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Pressure-induced referred pain areas are more expansive in individuals with a recovered fracture

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Abstract

Musculoskeletal trauma and pain can sensitize central pain mechanisms but whether these normalize upon recovery is unknown. This study compared the extent of pain referral in individuals recovered from a musculoskeletal trauma and healthy controls. Twenty pain-free participants recovered from a shoulder fracture and 20 age/gender matched controls participated in two experimental sessions (Day-0, Day-1) separated by 24 hours. On both days, pressure pain thresholds (PPTs) were measured bilaterally at infraspinatus, supraspinatus, trapezius, and gastrocnemius muscles. Referred pain towards the shoulder region was induced by a 60-s pressure stimulation (PPT+20%) at the infraspinatus muscle and recorded on an electronic body chart. Following Day-0 assessments, delayed onset muscle soreness (DOMS) was induced to challenge the pain systems by exercising the external rotators of the recovered/dominant shoulder. The size of pressure-induced pain referral on Day-0 did not differ between groups although there was a tendency for a smaller referred pain area in recovered group. PPTs at the infraspinatus muscle on the DOMS side was reduced on Day-1 in both groups (P=0.03). An expansion of pressure-induced pain referral was found in both groups following the DOMS protocol on Day-1 (P=0.05) with a relatively larger expansion (P=0.05) and higher frequency of pain in the shoulder (P=0.04) in the recovered pain group. Following complete recovery and absence of pain symptoms after a fracture, central pain mechanisms seem to normalize in the region of the trauma following recovery but when sensitized a heightened response can emerge. Such mechanisms could be important for recurrence of pain conditions.

Keywords: Referred pain, pressure algometry, pain mapping, muscle soreness, altered nociceptive processing

INTRODUCTION

Shoulder pain after a proximal humerus fracture has favorable prognosis provided that the fracture has no displacement [45; 46]. Approximately 50% of proximal humerus fracture patients, particularly complicated fractures, present with chronic shoulder pain at the 12 months follow-up [45]. Given that the periosteum is rich with nociceptors, shoulder pain can be easily provoked by fracture of the cortical bone, and is often perceived as sharp, stabbing and well-localized pain [8; 41; 43]. Pain after a proximal humerus fracture is typically felt locally in the anterior aspect of the shoulder [12].

It has been demonstrated in healthy individuals that referred pain from back muscles can be felt in the shoulder region [18], where pain from proximal humerus is also felt [12]. Interestingly, a stimulus applied to the maxillary sinus induced a pain experience at the site of a prior dental procedure [32], raising the possibility that subsequent to a strong nociceptive stimulus, the perceived location of referred pain may shift towards a recent locus of pain. The mechanism of referred pain and associated variable manifestation is not yet fully understood. Referred pain is considered a centrally mediated phenomenon [26] that can be facilitated by experimental pain. In combination with persistent pain models [18; 23; 25] increased pain and enlarged areas of referred pain were found in response to mechanical [23] or chemical [25] muscle stimulations. Ketamine-induced reduction in central pain sensitivity has been shown to reduce the area of pain referral from a nociceptive stimulus [28], underscoring the usefulness of pain referral mapping techniques as a proxy measure to assess central modulations of pain. Finally, experimental assessment of pain referral in chronic pain patients revealed expanded pain areas compared with asymptomatic controls [27], indicating that continuing pain sensitize this mechanism.

After a severe fracture, neuroplastic changes in the peripheral and central nervous systems likely contribute to sensitize the pain system. Several studies have demonstrated that neuroplasticity can last beyond tissue healing or cessation of peripheral nociception [30; 49] becoming `maladaptive´ [36; 40; 44]. In maladaptive neuroplasticity, sensitization of central pain mechanisms

is continued [5; 27; 44] and 'hyperalgesic priming' [34] may lead to altered nociceptive processing [13]. In the context of referred pain being perceived in previous injured and painful areas, but in the absence of tissue damage, it has been suggested that a type of neuroplasticity such as 'memory traces' [2] may play a role. However, it is not known if referred pain more often appears or is exaggerated in previously traumatized structures.

The purpose of this study was to investigate whether individuals fully recovered from a musculoskeletal fracture demonstrate facilitated pain sensitivity and referred pain compared with controls without a previous fracture. It was hypothesized that individuals with a history of proximal humerus fracture compared with healthy non-injured controls would have (1) increased pain sensitivity and (2) an enlarged pressure induced pain referral pattern towards the shoulder evoked by a painful pressure stimulus to the back muscles, which (3) would be further facilitated after inducing a persistent pain model in back muscles.

MATERIALS AND METHODS

Participants

Asymptomatic and pain-free subjects with a history of humerus fracture (fracture group, N=20) and controls without prior fracture matched for sex were included (control group, N=20). Participants in the fracture group were identified in a public hospital database and invited to participate. Inclusion criteria for the fracture group were subjects aged 18 to 65 years, with a prior fracture (without displacement) of the proximal third of the humerus and currently free of symptoms. Exclusion criteria were subjects with symptoms (e.g. pain), functional limitations, history of other fractures in the upper limb or any other pathology. Controls without any pain or history of fractures of the upper extremities were recruited from the university campus. In the control group, the mean age was 44 years (range 27-64 years), the mean weight was 69 kg (range 54-82 kg), and the average height was 171.5 cm (range 160-180 cm). In the fracture group the respective values were 54 years (range 37-67 years), the mean weight was 70.8 kg (range 54-82 kg), and the average height was 172.8 cm

(range 162-190 cm). The control and fracture groups included each 10 females. The participants received detailed information about the protocol and gave the informed consent prior to entering the study. All participants were naïve to the hypotheses and the methods used in the study. The local Ethics Committee approved the study (C.P - C.I. PI14/0071) which was conducted in accordance with the Helsinki Declaration. The study was performed in accordance with the CONSORT statement for non-pharmacological trials.

Protocol

This was a single blinded study, with a cross-sectional group comparison, conducted in two sessions (Fig. 1). For blinding purposes, the assessor performing all experimental procedures was unaware of the participants´ group allocation. All experimental procedures were explained by a research assistant, who also noted which side was the previously fractured side (controls indicated their dominant side). Participants were asked to attend two sessions in a hospital setting where the measurements took place on consecutive days (Day-0, Day-1), with 24 hours between sessions. In both sessions, pressure pain sensitivity at the infraspinatus, supraspinatus, lower trapezius and gastrocnemius muscles was assessed bilaterally. Following a 5 min break, the pain distribution resulting from suprathreshold pressure stimulation was assessed at the same location as pressure pain threshold recordings on the infraspinatus muscle, in the side with a previous fracture or in the dominant side for controls. In the fracture group, 65% of participants had the dominant side previously fractured. Following assessments on Day-0, delayed onset muscle soreness (DOMS) was induced by eccentric exercise of the shoulder external rotators on the side of the previous fracture or in the dominant side for the control group. The full protocol, including shoulder exercise was conducted in sitting position.

Pressure pain sensitivity

A handheld pressure algometer (*Algometer®, Somedic Senselab, Sweden*) with a 1 cm^2 probe (covered by a disposable latex sheath) was used to assess pressure pain thresholds (PPTs) bilaterally at four sites (Fig. 2): 1) 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). 2) The supraspinatus muscle (1 cm cranial to the midpoint of the scapular spine). 3) Lower trapezius muscle (4-5 cm lateral to the spinous process of the seventh thoracic vertebra). 4) The gastrocnemius muscle (in the distal third of the medial gastrocnemius muscle). The force was gradually increased at a constant rate of 30 kPa/s until the pressure stimulation became slightly painful where the subject pressed a button to stop the stimulation. This process was repeated 3 times with minimum 30 s between assessments and the average PPT value were extracted for further analysis.

Pressure-induced referred pain

Sustained pressure stimulation pain was applied by the handheld pressure algometer (*Algometer®, Somedic Senselab, Sweden*) with a 1 cm^2 probe at the infraspinatus muscle, at the same site as the infraspinatus PPT was recorded. The pressure was applied for 60 s at an intensity equivalent with 1.2 times the PPT assessed at the same day [18; 24]. This protocol has been shown to provoke pain referral patterns to the shoulder area likewise demonstrated by saline-induced pain in the infraspinatus muscle [18; 44]. Immediately after the pressure stimulation the participant was asked to draw the pain areas on a tablet-based application with an electronic body chart *(Navigate Pain, Aalborg University, Denmark)* [11]. The use of tablet-based recordings of pain drawings has been shown to be valid and reliable for assessing pain areas and comparable to paper recordings [10]. For data analysis, areas of referred pain and areas for "other sensations" were assessed separately and combined for both the front and back of the body (as referred symptoms). The size of the self-reported areas of pain referral and other sensations was automatically extracted and expressed in pixels. Moreover, in order to gain information about the distribution of the referred symptoms, the

body chart was subdivided in 15 different regions (Fig. 2) and the frequencies of referred symptoms in these regions were extracted [18]. Expansion of pain beyond the stimulation location, was considered referred pain [24]. Finally, in order to assess pain quality, the participant was asked to complete the McGill pain questionnaire [38].

Persistent pain model

At the end of the protocol on Day-0, all participants followed an exercise protocol consisting of eccentric exercise of the external rotator muscles of the shoulder. This was performed on the affected side (previous history of fracture) for the fracture group and on the dominant side for the control group with the objective to produce delayed onset muscle soreness (DOMS) on Day-1. The exercise consisted of externally rotating the shoulder against a resistance from a heavy elastic band (Black or Silver TheraBand™), performing four sets of as many times possible until failure, with 1 minute of rest between each set [18]. In short, the subject was in sitting position, resting the elbow 90º flexed on a table, maintaining the glenohumeral joint between 70º to 80º of flexion. This position reduces subacromial compression and permits maximal infraspinatus muscle activation during exercise [18]. Fatigue or failure was defined as the moment when it was not possible controlling the eccentric phase throughout full range of motion or keeping the upper limb stable. This way, mainly external rotators became fatigued and hence affected by DOMS, as eccentric contractions were not performed in other scapular muscles. On Day-1, the level of pain due to exercise was assessed with 6-point Likert scale where each number was anchored to a predefined description: 0) ‘absence of pain’, 1) ‘slight discomfort or minimal pain in the muscle’, 2) ‘moderate or slightly persisting soreness’, 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

Data were analyzed based on the results from normality tests (Shapiro-Wilk) and thereafter presented as median and interquartile ranges (IQR) or mean and standard deviations (SD), respectively. A comparison of persistent pain characteristics (Likert scores) between groups was made using unpaired tests (Mann-Whitney U, MWU). An analysis of variance (ANOVA) model was used for the PPTs with Site (bilateral infraspinatus, supraspinatus, lower trapezius and gastrocnemius muscles) and Time (Day-0, Day-1) as repeated measures and Groups (Fractured, Controls) as a between-group factor. Pain areas were logarithmically transformed to compensate for non-normal data distribution although non-transformed data are presented in figures and tables. The difference in log-transformed pain areas between days and the total number of body regions with pain, were analyzed by Student´s t-test. The log-transformed pain area data passed Shapiro-Wilk test for normality and were further analyzed by an ANOVA with Time as repeated measures and Groups as a between group factor. The Newman-Keul (NK) post-hoc test was used as correction. To compare the frequency of referred pain at each body region between days in both groups, Fisher exact test was used. Significance was accepted for $P \leq 0.05$.

RESULTS

In the fracture group, the average number of years from fracture until the assessment date was 2.5 years (range 1.1-7.5 years) and the specific locations of the fracture were the humeral head (35% of participants), humeral neck (20%), greater trochanter (30%), and lesser trochanter (15%). All participants indicated that the immediate pain after fracture was felt locally in the shoulder area, and that this pain was significantly reduced when medical management intervened. Since one of the inclusion criteria was “fracture without displacement”, the relevant medical management consisted of shoulder immobilization with a cast for a standard period (approximately 3 weeks) and without surgery. None of the participants had experienced an extended period of pain after the acute fracture episode. Finally, participants were not allowed to take any medication (e.g. pain medication or

Nonsteroidal anti-inflammatory drugs) during the experiment to avoid any potential effect on DOMS or pressure-induced referred pain.

Pressure pain sensitivity and induced persistent pain

A significant interaction was found between days and PPT-sites (Table 1; RM-ANOVA: $F_{(7,546)}$ = 4.44, *P*=0.00008). In the exercised side, the infraspinatus assessment site on Day-1 showed reduced PPT, compared to the same location on Day-0 (NK: *P*=0.03), and compared to the remaining of the PPT-sites on Day-1 (NK: *P*=0.00001). Only when gender was included as the only independent factor, a significant difference was found in the PPTs between males (391 ± 17) and females (304 ± 32) (RM-ANOVA, $F_{(1,38)}$ = 3.97, *P*=0.00). The median Likert score of induced pain on Day-1 was 3 (2-3 IQR) for controls and 2 (1-3 IQR) for the fracture group with no difference between the groups or between males and females (MWU: *P*=0.26). In both groups, all participants reported at least 1 on the exercised side and all scored 0 on the contralateral side.

Pressure-induced areas of pain referral

The sustained pressure-induced pain was reported in the infraspinatus region with referred pain to the back, posterior shoulder, anterior shoulder and chest regions (Fig. 3). A significant interaction was found in the size of the area of pain between days and groups (Table 2; RM-ANOVA: $F_{(1,38)}$ = 3.97, *P*=0.05). Compared with Day-0, the area of pain was larger on Day-1 in the fracture group (NK: *P*=0.0002) and the control group (NK: *P*=0.009). Although not significant, the fracture group demonstrated a tendency for smaller pain referral on Day-0 compared with controls (NK: *P*=0.1). When assessing the difference between Day-0 and Day-1, the fracture group demonstrated a greater increase in pain referral than controls (*t*-test, *P*=0.05; Table 2).

In general, all body regions tended to be more frequently affected by pain on Day-1 compared with Day-0 in both groups (Table 3). For the fracture group the regions “back” (Fisher exact test, *P*=0.04; Table 3) and “anterior shoulder” (Fisher exact test, *P*=0.05, Table 3) were

significantly more frequently affected by pain on Day 1, compared to Day 0. No similar changes were found in the control group (Fisher´s exact: *P*=0.08). The total number of body regions affected by pain was not significantly different at any day between fracture (Day-0: 4.25 ± 2.73 regions; Day-1: 4.8 ± 3.1 regions) and control (Day-0: 4.45 ± 2.46 regions; Day-1: 4.6 ± 1.98 regions) groups (RM-ANOVA: $F_{(1,38)} = 0.26$, *P*=0.91). Between Day-0 and Day-1, the increase in number of body regions affected by pain was not different between the fracture (0.55±2.65) and control (0.15±2.35) groups (t test: P=0.9).

The pain caused by sustained pressure stimulation in the control group was described on Day-0 as “Nagging (70% of participants)”, “Pressing” (60%) and “Annoying (50%)” whereas on Day-1 the most frequent were “Nagging (65%)”, “Hurting” (45%) and “Pressing” (35%). In the fracture group, sustained pressure stimulation produced pain on Day-0 described as “Pressing” (65%), “Nagging (60%)” and “Stabbing” (50%) whereas on Day-1, the most frequent were Sharp (50%), “Pressing (45%)”, Penetrating (45%) and “Stabbing” (45%).

At Day-0 during sustained pressure stimulation, a small number of participants reported ´other sensations´ than pain, both in the fracture group (15%) and the control group (40%). The majority of ´other sensations´ overlapped with the referred pain areas and was not analyzed further.

DISCUSSION

This is the first explorative study to investigate the effects of a fracture after complete recovery and the absence of pain, on measures of pain referral and sensitization. Despite having a comparable pain sensitivity profile, individuals with a previous shoulder fracture tended to show a reduced area of pain referral towards to the shoulder. These referred pain areas were enlarged when the pain system was challenged by persistent pain in a shoulder muscle and interestingly, a greater expansion of the referred pain area was seen in the previously fractured group compared with asymptomatic controls.

Pain sensitivity and referred pain following musculoskeletal injury

Increased pain sensitivity at the site of tissue injury may be attributed to peripheral [3] and central pain mechanisms [42; 55]. It is to be expected that pain sensitivity normalizes over time, i.e. returns to a pre-injury state, and does so in parallel with tissue healing [37] or the removal of peripheral nociceptive input (e.g. knee replacement in osteoarthrosis patients [29]). Further, a normalization of pain sensitivity seems dependent on the initial levels of pain and disability after injury [51]. Central pain mechanisms have been indicated as accountable for the transition from acute to chronic pain when recovering from an injury [5; 37; 49; 57], for chronic pain conditions with non-traumatic origin such as fibromyalgia, tension-type headache [56], and for complex regional pain syndrome [19], or other chronic pain condition associated with pain hypersensitivity [14]. However, compared to the role of pain mechanisms in persistent pain, it is under-investigated whether and to what extent these mechanisms can outlast the damage and pain resolution.

In combination with pain sensitivity assessment, referred pain assessment has been proposed as a useful clinical biomarker for the sensitization of the pain system [4; 18]. Despite pressure pain thresholds being similar between groups, in the previously fractured group the tendency of smaller referred pain areas at baseline conditions may indicate less responsive pain systems after such a traumatic event. Suggesting less active pain mechanisms in individuals that have successfully bounced back from a traumatic condition is highly relevant as it is the opposite path of the extensively investigated "sensitization" after tissue recovery [57]. Interestingly, it has been shown that pain during the first two weeks of a wrist fracture increases the likelihood of developing pain complications such as complex regional pain syndrome [17]. Although no pain ratings of the actual fracture were available in the medical records, none of the participants in the fracture group reported severe, long-lasting pain in the weeks after the fracture or maintained pain during immobilization. Referred pain was at baseline less frequently felt in the previously injured area than controls (40% of fractured vs 65% of controls felt pain in the anterior shoulder area after stimulation), which was also unexpected as previous research showed a shift in referred pain

towards such previous injured areas [32]. The fairly long time between the injury and current assessment may explain differences from previous findings. Interestingly, although the fracture group showed no higher frequency of referred pain to the previously injured area than the control group, only participants of the former used same descriptors for referred pain as those normally used to describe the pain of fracture e.g. sharp and stabbing [8; 41].

Multiple mechanisms may be involved in sensitization of the pain systems through neuroplasticity occurring following injury [15; 20], which may be expressed by augmented e.g. referred pain areas. Very little is known regarding an attenuated pain system after injury. Dar et al. [16] suggested that neurophysiological and cognitive mechanisms may be in play, explaining the reduced expression of pain mechanisms after severe injury.

In animal studies, latent local changes in the primary nociceptive afferents occur at the site of experimental inflammation, rendering them more sensitive to new inflammatory episodes. Increased pain sensitivity, observed as a facilitated withdrawal response to pressure stimulation even weeks after full resolution of that inflammation, is a mechanism suggested to relate to an increase in the activity of protein kinase C (PKCε) [9; 50]. Interestingly, PKCε is considered to play an important role in maintaining a latent, primed state at the nociceptor when there is no inflammatory mediator inducing hyperalgesia. The authors named this state “hyperalgesic priming” [48] and proposed it as having an important role in various chronic and recurrent pain conditions. In the current study, no group differences were found in pain sensitivity under basal conditions, and it was hypothesized that by sensitizing the stimulation area (infraspinatus muscle), group differences would emerge. However, the lack of group difference in pain sensitivity, seems to negate the possibility of hyperalgesic priming being the responsible mechanism for the apparent group differences in pain referral patterns between days.

Conditioned pain modulation (CPM) is a mechanism by which painful stimulation reduces the nociceptive response induced by another painful stimulation (test stimulus) applied in a distant body region [58]. The reduced efficiency of CPM has been associated with multiple chronic local and

widespread pain syndromes [39]. The present study did not investigate the CPM effect, however recent data demonstrated that the pressure-induced referred pain area was reduced in those healthy individuals presenting a more efficient CPM effect, suggesting that a reduced expression of referred pain might be modulated by engaging CPM mechanisms [47]. So far, it has not been demonstrated that a more efficient CPM-like mechanism could play a role after injury and pain resolution. Nevertheless, Dar et al. [16], hypothesized that a subclinical-below-pain-threshold nociceptive activity could be sufficient to activate descending pain control mechanisms. Such an explanation would be speculative as the CPM response has only been investigated during an acute induction of a painful conditioning stimulus. Moreover, the presence of DOMS enlarged the pain areas so subclinical nociceptive activity from the previously fractured area is not likely to be important for the reduced pain areas.

Challenging the pain system

In line with previous studies, the current study demonstrated that persistent pain models like DOMS can facilitate the central pain mechanism for pain referral and enlarge experimentally-induced referred pain areas [18; 23]. Enlarged referred pain areas after experimental stimulation have also been found in chronic pain populations e.g. osteoarthritis, low back pain, fibromyalgia [6], which has been linked to sensitized central pain mechanisms [27]. In the present study, the fracture group showed a stronger facilitation of referred pain than the control group when persistent pain was settled on Day-1, which could be interpreted as a sign of a more sensitive system. Additionally, in the fracture group the regions “back” and “anterior shoulder” were more frequently affected by referred pain on Day-1 than on Day-0. However, on Day-1 referred pain in fractured participants resembled controls´ referred pain (in terms of distribution, extension and frequency of body regions affected by pain), rather than exceeding it. Therefore, the stronger facilitation of referred pain observed in the fracture group could be better explained by a baseline state of inhibition rather than

an ongoing state of sensitization of the central pain mechanisms. These findings did not concur with the initial hypothesis.

Clinical implications and methodological considerations

The current explorative findings shed a light on the effect of a recovered injury on pain mechanisms in asymptomatic individuals, indicating that reduced referred pain response to suprathreshold pressure stimulation does not necessarily go hand-in-hand with less pain sensitivity in the previously affected area. In fact, it has been suggested that painful, suprathreshold stimulations are more useful than pain thresholds to detect sensitivity of the pain system [1; 7; 31]. Nevertheless, to explore whether higher pressure intensities produce larger areas of referred pain further studies are warranted, as this may demonstrate a stimulus-response function between pressure intensity and spatial characteristics of referred pain. Moreover, given the greater neuroplastic changes that seem to occur in those with higher pain intensity following a powerful nociceptive stimulus [21], recording information about initial pain ratings after fracture would be interesting. Unfortunately, initial pain ratings regarding fracture pain were not available on the medical records of the participants. Although it has been suggested that pain recall pain is as valid as momentary data for many patients [33], serious limitations have been pointed out [22], such as the risk of a recollection bias [35] or the low correspondence with momentary reports of pain [52]. Additionally, cross-sectional experimental pain studies using retrospective data tend to find difficulties in participants´ ability to report recalled pain without distortions [53; 54], which would make these data less reliable.

Conclusion

This study investigated a method to assess referred pain as a central pain mechanism in a group of pain-free participants with a history of shoulder fracture. Compared to controls, the findings revealed a tendency to reduced pressure-induced referred pain areas in previously fractured

participants. When challenging the pain system with exercise-induced soreness, a larger increase from baseline in pressure-induced referred pain areas was found in the fracture group compared with controls. Further studies involving groups with different musculoskeletal injuries are required to investigate the robustness of findings on pressure-induced referred pain.

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REFERENCES

[1] Abrishami A, Chan J, Chung F, Wong J. Preoperative pain sensitivity and its correlation with postoperative pain and analgesic consumption: a qualitative systematic review. Anesthesiology 2011;114(2):445-457.

[2] Albanese MC, Duerden EG, Rainville P, Duncan GH. Memory traces of pain in human cortex. J Neurosci 2007;27(17):4612-4620.

[3] Amaya F, Izumi Y, Matsuda M, Sasaki M. Tissue injury and related mediators of pain exacerbation. Curr Neuropharmacol 2013;11(6):592-597.

[4] Arendt-Nielsen L. Central sensitization in humans: assessment and pharmacology. Handb Exp Pharmacol 2015;227:79-102.

[5] Arendt-Nielsen L, Fernandez-de-Las-Penas C, Graven-Nielsen T. Basic aspects of musculoskeletal pain: from acute to chronic pain. The Journal of manual & manipulative therapy 2011;19(4):186-193.

[6] Arendt-Nielsen L, Graven-Nielsen T. Central sensitization in fibromyalgia and other musculoskeletal disorders. Current pain and headache reports 2003;7(5):355-361.

[7] Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 2009;10(6):556-572.

[8] BISHOP GH, LANDAU WM, JONES MH. Evidence for a double peripheral pathway for pain. Science 1958;128(3326):712-714.

[9] Bogen O, Alessandri-Haber N, Chu C, Gear RW, Levine JD. Generation of a pain memory in the primary afferent nociceptor triggered by PKCε activation of CPEB. J Neurosci 2012;32(6):2018-2026.

[10] Boudreau SA, Badsberg S, Christensen SW, Egsgaard LL. Digital Pain Drawings: Assessing Touch-Screen Technology and 3D Body Schemas. Clin J Pain 2016;32(2):139-145.

[11] Boudreau SA, Spence R, Vasov G, Egsgaard LL. Feature Extraction APP for Pain Profiles. In: W Jensen, KO Andersen, M Akay, editors. Replace, Repair, Restore, Relieve – Bridging Clinical and Engineering Solutions in Neurorehabilitation: Proceedings of the 2nd International Conference on NeuroRehabilitation (ICNR2014), Aalborg, 24-26 June, 2014. Cham: Springer International Publishing, 2014. pp. 853-854.

[12] Browner BD. Musculoskeletal emergencies E-Book: Saunders; 1 Har/Psc edition (September 7, 2012), 2012.

[13] Curatolo M. Diagnosis of altered central pain processing. Spine (Phila Pa 1976) 2011;36(25 Suppl):S200-204.

[14] Curatolo M, Müller M, Ashraf A, Neziri AY, Streitberger K, Andersen OK, Arendt-Nielsen L. Pain hypersensitivity and spinal nociceptive hypersensitivity in chronic pain: prevalence and associated factors. Pain 2015;156(11):2373-2382.

[15] Chen R, Cohen LG, Hallett M. Nervous system reorganization following injury. Neuroscience 2002;111(4):761-773.

[16] Dar R, Ariely D, Frenk H. The effect of past-injury on pain threshold and tolerance. Pain 1995;60(2):189-193.

[17] Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, Stanton TR. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. The journal of pain : official journal of the American Pain Society 2013;14(10):1001-1018.

[18] Domenech-Garcia V, Palsson TS, Herrero P, Graven-Nielsen T. Pressure-induced referred pain is expanded by persistent soreness. Pain 2016;157(5):1164-1172.

[19] Drummond PD, Finch PM. A disturbance in sensory processing on the affected side of the body increases limb pain in complex regional pain syndrome. Clin J Pain 2014;30(4):301-306.

[20] Elbert T, Rockstroh B. Reorganization of human cerebral cortex: the range of changes following use and injury. Neuroscientist 2004;10(2):129-141.

[21] Flor H, Diers M, Andoh J. The neural basis of phantom limb pain. Trends Cogn Sci 2013;17(7):307-308.

[22] Gendreau M, Hufford MR, Stone AA. Measuring clinical pain in chronic widespread pain: selected methodological issues. Best practice & research Clinical rheumatology 2003;17(4):575-592.

[23] Gibson W, Arendt-Nielsen L, Graven-Nielsen T. Delayed onset muscle soreness at tendon-bone junction and muscle tissue is associated with facilitated referred pain. Experimental brain research 2006;174(2):351-360.

[24] Gibson W, Arendt-Nielsen L, Graven-Nielsen T. Referred pain and hyperalgesia in human tendon and muscle belly tissue. Pain 2006;120(1-2):113-123.

[25] Gibson W, Arendt-Nielsen L, Taguchi T, Mizumura K, Graven-Nielsen T. Increased pain from muscle fascia following eccentric exercise: animal and human findings. Experimental brain research 2009;194(2):299-308.

[26] Graven-Nielsen T. Fundamentals of muscle pain, referred pain, and deep tissue hyperalgesia. Scandinavian journal of rheumatology Supplement 2006;122:1-43.

[27] Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nature reviews Rheumatology 2010;6(10):599-606.

[28] Graven-Nielsen T, Aspegren Kendall S, Henriksson KG, Bengtsson M, Sorensen J, Johnson A, Gerdle B, Arendt-Nielsen L. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain 2000;85(3):483-491.

[29] Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. Arthritis and rheumatism 2012;64(9):2907-2916.

[30] Heinricher MM. Pain Modulation and the Transition from Acute to Chronic Pain. Adv Exp Med Biol 2016;904:105-115.

[31] Hübscher M, Moloney N, Leaver A, Rebbeck T, McAuley JH, Refshauge KM. Relationship between quantitative sensory testing and pain or disability in people with spinal pain-a systematic review and meta-analysis. Pain 2013;154(9):1497-1504.

[32] HUTCHINS HC, REYNOLDS OE. Experimental investigation of the referred pain of aerodontalgia. J Dent Res 1947;26(1):3-8.

[33] Jamison RN, Raymond SA, Slawsby EA, McHugo GJ, Baird JC. Pain assessment in patients with low back pain: comparison of weekly recall and momentary electronic data. The journal of pain : official journal of the American Pain Society 2006;7(3):192-199.

[34] Kandasamy R, Price TJ. The pharmacology of nociceptor priming. Handb Exp Pharmacol 2015;227:15-37.

[35] Karimi Z, Pilenko A, Held SM, Hasenbring MI. Recall Bias in Patients with Chronic Low Back Pain: Individual Pain Response Patterns Are More Important Than Pain Itself! Int J Behav Med 2016;23(1):12-20.

[36] Kuner R. Spinal excitatory mechanisms of pathological pain. Pain 2015;156 Suppl 1:S11-17.

[37] Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10(9):895-926.

[38] Lazaro C, Caseras X, Whizar-Lugo VM, Wenk R, Baldioceda F, Bernal R, Ovalle A, Torrubia R, Banos JE. Psychometric properties of a Spanish version of the McGill Pain Questionnaire in several Spanish-speaking countries. Clin J Pain 2001;17(4):365-374.

[39] Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. J Pain 2012;13(10):936-944.

[40] Luo C, Kuner T, Kuner R. Synaptic plasticity in pathological pain. Trends Neurosci 2014;37(6):343-355.

[41] Mantyh PW. The neurobiology of skeletal pain. Eur J Neurosci 2014;39(3):508-519.

[42] Marcuzzi A, Dean CM, Wrigley PJ, Hush JM. Early changes in somatosensory function in spinal pain: a systematic review and meta-analysis. Pain 2015;156(2):203-214.

[43] Martin CD, Jimenez-Andrade JM, Ghilardi JR, Mantyh PW. Organization of a unique net-like meshwork of CGRP+ sensory fibers in the mouse periosteum: implications for the generation and maintenance of bone fracture pain. Neurosci Lett 2007;427(3):148-152.

[44] McGreevy K, Bottros MM, Raja SN. Preventing Chronic Pain following Acute Pain: Risk Factors, Preventive Strategies, and their Efficacy. Eur J Pain Suppl 2011;5(2):365-372.

[45] Olsson C, Nordquist A, Petersson CJ. Long-term outcome of a proximal humerus fracture predicted after 1 year: a 13-year prospective population-based follow-up study of 47 patients. Acta Orthop 2005;76(3):397-402.

[46] Olsson C, Petersson CJ. Clinical importance of comorbidity in patients with a proximal humerus fracture. Clin Orthop Relat Res 2006;442:93-99.

[47] Palsson TS, Doménech-Garcia V, Boudreau SA, Graven-Nielsen T. The extent of pain referral is reduced by a remote painful stimuls – indications for an endogenous modulation of referred pain, Proceedings of the EFIC® Pain Congress, 2017.

[48] Parada CA, Yeh JJ, Reichling DB, Levine JD. Transient attenuation of protein kinase Cepsilon can terminate a chronic hyperalgesic state in the rat. Neuroscience 2003;120(1):219-226.

[49] Pozek JP, Beausang D, Baratta JL, Viscusi ER. The Acute to Chronic Pain Transition: Can Chronic Pain Be Prevented? Med Clin North Am 2016;100(1):17-30.

[50] Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. Trends Neurosci 2009;32(12):611-618.

[51] Sterling M. Whiplash-associated disorder: musculoskeletal pain and related clinical findings. J Man Manip Ther 2011;19(4):194-200.

[52] Stone AA, Broderick JE, Shiffman SS, Schwartz JE. Understanding recall of weekly pain from a momentary assessment perspective: absolute agreement, between- and within-person consistency, and judged change in weekly pain. Pain 2004;107(1-2):61-69.

[53] Walentynowicz M, Bogaerts K, Van Diest I, Raes F, Van den Bergh O. Was it so bad? The role of retrospective memory in symptom reporting. Health psychology : official journal of the Division of Health Psychology, American Psychological Association 2015;34(12):1166-1174.

[54] Walentynowicz M, Van Diest I, Raes F, Van den Bergh O. Ways of encoding somatic information and their effects on retrospective symptom reporting. 2017;22(2):362-378.

[55] Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306(5944):686-688.

[56] Woolf CJ. Central sensitization: uncovering the relation between pain and plasticity. Anesthesiology 2007;106(4):864-867.

[57] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152(3 Suppl):S2-15.

[58] Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of psychophysical DNIC testing. Eur J Pain 2010;14(4):339.

FIGURE LEGENDS

Figure 1: Complete protocol followed in the study. PPTs: Pressure pain Thresholds. 60-s STPS: 60 seconds suprathreshold pressure stimulation. McGill: McGill Pain Questionnaire for measuring pain quality.

Figure 2: Anterior and posterior views of the body divisions used to quantify pain distribution and sites were pressure pain thresholds were measured.

Figure 3: Pressure-induced pain on Day-0 and Day-1 (DOMS), by suprathreshold stimulation in healthy and asymptomatic participants with a history of shoulder fracture. Stimulations were on the dominant side on healthy participants and on the side of injury for the rest of the participants. For illustration purposes all drawings are superimposed on the right side.

PPT (kPa)	Assessment site	Control group		Fracture group	
		Day-0	Day-1	Day-0	Day-1
Ipsilateral	**Infraspinatus**	355 ± 88	242 ± 83*#	348 ± 122	215 ± 56*#
	Supraspinatus	365 ± 84	317 ± 86	346 ± 108	323 ± 110
	Lower Trapezius	358 ± 107	322 ± 92	343 ± 108	314 ± 91
	Gastrocnemius	383 ± 70	359 ± 130	380 ± 82	350 ± 134
Contralateral	**Infraspinatus**	340 ± 74	324 ± 71	347 ± 99	337 ± 108
	Supraspinatus	389 ± 110	342 ± 85	359 ± 126	372 ± 151
	Lower Trapezius	378 ± 120	358 ± 106	369 ± 118	366 ± 97
	Gastrocnemius	374 ± 64	411 ± 122	365 ± 62	365 ± 163

Table 1: Mean (± SD, N= 20) pressure pain thresholds (PPTs) recorded on Day-0 and Day-1 for the two groups, on the ipsilateral (exposed to exercise after assessment on Day-0) and contralateral sides at the infraspinatus, supraspinatus, lower trapezius and gastrocnemius muscles. Significantly different compared with Day-0 (*, Repeated Measures - ANOVA, Newman-Keuls Post Hoc test: P=0.03) and the rest of the sites on Day-1 (#, Repeated Measures - ANOVA, Newman-Keuls Post Hoc test: P=0.00001). kPa: kilopascal.

	Control group		Fracture group	
	Day-0	**Day-1**	**Day-0**	**Day-1**
Total pain area	10255 ± 8132	15398 ± 8229*	6167 ± 4822	16707 ± 11043*
Area of pain drawn in front	3833 ± 3999	5195 ± 4172	2257 ± 3750	5966 ± 5785
Area of pain drawn in back	6421 ± 4849	10203 ± 5998	3911 ± 2863	10741 ± 6985
Total change between day 0 and day 1	5141 ± 6219		10539 ± 9093#	

Table 2: Mean (±SD) area of pain following 60-s pressure stimulation on the infraspinatus muscle at Day-0 and Day-1 (during delayed onset muscle soreness) and the total change between Day-0 and Day-1. The area is given by number of pixels out of a total 602931. Significantly different compared with Day-0 (*, Repeated Measures-ANOVA, Newman-Keuls post hoc test: P=0.009) and compared to controls (#, t-test: P=0.05).

Body region	Control group		Fracture group	
	Day-0	Day-1	Day-0	Day-1
Posterior head/neck	10	15	0	10
Supraspinal region	10	25	0	15
Infraspinatus region	100	100	100	100
Back	55	80	50	80*
Posterior shoulder	45	65	55	55
Posterior arm	15	30	30	25
Posterior forearm	0	5	0	5
Posterior hand	0	5	0	5
Anterior head/neck	5	5	5	15
Supraclavicular area	5	15	10	25
Chest region	40	50	30	55
Anterior shoulder	65	70	40	70*
Anterior arm	30	45	20	25
Anterior forearm	5	10	5	15
Anterior hand	10	1	0	15

Table 3: Percentages of participants (N=20 each group) that reported pain in the different body regions when sustained pressure stimulation was applied in the infraspinatus muscle on Day-0 and Day-1. Grey color: Body regions which were more frequently painful. Significantly higher frequency of pain, compared to Day-0 (Fisher exact test, $P \leq 0.05$).