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Title Page

Perceived Pain Extent is not associated with Physical, Psychological or Psychophysical Outcomes in Women with Carpal Tunnel Syndrome

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Abstract

Objective: Our aims were; 1, to investigate whether perceived pain extent, assessed from the pain drawing, relates to clinical, psychological and psychophysical outcomes in women with CTS; 2, to assess differences in pain extent depending on the presence of median or extra-median symptoms; and, 3, to investigate differences in pain extent according to severity (minimal, moderate or severe) or laterality (unilateral or bilateral) of CTS.

Methods: One hundred and forty (n=140) women with CTS completed pain drawings which were subsequently digitized allowing pain extent to be calculated. Clinical features including pain intensity (Numerical Pain Rating Scale, 0-10) and disability (Boston Carpal Tunnel Questionnaire), psychological features including depression (Beck Depression Inventory-BDI), and psychophysical (pressure pain and thermal pain thresholds) variables were assessed. Spearman rho correlation coefficients were used to reveal the correlations between pain extent and other outcomes. Differences in pain extent according to severity (minimal, moderate, severe) or laterality (unilateral, bilateral), and the presence of extra-median symptoms were also evaluated.

Results: No significant associations were identified between pain extent and clinical, psychological or psychophysical outcomes. Women with extra-median symptoms (88%) exhibited larger ($P<.001$) pain extent (total: 24.2±13.5%) than those women with median symptoms (12%, total: 12.2±6.9%). Pain extent was not significantly different depending on the severity or laterality of the symptoms.

Conclusions: Pain extent in the upper extremity was not associated with clinical, psychological or psychophysical variables and was not related to the severity or laterality of the symptoms in women with CTS.

Key words: carpal tunnel syndrome, pain area, pressure pain, sensitization.

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Introduction

Carpal tunnel syndrome (CTS) is the most common nerve entrapment of the upper extremity with a prevalence rate ranging from 6.3% to 11.7% depending on the diagnostic criteria applied (1). Women are more frequently affected by CTS than men (ratio 2:1) (2). The societal burden of CTS is substantial since patients often take time off from their work (3). The overall cost associated with CTS in the United States of America alone exceeds $2 billion annually (4).

Although CTS is traditionally considered as a peripheral neuropathy of the median nerve at the carpal tunnel, increasing evidence suggests that CTS is a heterogeneous pain disorder involving central and peripheral sensitization mechanisms (5). Some studies have reported that women with CTS exhibit widespread pressure pain hypersensitivity (6), bilateral thermal pain hyperalgesia (7), and enhanced wind-up in extra-median nerve territories (8) as manifestations of altered nociceptive processing. These sensory deficits are not associated with electrodiagnostic findings suggesting that sensitization is not related to the damage of the median nerve but rather can be present from the onset of the condition (9). A recent study confirming the hypothesis of altered central pain processing in CTS has shown that patients not only exhibit increased pain facilitation but that they also have reduced endogenous pain inhibition (10). Nevertheless, other studies have not found widespread sensory changes in patients with CTS without concomitant neck pain suggesting that there might be subgroups of subjects with CTS with varying levels of sensitivity (11). This hypothesis was supported by a recent study identifying a subgroup of women with CTS exhibiting higher pain sensitivity (12).

Pain drawings capture a graphic representation of the location and distribution of symptoms in people with pain by asking them to draw where they perceive their pain on a body chart. It is accepted that an expanded distribution of pain represents a clinical sign of central sensitization (13). In fact, some studies have reported the presence of pain spreading to extra-median areas (14) and to the upper extremity (15) as a potential manifestation of central sensitization in patients with CTS. Importantly, spreading of pain symptoms is not associated with the results of nerve conduction studies (16).

There is preliminary evidence suggesting that enlarged pain areas are associated with more severe pain, higher pressure pain hypersensitivity, higher disability or poorer psychological health in different chronic pain conditions such as painful knee osteoarthritis (17,18), whiplash-associated disorders (19) and fibromyalgia (20). Pain drawings may also assist clinicians in identifying people with CTS exhibiting higher pain sensitivity or more severe clinical features. Zanette et al found that subjects with CTS suffering from extra-median distribution of the symptoms reported higher pain intensity (14); however, this study did not investigate the size of the painful area nor the presence of concomitant symptoms in the upper extremity. No previous study has investigated if the size of the painful area (i.e. pain extent) is associated with clinical, psychological and psychophysiological outcomes in CTS. Thus, the aims of this study were: 1, to examine whether pain extent, extracted from pain drawings, was associated with clinical features, depression, widespread pressure pain hypersensitivity, or thermal pain hyperalgesia in women with CTS; 2, to determine the presence of median and extra-median symptoms from the pain drawings and to investigate the differences in pain extent between individuals with median or extra-median symptoms; and, 3, to investigate the differences in pain extent according to severity (minimal, moderate, severe) or laterality (unilateral or bilateral) of CTS.

Methods

Participants

Women with signs and symptoms compatible with CTS presenting at a local regional Hospital in Madrid (Spain) were screened for eligibility criteria (21). To be eligible, patients had to exhibit both clinical and electrophysiological findings of CTS including pain and paresthesia in the median nerve distribution, increasing symptoms during the night, and both a positive Tinel sign and positive Phalen sign. The electro-diagnostic examination had to reveal deficits of sensory and motor median nerve conduction according to the American Association of Electrodiagnosis (AAEM), the American Academy of Neurology (AAN), and the American Physical Medicine and Rehabilitation Academy (AAPM&R) guideline (22). Specifically, findings from the exam that were needed to confirm the diagnosis included: 1. median nerve distal sensory latency of the index finger (>3.60 ms) and/or 2. median nerve distal motor latency (> 4.20 ms). Sensory and motor conduction studies of the radial and ulnar nerves were also conducted to exclude multiple neuropathy. Patients were classified as minimal, moderate or severe CTS according to international guidelines (22).

Individuals were excluded if they exhibited any of the following criteria: 1. motor or sensory deficits in the ulnar or radial nerves; 2. older than 65 years; 3. previous surgery or steroid injections in the hand; 4. multiple diagnoses on the upper extremity (e.g., cervical radiculopathy); 5. cervical, shoulder, or upper extremity previous trauma; 6. any systemic disease causing CTS (e.g. diabetes mellitus, thyroid disease); 7. diagnosis of fibromyalgia syndrome; 8. pregnancy; or, 9. male gender. All participants signed the informed consent prior to their inclusion in the study. The local human research committee (PI01223-HUFA12/14) approved the study which was conducted according to the declaration of Helsinki.

Pain Drawings

All participants were instructed to complete a pain drawing indicating their pain location and extent on four different paper body charts of the hand and upper extremity: one reporting a palmar view of hand, one reporting a dorsal view of hand, one reporting a frontal view of the upper extremity and the last one reporting a dorsal view of the upper extremity. The four body charts were printed on an A4 sheet and participants were instructed to colour, using a pencil, every part of the body chart where they perceived pain symptoms. Participants were asked to report the pain that they usually experienced. Subsequently pain drawings on the paper body charts were copied onto a digital body chart by 2 trained operators using an image analysis software (Inkscape version 0.91). This procedure for digitizing pain drawings has shown high reliability (23,24). Pain extent was then computed using custom software developed with Matlab® and previously tested (25). The software calculates the amount of the pixels included on each pain drawing and any pain drawn outside of the body chart borders was not included in the analysis. Calculations were based on the number of pixels resulting from the size of the palmar and the dorsal view of the hand (palmar hand: 47175 pixels, dorsal hand: 41105 pixels) and the size of the frontal and the dorsal view of the upper extremity (frontal arm: 9980 pixels, dorsal arm: 10228 pixels) separately. Pain extent was expressed as the percentage of the total body chart area where the patient experienced pain (number of pixels with pain / total of pixels of the anatomical area x 100). Pain frequency maps were generated for the four different body charts bilaterally to illustrate where pain was most frequently perceived in the enrolled patients. Pain frequency maps were hence obtained by superimposing all the pain drawings performed on the same body chart from all participants.

Pain drawings involving the thumb (with or without the thenar eminence), index, and middle fingers (either palm or dorsum) were considered as median distribution; whereas symptoms involving the little and/or the ring finger were considered as an extra-median distribution. Further, any pain drawn including the upper extremity, excluding the hand, was considered as extra-median distribution.

Self-reported Clinical Measures

A 10-cm Numerical Pain Rating Scale (26) (NPRS; 0: no pain, 10: maximum pain) was used to assess the average intensity of hand pain, and worst and lowest level of hand pain experienced in the preceding week. The Spanish validated version (27) of the Boston Carpal Tunnel Questionnaire (28) (BCTQ) was used to assess the hand pain related-disability. It includes a functional status scale assessing the ability to perform eight common hand-related tasks, and a symptom severity scale assessing pain severity, numbness and weakness at night and during the day. Each item is answered on a 5-point scale (1: no complaint; 5: severe complaint) with higher scores indicating greater related-disability. This questionnaire is valid, reliable, and responsive for individuals with CTS (29).

Psychological Measures

Patients completed the Beck Depression Inventory (BDI-II) to obtain a measure of their level of depressive symptoms. This questionnaire consists of 21-item self-reported items assessing affective, cognitive, and somatic symptoms of depression (30). The BDI-II is easily adapted in most clinical conditions for detecting symptoms of depression (31).

Psychophysical Measures

In the current study, we also evaluated sensitivity to pressure and thermal pain to assess nociceptive gain processing. Pressure pain thresholds (PPT), the minimal amount of pressure where a sense of pressure first changes to pain, were measured bilaterally with an electronic algometer (Somedic AB©, Farsta, Sweden) over the median, ulnar and radial nerves, the articular pillar of C5-C6 joint, carpal tunnel, and tibialis anterior (6). The pressure was applied at an approximate rate of 30 kPa/sec. Participants were instructed to press the stop switch when the sensation changed from pressure to pain. The mean of three trials was calculated and used for the analysis. A 30-second rest period was provided between each trial to avoid temporal summation (32). The order of the assessment was randomized between participants. The reliability of algometry is high (33,34).

Thermal pain thresholds were assessed bilaterally with a Thermotest System (Somedic AB© Farsta, Sweden) over the carpal tunnel or thenar eminence (7). Patients were instructed to press a hand-controlled stop switch when the sensation changed from heat/cold to heat/cold pain (heat or cold pain threshold, HPT/CPT respectively). The mean of 3 trials at each region was calculated and used for the analysis. A rest of 5 seconds was allowed between trials. The order of the assessment was randomized. A systematic review concluded that the reliability of thermal pain thresholds on the hand is high (35).

Sample Size Calculation

The sample size was calculated using Ene 3.0 software (Autonomic University of Barcelona, Spain). The sample calculation was based on detecting significant moderate correlations (r=0.3) between the studied variables with an alpha level (α) of 0.05, and a desired power (β) of 95%. This generated a sample size of at least 135 subjects.

Statistical Analysis

Distribution of the data was tested with the Shapiro-Wilk test and non-normally distributed data were observed. Since no side-to-side differences in PPTs, HPTs or CPTs were found, the mean of both sides was used in the analysis. For the first objective, Spearman's correlation coefficients were computed to reveal the associations between pain extent with all clinical, psychological and psychophysical outcomes. Correlation was considered weak when $r_s<.3$, moderate when $.3<_{s_i} r_s<.7$, and strong when $r_s>.7$ (36). Statistical analysis was performed using R version 3.2.2. Significance was set to $\alpha=.05$ and the Bonferroni correction was applied (α-adjusted=.003) to account for multiple testing (37). For the second objective, a non-parametric Wilcoxon Rank Test was used to evaluate the differences in pain extent between those with median and extra-median symptoms. Finally, for the third objective, a non-parametric Kruskal-Wallis Test was used to evaluate the differences in pain extent accordingly to severity (minimal, moderate or severe) or laterality (left, right or bilateral).

Results

Two hundred (n=200) women with diagnosis of CTS between January 2015 and June 2017 were screened according to the eligibility criteria. Finally, 140 (70%) women satisfied all the eligibility criteria, agreed to participate, and signed the informed consent. The reasons for exclusion included: previous surgery (n=20), previous steroid injections (n=15), diabetes (n=10), whiplash (n=5), age above 65 (n=5), pain drawings not recognised by the software (n=5). Thirty-seven (26%) reported unilateral symptoms (28 right side, 9 left side), and the remaining 103 (74%) exhibited bilateral symptoms. Thirty-two (23%) presented minimal CTS, 62 (44%) moderate CTS and the remaining 46 (33%) severe CTS. The total pain extent was 22.1 ± 13.9% across the entire group of women with CTS, whereas pain extent for the hand and arm only was 25.7±16.1% and 5.8±10.6%, respectively. **Table 1** presents the clinical, psychological, and psychophysical measures of the entire sample. No significant associations were found between the pain extent and clinical, psychological or psychophysical variables in the total sample of women of CTS, except for CPT over the carpal tunnel and pain extent in the upper extremity (r=0.25; P=.002)

Pain frequency maps for women with CTS are illustrated in **Figure 1.** According to the pain drawings, 124 (88%) women exhibited extra-median symptoms and the remaining 16 (12%) women experienced median symptoms. Women with extra-median symptoms exhibited significantly larger (P<.001) total (24.2±13.5%) and hand (28.4±15.5%) pain extent than those with median symptoms (total: 12.2±6.9%; hand: 13.3±8.3%) as it is depicted in **Figure 2**.

The Kruskal-Wallis Test did not find significant differences for the total (F=1.396; P=.251), hand (F=1.674; P=.197) or arm (F=1.050; P=.353) pain extent between women with minimal (total: 26.1±14.4%; hand: 30.9±16.8%; arm: 5.0±7.0%), moderate (total: 21.3±12.4%; hand: 24.9±14.8%; arm: 5.2±10.2%) and severe (total: 22.7±14.1%; hand: 26.1±15.4%; arm: 7.9±13.1%) CTS. In addition, no significant differences in the total (F=.576; P=.563), hand (F=.646; P=.526), or upper extremity (F=.643; P=.527) pain extent were identified between those women with unilateral versus bilateral symptoms.

Discussion

The current study observed that the degree of pain extent was not associated with clinical, psychological or psychophysical variables in women with CTS. Additionally, no difference in pain extent was found depending on the severity or laterality of the symptoms.

It has been generally assumed that people with CTS should exhibit pain in the median nerve area; however, we observed that around 80% of our sample experienced extra-median symptoms. In fact, previous studies have reported a prevalence of extra-median symptoms in the hand or proximal upper extremity pain ranging from 40% to 50% (14-16), which is a lower rate than in the current study. Discrepancies in the prevalence of extra-median symptoms between the current and previous studies can likely be explained by the fact that our study is the first to include pain drawings of both the hand and upper extremity for describing extra-median symptoms, since Zanette et al (14) and Mansiz-Kaplan et al (16) only included the hands, whereas Zanette et al (15) only considered upper extremity symptoms. Further, previous studies only evaluated the presence of symptoms, but they did not assess the extent of pain. Thus, this is the first study to report the extent of pain as depicted by a novel method of pain drawing in a sample of women with CTS. In fact, our findings of a non-neuroanatomical distribution of pain in our sample of women with CTS is consistent with previous observations involving spinal nerves during both experimental and clinical studies (38,39).

Larger pain extent (13) and widespread pressure hypersensitivity (6,9) have been associated with stronger levels of sensitization. In the current study, pain extent in women with CTS with extra-median symptoms was larger than that in women with just median symptoms. These findings would agree with the hypothesis that the presence of extra-median symptoms (14-16) and larger pain areas (13) are clinical manifestations of central sensitization. The presence of central sensitization is supported by neuro-physiological studies investigating different quantitative sensory tests in individuals with CTS (5-10). Current results further support spreading of pain as a potential manifestation of sensitization mechanisms in women with CTS. Nevertheless, it should be noted that we did not find any significant association between pain extent and psychophysical outcomes

of sensitization, i.e., widespread pressure pain or thermal pain hypersensitivity (except CPT over the carpal tunnel). Current findings would agree with the results previously found in some primary headaches such as migraine (40) or tension-type headache (41) but contrast with those previously reported in painful knee osteoarthritis (18) where larger pain extent was associated with higher pressure pain sensitivity. Similarly, the current study did not find any significant association between pain extent and clinical, psychological, and related-disability outcomes in women with CTS which is also in disagreement with previous findings found on painful knee osteoarthritis (18), whiplash-associated disorders (19), and fibromyalgia (20) where larger pain extent was associated with higher intensity of pain or worse psychological variables. Previous studies suggest the relevance of pain drawing as an adjunct variable for evaluating patients; however, expanded pain drawings seem to be not always associated with psychological state (42), as in the current study.

One potential explanation for the discrepancy between studies may be related to the fact that knee osteoarthritis or whiplash-associated disorders are most typically nociceptive pain disorders whereas CTS is a neuropathic pain condition. It has been postulated that central sensitization progressively develops in musculoskeletal pain conditions such as painful knee osteoarthritis (18); whereas it seems that central sensitization is present in individuals with CTS from the beginning of their symptoms independently of electrodiagnostic findings (9). This hypothesis is supported by the results from the current study since pain extent or the presence of extra-median symptoms was not significantly different between women with minimal, moderate or severe CTS or between those with unilateral/bilateral symptoms. Since the electro-diagnostic examination classified women with CTS according to nerve conduction impairments; our results would support the well-known notion that pain features/manifestations are not correlated with potential nerve damage due to compression, even in case of a neurological condition and when considering the pain extent. Further, this assumption would explain the results previously found in women with fibromyalgia syndrome, a condition with a neuropathic component (43), where widespread pressure or thermal hyperalgesia was not associated with pain extent (20). Interestingly, in women with fibromyalgia syndrome (20)

and in those with CTS, pain extent was poorly associated with cold pain thresholds, a feature of neuropathic pain (44). It is possible that the association between pain extent and clinical, psychological or psychophysical measures is more complex in neuropathic pain conditions than in musculoskeletal pain disorders, or that pain extent would represent a different component of the pain spectrum in these conditions.

Finally, we should recognize that the current study has some potential limitations. First, we only included women with CTS recruited from one urban hospital. Therefore, our results should not be extrapolated to men with CTS. Multi-centre studies including men and women with CTS from the general population would help to strengthen the results. Second, we used sensitivity to pressure or thermal pain and pain extent for investigating central sensitization. We do not know if the use of dynamic, e.g., wind up or conditioned pain modulation, or self-reported, e.g., central sensitization inventory (CSI), outcomes would lead to different results. Finally, the role of other psychological variables, e.g., anxiety, sleep disorders was not either considered. Future studies evaluating the role of pain extent in the clinical evolution or as prognostic factor of treatment in CTS are needed.

Conclusions

This study used a reliable procedure to quantify pain extent in women with CTS and found that almost 80% of the patients exhibit extra-median symptoms. Pain extent was not associated with clinical, psychological or psychophysical variables in women with CTS and was not significantly different depending on the severity or laterality of the symptoms. Further research is needed to determine the role of pain extent in the clinical course and treatment prognosis of pain conditions.

References

1. Thiese MS, Gerr F, Hegmann KT, Harris-Adamson C, Dale AM, Evanoff B, Eisen EA, Kapellusch J, Garg A, Burt S, Bao S, Silverstein B, Merlino L, Rempel D. Effects of varying case definition on carpal tunnel syndrome prevalence estimates in a pooled cohort. Arch Phys Med Rehabil 2014; 95: 2320-6.
2. Bland JD, Rudolfer SM. Clinical surveillance of carpal tunnel syndrome in two areas of the United Kingdom, 1991-2001. J Neurol Neurosurg Psychiatry 2003; 74: 1674-9.
3. Foley M, Silverstein B, Pollisar N. The economic burden of carpal tunnel syndrome: long term earnings of CTS claimants in Washington State. Am J Ind Med 2007; 50: 155-172
4. Stapelton MJ. Occupation and carpal tunnel syndrome. ANZ J Surg 2006; 76: 494-6.
5. De-la-Llave-Rincón AI, Puentedura EJ, Fernández-de-las-Peñas C. New advances in the mechanisms and etiology of carpal tunnel syndrome. Discov Med 2012; 13: 343-8
6. Fernández-de-las-Peñas C, De-la-Llave-Rincón AI, Fernández-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
7. de-la-Llave-Rincón AI, Fernández-de-las-Peñas C, Fernández-Carnero J, Padua L, Arendt-Nielsen L, Pareja JA. Bilateral hand/wrist head and cold hyperalgesia, but not hypoesthesia, in unilateral carpal tunnel syndrome. Exp Brain Res 2009; 198:455-463
8. Zanette G, Cacciatori C, Tamburin S. Central sensitization in carpal tunnel syndrome with extraterritorial spread of sensory symptoms. Pain 2010; 148: 227-36
9. De-la-Llave-Rincón AI, Fernández-de-las-Peñas C, Laguarta-Val S, Alonso-Blanco C, Martínez-Pérez A, Arendt-Nielsen L, Pareja JA. Increased pain sensitivity is not associated with electrodiagnostic findings in women with carpal tunnel syndrome. Clin J Pain 2011; 27:747-754

10. Soon B, Vicenzino B, Schmid AB, Coppieters MW. Facilitatory and inhibitory pain mechanisms are altered in patients with carpal tunnel syndrome. PLoS One 2017; 12: e0183252.
11. Schmid AB, Soon BT, Wasner G, Coppieters MW. Can widespread hypersensitivity in carpal tunnel syndrome be substantiated if neck and arm pain are absent? Eur J Pain 2012; 16: 217-28
12. Fernández-de-las-Peñas C, Fernández-Muñoz JJ, Navarro-Pardo E, da-Silva-Pocinho R, Ambite-Quesada S, Pareja JA. Identification of subgroups of women with carpal tunnel syndrome with central sensitization. Pain Med 2016; 17:1749-56.
13. Arendt-Nielsen L, Graven-Nielsen T. Translational musculoskeletal pain research. Best Pract Res Clin Rheumatol 2011; 25: 209-26.
14. 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: 264-270.
15. Zanette G, Marani S, Tamburin S. Proximal pain in patients with carpal tunnel syndrome: a clinical neuro-physiological study. J. Peripher Nerv Syst 2007; 12: 91-97.
16. Mansiz-Kaplan B, Akdeniz-Leblecicier M, Yagci I. Are extra-median symptoms associated with peripheral causes in patient with carpal tunnel syndrome? Electrodiagnostic and ultrasonographic study. J Electromyogr Kinesiol 2018; 38: 203-207.
17. Wood L, Peat G, Thomas E, Duncan R. Knee osteoarthritis in community-dwelling older adults: are there characteristic patterns of pain location? Osteoarthritis Cartilage 2007; 15: 615-23.
18. Lluch Girbés E, Dueñas L, Barbero M, Falla D, Baert IA, Meeus M, Sánchez-Frutos J, Aguilella L, Nijs J. Expanded distribution of pain as a sign of central sensitization in individuals with symptomatic knee osteoarthritis. Phys Ther 2016; 96: 1196-207.

19. Falla D, Peolsson A, Peterson G, Ludvigsson ML, Soldini E, Schneebeli A, Barbero M. Perceived pain extent is associated with disability, depression and self-efficacy in individuals with whiplash-associated disorders. Eur J Pain 2016; 20: 1490-501.
20. Barbero M, Fernández-de-las-Peñas C, Palacios-Ceña M, Cescon C, Falla D. Pain extent is associated with pain intensity but not with widespread pressure or thermal pain sensitivity in women with fibromyalgia syndrome. Clin Rheumatol 2017; 36: 1427-1432
21. Chan L, Turner JA, Comstocl BA, Levenson LM, Hollingworth W, Heagerty P, Kliot M et al. The relationship between electro-diagnostic findings and patient symptoms and function in carpal tunnel syndrome. Arch Phys Med Rehabil 2007; 88: 19-24
22. American Association of Electro-diagnostic Medicine, American Academy of Neurology, American Academy of Physical Medicine and Rehabilitation. Practice parameter: electro-diagnostic studies in carpal tunnel syndrome. Neurology 2002; 58: 1589-92
23. Dos Reis FJ, de Barros E Silva V, de Lucena RN, Mendes Cardoso BA, Nogueira LC. Measuring the pain area: An intra- and inter-rater reliability study using image analysis software Pain Pract 2016; 16: 24-30
24. Persson AL, Garametsos S, Pedersen J. Computer-aided surface estimation of pain drawings - intra- and inter-rater reliability. J Pain Res 2011; 4: 135-41.
25. Barbero M, Moresi F, Leoni D, Gatti R, Egloff M, Falla D. Test-retest reliability of pain extent and pain location using a novel method for pain drawing analysis. Eur J Pain 2015; 19: 1129-38.
26. Jensen MP, Turbner JA, Romano JM, Fisher L. Comparative reliability and validity of chronic pain intensity measures. Pain 1999; 83: 157-162
27. Rosales RS, Benseny E, Díez 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

418 28. Levine DW, Simmons B, Koris M, Daltroy L, Hohl G, Fossel A, Katz J. A self-administered
419 questionnaire for the assessment of severity of symptoms and functional status in carpal
420 tunnel syndrome. J Bone Joint Surg Am 1993; 75: 1585-92
421 29. Carvalho-Leite J, Jerosch-Herold C, Song F. A systematic review of the psychometric
422 properties of the Boston Carpal Tunnel Questionnaire. BMC Musculoskeletal Disorders
423 2006; 7: 78
424 30. Beck AT, Steer RA, Brown GK. Beck Depression Inventory, 2nd ed. San Antonio, Texas;
425 The Psychological Corporation, 1996
426 31. Wang YP, Gorenstein C. Assessment of depression in medical patients: a systematic review
427 of the utility of the Beck Depression Inventory-II. Clinics 2013; 68: 1274-87
428 32. Nie H, Arendt-Nielsen L, Andersen H, Graven-Nielsen T. Temporal summation of pain
429 evoked by mechanical stimulation in deep and superficial tissue. J Pain 2005; 6: 348-355
430 33. Walton DM, Macdermid JC, Nielson W, Teasell RW, Chiasson M, Brown L. Reliability,
431 standard error, and minimum detectable change of clinical pressure pain threshold testing in
432 people with and without acute neck pain. J Orthop Sports Phys Ther 2011; 41: 644-50
433 34. Chesterson LS, Sim J, Wright CC, Foster NE. Inter-rater reliability of algometry in
434 measuring pressure pain thresholds in healthy humans, using multiple raters. Clin J Pain
435 2007; 23: 760-6
436 35. Moloney NA, Hall TM, Doody CM. Reliability of thermal quantitative sensory testing: a
437 systematic review. J Rehabil Res Dev 2012; 49: 191-207.
438 36. Dancey CP, Reidy J. Statistics without maths for psychology: Using SPSS for Windows.
439 New York: Prentice Hall. 2004.
440 37. Shaffer JP. Multiple hypothesis testing. Annu Rev Psychol 1995; 46: 561-584
441 38. Tanaka Y, Kokubun S, Sato T, Ozawa H. Cervical roots as origin of pain in the neck or
442 scapular regions. Spine 2006; 31: E568-73.
443

39. Murphy DR, Hurwitz EL, Gerrard JK, Clary R. Pain patterns and descriptions in patients with radicular pain: does the pain necessarily follow a specific dermatome? Chiropr Osteopat 2009; 17: 9
40. Fernández-de-las-Peñas C, Falla D, Palacios-Ceña M, Fuensalida-Novo S, Arias-Buría JL, Schneebeli A et al. Perceived pain extent is not associated with widespread pressure pain sensitivity clinical features, related-disability, anxiety, or depression in women with episodic migraine. Clin J Pain 2018; 34: 217-221.
41. Palacios-Ceña M, Barbero M, Falla D, Ghirlanda F, Arend-Nielsen L, Fernández-de-las-Peñas C. Pain extent is associated with the emotional and physical burden of chronic tension type headache, but not with depression or anxiety. Pain Med 2017; 18: 2033-2039
42. Carnes D, Ashby D, Underwood M. A systematic review of pain drawing literature: should pain drawings be used for psychologic screening? Clin J Pain 2006; 22: 449-457.
43. Üçeyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A et al. Small fibre pathology in patients with fibromyalgia syndrome. Brain 2013; 136: 1857-67.
44. De Medinaceli L, Hurpeau J, Merle M, Begorre H. Cold and post-traumatic pain: modelling of the peripheral nerve message. Biosystems 1997; 43:145-67

Legend of Figures

Figure 1: Pain frequency maps generated by superimposing the pain drawings of all women with carpal tunnel syndrome (n=140). The colour bar represents the frequency of coloured areas. Dark red indicates the most frequently reported area of pain

Figure 2: Pain frequency maps generated by superimposing the pain drawings of women with carpal tunnel syndrome with median (n=16) or extra-median (n=124) symptoms. The colour bar represents the frequency of coloured areas. Dark red indicates the most frequently reported area of pain.