

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

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**Abstract:** Dysfunction in the central nervous system is thought to underlie the movement disorders that commonly occur in complex regional pain syndrome (CRPS), with much of the literature focusing on reorganization of the primary motor cortex (M1). Presumed changes in the M1 representation of the CRPS-affected body part have contributed to new CRPS treatments, which are increasingly being integrated in the clinic. We systematically investigated the evidence for altered M1 function in CRPS. We adhered to rigorous systematic review procedure in our search strategy, risk-of-bias appraisal, and data extraction. Eighteen studies comprising 14 unique data sets were included. The included studies used several neuroimaging techniques, whose outcomes we grouped into M1 cortical excitability, spatial representation, reactivity, and glucose metabolism, and conducted meta-analyses where possible. Risk of bias across studies was high, mainly due to missing data and unblinded assessment of outcomes. No definitive conclusions can be drawn regarding M1 spatial representation, reactivity, or glucose metabolism in CRPS. There is limited evidence for bilateral M1 disinhibition in CRPS of the upper limb. **Perspective:** Despite widely held assumptions of primary motor cortex dysfunction in complex regional pain syndrome, there is only evidence to support bilateral disinhibition, and there is high risk of bias across the literature.

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**Key words:** Complex regional pain syndrome, neuroimaging, primary motor cortex, cortical reorganization, disinhibition, M1.

**D**iagnosis of complex regional pain syndrome (CRPS) is made on the basis of ongoing pain and dysfunction in several body systems, including the motor system. Movement disorders such as weakness, poor motor control, and/or dystonia are common in CRPS, particularly as the disease progresses.<sup>37,62</sup> The reported prevalence of

movement dysfunction in CRPS varies<sup>61</sup>; one prospective study into the neurologic symptoms of CRPS reported that 97% of 145 patients had motor disturbances of the affected limb.<sup>2</sup> Another, a retrospective study, reported that movement disorders were present in more than 65% of their sample of 185 CRPS patients, with dystonia the most common of these disorders.<sup>62</sup> Dysfunction in the central nervous system is thought to underlie the motor changes seen in CRPS.<sup>13,19,37</sup> Although it is highly unlikely that this dysfunction arises from a single structure alone, much of the existing literature focuses on functional reorganization of the primary motor cortex (M1). Evidence of change in M1 function, not only in CRPS but also in other pain states such as low back pain<sup>59</sup> and phantom pain,<sup>6</sup> has contributed to noninvasive management strategies in CRPS, such as graded motor imagery<sup>44</sup> and mirror therapy.<sup>39</sup>

Despite the accumulating evidence for motor disorders in CRPS, and the emerging evidence in support of motor-based treatments, there is no published systematic review of the literature. Without a formal

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interrogation of the literature, using an a priori defined search strategy and quality appraisal of studies, there is a clear risk that we have come to biased conclusions regarding the role of the motor cortex in this disorder. We aimed to determine the extent of altered function in the primary motor cortex in CRPS using a systematic review and meta-analysis of the literature. In light of the results of our recent systematic review into the function of the primary somatosensory cortex (S1) in CRPS,<sup>10</sup> we were specifically interested in the evidence for disinhibition and altered spatial representation in M1.

## Methods

### Search Strategy and Screening

Key words and Medical Subject Headings (MeSH) related to CRPS and its synonyms, neuroimaging, and the brain were used in Medline, Embase, and Web of Science (Appendix A), up to March 6, 2013. The reference lists of reviews in the field<sup>19,37,52,54,58</sup> were searched for any additional titles. Two independent investigators from within the team screened titles and abstracts, extracted data, and appraised risk of bias, with a third investigator from within the team involved in the process when consensus was not reached.

### Study Eligibility

Inclusion in the current review required studies to investigate the function of the primary motor cortex, use neuroimaging, report on adult humans with CRPS, and compare M1 function in CRPS to controls (ie, healthy participant or the unaffected side of CRPS patients). Neuroimaging was defined here as any experimental method by which images of human brain function are created, including, for example, magnetic resonance imaging (MRI), positron emission tomography (PET), magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS). In-press or accepted studies were included. No restriction was placed on year or language of publication. Case studies (and studies that provided imaging findings for only 1 participant), studies with incidental M1 findings (eg, activations in M1 that resulted from a paradigm primarily conducted to assess the sensory system), and studies in which CRPS patients did not make up at least 50% of the patient group were excluded from the current review.

### Data Extraction and Appraising Risk of Bias

Data extraction forms were custom-designed, piloted on 2 studies, and then used to extract the following data: 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 M1 (eg, motor-evoked potentials (MEPs), size of M1 cortical representation, M1 reactivity). Where a study included follow-up data, only baseline imaging data were extracted. Where a study reported on more than 1 control group, we extracted data from the pain-free control group only. If required data were not reported, we requested the data from study authors, contacting them a maximum of 3 times.

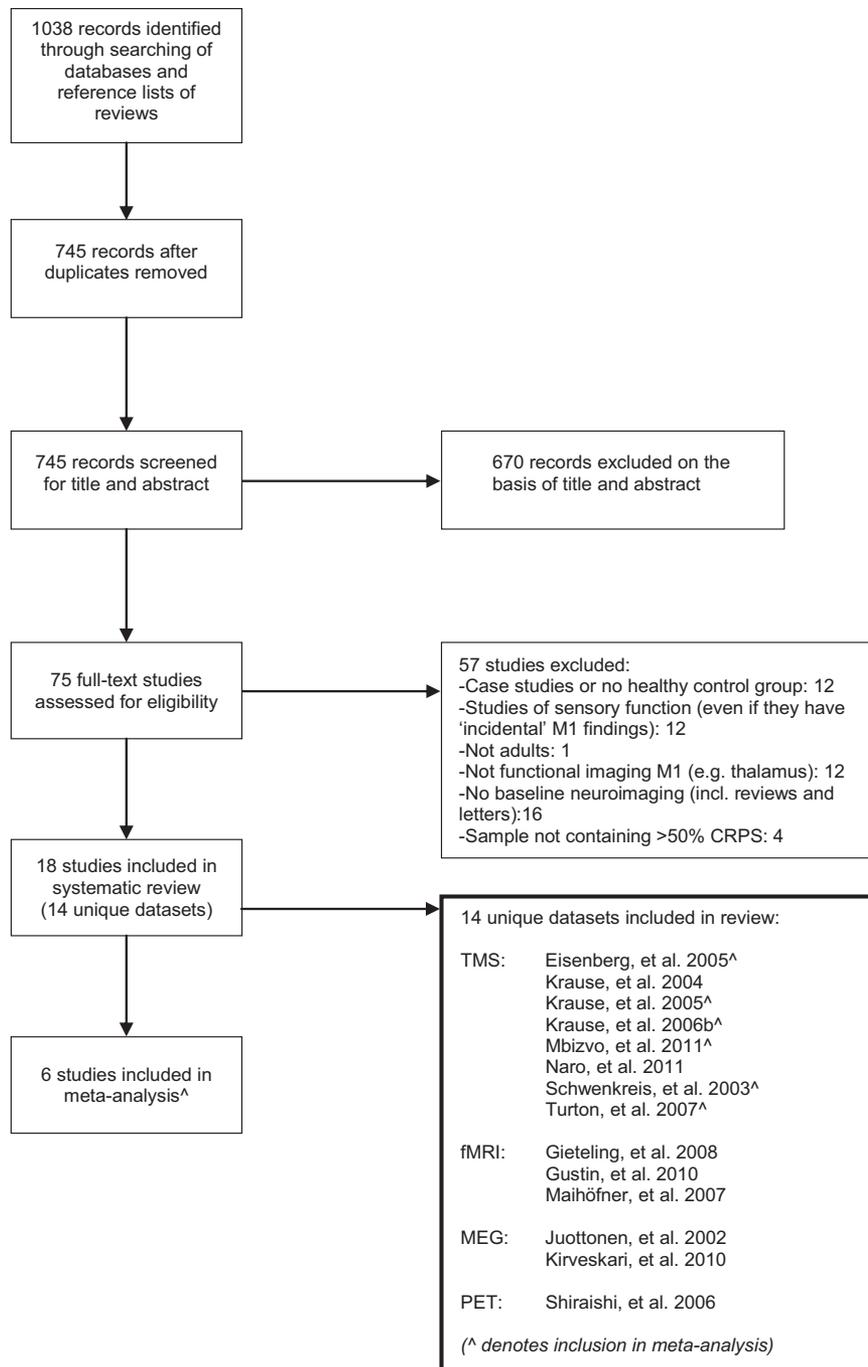
We based a risk of bias form on the STROBE statement<sup>64</sup> and items relevant to case-control studies from the Cochrane Collaboration tool for assessing risk of bias<sup>20,48</sup> (see Supplemental Table 1).

### Data Analysis

We grouped the included studies according to the outcomes they reported. Four main outcomes resulted: M1 cortical excitability, M1 spatial representations, M1 reactivity, and M1 glucose metabolism. The standardized mean difference (Hedge's *g*, the difference between means of each group divided by the pooled standard deviation) was calculated using Revman 5.0 (Cochrane Collaboration<sup>8</sup>), software used to construct and manage systematic reviews. This allowed for comparison of M1 function between CRPS patients and controls between studies. Effect estimates were interpreted according to Cohen's guidelines for effect sizes:  $\leq .2$  = small,  $.5$  = moderate,  $\geq .8$  = large.<sup>7</sup> Using a random-effects model, data were pooled for an outcome if we had access to data from at least 2 studies addressing that outcome. 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  $I^2 > 60\%$ .<sup>21</sup> All data are presented as effect estimates (95% confidence intervals).

## Results

A total of 1,038 studies were identified by the database search and hand-searching the reference lists of potentially eligible studies and 6 reviews.<sup>19,37,52,54,58</sup> After screening the title and abstract of all records, the full texts for 75 studies were sourced. Eighteen studies, comprising 14 unique data sets, 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), 12 studies that were not conducted to primarily assess the motor system/did not use motor paradigms (ie, studies evaluating sensory function, even if they presented M1 findings), 12 studies that did not investigate the function in M1 (ie, they were investigating structure or function of other brain areas), and 16 studies with no neuroimaging or no neuroimaging at baseline (including reviews or letters). (See Appendix B for a list of these excluded studies.) There were 4 samples that were reported on by 2 studies each: the samples of Gieteling et al,<sup>15</sup> Sinis et al,<sup>56</sup> Krause et al,<sup>30</sup> and Morgante et al<sup>42</sup>



**Figure 1.** Flow diagram detailing the screening and inclusion process for studies.

were included by Gieteling et al,<sup>14</sup> Gustin et al,<sup>16</sup> Krause et al,<sup>31</sup> and Naro et al,<sup>46</sup> respectively. Therefore, although 18 studies are included in the current review, risk of bias appraisal and data extraction were performed on 14 studies (see Fig 1 for list of included studies and those included in meta-analysis).

### Study Characteristics

All 18 of the included studies investigated CRPS of the upper limb, with 2 of these studies also recruiting people with CRPS of the lower limb.<sup>11,55</sup> The studies reported on a total of 169 cases of CRPS and 282 controls (unaffected

side or healthy controls). Ten studies used TMS to investigate excitability or spatial representation in the motor cortex<sup>11,28-31,38,42,46,51,60</sup>; 5 studies used functional MRI (fMRI) to investigate activation patterns with motor paradigms and map spatial representation in the motor cortex<sup>14-16,34,56</sup>; 2 studies used MEG to investigate motor cortex rhythms<sup>25,26</sup>; 1 study used PET to investigate widespread glucose metabolism.<sup>55</sup> Of the studies administering peripheral stimulation (including movement),<sup>14-16,25,26,34,56,60</sup> 3 studies administered stimulation that was perceived as painful by participants.<sup>14,15,26</sup> See Table 1 for study demographic information.

## Studies' Risk of Bias

There was an overall high risk of bias across the 14 studies (see Table 2). Excepting the conference abstracts, Naro et al<sup>46</sup> and Mbizvo et al,<sup>38</sup> and the letter, Krause et al,<sup>28</sup> from the appraisal, the bias across the remaining studies mainly arose from unblinded assessment of outcomes (ie, those who analyzed/interpreted the images were not blinded to the status of participants, or to which hemisphere was CRPS-affected) and from missing data. The 2 studies at lowest risk of bias overall were Krause et al<sup>31</sup> and Turton et al.<sup>60</sup> Notably, the only study to report consecutive sampling of participants was Eisenberg et al.<sup>11</sup>

There was a variety of CRPS diagnostic criteria used by the studies. Six studies<sup>16,25,26,34,51,60</sup> cited Stanton-Hicks et al,<sup>57</sup> with 1 of these<sup>26</sup> also citing Harden et al,<sup>18</sup> 1 study<sup>55</sup> cited Harden et al<sup>17</sup> and Boas,<sup>3</sup> 3 studies<sup>11,29,31</sup> cited Bruehl et al,<sup>5</sup> and 1 study<sup>14</sup> cited Merksey and Bogduk.<sup>40</sup> The letter<sup>28</sup> and the 2 conference abstracts<sup>38,46</sup> did not state the criteria used for diagnosis of their CRPS participants.

## Outcomes

### Cortical Excitability: TMS Studies

Ten studies investigated different parameters of cortical excitability using TMS. Six studies reported on the amplitude of the MEP at peripheral target forearm and hand muscles after stimulation of the motor cortex.<sup>28,29,31,38,51,60</sup> Five studies compared within participants, that is, between hemispheres (see Fig 2). There was no difference in MEP amplitude between hemispheres in CRPS patients, with a pooled effect estimate of  $-1.69$  ( $-3.43$ ,  $.05$ ). Six studies compared participants with healthy controls (see Fig 2). There was no difference in the MEP amplitude between CRPS patients and healthy controls, with a pooled effect estimate of  $-.75$  ( $-1.54$ ,  $.05$ ).

Three studies reported on motor threshold,<sup>28,31,51</sup> that is, the lowest TMS intensity needed to evoke MEPs in the target muscle when stimuli are applied to the motor cortex (refer to<sup>27</sup> for a review of TMS methods) (see Fig 3). Two of these studies compared findings within participants who had chronic CRPS; the pooled effect estimate of  $-.19$  ( $-.63$ ,  $.26$ ) indicating no difference between sides in the CRPS patients. Comparing chronic CRPS with healthy controls (see Fig 3) resulted in a pooled effect estimate of  $.24$  ( $-.24$ ,  $.72$ ), indicating no difference in motor threshold between the 2 groups.

Three studies used paired-pulse stimulation paradigms of the motor cortex, with a 1- to 4-ms interstimulus interval (ISI), to evaluate short-interval intracortical inhibition<sup>11,46,51</sup> (see Fig 4).<sup>11,46,47,54</sup> In addition, Eisenberg et al<sup>11</sup> presented data for the interaction of indirect waves (I-waves), also measuring cortical excitability via paired-pulse TMS with ISIs less than 4 ms. There was no difference when comparing hemispheres in participants with upper-limb CRPS (pooled effect estimate  $.63$  [ $-.28$ ,  $1.55$ ]) or when comparing hemispheres in participants with lower-limb CRPS

(pooled effect estimate  $.49$  [ $-.33$ ,  $1.31$ ]). Comparing upper-limb CRPS with healthy controls (see Fig 4) resulted in a pooled effect estimate of  $.89$  ( $.38$ ,  $1.40$ ), indicating a bilaterally higher MEP amplitude ratio of the test MEP in patients than in controls, that is, evidence of disinhibition. Consistent with these findings were those of Naro et al,<sup>46</sup> who reported significantly reduced short-interval intracortical inhibition in the CRPS-affected arm than in the healthy controls. No difference was demonstrated in the comparison of lower-limb CRPS with healthy controls, with a pooled effect estimate of  $.69$  ( $-.31$ ,  $1.69$ ).

Krause et al<sup>29</sup> investigated the silent period, normally defined as the time between the stimulus delivery and the return of voluntary activity, a measure believed to reflect inhibitory mechanisms at the motor cortex. They reported no difference in contralateral (patient mean  $52.62 \pm 11.9$  ms, control mean  $53.34 \pm 11.2$  ms) or ipsilateral (patient mean  $38.03 \pm 12.8$  ms, control mean  $27.63 \pm 11.4$  ms) cortical silent periods between CRPS and healthy controls.

Schwenkreis et al<sup>51</sup> examined intracortical facilitation using paired-pulse stimulation with a longer ISI (8–20 ms). They found no significant difference in intracortical facilitation between hemispheres of CRPS patients (affected hemisphere mean amplitude ratio  $136.7 \pm 96\%$  vs  $141.1 \pm 69.8\%$  for unaffected hemisphere), or between CRPS patients and control participants (controls mean amplitude ratio  $136 \pm 37.2\%$ ).

Turton et al<sup>60</sup> used TMS coupled with peripheral nerve stimulation, compared to the electromyographic response to TMS alone, in order to investigate sensorimotor interaction. They reported no difference (patients  $52.2 \pm 20.1\%$  vs controls,  $53.7 \pm 16.5\%$ ), thus demonstrating no evidence of abnormal suppression of electromyographic response in CRPS compared with healthy controls.

### Spatial Representations: TMS and fMRI Studies

Two studies used TMS to map the size and volume of the representation of the CRPS-affected hand in M1, comparing this with the unaffected hand and with healthy controls.<sup>31,38</sup> There was no difference when comparing the spatial representation of the CRPS-affected hand with that of the unaffected hand, with a pooled effect estimate of  $-.53$  ( $-1.42$ ,  $.36$ ) (see Fig 5). Similarly, there was no difference between CRPS and healthy controls, with a pooled effect estimate of  $.39$  ( $-.23$ ,  $1.00$ ) (see Fig 5). These 2 studies into spatial representation also mapped the center-of-gravity x- and y-coordinates for both patients and controls. Krause et al<sup>31</sup> reported larger variability in the center-of-gravity coordinates in CRPS, but no difference between hemispheres or groups. Mbizvo et al<sup>38</sup> reported on the difference between hemispheres, noting a greater asymmetry in the CRPS-affected hemisphere than the unaffected, and a tendency toward a lateral shift of the center of gravity in the CRPS-affected hemisphere.

Three studies investigated the M1 representation of the CRPS-affected hand with fMRI (measuring

Table 1. Study Demographics

| STUDY                             | MODALITY USED         | BASICS OF STIMULATION/<br>PARADIGM   | OUTCOMES ASSESSED  | CONDITION AND<br>COMPARISON  | CRPS PARTICIPANTS                     |                                     |  |  |   | Control Participants          |                      |
|-----------------------------------|-----------------------|--|--|--|---------------------------------------|-------------------------------------|--|--|---|-------------------------------|----------------------|
|                                   |                       |  |  |  | STUDY SIZE<br>(M/F)                   | MEAN AGE IN<br>YEARS                | MEAN RESTING<br>PAIN SCORE<br>AT BASELINE  | MEAN SYMPTOM<br>DURATION                           | MOTOR IMPAIRMENTS<br>(OBJECTIVE)  | STUDY SIZE (M/F)              | MEAN AGE IN<br>YEARS |
| Eisenberg et al <sup>11</sup>     | TMS; figure-of-8 coil | TMS applied to optimal scalp position M1. MEPs recorded with surface EMG from APB muscles of both wrists. Use of a single- and paired-pulse paradigm                               | rMT; aMT; MEP/M-wave amplitude ratio; CMCT; ICF; SICl; LICl; I-wave facilitation                                       | CRPS-type 1 (Bruehl et al <sup>5</sup> ) of the upper or lower limb vs unaffected side and healthy controls matched for age, gender, handedness                    | 12 total:<br>Hand (4/2)<br>Foot (5/1) | Hand:<br>33 ± 10<br>Foot:<br>32 ± 9 | VAS 0–10<br>Hand:<br>31 ± 41 months<br>Foot:<br>20 ± 21 months<br>Foot:<br>6.7 ± 2.3 | Hand:<br>31 ± 41 months<br>Foot:<br>20 ± 21 months | Motor/trophic changes in 11/12 subjects; immobility of affected limb in 11/12 | 14 (10/4)                     | 30.9 ± 12.7          |
| Gieteling et al, <sup>15*</sup> † | fMRI                  | Execution (painful) and imagined movement of wrist flexion/extension, both hands   | Cerebral activation, particularly in parietal cortex   | Reflex sympathetic dystrophy of the upper limb with dystonia and “normal” subjects   | 4 (gender not reported)               | Not reported                        | Not reported   | Not reported                                       | Presence of dystonia in all subjects  | 3 (gender not reported)       | Not reported         |
| Gieteling et al <sup>14</sup>     | fMRI at 3 T           | Execution (painful) and imagined movement of wrist flexion/extension, both hands   | Detection of activation in regions supporting primary motor function and higher-order motor control                    | CRPS (Merksey and Bogduk <sup>40</sup> ) and tonic dystonia of the right hand vs healthy controls matched for age. NB. Several patients had >1 CRPS-affected limb. | 8 (1/7)                               | 46.4 ± 6.0                          | Not reported   | 8.5 ± 3.0 years                                    | Presence of tonic dystonia in at least the right UL in all subjects           | 17 (2/15)                     | 42.9 ± 9.2           |
| Gustin et al <sup>16</sup>        | fMRI at 3 T           | Fist clenching of the affected and unaffected hands  | Detection of activation in pain processing, particularly sensory-discriminative, areas (before and after drug therapy) | CRPS of the upper limb (Stanton-Hicks et al <sup>57</sup> )<br>CRPS 1: 15<br>CRPS 2: 5   | 20 (8/12)                             | 50.9 ± 11.7                         | VAS 0–10<br>6.1 ± 2.3  | 16 ± 10 months                                     | Reduced ROM in all subjects   | Opposite limb used as control |                      |
| Juottonen et al <sup>25</sup>     | 306-channel MEG       | Compressed-air-driven tactile stimulation to index finger of both hands. Instructed to concentrate on the stimulus (+ somatosensory neuroimaging investigation, not included here) | Reactivity of the 20-Hz motor cortex rhythm (amplitude and duration of rebound) at rest and to tactile stimulation     | CRPS of the upper limb (Stanton-Hicks et al <sup>57</sup> ) vs unaffected side and healthy controls matched for age and gender                                     | 6 (0/6)                               | 45.4 ± 8.4                          | VAS 0–100<br>57.5 ± 17.8   | 42 ± 26 months                                     | Loss of strength, joint stiffness, tremor and restricted AROM in all subjects | 6 (0/6)                       | 45.1 (34–55) (range) |

Table 1. Continued

| STUDY                                  | MODALITY USED         | BASICS OF STIMULATION/<br>PARADIGM   | OUTCOMES ASSESSED  | CONDITION AND<br>COMPARISON   | CRPS PARTICIPANTS        |                          |   |                                      |   | Control Participants     |                            |
|--|-----------------------|--|--|---|--------------------------|--------------------------|---|--------------------------------------|---|--------------------------|----------------------------|
|  |                       |  |  |   | STUDY SIZE<br>(M/F)      | MEAN AGE IN<br>YEARS     | MEAN RESTING<br>PAIN SCORE<br>AT BASELINE | MEAN SYMPTOM<br>DURATION             | MOTOR IMPAIRMENTS<br>(OBJECTIVE)  | STUDY SIZE (M/F)         | MEAN AGE IN<br>YEARS       |
| Kirveskari et al <sup>26</sup>         | 306-channel MEG       | Single-pulse painful laser stimulation to the dorsum of both hands. Controls had 2 stimulation sessions: high intensity (VAS matched with patients) and low intensity (stimulation energy matched) | Reactivity of the 20-Hz motor cortex rhythm (amplitude and duration of rebound and suppression) at rest and to painful stimulation | CRPS of the upper limb (Stanton-Hicks et al <sup>57</sup> and Harden et al <sup>18</sup> ) vs unaffected side and healthy controls matched for age and gender | 8 (0/8)                  | 45.5 ± 10.5              | VAS 0–10<br>6.4 ± 1.8                     | 5.5 ± 3.1 years                      | Motor deficits in all subjects: reduced strength; ROM; difficulty in fine motor tasks                     | 8 (0/8)                  | 46.3<br>(28–52)<br>(range) |
| Krause et al <sup>28</sup><br>(letter) | TMS; circular coil    | TMS applied to optimal scalp position M1. MEPs recorded with surface EMG from long extensor muscles of both forearms   | rMT, MEP   | CRPS 1 of the upper limb vs unaffected side and healthy controls  | 11 (gender not reported) | Not reported             | Not reported                              | Not reported                         | Not reported  | 10 (gender not reported) | Not reported               |
| Krause et al <sup>29</sup>             | TMS; circular coil    | TMS applied to optimal scalp position M1. MEPs recorded with surface EMG from long extensor muscles of both forearms   | MEP; ICSP; cCSP ( <i>before and after a conditioning repetitive magnetic stimulation program</i> )                                 | CRPS 1 of upper limb (Bruehl et al <sup>5</sup> ) vs unaffected side and healthy controls   | 12 (2/10)                | 48.2 ± 15.6              | Not reported for all patients             | <6 months                            | Reduced AROM and weakness in 10/12 subjects; tremor in 3 subjects   | 10 (gender not reported) | 42.4 (only mean given)     |
| Krause et al <sup>30†</sup>            | TMS; figure-of-8 coil | TMS applied to hot spot on the motor cortex, MEPs recorded with EMG from long extensor muscles of both forearms  | Spatial representation in M1 (ie, size, volume); MEP; MT   | CRPS 1 (Bruehl et al <sup>5</sup> ) of the upper limb vs unaffected side and healthy controls   | 13 (4/9)                 | 37<br>(18–72)<br>(range) | Not reported for all patients             | 8 were <6 months<br>5 were >6 months | Reduced AROM in 8/14 subjects; weakness in 4; tremor in 2; hand closure in 1; reduced force in 2 subjects | 10 (4/6)                 | 38<br>(24–63)<br>(range)   |
| Krause et al <sup>31</sup>             | TMS; figure-of-8 coil | TMS applied to optimal scalp position M1. MEPs recorded with surface EMG from long extensor muscles of both forearms   | Spatial representation in M1 (ie, size, volume, COG, x- and y-coordinates); MEP; MT  | CRPS of the upper limb (Bruehl et al <sup>5</sup> ) vs unaffected side and healthy controls   | 14 (4/10)                | 37<br>(17–72)<br>(range) | Not reported for all patients             | 8 were <6 months<br>6 were >6 months | Reduced AROM in 9/14 subjects; weakness in 4; tremor in 2; hand closure in 1; reduced force in 2 subjects | 10 (gender not reported) | 38<br>(24–63)<br>(range)   |

Table 1. Continued

| STUDY                           | MODALITY USED      | BASICS OF STIMULATION/<br>PARADIGM   | OUTCOMES ASSESSED   | CONDITION AND<br>COMPARISON  | CRPS PARTICIPANTS   |                                   |   |                          |   | Control Participants    |                                      |
|---------------------------------|--------------------|--|---|--|---------------------|-----------------------------------|---|--------------------------|---|-------------------------|--------------------------------------|
|                                 |                    |  |   |  | STUDY SIZE<br>(M/F) | MEAN AGE IN<br>YEARS              | MEAN RESTING<br>PAIN SCORE<br>AT BASELINE | MEAN SYMPTOM<br>DURATION | MOTOR IMPAIRMENTS<br>(OBJECTIVE)  | STUDY SIZE (M/F)        | MEAN AGE IN<br>YEARS                 |
| Maihöfner et al <sup>34</sup>   | fMRI at 1.5 T      | Finger-tapping task at 1-Hz frequency, sequences of index finger to little finger reversed and repeated  | Detection of activation within the motor system during motor performance        | CRPS 1 of the upper limb (Stanton-Hicks et al <sup>57</sup> ) vs unaffected side and healthy controls matched for age and gender | 12 (2/10)           | 41.2 ± 8.7                        | NRS 0–10<br>3.92 ± .7                     | 52.2 ± 111<br>weeks      | Paresis present in all subjects; tremor present in 1 subject  | 12 (2/10)               | 43.2 ± 8.7                           |
| Mbizvo et al <sup>38*</sup>     | TMS                | TMS applied over motor hot spot. Peripheral measurements at first dorsal interosseus muscles, both hands   | Spatial representation in M1 (ie, size, volume, center-position); MEP           | CRPS of the upper limb vs unaffected side and healthy controls   | 5 (2/3)             | 50.6 ± 10.16                      | VAS 0-10<br>Not reported<br>for all       | 29.2 ± 28.8<br>months    | Weakness in 2 subjects; dystonia in 1 subject; mild stiffness in 2 subjects; no motor features in 1 subject | 9 (gender not reported) | Not reported                         |
| Morgante et al <sup>42*,†</sup> | TMS                | Peripheral recording from APB and FDI of both hands  | ICI; ICF; sensorimotor integration through SAI; synaptic plasticity through PAS | CRPS 1 of the upper limb vs unaffected side and healthy controls   | 10 (1/9)            | 55.5 ± 9.3                        | Not reported                              | 1.1 ± .6 years           | Fixed posture of the hand in all subjects   | 10 (1/9)                | 49.8 ± 4.5                           |
| Naro et al <sup>46*</sup>       | TMS                | Peripheral recording from APB and FDI of both hands  | ICI; ICF; sensorimotor integration through SAI; synaptic plasticity through PAS | CRPS 1 of the upper limb vs unaffected side and healthy controls   | 10 (1/9)            | 55.5 ± 9.3                        | Not reported                              | 1.1 ± .6 years           | Fixed posture of the hand in all subjects   | 10 (1/9)                | 49.8 ± 4.5                           |
| Schwenkreis et al <sup>51</sup> | TMS; circular coil | TMS applied over the vertex. MEPs recorded with surface EMG from FDI; both sides in patients and right hand only in controls. Use of a single- and paired-pulse paradigm | MT, MEP, ICI, ICF   | CRPS 1 of the upper limb (Stanton-Hicks et al <sup>57</sup> ) vs unaffected side and healthy controls                            | 25 (9/16)           | 50 (median)<br>(29–80)<br>(range) | VAS 0–10<br>3.5 ± 3.2                     | 26.1 ± 47.0<br>months    | Tremor in 5/25 subjects; dystonia in 1 subject  | 20 (10/10)              | 49<br>(median)<br>(20–78)<br>(range) |
| Shiraishi et al <sup>55</sup>   | PET                | <sup>18</sup> F-fluorodeoxyglucose PET   | Identification of active brain areas, via glucose metabolism                    | CRPS patients upper and lower limb (Harden et al <sup>17</sup> ; Boas <sup>3</sup> ) vs healthy controls                         | 18 (10/8)           | 40.7 ± 11.1                       | Not reported                              | 49.8 ± 59.2<br>months    | Not reported  | 13 (11/2)               | 38.7<br>(27–58)<br>(range)           |

Table 1. Continued

| STUDY                       | MODALITY USED                           | BASICS OF STIMULATION/<br>PARADIGM   | OUTCOMES ASSESSED  | CONDITION AND<br>COMPARISON  | CRPS PARTICIPANTS   |                      |   |                                  |   | Control Participants |                      |
|-----------------------------|---|--|--|--|---------------------|----------------------|---|----------------------------------|---|----------------------|----------------------|
|                             |   |  |  |  | STUDY SIZE<br>(MIF) | MEAN AGE IN<br>YEARS | MEAN RESTING<br>PAIN SCORE<br>AT BASELINE | MEAN SYMPTOM<br>DURATION         | MOTOR IMPAIRMENTS<br>(OBJECTIVE)            | STUDY SIZE (MIF)     | MEAN AGE IN<br>YEARS |
| Sinis et al <sup>56,†</sup> | fMRI BOLD at 3T;<br>(MEG <sup>‡</sup> ) | Fist clenching of the<br>affected and<br>unaffected hands;<br>(air-puff stimulation<br>of digits 1 and 5 <sup>‡</sup> )  | Identification of BOLD<br>signal, pre-and post-<br>treatment with<br>memantine   | CRPS of the upper limb<br>vs unaffected side   | 3 (2/1)             | 56 years             | VAS 0–10<br>9                             | Not reported<br>for all patients | Reduced ROM and<br>force in all<br>subjects | None                 |                      |
| Turton et al <sup>60</sup>  | TMS; figure-of-8 coil                   | TMS applied to optimal<br>scalp position M1.<br>MEPs recorded with<br>surface EMG from<br>APB muscle on<br>affected side in<br>patients; matching<br>side in controls.<br>Recording EMG<br>response to median<br>nerve stimuli paired<br>with subsequent<br>TMS. Compared<br>paired stimulation<br>with TMS alone. | Investigating<br>modulation of EMG<br>responses to TMS<br>induced by<br>concomitant median<br>nerve stimulation,<br>SAL. | CRPS 1 of the upper<br>limb (Stanton-Hicks<br>et al <sup>57</sup> ) vs healthy<br>controls matched for<br>age, gender,<br>handedness | 8 (1/7)             | 45 ± 13              | VAS 0–10<br>6.3 ± 1.4                     | 6.6 ± 4.9 years                  | Motor/trophic<br>changes in all<br>subjects | 8 (1/7)              | 45 ± 13              |

Abbreviations: EMG, electromyography; APB, abductor pollicis brevis muscle; rMT, resting motor threshold; aMT, active motor threshold; CMCT, central motor conduction time; ICI, intracortical inhibition; ICF, intracortical facilitation; SICI, short-interval intracortical inhibition; LICI, long-interval intracortical inhibition; VAS, visual analog scale; UL, upper limb; fMRI, functional MRI; ROM, range of motion; AROM, active range of motion; FDI, first dorsal interosseous muscle; SAL: short-latency afferent inhibition; PAS, paired-associative stimulation; iCSP, ipsilateral cortical silent period; cCSP, contralateral cortical silent period; COG, center of gravity; NRS, numerical rating scale; BOLD, blood oxygen-level dependent; 3T, 3 Tesla.

NOTE. All data reported as mean and standard deviation unless otherwise stated. All stimulation paradigms were nonpainful unless otherwise stated.

\*Conference abstract.

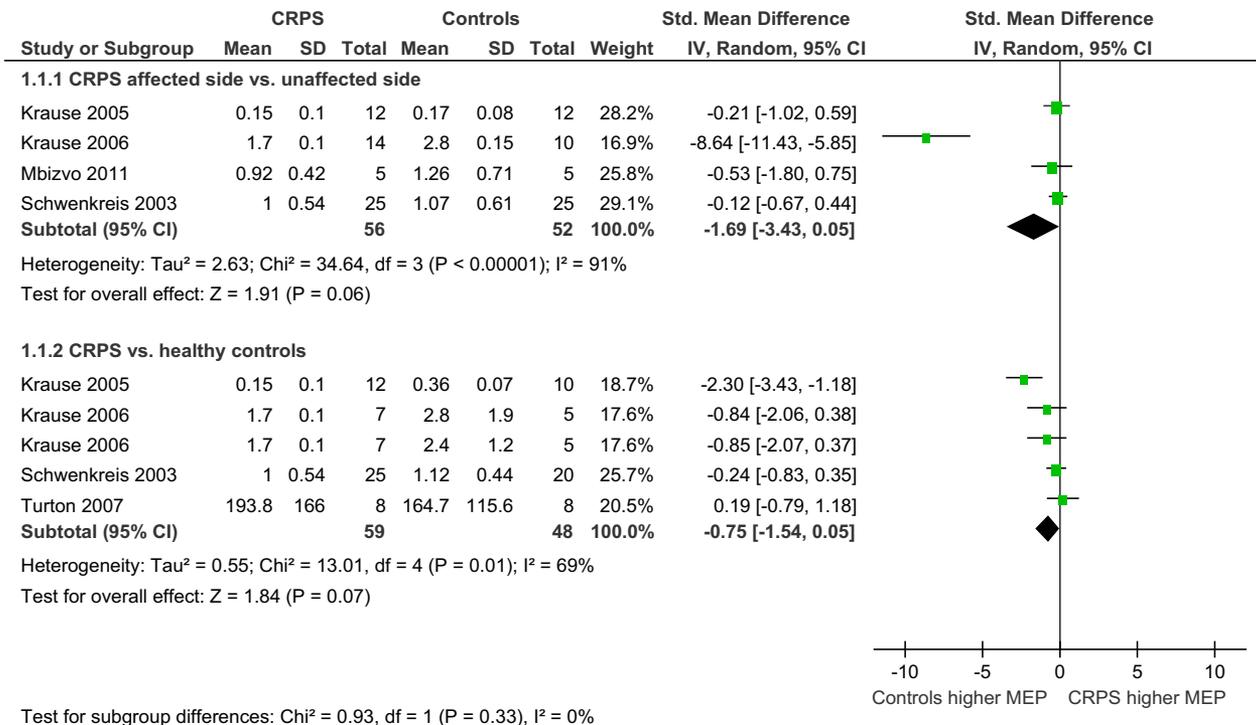
<sup>†</sup>Included in the current review but no data extraction or bias appraisal was completed, because the data set was duplicated by another study in the current review.

<sup>‡</sup>Somatosensory study; study outcomes not included in the current review.

**Table 2. Risk of Bias of Included Studies**

| STUDY  | SELECTION BIAS  |                        | DETECTION BIAS |                    | BLINDING | STATISTICAL METHODS |                        |                                  |                       |                      | REPORTING BIAS                  | PERFORMANCE BIAS  |
|--|-----------------|------------------------|----------------|--------------------|----------|---------------------|------------------------|----------------------------------|-----------------------|----------------------|---------------------------------|-------------------|
|  | SAMPLING METHOD | REPRESENTATIVE OF CRPS | CRPS DIAGNOSIS | DIAGNOSIS CONTROLS |          | OUTCOME ASSESSORS   | STUDY SIZE CALCULATION | BASELINE PATIENT CHARACTERISTICS | CONFOUNDING VARIABLES | MINIMAL MISSING DATA | MISSING DATA METHODS DESCRIBED? | OUTCOME REPORTING |
| Eisenberg et al <sup>11</sup>                    | ✓               | ✗                      | ✓              | ?                  | ?        | ?                   | ✓                      | ✓                                | ✓                     | N/A                  | ✗                               | ✓                 |
| Gieteling et al <sup>14</sup>                    | ?               | ✗                      | ✓              | ?                  | ?        | ?                   | ✓                      | ✓                                | ✓                     | N/A                  | ✓                               | ?                 |
| Gustin et al <sup>16</sup>                       | ?               | ✓                      | ✓              | ✓                  | ?        | ?                   | ✓                      | ✓                                | ✗                     | ✗                    | ✓                               | ✓                 |
| Juottonen et al <sup>25</sup>                    | ?               | ✗                      | ✓              | ?                  | ?        | ?                   | ✓                      | ✓                                | ✓                     | N/A                  | ✓                               | ✓                 |
| Kirveskari et al <sup>26</sup>                   | ?               | ✗                      | ✓              | ?                  | ?        | ?                   | ✓                      | ✓                                | ?                     | ✗                    | ✓                               | ✓                 |
| Krause et al <sup>28</sup> (letter)              | ?               | ?                      | ?              | ?                  | ?        | ?                   | ✗                      | ✗                                | ?                     | ✗                    | ?                               | ✓                 |
| Krause et al <sup>29</sup>                       | ?               | ?                      | ✓              | ✓                  | ?        | ?                   | ✗                      | ✓                                | ✓                     | N/A                  | ✓                               | ✓                 |
| Krause et al <sup>31</sup>                       | ?               | ✓                      | ✓              | ?                  | ?        | ?                   | ✓                      | ✓                                | ✓                     | N/A                  | ✓                               | ✓                 |
| Maihöfner et al <sup>34</sup>                    | ?               | ✓                      | ✓              | ✓                  | ?        | ?                   | ✓                      | ✓                                | ?                     | ✗                    | ✓                               | ✓                 |
| Mbizvo et al <sup>38</sup> (conference abstract) | ?               | ?                      | ?              | ?                  | ?        | ?                   | ✗                      | ✓                                | ?                     | ?                    | ✗                               | ✓                 |
| Naro et al <sup>46</sup> (conference abstract)   | ?               | ✗                      | ?              | ?                  | ?        | ?                   | ✓                      | ✗                                | ?                     | ✗                    | ✗                               | ?                 |
| Schwenkreis et al <sup>51</sup>                  | ?               | ✓                      | ✓              | ?                  | ?        | ?                   | ✗                      | ✓                                | ?                     | ✗                    | ✓                               | ✓                 |
| Shiraishi et al <sup>55</sup>                    | ?               | ?                      | ✓              | ✓                  | ?        | ?                   | ✗                      | ✗                                | ✓                     | N/A                  | ?                               | ✓                 |
| Turton et al <sup>60</sup>                       | ?               | ✗                      | ✓              | ✓                  | ?        | ?                   | ✓                      | ✓                                | ✓                     | N/A                  | ✓                               | ✓                 |

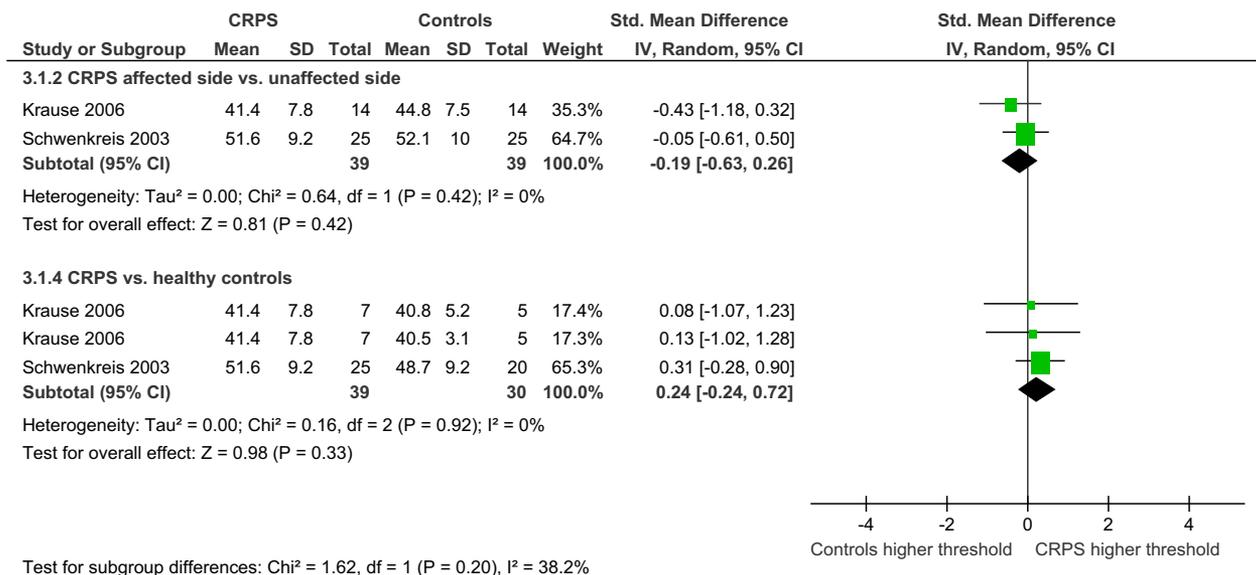
NOTE. ✓ = yes, or low risk of bias; ✗ = no, or high risk of bias; ? = unclear; N/A = criterion not applicable.



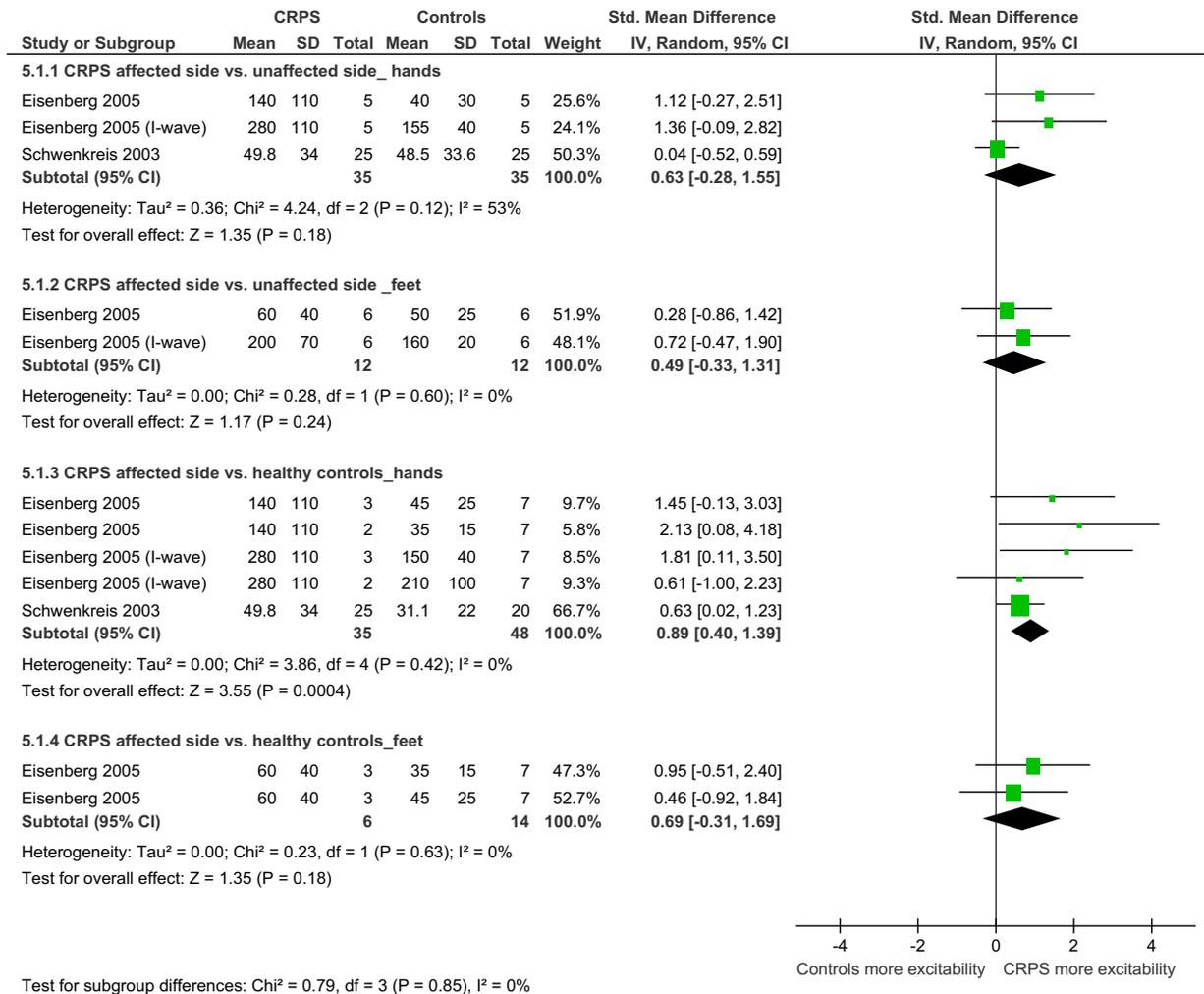
**Figure 2.** MEP amplitudes: a forest plot of standardized mean differences. The effect estimate of each study (standardized mean difference) is indicated by a box and its 95% confidence intervals (CIs) are marked with a horizontal line. The pooled effect estimate, and its 95% CIs, is denoted by the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

blood oxygen-level dependent [BOLD] contrast).<sup>14,16,35</sup> Gieteling et al<sup>14</sup> compared the activation that resulted from imagined and executed movements of both hands in CRPS patients and healthy controls. Patients demonstrated less activation than controls in the affected sensorimotor cortex during imagining of movement of the affected hand (study data were not available upon

our request). No between-group differences were found in any other conditions. Gustin et al<sup>16</sup> also compared movement of the CRPS-affected hand with that of the unaffected hand. They reported that movement of the CRPS-affected hand activated sensory regions relevant to pain processing; movement of both hands elicited activation in areas associated with motor function.



**Figure 3.** Motor thresholds: a forest plot of standardized mean differences. The effect estimate of each study (standardized mean difference) is indicated by a box and its 95% confidence intervals (CIs) are marked with a horizontal line. The pooled effect estimate, and its 95% CIs, is denoted by the diamond. Results are displayed for comparisons between hemispheres in CRPS patients, and comparisons between CRPS patients and non-CRPS controls.



**Figure 4.** Short-interval intracortical inhibition: a forest plot of standardized mean differences. The effect estimate of each study (standardized mean difference) is indicated by a box and its 95% confidence intervals (CIs) are marked with a horizontal line. The pooled effect estimate, and its 95% CIs, is denoted by the diamond. Results are displayed for comparisons between hemispheres in CRPS patients, and comparisons between CRPS patients and non-CRPS controls. Data are further divided into upper- and lower-limb CRPS.

Because of a lack of formal statistical comparison between hemispheres for motor function activation, this study provides little information to characterize motor function in CRPS.

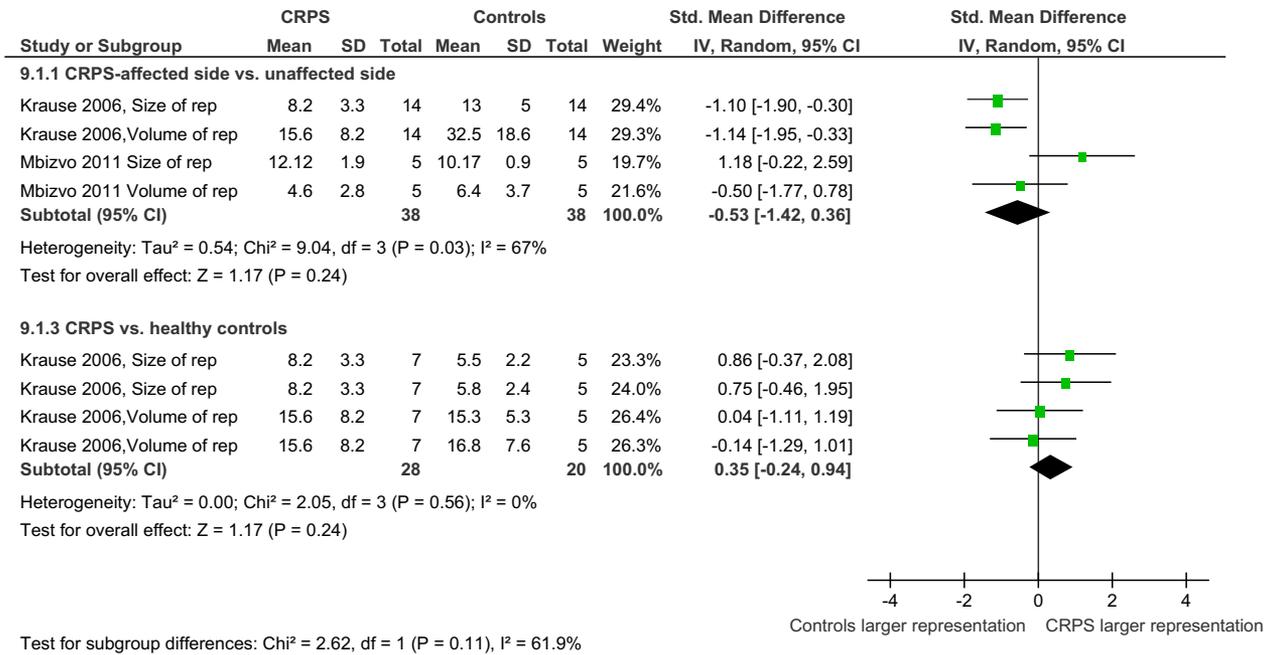
Maihöfner et al<sup>35</sup> compared the BOLD response to finger tapping in the CRPS-affected hand with that of the unaffected and with controls. They demonstrated more activation in M1 bilaterally during finger tapping on the CRPS-affected hand versus the unaffected hand (difference in cluster size in contralateral M1: 3,142,  $P < .0001$ ; ipsilateral M1: 554,  $P = .0001$ ) and the right hand in controls (difference in contralateral M1: 1,769,  $P = .0002$ ; ipsilateral M1: 3,250,  $P = .0003$ ).

**M1 Reactivity: MEG Studies**

Two studies used MEG to investigate for abnormalities in the 20-Hz rhythm that arises predominantly from the motor cortex.<sup>23</sup> Kirveskari et al<sup>26</sup> and Juottonen et al<sup>25</sup> investigated the spontaneous activity and changes in the reactivity of the 20-Hz rhythm to tactile<sup>25</sup> and noxious<sup>26</sup> laser stimulation. Both studies compared

within participants and to healthy controls. There was no difference between hemispheres or groups in the resting peak amplitude of the 20-Hz rhythm before stimulation in either of the 2 studies. Juottonen et al<sup>25</sup> reported no difference between hemispheres in the 20-Hz rebound duration after stimulation, or between hemispheres or groups for the average rebound amplitude. There was, however, evidence of a significantly shorter 20-Hz rebound duration in patients than healthy controls ( $P < .03$ ).

In the second study,<sup>26</sup> there were large differences in pain threshold between CRPS patients and healthy controls; therefore, the healthy controls in this study underwent 2 separate stimulation paradigms: a high-intensity stimulation (matched for visual analog scale scores with the patients), and a low-intensity stimulation (matched for stimulation energy with the patients). This study provided rebound amplitude and duration data, and suppression amplitude and duration data. The sum of these was expressed as reactivity amplitude. There was no difference between hemispheres in patients in



**Figure 5.** Spatial representation in M1: a forest plot of standardized mean differences. Data for representation size and volume are given. The effect estimate of each study (standardized mean difference) is indicated by a box and its 95% confidence intervals (CIs) are marked with a horizontal line. The pooled effect estimate, and its 95% CIs, is denoted by the diamond. Results are displayed for comparisons between hemispheres in CRPS patients, and comparisons between CRPS patients and non-CRPS controls.

any of these parameters, or between CRPS and healthy controls (either of the 2 stimulation conditions) in the rebound duration, the suppression duration, or the suppression amplitude. There was, however, a significant difference between the affected side of CRPS patients and the matched side of healthy controls undergoing the high-intensity stimulation in rebound amplitude ( $P = .05$ ) and in the summed reactivity amplitude ( $P = .03$ ).

### M1 Glucose Metabolism: A PET Study

Shiraishi et al<sup>55</sup> investigated the whole brain activity with <sup>18</sup>F fluorodeoxyglucose (FDG)-PET in CRPS patients and healthy controls. Regarding M1, they stated that patients showed contralaterally decreased glucose metabolism compared with controls.

## Discussion

We aimed to evaluate the evidence for altered function in the primary motor cortex in CRPS using a systematic review and meta-analysis of the literature. The findings suggest that there is no difference in the MEPs, motor thresholds, or cortical silent periods when comparing hemispheres in CRPS or comparing CRPS patients with healthy controls. Although there is no difference in intracortical inhibition between hemispheres, there is limited evidence of bilateral motor cortex disinhibition in CRPS of the upper limb, but not the lower limb. It is worth noting that the 1 TMS study that investigated lower-limb CRPS tested MEPs at an upper-limb site for all participants (ie, for upper- and lower-limb CRPS). It is possible that significant differences were not found for the lower-limb group because

disinhibition is specific to the M1 region representing the CRPS-affected body part. There is weak evidence of no abnormality in intracortical facilitation or suppression of the electromyographic response to paired-pulse stimulation in CRPS. There is no significant difference in size, volume, or center-of-gravity location between hemispheres or between groups. The fMRI studies investigating movement and imagined movement of the CRPS-affected hand reported on different outcomes; it was not suitable to pool their findings. The 2 MEG studies reporting on various components of the reactivity of the 20-Hz rhythm yielded mixed results. No definitive conclusion can be drawn from a single PET study on glucose metabolism.

As well as quantifying various aspects of motor cortex function in CRPS, an important aim of this review was to appraise the risk of bias in the existing literature. The variety in CRPS diagnosis employed by the studies might have moderated the results of the review. To address the potential problem of clinical heterogeneity in the pooled outcomes, we conducted sensitivity analyses based on disease duration and motor impairment. No differences in outcomes were seen based on these analyses (see Appendix C). The major issue that arose was the lack of blinding reported by the studies. That none of the studies in the current review, and only 1 study<sup>50</sup> in our recent review of S1 function,<sup>10</sup> reported on blinded statistical analysis might reflect the relative early stages we are currently at in functional neuroimaging analysis. It is well established, outside the world of neuroimaging, that blinded statistical analysis reduces the risk of bias in a study's results.<sup>41</sup> The lack of adequate methods for addressing missing data in neuroimaging studies was also highlighted in this review. There is a

high risk of bias in the conclusions of a study if only a nonrandom contingent of the recruited participants is included.

This review is the first to provide a comprehensive picture of the current state of functional imaging evidence in M1 for CRPS. Although we exhaustively searched the literature, we identified a limited number of original studies. This should be taken into account when interpreting the findings of our review. Because many different technologies and outcomes were included, the possibility of pooling the data was limited. Further, we were unable to obtain extra data from some authors.

We found no evidence of abnormality in MEPs or motor threshold. However, this finding cannot be interpreted to suggest that there is no change in cortical excitability levels—MEPs recorded at the periphery after M1 stimulation and the lowest TMS intensity needed to evoke consistent MEPs in peripheral target upper-limb muscles are not measures of cortical excitability; rather these single control stimuli reflect activity of the motor system in general.<sup>6,22,28</sup> This concept is important for the current review. The TMS studies varied in how clearly they stipulated their stimulation parameters; in some studies' methods it was not clear which outcomes were specifically being assessed and which physiologic mechanisms underpin these outcomes.

Motor cortex excitability is more appropriately addressed through paired-pulse stimulation paradigms that combine a subthreshold conditioning stimulus and a suprathreshold test stimulus at different ISIs to investigate intracortical inhibitory and facilitatory mechanisms.<sup>22,27,32,49</sup> In the current review, the pooled results of 2 such studies demonstrate evidence of a bilateral reduction in motor cortex inhibition in upper-limb CRPS.<sup>11,51</sup> Although there were only 3 studies that investigated this,<sup>11,46,51</sup> strength is added to the argument for motor cortex reorganization when these findings are interpreted alongside the evidence for bilaterally increased signal with movement of the CRPS-affected hand as detected with fMRI,<sup>34</sup> and bilaterally shorter rebound of the 20-Hz motor cortex rhythm in CRPS patients as detected with MEG.<sup>25</sup> That this functional reorganization seems to affect both hemispheres is interesting; Schwenkreis et al<sup>53</sup> compared motor cortex excitability in chronic neuropathic pain with that in chronic nociceptive pain and demonstrated that intracortical inhibition was unilateral, only affecting the hemisphere contralateral to the painful arm (after peripheral nerve lesion). The question is then, what is the difference between CRPS and other chronic painful conditions? What is observed clinically in CRPS—for instance, spreading of pain to other limbs, notably crossing the midline<sup>12</sup>—may be associated with the bilateral motor cortex effects seen here.

Evidence of bilateral motor cortex disinhibition conflicts with the existing evidence regarding disinhibition in the primary somatosensory cortex.<sup>10</sup> Lenz et al<sup>33</sup> found bilateral S1 cortical disinhibition compared with healthy controls (note however that there is also contention as to

whether or not this is in fact cortically mediated<sup>47</sup>), whereas van Rijn et al<sup>63</sup> demonstrated no difference in spatiotemporal interaction between CRPS and healthy controls, suggesting against S1 cortical disinhibition in CRPS. Despite conflicting results then, between S1 and M1, it seems that these changes, or lack thereof, are consistently bilateral.

Our recent systematic review demonstrated consistent evidence of a smaller S1 spatial representation of the CRPS-affected hand; in fact this was the only outcome that was significantly different between CRPS and non-CRPS controls.<sup>10</sup> It is intriguing then that we found no such difference in spatial representation in the primary motor cortex. This may be due to the nature of the stimulus used in a motor study, particularly with fMRI; a movement task of a CRPS-affected hand is arguably more difficult to standardize across participants than a sensory stimulation paradigm, and the mixed results in M1 spatial representation might reflect this. However it is also possible that spatial representation in M1, in contrast to S1, is not important with regards to CRPS signs and symptoms. Perhaps the motor dysfunction in CRPS is better characterized by changes in excitability and reactivity. There also remains the question of what is happening in the central nervous system in CRPS of the lower limb. The current review, together with our recent S1 review,<sup>10</sup> included only 3 studies that specifically recruited participants with lower-limb CRPS,<sup>11,36,55</sup> investigating different outcomes on a total of only 13 participants.

The aims of the fMRI investigations, though on the whole clearly stated, were different across the included studies and it was not feasible to pool findings. Two studies reported on the motor cortex as 1 part of widespread activations with given conditions.<sup>14,16</sup> When fMRI studies simply list the brain regions that activate or reach a certain threshold with a given condition, it is difficult to appreciate the reported effects or absence of effects. Indeed, there is a possibility that our search strategy did not source studies that may have in fact found activation in M1 but did not report on it. Also important in our critical appraisal is the statistical analyses used by the included fMRI studies, specifically the problem of correction for multiple comparisons. The 3 studies interpreted their results according to uncorrected, albeit conservative, probability values. In this way, the reader is not given an estimate of the percentage of false positives,<sup>1</sup> arguably crucial if we are comparing the results of the studies.

This review raises new questions concerning the efficacy of CRPS interventions that target the motor system. Graded motor imagery (GMI), which involves a progression from limb laterality training, to imagined movements and later to mirror movements, has supportive evidence from randomized controlled trials<sup>43,44</sup> and systematic reviews,<sup>4,9</sup> although it might be less effective when combined with a multimodal approach or when implemented incompletely.<sup>24</sup> GMI is based on the idea that implicit

motor imagery provides subthreshold inputs to M1 and reinstates normal inhibition.<sup>45</sup> The current finding seems consistent with that idea, although, importantly, the effect of graded motor imagery on disinhibition has not been evaluated. Clearly, further work is required, but the current review suggests that further investigation of bilateral motor cortex disinhibition might reveal important insights into how rehabilitation works when it does.

It seems that dysfunction of the motor cortex may be a bilateral phenomenon. As well as identifying the

surprisingly sparse literature that has so significantly contributed to our knowledge of motor cortex function in CRPS, the current review has highlighted the high risk of bias across the included studies, which needs to be addressed in future work.

## Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpain.2013.07.004>.

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63. van Rijn MA, van Hilten JJ, van Dijk JG: Spatiotemporal integration of sensory stimuli in complex regional pain syndrome and dystonia. *J Neural Transm* 116:559-565, 2009
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## 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, Post-traumatic 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\*, Electrophysiolog\*, EEG, MEG, Magnetoencephalogra\*, Positron emission tomography, PET, Voxel-based morphometry, VBM, CTscan, Computed tomography, Computerised axial tomography, Computerized axial tomography, transcranial magnetic stimulation, TMS, brain mapping.

Brain search terms: Brain\*, Cortic\*, Cortex, Gray matter, Grey matter, Central nervous system, Pain neuromatrix, Neuroanatom\*, Somatotop\*, nocicept\*, CNS, neuroplastic\*.

## 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):

Egloff N, Gander ML, Gerber S, von Kanel R, Wiest R: Chronic right-sided pain-associated nondermatomal somatosensory deficit following an accident [in German]. *Praxis* 99:797-801, 2010

Forss N, Kirveskari E, Gockel M: Mirror-like spread of chronic pain. *Neurology* 65:748-750, 2005

Hyman SA, Parris WC, Prysi NH, Skelley C, Lindsey K: Somatosensory evoked potentials are unchanged by reflex sympathetic dystrophy and by stellate ganglion block. *Clin J Pain* 7:226-229, 1991

Lai M-H, Wang T-Y, Chang C-C, Li T-Y, Chang S-T: Cerebellar diaschisis and contralateral thalamus hyperperfusion in a stroke patient with complex regional pain syndrome. *J Clin Neurosci* 15:1166-1168, 2008

Larbig W, Montoya P, Braun C, Birbaumer N: Abnormal reactivity of the primary somatosensory cortex during the experience of pain in complex regional pain syndrome: A magnetoencephalographic case study. *Neurocase* 12:280-285, 2006

Lin BF, Cherng CH, Fan YM, Wong CS, Huh BK, Yeh CC: Changes in regional cerebral blood flow and three-phase bone scan after repeated somatic nerve blocks for sympathetically independent pain. *Clin Nucl Med* 35:391-395, 2010

Moreau V, Berquin AD, Plaghki L: Laser-evoked potentials correlate with clinical evolution in a case of spontaneous and recurrent complex regional pain syndrome type I. *Clin J Pain* 23:375-379, 2007

Robberecht W, Van Hees J, Adriaensen H, Carton H: Painful muscle spasms complicating algodystrophy: Central or peripheral disease? *J Neurol Neurosurg Psychiatry* 51:563-567, 1988

Sinis N, Birbaumer N, Gustin S, Schwarz A, Bredanger S, Becker ST, Unertl K, Schaller HE, Haerle M: Memantine treatment of complex regional pain syndrome: A preliminary report of six cases. *Clin J Pain* 23:237-243, 2007

Steinstraesser L, Sand M, Steinau H-U, Stude P, Tegenthoff M: A case of cortical reorganisation demonstrated by means of functional MRI in a patient with a severe form of a complex regional pain syndrome. *J Plastic Reconstr Aesth Surg* 62:e542-e544, 2009

van de Beek W-JT, Vein A, Hilgevoord AAJ, van Dijk JG, van Hilten BJ: Neurophysiologic aspects of patients with generalized or multifocal tonic dystonia of reflex sympathetic dystrophy. *J Clin Neurophysiol* 19:77-83, 2002

Wu C-T, Fan Y-M, Sun C-M, Borel CO, Yeh C-C, Yang C-P, Wong C-S: Correlation between changes in regional cerebral blood flow and pain relief in complex regional pain syndrome type 1. *Clin Nucl Med* 31:317-320, 2006

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

Avanzino L, Martino D, van de Warrenburg BP, Schneider SA, Abbruzzese G, Defazio G, Schrag A, Bhatia KP, Rothwell JC: Cortical excitability is abnormal in patients with the "fixed dystonia" syndrome. *Mov Disord* 23:646-652, 2008

Egloff N, Sabbioni MEE, Salathe C, Wiest R, Juengling FD: Nondermatomal somatosensory deficits in patients with chronic pain disorder: Clinical findings and hypometabolic pattern in FDG-PET. *Pain* 145:252-258, 2009

Kishima H, Saitoh Y, Oshino S, Hosomi K, Ali M, Maruo T, Hirata M, Goto T, Yanagisawa T, Sumitani M, Osaki Y, Hatazawa J, Yoshimine T: Modulation of neuronal activity after spinal cord stimulation for

neuropathic pain; H(2)15O PET study. *Neuroimage* 49:2564–2569, 2010

Peyron R, Schneider F, Faillenot I, Convers P, Barral FG, Garcia-Larrea L, Laurent B: An fMRI study of cortical representation of mechanical allodynia in patients with neuropathic pain. *Neurology* 63:1838–1846, 2004

Twelve studies using paradigms aimed at investigating other systems (ie, sensory paradigms):

Forster C, Ringler R, Handwerker HO: Regional brain oxygenation during phasic and tonic painful stimulation. *Prog Brain Res* 129:303–311, 2000

Freund W, Wunderlich AP, Stuber G, Mayer F, Steffen P, Mentzel M, Schmitz B, Weber F: The role of periaqueductal gray and cingulate cortex during suppression of pain in complex regional pain syndrome. *Clin J Pain* 27:796–804, 2011

Freund W, Wunderlich AP, Stuber G, Mayer F, Steffen P, Mentzel M, Weber F, Schmitz B: Different activation of opercular and posterior cingulate cortex (PCC) in patients with complex regional pain syndrome (CRPS I) compared with healthy controls during perception of electrically induced pain: A functional MRI study. *Clin J Pain* 26:339–347, 2010

Lenz M, Hoffken O, Stude P, Lissek S, Schwenkreis P, Reinersmann A, Frettlöh J, Richter H, Tegenthoff M, Maier C: Bilateral somatosensory cortex disinhibition in complex regional pain syndrome type I. *Neurology* 77:1096–1101, 2011

Maihöfner C, Forster C, Birklein F, Neundörfer B, Handwerker HO: Brain processing during mechanical hyperalgesia in complex regional pain syndrome: A functional MRI study. *Pain* 114:93–103, 2005

Maihöfner C, Handwerker HO, Birklein F: Functional imaging of allodynia in complex regional pain syndrome. *Neurology* 66:711–717, 2006

Maihöfner C, Handwerker HO, Neundörfer B, Birklein F: Patterns of cortical reorganization in complex regional pain syndrome. *Neurology* 61:1707–1715, 2003

Pleger B, Ragert P, Schwenkreis P, Forster A-F, Wilimzig C, Dinse H, Nicolas V, Maier C, Tegenthoff M: Patterns of cortical reorganization parallel impaired tactile discrimination and pain intensity in complex regional pain syndrome. *Neuroimage* 32:503–510, 2006

Pleger B, Tegenthoff M, Ragert P, Forster A-F, Dinse HR, Schwenkreis P, Nicolas V, Maier C: Sensorimotor re-tuning [corrected] in complex regional pain syndrome parallels pain reduction. [Erratum appears in *Ann Neurol*. 2005 Apr;57(4):609]. *Ann Neurol* 57:425–429, 2005

Pleger B, Tegenthoff M, Schwenkreis P, Janssen F, Ragert P, Dinse HR, Völker B, Zenz M, Maier C: Mean sustained pain levels are linked to hemispherical side-to-side differences of primary somatosensory cortex in the complex regional pain syndrome I. *Exp Brain Res* 155:115–119, 2004

van Rijn MA, van Hilten JJ, van Dijk JG: Spatiotemporal integration of sensory stimuli in complex regional pain syndrome and dystonia. *J Neural Transm* 116:559–565, 2009

Vartiainen NV, Kirveskari E, Forss N: Central processing of tactile and nociceptive stimuli in complex regional pain syndrome. *Clin Neurophysiol* 119:2380–2388, 2008

Twelve studies which did not use imaging to investigate the function of M1 (ie, they were structural, or investigating function of other areas, majority were the thalamus). *This includes studies for which M1 data could not be separated from, for example, other motor areas—even after contacting authors:*

Apkarian AV, Thomas PS, Krauss BR, Szeverenyi NM: Prefrontal cortical hyperactivity in patients with sympathetically mediated chronic pain. *Neurosci Lett* 311:193–197, 2001

Eto F: Shoulder-hand syndrome following hemiplegia, 2: Clinicopathological study on the cerebral localization and its pathogenetic role [in Japanese (author's translation)]. *Nippon Ronen Igakkai Zasshi* 15:429–436, 1978

Fukui S: Evaluation of thalamic neural activity in CRPS type 1 patients by proton MR spectroscopy: A correlative study with rCBF. *J Anesth* 17:142–144, 2003

Fukui S, Shigemori S, Nosaka S: Changes in regional cerebral blood flow in the thalamus after electroconvulsive therapy for patients with complex regional pain syndrome type 1 (preliminary case series). *Reg Anesth Pain Med* 27:529–532, 2002

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

Fukumoto M, Ushida T, Zinchuk VS, Yamamoto H, Yoshida S: Contralateral thalamic perfusion in patients with reflex sympathetic dystrophy syndrome. *Lancet* 354:1790–1791, 1999

Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, Apkarian AV: The brain in chronic CRPS pain: Abnormal gray-white matter interactions in emotional and autonomic regions. *Neuron* 60:570–581, 2008

Iadarola MJ, Max MB, Berman KF, Byassmith MG, Coghill RC, Gracely RH, Bennett GJ: Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. *Pain*. 63:55–64, 1995

Kalita J, Vajpayee A, Misra UK: Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: a randomized controlled trial. *QJM* 99:89–95, 2006

Klase D, Bischof A, Haendler G, Spuck S, Rasche D, Tronnier V: Peripheral nerve stimulation: Lead position monitoring by reconstruction CT angiography—A technical report. *Acta Neurochir* 151:663–667; discussion 667, 2009

Thimineur M, Sood P, Kravitz E, Gudin J, Kitaj M: Central nervous system abnormalities in complex regional pain syndrome (CRPS): Clinical and quantitative evidence of medullary dysfunction. *Clin J Pain* 14:256–267, 1998

Walton KD, Dubois M, Llinas RR: Abnormal thalamocortical activity in patients with Complex Regional Pain Syndrome (CRPS) type I. *Pain* 150:41–51, 2010

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

Chojnowska E: Thalamic perfusion in reflex sympathetic dystrophy syndrome. *Lancet*. 355:494; author reply 495, 2000

Fonoff ET, Hamani C, Ciampi De Andrade D, Yeng LT, Marcolin MA, Jacobsen Teixeira M: Pain relief and functional recovery in patients with complex regional pain syndrome after motor cortex stimulation. *Stereotact Funct Neurosurg* 89:167–172, 2011

Forderreuther 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

Lang AE, Angel M, Bhatia K, Chen R, Fahn S, Hallett M, Schrag A, Thompson P: Myoclonus in complex regional pain syndrome. *Mov Disord* 24:314–316; author reply 316, 2009

Lee JYK, Baker K, Horenstein C, Deogaonkar MS, Machado AG, Lowe M, Phillips M, Stanton-Hicks M, Rezai AR: Functional magnetic resonance imaging of the brain during spinal cord stimulation for monoextremity complex regional pain syndrome. *Stereotact Funct Neurosurg* 85:35–36, 2007

Maihöfner C, Handwerker HO, Neundorfer B, Birklein F: Cortical reorganization during recovery from complex regional pain syndrome. *Neurology* 63:693–701, 2004

Maihöfner C, Neundorfer B, Birklein F, Handwerker HO: Mislocalization of tactile stimulation in patients with complex regional pain syndrome. *J Neurol* 253:772–779, 2006

Norris JW, West A: Thalamic perfusion in reflex sympathetic dystrophy syndrome. *Lancet* 355:495; author reply 495, 2000

Oaklander AL: Bilateral somatosensory cortex disinhibition in complex regional pain syndrome type I. *Neurology* 78:606; author reply 606–607, 2012

Picarelli H: The effects of repetitive transcranial magnetic stimulation (rTMS) over the motor cortex on complex regional pain syndrome patients. *Arq-Neuropsiquiatr* 70:751, 2012

Pleger B, Janssen F, Schwenkreis P, Völker B, Maier C, Tegenthoff M: Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. *Neurosci Lett* 356:87–90, 2004

Schwenkreis P, Maier C, Tegenthoff M: Motor cortex disinhibition in complex regional pain syndrome (CRPS)—A unilateral or bilateral phenomenon? *Pain* 115:219–220, 2005

Suarez A, Sacreste C, Papaianu M, Bouche B, Lemarie J: Repetitive transcranial magnetic stimulation in

chronic pain—Case series of 200 patients. 6th World Congress—World Institute of Pain, Miami Beach, FL, Blackwell Publishing, 2012, p 42

Wood PB: Variations in brain gray matter associated with chronic pain. *Curr Rheumatol Rep* 12:462–469, 2010

Zambo K, Perlaki G, Orsi G, Komoly S, Doczi T, Janszky J, Kovacs N, Balas I, Aradi M, Szabo Z, Schmidt E: Assessment of brain activity changes in long-term spinal cord stimulation by SPECT/CT and MRI fused technique. *Nucl Med Rev* 14:A18, 2011

One pediatric study:

Lebel A, Becerra L, Wallin D, Moulton EA, Morris S, Pendse G, Jasciewicz J, Stein M, Aiello-Lammens M, Grant E, Berde C, Borsook D: fMRI reveals distinct CNS processing during symptomatic and recovered complex regional pain syndrome in children. *Brain* 131:1854–1879, 2008

## Appendix C: Sensitivity Analyses

For each of the pooled outcomes, we evaluated whether there were differences between the individual studies in either disease duration or motor impairments of the complex regional pain syndrome (CRPS) sample. Because of the highly ambiguous way that motor impairments were reported by many studies, we had no reason to believe that the studies differed in their samples with regard to motor impairments. However, to combat the potential problem of heterogeneity or inappropriate pooling, we conducted a sensitivity analysis on an outcome when we were unsure as to whether there were meaningful differences in disease duration. Comparison of the pooled effect size with and without the study in question informed our decision as to whether pooling for that outcome was appropriate.

There were 2 outcomes for which sensitivity analyses were considered. Of these 2 outcomes, a formal sensitivity analysis was performed on one. Below we outline the decision making process for these outcomes.

Motor-evoked potential (MEP) amplitudes (Fig 2):

- All studies recruited chronic CRPS populations with the exception of Krause et al,<sup>29</sup> in which patients with CRPS of less than 6 months' disease duration were recruited. We constructed a forest plot without this sample present (see Fig C1 below). We compared the pooled effect estimates from the plot below with those from the existing forest plot, with its pooled effect estimate between sides:  $-1.69$  ( $-3.43$ ,  $.05$ ) and between groups:  $-.75$  ( $-1.54$ ,  $.05$ ). Because there was no substantial change to the pooled effect estimates resulting from removal of this study, a decision was made to retain the data from Krause et al<sup>29</sup> in the MEP forest plot.
- Krause et al<sup>31</sup>: Although this study recruited both an acute CRPS and a chronic CRPS group, the study's authors found no difference in interhemispheric asymmetry between the groups and therefore simply compared patients with controls. Hence, we did not conduct a sensitivity analysis with omission of this sample.

Motor thresholds (Fig 3):

- Krause et al<sup>31</sup>: See explanation above.

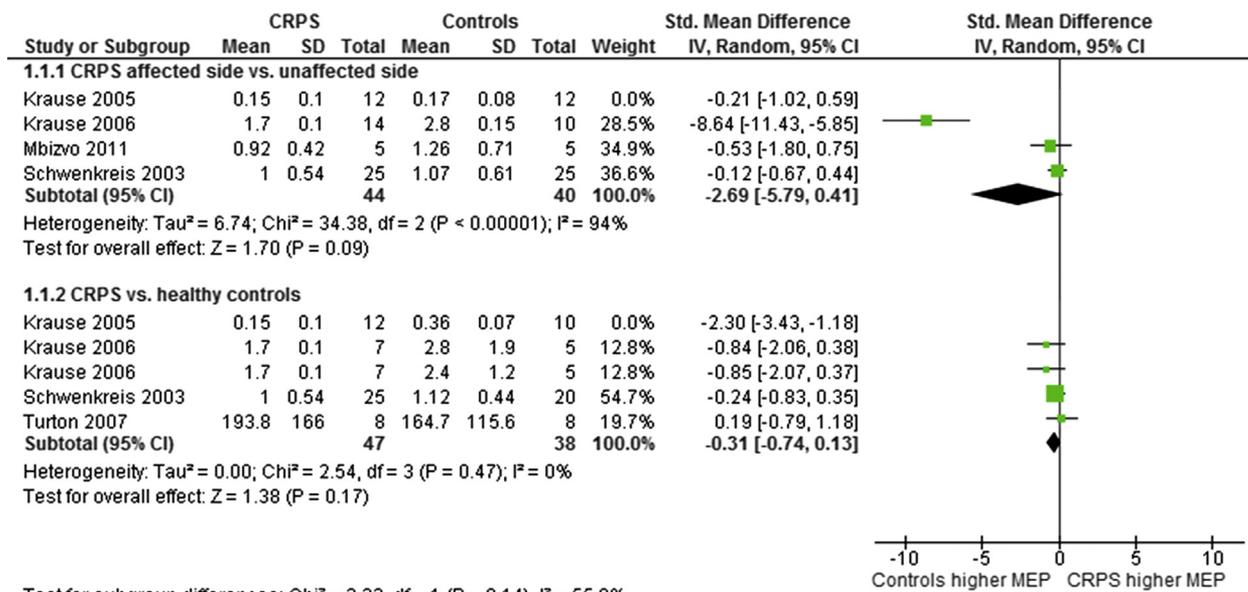


Figure C1. MEP amplitudes forest plot, omitting the data from Krause et al.<sup>29</sup>