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Original Research Article

Healthy Pain-Free Individuals with a History of Distal Radius Fracture Demonstrate an Expanded Distribution of Experimental Referred Pain Toward the Wrist

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Abstract

Objective. Nociception caused by injuries may sensitize central mechanisms causing expanded pain areas. After recovery, the status of such pain distribution and sensitivity mechanisms is unknown. The present study investigated whether individuals who have fully recovered from a distal radius fracture demonstrate increased pain sensitivity and expanded distribution of pressure-induced pain. **Design**. Cross-sectional single-blinded study. **Setting**. Clinical setting. **Subjects**. Twenty-three pain-free individuals with a history of painful distal radius fracture and 22 nonfractured, age/gender-matched controls participated in two experimental sessions (day 0, day 1) 24 hours apart. **Methods**. Pressure pain thresholds (PPTs) were recorded bilaterally at the extensor carpi radialis longus (ECRL), infraspinatus, and gastrocnemius muscles. Spatial distribution of pain was assessed following 60-second painful pressure stimulation at the ECRL (bilateral) and the infraspinatus muscles on the fractured or dominant side. Participants drew pain areas on a body map. After day 0 assessments, prolonged pain was induced by eccentric exercise of wrist extensors on the fractured/dominant side. **Results**. Compared with controls, pressure-induced ECRL pain in the fracture group referred more frequently toward the distal forearm ($P < 0.005$) on day 0. Both groups showed larger pain areas on day 1 compared with day 0 ($P < 0.005$), although the fracture group showed a larger relative change between days ($P < 0.005$). The fracture group showed larger pain areas on the fracture side compared with the contralateral side on both days ($P < 0.005$). **Conclusions**. Prolonged pain and recovered prior painful injuries like fractures may sensitize pain mechanisms manifested as expanded pain distribution. Pressure-induced referred pain can be a simple pain biomarker for clinical use.

Key Words: Referred Pain; Pressure Algometry; Muscle Soreness; Central Pain Mechanisms; Altered Nociceptive Processing

Introduction

The neuroanatomy linked with potential tissue trauma determines the location of pain within the body map as well as central mechanisms governing spreading pain and pain referral [1]. Interestingly, there is a diverse spatial distribution of pain among pain patients [2, 3] and in experimental pain models [1, 4], where a more common pain pattern is expected. Moreover, within clinical and experimental settings, clusters of pain are associated with pain history location [5, 6]. The spatial distribution of

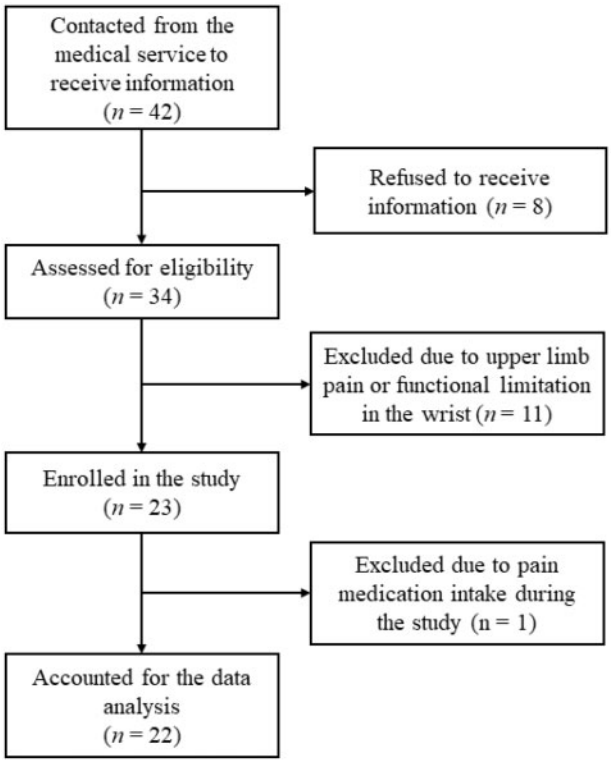

Figure 1. Flowchart depicting the recruitment process.

pain may be fundamental information of the pain system and a factor associated with relevant central mechanisms controlling the pain distribution.

The pattern of pain distant from the tissue trauma (referred pain) is highly variable and is considered a centrally mediated phenomenon [7, 8]. For instance, nociceptive stimulation of wrist extensor muscles can produce referred pain in the dorsal forearm and wrist [9, 10]. Individuals with tennis elbow pain exhibit larger referred pain areas from a standardized nociceptive stimulus in the forearm when compared with healthy controls [9], indicating sensitization of the mechanisms for referred pain. Interestingly, experimental models of prolonged muscle pain such as delayed-onset muscle soreness (DOMS) after eccentric exercise or intramuscular injection of nerve growth factor, expand the referred pattern of pain in healthy individuals [9–12]. A previous study showed that those who have recently recovered from an ankle sprain compared with controls more frequently present referred pain areas expanding toward the site of injury in response to pressure-induced pain [13]. Similar findings have been found in individuals years after resolution of a painful fracture [12] or days following the extraction of a painful tooth [14].

Severe pain is one of the major features immediately after a distal radius fracture [15, 16], with severity attenuating after bone stabilization [17, 18]. Following fractures, there are also initial changes in pain mechanisms contributing to the pain experience (e.g., peripheral neuroplasticity and sensitization) [19–21]. The sensitivity of pain mechanisms is normalized upon tissue recovery, together with the gradual decrease of pain within the first six months after fracture [15]. Nevertheless, sensitization may persist despite tissue repair and is associated with the transition from acute to chronic pain [20, 22–28]. However, less is known about the status of pain mechanisms in individuals who have successfully recovered from fracture pain.

The aim of this cross-sectional study was to investigate whether individuals who have fully recovered from a distal radius fracture (fracture group) demonstrate increased pain sensitivity and expanded distribution of pressure-induced pain within and remotely to the preinjury region compared with healthy controls (control group) without a history of distal radius fracture. It was hypothesized that the fracture group would demonstrate 1) increased pain sensitivity, 2) an expanded distribution of pain, referred toward the fracture site when provoked from the proximal forearm, and 3) an expanded distribution of pain referred to the arm and back provoked from pressure stimulation on the back, as compared with the control group. Moreover, the expansion of pain areas was hypothesized to be further facilitated after inducing a prolonged pain model in wrist extensors.

Methods

Participants

Asymptomatic individuals with a history of distal radius fracture were recruited via an accident and emergency unit database at a local public hospital (Figure 1). For

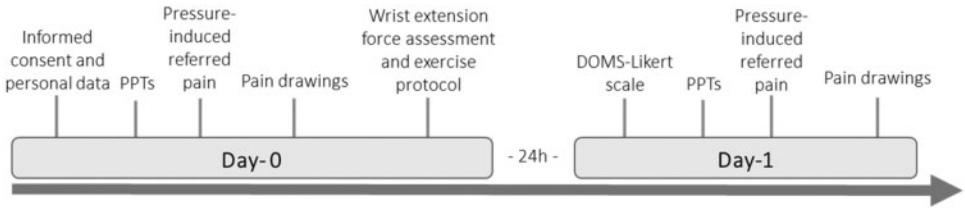

Figure 2. Timeline depicting the entire protocol followed in the study. DOMS = delayed-onset muscle soreness; PPT = pressure pain threshold.

inclusion in the fracture group, individuals needed to be between 20 and 80 years old, with a previous extra-articular fracture of the distal third of the radius that had recovered so that they were free of pain and any known functional limitations at inclusion. Exclusion criteria were a history of pain in the trunk, upper extremities, or head in the preceding three months, the presence of a specific pathology with pain as the main symptom (e.g., chronic low back pain or migraine) or another serious disease, history of other fractures in the upper limb, or pregnancy. Age- and sex-matched healthy controls were recruited from the university campus and the local community. Controls had to be pain-free at study participation and have no history of fracture in the upper extremities. Participants in both groups were not allowed to take medication that could potentially affect pain sensitivity (e.g., pain medication or nonsteroidal anti-inflammatory drugs) throughout the study. Based on a power of 80% and minimal detectable change (MDC) in the area of pressure-induced pain of 3,036 pixels, it was estimated that 22 participants were needed in each group. The MDC was obtained by applying the following formula: $MDC = 1.96*SEM*\sqrt{2}$ [29]. The values for calculating the SEM (the standard deviation and the square root of the sample size) were taken from a study using the same protocol [12]. A total of 45 healthy individuals were included in this study; 23 persons for the previously fractured group (mean age = 45 years, range = 21–79 years, 14 females) and 22 age- and gender-matched controls for the control group (mean age = 45 years, range = 21–80 years, 13 females). All participants received detailed information about the protocol and provided their informed consent before entering the study. The participants were naïve to the hypotheses and experimental methods. The study was approved by the local Ethics Committee (C.P.-C.I. PI16/094) and conducted in accordance with the Helsinki Declaration. The study was carried out in accordance with the STROBE statement for observational studies and registered on ClinicalTrials.gov (NTC03531801).

Procedure

This cross-sectional study was conducted during the period from October 2017 to June 2018. Participants were asked to attend two sessions in a hospital setting on two consecutive days (day 0 and day 1), with 24 hours between sessions (Figure 2). At the start of the day 0 session, demographic information, report of previously fractured side (dominant side for controls), date and initial treatment of fracture, and recall of pain intensity (0–10 numerical rating scale [NRS]) after the fracture were collected. Pressure pain sensitivity at the extensor carpi radialis longus (ECRL), infraspinatus, and gastrocnemius muscles was assessed bilaterally. Following a suprathreshold pressure stimulation, the distribution of pressure-induced pain and pain quality was recorded. The suprathreshold pressure stimulation was performed at the ECRL muscle (bilaterally) and on the infraspinatus muscle on the previously fractured side (dominant side for controls). Toward the end of the session on day 0, delayed-onset muscle soreness (DOMS) was induced by eccentric exercise of the extensor muscles of the wrist on the previously fractured or dominant side. The level of soreness from DOMS was assessed on day 1, and the sensitivity to pressure and suprathreshold pressure stimulation (similar to day 0) was performed. The exercise-induced DOMS constituted the prolonged pain model. A single assessor (VDG) trained in the protocol performed all algometric procedures. The assessor was blinded to the group allocation for each subject. All experimental procedures, including the eccentric exercise, were explained and demonstrated by a second researcher (PB) in charge of registering values of pressure pain thresholds and pressure-induced referred pain drawings.

Pressure Pain Sensitivity

A handheld pressure algometer (Algometer, Somedic Senselab, Hörby, Sweden) with a 1-cm^2 probe (covered by a disposable latex sheath) was used to assess pressure pain thresholds (PPTs) bilaterally at three sites (Figure 3): 1) the ECRL muscle; with the elbow pronated and flexed 90°, the exact point was situated 4–5 cm caudal on a line connecting the lateral epicondyle with the radial styloid process; 2) the infraspinatus muscle (the intermediate point between the inferior angle of the scapula, the spine of the scapula, and the medial border of the scapula); and 3) the gastrocnemius muscle (in the distal third of the medial gastrocnemius muscle). The six PPT sites were marked with semipermanent ink to ensure repeatability within and between sessions. The force was gradually increased with the pressure algometer at a constant rate of 30 kPa/s until the pressure stimulation became slightly

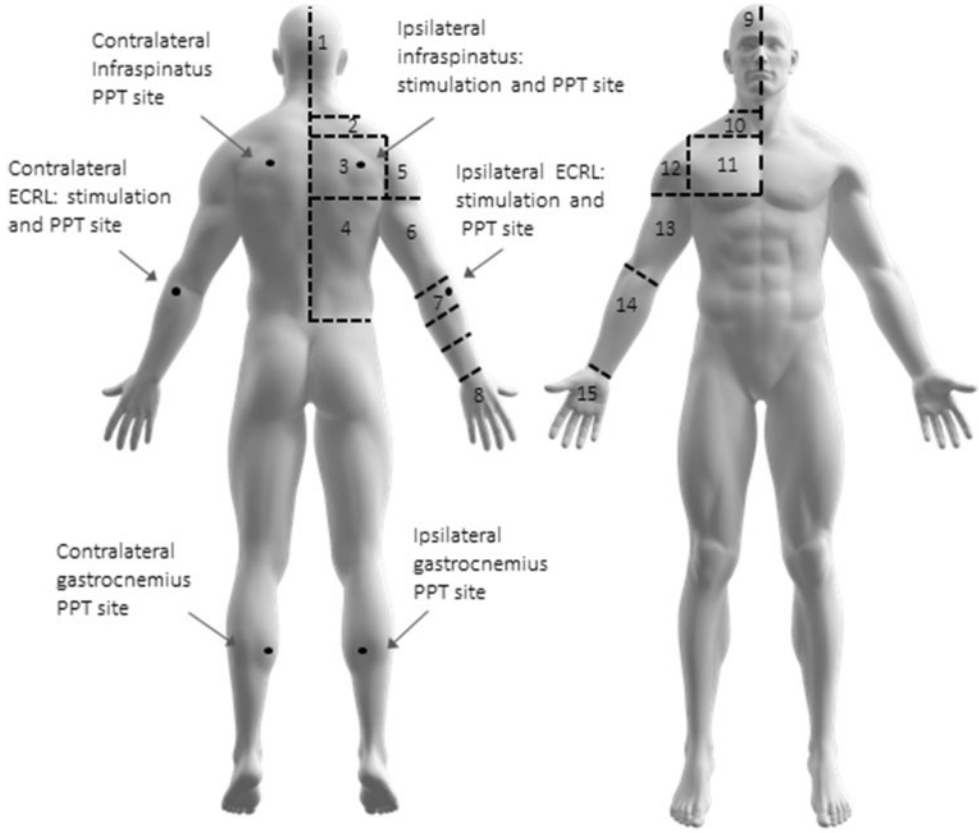

Figure 3. Body divisions used to quantify distribution of pain following the infraspinatus and bilateral extensor carpi radialis muscles, suprathreshold pressure stimulations, and sites where pressure pain thresholds were measured. The numbers code the regions used for assessing pain after the infraspinatus stimulation: 1) posterior head and neck, 2) supraspinal, 3) infraspinatus, 4) back, 5) posterior shoulder, 6) posterior arm, 7) posterior forearm, 8) posterior hand, 9) anterior head/neck, 10) supraclavicular, 11) chest, 12) anterior shoulder, 13) anterior arm, 14) anterior forearm, 15) anterior hand. The subdivisions of the forearm (region 7, proximal, mid, and distal forearm) were used for quantifying extensor carpi radialis stimulation.

painful, where the subject pressed a button to stop the pressure. This process was repeated twice, with a minimum of 30 seconds between assessments, and the average PPT value was extracted for further analysis.

Distribution of Pressure-Induced Referred Pain

Saline-induced experimental pain in the ECRL muscle frequently provokes referred pain to the dorsal forearm, wrist, and hand areas [30, 31], a pain distribution pattern similar to a sustained (60-second) suprathreshold pressure stimulation [11]. In the present study, a 60-second suprathreshold pressure stimulation pain applied with the handheld pressure algometer (Algometer, Somedic Senselab, Hörby Sweden) at three sites in the following order: 1) the ECRL muscle ipsilateral to the fractured side (dominant side for controls); 2) the contralateral ECRL muscle; and 3) the infraspinatus muscle ipsilateral to the previously fractured side (dominant side for controls). The pressure was applied on each site at an intensity equivalent to 1.2 times the PPTs assessed on the same day [11, 12, 32]. Between each suprathreshold pressure stimulation, a break of one to two minutes was observed. Immediately after each suprathreshold pressure stimulation, participants were asked to create a pain drawing, shading the pressure-induced pain areas to report any qualities such as numbness and tingling evoked by the stimulation. All drawings were digitally recorded on a full-body chart (anterior and posterior views) using the Android application Navigate Pain (version 1.0; Aalborg University, Denmark) as displayed on a handheld PC tablet (Airis OnePad 750, Infinity System, Spain). Digital pain drawings using the Navigate Pain tablet-based platform are a valid and reliable method for assessing pain areas and are comparable to paper recordings [33]. The size of the pressure-induced pain areas was automatically extracted and expressed in pixels. To measure the extent of the pain area, the body chart was divided into five different regions (Figure 3) for ECRL muscle stimulation [9] and 15 different regions for infraspinatus muscle (Figure 3) [11, 12]. An expanded pain area in the former distribution was considered "regional expansion," and an expanded pain area in the latter was considered "widespread expansion." The frequency of pressure-induced pain in each region was determined in addition to the frequency of pain referred beyond the stimulation site [11, 12, 32].

Model for Prolonged Muscle Pain

Following all assessments in the first session (day 0), all participants performed an eccentric exercise of the extensor muscles of the wrist (extensor carpi radialis longus, extensor carpi radialis brevis, and extensor carpi ulnaris muscles). The eccentric exercise was performed using the wrist of the previously fractured side (dominant side for controls). The objective was to produce DOMS within 24 hours (day 1). The exercise was performed using a custom-made device consisting of a handgrip with two parallel, flat metal plate brackets from which a weight was suspended [34]. An adjustable strap was attached around the hand to reduce finger flexor muscle activity and focus mechanical stress on the wrist extensor muscles. To maximize loading in the ECRL muscle, which is inserted at the base of the second metacarpal bone, the weight always hung from the medial metal plate bracket on the fractured side (dominant side for controls). The participants performed the exercise in sitting position, resting the elbow extended and the forearm pronated over a wedge on a table with an adjustable height, with the glenohumeral joint in 70–80° of flexion. A wedge with a 30° tilt was positioned under the forearm at the edge of the table to enable the full range of motion of the wrist extending 2 cm beyond the wedge. Each cycle of the exercise started from a maximal wrist extension position and ended in maximal wrist flexion. The duration of each cycle was standardized as a four-second eccentric contraction and one second of rest. A researcher (PB) moved the weight during the concentric contraction (returning back end-range extension) to minimize the amount of resisted concentric contraction. Each subject performed three five-minute sets separated by a two-minute rest interval. On average, individuals performed 140 (120–150) repetitions in total. The appropriate weight for resistance for each participant was calculated before the eccentric exercise by measuring the maximal wrist extension force with a digital dynamometer (Kern, Germany), which was attached to the custom-made device. This was done in the previously described position where the wrist was kept in a neutral position. In this position, a researcher (PB) applied a force perpendicular to the floor (the same direction as the weight). The maximum eccentric force was determined to be the force at which each subject could no longer prevent wrist flexion movement initiation [10]. The average value of the three trials was used for weight calculations. The first exercise set was performed at 90% maximum isometric force, with each subsequent set reduced in increments of 10% so that the final and third set was performed at 70% maximum isometric force. The progressive decrease in maximum isometric force was implemented for optimal performance without excessive fatigue [10]. On day 1, the level of pain due to exercise was assessed with six-point Likert scale where each number was anchored to a predefined description [12]: 0 = "complete absence of pain"; 1 = "slight discomfort or minimal pain in the muscle"; 2 = "moderate or slightly persisting soreness on palpation"; 3 = "a light muscle ache when lifting weights or moving objects"; 4 = "severe muscle discomfort that affected the capacity of moving the arm"; 5 = "a strong pain felt in the muscle that impeded movement or function of the arm."

Statistics

The analyses followed a previous protocol [12]. Data were analyzed based on the results from normality tests (Shapiro-Wilk) and after that presented as medians and interquartile ranges (IQRs) or means and standard deviations, respectively. A comparison of the level of pain due to the DOMS exercise protocol (Likert scores) between groups was made using unpaired tests (Mann-Whitney *U* [MWU]). An analysis of variance (ANOVA) was used for the PPTs with *site* (ECRL, infraspinatus and gastrocnemius muscles) as a dependent variable and *time* (day 0, day 1), *side* (fracture/dominant and nonfractured/nondominant), and *group* (fracture, control) set as fixed factors. Pain areas were logarithmically transformed to compensate for non-normal data distribution, although nontransformed data are presented in figures, tables, and text. The log-transformed pain area passed the Shapiro-Wilk test for normality and was further analyzed by an ANOVA with *time* and *side* as repeated-measures factors and *group* as a between-group factor. The log-transformed number of body regions did not pass the Shapiro-Wilk test and was therefore analyzed by the Mann-Whitney *U* or Wilcoxon test with the Bonferroni correction. The difference between days (relative change) in PPTs and the size of the pain area were calculated and analyzed using ANOVA or the Student *t* test. The Newman-Keuls (NK) post hoc test was used to account for multiple comparisons. The difference between days (relative change) in the total number of body regions affected by pain was calculated and analyzed using the Mann-Whitney *U* test. To compare the frequency of pain at each body region between days in both groups, a chi-square or Fisher exact test (for those cases where the frequency was 0) was used. Significance was set at $P < 0.05$.

Results

One female participant in the fracture group disclosed that she took pain medicine between day 0 and day 1, and therefore her data were excluded before data analysis. A full data set from 22 subjects in the fracture group and 22 subjects in the control group was available for data analysis.

All participants in the fracture group received standard conservative treatment of their injury, consisting of a firm cast for approximately four weeks. Additionally, before the stabilization of the wrist, three participants underwent surgical fixation of the radius bone. Demographic data and scores related to (recalled)

Table 1. Demographic data expressed in years, percentages (N = 22 per group), or scores on a 0–10 scale

Demographic Data	Fracture Group	Control Group
Age, mean (range), y	45 (21–79)	45 (21–80)
Proportion of males, %	41	41
Time from fracture, mean (range), y	7.9 (1–25)	
Recalled fracture pain (0–10 NRS), mean ± SD	5.2 ± 3.3	
Right dominance, %	95.5	86.4
Fractures on the right side, %	54.6	
Fractures on the dominant side, %	59.1	

NRS = numeric rating scale.

Table 2. Mean ± SD (N = 22) pressure pain thresholds assessed bilaterally on day 0 and day 1 for the fracture and control groups, on the ipsilateral (the exercised side after assessment on day 0) and contralateral sides at the extensor carpi radialis longus, infraspinatus, and gastrocnemius muscles

		Fracture Group, kPa		Control Group, kPa	
PPTs	Assessment Site	Day 0	Day 1	Day 0	Day 1
Ipsilateral	ECRL	214 ± 86.0	125 ± 57.5*,†	214 ± 86.5	133 ± 57.3*,†
	Infraspinatus	287 ± 96.4	231 ± 80.8	272 ± 85.5	243 ± 57.3
	Gastrocnemius	343 ± 127.0	278 ± 115.0	310 ± 93.2	283 ± 92.6
Contralateral	ECRL	212 ± 84.7	181 ± 62.5	218 ± 61.2	189 ± 69.5
	Infraspinatus	262 ± 75.7	237 ± 84.4	249 ± 70.3	253 ± 74.7
	Gastrocnemius	336 ± 121.3	289 ± 99.8	328 ± 121.4	290 ± 80.8

Significantly different compared with day 0 (*Newman-Keuls post hoc test: $P < 0.0001$) or the contralateral side (†Newman-Keuls post hoc test: $P < 0.001$).
ECRL = extensor carpi radialis longus; PPT = pressure pain threshold.

fracture pain are shown in Table 1. However, five out of 22 participants in the fracture group did not recall that they specifically had felt "intense pain," but described other symptoms such as dizziness or inflammation. For those who clearly recalled fracture-related acute pain, it was felt on the distal forearm/wrist and tended to subside within hours following the fracture event. Furthermore, none of the participants experienced severe, prolonged pain or complications during the recovery process.

Pressure Pain Sensitivity and Exercise-Induced Prolonged Pain

The ANOVA of PPTs revealed no group baseline difference in pain sensitivity. A significant interaction was detected between *days* and PPT *side* (ANOVA $F_{(3,166)} = 3$, $P = 0.03$) (Table 2), where the values on the ECRL PPTs on the fractured (dominant in controls) side were lower on day 1 compared with day 0 (NK $P = 0.00002$).

The Likert pain ratings due to exercise-induced prolonged pain (DOMS) on day 1 (IQR) were similar between groups 3 (2–3, MWU $P = 0.53$). One participant in each group indicated 0 (no pain) on the Likert scale.

Pain Area from Suprathreshold Pressure Stimulation on the ECRL Muscle

All participants felt pain in (or adjacent to) the stimulated body region following suprathreshold pressure stimulation of the ECRL muscle. In general, the area of pain spread distally, invading the mid part of the forearm in most of the participants in both groups (Figure 4, Table 3) and less frequently invading the distal forearm and hand. However, on day 0, the fracture group reported referred pain more frequently than the control group toward the mid (χ^2 $P = 0.04$) and distal forearm (the body region of the previous fracture; χ^2 $P = 0.003$) and the posterior arm (χ^2 $P = 0.02$) on day 1. No significant differences were found on day 1 between groups or in either group compared with day 0.

A significant *side* effect was found in the size of the pain area following the PPT stimulation bilaterally at the ECRL on day 0 (RM-ANOVA $F_{(1,42)} = 10.5$, $P = 0.002$) (Table 3) and day 1 (RM-ANOVA $F_{(1,42)} = 9.12$, $P = 0.004$) (Table 3). The fracture group demonstrated a larger referred pain area when stimulating on the ECRL muscle on the fracture side when compared with the contralateral ECRL muscle on day 0 (NK $P = 0.0005$) and day 1 (NK $P = 0.0002$). Moreover, a significant *time* effect was found in the pressure-induced pain area after the stimulation of the ECRL on the exercised side (fracture or dominant side; RM-ANOVA $F_{(1,42)} = 4.3272$, $P = 0.04$) (Table 4). Additionally, the fracture group showed a relatively larger change from day 0 to day 1 in the size of the referred pain area for the fracture (*t* test $P = 0.002$) and contralateral sides (*t* test $P = 0.004$).

No significant differences were found in the total number of body regions affected by pressure-induced pain on the ECRL muscle between days, sides, or groups (Wilcoxon and Mann-Whitney *U* tests $P > 0.05$)

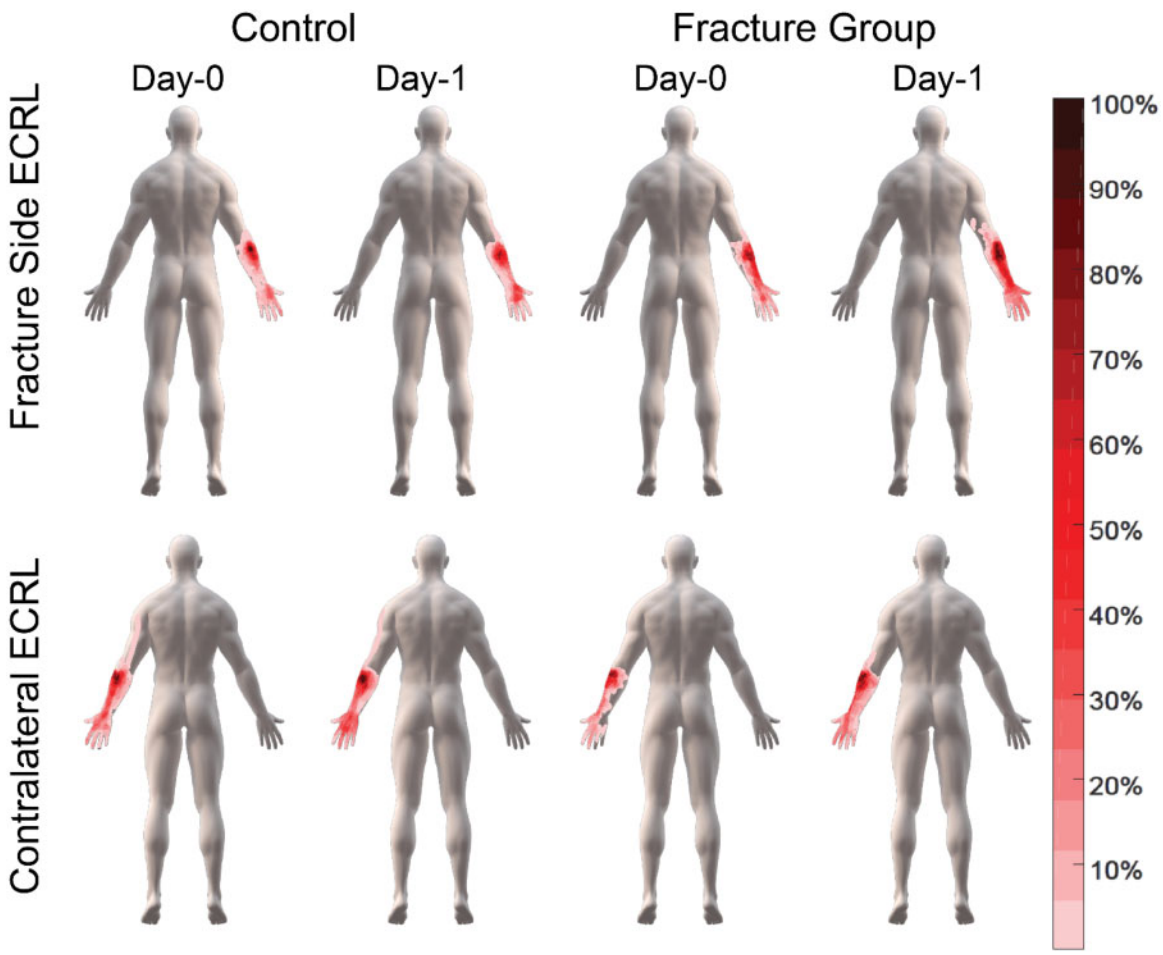

Figure 4. Distribution of pressure-induced referred pain following stimulation of the extensor carpi radialis longus (on both sides, although not at the same time) on day 0 and day 1 in healthy and asymptomatic participants with a history of radius fracture. Dark color was scaled as maximal (100%) overlying level for each side in 18 and 15 participants for the fracture (dominant for controls) and contralateral sides, respectively. If the fracture was on the left side, the pain drawings were mirrored and illustrated on the right side. Likewise, if the left side was dominant in control subjects, these drawings were mirrored and shown on the right side.

Table 3. Percentages of participants (N = 22 per group) indicating pain in the arm, forearm, and hand regions after suprathreshold pressure stimulation on the ipsilateral (fracture or dominant side) and contralateral extensor carpi radialis muscles at day 0 and day 1, 24 hours after induction of prolonged pain by exercise

	Fracture Group				Control Group			
	Day 0		Day 1		Day 0		Day 1	
Body Region	Ipsi	Contr	Ipsi	Contr	Ipsi	Contr	Ipsi	Contr
Posterior arm, %	5	0	32*	9	5	9	5	5
Proximal third of the forearm, %	91	95	95	86	95	91	77	91
Medial third of the forearm, %	95*	59	95	82	73	82	86	82
Distal third of the forearm, %	73*	27	64	41	27	36	41	36
Hand, %	64	41	64	41	45	45	64	55
Regions affected by pain, median (IQR)	2 (2–4)	2 (1–3)	4 (2–4)	2 (2–3)	2 (2–3)	2 (2–4)	3 (2–4)	3 (1–4)

Contra = contralateral; Ipsi = ipsilateral; IQR = interquartile range.
*Significantly more frequent compared with the control group on the same side and day (χ^2 test, $P < 0.05$).

(Table 3). For the relative change in total number of body regions from day 0 to day 1, no differences were found between sides or groups (Wilcoxon and Mann-Whitney U tests $P > 0.05$) (Table 3).

Pain Area from Suprathreshold Pressure Stimulation on the Infraspinatus Muscle

The pressure-induced pain area following stimulation of the infraspinatus muscle on day 0 and day 1 mainly

Table 4. Mean ± SD (N = 22) size of the pressure-induced pain area induced by stimulation of the ipsilateral (fracture or dominant side) and contralateral extensor carpi radialis longus and infraspinatus muscles sites on day 0 and day 1, 24 hours after induction of prolonged pain by exercise

	Fracture Group		Control Group	
Stimulation Site	Day 0	Day 1	Day 0	Day 1
Ipsilateral ECRL	1,717 ± 1,165.5*	2,580 ± 1,846.3*,†	1,588 ± 1,711.0	1,798 ± 1,633.6†
Contralateral ECRL	933 ± 877.2	1,618 ± 1,847.6	1,730 ± 1,752.7	1,982 ± 2,178.0
Ipsi. infraspinatus	4,003 ± 3,963.9	3,416 ± 3,597.9	1,590 ± 1,121.1	1,972 ± 1,421.4
Relative change from day 0 to day 1				
	Fracture Group		Control Group	
Ipsilateral ECRL	862 ± 1,353.8‡		210 ± 863.4	
Contralateral ECRL	686 ± 1,833.2‡		253 ± 1,031.6	
Ipsi. infraspinatus	−587 ± 3,231.0		382 ± 1,060.7	

Significantly different compared with the contralateral ECRL (*Newman-Keuls post hoc test $P < 0.001$), day 0 (†Newman-Keuls post hoc test $P < 0.05$), or the control group (‡t test $P < 0.005$).

ECRL = extensor carpi radialis longus; Ipsi = ipsilateral.

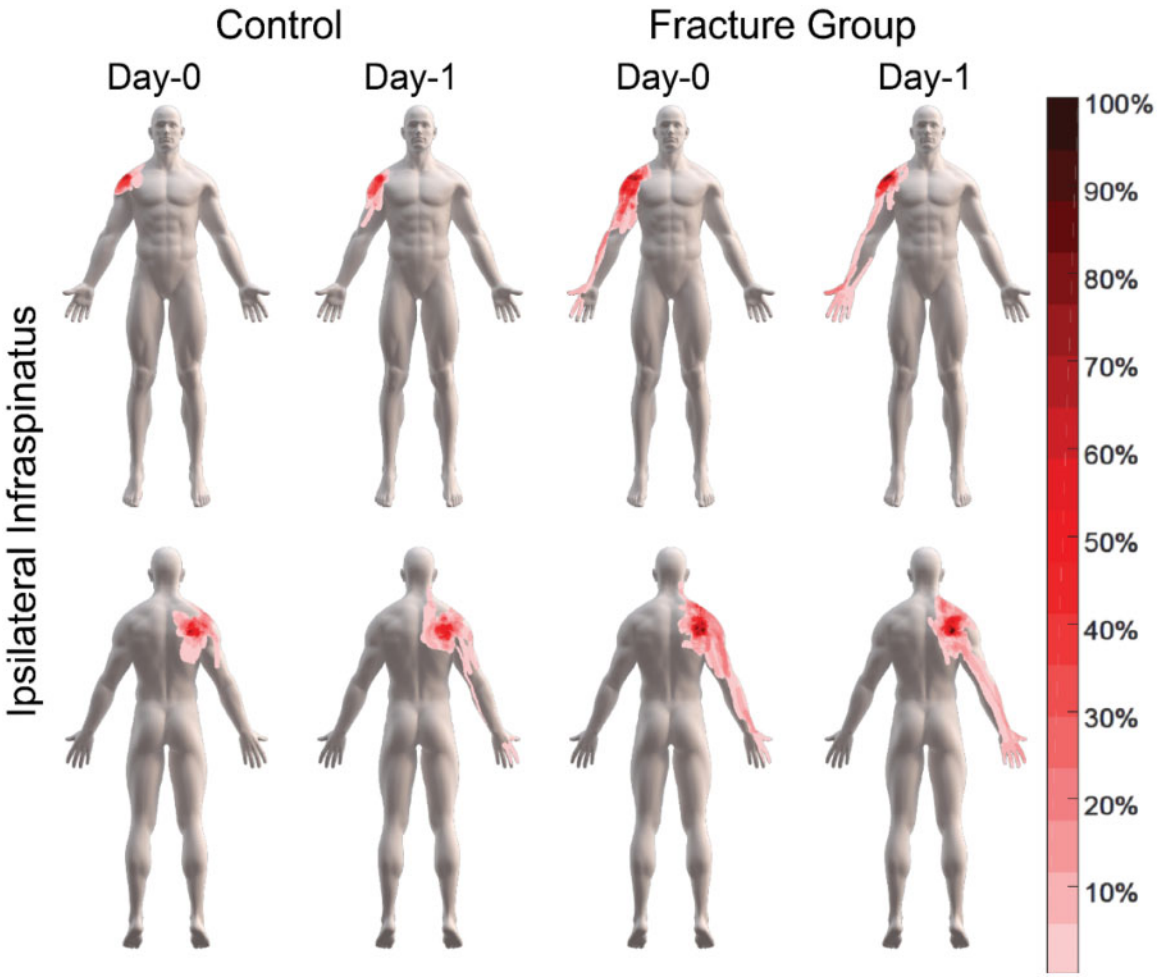

Figure 5. Distribution of pressure-induced referred pain following stimulation of the infraspinatus muscle (fracture side or dominant side in controls) on day 0 and day 1 in healthy and asymptomatic participants with a history of radius fracture. Dark color was scaled as maximal (100%) overlying level for each view (10 and 14 participants for the anterior and posterior body chart views, respectively). If the fracture was on the left side, the pain drawings were mirrored and illustrated on the right side. Likewise, if the left side was dominant in control subjects, these drawings were mirrored and shown on the right side.

Table 5. Percentages of participants (N = 22 per group) indicating pain in 15 body regions after suprathreshold pressure stimulation on the ipsilateral (fracture or dominant side) infraspinatus muscle at day 0 and day 1

	Fracture Group		Controls	
Body Region	Day 0	Day 1	Day 0	Day 1
Posterior head and neck, %	18	18	0	9
Supraspinal, %	36*	32	9	18
Infraspinatus, %	100	95	100	100
Back, %	18	27	14	23
Posterior shoulder, %	45	32	36	36
Posterior arm, %	32	14	9	14
Posterior forearm, %	14	14	0	5
Posterior hand, %	14	18	0	5
Anterior head/neck, %	0	0	0	0
Supraclavicular, %	14	14	5	0
Chest, %	59*	55*	27	23
Anterior shoulder, %	59	50	36	32
Anterior arm, %	36†	18	0	18
Anterior forearm, %	14	14	0	0
Anterior hand, %	14	18	0	0
Regions affected by pain, median (IQR)	4.5 (2–8)	4.5 (2–6)	2 (1–3)	3 (1–4)

IQR = interquartile range.

*Significantly more frequent compared with the control group (χ^2 test, $P < 0.05$).

†Significantly more frequent compared with the control group (Fisher exact test, $P < 0.05$).

spread across the stimulation and adjacent regions such as the posterior shoulder and supraspinal regions and referred to the anterior aspect of the shoulder and chest regions. To a lesser extent, pain also referred to the anterior and posterior arm regions (Figure 5, Table 5). Compared with controls, the fracture group showed higher frequencies of pain referred to the supraspinal (χ^2 $P = 0.03$), chest (χ^2 $P = 0.03$), and anterior arm (Fisher exact test $P = 0.004$) regions on day 0 and to the chest region on day 1 (χ^2 $P = 0.03$).The size of the pain area on day 0 and day 1 was not significantly different between groups or between days within the groups (Table 4). Additionally, no significant relative change was found in the size of the referred pain area between day 0 to day 1 within or between groups. Lastly, no significant between- or within-group differences were found for the total number of body regions covered by referred pain at day 0 or day 1.

Discussion

This study investigated whether a previous history of fracture is associated with regional expansion of pain distribution, and it is the first study to investigate the widespread expansion of pain distribution in this population. The main findings were that individuals who had recovered from a fracture at the distal radius demonstrate an expanded area of pain referred toward the previously fractured region, compared with the opposite side, which did not occur in individuals without a previous fracture. Despite the fact that exercise-induced prolonged pain expanded the pressure-induced pain area in both groups, the expansion of pain was further enhanced in those with a history of distal radius fracture.

Pain Sensitivity, Experimental Referred Pain, and Bone Pain After Fracture

Skeletal injuries are known to result in sensitivity changes of central pain mechanisms to a greater extent than injuries to other tissues such as muscle or skin [35], which may relate to the unique innervation properties of the bone [21]. An immediate increase in pain sensitivity is commonly seen following a musculoskeletal injury and is dependent on functional changes in the immune system [36] as well as peripheral [37] and central nervous system changes [19, 20, 22]. For some, these changes are maintained following tissue recovery [26, 38–40], potentially contributing to the development of maintained musculoskeletal pain [21, 26]. It is assumed, however, that for most people, these changes revert to normal following tissue recovery [38, 41]. In fact, recent evidence suggests that both the effectiveness of endogenous pain sensitivity control and the required pressure intensity to evoke remarkable pain may increase following recovery, which has been described as an adaptive response of the pain system [13]. An expanded referred pain area into the previously injured region was also described as part of this adaptive response following injury [13]. Recent findings indicate that stimulating musculoskeletal structures close to the previously fractured site results in a relatively larger expansion in pain referral area when compared with control [12] even though baseline pain sensitivity is comparable. In the current study, the expansion of the pain area is specific to the affected region and is not widespread, as evidenced by no differences (between groups or sessions) in pain referral from stimulating the infraspinatus muscle. These findings, together with previous studies investigating the sensitivity of central pain mechanisms after an injury [12, 13], indicate that

peripheral pain sensitivity is normalized following recovery, although parts of the nervous controlling pain distribution can remain sensitized. In line with the general population [42], most participants were right-handed in both groups (95.5% and 86.4% for the fracture and control groups, respectively). However, only 54.6% of individuals in the fracture group had the right side fractured. This mismatch implies that the right side was overrepresented as the exercise-induced pain side and the infraspinatus stimulation side in the control group. Specifically, 100% of controls vs. 59.1% of individuals in the fracture group had exercise-induced prolonged pain (DOMS) and infraspinatus stimulation on the dominant side Literature investigating the relationship between limb dominance and pain perception is scarce. However, some studies have found no relationship between these two variables when investigating the pain response to mechanical stimulus in neural tissue [43, 44]. Additionally, the fact that no differences between sides were found for the size of the area of pain in the control group rules out limb dominance as a potential confounding factor affecting the differences found in pain distribution.

Acknowledging that pain sensitivity is modality-specific where different methods for testing may indicate various levels of pain sensitivity in the same individuals [12, 45–47], it seems that stimulating at the pain threshold level does not reveal any evidence of pain hypersensitivity following recovery from injury and pain. Interestingly, stimulating above the pain threshold seems to unmask signs of sensitization. This unmasking was evidenced by the expanded pain referral spreading toward the previous injury [12–14], and these changes have been attributed to increased sensitivity of central pain mechanisms [11, 12, 48]. These previous findings are in line with the current study. First, the suprathreshold pressure stimulation on the fracture side provoked larger referred pain areas when the system was sensitized by exercise-induced prolonged pain (DOMS), compared with baseline and compared with the contralateral (non-injured) side. Second, the referred pain area spread more distally on the fracture side as the frequency of referred pain to the distal forearm was higher in the fracture group, compared with the control group, on day 0. Finally, individuals in the fracture group chose more adjectives to describe the quality of pain, compared with controls.

Fracture Pain

Initial pain due to wrist fractures is relevant to consider as the intensity of pain [49] and sensitivity [50] in the acute phase may predict future complications such as complex regional pain syndrome (CRPS) and the development of chronic pain [16]. However, there are other sources of pain associated with fracture that cannot be excluded as potential contributors to the findings of this study. For example, muscle injury is common in closed fractures [51], and it may contribute to pain after tissue healing via sensitization of neurons at the dorsal root ganglia [52]. Additionally, it has been shown that immobilization can induce sensitization of spinal cord neurons in animal models [53] and produce mechanical hyperalgesia in healthy individuals [54]. Unfortunately, the present study did not account for such manifestations, and therefore it was not possible to investigate the role of these additional factors. In the present study, participants recalled only fracture pain characteristics, including intensity, time, and location. Recalling the intensity of past pain experiences in patients has limitations [55], can be potentially biased [56], and has low correspondence with momentary pain [57]. However, there is also evidence showing that pain recall may be as valid as momentary pain reports [58]. The intensity of the pain experience was moderate and similar to previously reported pain values following distal radius fracture [16]. The pain was normally felt in the distal forearm and wrist regions, which are the same regions where experimental referred pain was more frequently reported in the fracture group compared with controls. The more frequent reports are in agreement with previous studies indicating a tendency of experimental referred pain to spread toward a previously injured area [12–14]. Nevertheless, attributing this finding only to the fracture should be done with caution, as the controls also tended to experience referred pain to the distal forearm and wrist, but it may explain some of the variance seen in the pain distribution in the general cohort [1].

Prolonged Experimental Pain Facilitates Pain Expansion

Eccentric exercise can induce prolonged pain (DOMS) and increase pain sensitivity [59], as shown in this study for the ECRL muscle. The sore ECRL muscle resulted in an expanded distribution of pressure-induced pain compared with the control condition (the contralateral side) in both groups. However, the fracture group demonstrated a relatively larger expansion than controls due to prolonged pain. According to this, a previous similar study obtained comparable results in both a pain-free fracture-recovered group and healthy controls [12]. Moreover, other experimental studies including only healthy controls, have obtained similar results [11, 48].

Neuroplastic Changes After Fracture

Several peripheral and central mechanisms may underlie and contribute to the sensitization of pain mechanisms after a fracture and returning back to normal following recovery. It has been shown in animals that inflammation can prime peripheral sensory nerve fibers, rendering them more sensitive to pressure stimulation weeks after recovery [60], potentially contributing to a generation of a “pain memory” [61] and episodic pain syndromes [60]. Therefore, it may be hypothesized that a primed

peripheral nervous system could influence not only pressure pain sensitivity but also pain referral in asymptomatic individuals. However, a recent study demonstrated an expanded referred pain area but not increased pain sensitivity in asymptomatic individuals recovered from fracture [12]; increased sensitivity of central pain mechanisms after a fracture has only been shown to occur when pain persists [22].

It is known that an upregulation of nociception-related neurotransmitters (e.g., dynorphin, calcitonin gen-related peptide [CGRP], and substance P) occurs in the spinal cord following skeletal injury [21, 36]. Likewise, other sensitizing molecules derived from glial activation can contribute to the unmasking of latent interneuron synapses at the dorsal horn and higher neural centers [62]. Moreover, changes in N-methyl-D-aspartate (NMDA) glutamate receptors have also been found, some of them related to the long-term potentiation of synapses like the phosphorylation of NMDA receptors [63]. Interestingly, these changes involve mechanisms that physiologically overlap with those considered relevant for the generation of referred pain, which was spread toward the previous fracture pain area (Figure 4). For example, referred pain is associated with synaptic reorganization of the sensory neurons at the dorsal horn after peripheral injury of the skeletal muscle [64, 65]. Additionally, referred pain can be reduced by ketamine, an NMDA antagonist, in both healthy volunteers [8] and patients [7]. Although speculative, the proposed mechanisms could, to some extent, explain the findings of the present study. Nevertheless, it is worth notice that despite being naïve to the study hypothesis, individuals with a history of fracture were asked to recall their fracture pain at the beginning of the experimental session. This fact may have exerted a confounding effect on the perception and report of the pressure-induced pain. However, as fracture pain is generally localized on the fracture site [18], it may be hypothesized that fracture pain memory biases would account for only a small proportion of the total referred pain area.

Clinical and Methodological Considerations

The finding of expanded distribution of pressure-induced referred pain despite normal pain sensitivity may be a useful biomarker for assessing the sensitivity of pain mechanisms in patients. The proposal of using pressure-induced pain as a pain biomarker is in line with other studies recommending the use of other modalities of suprathreshold painful stimulation in combination with pain thresholds to assess increased sensitivity of pain mechanisms [45, 46]. Nonetheless, only a few studies use suprathreshold pressure stimulation as a diagnostic tool in specific populations (clinical and nonclinical) and collectively indicate that suprathreshold pressure stimulation alone is insufficient for assessing pain mechanisms. With this in mind, the proposal of using pressure-induced referred pain [11] integrated into a battery of tests for assessing the pain mechanisms [12] is reinforced.

Conclusions

The present study used pressure-induced referred pain as a biomarker of sensitized pain mechanisms in asymptomatic individuals who had recovered from a distal radius fracture. Compared with the noninjured side, asymptomatic individuals demonstrated an expanded referred pain area for the fracture side, whereas no difference between sides was observed in healthy controls. Moreover, exercise-induced prolonged pain resulted in a significantly larger referred pain area in asymptomatic individuals with a history of previous fracture and healthy controls, although individuals with a history of fracture presented a relatively larger expansion from day 0 to day 1. These results indicate that prolonged pain and prior injuries like fracture may sensitize pain mechanisms, manifesting as expanded spatial distribution of pressure-induced referred pain.

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