Critical Review

Primary Somatosensory Cortex Function in Complex Regional Pain Syndrome: A Systematic Review and Meta-Analysis


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Abstract: That complex regional pain syndrome (CRPS) is associated with functional reorganization in the primary somatosensory cortex (S1) is widely accepted and seldom questioned. Despite more than a decade of research, there has been no systematic review of the CRPS literature concerning the changes in S1 function, and therefore the extent of these changes is unclear. Here we conduct a systematic review and meta-analysis to quantify the spatial and temporal aspects of S1 function in CRPS. A comprehensive search strategy identified functional neuroimaging studies of S1 in CRPS. We adhered to a rigorous systematic review protocol when extracting data and appraising risk of bias. Outcomes were grouped into spatial representation; activation levels, including disinhibition; peak latency of activation; and glucose metabolism. Meta-analysis was conducted where possible. Fifteen studies were included, all investigating upper-extremity CRPS. In patients with CRPS, the S1 spatial representation of the affected hand is smaller than that of the unaffected hand and that of non-CRPS controls; however, this evidence comes from only a few studies. There is no difference in activation, disinhibition, or latency of peripherally evoked S1 responses in CRPS. The risk of bias was high across studies, mainly from unclear sampling methods and unblinded analysis of outcomes.

Perspective: The evidence for a difference in function of the primary somatosensory cortex in CRPS compared with controls is clouded by high risk of bias and conflicting results, but reduced representation size seems consistent.

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Key words: Complex regional pain syndrome, neuroimaging, primary somatosensory cortex, cortical reorganization, S1.

Comprehensive regional pain syndrome (CRPS) involves multiple system dysfunction, severe pain, and disability. What causes CRPS is unknown and it is very difficult to treat effectively. Treatments that aim to "train the brain," which have shown promise in randomized controlled trials, were developed following reports that functional brain reorganization was associated with the development, maintenance, and treatment of CRPS. Many of these reports focus on the primary somatosensory cortex (S1), which holds a somatotopic map of the body's surface. Functional reorganization in S1 refers to a change in the response profile of S1 cells such that there is a shift in the location and/or magnitude of S1 activation evoked by cutaneous stimulation.
It is more than a decade since the first functional neuroimaging study of S1 in CRPS, yet there has been no systematic evaluation and meta-analysis of published findings. This is important because the sensorimotor cortex is widely assumed to be a suitable target for treatments, possibly because of the efficacy of such treatments in phantom limb pain. Without a systematic search and rigorous quality appraisal of the literature in CRPS, there is a high risk of selective literature sourcing and biased conclusions.

We aimed to quantify spatial and temporal aspects of the evoked response in S1 in people with CRPS. Specifically, we aimed to determine whether CRPS is associated with a difference in the S1 spatial representation of the affected body part and with altered S1 activity in terms of activation levels and latency of peripherally evoked responses.

Methods

Search Strategy and Screening

A sensitive search of MEDLINE, Embase, and Web of Science was conducted up to January 2, 2013. Free-text key words and Medical Subject Headings (MeSH) related to CRPS (and its synonyms), neuroimaging, and the brain were agreed upon by the investigators (Appendix A). The reference lists of several narrative reviews were hand-searched for any additional titles. Two independent investigators from within the team screened titles and abstracts, extracted data, and appraised risk of bias. In each case, the opinion of a third investigator from within the team was sought when consensus was not reached.

Study Eligibility

To be included, studies needed to 1) investigate the function of the primary somatosensory cortex (S1), 2) use neuroimaging, 3) report on adult humans with CRPS, and 4) compare S1 function in CRPS with controls (ie, healthy participant or the unaffected side). No restriction was placed on the duration of symptoms and year or language of publication. In-press or accepted studies were included. We excluded case studies (and studies that provided imaging findings for only 1 participant), studies with incidental S1 findings (eg, activations in S1 that resulted from a paradigm primarily conducted to assess the motor system), and studies in which CRPS patients did not make up at least 50% of the patient group.

Data Extraction and Risk of Bias

Custom-designed data extraction forms were used to extract the following study data (for both the patients and healthy controls, where applicable): study design, inclusion and exclusion criteria, source of study participants, participants’ age and gender, CRPS diagnostic criteria, pain intensity, CRPS duration, other clinical information given (eg, handedness), neuroimaging method, specifics of the investigative paradigm (eg, type and location of stimulation), and findings in S1 (eg, size of cortical representation, magnitude or latency of S1 activation, S1 glucose metabolism). If a study included follow-up data, only the baseline imaging data were extracted. If a study reported on more than 1 control group, only data from the pain-free control group were extracted. If required data were not reported in the study, we contacted authors a maximum of 3 times to request the data.

A risk of bias form was developed based on the STROBE statement and relevant items for case-control study designs from the Cochrane Collaboration’s tool for assessing risk of bias (see Supplementary Table 1).

Data Analysis

Studies were grouped according to the outcomes they reported on, resulting in 4 main outcomes:

- S1 spatial representation
- S1 activation levels—further divided into signal change, activation strength, and cortical disinhibition
- Peak latency of S1 responses
- S1 glucose metabolism

Where possible, the standardized mean difference (Hedge’s g—difference between means of each group divided by the pooled standard deviation) was calculated using Revman 5.0 (Cochrane Collaboration) to allow for comparison of S1 function in patients with CRPS versus controls between studies. Effect estimates were interpreted according to Cohen (Cohen’s $d$ —small; $d$ = moderate; $d$ = large). We pooled data for an outcome if we had data from at least 2 studies on that outcome, using a random-effects model. The $\chi^2$ test was used to detect statistically significant heterogeneity and the $I^2$ statistic to estimate the amount of heterogeneity. Statistically significant heterogeneity was considered present when $\chi^2$ P < .10. Substantial heterogeneity was considered present when $I^2$ >60%.

Results

We identified 1,027 studies. No additional titles arose from hand-searching the reference lists of potentially eligible studies and 6 reviews. Fifteen studies met the inclusion criteria. The inclusion process is detailed in Fig 1; notably, we excluded 12 case studies or studies with no healthy control group (or studies that only provided imaging data for 1 participant), 15 studies that were not primarily conducted to assess the sensory system/did not use sensory paradigms (ie, studies evaluating motor function, even if they presented S1 findings), 12 studies that did not investigate function in S1 (ie, they were investigating structure of S1, or function of other brain areas), and 13 studies with no baseline neuroimaging (ie, reviews and letters) (see Appendix B). Data are presented as effect estimates (95% confidence intervals [CIs]).

Study Characteristics

The included studies all presented unique data sets and investigated CRPS of the upper extremity, reporting on...
157 cases of CRPS and 197 controls (unaffected hand or healthy control group). Seven studies used functional magnetic resonance imaging (fMRI) 

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<tr>
<td>Risk of bias was high for many studies (see Table 2), mainly because of nonconsecutive or unclear sampling methods, unblinded assessment of neuroimaging outcomes, and unclear or selective reporting of outcomes. The studies with the lowest risk of bias were Freund et al, Pleger et al, and Maihöfner et al. In addition to their overall lower risk of bias, Pleger et al was the only study to report blinding of the study's outcome assessors (ie, outcome assessors were not aware whether the imaging was CRPS affected or control), and Freund et al and van Rijn et al were the only 2 studies to report recruitment of consecutive participants. A variety of diagnostic criteria was used to identify CRPS cases. Nine studies used Stanton-Hicks et al, 2 studies used Bruehl et al, 1 study used both Harden et al and Boas, 2 studies used Merksey et al, and 1 study used Harden et al; finally, 1 study was unclear regarding the diagnostic criteria used.</td>
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<th>Outcomes</th>
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<td>S1 Spatial Representation</td>
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<td>Five studies investigated the size of the representation of the CRPS-affected hand in S1, compared with that of the unaffected hand (see Fig 2). Four studies used MEG to record cortical responses to air-puff stimulation of the digits. One study used EEG to measure the cortical somatosensory-evoked potentials after electrical stimulation of the median and ulnar nerves. The pooled effect estimate of -1.08 (-1.58, -0.59) indicates that the representation size of the affected hand was smaller than that of the unaffected hand in CRPS patients. Although 3 studies compared CRPS with healthy controls (see Fig 2), data for the healthy controls were only reported by 2 studies. We were unable to obtain the data from the third study's authors. The pooled effect estimate was -1.09 (-1.86, -0.32), indicating that the representation size of the affected hand in CRPS patients was smaller than that of healthy controls.</td>
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</table>

One study measured the distance between the cortical representations of the hand and the lower lip. These authors observed a significantly shorter distance between the cortical representations of the hand and the lower lip in the CRPS-affected hemisphere (mean = 1.95 cm) compared with the unaffected hemisphere (mean = 2.76 cm). |

| S1 Activation Levels: Signal Change |
| Seven studies stimulated the CRPS-affected hand to investigate activation levels in S1 using fMRI (see Table 3). Six of these studies compared findings within participants (ie, affected vs unaffected hemisphere). Two studies used nonpainful paradigms; 1 used a graded nonpainful and painful stimulation paradigm; 1 used a paradigm of voluntary suppression of pain during painful stimulation; and finally Maihöfner et al imaged the effects of hyperalgesia and allodynia. The results were conflicting. Pleger et al reported a smaller cluster in the CRPS-affected hemisphere, Pleger et al reported a weaker blood oxygen level–dependent (BOLD) contrast in the CRPS-affected hemisphere, and Freund et al reported only a trend of S1 activation with stimulation of the CRPS-affected hand. In contrast to these results, however, Freund et al found no difference when comparing hemispheres. Maihöfner and colleagues compared hemispheres by providing identical stimuli to both sides but the stimulation was perceived as painful on the CRPS-affected side. (Note: The Maihöfner et al sample included 3 patients with lower-limb CRPS.) The cluster size was larger in the CRPS-affected hemisphere following stimulation of the CRPS-affected side. Four studies compared S1 activation in CRPS with healthy controls. Pleger et al reported a smaller activation in patients than in controls. However, Forster et al and Freund et al all reported no difference in the S1 activation between CRPS patients and healthy controls, using their painful stimulation paradigms. |

| S1 Activation Levels: Activation Strength |
| Six studies investigated the strength of the S1 response to hand stimulation, measuring cortical activation with MEG or EEG (see Fig 3). Five of these studies compared within participants. Two studies recorded SSEPs with median nerve stimulation, and 1 with ulnar nerve stimulation, resulting in 3 comparisons. Three studies used MEG to record responses to stimulation of the digits (D1 and D5); 2 studies used Merksey et al, and 1 study used Harden et al; finally, 1 study was unclear regarding the sample used. The pooled effect estimate of the studies evaluating nerve stimulation with SSEPs was -3.33 (-6.86, -0.20), suggesting no difference in strength of activation. However, the MEG studies evaluating digit stimulation yielded a pooled effect estimate of 2.02 (5.2, 3.53), consistent with findings from Juottonen et al, who reported a 25 to 55% stronger response in S1 to stimulation of the CRPS-affected hand than to stimulation of the unaffected hand. |

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Four studies compared the S1 activation levels in CRPS to healthy controls (see Fig 3). With regard to recording SSEPs, 2 studies stimulated the median nerve and 1 stimulated the ulnar nerve. One of these studies, van Rijn et al, measured both the N20 and N35 SSEP components, resulting in 5 comparisons. Two studies stimulated the index finger and recorded responses with MEG; Juottonen et al reported on 1 comparison and Vartiainen et al compared results to both the left and right hemispheres of controls, resulting in 2 comparisons. The pooled effect estimate of the EEG nerve stimulation studies, though close to significant at \( z = 0.41 \) (\( p = 0.68, 0.06 \)), and that of the MEG digit stimulation studies, \( z = 0.04 \) (\( p = 1.00, 0.91 \)), both indicate no difference in the strength or amplitude of the S1 response between groups.

### S1 Activation Levels: Cortical Disinhibition

Both Lenz et al and van Rijn et al investigated cortical disinhibition (see Fig 4), using different approaches. Lenz and colleagues compared between hemispheres and between CRPS patients and healthy controls; they recorded SSEPs with paired-pulse stimulation of the median nerve, reporting the paired-pulse ratio. They found no difference between hemispheres in paired-pulse ratio but a significantly increased paired-pulse ratio in CRPS (both hemispheres), compared with controls. van Rijn et al compared CRPS patients with dystonia to healthy controls and recorded SSEPs in spatially (simultaneous stimulation of the median and ulnar nerves vs mathematical sum of individually stimulating the 2 nerves) and temporally (single shocks vs paired shocks with interstimulus intervals of 20 and 40 ms) separated designs. The pooled effect estimate of .24 (\( z = 0.18, 0.67 \)) indicates no difference in cortical disinhibition between CRPS patients and controls in response to either spatial or temporal effects.

### Peak Latencies of S1 Responses

Four studies evaluated the difference in peak latency of S1 response to stimulation of the CRPS-affected hand versus the unaffected hand (see Fig 5). One study evaluated response to stimulation of both the median and ulnar nerves, recording SSEPs with EEG, resulting in 2 comparisons; 3 studies evaluated stimulation of the digits (D1 and D5; D2) using MEG, resulting in 4 comparisons. The pooled effect estimate of these studies, .14 (\( z = 0.43, 0.71 \)), suggests no difference between hands in terms of S1 response latency. Two studies investigated the difference in the latency of S1 responses between CRPS and healthy controls (see Fig 5). One study stimulated median and ulnar nerves, measuring SSEPs (both N20 and N35 components, resulting in 4 comparisons), and 1 study evaluated
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<td>Forster et al.</td>
<td>fMRI; BOLD at 1.5 T</td>
<td>Finger tapping, impact pain, tonic pain, light touch. Stimulated D2 and D3. Stimulation to both hands in patients; right hand in controls</td>
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<td>CRPS (Stanton-Hicks et al.(^{[62]})) vs healthy controls</td>
<td>7 (1/6)</td>
<td>27–68 (range)</td>
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<td>Freund et al.</td>
<td>fMRI; BOLD at 1.5 T</td>
<td>Graded electrical nonpainful and painful stimulation to D2 both hands. Instructed to concentrate on the stimulus</td>
<td>S1 signal change, to investigate for a generalized change in pain processing</td>
<td>CRPS type 1 (Stanton-Hicks et al.(^{[62]})) vs healthy controls</td>
<td>10 (5/5)</td>
<td>45 (28–61) (range)</td>
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<td>Freund et al.</td>
<td>fMRI; BOLD experiment with above</td>
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<td>CRPS type 1 (Stanton-Hicks et al.(^{[62]})) vs healthy controls</td>
<td>10 (5/5)</td>
<td>45 (28–61) (range)</td>
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<td>Juottonen et al.</td>
<td>306-channel, MEG</td>
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<td>Cortical SEFs to determine: Hand representation size (mm); strength of S1 activation (nAm) and latency of S1 responses (ms)</td>
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<td>45.4 (33–54) (range)</td>
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<td>CRPS (Harden et al.(^{[19]})) vs healthy controls (+ control group with nonneuropathic pain)</td>
<td>21 (9/12)</td>
<td>51 ± 10.8 (SD)</td>
<td>NRS 0–10</td>
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<td>Maihöfner et al.</td>
<td>37-channel MEG</td>
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<td>Cortical ECDs to determine: Hand representation size (mm); strength of S1 activation (nAm) and latency of S1 responses (ms)</td>
<td>CRPS upper limb (Stanton-Hicks et al.(^{[62]})) vs unaffected side</td>
<td>12 (3/9)</td>
<td>57.4 ± 18.7 (SEM)</td>
<td>NRS 0–100</td>
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\(^{[62]}\) Data obtained from Stanton-Hicks et al. (2012)
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<td>Maihöfner et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>fMRI; BOLD at 1.5 T</td>
<td>Painful pin-prick stimulation (over hyperalgesic skin) to affected limb; pin-prick to corresponding site on unaffected limb</td>
<td>S1 signal change, to explore central processing during hyperalgesia</td>
<td>10 patients with CRPS-1; 2 patients with CRPS-2 (Stanton-Hicks et al&lt;sup&gt;62&lt;/sup&gt;) vs unaffected side; 9 upper-limb affected; 3 lower-limb affected</td>
<td>Study Size (M/F): 12 (4/8)</td>
<td>Mean Age in Years: 45.3 ± 3.5 (SEM)</td>
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<td>Maihöfner et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>fMRI; BOLD at 1.5 T</td>
<td>Brush-evoked allodynia to affected side; brushing of the corresponding site on unaffected limb</td>
<td>S1 signal change, to explore allodynia-related brain areas—activations and deactivations</td>
<td>CRPS (Stanton-Hicks et al&lt;sup&gt;62&lt;/sup&gt;) vs unaffected side</td>
<td>Study Size (M/F): 12 (5/7)</td>
<td>Mean Age in Years: 47.5 ± 3.1 (SEM)</td>
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<td>32-channel EEG</td>
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<td>Mean Age in Years: 40 (19–64) (range)</td>
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<td>Pleger et al&lt;sup&gt;53&lt;/sup&gt;</td>
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<tr>
<td>Pleger et al&lt;sup&gt;52&lt;/sup&gt;</td>
<td>fMRI; BOLD at 1.5 T</td>
<td>Electrical stimulation to D2 on both hands.</td>
<td>S1 signal change (also an investigation of SII)</td>
<td>CRPS type 1 (Bruehl et al&lt;sup&gt;4&lt;/sup&gt;) vs unaffected side</td>
<td>Study Size (M/F): 17 (7/10)</td>
<td>Mean Age in Years: 40.1 ± 9.5 (SD)</td>
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<td>Shiraishi et al&lt;sup&gt;60&lt;/sup&gt;</td>
<td>PET</td>
<td>Identification of active brain areas, via glucose metabolism</td>
<td>CRPS patients (Harden et al&lt;sup&gt;18&lt;/sup&gt;; Boas et al&lt;sup&gt;2&lt;/sup&gt;) vs healthy controls. 14 upper-limb affected; 4 lower-limb affected</td>
<td>Not reported</td>
<td>Study Size (M/F): 18 (10/8)</td>
<td>Mean Age in Years: 10.4 (1–8) (range)</td>
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<td>Sinis et al&lt;sup&gt;61&lt;/sup&gt;</td>
<td>MEG</td>
<td>Pneumatic stimulation to D1 and D5 both hands. Also an fMRI motor study‡</td>
<td>Cortical SSEPs to determine hand representation size Before and after treatment</td>
<td>CRPS patients (IASP criteria not specified)</td>
<td>Study Size (M/F): 3 (2/1)</td>
<td>Mean Age in Years: 55.7 (ages: 60, 58, 49)</td>
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<td>Study</td>
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<td>Outcomes Assessed</td>
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<td>Somatosensory-evoked potentials</td>
<td>Electrical stimuli to median and ulnar nerves of both wrists; right arm in control group; investigated spatiotemporal interaction of nerve stimulation; Also recorded N9 and N14 components.</td>
<td>CRPS type 1 (Merksey et al[40]) vs healthy controls</td>
<td>33 (1/32)</td>
<td>39.7 ± 10.9 (SD)</td>
<td>Not reported</td>
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<td>9 years ± 6.4 (SD)</td>
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<td>Vartiainen et al[66]</td>
<td>306-channel MEG</td>
<td>Compressed-air tactile stimulation of D1, D2, and D5 of both hands. Instructed to concentrate on the stimulus; Also noxious laser stimulation—not an S1 investigation.</td>
<td>Cortical ECDs to determine: Hand representation size (mm); strength of S1 activation (nAm) and latency of S1 responses (ms)</td>
<td>8 (0/8)</td>
<td>45.5 (26–57) (range)</td>
<td>VAS 0–10 (5–8 (range)</td>
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<td>Chronic CRPS-type 1† (Stanton-Hicks et al[62]) vs healthy controls and unaffected side</td>
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<td>1–9 years (range)</td>
<td>9 (0/0)</td>
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<td>46 (28–57)</td>
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Abbreviations: T, Tesla; SEM, standard error of the mean; NRS, numerical rating scale; mA, milliamperes; nAM, nanoamperometers; SEFs, somatosensory-evoked fields; VAS, visual analog scale; SD, standard deviation; IASP, International Association for the Study of Pain; μV, microvolts; ECDs, equivalent current dipoles.

NOTE. All stimulation paradigms were nonpainful unless otherwise stated. All CRPS was upper limb, unless otherwise stated.

*Data from 6 of these patients were also used in Pleger et al.[53]
†Six of these patients also participated in Juottonen et al.[27]
‡Study outcomes not included in the current review.
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<td>N/A</td>
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<tr>
<td>Maihöfner et al34</td>
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<td>✹</td>
<td>✹</td>
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<tr>
<td>Maihöfner et al35</td>
<td>?</td>
<td>✹</td>
<td>✹</td>
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<tr>
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<td>?</td>
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<td>✹</td>
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<td>Shiaraishi et al85</td>
<td>?</td>
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<tr>
<td>Sinis et al61</td>
<td>?</td>
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<td>✹</td>
<td>✹</td>
<td>✹</td>
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<td>van Rijn et al65</td>
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<tr>
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<td>?</td>
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<td>✹</td>
<td>✔</td>
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<td>✘</td>
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<td>N/A</td>
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</table>

NOTE. ✔ = yes, or low risk of bias; ✘ = no, or high risk of bias; ? = unclear; N/A = criterion not applicable.
<table>
<thead>
<tr>
<th>Study</th>
<th>Cluster Size</th>
<th>t/z Score</th>
<th>Cluster Size</th>
<th>t/z Score</th>
<th>Comparison of Hemispheres in CRPS Patients</th>
<th>Any Further Comparisons Provided</th>
<th>Interpretations</th>
</tr>
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<tr>
<td>Forster et al(^1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None given</td>
<td>Cluster area no different in CRPS patients from healthy controls</td>
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<tr>
<td>Freund et al(^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>S1 activation only a trend with affected hemisphere minus unaffected hemisphere</td>
<td>No patient &gt;control/ control &gt;patient contrast exceeded 7 clusters</td>
<td>Trend only</td>
</tr>
<tr>
<td>Freund et al(^2)</td>
<td>Trend only</td>
<td></td>
<td>2 clusters found</td>
<td>z = 3.70 and 3.68</td>
<td>(Late phase of) tonic painful stimulation led to S1 activation in unaffected hemisphere; trend of activation in affected hemisphere</td>
<td>No suprathreshold clusters survived patient &gt;control contrast/control &gt;patient contrast</td>
<td>↓</td>
</tr>
<tr>
<td>Maihöfner et al(^4)</td>
<td>3150 mm(^3)</td>
<td>z = 8.14</td>
<td>881 mm(^3)</td>
<td>z = 4.65</td>
<td>Difference in signal: 2478 mm(^3), z = 5.57</td>
<td>Deactivation in S1 ipsilateral to painful pin-prick. 420 mm(^3), z = −3.80</td>
<td>↑</td>
</tr>
<tr>
<td>Maihöfner et al(^5)</td>
<td>3347 mm(^3)</td>
<td>z = 5.12</td>
<td>785 mm(^3)</td>
<td>z = 6.00</td>
<td>Difference in signal: 1857 mm(^3), z = 5.36</td>
<td>Deactivation in S1 ipsilateral to pain-free brushing. 702 mm(^3), z = −4.92</td>
<td>↑</td>
</tr>
<tr>
<td>Pleger et al(^6)</td>
<td>3 voxels</td>
<td>t = 4.3</td>
<td>34 voxels</td>
<td>t = 4.84</td>
<td>Difference in signal: 29 voxels, t = 4.4</td>
<td>Controls’ matched-hemisphere minus CRPS-hemisphere: 19 voxels, t = 6.6</td>
<td>↓</td>
</tr>
</tbody>
</table>

Abbreviation: N/A, not applicable.
index finger stimulation using MEG. When evaluating the N20 and N35 components, the results consistently demonstrate a nonsignificant effect estimate, suggesting no differences in latencies between groups. Although the MEG study yields significant large effect estimates for 2 comparisons (CRPS-affected hemisphere compared to both hemispheres of control participants), the overall pooled effect estimate of \(-0.68\) \([-1.50, 0.15]\) indicates no significant difference in S1 peak latency between groups.

**S1 Glucose Metabolism**

One study investigated activity in S1 with \(^{18}\)F-fluorodeoxyglucose PET in patients and healthy controls. They reported an inconsistent pattern of responsiveness; however, they concluded from their results that glucose metabolism in S1 is related to the area affected by pain in most cases.

**Discussion**

Our aim was to quantify spatial and temporal aspects of the evoked response in S1 in people with CRPS and to determine whether there is a difference in the S1 spatial representation of the affected body part. We found that in patients with CRPS the representation of the affected hand in S1 is smaller than both the unaffected hand and the hand of non-CRPS controls. The evidence suggests there is no difference in the activation strength in S1 comparing hemispheres in CRPS patients or comparing CRPS patients with non-CRPS controls. Two studies assessed cortical disinhibition in CRPS and had contrasting results. One study found bilateral sensory cortical disinhibition in S1 compared with non-CRPS controls; the other found no evidence of cortical disinhibition in CRPS patients with dystonia compared with non-CRPS controls. The results of this review demonstrate no significant differences in S1 peak latency after stimulation of the CRPS-affected and unaffected hands or comparing CRPS patients with non-CRPS controls. Finally, the results from 1 study on glucose metabolism in S1 present inconsistent and inconclusive patterns of neural activity.

Although we minimized threats to the validity of our own findings by using a comprehensive search strategy and adhering to standard methodology for systematic reviews, we acknowledge potential limitations. We were unable to retrieve additional data from several authors (mainly fMRI studies). Additionally, some studies did not report data on all of the participant groups that were recruited. Because we have included papers that aimed to investigate whole-brain activation in pain, it may be that we did not include studies that investigated S1 but did not report their findings. That unpublished nonsignificant findings threaten the validity of meta-analyses is well established.

In the included studies, there was an overall high risk of bias primarily introduced by nonconsecutive sampling, unblinded assessment of outcomes, and unclear or selective reporting of outcomes. These forms of bias are often associated with inflated effect sizes. Nonconsecutive sampling is important because some clinical signs that appear to be consistent with S1 reorganization, for example reduced tactile acuity, could enhance the likelihood that a patient is recruited to the study. It is interesting that imaging studies seldom report blinded data analysis, and may stem from the fact that current functional neuroimaging techniques are relatively new—the first fMRI experimentation in humans was in

**Figure 2.** Hand-size representation in S1: A forest plot of standardized mean differences. The effect estimate of each study (standardized mean difference) is indicated by a box and its 95% CIs are marked with a horizontal line. The pooled effect estimate, and its 95% CI, is denoted by the diamond. Results are displayed for comparisons between hemispheres in CRPS patients, and comparisons between CRPS patients and non-CRPS controls.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean CRPS</th>
<th>SD CRPS</th>
<th>Total CRPS</th>
<th>Mean Control</th>
<th>SD Control</th>
<th>Total Control</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
<th>IV, Random, 95% CI</th>
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<td></td>
<td></td>
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<tr>
<td>Juutinen 2002</td>
<td>7</td>
<td>3.2</td>
<td>6</td>
<td>12.5</td>
<td>3.7</td>
<td>6</td>
<td>13.6</td>
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<tr>
<td>Maihöfner 2003</td>
<td>8</td>
<td>3.8</td>
<td>12</td>
<td>13.7</td>
<td>7.8</td>
<td>12</td>
<td>34.1</td>
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<tr>
<td>Pleger 2004</td>
<td>1.1</td>
<td>1</td>
<td>7</td>
<td>3.2</td>
<td>1</td>
<td>7</td>
<td>13.3</td>
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<tr>
<td>Sinis 2006</td>
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<td>2.1</td>
<td>3</td>
<td>11.3</td>
<td>1.8</td>
<td>3</td>
<td>3.3</td>
<td>-2.29 [5.02, 0.44]</td>
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<tr>
<td>Vartiainen 2008</td>
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<td>5.7</td>
<td>12</td>
<td>10.5</td>
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<tr>
<td>Test for overall effect: Z = 4.30 (P &lt; 0.0001)</td>
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<tr>
<td><strong>2.1.2 CRPS vs healthy controls</strong></td>
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<tr>
<td>Pleger 2004</td>
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<td>7</td>
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<td>1.4</td>
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<td>11.45</td>
<td>9</td>
<td>57.9</td>
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<tr>
<td>Test for overall effect: Z = 2.76 (P = 0.006)</td>
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Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%
the early 1990s.\textsuperscript{55} Given that fMRI is still rapidly developing,\textsuperscript{56} there is likely to be much progress in the analysis and interpretation of imaging data. This could also underlie the apparent missing data or omission of results in some papers, or at least unclear aims or lack of regions of interest stipulated a priori. Use of inconsistent diagnostic criteria is also problematic because CRPS is diagnosed on the basis of signs and symptoms and the criteria for diagnosis have changed over the past 2 decades.\textsuperscript{4,19,20} Therefore, different studies may have investigated different underlying pathophysiologies.

There are consistent results of a smaller S1 representation of the CRPS-affected hand, from 5 studies investigating this outcome using MEG or EEG. Clarification with a more spatially precise method such as phase-encoded fMRI, which allows for fine-grained maps of single digits,\textsuperscript{3,38} may shed light on the biological mechanism by which the shrinkage occurs. One theory is that increased and ongoing nociceptive input leads to altered response profiles of cortical sensory neurons.\textsuperscript{36,54} Another is that reduced input from the periphery, because of lack of movement or less “weighting” assigned to the affected limb,\textsuperscript{30,48} leads to the altered response profile. Notably, a comparable shrinkage of S1 hand representation size, and a decrease in tactile acuity, following immobilization has been reported,\textsuperscript{32}

The only fMRI studies that found an increase in BOLD signal in the CRPS-affected hemisphere were those in which stimulation to the affected hand was painful.\textsuperscript{34,35} This raises the possibility that the hemisphere-specific increase in signal reflects upregulation within the somatosensory neuraxis, or perhaps the stimulus’s ability to capture attention,\textsuperscript{24} or that the S1 response to peripheral stimulation is purely intensity dependent. Adding weight to the possibility that other factors might contribute to BOLD changes is that the majority of MEG and EEG comparisons found no difference in the strength of S1 activation in response to nonpainful stimulation. There were 4 exceptions, but they are contrasting: 3 comparisons demonstrated higher activation in the CRPS-affected hemisphere than the unaffected,\textsuperscript{27,36} and 1 found lower activation in the CRPS-affected hemisphere than in healthy controls.\textsuperscript{31} The lack of consensus in activation strength might be explained by differences in methods. Small changes in activation may not be identified with fMRI using stimulation to a single site, or with standard analysis techniques. It may be that S1 activation can only be interpreted according to imaging technology and/or experimental paradigms.

![Figure 3](image-url)
The 2 studies of sensory cortex disinhibition had conflicting results. Lenz et al\textsuperscript{31} found changes in amplitude ratios indicative of bilateral cortical disinhibition in CRPS, whereas van Rijn et al\textsuperscript{65} found no difference in spatiotemporal interaction between CRPS and healthy controls, suggesting against cortical disinhibition in CRPS. That there is no clear consensus is important because cortical disinhibition is considered a key mechanism behind some of the behavioral findings in CRPS. Because S1 receptive fields are thought to be maintained by intracortical inhibition, reduced tactile acuity\textsuperscript{37,46} and the perception of a bigger limb\textsuperscript{43} are both consistent with the notion of cortical disinhibition.

The 2 studies of sensory cortex disinhibition had conflicting results. Lenz et al\textsuperscript{31} found changes in amplitude ratios indicative of bilateral cortical disinhibition in CRPS, whereas van Rijn et al\textsuperscript{65} found no difference in spatiotemporal interaction between CRPS and healthy controls, suggesting against cortical disinhibition in CRPS. That there is no clear consensus is important because cortical disinhibition is considered a key mechanism behind some of the behavioral findings in CRPS. Because S1 receptive fields are thought to be maintained by intracortical inhibition, reduced tactile acuity\textsuperscript{37,46} and the perception of a bigger limb\textsuperscript{43} are both consistent with the notion of cortical disinhibition.
with disinhibition. A similar behavioral effect observed during limb anesthesia or postsurgery has been attributed to the temporary loss of small-fiber inhibitory input, which has been shown in animals to evoke cortical disinhibition.\textsuperscript{28} In humans, nonphysiological stimulation of small-diameter fibers also induces distorted perceptions similar to those reported in CRPS,\textsuperscript{13} which suggests that cortical disinhibition can be evoked by both denervation and stimulation of the sensory afferents (see\textsuperscript{33} for a review). One possible answer to the disparity between the clinical and behavioral evidence of disinhibition and the neuroimaging evidence against it is that the behavioral and clinical effects are mediated by disinhibition elsewhere in the cortex. The posterior parietal cortex, which is critical for multimodal integration of sensory input and awareness, would seem a likely candidate.\textsuperscript{14} Clearly, again, further studies are required. What is more, that reports of disinhibition in the primary motor cortex in CRPS\textsuperscript{29} are subject to similar conjecture\textsuperscript{29} suggests that it is timely to apply the same rigorous methods to systematically synthesize that literature as we have done for S1.

The overall finding of no difference in latency between hemispheres or groups is important because it excludes the possibility that changes in cortical function simply reflect problems with transformation of the stimulus or transmission to the cortex. This has implications for clinical practice too: We can be confident that clinical tests, for example 2-point discrimination\textsuperscript{53} and mislocalization,\textsuperscript{37} are unlikely to be confounded by peripheral or spinal dysfunction.

It is important to recall that the current review extracted baseline imaging data. Stronger evidence for maladaptive cortical reorganization in CRPS arises from studies that prospectively map changes in cortical representation with treatment\textsuperscript{17} and correlate the reorganization with pain.\textsuperscript{36} Importantly, however, evidence of association between S1 functional changes and pain, or responses to treatment, does not shed light on causality, and the possibility remains that S1 functional changes simply reflect pain or disuse associated with CRPS. Disuse as a cause of S1 reorganization would conflict with data from amputees with and without phantom limb pain, where both groups are characterized by loss of sensory input but only the phantom limb pain group show S1 functional reorganization,\textsuperscript{10} although whether S1 changes cause pain remains an open debate.\textsuperscript{45} Clearly, longitudinal imaging studies that follow a patient from initial injury through to the development of CRPS are required. Such studies are problematic by virtue of the number of injured patients required to obtain a sufficient cohort of CRPS cases. However, recent development of a predictive model, whereby pain in the first 2 weeks after wrist fracture predicts subsequent development of CRPS (Moseley et al, 2012, unpublished data), makes a longitudinal imaging study more feasible. Further investigation into the nature of cortical reorganization, including consideration of posterior parietal and frontal cortices, should also help to elucidate the likely mechanisms of treatments targeted at cortical reorganization such as graded motor imagery,\textsuperscript{8,44} and tactile discrimination training.\textsuperscript{49} Critically, further studies should provide opportunities to improve upon current treatments and develop new treatments directly targeting cortical dysfunction.

This review identifies high risk of bias and a lack of consensus across the CRPS literature concerning S1. Our current thinking about the potential role of S1 reorganization in CRPS has stemmed from this literature. Aside from consistent demonstration of a smaller S1 representation of the CRPS-affected part, results vary between studies. Much of the variance might be a function of methodology, but we cannot know at this stage. Cortically targeted treatments of CRPS are being integrated in research and in the clinic. It is crucial that the research into mechanisms behind these treatments maintains a comparable pace.

**Acknowledgments**

We thank Neil O’Connell, Brunel University, for his advice on meta-analytical techniques and for review of earlier drafts of the manuscript. We thank Dr. Gian Domenico Iannetti, University College London, for his helpful advice on methodological issues.

**Supplementary Data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpain.2013.04.001.
45. Moseley GL: Making sense of "S1 mania"—Are things really that simple? Topical Iss Pain 5:121-134, 2006
63. Straube S, Derry S, Moore RA, McQuay HJ: Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. Cochrane Database Syst Rev;CD002918, 2010
Appendix A

Search Terms

CRPS search terms: Complex regional pain syndrome*; CRPS; Algodystrophy; Algoneurodystrophy; Shoulder-hand syndrome; Reflex sympathetic dystrophy; RSD; Sudek; Sudek’s atrophy; Sudeck; Sudeck’s atrophy; Causalgia; Sympathetically maintained pain; SMP; Posttraumatic dystrophy; Post-traumatic dystrophy.

Neuroimaging search terms: Imag*; Scan*; Neuroimag*; Neuroimag*; MRI; Magnetic resonance imaging; fMRI; functional magnetic resonance imaging; blood oxygen-level dependent contrast; BOLD contrast; Electroencephalogra*; Electrophysiology*; EEG; MEG; Magnetoencephalogra*; Positron emission tomography; PET; Voxel-based morphometry; VBM; CTscan; Computed tomography; Computerised axial tomography; Computerized axial tomography.

Brain search terms: Brain*; Cortic*; Cortex; Grey matter; Grey matter; Central nervous system; Sensor*; Pain.

Appendix B

Excluded Studies and Reasons for Exclusion

Twelve case studies (or studies providing imaging data for only 1 participant); studies with no healthy control group (eg, comparison to normative data or a control group with another pain disorder):


Primary Somatosensory Cortex Function in CRPS


Four studies of pain/pain disorders other than CRPS (or CRPS synonyms); or studies in which CRPS did not comprise >50% of the pain group:


Fifteen studies using paradigms aimed at investigating other systems (ie, majority were motor paradigms):

Di Pietro et al


Twelve studies that did not use imaging to investigate the function of S1 (ie, they were structural, or investigating function of other areas; majority related to the thalamus). This includes studies for which S1 data could not be separated from, for example, other sensory areas—even after contacting authors:


Fukui S, Shigemori S, Yamada N, Nosaka S: Chronic neuropathic pain with beneficial response to electroconvulsive therapy (ECT) and regional cerebral blood flow changes assessed by SPECT. Pain Clin 13:361-365, 2002


Thirteen studies with no reporting of baseline functional neuroimaging data (eg, letters or reviews):

Chojnowska E: Thalamic perfusion in reflex sympathetic dystrophy syndrome. Lancet 355:494, 2000; author reply 495
Förderreuther S: Clinical, electrophysiological and imaging findings in patients suffering from complex regional pain syndrome (CRPS). Klinische Neurophysiologie 35:237-242, 2004
Jankovic J, Van der Linden C: Dystonia and tremor induced by peripheral trauma: Predisposing factors. J Neurol Neurosurg Psychiatry 51:1512-1519, 1988
Oaklander AL: Bilateral somatosensory cortex disinhibition in complex regional pain syndrome type I. Neurology 78: 606, 2012; author reply 606-607
One pediatric study: