Can widespread hypersensitivity in carpal tunnel syndrome be substantiated if neck and arm pain are absent?

Annina B. Schmid a, Benjamin TC. Soon a, Gunnar Wasner b, Michel W. Coppieters a,⇑

⇑Centre of Clinical Research Excellence in Spinal Pain, Injury and Health, Division of Physiotherapy, School of Health and Rehabilitation Sciences, The University of Queensland, St. Lucia, Brisbane, QLD 4072, Australia

Department of Neurology, Division of Neurological Pain Research and Therapy, University Clinic of Schleswig-Holstein, Kiel, Germany

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A B S T R A C T

Recent studies demonstrated that patients with carpal tunnel syndrome (CTS) have signs of thermal and mechanical hyperalgesia in extra-median territories suggesting an involvement of central pain mechanisms. As previous studies included patients with shoulder/arm symptoms or neck pain, a potential influence of these coexisting disorders cannot be excluded. This study therefore evaluated whether widespread sensory changes (hypoesthesia or hyperalgesia) are present in patients with unilateral CTS in the absence of coexisting disorders. Twenty-six patients with unilateral CTS with symptoms localised to their hand and 26 healthy controls participated in the study. A comprehensive quantitative sensory testing (QST) protocol including thermal and mechanical detection and pain thresholds was performed over the hands (median, ulnar and radial innervation area), lateral elbows, neck and tibialis anterior muscle. Patients with CTS demonstrated thermal and mechanical hypoesthesia in the hand but not at distant sites. Thermal or mechanical hyperalgesia was not identified at any location with traditional QST threshold testing. However, patients with CTS rated the pain during thermal pain testing significantly higher than healthy participants. This was especially apparent for heat pain ratings which were elevated not only in the affected hand but also in the neck and tibialis anterior muscle. In conclusion, CTS alone in the absence of coexisting neck and arm pain does not account for sensory changes outside the affected hand as determined by traditional QST threshold testing. Elevated pain ratings may however be an early indication of central pain mechanisms.

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1. Introduction

Carpal tunnel syndrome (CTS) is an entrapment neuropathy of the median nerve at the level of the wrist. Despite this localised compression, patients frequently report symptoms outside the median nerve territory (Nora et al., 2005; Caliandro et al., 2006), which have been ascribed to central mechanisms (Zanette et al., 2006).

Recent studies used quantitative sensory testing (QST) to identify generalised disturbance of somatosensory function in patients with CTS (de la Llave-Rincon et al., 2009; Fernandez-de-las-Penas et al., 2009, 2010; Zanette et al., 2010). Vibration detection thresholds for example seem to be increased not only in the median nerve innervation area, but also in the ulnar and radial distribution areas (Lundborg et al., 1992; Tucker et al., 2007). Reports on thermal detection thresholds are conflicting. A recent study found normal thermal detection in patients with CTS (de la Llave-Rincon et al., 2009), whereas another study reported compromised cold detection in both the median and ulnar innervation territories (Goadsby and Burke, 1994). A possible explanation for sensory changes in the ulnar innervation area is the transmission of high carpal tunnel pressure into the Guyon’s canal (Ginanneschi et al., 2008). Hence, such spread of hypoesthesia may arguably be caused by a local mechanical effect rather than central mechanisms. Thermal or mechanical hypoesthesia has not yet been evaluated proximal to the hand. If found, the presence of central mechanisms may be further strengthened.

* Corresponding author. Tel.: +61 7 3365 1644; fax: +61 7 3365 1622.
E-mail address: m.coppieters@uq.edu.au (M.W. Coppieters).
Studies evaluating pain thresholds consistently identified widespread hyperalgesia in CTS. Decreased mechanical pain thresholds have been shown in both hands as well as over the cervical spine, arm and the tibialis anterior muscle in patients with unilateral CTS (Fernandez-de-las-Penas et al., 2009, 2010). Similarly, thermal hyperalgesia was identified in both hands in unilateral CTS (de la Llave-Rincon et al., 2009).

When interpreting these results of widespread hyperalgesia, it has to be considered that patients with CTS have a high prevalence of proximal symptoms such as neck pain and lateral elbow pain (Nora et al., 2004; Chow et al., 2005). Patients with lateral epicondylalgia or cervical disorders present with widespread sensory changes at similar sites as tested in CTS (Chien et al., 2008; Johnston et al., 2008; Fernandez-Carnero et al., 2009). Cervical and lateral elbow symptoms were not specifically listed as exclusion criteria in many studies reporting widespread hyperalgesia in patients with CTS (de la Llave-Rincon et al., 2009; Fernandez-de-las-Penas et al., 2009, 2010). Personal communication confirmed that almost all patients included in these studies reported episodes of neck pain. It is therefore uncertain whether the identified widespread findings can indeed be attributed to CTS or whether they may be a consequence of coexisting disorders.

The aim of this study was to explore whether the previously reported widespread sensory changes in patients with CTS can be ascribed to central mechanisms. Using a comprehensive QST protocol, we investigated whether the presence of hypoaesthesia and hyperalgesia in extramedian territories can be substantiated in patients with unilateral CTS who have no co-existing neck or arm disorders.

2. Methods

A cross-sectional design was used to evaluate quantitative sensory profiles of patients with CTS without neck or arm pain compared to healthy participants.

2.1. Participants

Twenty-six patients who met clinical (AAEM et al., 1993) and electrodiagnostic (AAEM et al., 2002) criteria for unilateral CTS participated in the study (14 females, 12 males; mean age (SD) = 49.3 (11.9); mean (SD) height = 169.8 cm (9.5); mean (SD) weight = 76.9 kg (15.3); severity of electrodiagnostic findings: mild: n = 5, moderate: n = 19, severe: n = 2). Patients were excluded if electrodiagnostic findings were indicative of peripheral neuropathies other than CTS, if bilateral hand symptoms were present (even if electrodagnostically negative on one side), if previous surgery or trauma to the upper/lower limb or neck was reported or if pregnancy related CTS, diabetes or any other medical, rheumatologic, orthopaedic or neurologic condition was present. Evidencing widespread symptoms of neck pain. It is therefore uncertain whether the identified widespread sensory changes at similar sites as tested in CTS (Chien et al., 2008; Johnston et al., 2008; Fernandez-Carnero et al., 2009). Cervical and lateral elbow symptoms were not specifically listed as exclusion criteria in many studies reporting widespread hyperalgesia in patients with CTS (de la Llave-Rincon et al., 2009; Fernandez-de-las-Penas et al., 2009, 2010). Personal communication confirmed that almost all patients included in these studies reported episodes of neck pain. It is therefore uncertain whether the identified widespread findings can indeed be attributed to CTS or whether they may be a consequence of coexisting disorders.

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2.2. Thermal detection and pain thresholds

Thermal detection and pain thresholds were measured using the Thermostest (Somedic AB, Farsta, Sweden) with a 12.5 cm² thermode. Thermal detection thresholds were measured before thermal pain thresholds. Thermal thresholds were determined by either an increase or decrease of 1°C increments from a baseline temperature of 30°C. The participants were asked to press a button once the cold/warm sensation first became detectable and the mean of three consecutive measures was recorded as the cold detection threshold (CDT) and warm detection threshold (WDT), respectively. For thermal pain thresholds, participants were asked to press the button once the cold/warm sensation first became painful. The mean of three repetitions was recorded as the cold pain threshold (CPT) and heat pain threshold (HPT), respectively (Rolke et al., 2006a). Cut-off temperatures were set at 5°C for the CPT and 50°C for the HPT.

2.3. Pain ratings during thermal pain thresholds

After determination of each thermal pain threshold, participants rated the intensity of their pain on a numerical pain rating scale from 0 (no pain at all) to 10 (maximum pain that can be imagined) (Kelly et al., 2005; Wasner and Brock, 2008). The mean of three pain ratings for each location was used for statistical analysis.

2.4. Vibration threshold

A vibrometer (Somedic AB, Stockholm, Sweden) with a 1 cm diameter probe was used at a constant frequency of 120 Hz and with a tissue displacement of 0.1 ± 400 μm. The participants were asked to indicate once they first became aware of the vibration sensation (perception threshold) and once the sensation disappeared (disappearance threshold). The mean of the perception and disappearance thresholds was recorded as the vibration threshold. The mean of three repetitions was used for analysis.

2.5. Pressure pain threshold (PPT)

Pressure pain thresholds were used to determine deep tissue hyperalgesia (Treede et al., 2002) and were measured with a digital algometer (Somedic AB, Farsta Sweden). Pressure was applied through a 1 cm² rubber plate at a constant rate of 40 kPa per second. The participants were asked to push a button as soon as the sensation of pressure changed to pain. Measurements were taken in triplicate and the mean was used for analysis (Treede et al., 2002).
2.6. Wind-up ratio (WUR)

Wind-up ratios were used to test for a frequency dependent increase in excitability of spinal cord neurons (Rolke et al., 2006a). Single and repeated trains of stimuli were delivered within a skin area of 1 cm² at a frequency of 1 Hz with a 256 mN von Frey hair. The participants were asked to rate the pain of the single stimulus as well as at the end of the train of stimuli using a numerical rating scale from 0 to 10. This procedure was repeated five times at each location. The mean of the pain rating of trains divided by the mean rating of the single stimuli is reported as the wind-up ratio (Rolke et al., 2006a).

2.7. Testing locations and procedure

Thermal detection and pain thresholds as well as vibration detection were determined bilaterally at the following anatomical locations: (a) over the dorsum of the second metacarpal (mid-shaft) (D2) and (b) over the palmar aspect of the first metacarpal (mid-shaft) (D1) (Tucker et al., 2007), bilaterally over the lateral epicondyles (LE) (Fernandez-Camero et al., 2009) as well as centrally on the neck over the spinous process of C6. PPT was measured over the thenar and hypothenar area of both hands as well as over LE and centrally over the C6 spinous process. A remote site over the tibialis anterior muscle (TA) on the unaffected side was chosen to assess potential generalised sensory changes when evaluating PPT and thermal pain thresholds (Chien et al., 2009). WUR was tested bilaterally over the thenar and LE as well as over the neck.

Fig. 1 summarises the tested sites and modalities. Identical sequences of testing were used for each participant starting with thermal detection and thermal pain thresholds, followed by wind-up ratios, vibration detection and pressure pain thresholds. The unaffected side was tested first, followed by the affected side and the method of limits was used to determine sensory thresholds. All QST measures were taken by the same experimenter. All instructions were given verbally in a standardised way as outlined by Rolke et al. (2006a).

2.8. Statistical analysis

To establish intratester reliability of each QST measure taken in triplicate, the intraclass correlation coefficient (ICC(2,3)) was calculated using the Spearman–Brown formula (Nee et al., 2010).

As both raw and log transformed data (Rolke et al., 2006b) were not normally distributed, non-parametric tests were used for statistical analysis in PASW 18 (SPSS Inc., Chicago, USA). Friedman’s two way analysis of variance for matched pairs (Conover, 1999) was used to compare data of patients with CTS (affected; unaffected side) with data of the healthy matched controls (matched to affected side for age, gender and hand dominancy; matched to unaffected side for age, gender and hand dominancy). Level of significance was set at \( p < 0.05 \). Post hoc pairwise multiple comparisons for Friedman tests were applied using the Bonferroni adjustment to correct for the a priori determined number of comparisons (three comparisons: affected versus unaffected; affected versus healthy matched affected; unaffected versus healthy matched unaffected; significance set at \( p < 0.016 \)).

3. Results

3.1. Reliability

Overall, the intra-examiner reliability was high. For cold detection, reliability coefficients ranged from 0.816 (95% confidence interval: 0.703, 0.889) to 0.947 (0.926, 0.963) and for warm detection from 0.951 (0.932, 0.965) to 0.983 (0.976, 0.988). For thermal pain thresholds, intra-examiner reliability ranged between 0.961 (0.926, 0.978) and 0.995 (0.989, 0.998) for cold pain and from 0.936 (0.734, 0.974) to 0.983 (0.957, 0.992) for heat pain. The overall reliability coefficients for pain ratings during thermal pain thresholds was 0.978 (0.974, 0.977). Reliability for vibration detection thresholds ranged from 0.906 (0.869, 0.933) to 0.980 (0.927, 0.986) and for PPT from 0.958 (0.934, 0.975) to 0.981 (0.966, 0.989). Reliability for WUR was 0.881 (0.853, 0.904).

3.2. Thermal detection thresholds

Cold detection on D1 was the only significantly different thermal detection threshold between groups (\( \chi^2(3) = 8.048, p = 0.045 \)). Post hoc tests revealed that cold detection thresholds in D1 of the affected hand in CTS were significantly increased compared to D1 of matched affected hands of control participants (\( p = 0.004 \)) (see Fig. 2).

Other detection thresholds did not reach statistical significance between groups (Cold D2 \( \chi^2(3) = 4.841, p = 0.184 \); Cold LE \( \chi^2(3) = 4.902, p = 0.179 \); Cold neck \( \chi^2(1) = 2.667, p = 0.102 \); Hot D1 \( \chi^2(3) = 3.988, p = 0.263 \); Hot D2 \( \chi^2(3) = 7.124, p = 0.068 \); Hot LE \( \chi^2(3) = 6.961, p = 0.073 \); Hot neck \( \chi^2(1) = 3.846, p = 0.050 \)). Median and interquartile ranges (IQR) are listed in Table 1A.

3.3. Vibration detection thresholds

Statistical comparison revealed significant group differences for vibration detection at D1 (\( \chi^2(3) = 12.692, p = 0.005 \)) and D2 (\( \chi^2(3) = 10.938, p = 0.012 \)). Post hoc comparisons revealed significantly higher vibration detection thresholds in the affected CTS hand at D1 compared to the healthy matched affected hand (\( p = 0.001 \)). At D2, vibration thresholds of the affected hand of patients with CTS were significantly higher than the matched affected hand of healthy participants (\( p = 0.004 \)) (see Fig. 2). Vibration detection at the elbow just marginally missed statistical significance (\( \chi^2(3) = 7.754, p = 0.051 \)) and for the neck was comparable between groups (\( \chi^2(1) = 2.462, p = 0.117 \)). Median and IQR of vibration detection thresholds are reported in Table 3A.
3.4. Thermal pain thresholds and pain ratings

None of the cold pain thresholds reached statistical significance between groups (D1: $\chi^2(3) = 2.702, p = 0.440$), D2 $\chi^2(3) = 3.212, p = 0.440$, LE $\chi^2(3) = 3.212, p = 0.207$, Neck $\chi^2(3) = 3.212, p = 0.207$, TA $\chi^2(3) = 3.212, p = 0.207$). Similarly, statistical analysis revealed no significant difference between groups for heat pain thresholds at all sites (D1 $\chi^2(3) = 5.641, p = 0.130$, D2 $\chi^2(3) = 5.502, p = 0.135$, LE $\chi^2(3) = 5.502, p = 0.135$, Neck $\chi^2(3) = 5.502, p = 0.135$, TA $\chi^2(3) = 5.502, p = 0.135$). Median and IQR for thermal pain thresholds are listed in Table 1B.

Interestingly, pain ratings for heat pain thresholds were significantly different between groups at all locations (D1 $\chi^2(1) = 9.916, p = 0.002$, D2 $\chi^2(1) = 9.916, p = 0.002$, LE $\chi^2(1) = 9.916, p = 0.002$, Neck $\chi^2(1) = 9.916, p = 0.002$, TA $\chi^2(1) = 9.916, p = 0.002$). Post hoc tests revealed that heat pain rating at D1 was significantly higher in the unaffected hand of patients with CTS compared to the hand in the control group matched to the unaffected side ($p = 0.010$). Heat pain ratings at D2 were significantly higher in the affected hand of patients with CTS compared to the matched affected hand of control participants ($p = 0.001$). Heat pain ratings over the neck and TA were significantly higher in patients compared to healthy controls (Neck $\chi^2(1) = 14.476, p = 0.001$, TA $\chi^2(1) = 14.476, p = 0.001$) (see Fig. 3). Pain ratings at LE of the affected side marginally missed Bonferroni adjusted significance compared to the values of the matched affected side in controls ($p = 0.021$).

Cold pain ratings were different at D1 ($\chi^2(3) = 13.758, p = 0.003$) and D2 ($\chi^2(3) = 9.029, p = 0.029$). Post hoc tests revealed significantly higher pain ratings in D1 of the affected hand of patients with CTS compared to the matched affected hand of control participants ($p = 0.001$) (see Fig. 3). None of the a priori comparisons of cold pain ratings at D2 reached significance in post hoc analysis. Pain ratings during cold pain testing at locations...
outside the hand were not significantly different between groups (LE \( \chi^2(3) = 4.313, p = 0.230 \); Neck \( \chi^2(1) = 1.190, p = 0.275 \); TA \( \chi^2(1) = 0.600, p = 0.439 \)). Median and IQR of pain ratings are reported in Table 2.

3.5. Pressure pain thresholds

PPT was significantly different over the hypothenar area (\( \chi^2(3) = 8.077, p = 0.044 \)). Patients with CTS exhibited higher pain thresholds in the unaffected hand compared to the healthy hand matched to the unaffected hand (\( p = 0.013 \)) (Fig. S1, see the online version at 10.1016/j.ejpain.2011.06.003). PPT at all other locations were not significantly different (Thenar \( \chi^2(3) = 2.077, p = 0.557 \); LE \( \chi^2(1) = 1.708, p = 0.635 \); Neck \( \chi^2(1) = 0.040, p = 0.841 \); TA \( \chi^2(1) = 1.960, p = 0.162 \)). Median and IQR of mechanical pain thresholds are specified in Table 3B.

3.6. Wind up ratio

Most participants with and without CTS did not indicate pain with a single stimulus or even repeated stimuli (\( \sim 88.5\% \)) indicating a clear absence of wind-up. Wind-up ratios were therefore in many cases impossible to determine (division by zero). There was no statistically significant difference between groups for wind-up ratios (WUR thenar \( \chi^2(3) = 6.600, p = 0.086 \); WUR LE \( \chi^2(3) = 4.655, p = 0.199 \); WUR neck \( \chi^2(1) = 0.000, p = 1.0 \)).

4. Discussion

This study revealed that patients with unilateral CTS have localised altered thermal and mechanical detection thresholds in the hand, but not at distant sites when the presence of coexisting neck or arm pain is strictly excluded. In contrast to other studies which did not exclude coexisting neck pain and interpreted the presence of widespread hyperalgesia as a sign of central sensitisation (de la Llave-Rincon et al., 2009; Fernandez-de-las-Penas et al., 2009, 2010), we did not identify reduced thermal or mechanical pain thresholds in any location. Interestingly though, the patients with CTS rated the pain during thermal pain testing significantly higher than healthy participants. This was especially apparent for heat pain ratings which were elevated in a widespread manner. The role of elevated pain ratings as a potential early indication of central pain mechanisms will be discussed.
Numerical pain ratings during thermal pain thresholds.

<table>
<thead>
<tr>
<th>Pain threshold</th>
<th>CTS</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Affected</td>
<td>Unaffected</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Cold D1</td>
<td>2.00 (4.00)</td>
<td>2.33 (3.80)</td>
</tr>
<tr>
<td>Cold D2</td>
<td>2.00 (4.00)</td>
<td>2.00 (4.00)</td>
</tr>
<tr>
<td>Cold LE</td>
<td>1.00 (3.00)</td>
<td>0.00 (2.00)</td>
</tr>
<tr>
<td>Cold neck</td>
<td>1.00 (2.00)</td>
<td>0.00 (1.00)</td>
</tr>
<tr>
<td>Cold TA</td>
<td>0.00 (2.00)</td>
<td>0.00 (1.00)</td>
</tr>
<tr>
<td>Hot D1</td>
<td>3.00 (4.00)</td>
<td>3.00 (4.00)</td>
</tr>
<tr>
<td>Hot D2</td>
<td>3.00 (4.00)</td>
<td>2.66 (4.00)</td>
</tr>
<tr>
<td>Hot LE</td>
<td>3.33 (4.00)</td>
<td>3.00 (4.00)</td>
</tr>
<tr>
<td>Hot neck</td>
<td>3.00 (2.67)</td>
<td>3.00 (2.83)</td>
</tr>
<tr>
<td>HOT TA</td>
<td>3.33 (4.00)</td>
<td>3.33 (4.00)</td>
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<tr>
<th>Pain threshold</th>
<th>Median (IQR)</th>
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<tbody>
<tr>
<td>PPT HT</td>
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<tr>
<td>PPT TH</td>
<td>434.00 (253.00)</td>
</tr>
<tr>
<td>PPT LE</td>
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<tr>
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<tr>
<td>PPT TA</td>
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<tr>
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<tr>
<td>PPT LE</td>
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<tr>
<td>PPT TA</td>
<td>520.67 (259.00)</td>
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<td>PPT LE</td>
<td>431.66 (287.50)</td>
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<tr>
<td>PPT neck</td>
<td>419.33 (143.00)</td>
</tr>
<tr>
<td>PPT TA</td>
<td>341.66 (287.50)</td>
</tr>
</tbody>
</table>

4.1. Detection thresholds

The findings of altered mechanical detection thresholds in the hand are in accordance with previous studies which reported elevated vibration thresholds in patients with CTS (Szabo et al., 1984; Imai et al., 1990; Lundborg et al., 1992; Laursen et al., 2006; Tucker et al., 2007). Some studies report altered thermal detection thresholds in the affected hand for cold but not warm stimuli. All locations outside the median nerve territory showed normal thermal detection thresholds which further weakens the hypothesis of a generalised impairment of somatosensory processing. The literature on thermal detection thresholds in patients with CTS is conflicting. Some studies report altered thermal detection thresholds in the affected hand (Westerman and Delaney, 1991; Goddsby and Burke, 1994; Lang et al., 1995; Tamburin et al., 2010) whereas others could not identify a significant thermal hypoaesthesia (Borg and Lindblom, 1988; de la Llave-Rincon et al., 2009). Ischemic nerve block which is known to affect predominantly myelinated fibres has been demonstrated to affect cold detection thresholds but not warm detection (Yarnitsky and Ochoa, 1991). Cold detection thresholds are therefore thought to depend on Aβ fibre function whereas warm detection is mediated by unmyelinated C-fibres (Fruhstorfer, 1984; Yarnitsky and Ochoa, 1991; Walk et al., 2009). The presence of cold but not warm hypoesthesia in our study may therefore reflect the preferential involvement of myelinated fibres in the included patient sample (Westerman and Delaney, 1991).
4.2. Pain thresholds

In contrast to previous studies reporting hyperalgesia as a reflection of central sensitisation (de la Llave-Rincon et al., 2009; Fernandez-de-las-Penas et al., 2009, 2010; Zanette et al., 2010), our sample of patients with CTS did not show signs of thermal or mechanical hyperalgesia. Wind-up ratios were also comparable to healthy participants. The only test which reached statistical significance was the PPT over the hypothenar area where notably the unaffected hand of patients demonstrated hypoalgesia compared to the healthy controls. Differences in patient populations may account for these divergent findings. With the exception of one publication (Zanette et al., 2010), studies which demonstrated widespread hyperalgesia did not strictly exclude coexisting neck pain (de la Llave-Rincon et al., 2009; Fernandez-de-las-Penas et al., 2009, 2010). Personal communication revealed that almost all patients in these studies (de la Llave-Rincon et al., 2009; Fernandez-de-las-Penas et al., 2009, 2010) reported concomitant neck pain (personal communication with C. Fernandez-de-las-Penas). This high proportion of coexisting neck pain in patients with CTS is in accordance with previously reported high prevalences of coexisting disorders such as neck pain (Pierre-Jerome and Bekkelund, 2003; Nora et al., 2004; Chow et al., 2005), shoulder/arm pain (Nora et al., 2004) or lateral epicondylalgia (Murray-Leslie and Wright, 1976) in patients with CTS. Neck disorders and lateral epicondylalgia have both been reported to lead to widespread hyperalgesia over the locations tested in those studies (Johnston et al., 2008; Fernandez-Carnero et al., 2009). A potential influence of coexisting disorders on previous findings of thermal and mechanical hyperalgesia can therefore not be excluded. In fact, our study suggests that CTS alone in the absence of neck or arm pain is not sufficient to alter mechanical or thermal pain thresholds.

To our knowledge, there is only one study using quantitative sensory testing in patients with CTS which rigorously excluded neck pain (Zanette et al., 2010). This study revealed that only patients with extramedian spread of symptoms showed signs of hyperalgesia in the median, radial and ulnar innervation area of the hand as well as in the forearm. As patients with proximal spread of symptoms (i.e. forearm, elbow, arm or anterior part of the shoulder) were included (Zanette et al., 2010), a potential influence of such proximal pain on hyperalgesia cannot completely be excluded. The present study complements the previous paper by Zanette et al. (2010) by including measurements at sites proximal to the elbow as well as on the asymptomatic side.

Despite the absence of hyperalgesia as determined by temperature or pressure readings, our study revealed that pain ratings at the thermal pain thresholds were significantly higher in the hand as well as at distant sites in patients with CTS as compared to healthy controls. Pain ratings at cold thresholds were elevated locally in the median nerve territory whereas heat pain ratings were elevated in a widespread manner including remote sites over the neck and the TA muscle. Although this distinct pattern is interesting, potential explanations remain speculative. Classically, local heat hyperalgesia is considered an indication for peripheral nociceptor sensitisation (Treede et al., 2004). However, peripheral sensitisation might not be responsible for the widespread nature of elevated pain ratings outside the median nerve territory observed in this study. Although the underlying mechanisms are not yet identified, heat hyperalgesia can be found in patients with central pain (Wasner, 2010). Considering the widespread distribution of the elevated pain ratings, central changes rather than peripheral nociceptor sensitisation are a plausible explanation.

A potential rationale for widespread elevated heat but not cold pain ratings may be distinct central processing of heat and cold stimuli. A particular subset of thalamic neurons responds exclusively to noxious heat whereas others respond as well to noxious cold (Lenz et al., 1993). Furthermore, the larger temperature differences that are needed for noxious cold to produce a similar pain perception as for noxious heat are another explanation (Morin and Bushnell, 1998). The inclusion of additional pain ratings at temperatures above pain threshold would further elucidate whether a steeper stimulus–response function may be responsible for an increase in heat pain ratings in patients with CTS. A potential peripheral substrate for the distinct findings for heat and cold pain ratings may be the different location of receptors for noxious heat and cold. Receptors that mediate noxious heat have been suggested to be superficially in the skin whereas receptors that mediate noxious cold are thought to be deeper (Morin and Bushnell, 1998). Another potential explanation could be the slightly higher – although not significantly different – heat pain thresholds in patients with CTS. Increased heat pain thresholds were however not consistently associated with higher pain ratings. For example, patients with CTS reported a higher pain rating at D2 on the affected side even though the difference in heat pain thresholds between groups was larger at D2 on the unaffected side where no difference in pain rating was present. We therefore believe that the statistically insignificant differences in heat pain thresholds are unlikely to be responsible for the identified higher pain ratings.

Even though the underlying mechanisms for the identified higher pain ratings remain speculative, a pre-existing generalised sensitivity to pain can be excluded as pain ratings were mainly elevated in the affected side and because the pain ratings to cold pain were not elevated outside the hand territory. Similarly, psychological factors which may account for elevated pain ratings in patient populations would not explain the differential effect on heat and cold pain ratings.

The present study could not reproduce previous reports of thermal and mechanical hyperalgesia in terms of temperature or pressure thresholds in patients with CTS (de la Llave-Rincon et al., 2009; Zanette et al., 2010). Potentially, a difference in disease severity of the included patient populations may account for these differences. Whereas the patient sample of the current study is comparable in terms of symptom duration and electrodiagnostic findings with previous studies (de la Llave-Rincon et al., 2009; Fernandez-de-las-Penas et al., 2009, 2010; Zanette et al., 2010), pain intensity ratings were substantially lower (mean VAS = 1.2 compared to 3.4–5.6 in previous studies (de la Llave-Rincon et al., 2009; Fernandez-de-las-Penas et al., 2009, 2010). The majority of patients reported paraesthesia but no or only mild hand pain as determined by the VAS (Jensen et al., 2003). This, together with lower ratings on the Boston carpal tunnel questionnaire, suggests that our patient population which was specifically limited to patients with symptoms restricted to the hand represented a milder form of CTS in terms of symptoms. Hypothetically, a progression of CTS symptom severity may be accompanied by the development of secondary pain sites as a manifestation of central mechanisms. Such a continuum would explain why we did not find thermal and mechanical hyperalgesia as determined by traditional QST threshold measurements in patients with symptoms limited to their hand. The presence of elevated pain ratings outside the median nerve territory may however be an early sign of potential involvement of central pain mechanisms in patients with CTS even in the absence of neck or arm pain. Further epidemiological studies are needed to elucidate whether coexisting disorders and widespread sensory changes develop over time, whether they are pre-existing or are only present in a distinct subgroup of patients with CTS. Future studies should include pain ratings at pain thresholds to further explore the possibility that pain ratings are more sensitive than quantitative sensory testing for detecting early signs of hyperalgesia in patients with mild neuropathic pain (Wasner and Brock, 2008).
Due to the design of the experiment, a potential order effect due to systematic testing of the unaffected side before the affected side has to be considered. In accordance with a recent publication (Maier et al., 2010), we decided to test the unaffected side first so that the patients perceived normal sensations before experiencing possible paradoxical sensations on the affected side. As there was no systematic trend of increased or decreased thresholds between sides and since the main findings of this study relate to the comparisons between patients and healthy participants, a potential order effect is unlikely.

In summary, patients with CTS in the absence of coexisting neck and arm pain present with hypoesthesia but not hyperalgesia in the median nerve innervation territory as determined by QST thresholds. Apart from elevated pain ratings during thermal pain testing, widespread signs of hyperalgesia were absent. CTS alone does therefore not account for sensory changes at distant sites as determined by traditional threshold testing. Future studies are however needed to clarify whether the identified elevated pain ratings during thermal pain testing are an early sign of involvement of central pain mechanisms in patients with CTS.

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Fig. S1. Pressure pain thresholds. Pressure pain thresholds (kPa) over the hypothenar. Lines represent median with dots marking single data points. Aff: affected CTS; unaff: unaffected CTS; m-aff: matched to affected healthy; m-unaff: matched to unaffected healthy.

Table S1
Demographic and clinical characteristics of patients with CTS.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom duration (months)</td>
<td>32.9</td>
<td>(37.7)</td>
</tr>
<tr>
<td>Hand pain intensity (VAS)</td>
<td>1.2</td>
<td>(1.8)</td>
</tr>
<tr>
<td>Boston Questionnaire symptom scale</td>
<td>2.6</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Boston Questionnaire function scale</td>
<td>0.6</td>
<td>(0.7)</td>
</tr>
<tr>
<td>LANSS</td>
<td>11.3</td>
<td>(5.9)</td>
</tr>
</tbody>
</table>

Classification of hand pain VAS
- No pain: 13 patients
- Mild pain: 11 patients
- Moderate pain: 1 patient
- Severe pain: 1 patient

Symptom distribution
- Median territory: 14 patients
- Extramedian territory: 12 patients

a Classification of the 100 mm hand pain VAS into no pain = 0–4 mm; mild pain = 5–44 mm; moderate pain = 45–74 mm; severe pain = 75–100 mm (Jensen et al., 2003).

b Classification of symptom distribution into “median” and “extramedian” territory was based on the interpretation of the hand diagrams (Zanette et al., 2006).