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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