Arthritis Care & Research
Vol. 62, No. 8, August 2010, pp 1055–1064
DOI 10.1002/acr.20189


ORIGINAL ARTICLE

# Pressure Pain Sensitivity Topographical Maps Reveal Bilateral Hyperalgesia of the Hands in Patients With Unilateral Carpal Tunnel Syndrome

CÉSAR FERNÁNDEZ-DE-LAS-PEÑAS,[1] PASCAL MADELEINE,[2] ALMUDENA MARTÍNEZ-PEREZ,[3] LARS ARENDT-NIELSEN,[2] RODRIGO JIMÉNEZ-GARCÍA,[4] AND JUAN A. PAREJA[3]

***Objective.*** **To assess topographical pressure pain sensitivity maps of the hand in patients with unilateral carpal tunnel syndrome (CTS) as compared with healthy subjects.**

***Methods.*** **A total of 20 women with CTS (ages 32–52 years) and 20 healthy matched women (ages 32–51 years) were recruited. Pressure pain thresholds (PPTs) were measured bilaterally over 30 locations of the palm of each hand by an assessor blinded to the subjects' conditions.**

***Results.*** **Patients showed lower PPTs in both hands in all of the measurement points as compared with controls ($P < 0.001$ for all). PPTs were lower in those points over the proximal phalanx of the fingers and the thenar eminency as compared with those points located over the distal phalanx of the fingers ($P < 0.001$). CTS patients showed lower PPT levels in dermatomes C6, C7, and C8 when compared with healthy controls ($P < 0.001$ for all), but without differences between dermatomes ($P = 0.4$). PPT was negatively correlated with both hand pain intensity and duration of symptoms ($P < 0.001$ for all).**

***Conclusion.*** **Our findings revealed bilateral generalized pressure pain hyperalgesia in unilateral CTS because lower PPT levels were found in all of the points. The pressure pain hyperalgesia was not uniformly distributed since PPTs were lower in points over the proximal phalanx of the fingers and the thenar eminency as compared with those points located over the distal phalanx of the fingers. The decrease in PPT levels was associated with the intensity and the duration of the pain symptoms, supporting a role of both peripheral and central sensitization mechanisms in this pain condition.**

## INTRODUCTION

Carpal tunnel syndrome (CTS) is a complex disorder associated with symptoms (pain and/or paresthesia) in the territory innervated by the median nerve of the hand. Although the etiology and pathology of CTS are under debate, there is some evidence involving the nociceptive system because different studies have reported functional deficits of nociceptive afferent in patients with CTS (1–4). More recent studies indicated additional involvement of central mechanisms. For instance, Zannete et al found that 45% of patients with CTS reported proximal pain (5) and spreading of their symptoms (6). Tucker et al (7) found a bilateral generalized increase in vibration thresholds in CTS demonstrating a generalized disturbance of somatosensory function rather than the existence of isolated peripheral neuropathy. Tecchio et al (8) and Napadow et al (9) found cortical remapping in the primary somatosensory cortex S1 in CTS patients that was correlated with patients' symptoms, supporting a role of central mechanisms in CTS.

Some studies had investigated nociceptive mechanisms by assessing mechanical hyperalgesia in deep tissues. For that purpose, pressure pain thresholds (PPTs) (10) have been investigated in different chronic conditions, e.g., whiplash (11,12), fibromyalgia (13), work-related disorders (14,15), tension-type headache (16,17), low back pain (18), osteoarthritis (19), and lateral epicondylalgia (20). These studies reported the presence of widespread mechanical pain sensitivity as a sign of generalized central

**Supported by a grant conceded by the Universidad Rey Juan Carlos and Comunidad de Madrid (reference CCG08-URJC/BIO-3469).**

**[1]César Fernández-de-las-Peñas, PT, PhD: Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain, and Aalborg University, Aalborg, Denmark; [2]Pascal Madeleine, PhD, Lars Arendt-Nielsen, DMSc, PhD: Aalborg University, Aalborg, Denmark; [3]Almudena Martínez-Perez, MD, Juan A. Pareja, MD, PhD: Fundación Hospital Alcorcón and Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain; [4]Rodrigo Jiménez-García, PhD: Universidad Rey Juan Carlos, Madrid, Spain.**

**Address correspondence to César Fernández-de-las-Peñas, PT, PhD, Facultad de Ciencias de la Salud, Universidad Rey Juan Carlos, Avenida de Atenas s/n, 28922 Alcorcón, Madrid, Spain. E-mail: cesar.fernandez@urjc.es.**

**Submitted for publication December 7, 2009; accepted in revised form March 1, 2010.**

nervous system hyperexcitability or central sensitization. In fact, we have recently shown bilateral widespread pressure hypersensitivity in CTS subjects associated with pain intensity and duration of pain symptoms (21). In a previous study, we reported a significant decrease in PPTs bilaterally over peripheral nerves of the arm, the C5–C6 zygapophyseal joint, and the carpal tunnel and tibialis anterior muscle, suggesting multisegmental sensitization or central sensitization in unilateral CTS (21). Nevertheless, recent evidence has shown that pressure pain hypersensitivity is not uniformly distributed within a region, as spatial changes in pressure pain sensitivity have been found in the cephalic region in different headache disorders (22,23) or shoulder pain (24,25). We have demonstrated the utility of multisite recordings for PPT mapping leading to a new imaging modality of muscle pain sensitivity (22–25). This technique enables us to visualize nonuniformity in muscle pressure pain sensitivity and, therefore, deep tissue hyperalgesia in a specific location of the body.

Li et al have recently reported high-resolution topographical mapping of thermal sensitivity in the hand in healthy subjects, showing that thermal sensitivity distribution over the hand is highly heterogeneous (26). To the best of our knowledge, no published studies have previously investigated topographical pressure pain sensitivity maps of the hand in patients with strictly unilateral painful CTS. In this study, we hypothesized heterogeneous topographical pressure pain sensitivity maps of the hand in patients with strictly unilateral CTS compared with healthy subjects highlighting different levels of hyperalgesia.

## SUBJECTS AND METHODS

**Subjects.** Consecutive patients diagnosed with CTS by an experienced neurophysiologist (AM-P) from the Neurology Department of Fundación Hospital Alcorcón were screened for eligibility criteria. The inclusion criteria consisted of both clinical and electrophysiologic signs of CTS (27). The patients had to present with pain and paresthesia within the median nerve distribution. Furthermore, patients had to exhibit at least 3 of the 4 following clinical findings: increasing symptoms during the night, positive Tinel's sign reproducing patients' symptoms, positive Phalen's sign reproducing patients' symptoms, or self-perceived hand strength deficits. Symptoms should have persisted for at least 6 months and should be strictly unilateral in order to assess a chronic condition. It has been found that patients with CTS can present with subclinical or "non-discomfort" CTS in the unaffected hand (28). In order to exclude these clinical pictures, we asked for any symptom or discomfort (paresthesia) in both hands. Clinical examination should have been negative in one hand.

In addition, the electrodiagnosis study should have revealed deficits of sensory and/or motor nerve conduction following the recommendations of the American Association of Electrodiagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation (29,30). Patients diagnosed with moderate (abnormal median nerve sensory velocity conduction and abnormal distal motor latency) or mild (abnormal median nerve sensory velocity conduction and normal distal motor latency) CTS were included in the study. A median nerve sensory conduction velocity slower than 40 mm/second and a median distal motor latency greater than 4.20 msec were considered abnormal (29,30). Sensory and motor conduction studies of radial and ulnar nerves were done to rule out radial or ulnar nerve involvement.

Patients were excluded if they exhibited any of the following criteria: 1) bilateral symptoms; 2) extreme/severe CTS; 3) any sensory or motor deficit for either the ulnar or radial nerve; 4) age >65 years; 5) history of wrist, upper extremity, or cervical spine trauma (whiplash); 6) previous wrist, upper extremity, or cervical surgery; 7) previously received a steroid injection; 8) multiple diagnoses for the upper extremity; 9) a history suggesting systemic disease is causing the CTS (e.g., diabetes mellitus, thyroid disease); 10) pregnancy; 11) a concomitant medical condition (e.g., rheumatoid arthritis, fibromyalgia); 12) involved with or seeking litigation at the time of the study; 13) presence of a score greater than 8 points on the Beck Depression Inventory II (BDI-II) (31); or 14) previous conservative (e.g., physiotherapy, electrotherapy) treatment.

Healthy control subjects were recruited from volunteers who responded to a local announcement and were excluded if they exhibited a history of upper extremity or neck pain, fractures, or any neurologic disorder. Healthy controls were matched on the basis of age and hand dominance. Matching for age was achieved by individually selecting the control subject with the closest available match for age of the patient with CTS, whereas hand dominance was controlled by matching the dominant arm, which was defined as the hand that the participants used for writing. Healthy controls received the same exploration as CTS patients related to depression and medication consumption. This study was supervised by the Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos. The project was approved by the local human research committee (FHA-URJC 033). All of the subjects signed an informed consent form prior to their inclusion.

**Self-reported measures.** A numerical pain rating scale (where 0 = no pain and 10 = maximum pain) (32) was used to assess the current level of hand pain and the worst and lowest level of pain experienced in the preceding week. Patients were asked to draw the distribution of their pain on an anatomic map (33). The pain area was calculated (arbitrary units) with a digitizer (Acecad D9000; Acecad).

The Spanish version (34) of the Boston Carpal Tunnel Questionnaire (BCTQ) (35), a self-report measure of functional limitation and symptom severity, was also used. This questionnaire evaluates 2 domains: the functional status scale evaluates the ability to perform 8 common hand-related tasks, whereas the symptom severity scale includes 11 items assessing hand pain severity, numbness, and weakness at night and during the day. Each question is answered on a 5-point scale (where 1 = no disability and

5 = very severe disability). Each BCTQ score (range 1–5) is calculated from the average of the score of the individual questions included in each subscale, with higher scores indicating greater severity. The BCTQ has been shown to be valid, reliable, and responsive for patients with CTS (36).

**Sample size determination.** The sample size determination and calculations were based on detecting at least clinically significant differences of 20% on PPT levels between both groups (37), with an alpha level of 0.05, a desired power of 80%, and an estimated interindividual coefficient of variation for PPTs of 20%. This generated a sample size of at least 16 participants per group.

**PPT assessment.** A PPT is defined as the amount of pressure where a sense of pressure changes to pain (38). An electronic algometer (Somedic) was used to measure the PPT. The algometer consists of a 1-$cm^2$ rubber-tipped plunger mounted on a force transducer. The pressure was applied at a rate of 30 kPa/second. The participants were instructed to press a switch when the sensation changed from pressure to pain. Three PPT measurements (intraexaminer reliability) were taken at each point with a 20-second interval in between 2 consecutive points, with randomization in the order of the points' assessments. The reliability of pressure algometry has been found to be high (intraclass correlation coefficient [ICC] 0.91, 95% confidence interval [95% CI] 0.82–0.97) (39). Averaged PPT values over the 30 locations were interpolated using an inverse distance weighted interpolation (40) for graphical purposes to have an easy reading of the PPT distribution over both hands. The inverse distance weighted interpolation consists of computing PPT values to unknown locations by using mean scores from the set of known PPT values and locations (41,42).

**Topographical pressure pain sensitivity maps of the hand.** The study protocol was the same for patients and controls. All of the examinations were performed in a quiet, draught-free, temperature- and humidity-controlled laboratory (mean ± SD temperature 24°C ± 1°C, relative humidity 25–35%). All of the participants had abstained from vigorous exercise on the previous day. The participants were not allowed to take analgesics or a muscle relaxant through the 72 hours prior to the examination. Subjects were asked to take a seated position on an examination bed. PPT levels were measured bilaterally over 30 locations (Figure 1A) on each hand by an assessor (CF-d-l-P) blinded to the subjects' conditions. All of the PPT measurements were done by the same assessor. Each location was marked with a pencil as thumb: distal phalanx (point 1), proximal phalanx (point 2), and thenar eminency (point 3); index finger: distal phalanx (point 4), middle phalanx (point 5), and proximal phalanx (point 6); middle finger: distal (point 7), middle (point 8), and proximal (point 9) phalanx; fourth finger: distal (point 10), middle (point 11), and proximal (point 12) phalanx; fifth finger: distal (point 13), middle (point 14), and proximal (point 15) phalanx; and head of the fifth (point 16), fourth (point 17), third (point 18), and second (point 19) metacarpal bones. For points 20–27, 2-cm equidistant points over each metacarpal bone were marked (20–24 over the second metacarpal bone, 21–25 over the third metacarpal bone, 22–26 over the fourth metacarpal bone, and 23–27 over the fifth metacarpal bone). Finally, one point over the lower end of the hypothenar eminency (point 28), over the carpal tunnel (point 29), and over the lower end of the thenar eminency (point 30) were also assessed (Figure 1A). The measured spots were located in the 3 dermatomes C6, C7, and C8 (Figure 1B).

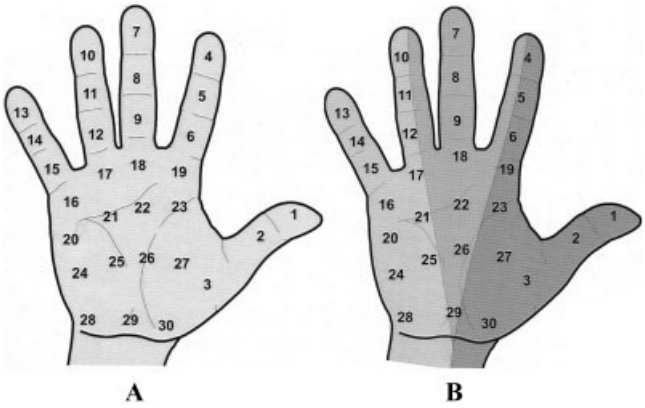


**Figure 1.** Schematic representation of the 30 points for pressure pain threshold assessment without (**A**) and with (**B**) hand dermatomes.

**Data analysis.** We focused the main analysis on topographical pain maps investigating PPTs on each isolated points; moreover, a complementary analysis by dermatomes was also done. In such a way, PPT levels from those points (1–6, 19, 23, 27, and 30) located over the dermatome C6, those points (7–9, 18, 22, 26, and 29) located over the dermatome C7, and those points (10–17, 20, 21, 24, 25, and 28) located over the dermatome C8 were pooled.

**Statistical analysis.** Data were analyzed with the SPSS statistical package, version 14.0 (SPSS). Results are expressed as mean and 95% CI. The Kolmogorov-Smirnov test was used to analyze the normal distribution of the variables (*c* values greater than 0.05). Quantitative data without a normal distribution (i.e., pain history, pain area, current level of pain, and lowest and worst level of pain in the preceding 24 hours) were analyzed with nonparametric tests, whereas data with a normal distribution (PPT) were analyzed with parametric tests. The ICC was used to assess the intraexaminer reliability of PPT levels. A multilevel (mixed-effect) analysis of variance (ANOVA) was applied to detect differences in PPTs, with side (dominant/nondominant, symptomatic/nonsymptomatic) and assessed points (from 1–30) as within-subject variables and with group (patients or controls) as the between-subject variable. A three-way ANOVA test was used to evaluate the differences in PPTs, with dermatome (C6, C7, and C8) and side (dominant/nondominant, symptomatic/nonsymptomatic) as within-subject factors and with group (patients, controls) as the between-subject factor. Post hoc comparisons were done with the Bonferroni test. Finally,

the Spearman's rank correlation ($r_s$) test was used to analyze the association between PPTs, the clinical variables relating to symptoms, and the scales of the BCTQ. The statistical analysis was conducted at a 95% confidence level and a $P$ value less than 0.05 was considered statistically significant.

## RESULTS

**Demographic and clinical data of the patients.** One hundred two consecutive patients with CTS were screened between March 2008 and March 2009 for possible eligibility criteria. Finally, a total of 20 women ages 32–52 years (mean ± SD 43 ± 4 years) presenting with unilateral CTS satisfied all of the criteria and agreed to participate. The reasons for exclusion were bilateral symptoms (n = 40), fibromyalgia (n = 15), whiplash syndrome (n = 5), previous surgery (n = 14), pregnancy (n = 4), and diabetes mellitus (n = 4). In addition, 20 matched healthy women ages 32–51 years (mean ± SD 43 ± 3 years) without upper extremity symptoms were also included. There were no statistical age differences between cases and controls ($P$ = 0.763). All of the participants were right hand dominant. Fifteen (75%) had their right hand affected and the remaining 5 (25%) had the left hand affected. None of the patients were taking any analgesic drug (antidepressants, γ-aminobutyric acid–ergic medications, or long-acting benzodiazepine) at the time the study was conducted.

The mean ± SD duration of hand pain was 3.4 ± 1.2 years (95% CI 2.4–4.4) and the mean ± SD pain area on the affected hand was 14.3 ± 6.5 $cm^2$ (95% CI 11.3–17.4). The mean ± SD current level of hand pain was 5.6 ± 0.7 (95% CI 5.3–5.9) and the mean ± SD worst level of pain experienced in the preceding week was 7.5 ± 0.8 (95% CI 7.0–7.8), whereas the mean ± SD lowest level of pain in the preceding week was 3.0 ± 0.5 (95% CI 2.7–3.3). The mean ± SD BCTQ functional status scale score was 2.5 ± 0.6 (95% CI 2.2–2.8) and the mean ± SD BCTQ symptom severity scale score was 2.8 ± 0.5 (95% CI 2.6–3.1). A significant positive correlation between duration of pain history and current level of hand pain ($r_s$ = 0.5, $P$ = 0.03) was found. No significant correlation between either scale (functional status or symptom severity) of the BCTQ and clinical pain features was found.

**Pressure pain sensitivity map of the hand.** The intraexaminer repeatability of PPT readings ranged from 0.90–0.93 in patients and from 0.89–0.94 in controls, suggesting high repeatability of the PPT data. The SEM ranged from 5.3–7.2 kPa, depending on the assessed point.

The ANOVA detected significant differences in mean PPTs between groups (F = 95.9, $P < 0.001$), sides (F = 22.1, $P < 0.001$), and between measurement points (F = 13.3, $P < 0.001$). General post hoc comparisons revealed 1) lower PPTs for CTS patients compared with healthy controls in all of the measurement points ($P < 0.001$ for all measurement points) (Table 1); 2) higher PPTs in the affected arm within CTS patients and in the dominant side within controls when compared with the unaffected/nondominant side ($P < 0.01$ for both); and 3) lower PPT levels in points over the proximal phalanx of the fingers ($P < 0.01$ for points 6, 9, 12, and 15) and the thenar eminency ($P < 0.01$ for points 3, 23, 30, and 27) as compared with points located over the distal phalanx of the fingers (points 1, 4, 7, and 10).

In addition, significant interactions between group and point (F = 4.1, $P < 0.001$) and between group × point × side (F = 1.5, $P$ = 0.02) were found. Within the patient group, the affected side showed higher PPTs in points 2 ($P$ = 0.021), 3 ($P$ = 0.019), 6 ($P$ = 0.024), 9 ($P$ = 0.012), 14 ($P$ = 0.016), and 15 ($P$ = 0.028), and lower PPT levels in points 12 ($P$ = 0.031), 17 ($P$ = 0.025), 20 ($P$ = 0.034), and 29 ($P$ = 0.021), compared with the unaffected side (Figure 2). Within the control group, the dominant side showed higher PPTs in points 8 ($P$ = 0.022), 10 ($P$ = 0.017), 11 ($P$ = 0.029), 12 ($P$ = 0.028), 17 ($P$ = 0.020), and 18 ($P$ = 0.028) compared with the nondominant side (Figure 3). Table 2 summarizes PPTs of each point for both sides (symptomatic or nonsymptomatic) within CTS patients, and Table 3 shows PPTs of each point for both sides (dominant or nondominant) within healthy controls.

**Pressure pain sensitivity of C6, C7, and C8 dermatomes.** The ANOVA revealed significant differences between groups (F = 93.1, $P < 0.001$), but not between dermatomes (F = 1.1, $P$ = 0.4), for PPT levels. In such a way, patients with CTS showed lower mean ± SD PPTs ($P < 0.001$ for all) in all dermatomes (C6 affected: 271.4 ± 40.9 kPa, C6 unaffected: 265.5 ± 32.7 kPa; C7 affected: 265.8 ± 28.7 kPa, C7 unaffected: 258.5 ± 30.1 kPa; C8 affected: 266.1 ± 35.2 kPa, C8 unaffected: 262.0 ± 29.5 kPa) when compared with healthy controls (C6 dominant: 430.7 ± 42.2 kPa, C6 nondominant: 429.3 ± 39.7 kPa; C7 dominant: 447.1 ± 39.0 kPa, C7 nondominant: 436.5 ± 37.9 kPa; C8 dominant: 439.7 ± 38.2 kPa, C8 nondominant: 429.9 ± 35.3 kPa), but without differences between dermatomes.

**Pressure sensitivity and clinical features in patients with CTS.** Finally, significant negative correlations between duration of pain symptoms and PPTs were found over points 1, 3, 4, 6, 9, 14, 15, 20, 22, and 30 ($-0.6 < r_s < -0.5$; $P < 0.01$) on the affected side and with PPTs over points 6, 15, 23, and 28 ($-0.7 < r_s < -0.6$; $P < 0.01$) on the unaffected side. In such a way, the longer the duration of pain history, the lower the PPT levels.

In addition, mean pain intensity was also negatively correlated with PPT levels over points 4 ($r_s = -0.7$, $P < 0.001$), 8 ($r_s = -0.45$, $P$ = 0.04), 18 ($r_s = -0.5$, $P$ = 0.01), 27 ($r_s = -0.45$, $P$ = 0.04), and 28 ($r_s = -0.6$, $P$ = 0.007) within the affected side, and with points 4 ($r_s = -0.55$, $P$ = 0.009) and 24 ($r_s = -0.6$, $P$ = 0.006) on the unaffected side. In such a way, the greater the pain intensity, the lower the bilateral PPT levels.

## DISCUSSION

The current study showed the ability of topographical mapping of pressure pain sensitivity to detect bilateral pain hyperalgesia in patients with strictly unilateral CTS as compared with healthy controls. In addition, lower PPT

**Table 1. Mean pressure pain thresholds of both sides over each assessed point in patients with unilateral carpal tunnel syndrome and healthy controls***

| | Mean (95% CI) kPa |
|---|---|
| Point 1 | |
| Patients with CTS | 317.1 (303.1–331.1) |
| Healthy controls | 458.1 (448.1–468.0) |
| Point 2 | |
| Patients with CTS | 278.1 (270.2–285.9) |
| Healthy controls | 429.4 (419.6–439.2) |
| Point 3 | |
| Patients with CTS | 252.5 (241.3–263.6) |
| Healthy controls | 394.1 (380.9–407.4) |
| Point 4 | |
| Patients with CTS | 279.1 (268.8–289.3) |
| Healthy controls | 449.7 (438.8–460.7) |
| Point 5 | |
| Patients with CTS | 263.9 (246.7–261.2) |
| Healthy controls | 442.0 (429.0–454.9) |
| Point 6 | |
| Patients with CTS | 253.9 (243.5–264.2) |
| Healthy controls | 424.7 (411.6–438.0) |
| Point 7 | |
| Patients with CTS | 265.6 (255.7–275.6) |
| Healthy controls | 458.3 (445.0–471.7) |
| Point 8 | |
| Patients with CTS | 260.9 (255.5–266.3) |
| Healthy controls | 448.4 (436.9–460.0) |
| Point 9 | |
| Patients with CTS | 250.1 (238.0–262.3) |
| Healthy controls | 426.3 (414.1–438.5) |
| Point 10 | |
| Patients with CTS | 285.2 (275.7–294.8) |
| Healthy controls | 442.5 (429.4–455.6) |
| Point 11 | |
| Patients with CTS | 269.7 (261.9–277.5) |
| Healthy controls | 444.1 (433.5–454.6) |
| Point 12 | |
| Patients with CTS | 254.6 (243.7–265.4) |
| Healthy controls | 404.2 (391.7–416.6) |
| Point 13 | |
| Patients with CTS | 250.4 (243.7–257.2) |
| Healthy controls | 446.7 (433.4–460.0) |
| Point 14 | |
| Patients with CTS | 268.7 (257.6–279.8) |
| Healthy controls | 428.9 (417.8–440.1) |
| Point 15 | |
| Patients with CTS | 247.9 (236.9–259.0) |
| Healthy controls | 415.4 (402.5–428.4) |
| Point 16 | |
| Patients with CTS | 268.4 (258.8–278.1) |
| Healthy controls | 436.1 (425.6–446.5) |
| Point 17 | |
| Patients with CTS | 243.4 (233.5–253.3) |
| Healthy controls | 433.5 (424.2–442.7) |
| Point 18 | |
| Patients with CTS | 266.4 (256.9–275.9) |
| Healthy controls | 440.8 (433.2–448.4) |
| Point 19 | |
| Patients with CTS | 274.1 (267.3–281.0) |
| Healthy controls | 444.0 (434.1–453.9) |
| Point 20 | |
| Patients with CTS | 255.2 (245.7–264.7) |
| Healthy controls | 433.6 (423.5–443.7) |
| Point 21 | |
| Patients with CTS | 260.0 (251.0–269.2) |
| Healthy controls | 433.7 (422.5–444.9) |
| Point 22 | |
| Patients with CTS | 251.5 (243.8–259.4) |
| Healthy controls | 424.6 (410.7–438.5) |
| Point 23 | |
| Patients with CTS | 256.0 (245.9–266.0) |
| Healthy controls | 413.7 (399.1–428.4) |
| Point 24 | |
| Patients with CTS | 266.7 (258.7–274.6) |
| Healthy controls | 442.2 (430.6–453.8) |
| Point 25 | |
| Patients with CTS | 282.9 (272.2–293.7) |
| Healthy controls | 454.9 (445.5–464.2) |
| Point 26 | |
| Patients with CTS | 265.4 (255.7–275.1) |
| Healthy controls | 431.1 (420.7–441.5) |
| Point 27 | |
| Patients with CTS | 268.6 (256.4–280.8) |
| Healthy controls | 413.1 (402.8–423.3) |
| Point 28 | |
| Patients with CTS | 279.0 (268.5–289.4) |
| Healthy controls | 436.5 (426.6–446.5) |
| Point 29 | |
| Patients with CTS | 275.1 (266.7–283.4) |
| Healthy controls | 463.0 (451.5–474.4) |
| Point 30 | |
| Patients with CTS | 251.4 (241.2–261.6) |
| Healthy controls | 431.2 (419.1–443.4) |

(continued)

**Table 1. *(Cont'd)***

* 95% CI = 95% confidence interval; CTS = carpal tunnel syndrome.

levels were found at distant points, supporting the hypothesis of central sensitization in CTS. Importantly, the decrease in PPTs was associated with the intensity and the duration of the pain symptoms, supporting a role of the peripheral input in driving the central sensitization in CTS.

The bilateral hyperalgesia found in both hands in patients with strictly unilateral CTS suggests a generalized pressure hyperalgesia. In addition, we also found higher PPTs within the affected arm of the patients and within the dominant side in controls, which most likely reflect a side-to-side dominance of pressure pain sensitivity. Furthermore, higher PPT values at the symptomatic hand in patients with CTS may be related to sensory disturbances related to the symptomatic region, since these patients usually experience hypoesthesia or paresthesia. Nevertheless, despite side dominance, patients with unilateral CTS showed bilateral pressure hyperalgesia as compared with controls.

In fact, the generalized pressure hyperalgesia was supported by the fact that the PPT was not significantly different between dermatomes (C6, C7, or C8), in line with recent results obtained in osteoarthritis patients (43) suggesting that mechanical sensitivity is not related to particular sensitized segments. Our results disagree with those previously found by Li et al (26), who demonstrated that

**Table 2. Pressure pain thresholds of each assessed point in either the affected or nonaffected hand in patients with unilateral carpal tunnel syndrome**

| | Mean (95% confidence interval) kPa |
|---|---|
| Point 1 | |
| Symptomatic side | 326.3 (302.5–350.1) |
| Nonsymptomatic side | 307.8 (291.8–323.9) |
| Point 2 | |
| Symptomatic side | 290.5 (279.2–301.9) |
| Nonsymptomatic side | 265.5 (257.1–274.0) |
| Point 3 | |
| Symptomatic side | 264.4 (245.1–283.7) |
| Nonsymptomatic side | 240.5 (230.3–250.8) |
| Point 4 | |
| Symptomatic side | 282.7 (266.3–299.2) |
| Nonsymptomatic side | 275.4 (261.8–289.0) |
| Point 5 | |
| Symptomatic side | 248.7 (238.1–259.4) |
| Nonsymptomatic side | 259.2 (249.1–269.2) |
| Point 6 | |
| Symptomatic side | 262.5 (245.4–279.5) |
| Nonsymptomatic side | 245.3 (233.2–257.4) |
| Point 7 | |
| Symptomatic side | 272.1 (257.6–286.7) |
| Nonsymptomatic side | 259.2 (244.8–273.4) |
| Point 8 | |
| Symptomatic side | 264.0 (256.8–271.3) |
| Nonsymptomatic side | 257.8 (249.3–266.3) |
| Point 9 | |
| Symptomatic side | 263.3 (241.9–284.6) |
| Nonsymptomatic side | 236.9 (226.1–247.7) |
| Point 10 | |
| Symptomatic side | 292.9 (277.7–308.0) |
| Nonsymptomatic side | 277.6 (265.7–289.5) |
| Point 11 | |
| Symptomatic side | 274.8 (261.7–287.9) |
| Nonsymptomatic side | 264.6 (255.5–273.8) |
| Point 12 | |
| Symptomatic side | 246.0 (227.9–264.0) |
| Nonsymptomatic side | 263.2 (250.5–275.9) |
| Point 13 | |
| Symptomatic side | 256.7 (247.8–265.7) |
| Nonsymptomatic side | 244.2 (234.1–254.2) |
| Point 14 | |
| Symptomatic side | 281.2 (261.7–300.8) |
| Nonsymptomatic side | 256.2 (247.0–265.4) |
| Point 15 | |
| Symptomatic side | 255.6 (237.4–273.8) |
| Nonsymptomatic side | 240.3 (226.9–253.7) |
| Point 16 | |
| Symptomatic side | 274.6 (260.7–288.4) |
| Nonsymptomatic side | 262.3 (248.2–276.4) |
| Point 17 | |
| Symptomatic side | 230.5 (222.2–238.7) |
| Nonsymptomatic side | 256.3 (239.4–273.2) |
| Point 18 | |
| Symptomatic side | 268.4 (257.0–279.8) |
| Nonsymptomatic side | 264.4 (248.1–280.7) |
| Point 19 | |
| Symptomatic side | 276.2 (268.2–284.0) |
| Nonsymptomatic side | 272.2 (260.2–284.1) |
| Point 20 | |
| Symptomatic side | 245.2 (233.3–257.1) |
| Nonsymptomatic side | 265.3 (250.8–279.7) |
| Point 21 | |
| Symptomatic side | 267.6 (256.3–279.0) |
| Nonsymptomatic side | 252.5 (238.1–266.9) |
| Point 22 | |
| Symptomatic side | 255.7 (245.3–266.2) |
| Nonsymptomatic side | 247.4 (235.1–259.6) |
| Point 23 | |
| Symptomatic side | 252.4 (236.2–268.6) |
| Nonsymptomatic side | 259.6 (246.4–272.8) |
| Point 24 | |
| Symptomatic side | 269.0 (255.7–282.4) |
| Nonsymptomatic side | 264.3 (254.5–274.2) |
| Point 25 | |
| Symptomatic side | 290.7 (273.9–307.5) |
| Nonsymptomatic side | 275.2 (261.2–289.3) |
| Point 26 | |
| Symptomatic side | 270.7 (257.6–283.8) |
| Nonsymptomatic side | 260.0 (245.1–275.0) |
| Point 27 | |
| Symptomatic side | 264.7 (244.5–285.0) |
| Nonsymptomatic side | 272.5 (257.0–288.0) |
| Point 28 | |
| Symptomatic side | 274.2 (258.6–289.7) |
| Nonsymptomatic side | 283.7 (268.7–298.8) |
| Point 29 | |
| Symptomatic side | 266.5 (254.3–278.7) |
| Nonsymptomatic side | 283.7 (272.4–295.0) |
| Point 30 | |
| Symptomatic side | 245.7 (233.4–257.9) |
| Nonsymptomatic side | 257.1 (240.0–274.2) |

thermal sensitivities were not uniformly distributed within hand dermatomes, with C7 being more sensitive than C8 to cold stimulation. It is known that the size of the stimulated skin area, the skin thickness, and the thermoreceptive density of nociceptive receptors may be factors affecting thermal sensations. It may be that hand dermatomes may have differences in the density of thermoreceptive nociceptors, explaining the differences in cold stimulation. Nevertheless, the results of the current study do not show the same distribution for mechanical pain nociceptors since PPTs showed no significant difference between dermatomes, arguing for pain modality specificity.

Pressure pain hyperalgesia has been found to be related to specific anatomic locations, e.g., muscle belly versus musculotendinous junctions. Nie et al have reported that muscle belly locations had greater pressure pain hyperalgesia when compared with musculotendinous junctions in the upper trapezius muscle (25). Spatial differences in mechanical pain sensitivity can be explained by the fact that belly sites have greater thickness than musculotendinous ones (44). In parallel, underlying bone structures in the musculotendinous junctions can provide increased tissue hardness, resulting in generally higher PPT levels than those seen in muscle belly. Furthermore, differences in the

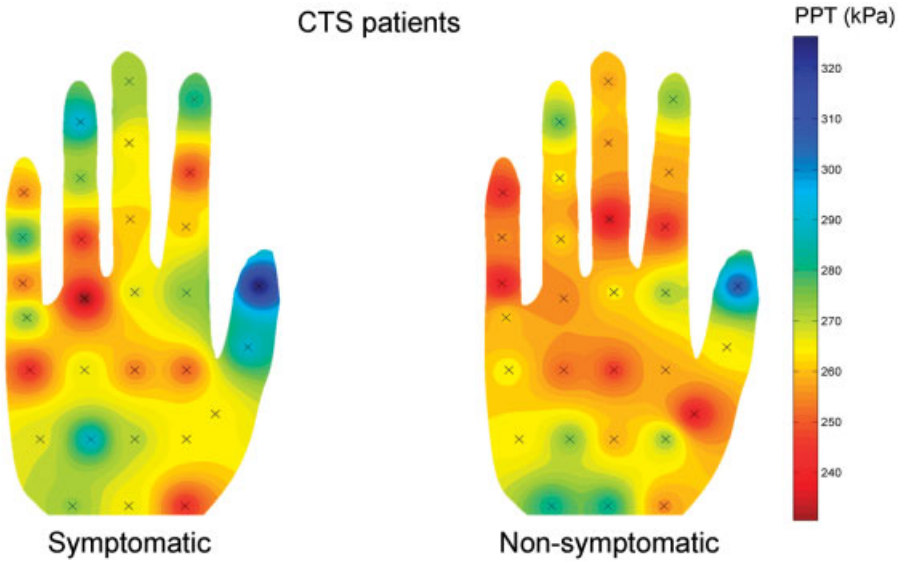


**Figure 2.** Average pressure pain threshold (PPT) maps for patients with unilateral carpal tunnel syndrome (CTS). × shows the measured points.

density of group III and IV afferents among musculotendinous junctions and muscle belly (45) and different concentrations of inflammatory mediators such as neuropeptides, cytokines, and catecholamines (46) can also explain these differences in PPTs. We should also consider that the area of the algometer probe used in the present study was 1 $cm^2$. PPTs are reported to decrease when the probe area is increasing from 0.5–2 $cm^2$ (47). Therefore, changes in the probe area would also result in changes in the spatial summation of pressure pain due to potential overlap between pressure-sensitive receptive fields of the palm of the hand. Further studies are needed to delineate the effects of probe size in PPT topographical maps in both healthy and patient populations.

Our results demonstrated that pressure hyperalgesia is not uniformly distributed over the palm of the hand since PPTs were lower in points over the proximal phalanx of the fingers and the thenar eminency as compared with those points located over the distal phalanx of the fingers in both patients and controls. Lower PPT levels over the thenar eminency are expected since this region houses the muscles of the thumb. Additionally, it was also expected that the distal phalanx of the finger would have lower pressure hyperalgesia, since it is usually seen in clinical practice that distal points are less hypersensible to pain than proximal points.

Because pressure pain sensitivity is not uniformly distributed over the palm of the hand in both patients with CTS and controls, anatomic locations should be precisely determined for pressure sensitivity examinations in clinical and research applications.

Our results argue for further evidence of both peripheral

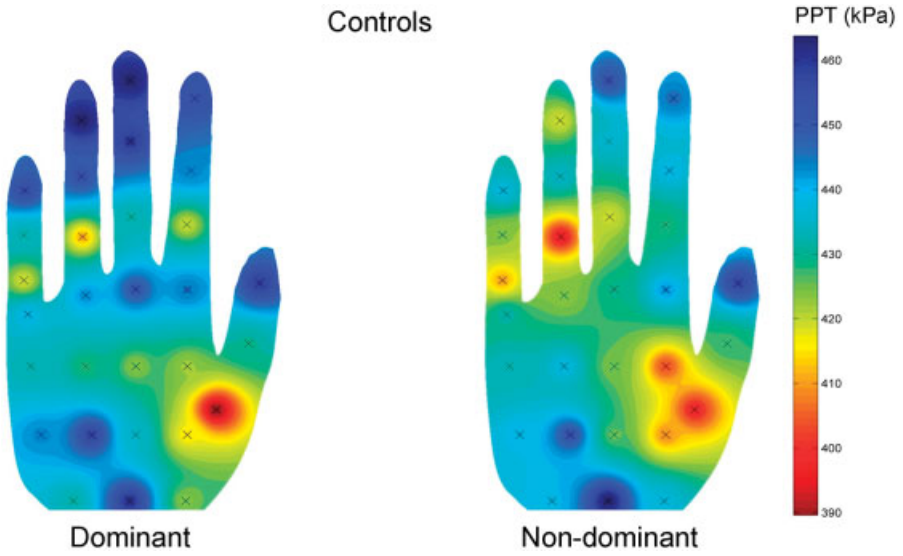


**Figure 3.** Average pressure pain threshold (PPT) maps for healthy control subjects. × shows the measured points.

**Table 3. Pressure pain thresholds of each assessed point in either the dominant or nondominant hand in healthy subjects**

| | Mean (95% confidence interval) kPa |
|---|---|
| Point 1 | |
| Dominant side | 459.2 (445.8–472.5) |
| Nondominant side | 456.9 (440.8–473.0) |
| Point 2 | |
| Dominant side | 431.0 (422.3–439.7) |
| Nondominant side | 427.7 (409.2–446.3) |
| Point 3 | |
| Dominant side | 389.5 (368.0–411.1) |
| Nondominant side | 398.7 (381.4–416.0) |
| Point 4 | |
| Dominant side | 453.6 (434.5–472.6) |
| Nondominant side | 445.9 (433.3–458.5) |
| Point 5 | |
| Dominant side | 444.3 (424.5–464.1) |
| Nondominant side | 439.6 (420.9–458.3) |
| Point 6 | |
| Dominant side | 420.5 (404.7–436.4) |
| Nondominant side | 429.0 (406.5–451.5) |
| Point 7 | |
| Dominant side | 464.6 (443.7–485.5) |
| Nondominant side | 452.1 (433.8–470.4) |
| Point 8 | |
| Dominant side | 459.9 (442.2–477.6) |
| Nondominant side | 436.9 (422.4–451.5) |
| Point 9 | |
| Dominant side | 432.8 (415.6–449.9) |
| Nondominant side | 419.8 (401.2–438.3) |
| Point 10 | |
| Dominant side | 465.3 (444.6–486.1) |
| Nondominant side | 419.8 (410.5–429.1) |
| Point 11 | |
| Dominant side | 452.6 (437.6–467.6) |
| Nondominant side | 435.5 (420.4–450.6) |
| Point 12 | |
| Dominant side | 411.7 (392.4–431.0) |
| Nondominant side | 396.7 (379.8–413.5) |
| Point 13 | |
| Dominant side | 454.7 (433.9–475.5) |
| Nondominant side | 438.7 (421.0–456.4) |
| Point 14 | |
| Dominant side | 433.9 (419.6–448.2) |
| Nondominant side | 423.9 (405.8–442.1) |
| Point 15 | |
| Dominant side | 419.5 (398.8–440.2) |
| Nondominant side | 411.4 (393.7–428.8) |
| Point 16 | |
| Dominant side | 439.8 (425.9–453.7) |
| Nondominant side | 432.3 (415.6–449.1) |
| Point 17 | |
| Dominant side | 443.0 (434.2–451.7) |
| Nondominant side | 424.0 (407.9–440.1) |
| Point 18 | |
| Dominant side | 451.4 (442.4–460.4) |
| Nondominant side | 430.1 (419.1–441.1) |
| Point 19 | |
| Dominant side | 445.5 (432.9–458.1) |
| Nondominant side | 442.6 (426.1–459.1) |
| Point 20 | |
| Dominant side | 432.9 (415.6–450.2) |
| Nondominant side | 434.4 (422.1–446.7) |
| Point 21 | |
| Dominant side | 428.4 (410.4–446.3) |
| Nondominant side | 439.1 (424.4–453.8) |
| Point 22 | |
| Dominant side | 424.3 (404.4–444.1) |
| Nondominant side | 425.1 (403.7–446.4) |
| Point 23 | |
| Dominant side | 423.1 (397.8–448.3) |
| Nondominant side | 404.4 (388.2–420.7) |
| Point 24 | |
| Dominant side | 444.2 (427.3–461.0) |
| Nondominant side | 440.3 (422.7–457.9) |
| Point 25 | |
| Dominant side | 457.5 (442.9–471.9) |
| Nondominant side | 452.3 (439.3–465.4) |
| Point 26 | |
| Dominant side | 436.0 (421.5–450.5) |
| Nondominant side | 426.2 (410.3–442.1) |
| Point 27 | |
| Dominant side | 416.3 (399.4–433.1) |
| Nondominant side | 409.9 (396.8–423.0) |
| Point 28 | |
| Dominant side | 432.7 (417.8–447.7) |
| Nondominant side | 440.3 (426.0–454.7) |
| Point 29 | |
| Dominant side | 460.9 (441.8–480.0) |
| Nondominant side | 465.1 (450.6–479.5) |
| Point 30 | |
| Dominant side | 424.5 (404.5–444.5) |
| Nondominant side | 438.0 (423.0–453.0) |

and central sensitization mechanisms in CTS patients, since bilateral and generalized pressure pain hyperalgesia were found in patients experiencing unilateral symptoms. In fact, the involvements of peripheral and central sensitization mechanisms have also been reported in several local pain syndromes, e.g., work-related disorders (14,15), tension-type headache (16,17), low back pain (18), osteoarthritis (19), lateral epicondylalgia (20), or unilateral shoulder pain (24). This clinical evidence agrees with findings in animal models where unilateral localized musculoskeletal pain causes segmental sensitization of contralateral areas (48), which may explain our bilateral hyperalgesia in the unaffected hand. It is hypothesized that the presence of sensitization mechanisms in local pain syndromes suggests that sustained peripheral noxious input to the central nervous system can play a role in the initiation and maintenance of these sensitization mechanisms. In fact, in our study we found that the decrease in PPTs was associated with the intensity and the duration of the pain symptoms, supporting an interaction between peripheral and central sensitization mechanisms. Therefore, in patients with CTS, the compression of the median nerve in the carpal tunnel may act as a trigger factor for establishing a neurogenic inflammation on its nervi nervo-

rum (49,50), and therefore initiate different potent sensitization mechanisms.

Finally, we should recognize the limitations of this study. First, we only included women with mild to moderate CTS and with strictly unilateral symptoms. Previous studies have shown that women have a less efficient pain habituation and a greater susceptibility to the development of temporal summation of mechanically evoked pain (51) than men. Population-based epidemiologic studies with greater sample sizes including both men and women are needed to permit a more generalized interpretation of these results. Furthermore, pressure pain sensitivity can be influenced by psychological status (depression or anxiety), although this is unlikely because in the current study, patients with depression status were excluded (>8 points on the BDI-II). In addition, it is also possible that beliefs related to possible interventions (e.g., physical therapy) could influence the pressure-sensitive heterogeneity, although this is unlikely since all of the patients had never received treatment. Finally, it would be interesting to assess topographical pressure sensitivity maps in dermatomes innervated by spinal segments above or below those dedicated to the median nerve, i.e., the shoulder region (C5 nerve root), to confirm the presence of central sensitization in this patient population.

In conclusion, topographical mapping of pressure pain sensitivity in patients with strictly unilateral CTS showed significant generalized hyperalgesia. In addition, extrasegmental sites to the median nerve also showed hyperalgesia in patients with strictly unilateral symptoms, indicating sensitization. Furthermore, the hyperalgesia was associated with the intensity and the duration of the pain symptoms, supporting a role of the peripheral input to drive the central sensitization in CTS.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Fernández-de-las-Peñas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Fernández-de-las-Peñas, Madeleine, Martínez-Perez, Arendt-Nielsen, Jiménez-García, Pareja.

**Acquisition of data.** Fernández-de-las-Peñas, Madeleine, Martínez-Perez, Arendt-Nielsen, Jiménez-García, Pareja.

**Analysis and interpretation of data.** Fernández-de-las-Peñas, Madeleine, Martínez-Perez, Arendt-Nielsen, Jiménez-García, Pareja.

## REFERENCES


1. Lang E, Claus D, Neundorfer B, Handwerker H. Parameters of thick and thin nerve-fiber functions as predictors of pain in carpal tunnel syndrome. Pain 1995;60:295–302.
2. Arendt-Nielsen L, Gregersen H, Toft E, Bjerring P. Involvement of thin afferents in carpal tunnel syndrome: evaluated quantitatively by argon laser stimulation. Muscle Nerve 1991; 14:508–14.
3. Westerman RA, Delaney CA. Palmar cold threshold test and median nerve electromyography in carpal tunnel compression neuropathy. Clin Exp Neurol 1991;28:154–67.
4. Goadsby P, Burke D. Deficit in the function of small and large afferent fibers in confirmed cases of carpal tunnel syndrome. Muscle Nerve 1994;17:614–22.
5. Zanette G, Marani S, Tamburin S. Proximal pain in patients with carpal tunnel syndrome: a clinical-neurophysiological study. J Peripher Nerv Syst 2007;12:91–7.
6. Zanette G, Marani S, Tamburin S. Extra-median spread of sensory symptoms in carpal tunnel syndrome suggests the presence of pain-related mechanisms. Pain 2006;122:264–70.
7. Tucker AT, White PD, Kosek E, Pearson RM, Henderson M, Coldrick AR, et al. Comparison of vibration perception thresholds in individuals with diffuse upper limb pain and carpal tunnel syndrome. Pain 2007;127:263–9.
8. Tecchio F, Padua L, Aprile I, Rossini PM. Carpal tunnel syndrome modifies sensory hand cortical somatotopy: a MEG study. Hum Brain Mapp 2002;17:28–36.
9. Napadow V, Kettner N, Ryan A, Kwong KK, Audette J, Hui KK. Somatosensory cortical plasticity in carpal tunnel syndrome: a cross-sectional fMRI evaluation. Neuroimage 2006;31:520–30.
10. Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC. Gender differences in pressure pain threshold in healthy humans. Pain 2003;101:259–66.
11. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and associated with poor recovery. Pain 2003;104:509–17.
12. Scott D, Jull G, Sterling M. Widespread sensory hypersensitivity is a feature of chronic whiplash-associated disorder but not chronic idiopathic neck pain. Clin J Pain 2005;21:175–81.
13. Desmeules JA, Cedraschi G, Rapiti E, Baumgartner E, Finckh A, Cohen P, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum 2003;48:1420–9.
14. Madeleine P, Lundager B, Voigt M, Arendt-Nielsen L. Sensory manifestations in experimental and work-related chronic neck-shoulder pain. Eur J Pain 1998;2:251–60.
15. Greening J, Lynn B. Vibration sense in the upper limb in patients with repetitive strain injury and a group of at-risk office workers. Int Arch Occup Environ Health 1998;71:29–34.
16. Fernandez-de-las-Penas C, Cuadrado ML, Ge HY, Arendt-Nielsen L, Pareja JA. Increased pericranial tenderness, decreased pressure pain threshold and headache clinical parameters in chronic tension type headache patients. Clin Pain 2007;23:346–52.
17. Fernandez-de-las-Penas C, Coppieters MW, Cuadrado ML, Pareja JA. Patients with chronic tension type headache demonstrate increased mechano-sensitivity of the supra-orbital nerve. Headache 2008;48:570–7.
18. O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. Eur J Pain 2007;11:415–20.
19. Bajaj P, Bajaj P, Graven-Nielsen T, Arendt-Nielsen L. Osteoarthritis and its association with muscle hyperalgesia: an experimental controlled study. Pain 2001;93:107–14.
20. Fernandez-Carnero J, Fernandez-de-las-Penas C, de la Llave-Rincon AI, Ge HY, Arendt-Nielsen L. Widespread mechanical pain hypersensitivity as sign of central sensitization in unilateral lateral epicondylalgia: a blinded, controlled study. Clin J Pain 2009;25:555–61.
21. Fernandez-de-las-Penas C, de la Llave-Rincon AI, Fernandez-Carnero J, Cuadrado ML, Arendt-Nielsen L, Pareja JA. Bilateral widespread mechanical pain sensitivity in carpal tunnel syndrome: evidence of central processing in unilateral neuropathy. Brain 2009;132:1472–9.
22. Fernandez-de-las-Penas C, Ge HY, Cuadrado ML, Madeleine P, Pareja JA, Arendt-Nielsen L. Bilateral pressure pain sensitivity mapping of the temporalis muscle in chronic tension type headache. Headache 2008;48:1067–75.
23. Fernandez-de-las-Penas C, Madeleine P, Cuadrado ML, Ge HY, Arendt-Nielsen L, Pareja JA. Pressure pain sensitivity mapping of the temporalis muscle revealed bilateral pressure hyperalgesia in patients with strictly unilateral migraine. Cephalalgia 2009;29:670–6.
24. Ge HY, Fernandez-de-las-Penas C, Madeleine P, Arendt-

Nielsen L. Topographical mapping and mechanical pain sensitivity of myofascial trigger points in the infraspinatus muscle. Eur J Pain 2008;12:859–65.
25. Nie H, Kawczynski A, Madeleine P, Arendt-Nielsen L. Delayed onset muscle soreness in neck/shoulder muscles. Eur J Pain 2005;9:653–60.
26. Li X, Petrini L, Defrin R, Madeleine P, Arendt-Nielsen L. High resolution topographical mapping of warm and cold sensitivities. Clin Neurophysiol 2008;19:2641–6.
27. Chan L, Turner JA, Comstocl BA, Levenson LM, Hollingworth W, Heagerty P, et al. The relationship between electrodiagnostic findings and patient symptoms and function in carpal tunnel syndrome. Arch Phys Med Rehabil 2007;88:19–24.
28. Padua L, Padua R, Nazzaro M, Tonali P. Incidence of bilateral symptoms in carpal tunnel syndrome. J Hand Surg Br 1998; 23:603–6.
29. American Association of Electrodiagnostic Medicine, American Academy of Neurology, American Academy of Physical Medicine and Rehabilitation. Practice parameter for electrodiagnostic studies in ulnar neuropathy at the elbow: summary statement. Muscle Nerve 1999;22:S141–67.
30. American Association of Electrodiagnostic Medicine, American Academy of Neurology, American Academy of Physical Medicine and Rehabilitation. Practice parameter: electrodiagnostic studies in carpal tunnel syndrome. Neurology 2002;58:1589–92.
31. Beck AT, Steer RA, Brown GK. Beck Depression Inventory. 2nd ed. San Antonio (TX): Psychological Corporation; 1996.
32. Jensen MP, Turbner JA, Romano JM, Fisher L. Comparative reliability and validity of chronic pain intensity measures. Pain 1999;83:157–62.
33. Katz JN, Stirrat CR. A self-administered hand diagram for the diagnosis of carpal tunnel syndrome. J Hand Surg Am 1990; 15:360–3.
34. Rosales RS, Benseny E, Diez de la Lastra-Bosch I. Evaluation of the Spanish version of the DASH and carpal tunnel syndrome health-related quality of life instruments: cross cultural adaptation process and reliability. J Hand Surg 2002; 27A:334–43.
35. Levine DW, Simmons B, Koris M, Daltroy L, Hohl G, Fossel A, et al. A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. J Bone Joint Surg Am 1993;75:1585–92.
36. De Carvalho Leite JC, Jerosch-Herold C, Song F. A systematic review of the psychometric properties of the Boston Carpal Tunnel Questionnaire. BMC Musculoskelet Disord 2006;7:78.
37. Prushansky T, Dvir Z, Defron-Assa R. Reproducibility indices applied to cervical pressure pain threshold measurements in healthy subjects. Clin J Pain 2004;20:341–7.
38. Vanderweeen L, Oostendorp RA, Vaes P, Duquet W. Pressure algometry in manual therapy. Man Ther 1996;1:258–65.
39. Chesterson LS, Sim J, Wright CC, Foster NE. Inter-rater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. Clin J Pain 2007;23: 760–6.
40. Shepard D. A two-dimensional interpolation function for irregularly-spaced data. In: Proceedings of the 23rd Association for Computing Machinery (ACM) national conference; 1968 Aug 27–29. p. 517–24.
41. Binderup AT, Arendt-Nielsen L, Madeleine P. Pressure pain threshold mapping: a new imaging modality of muscle sensitivity to pain. IEEE Student Branch 2008:4s.
42. Binderup AT, Arendt-Nielsen L, Madeleine P. Pressure pain threshold mapping of the trapezius muscle reveals heterogeneity in the distribution of muscular hyperalgesia after eccentric exercise. Eur J Pain 2009. E-pub ahead of print.
43. Imamura M, Imamura ST, Kaziyama HH, Targino RA, Hsing WT, de Souza LP, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. Arthritis Rheum 2008;59: 1424–31.
44. Andersen H, Arendt-Nielsen L, Daneskiold-Sansoe B, Graven-Nielsen T. Pressure pain sensitivity and hardness along human normal and sensitized muscle. Somatosens Mot Res 2006;23:97–109.
45. Andres KH, von During M, Schmidt RF. Sensory innervation of the Achilles tendon by group III and IV afferent fibers. Anat Embryol (Berl) 1985;172:145–56.
46. Shah JP, Danoff JV, Desai MJ, Parikh S, Nakamura LY, Phillips TM, et al. Biochemicals associated with pain and inflammation are elevated in sites near to and remote from active myofascial trigger points. Arch Phys Med Rehabil 2008;89: 16–23.
47. Defrin R, Ronat A, Ravid A, Peretz C. Spatial summation of pressure pain: effect of body region. Pain 2003;106:471–80.
48. Sluka KA, Kalra A, Moore SA. Unilateral intramuscular injections of acidic saline produce a bilateral, long-lasting hyperalgesia. Muscle Nerve 2001;24:37–46.
49. Bove G, Light A. The nervi nervorum: missing link for neuropathic pain? Pain Forum 1997;6:181–90.
50. Watkins L, Maier S. Neuropathic pain: the immune connection. Pain Clin Updated 2004;13:1–4.
51. Sarlani E, Greenspan JD. Gender differences in temporal summation of mechanically evoked pain. Pain 2002;97:163–9.