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Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb

G. Lorimer Moseley,[1] Alberto Gallace[2,3] and Charles Spence[3]

1 PaiN Group & Department of Physiology, Anatomy & Genetics, University of Oxford, UK and Prince of Wales Medical Research Institute & School of Medical Sciences, University of New South Wales, Sydney, Australia
2 Department of Psychology, University of Milano-Bicocca, P.zza dell'Ateneo Nuovo 1, 20126 Milano, Italy
3 Department of Experimental Psychology, Oxford University, South Parks Road, Oxford OX1 3UD, UK

Correspondence to: G. Lorimer Moseley,
Prince of Wales Medical Research Institute,
Cnr Easy & Barker Streets,
Randwick, 2031,
Australia
E-mail: lorimer.moseley@gmail.com

Complex regional pain syndrome (CRPS) occurs after stroke, but most cases develop after peripheral trauma and without evidence of brain trauma. However, CRPS is associated with symptoms that appear similar to those observed in patients suffering from hemispatial neglect. Ten participants (four males) with CRPS of one arm performed temporal order judgements of pairs of vibrotactile stimuli, one delivered to each hand, at one of 10 possible stimulus onset asynchronies, under two conditions: arms held each side of the midline and arms crossed over the midline. Participants released a foot switch to indicate which hand had been stimulated first. The order of conditions was randomized and the foot under which the switch was positioned was counterbalanced. There were two blocks of 150 trials in each condition. The stimulus onset asynchronicity at which the participants were equally likely to select either hand, the point of subjective simultaneity (PSS), was compared between conditions and between those with left or right-sided symptoms. When arms were not crossed, the participants prioritized stimuli from the unaffected limb over those from the affected limb (mean $\pm$ SD PSS = 25 $\pm$ 7.5 ms) and the magnitude of the PSS strongly related to the degree to which the affected hand was cooler than the unaffected hand ($r = 0.942$, $P < 0.001$). When the arms were crossed, the effect was reversed: the participants prioritized stimuli from the affected limb over those from the unaffected limb [PSS = –18 $\pm$ 13 ms; main effect of condition $F\ (1, 9) = 98.6$, $P < 0.001$]. There was no effect of the side of symptoms. These results show that CRPS is associated with a deficit in tactile processing that is defined by the space in which the affected limb normally resides, not by the affected limb itself, and which relates to the relative cooling of the affected limb. This pattern is consistent with data from those with hemispatial neglect after stroke and raises the possibility that chronic CRPS involves a type of spatial neglect.

Keywords: Reflex sympathetic dystrophy; temporal order judgments; CRPS; neglect; neuropathic pain

Abbreviations: CRPS = complex regional pain syndrome; JND = just noticeable difference; PSS = point of subjective simultaneity; TOJs = temporal order judgements

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Introduction

Complex regional pain syndrome (CRPS) is usually initiated by peripheral trauma with (CRPS type II) or without (CRPS type I) identifiable peripheral nerve injury (Bruehl *et al*., 1999). The disorder is characterized by severe pain and the disruption of blood flow, sweating and motor function, usually confined to one arm or leg. CRPS is essentially a clinical diagnosis based on a range of symptoms and signs (Bruehl *et al*., 1999), and is widely considered to be a disorder of the central nervous system, although peripheral inflammatory factors are probably more important in the initiation of the disorder (Janig and Baron, 2002).

A commonly reported characteristic of CRPS that has received a great deal of attention is the presence of symptoms that appear similar to those observed in patients suffering from hemispatial neglect, which is a neurological syndrome that occurs after certain types of brain damage (see Bisiach and Vallar, 2000; Vallar, 2001 for reviews). Such patients often ignore stimuli presented on the contralesional side of space, or the contralesional side of their body, or both. Hemispatial neglect patients may also fail to recognize their contralesional limb as belonging to their own body (a condition known as 'somatoparaphrenia' (e.g. Bottini *et al*., 2002; see Vallar and Ronchi, (in press), for a recent review) and sometimes even to try to harm, and/or remove their paretic limb (a condition known as 'misoplegia' (Loetscher *et al*., 2006). Similarly, CRPS patients often position their affected limb out of view; they report that the limb doesn't belong to them anymore (Lewis *et al*., 2007); that they have to concentrate their efforts to make the limb move and that unless they focus their attention on it, the limb lies still, like a dead weight (Galer and Jensen, 1999). Both patients with post-stroke hemispatial neglect (Coslett, 1998) and patients with CRPS (Schwoebel *et al*., 2001; Moseley, 2004), have difficulty in discriminating the laterality of a pictured limb if it corresponds to their affected side.

Despite the vigour of the debate, no one has yet undertaken an empirical evaluation of whether or not the human brain prioritizes tactile information from one side of the body over the other in patients with CRPS. This is important because up to now all the findings that seem consistent with hemispatial neglect can also be explained by other mechanisms. The common approach to investigating spatial or somatotopically defined biases in processing involves temporal order judgements (TOJ; e.g. Spence *et al*., 2001; Vibell *et al*., 2007), which are generally held to index genuinely perceptual effects unconfounded by the need to make rapid behavioural responses. In a typical TOJ task, pairs of tactile stimuli are presented, one to either hand, and participants are instructed to respond according to which hand they perceive to have been stimulated first. If a bias in information processing occurs toward a particular side of the body/space, the point of subjective simultaneity (PSS: i.e. the point at which participants perceive the two stimuli as occurring at the same time) should be shifted accordingly. That is, TOJs are used to study perceptual latency because they can effectively show a speeding-up (i.e. prioritization) or slowing down of neural processing related to the stimuli presented. Patients with hemispatial neglect prioritize information from the ipsilesional side over that from the contralesional side (Rorden *et al*., 1997; Guerrini *et al*., 2003; Baylis *et al*., 2004; Berberovic *et al*., 2004; Sinnett *et al*., 2007). Accordingly, we hypothesized that patients with CRPS might prioritize tactile information from the unaffected side over that from the affected side.

Methods

Participants

Patients who had CRPS Type 1 of one upper limb, initiated by trauma to the limb, and diagnosed according to recommended criteria for research (Bruehl *et al*., 1999), were eligible to take part in this study. The presence of peripheral nerve injury was excluded by full clinical examination from an experienced neurologist. Patients were excluded if they had any symptoms in the opposite limb or either leg; any unresolved neurological or orthopaedic injury, pain elsewhere, diabetes, any dermatological condition that might disrupt sensation, a known psychiatric disorder, an inability to read and understand spoken English, or a known diagnosis of dyslexia. These criteria yielded a convenience sample of 10 patients (four males, mean $\pm$ SD age = 37 $\pm$ 11 years; duration since onset = 31 $\pm$ 23 months; Table 1). All of the participants had taken part in a separate and unrelated study, concerning the effect of visual distortion of the limb on pain and swelling (Moseley *et al*., 2008b) between 7 and 78 days (mean = 31 days) prior to this study. All of the participants gave written informed consent. All procedures were approved by the institutional ethics committees and conformed to the Declaration of Helsinki. No attempt was made to control medication intake, although all medications were recorded (Table 1). To standardize or wash-out medications is not feasible, nor ethical, in this patient group.

Materials and Methods

Tactile thresholds were evaluated in order to ensure the experimental stimuli were, in fact, presented at a suprathreshold level. Tactile stimuli were 140% of the tactile threshold for each hand for each participant. Tactile stimuli (10 ms duration; 290 Hz) were generated by a TE-22 signal generator and were presented via bone conduction vibrators (Part no. VBW32, Audiological Engineering Corp. Somerville, MA, USA; vibrating surface 1.6 cm $\times$ 2.4 cm), each placed inside a 100 mm $\times$ 100 mm $\times$ 100 mm foam cube. The signal generator was driven by a custom program, written in Matlab Version r13 (Mathworks, Naticks, MA, USA). Two tactile stimuli were presented in each trial, one delivered to either vibrator. There were 10 possible stimulus onset asynchronies between the two vibrotactile stimuli ($\pm$120, $\pm$60, $\pm$30, $\pm$15 or $\pm$5 ms; negative values indicate that the affected side was stimulated first) and they were presented equiprobably in a randomized order (i.e. we used the method of constant stimuli) (Spence *et al*., 2001). In the TOJ task, the participant had to release one of two foot pedals, one positioned under the toes and the other under the heel. The response foot was alternated between blocks of trials (see the protocol below). Half of the participants released the pedal under their toes for left hand first responses (and their heel for right first responses) while the other half of participants did the opposite. The participants held one foam cube in either hand such that their index finger rested on top of the vibrator.

Table 1 Participant characteristics

	Sex, age	Part	Dur.	Size^{ratio}	TPD^{ratio}	P$^{2\ day}$	Cognitive neglect	Motor neglect	Medication^{week}
A	M, 34	L wrist #	18	1.08	1.18	6	6	7	Gabapentin, amitriptyline
B	F, 23	L wrist #	17	1.02	1.16	4	6	8	Gabapentin, paracetamol, codeine
C	F, 26	L wrist #	15	0.93	1.17	5	6	7	Oral morphine, paracetamol
D	F, 45	R wrist #	43	0.95	1	4	3	8	Nil reported
E	F, 34	R finger dislocation	79	1.00	1.07	6	5	5	Nortriptyline, aspirin, cannabis
F	M, 21	L blunt trauma	46	1.05	1.09	3	8	5	Paracetamol, codeine
G	M, 48	L thumb dislocation	27	1.23	1.12	6	6	8	Gabapentin, amitriptyline, paracetamol
H	F, 53	L wrist #	56	1.18	1.04	5	5	3	Nil reported
I	M, 47	L wrist #	9	1.10	1.08	4	4	3	Nil reported
J	F, 39	R arm #	9	1.00	1.13	5	5	7	Amitriptyline
	Mean (SD)		31.9 (23.3)	1.05 (0.10)	1.10 (0.06)	4.8 (1.0)	5.4 (1.3)	6.1 (2.0)	

Age is in years, L = left; R = right; # = simple fracture; Dur. = duration in months; Size^{ratio} = mean circumference of digits 2–4 on affected side/same measures on unaffected side; TPD = two point discrimination threshold on the affected side/same measure on unaffected side; P$^{2\ day}$ = average pain over last 2 days, as measured on a 0–10 point numerical rating scale; Medication^{week} = reportedly taken within the previous week.

Assessment

Patients were assessed via a routine clinical interview and physical examination (Table 1 and Supplementary Table 1). In addition, participants completed a five-item questionnaire on symptoms of neglect (Galer and Jensen, 1999), adapted for use with a 5-point Likert scale response (Frettloh *et al*., 2006), and completed a 100 mm visual analogue scale in response to the question: 'How strong is your sense of ownership over the affected limb?', anchored at left with 'Very weak—I feel like the limb doesn't belong to me at all' and at right with 'Normal—the same as my other limbs'. The distance from the left anchor to the participant's mark was used in secondary analyses. The following assessments were used for statistical analysis:

(i) Skin temperature was measured by means of a hand-held AutoPro laser thermometer (Raytek® Santa Cruz, CA, USA; accuracy ±1% of reading). Five readings of skin temperature on the two sides were taken from two standardized sites on the back of the hand and one on the front of the hand. Skin temperature on the two sides was compared between sides using a paired *t*-test. To minimize the likelihood of a Type 1 error, we set $P<0.01$. Skin temperature on the affected side minus that on the unaffected side was used for analysis.

(ii) Static two-point discrimination threshold was assessed according to the method described in detail elsewhere (Moseley *et al*., 2008c). The average of an ascending run and a descending run was used for analysis.

(iii) Swelling was estimated using Jobzt finger tape to obtain the average circumference at the midpoint of the proximal phalanx of the first three digits.

These measures were expressed as a proportion of the same measures obtained from the unaffected limb (Table 1).

(iv) Average pain over the last 2 days. Patients completed a numerical rating scale anchored with 'No pain' on the left and 'Worst possible pain' on the right, in response to the question 'How would you rate your average pain over the last 2 days?'

Protocol

Data were collected in a dimly-lit room. The participants sat with arms resting on a padded bench. The height of the seat and the bench, and the orientation of their arms were adjusted to make the participant as comfortable as possible, with the constraint that both arms were in a similar orientation relative to the participant's midline. Shins were vertical and thighs were horizontal. The foot pedal was fixed to a wooden board underneath the feet. The order of conditions was determined via a random numbers generator table. There were two conditions, which were identical except that one involved crossing the limbs across the midline so that the hands were placed in the opposite hemispace. In both conditions, the participants responded by indicating which hand had been stimulated first.

Participants completed two practice blocks of 50 trials of the given condition, interspersed with a 2 min rest. Pain and swelling were reassessed. After a further 4 min rest, data collection began. For each condition, two blocks of 150 trials were interspersed with a 4 min rest, or until pain had returned to pre-trial level.

Analyses

Responses were processed to yield two primary outcome variables: The PSS and the just noticeable difference (JND). The proportion of correct responses at each stimulus onset asynchronicity was converted into *z*-scores using a standardized normal distribution. The best-fitting straight line was computed for each participant and the slope and intercept values were derived. The PSS refers to the point at which observers report the two events (right stimulus first and left stimulus first) equally often. This is considered equivalent to the stimulus onset asynchronicity at which participants perceive the two stimuli as occurring at simultaneously. By convention, the JND indicates the difference between values needed to get 25% versus 75% correct (Spence, 2009).

Repeated measures analyses of variance (ANOVAs) were used to compare the PSS and JND between conditions. The within-participant factor was condition (uncrossed or crossed) and the between-participant factor was side of symptoms. Pain, swelling and skin temperature before and after each block of trials, were compared using paired *t*-tests. We also compared pain, swelling and skin temperature immediately after each block between the two experimental conditions, using paired *t*-tests. To increase the likelihood of detecting an effect of data collection on signs and symptoms, which might confound our results, significance for these analyses was set at $P<0.1$.

We used linear regression to compare the PSS during one condition to the PSS during the other, and the PSS during the normal, uncrossed posture, to pain over the last 2 days, swelling and two-point discrimination threshold. We used linear regression to relate PSS to skin temperature, recorded immediately after the completion of the second block of TOJ trials. Finally, we used linear regressions to relate PSS to self-reported symptoms of cognitive and motor neglect, and to the visual analogue scale on the sense of ownership over the affected limb.

Results

Tactile thresholds

Tactile threshold, as determined by the intensity of the vibrotactile stimulus at which participants reliably responded, was greater on the affected side (mean ± SD difference = 9.3% ± 4.8%). Experimental stimuli were 140% of threshold for all participants.

Arms uncrossed

Patients with CRPS prioritized tactile stimuli from the unaffected arm over identical stimuli from the affected arm. That is, the tactile stimulus delivered to the affected arm had to be presented 25 ms earlier than an identical stimulus delivered to the same location on the unaffected arm, for the two stimuli to be perceived as occurring at the same time (mean ± SD PSS = 25 ± 7.5 ms; Fig. 1). The JND was 28 ± 1.7 ms. There was no difference in PSS or JND between those who had CRPS of the left arm and those who had CRPS of the right arm (not significant).

Arms crossed

When patients performed the task with their arms crossed, prioritization of tactile stimuli was reversed such that the participants now prioritized stimuli from the affected arm over stimuli from the unaffected arm. That is, the tactile stimulus delivered to the *unaffected* arm had to be delivered 18 ms earlier than an identical stimulus to the affected arm, for the stimuli to be perceived as occurring at the same time (mean ± SD PSS = –18 ± 13 ms). The difference in the PSS between these conditions was significant [main effect of condition $F(1, 9) = 327.5$, $P < 0.001$]. The PSS in one condition was negatively related to that in the other condition [r = –0.795, $F(1, 8) = 13.73$, $P = 0.006$]. The JND was larger (indicating that the participants found the task harder) when their arms were crossed (69 ± 11 ms) than when their hands were placed in the normal, uncrossed, posture [main effect of Condition $F(1, 9) = 98.6$, $P < 0.001$].

Skin temperature difference between arms did not change during the normal, arms uncrossed condition (not significant), but the affected arm was warmer after the arms uncrossed condition than it was before [$t(9) = 3.25$, $P = 0.01$], although it remained cooler on average than the unaffected hand (mean ± SD difference between hands = 0.36 ± 0.37°). Pain and swelling were no different before and after data collection in either condition (not significant).

Relating PSS to clinical assessments

The PSS in the normal, uncrossed, posture was strongly related to skin temperature difference between the arms [$r = 0.942$, $F(1, 8) = 63.23$, $P < 0.001$; Fig. 2]. That is, for every millisecond earlier the affected limb had to be stimulated in order for the two stimuli to be perceived as simultaneous, the affected arm was 0.05° cooler than the unaffected arm (unstandardized $B = 0.051$, $t = 7.95$, $P < 0.001$). The relationship between PSS and skin temperature was weaker, but still significant, for the hands crossed condition [$r = 0.719$, $F(1, 8) = 8.58$, $P = 0.02$]. The PSS did not relate to any of the other clinical assessments (not significant).

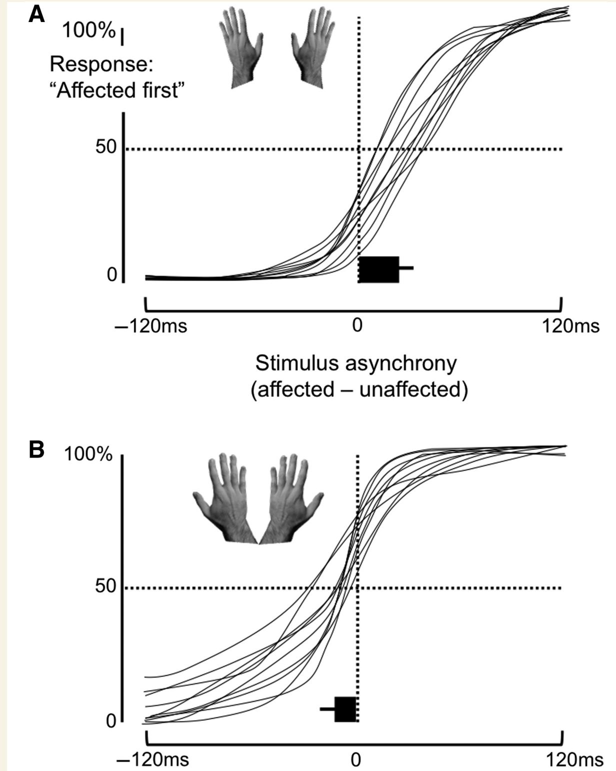

Figure 1 Mean response curves for all participants. (**A**) Arms uncrossed: proportion of stimuli in which the participant judged that the affected arm was stimulated first; response: 'affected arm first' (y-axis), and actual stimulus asynchrony, affected side minus unaffected side (x-axis). Vertical broken line indicates the point at which both stimuli were equally likely to occur first and horizontal broken line indicates the point at which the stimuli were equally like to be *judged* as occurring first. Solid panel with error bar denotes the mean and standard deviation of the PSS (the stimulus asynchrony at which the stimuli were equally likely to be judged as occurring first). Note that the PSS occurs when the stimulus to the affected arm precedes that to the unaffected arm. (**B**) Arms crossed. Note the PSS now occurs when the stimulus to the unaffected arm precedes that to the affected arm.

Relating PSS to self-reported symptoms of cognitive and motor neglect and the sense of ownership over the limb

The PSS in the normal, uncrossed, posture was not related to symptoms of cognitive or motor neglect, as assessed via a self-report questionnaire (Galer and Jensen, 1999) (symptoms of cognitive neglect: B = –0.99, t = –2.3, $P = 0.06$; symptoms of motor

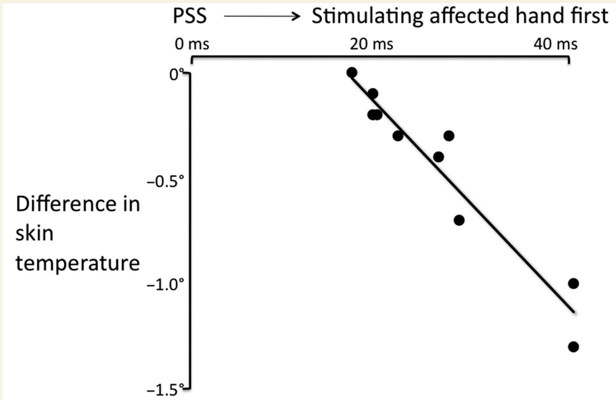

Figure 2 Scatterplot and trendline for the timing of two stimuli, one to either hand, at which the participants perceive the two stimuli as occurring at the same time (PSS; *x*-axis) and the skin temperature on the back of the affected hand, relative to the unaffected hand.

neglect: $B = -0.67$, $t = -2.1$, $P = 0.09$). The PSS was, however, related to participants' sense of ownership over their affected limb ($B = -0.64$, $t = -13.9$, $P < 0.01$).

Discussion

We hypothesized that patients with CRPS would prioritize tactile input from the unaffected arm over that from the affected arm, which would be consistent with the results reported in studies of patients with spatial neglect (e.g. Rorden *et al*., 1997; Baylis *et al*., 2004; Berberovic *et al*., 2004; Sinnett *et al*., 2007). Our results support that hypothesis and extend it by showing that the bias in tactile information processing shown by the CRPS patients is 'spatially' rather than 'somatotopically' defined. That is, when the arms were crossed over the midline so that the unaffected arm was placed in the space normally occupied by the affected arm, tactile stimuli from the affected arm were prioritized over those from the unaffected arm. The effect does not simply show that patients with CRPS perform poorly on the tactile TOJ task. Rather, the JND during the uncrossed condition was similar to that considered to reflect TOJ optimal performance (Hirsh and Sherrick, 1961; Spence *et al*., 2001) and the increased JND during the uncrossed condition was similar to that observed in healthy subjects who are not required to give speeded responses (Yamamoto and Kitazawa, 2001).

A processing bias away from the affected side seems consistent with a delay in left/right arm recognition when a pictured arm corresponds to their affected side (Schwoebel *et al*., 2002; Moseley, 2004). According to extensive research on the left/right judgement task, it involves first making an initial judgement, mentally manoeuvring one's own arm to match the picture, then responding (Parsons, 2001). The results of experiments that have investigated the effect of pain on the left/right judgement task (Moseley *et al*., 2005; Hudson *et al*., 2006; McCormick *et al*., 2007) suggest that the delay in this task experienced by patients with CRPS is probably related to a bias in the initial judgment, toward selecting the unaffected limb. That is, the mental movement of that limb suggests that the initial judgment was incorrect, which delays the final response. Thus, the results of the left/right judgement task suggest that CRPS patients have a bias in the processing of visual body-relevant information away from the affected side. The results obtained in the present study using the tactile TOJ task, suggest that they also have a bias in processing of tactile information away from the affected side.

The current findings are similar to those that have been reported previously in studies of patients affected by hemispatial neglect. Specifically, it has been shown that in patients with this deficit, tactile stimuli delivered on the left side of the body need to be presented at least 200 ms before stimuli on the right side in order for them to be perceived as simultaneous (e.g. Guerrini *et al*., 2003). Similar results have been obtained by using auditory (e.g. Karnath *et al*., 2000; Sinnett *et al*., 2007) and visual stimuli (e.g. Rorden *et al*., 1997; Baylis *et al*., 2002; Cate and Behrmann, 2002).

Other clinical and experimental phenomena observed in patients with CRPS have also been observed in patients with post-stroke hemispatial neglect. For example, when patients place their affected (CRPS) or neglected (neglect) arm behind a mirror and watch the reflected image of their opposite arm being touched, they perceive a touch as occurring on the arm behind the mirror (Halligan *et al*., 1992; Halligan *et al*., 1996; Acerra and Moseley, 2005); CRPS patients show decreased perfusion of the thalamus contralateral to the affected body part (Iadarola *et al*., 1995) and ipsilateral hemisensory impairment (Rommel *et al*., 1999; Drummond and Finch, 2006), both of which increase with the duration of the disorder, and certain neglect patients show focal depressions in the thalamus (Vongiesen *et al*., 1994) and are characterized by hemisensory impairment (Bisiach *et al*., 1979). Finally, both neglect patients (Bisiach *et al*., 1999) and those with CRPS (Cohen *et al*., 2008) demonstrate difficulties interpreting visuospatial perceptual stimuli such as the Necker cube (Necker, 1832). Given this set of similarities between neglect and CRPS one might wonder whether similar interpretations can be adopted to account for, at least up to a certain extent, the symptoms of both groups of patients.

A bias in tactile processing away from a painful body part would not be predicted by the current understanding of pain and attention, which emphasizes the priority given to pain-relevant stimuli (Eccleston and Crombez, 2005). Initial data using TOJ of visual or noxious stimuli do not demonstrate a clear spatial prioritization towards painful stimuli (Zampini *et al*., 2007), although we have established that physically threatening visual stimuli impart a bias towards the threatened side (Van Damme *et al*., 2009). Data from other experimental paradigms strongly suggest that spatial attention is prioritized toward the site of pain, or of impending pain, but potential confounders make a definitive conclusion at this stage difficult (see Van Damme *et al*., 2009 for a recent review). Nonetheless, a possible explanation for the current finding in CRPS patients is that the shift in tactile attention is an implicit strategy to limit the provocation of pain—there is certainly evidence that the expectation of pain shifts spatial attention toward the expected site of pain (Zampini *et al*., 2007). Indeed, in CRPS, perceptual disturbances consistent with a 'disowning' of the affected part—one research group has suggested that CRPS involves a kind of autotomy—become more common as the condition persists (Lewis *et al*., 2007).

An important aspect of the present findings is that the bias in tactile processing is related to a space-based rather than a somatotopic-based frame of reference. That is, tactile information presented on the side of space that generally corresponds to the anatomical position of the unaffected limb is prioritized, regardless of the actual position of the limb. It seems then that the withdrawal of attention from the affected limb acts upon space rather than a specific body part. This consideration appears to be in agreement with the idea that a high order mechanism is responsible for the occurrence of CRPS (Janig and Baron, 2002). Why then is a spatial frame involved in the prioritization of tactile information in CRPS patients? This might simply be due to the fact that under normal conditions the affected limb is placed most of the time in the side of space that corresponds to the equivalent side of the body. As a consequence a simple mechanism to protect the affected body part against provocation would be to draw attention away from that side of space. An alternative and more speculative explanation remains possible, however. Namely, that in order to organize coherent movements for the avoidance of pain, the cognitive system must integrate information from the body surface (provided by the sensory receptors located in the skin) with proprioceptive information regarding the configuration of the limbs in space. It has been proposed that in order to integrate this information, stimuli on the body must be transformed from locations on the skin to locations in external space (Yamamoto and Kitazawa, 2001; Kitazawa, 2002; Haggard and Wolpert, 2005; Gallace and Spence, 2008) although this transformation depends to a certain extent on the specific nature of the task to be performed (Gallace *et al*., in press). The possibility that noxious stimuli are automatically re-coded using a spatial frame of reference might provide a further explanation to the spatial effect reported in the present study. Unfortunately, however, as far as pain is concerned, the role of external space coordinates for the mapping and response to noxious stimuli still needs to be investigated.

The second important and new result of the current study concerns the relationship between the PSS and skin temperature difference between hands. The earlier the affected arm had to be stimulated for the stimuli to be perceived as occurring simultaneously, the cooler the affected hand, relative to the unaffected one. We can exclude the possibility that the decreased temperature caused the shift in PSS because the PSS was immediately reversed when patients crossed their arms even though skin temperature of the affected hand remained cooler than that of the unaffected hand. That said, the affected arm was significantly warmer after the condition in which the arms were crossed than it was before that condition, which raises the possibility that crossing the arms raised skin temperature of the affected arm. These findings are important because they provide the first link in a patient population between spatial neglect and skin temperature control. Directly relevant to this is a study that induced a limb-specific decrease in skin temperature, and a shift in the PSS, in healthy volunteers, by psychologically inducing a sense of disownership of one arm via the illusory ownership of an artificial counterpart (Moseley *et al*., 2008a). The magnitude of the shift in PSS and the decrease in skin temperature was similar to that observed here. Although deficits in body ownership and temperature dysregulation are characteristic of many neurological and psychiatric disorders, that the two might be related has only recently been proposed (Moseley *et al*., 2008*a*). We did not detect a relationship between PSS and swelling, but our approach and sample may have left us underpowered to detect such an effect. Relevant to the possibility is the finding that the increase in swelling evoked by movement in patients with CRPS is decreased if patients watch the movement through a lens that makes the limb look further away than it really is, and thus outside of the space it actually occupies (Moseley *et al*., 2008*b*). Together, these studies imply that a spatial frame of reference influences cortical mechanisms that modulate cutaneous vasoconstriction. They also strongly suggest that higher order processes might impart a top-down effect on both tactile processing and tissue regulation in CRPS. That would certainly be consistent with the observation that CRPS occurs without peripheral trauma, for example after 2–12% of strokes (Davis *et al*., 1977; Braus *et al*., 1994; Petchkrua *et al*., 2000) or in association with severe psychological stress (Grande *et al*., 2004).

An elegant series of experiments in healthy volunteers clearly demonstrated that crossing the arms and making speeded TOJ results in paradoxical responses for stimulus onset asynchronies of $<$300 ms (Yamamoto and Kitazawa, 2001). On the basis of their data, the authors proposed that neurons have cutaneous receptive fields located on the hands, but organized in spatial coordinates, such that the spatial representation of the stimulus requires the dynamic remapping based on the location of the hands in space. Limiting the time permitted for a response to $\sim$300 ms prevents this remapping from taking place and results in paradoxical judgements. That we did not observe a paradoxical response pattern when the arms were crossed reflects our long response window. That the JND during the arms crossed condition was less than that reported for healthy controls (Shore *et al*., 2002) may reflect a further impact on the remapping process, but it is not possible to determine this on the basis of the current work alone. Importantly, the dysfunction we have observed here in people with CRPS is not consequent to frank damage to cortical tissue, which underpins post-stroke hemispatial neglect (although, importantly, hemispatial neglect is generally held to not involve damage to sensory processing substrates) (Vallar *et al*., 1991; Walker *et al*., 1991).

Taken together, the spatial rather than the somatotopic nature of the shift in tactile processing observed in the current study, and the proposal put forward by Yamamoto and Kitazawa (2001), implies candidate neural mechanisms. One region likely to be involved is the posterior parietal cortex, which is thought to be important in the integration of visual, tactile and proprioceptive input for the construction of personal and extrapersonal space (Grefkes and Fink, 2005). Posterior parietal cortex activity during finger movements correlates with the extent of motor impairment in patients with CRPS (Maihofner *et al*., 2007), and is critical for the spatial processing involved in the left/right hand judgement task (Parsons, 2001), on which patients with CRPS perform poorly (Moseley, 2004). It is also worth noting that the posterior parietal cortex is one of the areas of the brain that is often damaged in patients affected by unilateral spatial neglect (Vallar, 2001) and sometimes in disorders that involve delusions of disownership of left-sided body parts such as somatoparaphrenia (e.g. see Vallar and Ronchi, in press for a review). What is more, transcranial magnetic stimulation over the right posterior parietal cortex of neurologically normal participants induces neglect in a space-based frame of reference (Muggleton *et al*., 2006). Even more relevant here is the suggestion that sensory signals from many sensory modalities, as well as efferent copy signals from motor structures, converge in the posterior parietal cortex in order to be recoded into common spatial representations (Andersen *et al*., 1997). This mechanism allows the sensory locations of input signals to be remapped into the appropriate motor coordinates required for making directed movements. Given that the perception of noxious stimuli is likely to generate an appropriate avoidance movement, it is plausible to think that these kinds of stimuli are converted into common spatial representations sustained by the posterior parietal cortex.

Another candidate area that also receives converging signals from both hands and might be involved in this spatial remapping is the primary sensory cortex (S1) (Iwamura *et al*., 1994; Iwamura, 1998). Robust and substantial reorganization of S1 has been observed in people with chronic CRPS (Maihofner *et al*., 2003; Pleger *et al*., 2006) and resolution of symptoms coincides with normalization of cortical changes (Maihofner *et al*., 2004). In fact, directly targeting cortical changes via tactile discrimination training reduces pain and disability associated with CRPS (Moseley *et al*., 2008c; Moseley and Wiech, 2009). These findings raise the possibility that such training enhances spatial representation, which would be reflected in decreased PSS after training.

At first glance, the current results seem to contrast with the visuospatial perceptual disturbances observed in five patients with CRPS (Sumitani *et al*., 2007b)—patients' perceived midline, on a blindfolded pointing task, was shifted toward the affected side, which is opposite to that observed in patients with spatial neglect (Bisiach *et al*., 1983; Marshall and Halligan, 1990). That finding would suggest a bias in spatial representation opposite to that observed in the current study. Several factors are relevant to this apparently contrasting result. First, the deviation in perceived midline was reversed during anaesthetic blockade of the affected arm, rather than simply normalized and a subsequent case study suggested that prism glasses that shifted the visual field towards the affected side, exacerbated pain (Sumitani *et al*., 2007*a*). Second, wearing prism glasses that shifted the visual field away from the affected limb had no immediate effect but was associated with a substantial reduction in pain 2 weeks later (Sumitani *et al*., 2007*a*). This time-lag is substantially greater than the effect observed in patients with unilateral neglect, where a large effect is observed within 2 hours (Rossetti *et al*., 1998). Third, the direction of the effect of prism glasses in CRPS is opposite to that observed in patients with neglect. These findings seem broadly consistent with our proposal that the bias in tactile processing observed in the current study might initially serve to oppose the provocation of pain. That is, our data may be evidence of an implicit strategy to achieve the same effect as that imparted by shifting the visual field away from the affected side. Alternatively, perhaps prism adaptation provides a potent visuospatial perturbation that triggers recalibration of multisensory visuospatial representation, such as has been proposed for the amelioration of phantom limb pain after caloric stimulation (Andre *et al*., 2001). Indeed, although a single case study suggested that different prisms had different short term effects (Sumitani *et al*., 2007*a*), the long-term effect in patients with CRPS of prisms that cause a shift towards the affected side has not been investigated. A generic effect of shifting the visual field would be consistent with the proposal that the effect of prism adaptation in spatial neglect involves triggering autonomous active processes involved in brain plasticity relating to multisensory integration and spatial representation (Frassinetti *et al*., 2002). A final consideration is that the patients in the current study were more chronic (mean duration = 31 months) than those used in study by Sumitani *et al*. (2007*a*) (mean duration = 14 months). Early CRPS is more likely to involve a relatively hot limb than a relatively cold one and it is possible that the transition from hot CRPS to cold CRPS is also associated with a shift in spatially defined tactile processing. Our finding that PSS relates to the cooling of the affected limb would seem consistent with this possibility.

It has been suggested that commonalities between stroke and CRPS raises the possibility that management approaches in one condition may be useful in the other (Acerra *et al*., 2007). The current results support this suggestion, particularly as it relates to the application of strategies of proven effectiveness for post-stroke neglect, to CRPS. For example, transcutaneous nerve stimulation (Vallar *et al*., 1995), neck muscle vibration (Karnath *et al*., 1993), vestibular caloric stimulation (Rubens, 1985), optokinetic stimulation (Vallar *et al*., 1993) and prism adaptation (Girardi *et al*., 2004) have all been shown to temporarily alleviate certain symptoms of the unilateral spatial neglect syndrome. Prism adaptation also reduces the bias observed in TOJ of neglect patients (Berberovic *et al*., 2004), but preliminary evidence from the work discussed earlier is difficult to interpret (Sumitani *et al*., 2007*a*). Interestingly, it has been suggested that the common factor underlying such experimental manipulations may be that they all affect the 'higher-order' levels of processing required to support an egocentric representation of external space (Vallar *et al*., 1993; Nico, 1999). Consequently, if spatial representations and/or mechanisms related to the orientation of spatial attention are involved in some of the symptoms of CRPS one should expect an effect of these manipulations also on this syndrome.

Finally, cognitive and motor neglect scores as determined by a self-report questionnaire that has some clinical utility (Galer and Jensen, 1999), did not relate to PSS, but it seems likely that our study was underpowered to detect a relationship ($P < 0.1$ for both). Participants' sense of ownership over their affected limb strongly related to PSS, such that a larger PSS during the normal, uncrossed posture was related to a smaller sense of ownership over the affected limb. These analyses were not a primary aim of the current study but are useful because they generate the hypothesis that the degree to which patients with CRPS prioritize away from the space in which their affected limb normally resides can be estimated using self-report questionnaires, and that PSS relates to patients' experience of their limb. Furthermore, these self-report measures suggest that several sensory modalities might be affected in CRPS. We have only tested within the tactile domain, but that hemispatial neglect is a multimodal problem suggests further work interrogating visual, auditory and higher order processing is warranted.

In summary, the current results demonstrate that patients with CRPS, a clinical presentation of severe pain, autonomic and motor dysfunction, usually confined to a specific limb and initiated by minor trauma to that limb, prioritize tactile information from the unaffected side of their body and the extent of the prioritization shift directly relates to the decrease in skin temperature on the affected limb. Our results also show that this bias in tactile processing is a spatial, not somatotopic effect, and is similar to what has been often reported in patients with spatial neglect after stroke, yet all the participants here had sustained an injury to their arm, not their brain. This finding raises the possibility that strategies that have been successfully used for the improvement of neglect symptoms may also be helpful in CRPS.

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Supplementary material

Supplementary material is available at *Brain* online.

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