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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.***

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

Complex regional pain syndrome (CRPS) involves multiple system dysfunction, severe pain, and disability. What causes CRPS is unknown[39] and it is very difficult to treat effectively.[5,63] Treatments that aim to "train the brain," which have shown promise in randomized controlled trials,[42,44] were developed following reports that functional brain reorganization was associated with the development, maintenance, and treatment of CRPS.[36,39,47,64] Many of these reports focus on the primary somatosensory cortex (S1), which holds a somatotopic map of the body's surface.[51] 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.[25]

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It is more than a decade since the first functional neuroimaging study of S1 in CRPS,[11] 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,[1,47] possibly because of the efficacy of such treatments in phantom limb pain.[9] 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.[16]

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[21,39,58,59,64] 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[67] and relevant items for case-control study designs from the Cochrane Collaboration's tool for assessing risk of bias[22,50] (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[7]) to allow for comparison of S1 function in patients with CRPS versus controls between studies. Effect estimates were interpreted according to Cohen ($\leq$.2 = small; .5 = moderate; $\geq$.8 = large).[6] We pooled data for an outcome if we had data from at least 2 studies on that outcome, using a random-effects model. The χ^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 χ^2 $P < .10$. Substantial heterogeneity was considered present when I^2 >60%.[23]

Results

We identified 1,027 studies. No additional titles arose from hand-searching the reference lists of potentially eligible studies and 6 reviews.[21,39,58,59,64] 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