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Original experimental

An exploration into the cortical reorganisation of the healthy hand in upper-limb complex regional pain syndrome

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HIGHLIGHTS

- Recent findings indicated an enlarged representation of the healthy hand in S1 in CRPS.
- The enlarged S1 healthy hand representation is not related to compensatory hand use.
- The enlarged S1 healthy hand representation does not relate to pain duration.
- Our findings suggest that the enlarged S1 healthy hand representation may be pre-existing.

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ABSTRACT

Background and aims: Recent evidence demonstrated that complex regional pain syndrome (CRPS) is associated with a larger than normal somatosensory (S1) representation of the healthy hand. The most intuitive mechanism for this apparent enlargement is increased, i.e. compensatory, use of the healthy hand. We investigated whether enlargement of the S1 representation of the healthy hand is associated with compensatory use in response to CRPS. Specifically, we were interested in whether the size of the S1 representation of the healthy hand is associated with the severity of functional impairment of the CRPS-affected hand. We were also interested in whether CRPS duration might be positively associated with the size of the representation of the healthy hand in S1.

Methods: Using functional magnetic resonance imaging (fMRI) data from our previous investigation, the size of the S1 representation of the healthy hand in CRPS patients ($n = 12$) was standardised to that of a healthy control sample ($n = 10$), according to hand dominance. Responses to questionnaires on hand function, overall function and self-efficacy were used to gather information on hand use in participants. Multiple regression analyses investigated whether the S1 representation was associated with compensatory use. We inferred compensatory use with the interaction between reported use of the CRPS-affected hand and (a) reported overall function, and (b) self-efficacy. We tested the correlation between pain duration and the size of the S1 representation of the healthy hand with Spearman's rho.

Results: The relationship between the size of the S1 representation of the healthy hand and the interaction between use of the affected hand and overall function was small and non-significant ($\beta = -5.488 \times 10^{-5}$, 95% C.I. −0.001, 0.001). The relationship between the size of the S1 representation of the healthy hand and the interaction between use of the affected hand and self-efficacy was also small and non-significant ($\beta = -6.027 \times 10^{-6}$, 95% C.I. −0.001, 0.001). The S1 enlargement of the healthy hand was not associated with pain duration (Spearman's rho = −0.14, $p = 0.67$).

Conclusion: Our exploration did not yield evidence of any relationship between the size of the healthy hand representation in S1 and the severity of functional impairment of the CRPS-affected hand, relative to overall hand use or to self-efficacy. There was also no evidence of an association between the size of the healthy hand representation in S1 and pain duration. The enlarged S1 representation of the healthy hand does not relate to self-reported function and impairment in CRPS.

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Implications: While this study had a hypothesis-generating nature and the sample was small, there were no trends to suggest compensatory use as the mechanism underlying the apparent enlargement of the healthy hand in S1. Further studies are needed to investigate the possibility that inter-hemispheric differences seen in S1 in CRPS may be present prior to the development of the disorder.

1. Introduction

It is widely accepted that complex regional pain syndrome (CRPS) is associated with functional reorganisation in the region of the primary somatosensory cortex (S1) that represents the painful limb [1–3]. Specifically, there is evidence that the spatial representation of the CRPS-affected hand in S1 is smaller than that of the healthy hand ([4–7]; for meta-analytic review see Di Pietro et al. [8]). Evidence that the CRPS-affected hand representation is also smaller than that of controls is not as compelling [8], but, nonetheless, the conventional view is that CRPS is associated with shrinkage of the S1 representation of the affected hand. This, together with evidence of altered function of the primary motor cortex in CRPS [9], has contributed to novel non-invasive therapies for CRPS that were theoretically aimed at normalising the maladaptive cortical reorganisation [10,11].

We recently conducted the largest study to date investigating S1 spatial representation in people with upper limb CRPS and healthy controls, using functional magnetic resonance imaging (fMRI) [12]. Our results were contrary to the prevailing view. While we confirmed hemispheric differences in spatial representation of the hand in people with CRPS, we clearly showed that S1 representation of the *healthy* hand in CRPS was larger than the hand representation of healthy controls, as opposed to the S1 representation of the affected hand being smaller than the hand representation of healthy controls. We also found that there was no correlation between pain duration and the size of the S1 representation of either hand in CRPS patients [12]. These intriguing findings clearly require further exploration.

That enlargement of the S1 representation of a body part reflects use and training of that body part has long been established in both humans [13,14] and animals [15]. Based on such principles of use-dependent neuroplasticity, we were interested in whether the S1 representation of the healthy hand is associated with altered hand use in response to CRPS. Specifically, we were interested in whether the size of the healthy hand representation in S1 is associated with the severity of functional impairment of the CRPS-affected hand. For example, one might hypothesise that decreased function or use of the CRPS-affected hand is associated with an increased representation size of the healthy hand, due to increased function or use of the healthy hand. However, only considering the function of the CRPS-affected hand does not capture use of the healthy hand. That is, one might expect a larger healthy hand S1 representation in those that have the combination of poor CRPS-hand function but high overall upper extremity function (i.e. high function when either/both hand(s) can be used) than in those that have low overall upper extremity function (i.e. not using either hand) or in those with high CPRS hand function. Thus, to capture this balance between CRPS-hand use and healthy hand use, we used a questionnaire-based measure of compensatory hand use and explored its relationship to healthy hand representation in S1. Last, as CRPS of longer duration may result in extended compensatory use of the healthy hand, our secondary aim was to investigate whether we would find a positive relationship between the size of the healthy hand in S1 and the duration of CRPS, after standardisation of hand representation according to hand dominance.

2. Methods

2.1. Participants

We recruited a convenience sample of patients who were over 18 years old and who had received a diagnosis of unilateral upper-limb CRPS from a pain physician, hand therapist, general practitioner or physiotherapist. All participants were recruited as part of a wider investigation of functional reorganisation in CRPS, the protocol of which is presented elsewhere [12]. That is, the sample reported on here is the same as that reported on previously, and the neuroimaging data have been taken directly from our previous publication, for further exploration. Participants were excluded if they could not speak English or had uncontrolled psychiatric conditions that precluded successful participation in the study. Routine MRI safety protocols were adhered to.

2.2. Ethics

All participants provided informed written consent. All procedures conformed to the Declaration of Helsinki and approval for the study was granted by the Institutional Human Research Ethics Committee.

2.3. fMRI mapping of the size of the hand in S1

The fMRI protocol is presented in detail elsewhere [12]. Echo-planar images (EPI) were acquired on a 3T MRI scanner (Philips Achieva; Neuroscience Research Australia), using a 32-channel head coil. A custom script was written on MATLAB (version 7.10; Mathworks, Natick, MA, USA) in order to deliver MRI-compatible vibrotactile stimulation (Piezotactile Stimulator PTS-C2, http://dancerdesign.co.uk) to two probes, fitted to the first (D1) and fifth (D5) digit respectively. Stimulation was delivered in a randomised, block-design [16] at a frequency of 23 Hz [16–18] and a fixed amplitude of 280 microns [19–21]. Participants were asked to concentrate their attention on the stimuli [4,7]. fMRI data were analysed using Statistical Parametric Mapping version 8 software (Wellcome Trust Centre for Neuroimaging, University College London, UK). Right and left hand sessions were evaluated separately. After pre-processing and first-level statistics were employed uniformly across right-hand and left-hand sessions for all participants, activation maxima in response to stimulation of each digit were located within a bilateral S1 mask determined a priori ($p < 0.05$ uncorrected) [22,23]. The distance between activation maxima was calculated for both hands as a measure of hand representation size [24]. This was performed by a member of the research team (ML) who was blinded to all clinical information (i.e. unaware of which hand was affected by CRPS).

While our previous investigation confirmed that the apparently larger representation of the healthy hand in CRPS was not a function of the inherent differences in hand representation size in healthy controls, limitations in study size meant that we could not statistically evaluate whether hand representation in CRPS might vary depending on whether CRPS affects the dominant or non-dominant hand [12]. Thus, in the current study, the size of the S1 representation of the healthy hand in participants with CRPS was standardised to the mean representation size of the corresponding hand in the previously recruited healthy control sample. The method was as follows: if CRPS affected the patient's dominant hand, their healthy hand was their non-dominant hand and was therefore standardised to the mean representation size of the non-dominant hand in controls. Conversely, in patients with CRPS of the non-dominant hand, the healthy hand was their dominant hand and was therefore standardised to the mean representation size of the dominant hand in controls. Thus the extent of the healthy hand representation size in patients was expressed as a proportion of the mean representation size in controls. As a last step, each proportion was log-transformed, to ensure that proportions of the same ratio (regardless of the raw values) were represented symmetrically and at the same interval along the scale.

2.4. Measures

In addition to the collection of functional imaging and clinical information, including assessment of pain duration, participants completed the Patient-Rated Wrist and Hand Evaluation (PRWHE) [25], the shortened version of the Disabilities of the Arm, Shoulder and Hand (QuickDASH) [26], and the Pain Self-Efficacy Questionnaire (PSEQ) [27]. The responses to the function items of the PRWHE (10 items all pertaining to function of the painful hand) were summed and subtracted from 100 so that a higher score indicated higher function. The QuickDASH score (11 items all pertaining to the ability to carry out daily tasks, *irrespective of hand*) was calculated as per the author's instructions [26] and then subtracted from 100, so that a higher score indicated higher function. The PSEQ assesses one's confidence to achieve valued outcomes, despite pain. Answers to the 10 items of the scale were summed; a higher score indicated stronger self-efficacy.

2.5. Reported compensatory hand use and the healthy hand S1 representation size

We operationalised compensatory use of the healthy hand as the interaction between the reported use of the CRPS-affected hand (PRWHE score) and overall function (QuickDASH score) (Model 1), and as the interaction between the PRWHE score and reported self-efficacy (PSEQ score) (Model 2). Patients who reported decreased use of their affected hand and high overall function or self-efficacy, for example, were considered to have increased or compensatory use of their healthy hand. Self-efficacy beliefs determine whether people are likely to engage in valued activities [28], and have been shown to play a key role in the disability associated with painful conditions [29]. We considered the use of objective measures to assess arm movement; however pilot testing suggested that activity sensors, such as the 'Actical' (Philips), did not provide reliable data on individual arm movement. This was confirmed by the manufacturer. Moderate to strong relationships between objective and subjective measures of arm function have been demonstrated for conditions with unilateral functional impairment, for example stroke [30] and rheumatoid arthritis [31].

2.6. Statistics

Analyses were performed with SPSS Version 21 (IBM Corporation, New York). Data were checked for normality using visual inspection and the Shapiro–Wilk statistic. Two multiple regression models investigated the relationship between the size of the S1 representation of the *healthy* hand (standardised to controls and log-transformed as above; dependent variable) and compensatory use of the healthy hand (independent variable), using an interaction term of PRWHE × QuickDASH (Model 1) and PRWHE × PSEQ (Model 2). Unstandardised β were interpreted as follows: a regression coefficient of, for instance, 0.013 indicated a 1.3% increase in S1 hand representation size for every 1 unit increase in compensatory hand use (interaction term). The correlation between pain duration and the size of the S1 representation of the healthy hand was tested with Spearman's rho. Results below are presented as mean ± SD unless otherwise stated.

3. Results

Twelve patients with CRPS of the upper limb were included in the study (3 male, 9 female; age 50.4 ± 12.2 years; one left-handed, one ambidextrous). Seven patients presented with CRPS of the dominant hand; five patients had CRPS of the non-dominant hand. See Table 1 for patient characteristics. Ten healthy controls were included in the study (3 male; age 44.4 ± 14.2 years; one left-handed).

The median pain duration for the CRPS patients was 27 months ± 43 (4–45). The mean PRWHE score of the CRPS patients was 46 ± 30 out of 100 (range 3–91). The mean QuickDASH score was 54 ± 29 out of 100 (range 2–91). The mean PSEQ score was 33 ± 20 out of 60 (range 0–60).

In the CRPS group, the mean ± SD representation size of the affected hand in S1 was 15.02 mm ± 5.08; the healthy hand was 19.98 mm ± 7.14. In the healthy controls, the mean representation size of the dominant hand was 18.09 mm ± 4.45. Because the data for the non-dominant hand in controls were non-normally distributed, we took the conservative approach of using the mean, that is 13.03 mm ± 4.59, which was larger than the median (12.21 mm ± 3.91 (IQR)), and thus minimised our chance of a false positive finding. The standardised mean healthy hand representation size (i.e. prior to the final log transformation) in patients with CRPS of the dominant hand was 1.84 (i.e. the size of the healthy hand representation expressed as a proportion of the size of the non-dominant hand in controls). The standardised mean healthy hand representation size in patients with CRPS of the non-dominant hand was 0.80 (i.e. the size of the healthy hand representation expressed as a proportion of the size of the dominant hand in controls).

3.1. Reported compensatory hand use and the healthy hand S1 representation size

There was no significant relationship between the size of the S1 representation of the healthy hand and function of the CRPS-affected hand (i.e. PRWHE score), or overall function (i.e. QuickDASH score) or the interaction term PRWHE × QuickDASH; that is, the size of S1 representation of the healthy hand was not associated with function of the CRPS-affected hand relative to overall function (for Model 1 results see Table 2). With each of the unstandardised coefficients, even the upper bound of the 95% C.I. indicated that there was no meaningful relationship with the S1 representation of the healthy hand. Similarly, there was no significant relationship between the size of the S1 representation of the healthy hand and self-efficacy (i.e. PSEQ score), or the interaction term PRWHE × PSEQ; that is, the size of the S1 representation of the healthy hand was not associated with function of the CRPS-affected hand relative to overall confidence to achieve valued outcomes (for Model 2 results see Table 2). Finally, there was no relationship between the standardised size of the S1 representation of the healthy hand and the duration of CRPS signs and symptoms (Spearman's rho = −0.14, p = 0.67).

Table 1
Demographics and clinical information of CRPS participants.

Patient number, gender, age	CRPS location	Pain duration (months)	Pain intensity (0–10)[a]	Hand dominance (reported)	Pain in other locations
#1 Male 36 y/o	L	30	8	R	R UL and L LL
#2 Female 45 y/o	R	42	6	R	R face
#3 Female 39 y/o	L	2	5	R	None
#4 Female 46 y/o	R	2	2	R	None
#5 Female 52 y/o	R	29	8	R	L UL, R side face, R LL
#6 Male 66 y/o	L	120	4	R	R UL, LBP
#7 Male 34 y/o	L	3	3	Ambidextrous	None
#8 Female 60 y/o	R	180	7.5	R	L UL, L LL
#9 Female 56 y/o	R	25	2	R	None
#10 Female 44 y/o	L	48	7	R	Bilateral LL
#11 Female 53 y/o	R	19	4	R	None
#12 Female 74 y/o	R	4	3	L	None

CRPS = complex regional pain syndrome; y/o = years old; R = right; L = left; Bil. = bilateral; UL = upper limb; LL = lower limb.

[a] Resting average pain intensity over last two days. "How would you rate your average pain at rest over the last two days? Please rate from 0 to 10, with 0 being no pain at all and 10 being the worst pain you can imagine."

Table 2
Results of multiple regression analyses investigating various relationships with the S1 representation of the healthy hand in CRPS.

	Unstandardised β[a]	Standardised Beta[b]	95% CI around unstandardised β
PRWHE score (Model 1)	0.013	0.744	−0.05, 0.076
QuickDASH score (Model 1)	−0.009	−0.493	−0.044, 0.026
PRWHE × QuickDASH (Model 1)	-5.488×10^{-5}	−0.327	−0.001, 0.001
PRWHE score (Model 2)	0.000	0.020	−0.060, 0.061
PSEQ score (Model 2)	−0.001	−0.022	−0.058, 0.057
PRWHE × PSEQ (Model 2)	-6.027×10^{-6}	−0.024	−0.001, 0.001

PRWHE = Patient-Rated Wrist and Hand Evaluation; QuickDASH = shortened version of the Disabilities of the Arm, Shoulder and Hand; PSEQ = Pain Self-Efficacy Questionnaire.

[a] Unstandardised β expressed in original units of each scale.

[b] Standardised coefficient after all variables' conversion to z-scores.

3.2. Post hoc exploratory analysis of side of CRPS (dominant vs non-dominant hand)

Due to differences seen in the standardised S1 hand representation size between those with CRPS of the dominant versus non-dominant hand, we repeated the multiple linear regression analyses (Model 1 and Model 2), controlling for 'CRPS side' (dominant or non-dominant) as a confounder. In Model 1, when controlling for CRPS side, the results were unchanged: no significant relationships were found between the S1 representation of the healthy hand and any of the existing variables (see Table 3). In Model 2 (PSEQ), when controlling for CRPS side, it is worth noting that the relationship between S1 representation of the healthy hand and PRWHE score was significant ($\beta = -0.028$, 95% C.I. −0.055, −0.001; see Table 3 for full results). Ideally, we would further explore the relationship between S1 representation of the healthy hand and inferred compensatory use to see if it differed based on which side was affected by CRPS (dominant versus non-dominant). However, due to the small numbers of participants when we divided participants into those with CRPS of the non-dominant hand ($n = 5$) and dominant hand ($n = 7$), we were unable to repeat the linear regression analyses (Model 1 and Model 2) separately in these groups (see Supplementary Figs. 1 and 2 for post hoc exploration of dominance in each Model).

4. Discussion

We investigated whether there would be a positive relationship between the size of the healthy hand representation in S1 and the severity of functional impairment of the CRPS-affected hand relative to overall hand use and self-efficacy. Our exploration did not yield evidence of this. That is, the apparent enlargement of the S1 representation of the healthy hand does not appear to reflect the extent to which the affected hand is incapacitated by CRPS. Taken together, the results from two measures of disability suggest that enlarged representation in S1 of the healthy hand may not reflect use-dependent changes in CRPS.

Table 3
Results of post hoc multiple regression analyses investigating various relationships with the S1 representation of the healthy hand in CRPS.

	Unstandardised β[a]	Standardised Beta[b]	95% CI around unstandardised β
PRWHE score (Model 1)	−0.022	−1.289	−0.053, 0.010
QuickDASH score (Model 1)	−0.008	−0.432	−0.023, 0.008
PRWHE × QuickDASH (Model 1)	0.000	1.702	0.000, 0.001
CRPS side (Model 1)	−0.980	−0.995	−1.374, −0.587
PRWHE score (Model 2)	−0.028	−1.639	−0.055, −0.001
PSEQ score (Model 2)	−0.002	−0.092	−0.026, 0.021
PRWHE × PSEQ (Model 2)	0.000	1.751	0.000, 0.001
CRPS side (Model 2)	−0.995	−1.010	−1.357, −0.632

PRWHE = Patient-Rated Wrist and Hand Evaluation; QuickDASH = shortened version of the Disabilities of the Arm, Shoulder and Hand; PSEQ = Pain Self-Efficacy Questionnaire.
[a] Unstandardised β expressed in original units of each scale.
[b] Standardised coefficient after all variables' conversion to z-scores.

4.1. Past findings: S1 representation of the hand

Our finding is surprising and appears to challenge established principles of neuroplasticity insofar as increased cortical representation of the hand in S1 did not seem to relate to use of the hand. It is important to note, however, a key difference in our neuroimaging 'representation' measure and that used by past studies. The D1–D5 distance was used here as a measurement of S1 representation size (as recommended by Jung et al. [24]); however, in their seminal studies of use and S1 representation, Elbert et al. [13] and Pascual-Leone and Torres [14] demonstrated increases in the magnitude, or strength, of the activation with digit simulation.

One possible explanation for the current finding is that the difference in representation size between hemispheres in these patients is unrelated to the signs and symptoms of CRPS, and might simply reflect what is found in healthy controls. There is indeed evidence of asymmetry between hemispheres in healthy controls. Studies using electroencephalography (EEG) have demonstrated that the left hemisphere shows a stronger response to peripheral electrical stimulation [24,32] than the right, in both left-hand dominant and right-hand dominant people. Furthermore, a healthy participants study that used a similar paradigm to ours, but with magnetoencephalography (MEG) not fMRI, showed larger S1 representation of the hand in the left hemisphere than in the right hemisphere in all right-hand dominant and most left-hand dominant participants [33]. Although it is important to consider our findings in the context of the seemingly consistent patterns of asymmetry seen in healthy participants, it would seem that these patterns do not explain our result, because in our sample the healthy hand was represented in different hemispheres.

It is important to note, however, the potential differences in the S1 representation of the hands, based on whether the dominant or the non-dominant hand is affected by CRPS. Our previous study [12] demonstrated a larger than usual representation of the healthy hand, and the finding was independent of the inherent differences in hand representation we found in healthy controls. However, the investigation did indeed yield evidence of a difference in the representation of the hands in controls, and furthermore a suggestion that a different pattern of S1 representation might arise when CRPS affects the non-dominant hand – the group of patients with CRPS of the non-dominant hand was perhaps too small to affect the overall average in our previous study [12]. For these reasons it was important here to account for the effects of hand dominance, by expressing hand representation size in patients as a proportion of that in healthy controls. In doing so, it appears that there might indeed be a difference in S1 hand representation based on the side affected by CRPS, but the sample is small and this question ultimately requires evaluation with a larger sample before any conclusion can be made.

4.2. Relationship between S1 representation and pain duration

Our secondary aim was to explore the relationship between the size of the healthy hand in S1 and the duration of CRPS; the findings of the study did not support this notion either. One interpretation of this finding is that the difference in hemispheres may be premorbid, whereby the S1 representation of the non-dominant hand is larger than that of the dominant hand, before the onset of CRPS. In this case such a difference might reflect a vulnerability to the condition. This possibility, although speculative, is novel, plausible and offers important potential for future study. Alternatively it may be that the difference between hemispheres occurs early in the course of the disease, for example, soon after injury or during immobilisation. Relevant to this is the report of an increase in the magnitude of cortical activation with sensory stimulation and movement of the *non*-immobilised (non-dominant) hand following short-term immobilisation (72 h) of the other (dominant) hand, in a healthy control group [34].

To our knowledge, the correlation between pain duration and the size of the S1 representation of the *healthy* hand has not been tested previously. In fact, little is known about the correlation between pain duration and the size of the S1 representation of the CRPS-affected hand. Of the four existing studies into S1 spatial representation in CRPS, two studies did not present correlation data on pain duration [6,7] and two studies present evidence of no correlation [4,5]. It is possible that our study was underpowered to detect a relationship between pain duration and S1 representation, however the size of the non-significant correlation was small and as such it is unlikely that this relationship would be meaningful even if it was detectable in a large sample. Of further note is that the apparent direction of the correlation observed here suggests that, if anything, the healthy hand may become *smaller* in its representation over time. Again, this seems worthy of further longitudinal investigation.

4.3. Considering hemispheric interactions and lateralisation

Most of the existing studies on dominance in healthy populations have investigated the primary motor cortex (M1), not S1. Previous findings in M1 include asymmetry in both structure and function, and a correlation between hand-dominance and the degree of hand motor representation [33,35,36]. It is intuitive that enhanced use of the dominant hand would impart some effect on somatosensory-processing regions, but function is related more closely to movement, and somatosensory representation appears to vary independently of motor function, with the latter being more clearly lateralised according to dominance [32]. An obvious target for future work on CRPS-related functional impairment would be to investigate alterations to hand representation in M1.

Another phenomenon more extensively investigated in the motor domain than in the somatosensory domain, in healthy populations, is inter-hemispheric interaction [37]. Abnormal, or more specifically, decreased inter-hemispheric inhibition has been found in CRPS in both the primary motor [9,38] and in the primary somatosensory [39] cortices. It certainly seems plausible that a lack of inhibition by the CRPS-affected hemisphere on the healthy hemisphere might explain the apparently enlarged healthy hand representation that is unexplained by compensatory use; however, we cannot definitely claim this on the basis of the current results.

4.4. Limitations

It is important to highlight the hypothesis-generating nature of this study. Intriguing questions of neuroplasticity were addressed but not answered definitively. There were several limitations of the current study. We recruited a small sample, and the group was heterogeneous in CRPS signs and symptoms. As such, the study may have been underpowered to detect the relationships we were looking for. However, that there was no sign of a trend in either of the main analyses suggests that if a relationship does in fact exist, it is likely to be very small and therefore unlikely to completely explain the phenomenon of use-dependent plasticity. We also relied on self-report of function and we inferred use of the healthy hand through comparisons of CRPS-affected hand function and overall hand function. Subjective measures of hand function have demonstrated moderate to strong relationships with key objective hand function tests in patients with rheumatoid arthritis of the hands [31], and self-report questionnaires of hand use and accelerometry have been found to be significantly related in stroke [30]. However, to our knowledge this relationship has not been yet been established in CRPS. An objective and direct measure of healthy hand function would provide more comprehensive assessment.

4.5. Final considerations

A final consideration relates to the emerging picture of spatially-defined deficits in CRPS, as distinct from somatotopically-defined deficits. These deficits are best exemplified by delivering identical tactile stimuli, at varying interstimulus intervals, to both hands of someone with CRPS of one hand, and having them make temporal order judgments (TOJ) of the stimulus pairs. When the hands are held in front of the body, on either side of the midline, the stimulus delivered to the affected hand is processed slower than the stimulus delivered to the unaffected hand. However, when the hands are crossed, the relationship is reversed, demonstrating that the deficit relates to which side of the midline the stimulus occurs, not which hand is stimulated [40,41]. Moreover, the deficit extends to thermoregulation, with the hand on the affected side of space being cooler than the hand on the healthy side [42]. Spatially-defined deficits have also been observed in people with unilateral back pain [43] and unilateral knee pain [44]. It seems reasonable to suggest that the relationship between S1 changes and usage in CRPS are more complex than they have appeared – perhaps dysfunction of neurological mechanisms underpinning spatial processing and the integration of bodily representations plays an important interactive role [45].

Previous studies have demonstrated that the S1 cortical representation of the affected hand in CRPS is smaller than that of the healthy hand [4–7]. Those results were consistent regardless of whether CRPS affected the left or right hand. So while it may be argued, on the basis of the cortical asymmetries seen in healthy populations, that the interhemispheric differences found in CRPS are unrelated to the disorder, this conclusion seems highly unlikely. It is more than feasible that the size of the S1 representation of the healthy hand would relate to the incapacity of the affected hand, according to established principles of use-dependent neuroplasticity. However, our preliminary findings do not provide support for this proposal; they instead raise the tantalising possibility that abnormal hemispheric asymmetry, such that the non-dominant hand is abnormally large in its representation, might reflect a vulnerability for the condition, or a marker of initial response to injury or immobilisation. This possibility clearly requires more investigation, but represents a potentially critical new direction in our pursuit of explanations for why a small proportion of people develop CRPS after peripheral trauma whereas the vast majority do not. That the S1 representation of the healthy hand might become smaller in size over time is consistent with both possibilities and warrants further investigation.

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Ethical issues

Please see Section 2.2.

Conflicts of interest

The authors report no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.sjpain.2016.06.004.

References

[1] Bruehl SP. An update on the pathophysiology of complex regional pain syndrome. Anesthesiology 2010;113:713–25.

[2] Marinus J, Moseley GL, Birklein F, Baron R, Maihofner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol 2011;10:637–48.
[3] Schwenkreis P, Maier C, Tegenthoff M. Functional imaging of central nervous system involvement in complex regional pain syndrome. Am J Neuroradiol 2009;30:1279–84.
[4] Juottonen K, Gockel M, Silen T, Hurri H, Hari R, Forss N. Altered central sensorimotor processing in patients with complex regional pain syndrome. Pain 2002;98:315–23.
[5] Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. Neurology 2003;61:1707–15.
[6] 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 2004;155:115–9.
[7] Vartiainen NV, Kirveskari E, Forss N. Central processing of tactile and nociceptive stimuli in complex regional pain syndrome. Clin Neurophysiol 2008;119:2380–8.
[8] Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, Stanton TR. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain 2013;14:1001–18.
[9] Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, Stanton TR. Primary motor cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain 2013;14:1270–88.
[10] McCabe CS, Haigh RC, Ring EF, Halligan PW, Wall PD, Blake DR. A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). Rheumatology 2003;42:97–101.
[11] Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. Pain 2004;108:192–8.
[12] Di Pietro F, Stanton TR, Moseley GL, Lotze M, McAuley JH. Interhemispheric somatosensory differences in chronic pain reflect abnormality of the Healthy side. Hum Brain Mapp 2015;36:508–18.
[13] Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased cortical representation of the fingers of the left hand in string players. Science 1995;270:305–7.
[14] Pascual-Leone A, Torres F. Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. Brain 1993;116:39–52.
[15] Merzenich MM, Kaas JH, Wall J, Nelson RJ, Sur M, Felleman D. Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. Neuroscience 1983;8:33–55.
[16] Nelson AJ, Chen R. Digit somatotopy within cortical areas of the postcentral gyrus in humans. Cereb Cortex 2008;18:2341–51.
[17] Jones LA, Lederman SJ. Neurophysiology of hand function. In: Human hand function. New York: Oxford University Press; 2006. p. 24–43.
[18] Tommerdahl M, Delemos KA, Whitsel BL, Favorov OV, Metz CB. Response of anterior parietal cortex to cutaneous flutter versus vibration. J Neurophysiol 1999;82:16–33.
[19] Butterworth S, Francis S, Kelly E, McGlone F, Bowtell R, Sawle GV. Abnormal cortical sensory activation in dystonia: an fMRI study. Mov Disord 2003;18:673–82.
[20] Francis ST, Kelly EF, Bowtell R, Dunseath WJR, Folger SE, McGlone F. fMRI of the responses to vibratory stimulation of digit tips. Neuroimage 2000;11:188–202.
[21] Nelson AJ, Staines WR, Graham SJ, McIlroy WE. Activation in SI and SII: the influence of vibrotactile amplitude during passive and task-relevant stimulation. Cogn Brain Res 2004;19:174–84.
[22] Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 2005;25:1325–35.
[23] Weibull A, Björkman A, Hall H, Rosén B, Lundborg G, Svensson J. Optimizing the mapping of finger areas in primary somatosensory cortex using functional MRI. Magn Reson Imaging 2008;26:1342–51.
[24] Jung P, Baumgärtner U, Magerl W, Treede R-D. Hemispheric asymmetry of hand representation in human primary somatosensory cortex and handedness. Clin Neurophysiol 2008;119:2579–86.
[25] MacDermid JC. Development of a scale for patient rating of wrist pain and disability. J Hand Ther 1996;9:178–83.
[26] Beaton DE, Wright JG, Katz JN. Development of the QuickDASH: comparison of three item-reduction approaches. J Bone Joint Surg 2005;87:1038–46.
[27] Nicholas MK. Self-efficacy and chronic pain. In: Annual conference of the British Psychological Society. 1989.
[28] Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev 1977;84:191–215.
[29] Arnstein P. The mediation of disability by self efficacy in different samples of chronic pain patients. Disabil Rehabil 2000;22:794–801.
[30] van der Pas SC, Verbunt JA, Breukelaar DE, van Woerden R, Seelen HA. Assessment of arm activity using triaxial accelerometry in patients with a stroke. Arch Phys Med Rehabil 2011;92:1437–42.
[31] O'Connor D, Kortman B, Smith A, Ahern M, Smith M, Krishnan J. Correlation between objective and subjective measures of hand function in patients with rheumatoid arthritis. J Hand Ther 1999;12:323–9.
[32] Jung P, Baumgärtner U, Bauermann T, Magerl W, Gawehn J, Stoeter P, Treede R-D. Asymmetry in the human primary somatosensory cortex and handedness. Neuroimage 2003;19:913–23.
[33] Sörös P, Knecht S, Imai T, Gürtler S, Lütkenhöner B, Ringelstein EB, Henningsen H. Cortical asymmetries of the human somatosensory hand representation in right- and left-handers. Neurosci Lett 1999;271:89–92.
[34] Weibull A, Flondell M, Rosen B, Bjorkman A. Cerebral and clinical effects of short-term hand immobilisation. Eur J Neurosci 2011;33:699–704.
[35] Amunts K, Schlaug G, Schleicher A, Steinmetz H, Dabringhaus A, Roland PE, Zilles K. Asymmetry in the human motor cortex and handedness. Neuroimage 1996;4:216–22.
[36] Volkmann J, Schnitzler A, Witte OW, Freund H-J. Handedness and asymmetry of hand representation in human motor cortex. J Neurophysiol 1998;79: 2149–54.
[37] Ragert P, Nierhaus T, Cohen LG, Villringer A. Interhemispheric interactions between the human primary somatosensory cortices. PLoS ONE 2011;6:e16150.
[38] Schwenkreis P, Scherens A, Rönnau A-K, Höffken O, Tegenthoff M, Maier C. Cortical disinhibition occurs in chronic neuropathic, but not in chronic nociceptive pain. BMC Neurosci 2010;11:1–10.
[39] Lenz M, Hoffken O, Stude P, Lissek S, Schwenkreis P, Reinersmann A, Frettloh J, Richter H, Tegenthoff M, Maier C. Bilateral somatosensory cortex disinhibition in complex regional pain syndrome type I. Neurology 2011;77: 1096–101.
[40] Moseley GL, Gallace A, Spence C. Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb. Brain 2009;132:3142–51.
[41] Moseley GL, Gallace A, Iannetti GD. Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome. Brain 2012;135:3676–86.
[42] Moseley GL, Gallace A, Di Pietro F, Spence C, Iannetti GD. Limb-specific autonomic dysfunction in complex regional pain syndrome modulated by wearing prism glasses. Pain 2013;154:2463–8.
[43] Moseley GL, Gallagher L, Gallace A. Neglect-like tactile dysfunction in chronic back pain. Neurology 2012;79:327–32.
[44] Stanton TR, Lin C-WC, Smeets RJEM, Taylor D, Law R, Lorimer Moseley G. Spatially defined disruption of motor imagery performance in people with osteoarthritis. Rheumatology 2012;51:1455–64.
[45] Reid E, Wallwork SB, Harvie D, Chalmers KJ, Gallace A, Spence C, Moseley GL. A new kind of spatial inattention associated with chronic limb pain? Ann Neurol 2016;79:701–4.