Muscle Hyperalgesia Correlates With Motor Function in Complex Regional Pain Syndrome Type 1


*Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands.
†Department of Biomechanical Engineering, Delft University of Technology, Delft, The Netherlands.
‡MIRA, Institute for Biomechanical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands.
§Noldus Information Technology BV, Wageningen, The Netherlands.

Abstract: At present it is unclear if disturbed sensory processing plays a role in the development of the commonly observed motor impairments in patients with complex regional pain syndrome (CRPS). This study aims to investigate the relation between sensory and motor functioning in CRPS patients with and without dystonia. Patients with CRPS of the arm and controls underwent comprehensive quantitative sensory testing and kinematic analysis of repetitive finger movements. Both CRPS groups showed thermal hypoesthesia to cold and warm stimuli and hyperalgesia to cold stimuli. A decreased pressure pain threshold reflecting muscle hyperalgesia emerged as the most prominent sensory abnormality in both patient groups and was most pronounced in CRPS patients with dystonia. Moreover, the decreased pressure pain threshold was the only nociceptive parameter that related to measures of motor function in both patients and controls. CRPS patients with dystonia had an increased 2-point discrimination as compared to controls and CRPS patients without dystonia. This finding was also reported in other types of dystonia and has been associated to cortical reorganization in response to impaired motor function. We hypothesize that increased sensitivity of the circuitry mediating muscle nociception may play a crucial role in impaired motor control in CRPS.

Perspective: This is the first study linking a sensory dysfunction, ie, muscle hyperalgesia, to motor impairment in CRPS. Circuitries mediating muscle nociception may therefore play an important role in impaired motor control in CRPS.

© 2013 by the American Pain Society

Key words: Complex regional pain syndrome, dystonia, quantitative sensory testing, motor impairments, pressure pain threshold.

Pain is intimately linked to changes in motor behavior. This may vary from findings that noxious stimuli are associated with nociceptive protective motor responses in experimental research to the occurrence of disabling abnormalities in motor control in conditions where pain has turned chronic. Complex regional pain syndrome (CRPS) is an example of a chronic pain condition in which motor impairments are commonly observed. Reported motor impairments in CRPS may vary from mild slowness of movement (bradykinesia) to prominent abnormal posturing (tonic dystonia). One of the central nervous system’s primary integrative functions is to use sensory information to control movement. Disturbances of this integrative function may lead to inappropriate motor performance. Against this background, it can be assumed that the pain and sensory disturbances found in CRPS contribute to the motor impairments of this condition. Several sensory abnormalities, including thermal and mechanical hyperalgesia and hypoesthesia, have been observed in CRPS, but it remains unclear if these sensory abnormalities...
Dysfunctions play a role in motor dysfunction in this syndrome. Additionally, studies have not evaluated tactile acuity and hand laterality judgments in combination with quantitative sensory testing (QST) measurements in the same study. Hand laterality judgments are used to examine the integrity of the cortical body scheme, which can be influenced by peripheral factors. Moreover, studies in CRPS have shown that patients take longer to recognize their affected hand and also found that this effect is related to the extent of pain.

Investigating both CRPS patients with and those without dystonia using the same comprehensive sensory test protocol in combination with a detailed quantitative examination of motor performance would allow drawing a clear conclusion regarding the role of sensory dysfunction in motor disturbances in CRPS. The aims of this study were therefore 1) to compare sensory function at different levels of the nervous system in CRPS patients with dystonia to that of CRPS patients without dystonia and healthy controls; and 2) to examine the relation between sensory functions and motor performance in the 3 groups.

Methods
Participants
All patients who were registered at our department with the diagnosis of dystonia in the context of CRPS were approached to participate in this study. Forty-eight patients with CRPS type 1 of the upper limb (with dystonia, n = 31; without dystonia, n = 17) and 42 age- and sex-matched healthy controls participated in this study between May 2009 and February 2011 (Table 1). CRPS was diagnosed according to criteria of the International Association for the Study of Pain. Tonic dystonia was defined as a condition in which continuous muscle contractions lead to abnormal postures, from which return to a neutral position is not possible or is possible only with great difficulty. The severity of the dystonia was assessed with the Burke Fahn Marsden (BFM) scale. Patients were excluded if they had lesions or diseases of the central nervous system, a genetic form of dystonia, or other conditions than CRPS that could account for the presence of dystonia. Healthy controls were not included if they had a history of lesions or diseases of the central or peripheral nervous system, or other conditions associated with pain and/or limited function of the extremities. The most affected hands of patients were included in the analysis.

Assessment of Pain
Patients were asked to rate their mean pain over the last week on a numeric rating scale (NRS), ranging from 0 to 10, where 0 is no pain, and 10 the worst pain imaginable. Moreover, patients filled out the McGill Pain questionnaire (MPQ) in which they had to indicate which words applied to their pain in the week before the measurement. The Pain Rating Index of the MPQ was used in the analysis.

Sensory Testing
The following QST measures were investigated according to the protocol developed by the German Network of Neuropathic Pain: warm detection threshold, cold detection threshold, heat pain threshold, cold pain threshold, pressure pain threshold, vibration detection threshold, and wind-up ratio. All tests were performed

<table>
<thead>
<tr>
<th>Table 1. Demographic and Clinical Information of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRPS WITH DYSTONIA</strong></td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>Age (mean, SD) in years</td>
</tr>
<tr>
<td>Disease duration (median, IQR) in years</td>
</tr>
<tr>
<td>Type of trauma, precipitating event</td>
</tr>
<tr>
<td>Soft tissue trauma</td>
</tr>
<tr>
<td>Fracture</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Spontaneous</td>
</tr>
<tr>
<td>No. of patients with 2 affected hands</td>
</tr>
<tr>
<td>BFM score (mean, SD)</td>
</tr>
<tr>
<td>NRS pain score (range, 0–10; mean, SD)</td>
</tr>
<tr>
<td>MPQ: Pain Rating Index (mean, SD)</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; IQR, interquartile range.

NOTE. P values for age and sex are based on comparisons between the 3 groups, while P values for the other variables are based on comparing the 2 CRPS groups; P values < .05 were considered significant.

*Chi-square tests.
† Chi-square tests.
‡ Mann-Whitney U tests.
§t-tests.
by a trained examiner in a quiet room where the temperature was held constant at 22 to 23°C. The assessor was not blinded to the subject's disease status. A 3 × 3-cm Peltier element (TSA 2001-II; Medoc, Ramat Yishai, Israel) was used to test thermal sensation (warm and cold detection thresholds, heat and cold pain thresholds). All tests were performed at the dorsum of the hands. The method of limits was used with temperatures increasing at a rate of 1°C/second, starting from the baseline temperature of 32°C, and with an interstimulus interval of 10 seconds. The safety cutoffs were 0° and 50°C. Patients were instructed to press a “stop” button when they felt the slightest change in temperature when testing detection thresholds, or at the first burning or stinging sensation when testing pain thresholds. When subjects did not perceive a detection or pain threshold, the maximum value was noted. The pressure pain threshold was measured over the m. abductor pollicis brevis with an electronic algometer (FPX50; Wagner Instruments, Greenwich, CT). A Vibrometer (Type II; Somedic, Stockholm, Sweden) was used to test the vibration detection threshold on the first metacarpal bone; the probe was held with a constant pressure of 450 gms, which was maintained with feedback displayed on the vibrometer. To assess the wind-up ratio, a custom-made pinprick of 256 mN was used. The pain score on a 0 to 100 NRS perceived after 1 stimulus was compared to the rating after a train of 10 successive stimuli applied at rate of 1/second. The pain rating after the train of stimuli was divided by the rating of the first stimulus. The wind-up ratio was not calculated when the first pain rating was scored zero. The mean of 3 measurements was calculated and used for further analysis, except for the wind-up ratio, which was performed only once.

**Two-Point Discrimination**

The 2-point discrimination was assessed with an aesthesiometer (Baseline; Fabrication Enterprises, White Plains, NY) and the stimuli were applied at the dorsum of the hands. After the instruction the participants were blindfolded. Testing started with 0-mm distance between the 2 points, gradually increasing the steps (steps of 1 mm, interstimulus interval of 7 seconds) until the subject was able to detect 2 points instead of 1. Then this distance was tested again; the value was registered when the subject confirmed the detection of 2 points during the repetition, or when only 1 point was detected the test continued with an increase of 1 mm. The mean of 3 measurements was calculated and used for further analysis.

**Hand Laterality Judgment Task**

In the hand laterality judgment task patients had to recognize the laterality of hands that were presented on a screen using the Recognise online program (Neuro Orthopaedic Institute, Adelaide, Australia). This program displayed 20 images of hands in varying poses, and patients were asked to indicate, with the keys “A” and “D” on the keyboard, whether a left or right hand was displayed. The mean accuracy as well as the response time of the correct responses were calculated over 2 trials.

**Motor Task**

A finger tapping task was used as an objective measurement of the motor abilities.54 A small strip of 2-cm-wide adhesive green tape was attached around the tip of the thumb and blue tape around the tip of the index finger. The lower arm was fixed to ensure the movement was performed in the horizontal plane. Participants were instructed and encouraged to open and close the thumb and index finger as fast as possible, and with the widest possible amplitude, for 30 seconds. All participants were able to watch their active hand. The movements were recorded with a digital color video camera at a frame rate of 60 Hz (Basler A601fc; Basler AG, Ahrensburg, Germany). The camera was mounted vertically on a stand above the area where the task was performed and was connected to a computer equipped with video tracking software (EthoVision Color-Pro 3.0; Noldus Information Technology, Wageningen, The Netherlands). The software was calibrated to convert the pixels to distance in the approximated plane of the finger movement. The video tracking software program calculated the X-Y coordinates of the centers of the colored tape at both fingertips and the distance between them as a function of time. Patients were excluded from this task when they were not able to voluntarily move their thumb and/or index finger. From the distance between the fingertips, we calculated 3 kinematic measures: mean velocity (velocity; cm/s), mean maximum amplitude (amplitude; cm), and mean frequency (frequency; Hz/s). We considered velocity as the most important measure because this parameter is the product of frequency and amplitude, and thus reflects the combined information. Both other measures were included to evaluate if any differences that would emerge between groups were caused by differences in amplitude, frequency, or both.

**Statistics**

Differences between baseline characteristics of patients and healthy controls were assessed with analysis of variance and t-tests for normally distributed continuous data, with the Kruskal-Wallis and Mann-Whitney U tests for non-normally distributed data, while frequencies and proportions were assessed with chi-square tests. Not all QST parameters were normally distributed, not even after log or other transformations (as determined by the Kolmogorov-Smirnov test and inspection of the normality plots); therefore, nonparametric statistics were used for all QST comparisons. Group comparisons for the QST data, 2-point discrimination, hand laterality judgment, and motor tasks were performed with the Kruskal-Wallis test, while Mann-Whitney U tests were used for post hoc comparisons. To investigate whether motor impairments were related to the outcomes of the sensory assessments, correlations between finger tapping amplitude, frequency, and velocity on the one hand and the pain score and all QST parameters on the other hand were calculated using Spearman’s rank order
Results

Sensory Testing

CRPS patients with dystonia showed sensory dysfunction at multiple levels compared to healthy controls (Table 2). In particular they showed a loss of function for warmth detection (\(P = .011\)), cold detection (\(P = .002\)), vibration detection \((P < .001)\), and 2-point discrimination \((P < .001)\). Moreover a gain of function was found for cold pain \((P = .006)\) and pressure pain \((P < .001)\).

CRPS patients without dystonia were less impaired in sensory functions compared to the CRPS with dystonia patients. They had a loss of function for the non-nociceptive stimuli warmth detection \((P = .007)\) and cold detection \((P = .003)\), and a gain of function for cold pain \((P = .017)\) and pressure pain \((P < .001)\).

The wind-up ratio did not differ between healthy controls and either patient group, but compared to healthy controls, pain levels after the first pinprick were significantly higher in CRPS patients with dystonia \((P = .001)\).

Baseline characteristics did not differ between CRPS patients with dystonia and CRPS patients without dystonia (Table 1). Compared to CRPS patients without dystonia, CRPS patients with dystonia had a larger gain of function for pressure pain \((P = .026)\).

Two-Point Discrimination

CRPS patients with dystonia had a larger loss of function for 2-point discrimination compared to CRPS patients without dystonia \((P < .001)\).

Table 2. Results of QST Measurements and Finger Tapping

<table>
<thead>
<tr>
<th>Measure</th>
<th>CRPS With Dystonia</th>
<th>CRPS Without Dystonia</th>
<th>Healthy Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm detection, °C</td>
<td>36.4 (34.7–43.5)*</td>
<td>36.4 (35.3–43.2)*</td>
<td>35.2 (33.4–36.1)</td>
<td>.007</td>
</tr>
<tr>
<td>Cold detection, °C</td>
<td>29.4 (28.0–30.9)*</td>
<td>30.0 (28.4–30.6)*</td>
<td>30.9 (30.1–31.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Heat pain, °C</td>
<td>41.7 (35.6–48.0)</td>
<td>44.7 (38.9–48.1)</td>
<td>43.7 (40.8–47.6)</td>
<td>.409</td>
</tr>
<tr>
<td>Cold pain, °C</td>
<td>26.5 (4.8–30.0)*</td>
<td>24.5 (12–26.7)*</td>
<td>13.8 (4.9–22.5)</td>
<td>.006</td>
</tr>
<tr>
<td>Pressure pain, kg/cm</td>
<td>2.0 (1.0–3.8)*</td>
<td>3.4 (2.2–5.6)</td>
<td>6.1 (4.9–6.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vibration detection, µm</td>
<td>.45 (.40–5.5)*</td>
<td>.35 (.20–1.05)</td>
<td>.22 (17–41)</td>
<td>.001</td>
</tr>
<tr>
<td>Wind-up ratio</td>
<td>1.4 (1–2)</td>
<td>1.4 (1–3.4)</td>
<td>2.0 (1–3)</td>
<td>.525</td>
</tr>
<tr>
<td>2-point discrimination, mm</td>
<td>27 (22–48)*</td>
<td>18 (13–23)*</td>
<td>19 (13–23)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NOTE: All measures are presented as median (interquartile range). Overall statistical comparisons were performed with the Kruskal-Wallis test; post hoc comparisons between groups with the Mann-Whitney U test. \(P\) values < .05 were considered significant. All sensory measures were performed in 29 or 30 of the CRPS patients with dystonia, except the vibration threshold and the 2-point discrimination (both \(N = 26\); in all 17 CRPS patients without dystonia, except 2-point discrimination \(N = 15\); and in all 42 controls, except vibration threshold \(N = 36\) and 2-point discrimination \(N = 41\). Missing values for the vibration threshold were mainly caused by temporary malfunctioning of this instrument. The finger tapping task was performed in 19 of the 31 CRPS patients with dystonia, 16 of the 17 CRPS patients without dystonia and in all 42 controls. Missing values in CRPS patients with dystonia were the result of the abnormal postures \(n = 9\), software failure \(n = 1\), severe allodynia \(n = 1\), and time constraints \(n = 1\). *Significant difference compared to controls. | Significant difference between CRPS with dystonia and CRPS patients without dystonia.

Hand Laterality Judgment

Overall tests showed a significant difference in response time \((P = .017)\) but not in accuracy of the hand laterality task \((P = .288)\). Post hoc tests showed that CRPS patients without dystonia were faster in recognizing their affected hand than CRPS patients with dystonia \((P = .004)\).

Motor Tasks

On the 30-second finger tapping task, all 3 finger tapping parameters, ie, velocity, amplitude, and frequency, were significantly different between the 3 groups (Table 2). Missing values were mostly due to the inability to voluntarily move the thumb and index finger in CRPS patients with dystonia (for detailed description of missing values see footnote Table 2).

CRPS patients with dystonia had a lower velocity than the control group \((P < .001)\) and exhibited a lower amplitude \((P < .001)\) and frequency \((P < .001)\). CRPS patients without dystonia also displayed a lower velocity \((P = .004)\) and amplitude \((P = .004)\), but not frequency \((P = .676)\) on the finger tapping task compared to the control group. CRPS patients with dystonia had a lower velocity \((P = .001)\) and frequency \((P = .002)\), but did not differ in amplitude \((P = .172)\) compared to CRPS patients without dystonia.

Relations Between Pain, Sensory Function, and Motor Performance

In CRPS patients with dystonia, correlations between pain scores and somatosensory tests showed only a significant correlation between the MPQ and the 2-point discrimination \((P = .005)\). The pressure pain threshold...
was significantly correlated with the finger tapping velocity ($P = .008$) and frequency ($P = .036$), as well as the BFM score ($P = .008$) (Table 3). The finger tapping task was correlated with neither the pain scores nor the BFM (data not shown).

The NRS score of CRPS patients without dystonia was correlated with the response time on the laterality task ($P = .034$). A significant correlation between pressure pain threshold and finger tapping velocity was found ($P = .044$). No other relations were found between pain and somatosensory measures, or between pain and finger tapping parameters.

In healthy controls the frequency of finger tapping was significantly correlated with the heat pain threshold ($P = .012$), pressure pain threshold ($P = .028$), and response time on the laterality task ($P = .004$).

### Discussion

Prior studies revealed that loss of thermal detection and hyperalgesia to cold and blunt pressure are commonly observed in patients with CRPS, regardless of the presence of dystonia. In this study, these findings were reproduced. In accordance with earlier studies, a decreased pressure pain threshold emerged as the most prominent sensory abnormality. We also found that CRPS patients with dystonia had a lower pressure pain threshold than CRPS patients without dystonia. Most importantly, pressure pain threshold was the only measure of nociceptive function that related to measures of motor function. In both CRPS groups, pressure pain threshold correlated with finger tapping velocity, whereas in CRPS patients with dystonia, pressure pain threshold also correlated with the BFM score, a clinical measure of dystonia severity. Recently, a correlation was found between pressure pain threshold and hand dexterity as measured by the Sequential Occupational Dexterity Assessment in patients with CRPS. This relation was established by using a dynamic causal modeling approach, and against expectations, the pressure pain threshold was predicted by impaired hand dexterity. Our study highlights the role of this sensory abnormality across the spectrum of motor deficits in patients with CRPS and may provide an important clue on the neural basis underlying impaired motor control in CRPS.

The pressure pain threshold is obtained through pressure algometry, a commonly used technique for quantification of pain from deeper tissue, and predominantly reflects muscle nociception, as cutaneous analgesia has a marginal influence on the test response. The primary afferents of muscle nociception are Class III and IV fibers, which correspond to Aδ and C fibers of the skin. Class III and IV afferents end predominantly in free nerve endings in fascia and muscle, near small blood vessels, although Class III fibers have been shown to also end in other receptors like the paciniform corpuscle, which respond to dynamic mechanical stimuli. The lower pressure pain threshold found in CRPS patients thus reflects muscle hyperalgesia and is most prominent in CRPS patients with dystonia. This latter finding questions whether continuous muscle contractions may contribute to muscle hyperalgesia. However, in healthy controls, higher muscle contraction levels were associated with higher pressure pain thresholds; and in patients with writer’s cramp and cervical dystonia, no differences in pressure pain thresholds of the hand and neck muscles were found in comparison with healthy controls. Together this indicates that the presence of muscle contractions per se seems an unlikely explanation for muscle hyperalgesia. Alternatively, muscle hyperalgesia may result from increased sensitivity of peripheral nociceptive afferents (peripheral sensitization) or from spinal neurons involved in nociceptive processing (central sensitization). Following tissue damage, which commonly precedes the onset of CRPS, mediators of inflammation released at the site of tissue injury sensitize the peripheral nociceptors, which in turn enhances sensory neuron background activity, lowers mechanical thresholds, and increases activity in response to suprathreshold stimuli. Additionally, vasomotor dysfunction, a common feature of CRPS, causes deep tissue ischemia, which may also lead to activation of muscle nociceptors, ectopic activation of sensory afferents, and inflammation. In CRPS

---

**Table 3. Correlation Coefficients of Sensory Profile Measurements With Finger Tapping Parameters**

<table>
<thead>
<tr>
<th>CRPS with dystonia</th>
<th>WDT</th>
<th>CDT</th>
<th>HPT</th>
<th>CPT</th>
<th>PPT</th>
<th>VDT</th>
<th>WUR</th>
<th>2PD</th>
<th>ACCURACY</th>
<th>RESPONSE TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity</td>
<td>0.15</td>
<td>-0.08</td>
<td>0.42</td>
<td>-0.19</td>
<td>0.59*</td>
<td>0.38</td>
<td>-0.01</td>
<td>0.19</td>
<td>-0.14</td>
<td>-0.15</td>
</tr>
<tr>
<td>Amplitude</td>
<td>0.13</td>
<td>0.17</td>
<td>0.38</td>
<td>-0.12</td>
<td>0.37</td>
<td>0.23</td>
<td>0.03</td>
<td>-0.06</td>
<td>-0.13</td>
<td>0.35</td>
</tr>
<tr>
<td>Frequency</td>
<td>0.12</td>
<td>-0.22</td>
<td>0.30</td>
<td>-0.15</td>
<td>0.48*</td>
<td>0.41</td>
<td>-0.39</td>
<td>0.23</td>
<td>-0.06</td>
<td>-0.42</td>
</tr>
<tr>
<td>CRPS without dystonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity</td>
<td>-0.05</td>
<td>0.18</td>
<td>-0.15</td>
<td>0.16</td>
<td>0.51*</td>
<td>-0.02</td>
<td>-0.49</td>
<td>-0.11</td>
<td>0.18</td>
<td>0.23</td>
</tr>
<tr>
<td>Amplitude</td>
<td>-0.12</td>
<td>-0.04</td>
<td>-0.15</td>
<td>0.14</td>
<td>0.49</td>
<td>0.02</td>
<td>-0.41</td>
<td>-0.16</td>
<td>0.25</td>
<td>0.42</td>
</tr>
<tr>
<td>Frequency</td>
<td>0.26</td>
<td>0.30</td>
<td>0.14</td>
<td>0.18</td>
<td>0.15</td>
<td>-0.18</td>
<td>-0.20</td>
<td>-0.18</td>
<td>0.14</td>
<td>-0.27</td>
</tr>
<tr>
<td>Healthy controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity</td>
<td>-0.06</td>
<td>0.14</td>
<td>0.08</td>
<td>-0.02</td>
<td>0.31</td>
<td>0.08</td>
<td>-0.17</td>
<td>-0.05</td>
<td>0.12</td>
<td>0.04</td>
</tr>
<tr>
<td>Amplitude</td>
<td>-0.11</td>
<td>0.06</td>
<td>-0.10</td>
<td>0.06</td>
<td>0.13</td>
<td>0.10</td>
<td>-0.18</td>
<td>-0.01</td>
<td>0.17</td>
<td>0.24</td>
</tr>
<tr>
<td>Frequency</td>
<td>0.22</td>
<td>0.11</td>
<td>0.39*</td>
<td>-0.11</td>
<td>0.36*</td>
<td>-0.17</td>
<td>-0.04</td>
<td>0.07</td>
<td>-0.08</td>
<td>-0.45*</td>
</tr>
</tbody>
</table>

Abbreviations: WDT, warm detection threshold; CDT, cold detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; PPT, pressure pain threshold; VDT, vibration detection threshold; WUR, wind-up ratio; 2PD, 2-point discrimination.

NOTE. Overall statistical comparisons calculated by Spearman’s rank order correlation; *P values < .05 were considered significant.

*Significant correlation.
patients, experimentally induced muscle acidosis in the first interosseous muscle of the hand led to an enhanced pain response of the affected side compared to the unaffected side and to healthy controls. These findings underscore the importance of increased sensitivity of the muscle nociceptors of the affected extremity in CRPS. Peripheral sensitization may play an important role in muscle hyperalgesia because intramuscular infusion of lidocaine attenuated muscle hypersensitivity in patients with chronic musculoskeletal pain.

Peripheral sensitization initiates—and possibly also maintains—central sensitization, which is associated with changes in anatomical and functional connectivity of spinal neurons that subserve nociception. Under these circumstances, which are thought to be particularly relevant in patients with CRPS, spinal nociceptive neurons are more excitable to peripheral input. Central sensitization is also associated with the development of hyperalgesia, allodynia, and the spreading of pain to adjacent noninjured areas. It seems unlikely that central sensitization only involves pathways that deal with nociception and not those that mediate a motor response to noxious stimuli. Indeed, in animal studies, central sensitization enhances nociceptive withdrawal reflexes and impairs spinally mediated simple motor learning tasks. However, these studies only evaluated cutaneous nociception and therefore do not inform on the role of muscle nociception in motor behavior. The effect of muscle nociceptor stimulation on motor function has been extensively investigated in studies applying acute experimental pain to healthy human controls. Although these studies reveal that, depending on the type of test condition (relaxed, isometric, or dynamic muscle contractions), experimental muscle pain influences the recruitment of muscle fibers, there is no convincing evidence for the development of increased muscle tone. Notably, these findings reflect acute experimental pain and cannot be directly extrapolated to conditions with chronic pain. Nevertheless, increasing evidence suggests that central sensitization may impair motor processing in CRPS. In patients with chronic CRPS, impairment of repetitive finger movements and drawing skills of the nonaffected extremity have been found that can only be explained by impaired central motor processing. Central sensitization is associated with a decrease of tonic and phasic action of inhibitory interneurons, which receive extensive sensory and supraspinal input and play a crucial role in the regulation of muscle tone and sensory perception. When these interneurons are impaired, motor neurons are exposed to uninhibited sensory and supraspinal input. Dystonia and pain in patients with CRPS respond to intrathecal administration of baclofen, a major neurotransmitter involved in central inhibition. Baclofen mimics the actions of gamma-aminobutyric acid (GABA) on the presynaptic GABA$_B$ receptor, and activation of this receptor inhibits the sensory input to motor neurons in the spinal cord. Collectively our findings suggest that circuitry mediating muscle nociception may contribute to the impaired motor control of patients with CRPS and that peripheral and, especially, central sensitization may play an important role. Given that our findings are based on correlations, definite inferences about causality cannot be made. In theory a third variable (eg, disease severity) could cause dystonia as well as more severe muscle hyperalgesia, which would also result in a significant correlation. However, given that the disease duration and pain scores were similar across both CRPS groups, we consider this less likely.

Motor impairments in CRPS have also been associated with changes in cortical networks involved in nociceptive processing and higher order motor control. However, from these studies it remains unclear if cortical changes are secondary to more distally localized spinal or peripheral changes in circuitry mediating nociception. We found that CRPS patients with dystonia performed worse on 2-point discrimination of the hands compared to CRPS patients without dystonia. Changes of 2-point discrimination—a measure of spatial tactile acuity—are associated with cortical reorganization. The impaired discrimination thresholds in CRPS patients with dystonia as compared to CRPS-only patients may reflect more prominent cortical reorganization as a result of a more impaired motor function because the pain scores of both groups were similar. This is further supported by the fact that higher 2-point discrimination thresholds have also been demonstrated in other forms of focal and generalized dystonia. Whereas previous studies found higher discrimination thresholds in CRPS patients without dystonia as compared to healthy controls, this finding was not confirmed in this study. The discrepancy between these findings may be the result of the relatively small group of CRPS patients without dystonia investigated, or it might be due to the measurement of different sites. Because dystonia patients frequently display flexion postures of the hand, measurements in this study were performed at the dorsum of the hand, whereas previous studies measured 2-point discrimination at the fingertip of the affected hands.

A test that involves a more cognitive task is the hand laterality judgment. Using this test is relevant because there is evidence that CRPS patient with and without dystonia experience disturbances of body perception. Although CRPS patients with dystonia were significantly slower than patients without dystonia on the hand laterality judgment task, we observed no difference between both patient groups and healthy controls.

Compared to these studies, our healthy control group performed worse, while our CRPS patients without dystonia were faster in recognizing their affected limb. Differences between studies could also have arisen from the number and type of images displayed, which varied from line drawings to pictures and from easy to difficult.
We examined whether variation in difficulty of the displayed pictures between groups could explain our findings, but no differences were observed. Interestingly, when the effects of (the expectation of) experimental induced hand pain were investigated, longer response times were shown toward the noninjected hand. These findings might reflect disturbed information processing and may provide interesting clues for future research in unraveling the development of body matrix disruptions in patients where the pain has turned chronic.

A few methodological issues must be considered when interpreting the results of this study. First, due to the physical characteristics of the condition, the assessor could not be blinded to the subject's disease status. A second limitation of this study is the relatively small sample size of the CRPS without dystonia patient group. This fact, combined with the relatively long disease duration of the patients in our study, could account for differences with other studies. However, both patient groups were similar with respect to pain levels and disease duration, allowing us to optimally control for these potentially confounding factors. Another point to consider is that we did not quantify disuse and therefore cannot rule out that this may have contributed to the differences between the CRPS patient groups.

To summarize, our findings suggest that circuitry mediating muscle hyperalgesia may play an important role in the motor impairments of CRPS. Longitudinal research is warranted to evaluate if changes in muscle hyperalgesia are associated with changes in muscle tone. Abnormalities of 2-point discrimination in CRPS patients with dystonia are in line with those reported in other causes of dystonia, and likely are associated with cortical reorganization in response to the more impaired motor function and decreased sensory input. The profile of other sensory disturbances in both CRPS patient groups agrees with findings of earlier studies and is likely attributable to the mechanisms that underpin disturbed sensory processing in this condition.

References


23. Kemler MA, Schouten HJ, Gracely RH: Diagnosing sensory abnormalities with either normal values or values from contralateral skin: Comparison of two approaches in complex regional pain syndrome I. Anesthesiology 93: 718-727, 2000


34. Moseley GL: Why do people with complex regional pain syndrome take longer to recognize their affected hand? Neurology 65:773, 2005


38. Moseley GL, Sim DF, Henry ML, Souvis T: Experimental hand pain delays recognition of the contralateral hand—evidence that acute and chronic pain have opposite effects on information processing? Brain Res Cogn Brain Res 25: 188-194, 2005


