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Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome

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Numerous clinical conditions, including complex regional pain syndrome, are characterized by autonomic dysfunctions (e.g. altered thermoregulation, sometimes confined to a single limb), and disrupted cortical representation of the body and the surrounding space. The presence, in patients with complex regional pain syndrome, of a disruption in spatial perception, bodily ownership and thermoregulation led us to hypothesize that impaired spatial perception might result in a spatial-dependent modulation of thermoregulation and bodily ownership over the affected limb. In five experiments involving a total of 23 patients with complex regional pain syndrome of one arm and 10 healthy control subjects, we measured skin temperature of the hand with infrared thermal imaging, before and after experimental periods of either 9 or 10 min each, during which the hand was held on one or the other side of the body midline. Tactile processing was assessed by temporal order judgements of pairs of vibrotactile stimuli, delivered one to each hand. Pain and sense of ownership over the hand were assessed by self-report scales. Across experiments, when kept on its usual side of the body midline, the affected hand was $0.5 \pm 0.3^{\circ}$C cooler than the healthy hand ($P < 0.02$ for all, a common finding in cold-type complex regional pain syndrome), and tactile stimuli delivered to the healthy hand were prioritized over those delivered to the affected hand. Simply crossing both hands over the midline resulted in (i) warming of the affected hand (the affected hand became $0.4 \pm 0.3^{\circ}$C warmer than when it was in the uncrossed position; $P = 0.01$); (ii) cooling of the healthy hand (by $0.3 \pm 0.3^{\circ}$C; $P = 0.02$); and (iii) reversal of the prioritization of tactile processing. When only the affected hand was crossed over the midline, it became warmer (by $0.5 \pm 0.3^{\circ}$C; $P = 0.01$). When only the healthy hand was crossed over the midline, it became cooler (by $0.3 \pm 0.3^{\circ}$C; $P = 0.01$). The temperature change of either hand was positively related to its distance from the body midline (pooled data: $r = 0.76$, $P < 0.001$). Crossing the affected hand over the body midline had small but significant effects on both spontaneous pain (which was reduced) and the sense of ownership over the hand (which was increased) ($P < 0.04$ for both). We conclude that impaired spatial perception modulated temperature of the limbs, tactile processing, spontaneous pain and the sense of ownership over the hands. These results show that complex regional pain syndrome involves more complex neurological dysfunction than has previously been considered.

Keywords: spatial perception; neglect; chronic pain; autonomic nervous system; cortical body matrix
Abbreviations: CRPS = complex regional pain syndrome

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Introduction

Perception of sensory events occurring in, on or around the body is disrupted in a range of neurological and psychiatric conditions, including schizophrenia, autism, epilepsy, neuropathic pain, anorexia nervosa and bulimia. Disruption of temperature regulation and disrupted bodily awareness have also been associated with these conditions (e.g. Slade, 1985; Priebe and Rohricht, 2001; Boesebeck and Ebner, 2004; Chong and Castle, 2004; Moseley, 2005; Papezová *et al*., 2005; Holtkamp *et al*., 2007). In patients suffering from brain damage, evidence of deficits of spatial perception is typified by unilateral spatial neglect, a condition in which sensory stimuli from the contralesional side of space are given less weighting (and thus neglected) than stimuli from the ipsilesional side of space (Bisiach and Luzzatti, 1978). Remarkably, a similar phenomenon has been observed in people without CNS damage but who have chronic complex regional pain syndrome (CRPS) triggered by peripheral tissue injury (Moseley *et al*., 2009). In CRPS, impaired perception of space is thought to extend beyond tactile stimuli and, possibly, beyond the affected area (see Legrain *et al*., 2012 for a review).

Disrupted thermoregulation is an important diagnostic sign of CRPS, but the disease is also characterized by disrupted tactile processing and a reduced sense of ownership over the affected limb [see Marinus *et al*., 2011 for a review; see also Vallar and Ronchi (2009) for a recent review on the deficit of body ownership affecting neglect patients]. In fact, the extent of impaired perception of space relates the extent to which the affected limb is cooler than the healthy limb (Moseley *et al*., 2009). This observation raises the intriguing possibility that, in patients with CRPS, there are inter-relations between spatial perception, sense of body ownership and efferent bodily systems, most notably the autonomic nervous system. Support for this possibility comes from a series of experiments performed on healthy volunteers in which cooling of one arm was induced by the illusion of ownership over an artificial limb situated within the space immediately surrounding the body (Moseley *et al*., 2008*a*; Hohwy and Paton; 2010)—the 'peripersonal' space (Rizzolatti *et al*., 1981). In fact, the results of those experiments lead to the suggestion that a network of brain areas, called the 'cortical body matrix' (Moseley *et al*., 2012*a*), might be responsible for the integration of somatotopical and multimodal spatial frames of reference, with the ultimate aim of regulating and protecting the body integrity both at a behavioural or a perceptual level, and at a homeostatic level.

In this study, we undertook five experiments on patients with unilateral upper limb CRPS. We aimed to determine whether disrupted spatial perception might modulate thermoregulation and somatosensory processing in people with unilateral CRPS of one arm. Our primary hypotheses were that the position of either hand, relative to the body midline, would modulate thermoregulation, spontaneous pain and the sense of ownership of that hand.

Materials and methods

Participants

There were five separate experiments. A total of 23 patients with unilateral upper limb CRPS participated. Some patients participated in more than one experiment (Supplementary Table 1 shows all patient details, extra characteristics of the clinical assessment, which patients participated in which experiments and specifies the number of patients who participated in each experiment). Which participants participated in which experiments was entirely determined by convenience; as data were collected over a 2-year period and patients were no longer eligible once they had commenced treatment. Ten healthy volunteers also participated in Experiments 1 and 2. All patients had been diagnosed with CRPS according to established criteria (Bruehl *et al*., 1999). None of the participants had sustained demonstrable peripheral nerve or CNS damage. All patients were identified as having 'cold-type CRPS' (the dominant form of chronic CRPS, in which the affected arm is cooler than the unaffected arm) (Marinus *et al*., 2011) by satisfying three criteria: (i) the patient reported that the affected limb usually felt cooler than the other one; (ii) the patient reported that the affected limb seldom felt warmer than the other one; and (iii) the affected limb was significantly cooler than the healthy limb, as assessed by three thermal imaging snapshots taken 3 min apart at three standard sites on both hands. All healthy controls had no diagnosis of psychiatric or neurological illness that would affect blood flow. All experiments conformed to the Declaration of Helsinki. All participants provided written informed consent, and ethics approval was granted by the institutional ethics committee.

Protocol

Experiment 1

This experiment tested the hypotheses that (i) in patients with CRPS, skin temperature of either hand is lower when the hand is on the affected side of space (in respect to the body midline) than when it is on the healthy side of space; and (ii) the extent to which tactile stimuli from the affected side of space are given less weighting than those from the healthy side of space relate to the difference in skin temperature between the hands, regardless of whether the hands are uncrossed or crossed.

Ten patients and 10 age- and gender-matched controls participated in this experiment (Supplementary Table 1). Participants sat at a table. They were advised to find a comfortable sitting position and to rest their arms on the table in front of them. Baseline temperature was assessed by means of infrared thermal imaging and processed with the camera software [FLIR SC620 Camera and FLIRQuickreport, FLIR Systems; sensitivity <40 mK, field of view = $24^\circ \times 18^\circ$). For baseline measures, the average temperature was obtained from readings focused on the middle of the back of the hand, and on the tip of the second and fourth digits. After baseline measures, there were six experimental periods of 9 min each. During three periods, participants rested their arms in front of them so that the hands were equidistant, ~12 cm from the midline and uncrossed. For the other three periods, participants crossed their arms so that their hands were on the opposite side of the body midline (with reference to their usual position), ~8 cm from the midline and equidistant from it. Participants self-selected which arm went over which. The order of conditions, crossed or uncrossed, was balanced across participants. Hypothesis (i) was tested by measuring skin temperature recordings, at the beginning and end of each period. The camera was focused on a marked point at the centre of the back of each hand. Data were statistically analysed (PASW Statistics18, SPSS Inc) by an investigator who was blinded to the experimental conditions and naïve about the study. A three-way repeated measures ANOVA was performed on change in temperature between the beginning and the end of each experimental condition, with 'hand' (two levels: healthy and affected) and 'position' (two levels: uncrossed and crossed) as within subject factors, and 'group' (two levels: patients and controls) as between subject factors. A Greenhouse-Geisser correction for non-sphericity was applied. Cohen's *d* was used to determine effect size.

Hypothesis (ii) was tested by means of temporal order judgements. At the completion of the first period in each position, participants performed the temporal order judgement task. Vibrotactile stimuli (10 ms duration; 290 Hz frequency) were delivered through in-house stimulators (surface 1.6×2.4 cm) that were fixed to the pad of the index finger of either hand with tape. Stimuli were delivered at 140% of the mean vibrotactile threshold for each hand of patients with unilateral CRPS, a figure we had determined in previous work that used the same experimental set-up (Moseley *et al*., 2009). When necessary, stimuli were adjusted so that they were perceptually equivalent between sides. A trial consisted of a pair of stimuli, one from each vibrator in counterbalanced random order, separated by different stimulus-onset asynchronies: +10, +30, +60, +120 or +240 ms. Participants wore ear protectors so that they could not hear the sound eventually generated by the activation of the vibrator. Participants judged which of the two stimuli occurred first and responded verbally. The stimulus locations (right and left) were assigned numerical identifiers ('1' or '2') and this was alternated between participants to avoid the possibility that a bias towards '1' or '2' could confound the data. Verbal responses were recorded by an investigator blinded to stimulus-onset asynchronies and unable to detect the timing of the stimuli. After a practice batch of 50 trials, participants completed two batches of 150 trials, separated by 3 min rest.

The primary outcome variable for temporal order judgement was the point of subjective simultaneity. The point of subjective simultaneity is that stimulus onset asynchrony at which participants are equally likely to report either stimulus as occurring first. The point of subjective simultaneity is considered equivalent to the temporal arrangement of the stimuli at which they are perceived as simultaneous. The proportion of correct responses at each stimulus-onset asynchrony was converted into *z*-scores using a standardized normal distribution. Linear function computed the best-fitting sigmoidal line. The slope and intercept values were derived to calculate mean and 95% confidence interval for point of subjective simultaneity. We compared point of subjective simultaneity between positions with a paired *t*-test and we undertook a regression between point of subjective simultaneity and difference in skin temperature between hands to determine a Pearson's *r*. We also calculated the just noticeable difference, which indicates the difference between values needed to get 25 versus 75% correct and is negatively related to the sensitivity of the participant's responses (Spence, 2009).

Experiment 2

This experiment aimed to determine whether proprioception alone could drive the effect in observed patients with CRPS, in which case the patients' results of Experiment 1 would be replicated without visual information about hand position. We did not include controls in Experiment 2 because there was clearly no effect observed in Experiment 1 in controls, and this experiment aimed to clarify the effect observed in Experiment 1 in patients. The hypotheses of this experiment were identical to those of Experiment 1. The same patients who participated in Experiment 1 undertook Experiment 2 on a separate day, with a mean [±standard deviation (SD)] delay of 23 ± 9 days. The protocol was identical, except that participants were blindfolded during each period. That is, the blindfold was applied before the participant adopted the required position. Hand position was adjusted in response to verbal feedback from the investigator. At this stage, investigators and participants did not know the results of the first experiment. We applied exactly the same statistical analyses as those used in Experiment 1.

Experiment 3

This experiment aimed to determine whether, in patients with CRPS, there is an effect of the location of each hand, relative to the midline, on (i) the sense of ownership over the hand; and (ii) spontaneous pain. The hypotheses were (i) that the sense of ownership over the hand would be greater when it had been placed on the healthy side of the body midline than if it was kept on the (usual) affected side; and (ii) that spontaneous pain would be less intense when the hand had been held on the healthy side of the body midline than when it was held on the (usual) affected side. Eight of the patients who had participated in the first two experiments also participated in Experiment 3, 8 ± 8 days later (Supplementary Table 1). There were two experimental periods of 10 min with the hands uncrossed and two periods of 10 min with the hands crossed. The periods were longer in this experiment than in Experiments 1 and 2 because this experiment had fewer conditions. The order of conditions was again randomized. Before and immediately after each period, with the hands still in place, participants completed two pairs of 101-point numerical rating scales (NRS), in random order. To familiarize the participant with the NRS, they were shown a visual analogue scale, with marks and numbers every 10 points. In this sense, the tool was like a visual analogue scale with numbers attached so that the participant could verbally select a number that best coincided with their chosen mark on the visual analogue scale.

The first pair of NRSs concerned pain. The first question related to the affected hand. The question was 'How painful is your affected hand right now?' The second NRS related to the other hand. The question was 'How painful is your other hand?' These NRSs were anchored at left with 'Not at all' and at right with 'As bad as it could be'.

The second pair of NRSs concerned the sense of ownership over the hand. The first NRS related to the affected hand. The question was: 'How would you rate your sense of ownership over your affected hand right now?' The second NRS related to the unaffected hand. The question was 'How would you rate your sense of ownership over your other hand right now?' These NRSs were anchored at left with 'It feels like I don't own it at all' and at right with 'It feels like I own it completely'.

Data for both conditions in each position were pooled. A two-way repeated measures ANOVA was performed on average sense of ownership ratings, with 'hand' (two levels: affected and healthy) and 'position' (two levels: crossed and uncrossed) as experimental factors. A Greenhouse-Geisser correction for non-sphericity was applied. Because the healthy hand was not painful in either condition, a paired *t*-test compared pain in the affected hand between the uncrossed and crossed conditions. A Bonferroni correction for multiple measures was applied.

After participants had completed the NRS, they were asked the following open-ended questions: 'How does your affected hand feel right now?' and 'How does your other hand feel right now?' Responses that related to swelling, pain, temperature or perceived location or posture were recorded.

Experiment 4

This experiment aimed to determine if any effect of crossing the arms was dependent on the arms crossing each other, rather than crossing the midline. The hypothesis of this experiment was that skin temperature of either hand would be lower on the affected side of the body midline than on the healthy side of the body midline, even when the hands were not crossed. Ten patients with CRPS participated in this experiment, six of whom had not participated in any previous experiments (Supplementary Table 1). Four of the participants from Experiments 1–3 also participated in this experiment, without knowing the results of previous experiments.

In this experiment, there were three experimental periods of 10 min, which were undertaken in random order. For all periods, participants sat with their arms resting on the table in front of them. In one period, participants held their hands comfortably ~10 cm equidistant from the midline. This was called the 'uncrossed' position. In another period, participants held their affected hand ~8 cm over the midline so that it rested adjacent to their healthy hand. That is, both hands were on the healthy side of the midline. This was called the 'both healthy' position. For the final period, participants held the healthy hand ~8 cm over the midline so that it rested adjacent to their affected hand. That is, both hands were on the affected side of the midline. This was called the 'both affected' position. Temperature was recorded and statistically analysed as in Experiments 1 and 2. A two-way repeated measures ANOVA was undertaken on hand temperature, with 'hand' (two levels: affected and healthy) and position (three levels: uncrossed, both affected, and both healthy) as experimental factors. A Greenhouse-Geisser correction for non-sphericity was applied.

Experiment 5

This experiment tested the hypothesis that the observed change in skin temperature is positively related to how far the hand is placed in relation to its usual position in external space. Seven new patients with CRPS participated in this experiment (Supplementary Table 1). Patients held their hands comfortably ~15 cm equidistant from the midline. This location of their hands was designated 'the bookends'. They were then asked to self-select four locations equally distributed between the bookends and to number them from 2 to 5, with the left bookend being '1' and the right bookend being '6'. They were then asked to put either their left or right hand (alternated between participants) at each of the six locations, while the other, non-moving hand stayed at its bookend. The order of locations was randomized. Participants held their hand in each location for 9 min. The perpendicular distance from the tip of the middle finger to the midline was recorded. Temperature was recorded and expressed as a difference between that observed when the hand was at its 'bookend'. The distance between the position of the affected hand and its usual position was expressed as a positive value while the distance between the position of the healthy hand and its usual position was expressed as a negative value. We pooled the data from both hands and used linear regression to relate the difference in position and the difference in temperature, relative to the usual position bookend.

Analyses on pooled data

We also investigated whether the duration of CRPS, or average pain over the last 2 days, relates to the extent of spatially dependent effects on temperature of the affected hand. At initial interview, each participant rated their average pain over the last 2 days on a 0–10 NRS, anchored at left with 'no pain at all' and at right with 'worse possible pain'. None of our experiments were sufficiently powered in isolation to undertake this analysis, so we determined, for each participant, an effect size of the shift in temperature associated with crossing the midline for each hand. For this analysis, because both temperature and distance are interval measures, we undertook a linear regression, calculating Pearson's *r*. We related the effect size to the duration of CRPS using linear regression and Pearson's *r*. Because pain is an ordinal variable, we related effect size to pain by calculating Spearman's *r*. That is, we undertook four analyses—two for the affected and two for the healthy hand. For those who participated in more than one experiment, only data from their first experiment were analysed. Because these were secondary analyses, we did not correct for multiple comparisons.

Results

Results are reported as mean ± SD. Corrected *P*-values are shown.

Experiment 1

Skin temperature

The temperature of both the affected and healthy hand was dependent on their location in external space, in respect to the body midline. In other words, patients had a cold side of space and a warm side of space. The critical statistical result was a 'hand' × 'position' interaction [$F(1,9) = 34.7$; $P < 0.001$; $\eta^2 = 0.65$]. There was no main effect of 'hand' or 'position' ($P > 0.17$ for both). That is, the temperature of either hand was cooler when that hand was on the affected side of the body midline than when it was on the healthy side of the body midline. Specifically, when the arms were uncrossed and equidistant from the midline, the affected hand was cooler than the healthy one [0.5 ± 0.3°C; $t(9) = 4.18$, $P = 0.005$], which is a common finding in patients with cold-type CRPS (Birklein *et al.*, 1998). When the hands had been crossed over the body midline for 9 min, the temperature of both hands had changed. The affected hand had become 0.4 ± 0.3°C warmer than it was in the uncrossed condition ($P = 0.01$; effect size, Cohen's $d = 0.35$) and the healthy hand had become 0.3 ± 0.3°C cooler than it was in the uncrossed condition ($P = 0.02$; Cohen's $d = 0.28$), but the healthy hand was not cooler than the affected one after 9 min with the hands crossed [temperature of healthy hand − affected hand = 0.2 ± 0.3°C; $t(9) = 1.94$, $P = 0.14$]. Therefore, the hypothesis that skin temperature of either hand is lower when the hand is on the affected side of the body midline than when it is on the healthy side of the body midline, was supported.

Temporal order judgement task

As it has been shown previously (Yamamoto and Kitazawa, 2001; Moseley *et al.*, 2009), crossing the hands over the midline also affected tactile processing. Tactile stimuli delivered to a hand that was held on the healthy side of the body midline were prioritized over identical tactile stimuli delivered to a hand held on the affected side of the body midline, regardless of which hand was where. That is, when the hands were uncrossed, a stimulus to the index finger of the affected hand needed to occur ~17 ms before an identical stimulus to the index finger of the healthy hand, for the two stimuli to be perceived as being simultaneous (17.1 ± 10.0 ms; Fig. 1). This result confirmed our previous finding (Moseley *et al.*, 2009).

When the hands were crossed over the midline, the opposite situation was observed: the stimulus to the healthy hand needed to occur before the stimulus to the affected hand (point of

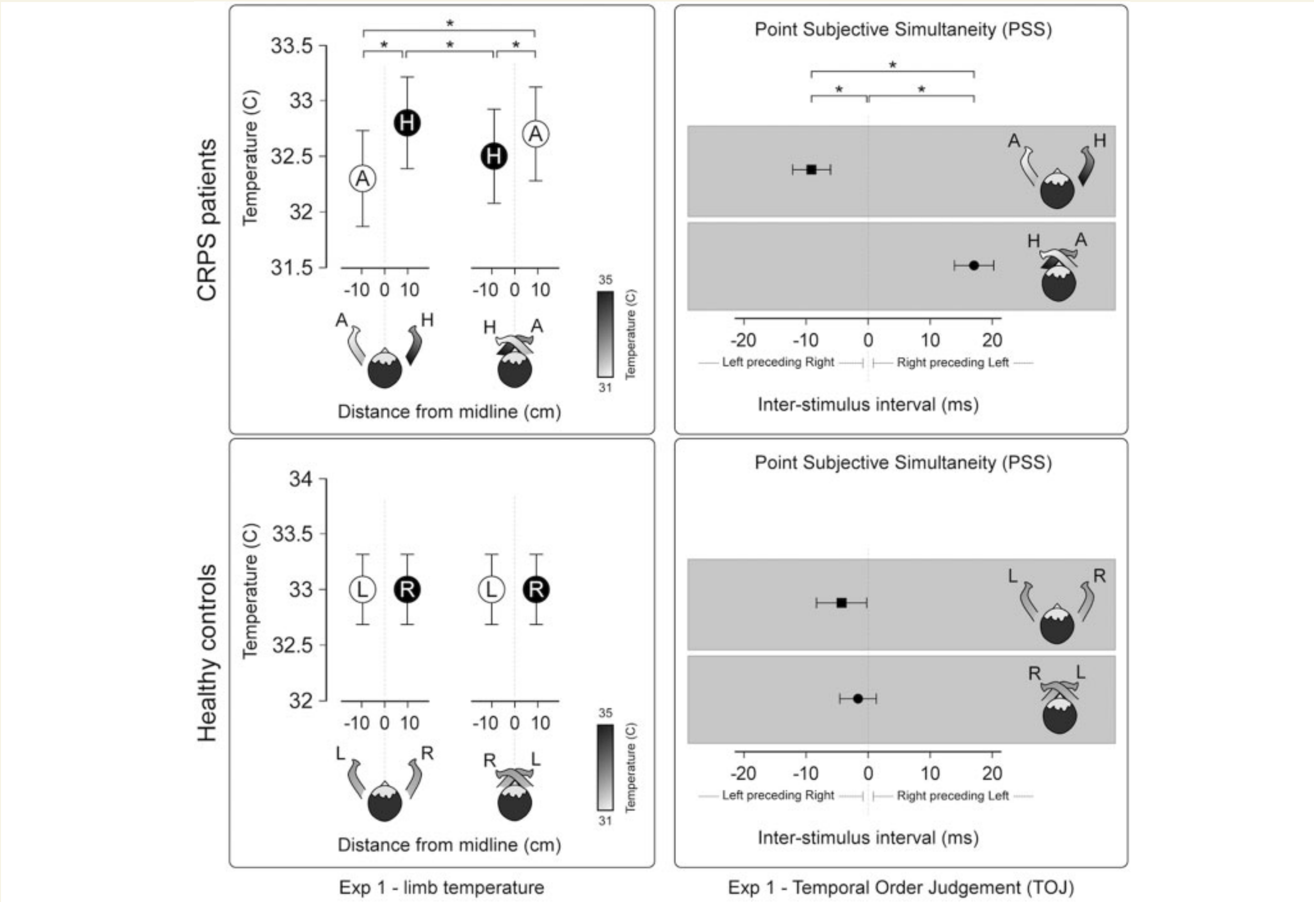

Figure 1 Experiment 1. *Left*: Mean (circles) and SD (error bars) temperature of the affected (open circle 'A'; or left hand, open circle 'L' for controls) and healthy (filled circle 'H'; or right hand, filled circle 'R' for controls) hands, after the hands had been held uncrossed or crossed over the midline for 9 min. Horizontal axis shows approximate distance from the midline. Asterisk denotes significant difference on Wilcoxon pair test ($P < 0.01$). *Right*: Temporal order judgement (TOJ) results: mean (shapes) and SD (error bars) point of subjective simultaneity (PSS) after the hands had been held uncrossed or crossed over the body midline for 9 min, in patients with unilateral CRPS (*top*) and healthy controls (*bottom*). Asterisk denotes significant difference ($P < 0.01$).

subjective simultaneity = −9.1 ± 9.7 ms). Point of subjective simultaneity was different between the hands uncrossed and crossed [26.2 ± 13.1 ms, $t(9) = 6.50$; $P = 0.001$; Fig. 1]. Point of subjective simultaneity was positively related to the difference in temperature between the hands, regardless of whether the hands were crossed or not (Pearson's $r = 0.8$, $P < 0.01$ for both). That is, the larger the tactile processing bias as reflected by the difference in point of subjective simultaneity from zero, the larger the difference in skin temperature between the hands. Therefore, the hypothesis that the extent to which tactile stimuli from the affected side of space were given less weighting than those from the healthy side of space would relate the difference in skin temperature between the hands, regardless of whether the hands were uncrossed or crossed, was supported.

As expected, the just noticeable difference was significantly larger when the arms were crossed (62.3 ± 13.1 ms) than when they were uncrossed [38.1 ± 10.3 ms; $t(9) = 5.8$; $P < 0.001$], which indicates that the smallest interval that could reliably be noticed by patients was larger when they had their arms crossed than they were when they had their arms uncrossed.

Healthy controls

When we undertook these experiments in a group of 10 healthy volunteers (six females, Supplementary Table 1), we did not replicate the results that were obtained on patients. That is, skin temperature was not different between hands regardless of hand location [difference = 0.0 ± 0.1°C; 'hand' × 'position' interaction: $F(1,9) = 0.054$, $P = 0.82$]. Similarly, there was no side-dependent prioritization of tactile stimuli [point of subjective simultaneity = 4.5 ± 9.2 ms for uncrossed hands and 2.0 ± 6.9 ms for crossed hands; $t(9) = 0.89$, $P = 0.56$; Fig. 1].

For healthy controls, as it was for patients, the smallest interval that could reliably be noticed was larger when they had their arms crossed (just noticeable difference = 56.0 ± 9.9 ms) than when they had their arms uncrossed [just noticeable difference = 35.6 ± 10.8 ms; $t(9) = 5.7$; $P = 0.003$].

Patients versus controls

The critical result with regards to the difference between patients and controls was a significant 'hand' × 'position' × 'group' interaction: [$F(1,18) = 33.8$; $P < 0.001$; $\eta^2 = 0.65$], indicating that crossing the hands caused a significant change of hand temperature in patients but not in controls.

Experiment 2

Skin temperature without vision

When the above experiment was repeated in patients who were blindfolded, the results were virtually identical. The affected hand was cooler than the healthy one [by $0.4 \pm 0.4°C$; $t(9) = 4.14$, $P = 0.008$], but when the hands had been crossed over the midline for 9 min, the temperature of the affected hand had significantly increased [by $0.4 \pm 0.4°C$; $t(9) = -5.2$, $P = 0.003$; Cohen's $d = 0.27$], and the temperature of the healthy hand, now on the affected side of the body midline, had decreased [by $0.3 \pm 0.3°C$; $t(9) = 5.06$, $P = 0.003$; Cohen's $d = 0.23$]. The healthy hand was not cooler than the affected one after 9 min with the hands crossed [temperature of healthy hand − affected hand = $0.2 \pm 0.3°C$; $t(9) = 1.97$, $P = 0.14$]. Again, the critical statistical result was a significant 'hand' × 'position' interaction [$F(1,9) = 33.50$; $P < 0.001$; $\eta^2 = 0.78$; Fig. 2].

Temporal order judgement task without vision

To be perceived as being simultaneous, stimuli to the hand held on the affected side of space had to occur before stimuli to the hand held on the healthy side of space, whether the hands were uncrossed (point of subjective simultaneity = 16.3 ± 11.7 ms) or crossed over the body midline (point of subjective simultaneity = -8.3 ± 9.1 ms). The difference in point of subjective simultaneity between the hands uncrossed and crossed was again significant [$t(9) = 5.45$; $P = 0.001$; Fig. 2]. Again, just noticeable difference was larger with the arms crossed (68.4 ± 13.0 ms) than with them uncrossed [43.3 ± 18.0 ms; $t(9) = 3.9$, $P = 0.024$].

Experiment 3

Sense of ownership over the hands

When participants had their arms uncrossed, they had a lower sense of ownership over their affected hand than over their healthy hand, which is a common observation in CRPS (Lewis *et al*., 2007). Crucially, this sense of ownership was also affected by the location of the hand in space. For the affected hand, where 10 = 'It feels like I own it completely', the sense of ownership over the hand in its usual position was 5.9 ± 1.7. When that hand had been held beyond the midline, in the healthy side of space, for 10 min, the sense of ownership increased to 7.1 ± 1.8 (Cohen's $d = 0.68$). For the healthy hand, the sense of ownership of the healthy hand in its usual position was always rated 10, meaning that the participants felt they fully owned their hand. When that hand was held in the affected space for 10 min, the sense of ownership decreased to 8 ± 1.3. The critical statistical result was a significant 'hand' × 'position' interaction [$F(1,6) = 22.3$; $\eta^2 = 0.79$; $P = 0.003$]. Therefore, the hypothesis that the sense of ownership over either hand would be greater when it was held on the healthy side of the body midline than if it was held on the (usual) affected side of the body midline, was supported.

Pain

The affected hand was significantly less painful when the hands had been crossed for 10 min than when they had been uncrossed [$t(6) = -3.3$; $P = 0.032$; difference = 4 ± 3 mm on a 100-mm scale; Cohen's $d = 0.34$]. Therefore, the hypothesis that the affected hand would hurt less when it had been held on the healthy side of the body midline than when it was held on the (usual) affected side of the body midline was statistically supported. Notably, the degree to which pain was reduced is smaller than that considered clinically important in treatment studies.

Open-ended questions

When participants were asked the open-ended question 'How does the hand feel?', seven out of eight participants reported at the end of the 10-min period with their affected hand on the healthy side of the body midline, that the hand felt 'slightly' (5/8), 'a bit' (1/8) or 'moderately' (1/8) less swollen. Four participants reported that their affected hand felt 'warmer' (2/8) or 'less cold' (2/8). Other reports were 'less weird' (3/8), 'less fuzzy' (2/8) and 'more real' (1/7). Remarkably, two participants also reported at the end of the 10-min period with the healthy hand in the affected space, that the healthy hand felt 'slightly swollen'. There were no other reports relevant to the current experiment.

Experiment 4

Crossing the hands or crossing the body midline?

This experiment tested the possibility that the observed changes in hand temperature depended on the arms actually being crossed over each other, rather than on one arm being on one or the other side of the body midline. When only the affected hand was held over the body midline, it became warmer than it was in the uncrossed position [by $0.5 \pm 0.3°C$; $t(9) = -7.17$, $P = 0.01$; Cohen's $d = 0.32$]. When only the healthy hand was crossed over the body midline, it became cooler than it was in the uncrossed position [by $0.3 \pm 0.3°C$; $t(9) = 9.35$, $P = 0.015$; Cohen's $d = 0.30$; Fig. 3]. Crossing one hand over the body midline did not affect the temperature of the other hand. For this analysis, there were significant main effects of 'hand' [$F(1,9) = 27.3$; $\eta^2 = 0.75$; $P = 0.001$] and 'position' [$F(2,18) = 16.6$; $P < 0.001$; $\eta^2 = 0.65$], but the critical statistical result was a significant 'hand' × 'position' interaction [$F(2,18) = 53.12$; $P = 0.001$; $\eta^2 = 0.86$]. Therefore, the hypothesis that skin temperature of either hand would be lower on the affected side of the body midline than on the healthy side of the body midline even when the hands were not crossed over each other, was supported.

Experiment 5

Relating skin temperature to the distance beyond midline

Patients undertook this task with one hand or the other (alternated between patients) because the time that was needed for us to assess both hands on all patients was not tolerated. Four patients performed the task with their affected hand and three patients performed it with their healthy hand. For either hand,

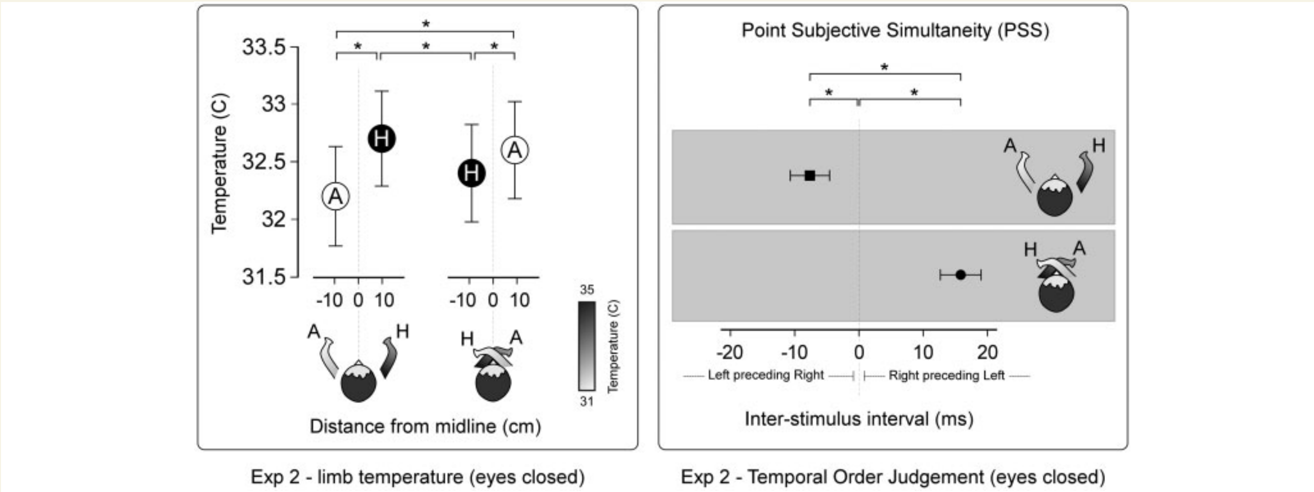

Figure 2 Experiment 2. Temperature (*left* panel) and temporal order judgement (*right* panel) results for Experiment 2, which was identical to Experiment 1 except that patients were blindfolded. Thus, this experiment removes the impact of vision on the observed effect. Results are similar to those for Experiment 1. PSS = point of subjective simultaneity.

there was no change in temperature when the hand was positioned for 10 min anywhere on the ipsilateral side of the midline. However, when the hand was positioned for 10 min beyond the midline, the change in temperature was positively related to the distance from the midline ($r = 0.76$, $P < 0.01$; Fig. 4). Therefore, the hypothesis that the change in skin temperature is positively related to how far beyond the midline the hand is held, was supported.

Pooled data: does the spatially defined effect on skin temperature relate to the duration of complex regional pain syndrome or baseline pain?

There was no relationship between the size of the spatially dependent effect on hand temperature and duration of CRPS ($P > 0.23$ for both). Average pain over the last two days was positively related to the spatially dependent effect on temperature of the affected hand (Spearman's $r = 0.475$, $P = 0.034$) and temperature of the healthy hand (Spearman's $r = 0.532$, $P = 0.016$).

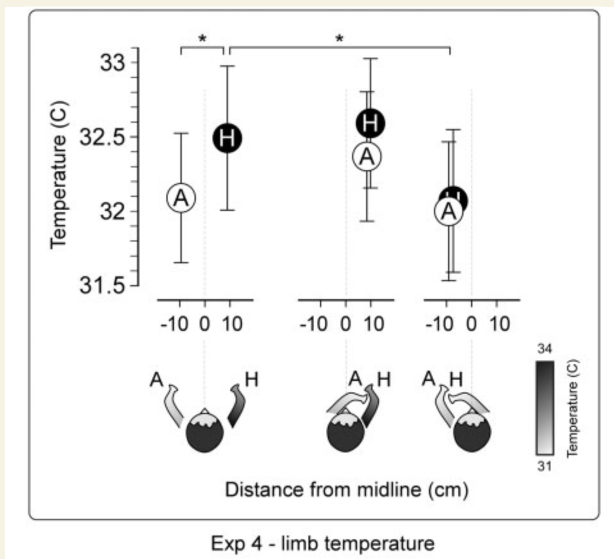

Figure 3 Experiment 4. Mean (shapes) and SD (error bars) temperature for the affected (open circle 'A') and healthy (filled circle 'H') hands, after 10 min with the hands uncrossed (*left*), with both hands on the healthy side of space (*middle*) and with both hands on the affected side of space (*right*). Asterisk denotes significant difference ($P < 0.01$).

Discussion

The experiments reported here clearly show that, in patients with unilateral upper limb CRPS, thermoregulation of either limb is disrupted according to a space-based rather than somatotopic frame of reference. That is, in these patients, the location of either hand relative to the body midline affects the skin temperature of that hand. That the temperature of a single limb can be disrupted after peripheral trauma (Janig and Baron, 2003), stroke (Riedl *et al*., 2001) and several psychiatric conditions (Moseley *et al*., 2008*a*) is well established. However, that thermoregulation and sense of bodily ownership can be disrupted by changing the position of the hand in space, relative to the body midline, is an entirely new finding, supporting the idea of a tight and powerful relation between both somatotopical and spatial processing, the sense of ownership over the hand, and homeostatic regulation.

CRPS is characterized by an array of efferent system dysfunction that appears to be distributed across a specific body part rather than a nerve or nerve root distribution. For example, the sensory dysfunction (Mailis-Gagnon, 2006) affects the whole limb and sometimes the entire hemibody, (Janig and Baron, 2002; Mailis-Gagnon, 2006) and, similarly, the motor dysfunction extends beyond the injured area to affect the entire limb, sometimes resulting in severe fixed dystonia (van de Beek *et al*., 2002). The current results raise the possibility that altered spatial processing might contribute to the maintenance of CRPS through an effect on autonomic and

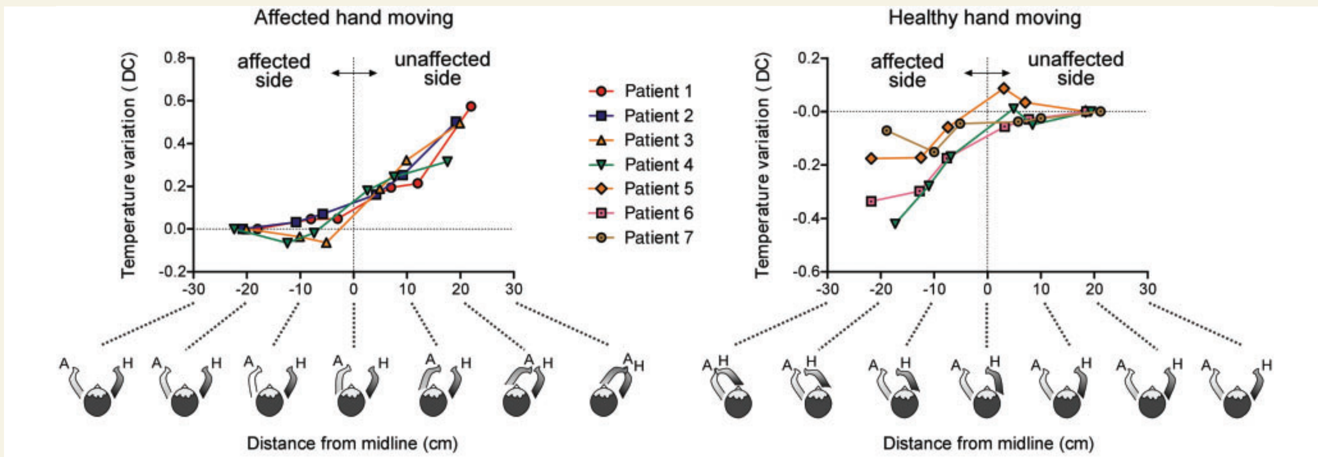

Figure 4 Results of Experiment 5. Individual patient data for the temperature variation (%) of the affected hand (*left* panel) and healthy hand (*right* panel) from baseline. Baseline was determined with the hands held uncrossed and equidistant from the body midline. Each position was self-selected and temperature was recorded after the patients kept the position for 9 min. The order of position was randomized. Horizontal axis shows the distance of the hand from the body midline. Negative values indicate the affected side and positive values indicate the healthy side. *Left* panel: Note that hand temperature is relatively constant while the affected hand is kept on the affected side of space, but that temperature linearly increases with the distance beyond the midline. *Right* panel: The opposite pattern is observed for the healthy hand—hand temperature is relatively constant while the healthy hand is kept on the healthy side of space, but the temperature decreases with the distance beyond the midline. Data were collected from one hand only in each patient.

sensory dysfunction. That there was no relationship between the extent of the disruption in spatial perception and the duration of CRPS suggests against the possibility that the phenomenon is simply a consequence of having CRPS for an extended period. That said, our cohort only included people with chronic cold-type CRPS so it remains possible that if acute patients were also included, a duration effect would be observed, although at the acute stage, patients might be more likely to be 'warm type' (Marinus *et al*., 2011). We should be cautious, however, in extrapolating clinical implications of the current results. Indeed, the magnitudes of the observed effects are small, and further work is required to clarify this issue.

That disrupted high-order spatial representations can modulate thermoregulation would be predicted according to the recent theory of a multisensory 'cortical body matrix', by which brain-grounded maps of the body and the space around it are integrated with the purpose to maintain the psychological (bodily awareness and ownership) and homeostatic integrity of the body (Moseley *et al*., 2012*a*). The cortical body matrix theory does not suppose a single network of neurons—there is substantial evidence that different frames of reference are subserved by distinct sub-populations of neurons within parietal and frontal cortices (Driver and Spence, 1998)—but an integrated matrix of neuronal loops. Our results are in agreement with that theory insofar as they clearly show a spatially defined modulation of skin temperature, but further studies are necessary to demonstrate whether or not the theory is a useful one within this domain.

The potential implications of the current work extend to a range of complex persistent pain states, including chronic pelvic pain and fibromyalgia (Janig and Foreman, 2011), which are characterized by disruption of multiple efferent systems, disrupted somatotopic and spatial perception and disrupted bodily awareness or ownership. Although non-lateralized painful conditions may not involve midline-based disruptions, there is evidence that patients with unilateral chronic back pain display ipsilateral disruption of somatotopic perception (Flor *et al*., 1997), bodily awareness (Moseley, 2008*a*) and spatial perception (Moseley *et al*., 2012*b*).

We observed almost identical results of disrupted thermoregulation according to a space-based frame of reference, whether participants had their eyes open or closed. This shows that although vision may be dominant under many conditions of stimulus presentation (Eimer and Driver, 2000), proprioceptive cues alone are sufficient to drive the observed effect. Vision and proprioception are not mutually additive for the effect, which is consistent with the notion of a ceiling effect in the contribution of vision and proprioception to the representation of our limbs in external space (Sambo *et al*., 2012).

The current results are certainly not the first to show tactile, autonomic and perceptual dysfunction delineated by the body midline. Indeed, hemispatial dysfunction is pathognomonic of the post-stroke condition of unilateral neglect, which can occur after damage to a number of cortical structures involved in spatial attention and spatiomotor performance (Buxbaum *et al*., 2004). Although there is no evidence of primary cortical damage in CRPS, marked functional changes in the response profile of the primary sensory cortex (S1) areas that represent the affected body area have been observed (Juottonen *et al*., 2002; Maihöfner *et al*., 2003; Pleger *et al*., 2004). On the grounds that sensory awareness depends on the integration of sensory input according to both somatotopic and spatial frames of reference (Gallace and Spence, 2008), it seems reasonable to suggest that the spatial perception deficit observed here might result not only from damage to spatiomotor areas but also from sustained abnormal somatosensory input (Moseley *et al*., 2012*a*). The mechanism by which sustained abnormal somatosensory input might induce a spatially defined disruption is not clear. The current results are consistent with current thought in the pathophysiology of chronic CRPS, which emphasizes cortical and autonomic dysfunction (Marinus *et al*., 2011). However, although S1 reorganization has been emphasized in the extant literature (Marinus *et al*., 2011), our results uphold the assertion that CRPS does not simply affect somatotopic representation in S1, but multiple multisensory representations of space (Legrain *et al*., 2012). Perhaps, because the affected hand is held immobile in the same spatial position, the representation of the space itself takes on the 'CRPS signature'.

It is important to note that although aspects of the chronic CRPS presentation appear similar to post-stroke neglect, and there is preliminary evidence that patients with CRPS display shifts in visual attention (Sumitani *et al*., 2007*a*, *b*), there are important differences between these two clinical conditions. For example, results of classic tests of neglect such as the line bisection task appear normal (Förderreuther *et al*., 2004) or are no different from those obtained from non-CRPS patients with pain (Kolb *et al*., 2012). Therefore, although the building body of data from people with CRPS appears consistent with parietal dysfunction, this dysfunction seems to be distinct from the classical neglect that is observed after stroke.

Experiments in healthy volunteers and patients with CRPS corroborate the idea that high-order representations of the body and space can exert a top-down influence over efferent body systems. For example, the rubber hand illusion is a simple cognitive manipulation that exploits the brain's predilection for congruent multisensory input and induces the vivid sense that one hand has been 'replaced' by a prosthetic counterpart (Botvinick and Cohen, 1998). It is worth noting here that the rubber hand illusion also induces a limb-specific drop in temperature (Moseley *et al*., 2008*a*) and an increased reactivity to histamine (Barnsley *et al*., 2012) of the real hand, the one that has been somehow 'replaced'. The magnitude of these effects is positively related to a shift in the prioritization of tactile inputs from the actual arm (as reflected by the point of subjective simultaneity), and to the vividness of the illusion of ownership over the rubber hand.

The most obvious mechanism underlying the observed change in temperature would involve changes in autonomic nervous system activity, which modulates blood flow by controlling vasoconstriction, or sweating, or both (Birklein *et al*., 1998). It is likely that anatomical projections from the posterior parietal cortex, which are critical for mapping external space (Andersen, 1995), to autonomic control centres in the insula and brainstem (Augustine, 1996) contribute to the observed effect. Perhaps this offers an explanation for the temperature gradient observed in Experiment 5: one might speculate that a gradient of strength might codify for spatial positions further apart from the midline. Indeed, the influence on thermoregulation seems dependent on the distance between the current position of the limb and where the pain is usually spatially mapped. Involvement of both hands is not altogether surprising—sub-clinical alterations in cortical processing of somatosensory input arising from both hands have already been observed in people with unilateral CRPS (Thimineur *et al*., 1998; Schwenkreis *et al*., 2003). However, that the involvement of the non-painful limb might indirectly result from dysfunction of spatial perception has not been considered. Descending projections from the posterior parietal cortex to autonomic centres in the brainstem (Porreca *et al*., 2002) could feasibly result in altered sympathetic tone when limbs are placed in the affected side of space.

An important question that remains to be answered is whether persistent pain is a cause or a consequence of the effects observed here, or both a cause and consequence, or neither. It is notable that average intensity of spontaneous pain over the past 2 days was moderately related to the magnitude of the spatially dependent effect on hand temperature of either hand. That the relationship was present for both hands suggests against a real-time effect of pain on limb temperature because the unaffected hand did not hurt when it crossed the midline, but it did change temperature. Relevant to this is the finding from Experiment 3, that pain was significantly reduced by placing the painful hand across the midline. Nonetheless, it raises the possibility that spontaneous pain is modulated by this deficit in spatial perception, a possibility that further research might elucidate. It is notable that treatment that normalizes the cortical representation of the affected body part is beneficial in both phantom limb pain and CRPS (Flor *et al*., 2001; Moseley *et al*., 2008*b*; Moseley and Wiech, 2009), an observation that raises the possibility of new treatments that target the disrupted cortical body matrix. Currently, many treatments for pain states still focus on a peripheral or spinal nociceptive driver. For example, common treatments for chronic CRPS are sympathetic nerve periods, spinal cord stimulation, systemic analgesics (Forouzanfar *et al*., 2002) and, in severe cases, amputation (Guttmann and Wykes, 2008). Even physical and occupational therapy tends to focus on the affected limb (Oerlemans *et al*., 2000). However, these peripherally targeted approaches are largely unsuccessful (Daly and Bialocerkowski, 2009). Critically though, the failure of peripherally targeted approaches on the one hand, and the association between central pathology and pain on the other, do not prove that central pathology causes pain. In fact, we rely instead on theoretical models, for example, the sensory–motor incongruence theory, which proposes that disruption of the cortical proprioceptive representation causes pain (Harris, 1999).

Experimental evidence for such theories is, however, not convincing. For example, experimental disruption of cortical proprioceptive representation does not evoke pain in healthy volunteers (Moseley *et al*., 2006; see Wand *et al*., 2011 for review). However, the possibility remains that cortical reorganization is not sufficient to cause pain in a normal healthy nociceptive/pain system, but it is sufficient to cause pain in a sensitized system such as that in chronic pain. Consistent with this possibility is the result of Experiment 3, which showed an effect of spatial location of the hand on pain. Importantly, the effect, albeit statistically significant, was too small to be clinically important. A more substantial effect was observed on the sense of ownership over the hand. That disruption of bodily ownership is a common and distressing characteristic of pathological pain syndromes has been suggested by quantitative (Moseley, 2005, 2008) and qualitative (Lewis *et al*., 2007) studies, so it seems possible that modifying the location of the hand might offer a short-term clinical benefit. However, speculation beyond this is not justified on the basis of the current data, and further research is required to clarify how best to capture the current findings within a clinical context.

Regardless of its underlying mechanisms, the influence, in patients with CRPS, of the position of a hand in space over its temperature, demonstrates a more complex interrelationship between cortical maps of space, and body temperature regulation, than has previously been considered. The result adds to a growing body of evidence for cortical disruption in CRPS (Marinus *et al*., 2011) and strengthens previous assertions about the similarities between CRPS and stroke (Acerra *et al*., 2007). Beyond CRPS, that these cortical maps can exert a top-down effect on physiological bodily functions at all extends Descartes' notion of mind–body unity (Descartes, 1644) to a new level. This finding may also have direct clinical and practical implications for the wide range of disorders characterized by disrupted spatial representation and thermoregulation (Moseley *et al*., 2008).

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Supplementary material

Supplementary material is available at *Brain* online.

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