.9^\circ$ , see Figure 2, open circles), which also differed significantly from zero,  $t(44) = -3.82$ ,  $p < .01$ .

The fact that the direction of matching errors were reversed when the conditioning sequence was alternated from the indicator to the reference limb supports the role for muscle spindles in position sense as measured by arm matching. Further, persons with chronic unilateral limb pain seem to generate spindle signals for limb position sense in the same way as pain-free controls.

#### *Pointer Trials After Flexion Conditioning*

In this task, participants moved the indicator paddle to match the position of the reference arm, which was flexion conditioned and hidden from view.

A mixed model ANOVA examined whether position errors, during pointing, differed for the painful limb or side in participants with upper- or lower-limb pain. There was no main effect of limb side (i.e., whether the reference limb was the painful or pain-free side of the body for pain groups) on position errors,  $F(1, 28) = .28$ ,  $p = .60$ ,  $\eta_p^2 = .01$ , nor was there a difference between those with upper- or lower-limb pain,  $F(1, 28) = .27$ ,  $p = .61$ ,  $\eta_p^2 = .01$ . When the painful limb or side acted as the reference arm, all participants made pointing errors towards extension (control:  $3.1^\circ \pm 1.8^\circ$ ; upper-limb pain:  $1.3^\circ \pm 3.3^\circ$ ; lower-limb pain:  $6.0^\circ \pm 2.7^\circ$ ) which were significantly different from zero,  $t(44) = 2.41$ ,  $p < .05$ , see Figure 3, filled circles. Similar errors were observed when the pain-free arm acted

as the reference, shown in the open circles (controls:  $2.3^\circ \pm 2.0^\circ$ ; upper-limb pain:  $1.9^\circ \pm 1.8^\circ$ ; lower-limb pain:  $4.1^\circ \pm 2.3^\circ$ ), which were also significantly different from zero,  $t(44) = 2.42$ ,  $p < .05$ .

A repeated measures ANOVA, including reference limb side as a within subjects factor, found no significant difference in pointing errors between pain-free control, upper-limb pain, and lower-limb pain groups on position errors in the pointing task,  $F(2, 42) = .15$ ,  $p = .87$ ,  $\eta_p^2 = .01$ .

#### *Comparison Between Pointer And Matching Trials After Flexion Conditioning*

Finally, a repeated measures ANOVA examined position errors between the pointer and matching tasks, across limbs (reference limb: painful side/pain-free side) and the pain groups (upper-limb pain/lower-limb pain/pain-free control) for the flexion condition task only. There was a significant effect of task,  $F(1, 42) = 6.60$ ,  $p < 0.05$ ,  $\eta_p^2 = 0.14$ , with the matching task producing errors in the direction of flexion ( $3.30^\circ \pm 1.19^\circ$ ) whereas the pointing task did not generate significant errors ( $0.06^\circ \pm 0.52^\circ$ ). However, these effects were not enhanced as a function of limb side ( $p = .92$ ), nor did they interact with group membership ( $p = .77$ ). Table 2 summarises the statistical analyses performed.

## **Discussion**

Awareness of limb position is derived from peripheral inputs that signal information about length changes in the muscle, and higher-order body representations, that provide a point of reference and recognition of ownership of the muscle itself [52]. At the periphery, previous studies on limb position sense in chronic pain did not control for the thixotropic behaviour of the muscle spindle receptors leading to conflicting results and interpretations [1; 4; 31; 49; 59]. Therefore, it was unclear whether disturbances to position sense in persons with chronic pain occurred at the level of the muscle spindles, or in higher-order brain regions. This is the first study to use thixotropic muscle conditioning in two distinct position sense tasks aimed at testing the peripheral and central components of position sense in chronic pain. The results have shown that under several conditioning protocols and position sense tasks, position errors were comparable between persons who are pain-free and those who report unilateral upper- and lower-limb pain.

Afferent signals from both arms are thought to be involved in an arm matching task [24; 61; 63]. If chronic pain leads to disruption to the generation or transmission of afferents signals from the painful limb(s), then this would be expected to bring about systematic matching errors when compared to persons who are pain-free. The direction of errors should be reversed when the painful arm alternates from acting as the reference arm to the indicator arm. Overall, matching errors were

no different when the painful limb was used to indicate the position of the non-painful arm. Our findings are consistent with previous studies that demonstrated that muscle spindle discharge is not affected by painful stimulation, induced via hypertonic saline injections, of group III and IV afferents [3; 10].

Moreover, we examined position sense after conditioning one arm with a flexion contraction followed by a stretch and the other arm with a flexion contraction only, which results in asymmetrical spindle activity between the two arms. As a result, participants match the arm positions by 'listening' to very different spindle firing rates. However, there were no differences in position sense between groups. In fact all participants made matching errors of approximately 8° towards extension when the *indicator* arm was flexion conditioned and stretched. These errors were presumably driven by the high flexor spindle signal in the reference arm. When the *reference* arm was flexion conditioned and stretched, there was an approximate 13° shift towards flexion. This is consistent with a lower spindle signal in the reference arm, being matched by a higher flexor spindle signal in the indicator arm. As the matching errors did not differ across groups it appears that both arms contribute equally to the matching process and this is not disrupted by the presence of chronic limb pain. In other words, it appears that muscle spindle function is relatively undisturbed in the presence of chronic pain.

It has been shown that there are considerable changes in the sensory [11] and motor cortices [30] associated with chronic pain [12; 36]. Moreover, disturbances in the motor representation of a painful limb have been inferred from reduced accuracy [6] or slower response time [55] in laterality judgement tasks when the depicted limb represents the affected limb. In these tasks, the participant must decide as quickly as possible whether an image of a body part (e.g., a hand or foot) belongs to the left or right side of the body, requiring them to mentally rotate their own limb [47; 48]. However, this does not involve reference to afferent input from those body parts. In fact, when doing these tasks participants must inhibit any actual movements in the limbs and perform the task using mental rotation only.

It seems plausible that disturbances to body representations may manifest in disturbances to perceived position sense. Given that matching errors were comparable across all groups, we used a pointer task, which is believed to derive input from the body schema and other exteroceptive sources [51]. However, we found that regardless of whether participants pointed to the painful or non-painful arm, the errors always lay into extension, which is consistent with previous experiments on pointing in healthy individuals [60]. In other words, participants consistently perceive the forearm to be more extended than it really was regardless of whether it was the painful arm or not. This

supports the idea that the mental representation of the body parts at rest is naturally distorted [32; 33], and that this does not appear to change when the limb is chronically painful.

The present findings conflict somewhat with previous research investigating proprioception in chronic pain [4; 31]. For instance, Brumange et al. [4] vibrated the multifidus muscles in patients with chronic lower back pain and found a shortening illusion in participants with chronic pain, compared to controls. This is the opposite effect expected from muscle vibration, which typically induces lengthening illusions by increasing the spindle discharge rate. However, the differences between the present findings and those of Brumange et al. may be explained by the position sense tasks employed. Brumange et al. used a lumbosacral repositioning task, which requires the participant to reproduce a previously remembered afferent state, i.e. postural position. Similarly, Lewis et al. [31] found bilateral position sense disturbances in individuals with unilateral Chronic Regional Pain Syndrome (CRPS) when asked to position their arm in accordance to hours of a clock face. In contrast, participants in our study presumably utilised concurrent afferent signals to make a positional judgement, during the matching trials. It appears that even in the context of chronic unilateral pain, the spindle afferent signals from both arms are 'listened to' equally, as the magnitude of the errors was comparable across groups, and when the type of conditioning was alternated between the two arms. The implications of these findings are that (i) spindle function is preserved in the presence of chronic pain; and (ii) the retrieval of body schema information is also intact.

While we accept that motor, sensory and regulatory dysfunctions are associated with many chronic pain conditions, it may be possible that they do not specifically rely on afferent proprioceptive inputs and instead involve multiple inputs and/or frames of reference. Longo [32] has argued for the existence of multiple body representations. One of these operates largely outside of consciousness, i.e., the body schema, and another implicit representation forms the way we consciously perceived our bodies (i.e. the body image). Indeed several studies have highlighted the distortions in the way the body feels to the pain patient as relating to the body image [31; 34; 62]. Under instances where conflicting proprioceptive and visual sensory feedback is present, vision often overrides the former [17; 23; 24; 27]. Indeed, in the case of chronic neck pain, when visual feedback is manipulated to overstate neck rotation, pain occurs earlier during the neck rotation movement [20]. Future investigations should disentangle the inputs that build and maintain the body representation, with a focus on the associated threat cues, particularly vision, that evoke pain symptoms.

Several limitations of this study should be considered. First, the pain aetiology was heterogeneous within and across upper-limb and lower-limb pain participants. Patients presented with pain arising

from a range of conditions such clinically diagnosed CRPS to pain associated with varicose veins. Our study endeavoured to examine disturbances in position sense in relation to unilateral chronic pain regardless of pain condition or mechanism (excluding those with inflammation, diabetes or widespread pain); however, this should be tested more thoroughly in the future. We attempted to reduce other variabilities such as pain duration, average pain intensity, gender and age by matching these factors across the groups. Nevertheless, there was a significant difference of pain severity, as reported by the Brief Pain Index, between groups, with the upper-limb pain cohort reporting slightly higher pain severity than the lower-limb group. However, the groups did not differ in their fear of exacerbating their pain through movement. Finally, it should be emphasised that the study was probably underpowered and the findings should be treated carefully.

### *Conclusions*

This is the first study to examine position sense in persons with chronic pain while controlling for muscle spindle discharge rates using thixotropic muscle conditioning. This technique is thought to manipulate background spindle afferent discharge, leading to illusions of limb displacement in the absence of vision. We have shown that position errors in persons with chronic pain were comparable to healthy controls. Further, it appears that both the affected and pain-free limbs are involved equally when matching the relative position of one arm with the other. These findings indicate that people with chronic pain respond to thixotropic muscle conditioning, leading to reproducible and predictable errors in position sense consistent with their pain-free counterparts. Thixotropic conditioning could be extended to test reflexes and muscle stiffness, often disturbed in chronic pain disorders [22], to further elucidate the signalling behaviour of spindles in chronic pain.

### **Acknowledgements**

The authors have no conflict of interests to declare. We would like to thank Prof Uwe Proske and Dr Trevor Allen for their constructive feedback in improving this manuscript.

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Table 1

Demographic characteristics and pain profile of participants.

|                            |         | Upper-limb pain | Lower-limb pain | Controls    | p-values |
|----------------------------|---------|-----------------|-----------------|-------------|----------|
| <b>Sex</b>                 | M:F     | 8:7             | 6:9             | 5:10        |          |
| <b>Age</b>                 | mean±SD | 38.4 ± 16.5     | 34.0 ± 14.3     | 36.3 ± 10.9 |          |
| <b>Affected-Side</b>       | L:R     | 6:9             | 9:6             | -           |          |
| <b>Aetiology</b>           |         |                 |                 |             |          |
| <b>Fracture</b>            | n (%)   | 27%             | 27%             |             |          |
| <b>CRPS</b>                | n (%)   | 6%              | 7%              |             |          |
| <b>Muscular/Tendon</b>     | n (%)   | 20%             | 26%             |             |          |
| <b>Unknown/Other</b>       | n (%)   | 47%             | 40%             |             |          |
| <b>Pain Duration (yrs)</b> | mean±SD | 6.1 ± 4.9       | 4.6 ± 3.6       | -           |          |
| <b>Average Pain (0-10)</b> | mean±SD | 7.1 ± 2.4       | 5.6 ± 1.5       | -           |          |
| <b>BPI Severity</b>        | mean±SD | 6.4 ± 2.2       | 4.9 ± 1.7*      | -           | p = .04  |
| <b>BPI Interference</b>    | mean±SD | 3.9 ± 2.7       | 3.8 ± 2.3       | -           |          |
| <b>TSK</b>                 | mean±SD | 34.4 ± 5.3      | 37.1 ± 6.4      | -           |          |
| <b>DASS: Depression</b>    | mean±SD | 10.4 ± 9.7      | 11.7 ± 9.0*     | 1.1 ± 2.6*  | p = .00  |
| <b>DASS: Anxiety</b>       | mean±SD | 9.7 ± 7.0       | 10.9 ± 10.4*    | 1.7 ± 2.4*  | p = .00  |
| <b>DASS: Stress</b>        | mean±SD | 16.0 ± 8.6      | 18.9 ± 8.0*     | 3.2 ± 3.3*  | p = .00  |

Note: BPI = Brief Pain Inventory, TSK = Tampa Scale of Kinesiophobia, DASS = Depression, Anxiety and Stress Scale. \* indicates significant differences as tested by oneway ANOVA, Bonferroni post-hoc, compared to the upper-limb pain group.

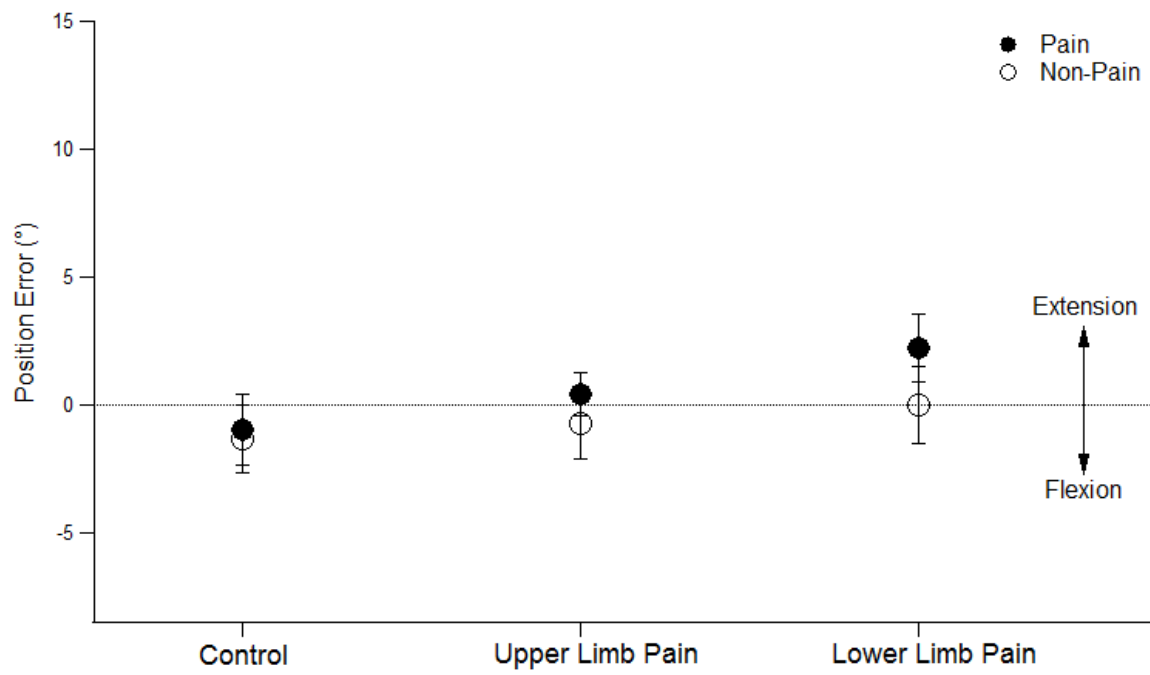
Table 2

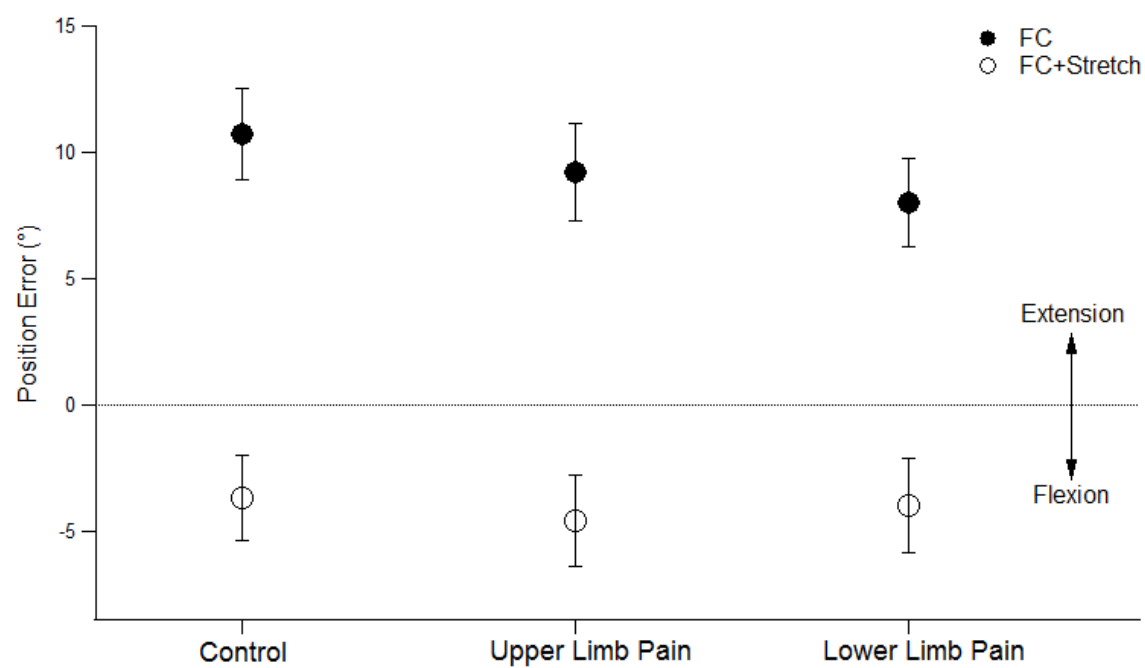
Result of ANOVAs on position errors.

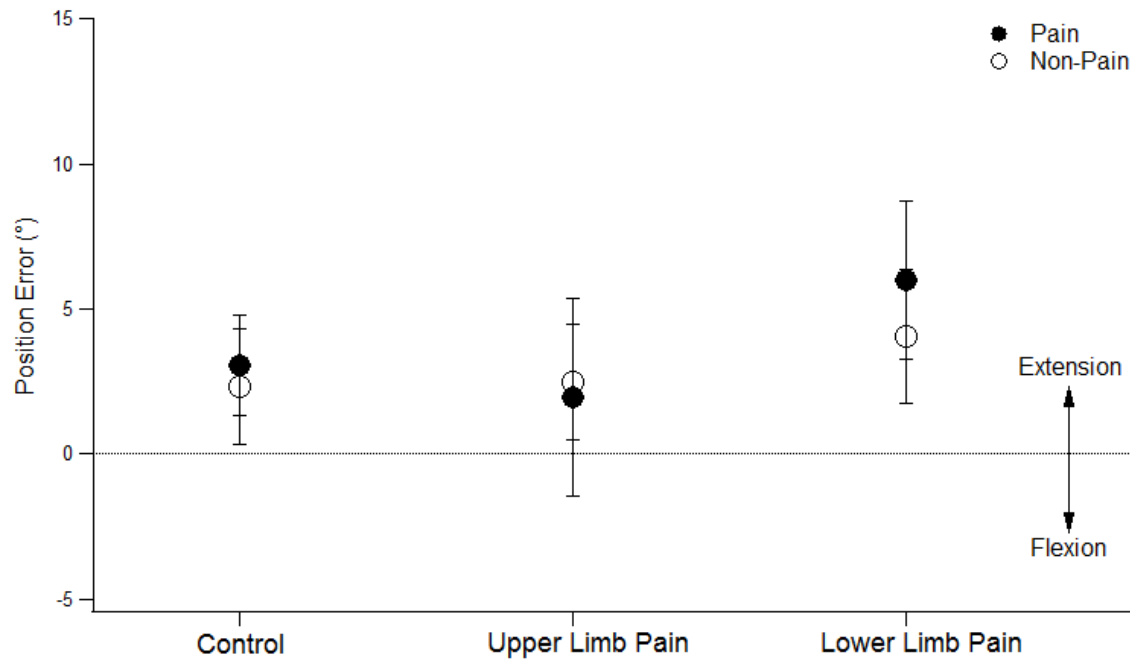
|                           | Analysis                              | Outcome        | Effect            | F Value          | Sig  | $\eta_p^2$ | Observed Power |
|---------------------------|---------------------------------------|----------------|-------------------|------------------|------|------------|----------------|
| Matching Bilateral FC     | Mixed model ANOVA (ULP/LLP)           | Position Error | Limb Side         | F(1, 28) = 0.81  | .38  | .03        | .14            |
|                           |                                       |                | Limb Side X Group | F(1, 28) = .29   | .59  | .01        | .08            |
|                           | Univariate ANOVA (ULP/LLP/CON)        | Position Error | Group             | F(2, 42) = 1.73  | .19  | .08        | .34            |
| Asymmetrical Conditioning | Mixed model ANOVA (ULP/LLP/CON)       | Position Error | Cond              | F(1, 42) = 57.03 | .00* | .58        | 1.00           |
|                           |                                       |                | Cond X Group      | F(2, 42) = .23   | .80  | .80        | .08            |
| Pointing FC               | Mixed model ANOVA (ULP/LLP)           | Position Error | Limb Side         | F(1, 28) = .28   | .60  | .01        | .08            |
|                           |                                       |                | Limb Side X Group | F(1, 28) = .27   | .61  | .01        | .08            |
|                           | Repeated measures ANOVA (ULP/LLP/CON) | Position Error | Limb Side X Group | F(2, 42) = .15   | .87  | .01        | .07            |

|                             |                                       |                |              |                 |       |     |     |
|-----------------------------|---------------------------------------|----------------|--------------|-----------------|-------|-----|-----|
| <b>Matching vs Pointing</b> | Repeated measures ANOVA (ULP/LLP/CON) | Position Error | Task         | F(1, 42) = 6.60 | 0.01* | .14 | .71 |
|                             |                                       |                | Task X Group | F(2, 42) = .26  | .77   | .01 | .09 |
|                             |                                       |                | Limb Side    | F(1, 42) = .92  | .34   | .02 | .16 |

Note: \*indicates  $p < 0.05$  significant main effects. Interaction effects were indicated by X. The between factor was group (ULP = upper limb pain, LLP = lower limb pain, CON = controls), and within-subject factors were limb side (painful/non-painful), cond (muscle conditioning: flexion conditioning vs flexion conditioning with stretch), and task (matching vs pointing).







## Figure Captions

### FIGURE 1

**Matching errors after bilateral flexion conditioning.** Errors (Mean  $\pm$  SEM) are shown for 45 participants. Blindfolded participants performed approximately 50% MVC contractions in both elbow flexor muscles prior to declaring a match. The filled circles show matching errors when the painful arm, or side (as was the case for the lower-limb group), acted as the reference arm. In another trial, the non-painful arm acted as the reference arm, which was matched with the contralateral, painful indicator arm, shown in the open circles. For the control group, the reference arm was randomly assigned. The zero line indicates a perfect match. Repeated measures ANOVA found no significant differences across groups under both trials ( $p>0.05$ ).

### FIGURE 2

**Matching errors after asymmetrical conditioning: flexion contraction and stretch.** In these trials, the painful side acted as the reference arm. For the filled circles, the reference arm was flexion conditioned as described previously. The indicator arm also performed the flexion contraction, but was subsequently moved by the experimenter from the vertical position into elbow extension. From the extended position, the subject moved their arm to match the position of the reference. This resulted in matching errors of 8° or more degrees into extension. In another trial, represented by the open circles, the conditionings of the arms were reversed. The painful reference arm performed a contraction and stretch, while the indicator arm performed the flexion contraction only. There was a significant effect of conditioning on matching errors ( $p<0.01$ ), with no difference between groups. Position errors are expressed as mean  $\pm$  SEM for 45 participants. Dotted line indicates zero error.

### FIGURE 3

**Pointing errors after flexion conditioning.** The filled circles show pointing errors after flexion conditioning of the painful arm. Position errors when the non-painful was pointed to (acting as the reference) are shown by the open circles. Participants were asked to indicate the position of the reference arm, which was hidden from view, by manoeuvring the angle of the contralateral paddle.

Repeated measures ANOVA found no difference in pointing errors ( $p>0.05$ ). Dotted line represents the zero line.

ACCEPTED MANUSCRIPT

Table 1

Demographic characteristics and pain profile of participants.

|                            |          | Upper-limb<br>pain | Lower-limb<br>pain | Controls   | p-values |
|----------------------------|----------|--------------------|--------------------|------------|----------|
| <b>Sex</b>                 | M:F      | 8:7                | 6:9                | 5:10       |          |
| <b>Age</b>                 | mean±SEM | 37.7 ± 4.2         | 34.0 ± 3.7         | 36.3 ± 2.8 |          |
| <b>Affected-Side</b>       | L:R      | 6:9                | 9:6                | -          |          |
| <b>Aetiology</b>           |          |                    |                    |            |          |
| <b>Fracture</b>            | n (%)    | 27%                | 27%                |            |          |
| <b>CRPS</b>                | n (%)    | 6%                 | 7%                 |            |          |
| <b>Muscular/Tendon</b>     | n (%)    | 20%                | 26%                |            |          |
| <b>Unknown/Other</b>       | n (%)    | 47%                | 40%                |            |          |
| <b>Pain Duration (yrs)</b> | mean±SEM | 5.0 ± 1.3          | 4.3 ± 0.85         | -          |          |
| <b>Average Pain (0-10)</b> | mean±SEM | 7.4 ± 0.4*         | 5.9 ± 0.5          | -          | p < 0.05 |
| <b>BPI Severity</b>        | mean±SEM | 6.4 ± 0.6          | 5.1 ± 0.5          | -          |          |
| <b>BPI Interference</b>    | mean±SEM | 4.0 ± 0.7          | 4.3 ± 0.7          | -          |          |
| <b>TSK</b>                 | mean±SEM | 34.4 ± 1.4         | 37.3 ± 1.6         | -          |          |
| <b>DASS: Depression</b>    | mean±SEM | 10.4 ± 2.5*        | 11.7 ± 2.3*        | 1.1 ± 0.7  | p < 0.01 |
| <b>DASS: Anxiety</b>       | mean±SEM | 9.7 ± 1.8*         | 10.9 ± 2.7*        | 1.7 ± 0.6  | p < 0.01 |
| <b>DASS: Stress</b>        | mean±SEM | 16.0 ± 2.2*        | 18.9 ± 2.1*        | 3.2 ± 0.8  | p < 0.01 |

**Notes:** Values are expressed as mean ± SEM.

BPI = Brief Pain Inventory, TSK = Tampa Scale of Kinesiophobia, DASS = Depression, Anxiety and Stress Scale. Asterisks show significant differences between groups.

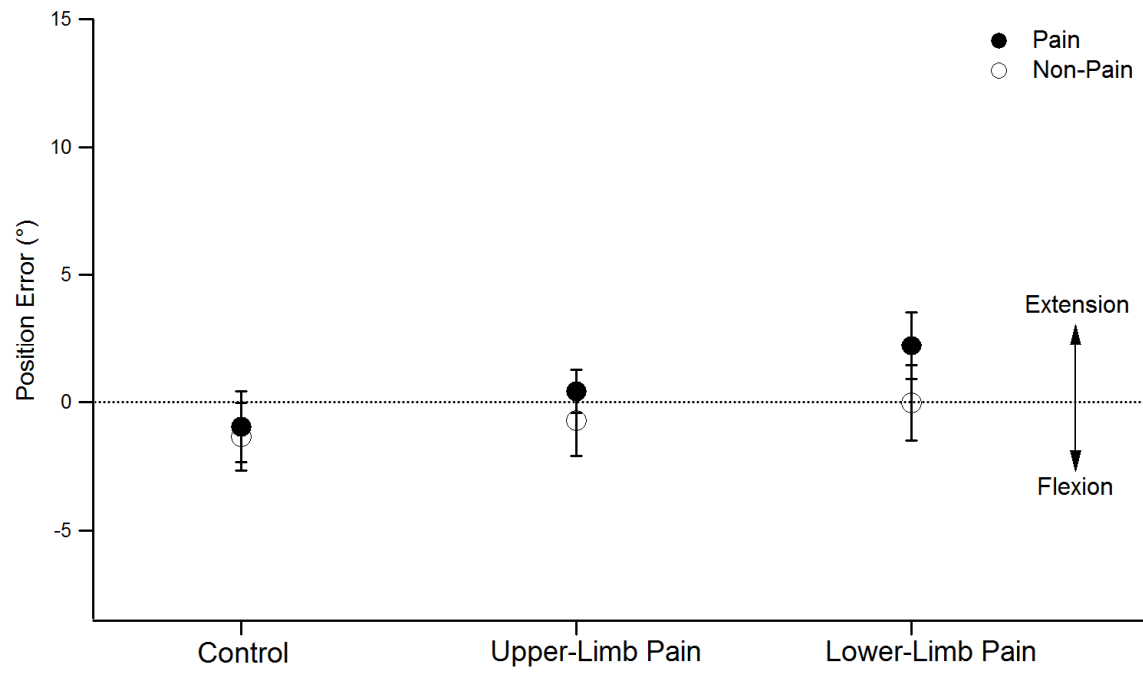
Table 2

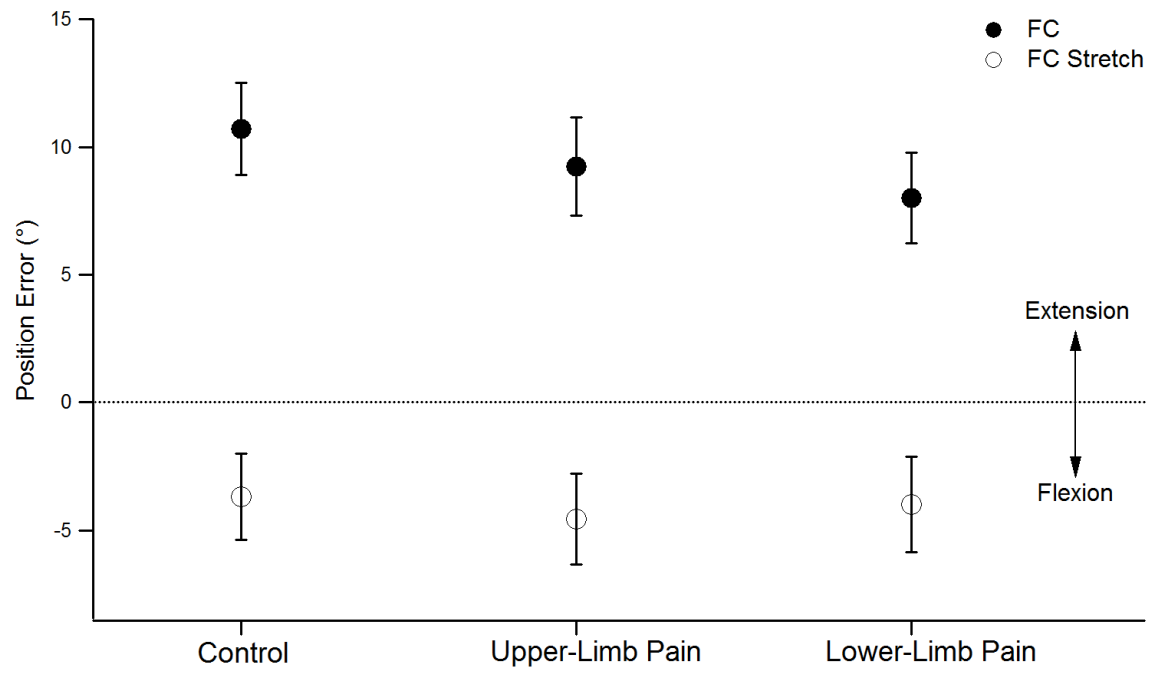
Result of ANOVAs on position errors.

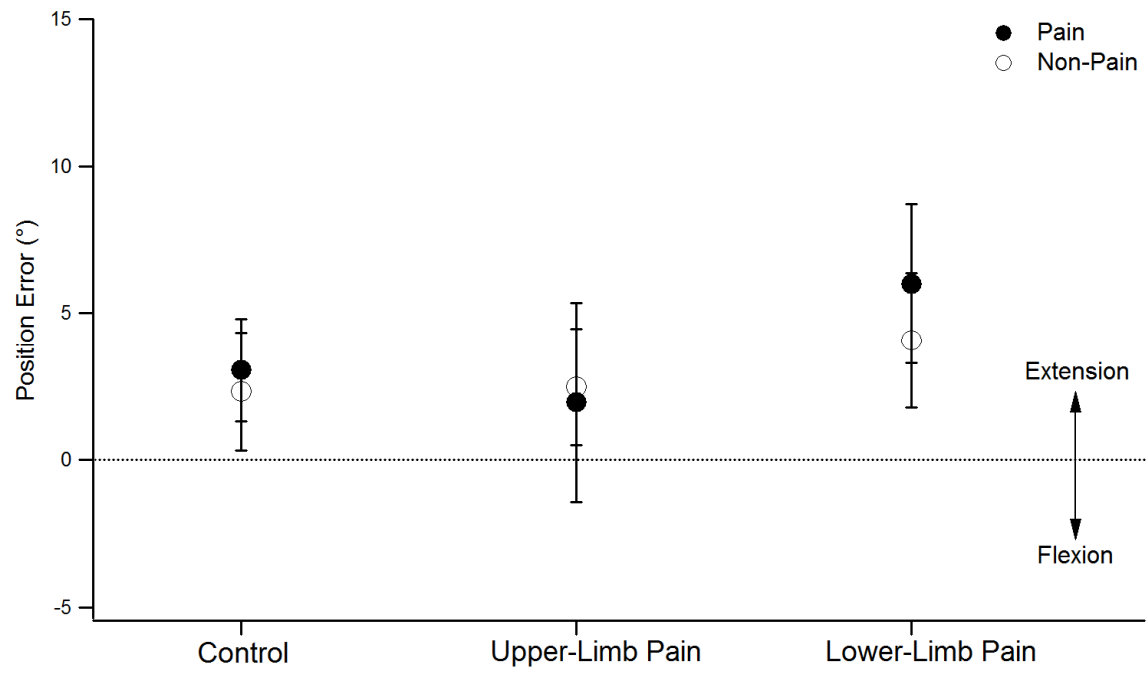
|                                  | Analysis                              | Outcome        | Effect            | F Value          | Sig  | $\eta_p^2$ | Observed Power |
|----------------------------------|---------------------------------------|----------------|-------------------|------------------|------|------------|----------------|
| <b>Matching Bilateral FC</b>     | Mixed model ANOVA (ULP/LLP)           | Position Error | Limb Side         | F(1, 28) = 0.81  | .38  | .03        | .14            |
|                                  |                                       |                | Limb Side X Group | F(1, 28) = .29   | .59  | .01        | .08            |
|                                  | Univariate ANOVA (ULP/LLP/CON)        | Position Error | Group             | F(2, 42) = 1.73  | .19  | .08        | .34            |
| <b>Asymmetrical Conditioning</b> | Mixed model ANOVA (ULP/LLP/CON)       | Position Error | Cond              | F(1, 42) = 57.03 | .00* | .58        | 1.00           |
|                                  |                                       |                | Cond X Group      | F(2, 42) = .23   | .80  | .80        | .08            |
| <b>Pointing FC</b>               | Mixed model ANOVA (ULP/LLP)           | Position Error | Limb Side         | F(1, 28) = .28   | .60  | .01        | .08            |
|                                  |                                       |                | Limb Side X Group | F(1, 28) = .27   | .61  | .01        | .08            |
|                                  | Repeated measures ANOVA (ULP/LLP/CON) | Position Error | Limb Side X Group | F(2, 42) = .15   | .87  | .01        | .07            |

|                             |                                       |                |              |                 |       |     |     |
|-----------------------------|---------------------------------------|----------------|--------------|-----------------|-------|-----|-----|
| <b>Matching vs Pointing</b> | Repeated measures ANOVA (ULP/LLP/CON) | Position Error | Task         | F(1, 42) = 6.60 | 0.01* | .14 | .71 |
|                             |                                       |                | Task X Group | F(2, 42) = .26  | .77   | .01 | .09 |
|                             |                                       |                | Limb Side    | F(1, 42) = .92  | .34   | .02 | .16 |

Note: \*indicates  $p < 0.05$  significant main effects. Interaction effects were indicated by X. The between factor was group (ULP = upper limb pain, LLP = lower limb pain, CON = controls), and within-subject factors were limb side (painful/non-painful), cond (muscle conditioning: flexion conditioning vs flexion conditioning with stretch), and task (matching vs pointing).







# **Proprioception in chronic pain: Muscle spindles provide accurate proprioceptive position information in persons with unilateral limb pain**

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## **Highlights**

- Peripheral and central mechanisms of position sense were assessed in unilateral chronic pain patients.
- A muscular contraction or stretch prior to a position sense measurement was used to modulate muscle spindle activity.
- The unilateral chronic pain groups produced position errors comparable to healthy controls.
- Both painful and non-painful limbs are involved in limb matching.
- Lateralised pain, whether in the arm or leg, does not influence forearm position sense.