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Limb-specific autonomic dysfunction in complex regional pain syndrome modulated by wearing prism glasses

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In unilateral upper-limb complex regional pain syndrome (CRPS), the temperature of the hands is modulated by where the arms are located relative to the body midline. We hypothesized that this effect depends on the perceived location of the hands, not on their actual location, nor on their anatomical alignment. In 2 separate cross-sectional randomized experiments, 10 (6 female) unilateral CRPS patients wore prism glasses that laterally shifted the visual field by 20°. Skin temperature was measured before and after 9-minute periods in which the position of one hand was changed. Placing the affected hand on the healthy side of the body midline increased its temperature (Δ°C = +0.47 ± 0.14 °C), but not if prism glasses made the hand appear to be on the body midline (Δ°C = +0.07 ± 0.06 °C). Similarly, when prism glasses made the affected hand appear to be on the healthy side of the body midline, even though it was not, the affected hand warmed up (Δ°C = +0.28 ± 0.14 °C). When prism glasses made the healthy hand appear to be on the affected side of the body midline, even though it was not, the healthy hand cooled down (Δ°C = −0.30 ± 0.15 °C). Friedman's analysis of variance and Wilcoxon pairs tests upheld the results ($P < 0.01$ for all). We conclude that, in CRPS, cortical mechanisms responsible for encoding the perceived location of the limbs in space modulate the temperature of the hands.

1. Introduction

Complex regional pain syndrome (CRPS) is characterized by severe pain, with autonomic, sensory, and endocrine dysfunction [10]. Chronic CRPS is associated with disrupted spatial perception [23]. For example, stimuli delivered to the hand placed in the affected side of space (ie, the side of space where the painful hand is usually located) are given less weighting than identical stimuli delivered to the hand placed in the unaffected side, regardless of which hand is where [20]. This phenomenon is similar to that observed in poststroke patients who develop hemispatial neglect [2], and a similar spatially defined deficit has recently been observed in people with unilateral chronic back pain [17].

This spatially defined deficit relates to thermoregulation – patients with CRPS have a "cool side of space" [18]. One issue that remains to be resolved is whether the midline-dependent effect on skin temperature of either hand is caused by the actual anatomical configuration of the limb, or by the perceived location of the hand, as a result of the integration of somatotopic and external space frames of reference. Prism glasses that laterally shifted the visual field were used to investigate this issue. We hypothesized that skin temperature of either hand would depend on the perceived location of the hand relative to the body midline, not on its actual location.

2. Materials and methods

2.1. Participants

A convenience sample of 10 patients (6 females) who satisfied the diagnostic criteria for CRPS [4] and were identified as having "cold-type CRPS" of one hand by clinical assessment, and were naïve to experiments in our research group, participated (Table 1). Seven patients had CRPS affecting the left arm. No patient wore prescription glasses. Sample size was based on detecting a large effect with no dropouts, 80% power, and alpha set at 0.05. All experiments conformed to the Declaration of Helsinki. All participants provided

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Table 1
Participant characteristics.

ID	Side	Trigger	Months	Age	M/F	Treatments	Medications
1	L	Dislocated finger	28	33	F	PT, GMI	Gaba, paracet, ketamine
2	L	Wrist fracture	32	46	M	TDT, GMI,	Gaba, paracet,
3	L	Wrist fracture	13	40	F	PT, mirror	Morphine, Gaba, ketamine
4	L	STI	20	24	F	PT, mirror, SCS	Morphine, Gaba
5	L	Hand fracture	48	28	F	PT, Hydro	Tricyc, paracet, morphine
6	L	Wrist fracture	54	33	F	PT, Mirror therapy	Gaba, paracet,
7	R	STI	47	46	M	PT, Mirror therapy	Ketamine, Tricyc
8	R	Wrist fracture	39	35	M	PT, PMP	Ketamine, Tricyc, Gaba
9	R	Wrist fracture	67	23	M	PT, PMP	Paracet, Tricyc
10	L	Wrist fracture	90	46	F	PT, mirror, SCS	Morphine, Gaba, ketamine

Side, affected side; Trigger, injury that triggered complex regional pain syndrome; Months, duration since injury in months; Age, age of participant in years; M/F, male or female; L, left; R, right; Treatments, treatments that the participant has received prior to recruitment in the present study; PT, physical therapy; GMI, graded motor imagery; TDT, tactile discrimination training; mirror, mirror therapy; STI, soft tissue injury; SCS, spinal cord stimulator; Hydro, hydrotherapy; PMP, multidisciplinary pain management programme; Gaba, gabapentin; paracet, paracetamol; Ketamine, low-dose infusion over 3–5 days; Tricyc, tricyclic antidepressants.

written informed consent and ethics approval was granted by the institutional ethics committee.

2.2. Protocol

2.2.1. Experiment 1

All testing was undertaken in a temperature- and humidity-controlled room. Participants sat comfortably with their hands resting on a plastic table in front of them, such that the hands were equidistant from the body midline at a distance similar to the distance between their shoulders. No advice was given about maintaining head position or orientation. After 12 minutes in this baseline posture, temperature recordings were obtained using infrared thermal imaging (FLIR SC620: field of view = 24°; accuracy 2% of reading; sensitivity to change < 40 mK). The camera was positioned 130 cm above the table, with the centre of the field of view at the midpoint between the 2 hands. A specific point on the hand was chosen and marked with a felt pen. The point corresponded to 3 cm proximal to the 4th metacarpophalangeal joint (Supplementary Fig. S1). Temperature data were stored and analysed using custom software (FLIRQuickreport, FLIR Systems, Täby, Sweden).

Prism glasses that shifted the visual field by 20° were fixed to glass frames, such that the visual field could be shifted to the left or to the right. Cardboard was fixed around the glasses in order to eliminate any external visual cues. Participants placed their healthy hand out of view, on their lap. They sat comfortably, closed their eyes, and then put on the glasses and opened their eyes. They were advised to keep their head facing approximately forwards. The direction in which the visual field was shifted was alternated between participants. The participants then placed their affected hand on an angled platform, made of plastic, which was placed in front of them so that they could easily see their hand. Paper was fixed to the platform and was replaced for each patient. Participants were asked to position their affected hand on the table. So that their affected hand was in line with the body midline. For some participants, the actual location of the affected hand was on the affected side of the true body midline. For other participants, it was on the healthy side of the true body midline. For all participants, the perceived location of the affected hand was on the perceived body midline. In this manner, the perceived and actual locations of the affected hand were dissociated. The actual location of the hand, relative to the body midline, was measured and noted, and marked on the platform. Participants stayed in this position for 9 minutes. Skin temperature was recorded at the beginning and end of this period. At the end, participants closed their eyes, removed the glasses, adopted a comfortable position with their hands in their lap, opened their eyes again, and then rested for 15 minutes. At the end of the 15-minute rest period, the participants once again wore the glasses, but this time the prisms were reversed, so that the visual field was laterally shifted in the opposite direction. The above procedure was repeated. After another 15-minute rest, 2 more conditions were undertaken, separated by a 15-minute rest period, but in these conditions participants did not wear the prism glasses. However, their hand was positioned in the same location as it had been during the corresponding earlier condition when they were wearing the prism glasses (Table 2, Fig. 1). That is, although the direction in which the prisms shifted the visual field was alternated between participants, all participants undertook the prism glasses conditions first.

2.2.2. Analyses

Temperature data were transferred to statistical software (PASW Statistics 18, SPSS Inc, Chicago, IL, USA) by an investigator who was blind to the experimental conditions and naïve about the study. Temperature recorded at the end of each period was subtracted from that recorded at the beginning of that period to measure a temperature change (Δ°C).

Because we had a small sample, under advice from a statistician, we undertook nonparametric statistical analyses. First, we performed a Friedman's analysis of variance (ANOVA) to compare Δ°C of the affected hand during the 4 conditions (see Table 2; Fig. 1). Because we were undertaking 2 experiments on the one sample, we corrected for multiple measures such that α was set at 0.025. If the Friedman's ANOVA was significant at this α, Wilcoxon paired tests were performed to compare the changes in temperature between the 2 conditions that had the hand in the same actual location but in different perceived locations (Conditions 1 & 2, and Conditions 3 & 4; Table 2; Fig. 1).

2.2.3. Experiment 2

The same patients participated in Experiment 2, 1 week after they had taken part in Experiment 1. This experiment also involved the prism glasses, but this time the participants placed their affected hand on the perceived opposite side of space, about 4 cm beyond the perceived body midline. The prism glasses shifted the visual field in the opposite direction. That is, the perceived location of the hand was beyond the actual body midline, but the actual location of the hand corresponded approximately to the actual body midline. There were 4 conditions: 2 in which the affected hand was located on the actual body midline and the prism glasses were either worn or not worn, and 2 in which the healthy hand was located on the actual body midline and the prism glasses were either worn or not worn (see Table 3). Whether or not the prism glasses were worn first, and whether the affected hand or the healthy hand was tested first, was adjusted in a predefined order, across participants (Supplementary Table S1).

Table 2
The perceived and true location of the affected hand during each experimental condition in Experiment 1.

Condition	1	2	3	4
Hand	Affected	Affected	Affected	Affected
Perceived location	20° to the healthy side of midline	On the midline	20° to the affected side of midline	On the midline
True location	20° to the healthy side of midline	20° to the healthy side of midline	20° to the affected side of midline	20° to the affected side of midline
Analysis 1	Friedman's ANOVA on Δ°C			
Analysis 2	Wilcoxon pairs on Δ°C		Wilcoxon pairs on Δ°C	

ANOVA, analysis of variance.

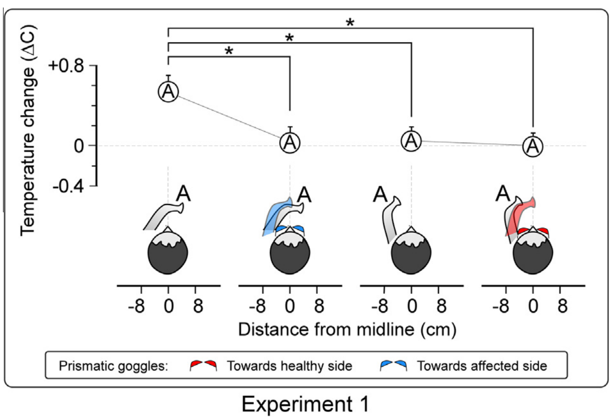

Fig. 1. Results of Experiment 1: the affected hand (A) became warmer when it was placed on the healthy side of space, about 40 mm beyond the body midline (left figurine). However, when the participant wore prismatic goggles (blue) that shifted the apparent location of the limb toward the affected side of the visual field, this warming effect disappeared. Simply inducing a shift in visual field did not cause the effect: when goggles that shifted the visual field toward the healthy side (red) were worn so that the affected hand appeared to be on the body midline, there was no effect on temperature (right figurine). Error bars represent SD. Asterisk denotes significance of Friedman's analysis of variance and Wilcoxon pairs tests, $P < 0.03$.

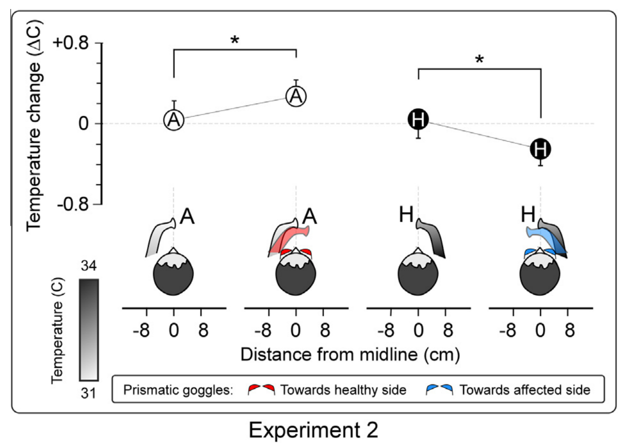

Fig. 2. Results of Experiment 2: The affected hand (A) became warmer when the patient wore prismatic goggles that shifted the visual field toward the healthy side (red), so that the perceived location of the hand was on the healthy side of space, about 4 cm beyond the body midline, even though the true location of the hand was on the midline (second figurine from left). Similarly, the healthy hand (H) became cooler when the patient wore prism glasses that shifted the visual field towards the affected side (blue), so that the perceived location of the hand was on the affected side of space, about 4 cm beyond the body midline, even though the true location of the healthy hand was on the midline (right figurine). Shapes represent mean, and error bars represent SD. Asterisk denotes significance of Friedman's analysis of variance and Wilcoxon pairs tests, $P < 0.03$.

2.2.4. Analyses

Nonparametric statistical analysis again consisted of a Friedman's ANOVA on Δ°C. If the ANOVA was significant at $\alpha = 0.025$, a Wilcoxon pairs test compared Δ°C between the 2 conditions that involved the affected hand and the 2 conditions that involved the healthy hand (Conditions 1 & 2; and Conditions 3 & 4; Table 3; Fig. 2).

3. Results

3.1. Experiment 1

After the baseline period, the affected hand was cooler than the healthy hand (mean ± SD = −0.40 ± 0.30 °C; $P = 0.01$). When the hands were held in this position without the participants wearing

Table 3
The perceived and true location of the affected hand (conditions 1 & 2) and healthy hand (conditions 3 & 4) during each experimental condition in Experiment 2.

Condition	1	2	3	4
Hand	Affected	Affected	Healthy	Healthy
Perceived location	On the midline	20° to the healthy side of midline	On the midline	20° to the affected side of midline
True location	On the midline	On the midline	On the midline	On the midline
Analysis 1	Friedman's ANOVA on Δ°C			
Analysis 2	Wilcoxon pairs on Δ°C		Wilcoxon pairs Δ°C	

ANOVA, analysis of variance.

the prism glasses, there was no change in temperature of the affected hand (Condition 3: Δ°C = +0.05 ± 0.07 °C; interquartile range [IQR] +0.02–0.1 °C).

When participants wore prism glasses, the perceived midline at the depth of the platform was shifted from the actual midline, by 42 ± 5 mm to the left or by 39 ± 7 mm to the right, depending on the condition. Importantly, when the perceived location of the affected hand was on the perceived body midline, there was a very small increase in temperature of the affected hand, no matter whether its actual location was 40 mm to the affected side (Condition 4: Δ°C = 0.05 ± 0.05 °C; IQR 0.01–0.09 °C) or 40 mm to the healthy side (Condition 2: Δ°C = 0.07 ± 0.06 °C; IQR 0.02–0.10 °C; see Fig. 1). That is, the affected hand became slightly warmer if it was held for 9 minutes on the perceived body midline.

The skin temperature of the affected hand increased when participants were not wearing prism glasses and the affected hand was positioned on the healthy side of space, about 40 mm beyond the actual body midline (Condition 1: Δ°C = +0.47 ± 0.14 °C; IQR 0.34–0.62 °C). The result that most clearly upholds the hypothesis is our finding that this large effect was significantly mitigated when participants wore prism glasses so that the *perceived* location of the hand was on the perceived body midline (Condition 2: Δ°C = +0.07 ± 0.06 °C; IQR 0.02–0.10 °C; Fig. 1). The critical statistical results were a significant Friedman's ANOVA [χ^2 (3) = 18.36; Kendall's W = 0.612; $P < 0.001$] and a significant Wilcoxon pairs test between Condition 1 and Condition 2 ($z = 2.8$, $P < 0.005$; see Supplementary Table S2 for full Wilcoxon ranks).

Room temperature varied between 22.1 °C and 22.3 °C; humidity varied between 36% and 39% throughout the experiment.

3.2. Experiment 2

After the participants sat for 12 minutes with the hands equidistant from the body midline and shoulder-width apart, the affected hand was cooler than the healthy hand as expected (−0.50 ± 0.30 °C; $P < 0.01$).

The prism glasses had the same effect on perceived location of the body midline as that observed in Experiment 1. When participants wore prism glasses, they were instructed to keep their affected hand about 40 mm beyond their perceived midline. In this location, the affected hand was on the actual midline, yet it nevertheless became warmer (Condition 2: Δ°C = +0.28 ± 0.14 °C; IQR 0.17–0.36 °C; Fig. 2). Critically, when the affected hand was held in the same location but participants did not wear prism glasses, it did not become warmer (Condition 1: Δ°C = +0.04 ± 0.18 °C; IQR −0.04–0.06 °C). When the participants wore prism glasses and kept their healthy hand about 40 mm beyond the perceived midline, the healthy hand was on the actual midline. During the 9 minutes in this location, the temperature of the healthy hand dropped (Condition 4: Δ°C = −0.30 ± 0.15 °C; IQR −0.13 to −0.42 °C; Fig. 2). Once again, when the hand was held in this same location, but participants did not wear prism glasses, there was no reduction in temperature (Condition 3: Δ°C = +0.03 ± 0.20 °C; IQR −0.02–0.09 °C; Fig. 2). The critical statistical results were a significant Friedman's ANOVA (χ^2 (3) 22.0; Kendall's W = 0.732; $P < 0.001$), and a significant Wilcoxon pairs tests for Conditions 1 and 2 ($z = 2.09$; $P = 0.037$) and Conditions 3 and 4 ($z = 2.60$; $P = 0.009$).

Room temperature varied between 22.1 °C and 22.3 °C. Humidity varied between 36% and 39% throughout.

4. Discussion

We hypothesized that the skin temperature of either hand would depend on the perceived location of the hand relative to the body midline, not on the anatomical configuration of the arm or the actual location of the hands. The results reported here uphold this hypothesis and show that the space-based disruption of thermoregulation of the hands in patients with unilateral upper-limb cold-type CRPS is not caused by mechanical or postural effects, muscle activity, or articular alignment. Rather, our results implicate the crucial role of a cortical representation of the hand's location within a body-centred, or space-centred, frame of reference. These results highlight the close relationship that exists between the cortical maps of the body in external space and the homeostatic regulation of the body itself.

We have previously demonstrated that people with chronic unilateral cold-type CRPS of one hand have an affected, and cold, side of space and that when either hand is placed in the side of space where the affected hand is usually located, the temperature of that hand is reduced [20]. The magnitude of such a temperature change relates to the extent to which tactile stimuli delivered to the hand placed in the healthy side of space are prioritized over identical stimuli delivered to the hand placed in the affected side, as well as to the sense of ownership that the patient feels over their hand. Moreover, the magnitude of the temperature change when one hand crosses the midline is directly related to how far beyond the midline the hand is located [18]. The current findings confirm that the observed changes in hand temperature genuinely depend on the cortical spatial representation of the hand. Importantly, the observed effects were detected using a rigorous double dissociation design and conservative nonparametric statistics.

It is well known that visual input can dramatically bias proprioceptive information [7]. Our previous work has demonstrated that this midline-dependent effect is still present when visual information is not available (that is, patients close their eyes). Notably, vision and proprioception are not mutually additive, consistent with the notion of a ceiling effect in the contribution of vision and proprioception to the effects of changing the position of limbs in external space on somatosensory processing (eg, [27]).

That the efferent system dysfunctions that characterize CRPS do not follow a nerve or root distribution is now well established. Indeed, signs and symptoms affect a limb segment, or a whole limb, or sometimes an entire hemibody, and frequently spread from one hand to the other or from one hand to the ipsilateral foot [31]. The substantial deficits in the ability of CRPS patients to mentally rotate the affected limb [15] might also be explained by disruption to spatial reference frames, which are critical for the mental rotation of body parts as well as external objects [1]. Taken together, then, these findings strongly support the notion that CRPS signs and symptoms are related to a dysfunction in the cerebral cortex – where the *perceived* location of the hand is generated.

Our findings are consistent with the recent proposal of a disrupted "cortical body matrix" in CRPS [19]. The cortical body matrix refers to a network of neural activities that integrates the regulation and protection of the body at both a physiological and perceptual level. That proposal integrates not just somatotopic and limb-centred frames of reference, but also body-centred frames of reference. Disruption of this cortical body matrix could underpin the multiple-system dysfunction that is observed not only in CRPS [19], but in a wide range of disorders. Indeed, body integrity is disrupted both physiologically and perceptually in several disorders (see [21] for a list). Could these disorders share a common pattern of disruption of key cortical structures that subserve the correct representation of the body in external space? Further research is clearly required, but the growing body of experimental and clinical evidence suggests that the link between somatosensory processing and homeostatic control of the body and its cortical representation is strong.

The notion that spatial reference frames play a role in the efferent homeostatic control of the limbs in CRPS patients also agrees with the growing body of evidence showing side-specific problems with motor imagery [15,22,28] and the efficacy of repeated mental rotation of body parts for the treatment of chronic CRPS [3,6,12–14]. The mental rotation of body parts and objects depends on intact spatial reference frames. In CRPS patients, repeated training of mental rotation reduces pain, autonomic and tactile dysfunction, and decreases the sense, which is common in CRPS [8], of disownership over the affected limb [12,13,16]. Importantly, clinical improvements relate closely to improvement of mental rotation abilities [13], and this effect is not due simply to sustained attention to the limb [14]. The results reported here raise the possibility that the previously proposed mechanism for the clinical effect of graded motor imagery, that it reinstates normal motor patterns in a sub-threshold manner [14], is incomplete. Perhaps the mechanism underlying this effect relates instead, or as well, to reinstating the normal representations of body districts in external frames of reference, or the transformation between different frames of reference.

It is important to note that prisms have successfully been adopted for the temporary treatment of hemispatial neglect. In particular, short periods of adaptive pointing toward targets, visually displaced rightward by prisms, can ameliorate many clinical symptoms of right-hemisphere neglect patients [9,11,24,25]. It has been suggested that the improvement observed in these patients is related to the compensation for the visual field displacement that is induced by prisms. In fact, during the adaptation procedure, patients implicitly deviate their motor programs toward the left (and otherwise neglected) side of space, resulting in a leftward recalibration of their sensorimotor systems (eg, [29]). The neural basis of this effect would appear to be related to a restored activation of those brain networks that control spatial attention and awareness (and, in particular, the frontoparietal areas), which are damaged in neglect patients (eg, [26]).

Similarly encouraging results have been obtained from initial studies of prism adaptation in CRPS. Adaptation to displacement of the visual fields has been shown to decrease pain as well as other CRPS pathological features, for example, autonomic signs, when the visual field is shifted toward the unaffected side [5,30]. Furthermore, evidence exists for exacerbation of pain when CRPS patients adapt to a shift in the visual field toward their affected side [30]. Such findings strengthen the notion of cerebral mechanisms underpinning the clinical picture of CRPS, suggesting that the shift in attention away from the affected side of space in CRPS may be a suitable target for therapy.

Our study is not without limitations. First, the results are limited in their generalizability to people identified as having cold-type CRPS. This means that those patients whose limb temperature fluctuates randomly and substantially would have been excluded from this study. It is also possible that the wider implications of this study for the cortical body matrix idea are less pertinent to non-cold-type CRPS. Related to this is our approach to take single measures of temperature before and after periods, rather than continuously monitor it throughout testing. It is possible that the properties of our furniture and props affected our results – we did use plastic, but we did not measure how much the surfaces drained heat from body parts. That our results depended on limb-specific effects suggests that this was not a major threat to validity, but future experiments might benefit from verifying that this is the case. We included patients who were diagnosed according to criteria that have subsequently been updated. This should be taken into consideration when interpreting the results, but we contend that it does not undermine the main findings. Finally, although patients had participated in a range of experiments, they were not engaged in treatment at the time of the experiment. We do not expect that treatments they had received would affect our results, even though mirror therapy and graded motor imagery both involve visuomotor integration, but we cannot exclude this possibility altogether.

In summary, the results clearly demonstrate that, in patients with cold-type CRPS of one arm, the space-based disruption of thermoregulation of either hand is not determined by anatomical factors related to the location or configuration of the hands, but genuinely depends on the cortical representation of the hand's location within a body-centred frame of reference. These findings extend a growing body of evidence that implicates disruption of mechanisms within the cerebral cortex, in the multiple-efferent-system dysfunction seen in CRPS. Further research is required to determine whether modulation of spatial perception might offer an effective treatment for unilateral CRPS, and possibly for a wide range of neurological disorders that are characterized by dysfunction in both spatial perception and thermal regulation.

Conflict of interest

The authors have no conflicts of interest.

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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.pain.2013.07.026.

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