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Space-based bias of covert visual attention in complex regional pain syndrome

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Some patients with complex regional pain syndrome report that movements of the affected limb are slow, more effortful, and lack automaticity. These symptoms have been likened to the syndrome that sometimes follows brain injury called hemispatial neglect, in which patients exhibit attentional impairments and problems with movements affecting the contralesional side of the body and space. Psychophysical testing of patients with complex regional pain syndrome has found evidence for spatial biases when judging visual targets distanced at 2 m, but not in directions that indicate reduced attention to the affected side. In contrast, when judging visual or tactile stimuli presented on their own body surface, or pictures of hands and feet within arm's reach, patients with complex regional pain syndrome exhibited a bias away from the affected side. What is not yet known is whether patients with complex regional pain syndrome only have biased attention for bodily-specific information in the space within arm's reach, or whether they also show a bias for information that is not associated with the body, suggesting a more generalized attention deficit. Using a temporal order judgement task, we found that patients with complex regional pain syndrome processed visual stimuli more slowly on the affected side (relative to the unaffected side) when the lights were projected onto a blank surface (i.e. when no bodily information was visible), and when the lights were projected onto the dorsal surfaces of their uncrossed hands. However, with the arms crossed (such that the left and right lights projected onto the right and left hands, respectively), patients' responses were no different than controls. These results provide the first demonstration of a generalized attention bias away from the affected side of space in complex regional pain syndrome patients that is not specifically related to bodily information. They also suggest a separate and additional bias of visual attention away from the affected hand. The strength of attention bias was predicted by scores on a self-report measure of body perception distortion; but not by pain intensity, time since diagnosis, or affected body side (left or right). At an individual level, those patients whose upper limbs were most affected had a higher incidence of inattention than those whose lower limbs were most affected. However, at a group level, affected limb (upper or lower) did not predict bias magnitude; nor did three measures designed to assess possible asymmetries in the distribution of movements across space. It is concluded that inattention in near space in complex regional pain syndrome may arise in parallel with a distorted perception of the body.

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Abbreviations: CRPS BPDS = Bath CRPS Body Perception Disturbance Scale; CRPS = complex regional pain syndrome; JND = just noticeable difference; PSS = point of subjective simultaneity; TOJ = temporal order judgement; TSK = Tampa Scale for Kinesiophobia

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Introduction

In some chronic pain conditions—including phantom limb pain, repetitive strain injury, whiplash, and musician's dystonia—symptoms arise that cannot be explained by pathology of the affected body part. Patients with complex regional pain syndrome (CRPS) demonstrate severe pain, swelling and motor dysfunction in a limb, and also perceptual changes that suggest altered cortical signalling for sensation and movement (Schwoebel *et al.*, 2001; Förderreuther *et al.*, 2004; Robinson *et al.*, 2011). They also report that movements of the affected limb are slow, effortful, and lack automaticity (Galer *et al.*, 1995; Galer and Jensen, 1999). Slowed movements and feelings of estrangement from the affected limb(s) in patients with CRPS were first referred to as 'neglect-like' symptoms by Galer *et al.* (1995) because of their resemblance to the syndrome of hemispatial neglect ('neglect'), which may follow brain injury. Brain-lesioned patients with neglect show inattention and motor impairments affecting the contralesional side of the body and space (Bisiach and Vallar, 2000; Parton *et al.*, 2004). The term 'neglect-like' has since been used widely by both researchers and clinicians. However, as the authors later emphasized, there are also many differences between the unusual experiences and lateralized motor and sensory deficits of patients with CRPS, and the symptoms of patients with hemispatial neglect following brain injury. Thus, we reserve the term 'neglect' for the syndrome that follows brain injury, and we refer to 'inattention' or 'biased attention' when referring to the hypothesized sensory imbalance of patients with CRPS. Notably, pain and other symptoms might be alleviated in patients with CRPS treated with prism adaptation (Sumitani *et al.*, 2007*a*; Bultitude and Rafal, 2010; Christophe *et al.*, 2016), a promising behavioural treatment for neglect following brain injury (Rossetti *et al.*, 1998; Luauté *et al.*, 2006; Serino *et al.*, 2006, 2009; Shiraishi *et al.*, 2008, 2010; Mizuno *et al.*, 2011; Saevarsson *et al.*, 2012; Rode *et al.*, 2014; Làdavas *et al.*, 2015). Finding that a treatment for neglect also helps patients with CRPS suggests that a bias in spatial attention might contribute to the manifestation and maintenance of the condition.

Despite the beneficial effects of prism adaptation on CRPS, there is little direct evidence of biased spatial attention in those with the condition (for a review see Torta *et al.*, 2016). Indeed, Punt *et al.* (2013) argued that the motor impairments that first prompted the use of the term 'neglect-like' with regards to CRPS could be better categorized as learned non-use. Testing sensory processing, rather than motor function, in CRPS could provide more certain information about whether altered spatial perception plays a role in physical CRPS symptoms.

Several studies have examined the performance of patients with CRPS on tests of visual attention, with mixed results. When tested with classic pen-and-paper tests of neglect, such as figure copying and line bisection, patients with CRPS show none of the omissions or displacements that would indicate problems with directing attention to the affected side of space (Förderreuther *et al.*, 2004; Robinson *et al.*, 2011; Kolb *et al.*, 2012; Reinersmann *et al.*, 2012; but see Cohen *et al.*, 2013, for an example of one patient whose drawing of a house appears to lack detail on one side). Patients with CRPS also exhibited no bias on a task that is highly sensitive to the allocation of visual attention and involves making saccades to cued and uncued targets (Filippopulos *et al.*, 2015). These studies suggest that any spatial bias in patients with CRPS is likely subtle at best, and might not affect overt visual attention.

Directly counter to the hypothesis that attention is biased away from the affected side, Sumitani *et al.* (2007*b*, 2014) and Uematsu *et al.* (2009) reported that when judging when a point of light was positioned straight ahead of their body midline in a darkened room, patients with CRPS were biased towards the 'affected' side of space. The researchers interpreted this as evidence for over-representation of the affected side of space due to exaggerated somatosensory input from the affected limb. Other groups, however, have reported that straight-ahead judgements made by patients with CRPS were biased toward the left visual field regardless of the side of the body that was affected (Reinersmann *et al.*, 2012), or else were unbiased (Kolb *et al.*, 2012; Christophe *et al.*, 2016). No study has so far provided evidence of a visual straight-ahead bias away from the affected side in CRPS. Therefore, although there may be measurable changes in spatial perception in patients with CRPS, these might not always manifest themselves as a bias away from the affected limb. Significantly deviated visual straight ahead judgements were only observed when patients with CRPS were tested in darkened rooms and not when the rooms were well illuminated, suggesting that patients have problems with coding the location of visual information in relation to the body ('egocentric' reference frame) that are overcome when spatial information can be coded with reference to the surrounding environment ('allocentric' reference frame). The evidence from visual straight-ahead judgements of patients with CRPS indicates a potential role of bodily information in driving spatial bias in CRPS, since perception of visual straight-ahead is directly influenced by felt information about body orientation (Biguer *et al.*, 1988; Roll *et al.*, 1991; Taylor and McCloskey, 1991; Karnath *et al.*, 1994).

A failure to detect a spatial attention bias in earlier work may relate to the nature of the task used. Using a sensitive test of tactile attention, Moseley *et al.* (2009) provided the first objective evidence that patients with CRPS have an attentional bias away from the affected side. Patients with CRPS processed touch applied to the affected hand more slowly as compared to the unaffected hand, resembling tactile processing biases that have been reported in patients with neglect following brain injury (Smania and Aglioti, 1995). This pattern reversed when the hands were crossed, suggesting that patients with CRPS exhibit deficits in attending to the side of space within which their affected limb normally resides rather than to the affected limb itself.

In a recent set of studies, patients with CRPS again showed attentional biases for tactile stimuli, when bisecting horizontal lines that were overlaid onto the affected body part, and when bisecting horizontal lines that were overlaid on the unaffected forearm when it was positioned in the affected side of space (Reid *et al.*, 2016). Patients exhibited no attentional biases, however, for auditory stimuli, for standard line bisection in which lines were presented on pieces of paper that were otherwise blank, or when bisecting horizontal lines on the unaffected forearm when it was positioned in the unaffected side of space. Furthermore, the researchers presented evidence that when mentally rotating pictures of hands, patients with upper limb CRPS were slower to identify the laterality of pictures of hands that corresponded to their affected hand relative to pictures of hands that corresponded to their unaffected hand, but this difference only arose when the pictures were presented in the affected side of space. The same pattern was displayed by patients with lower limb CRPS when mentally rotating pictures of feet. The authors interpreted this pattern of deficits, which they termed 'somatospatial inattention', as an impaired capacity to integrate bodily information with spatial processing. One way to explore whether spatial processing deficits in CRPS are indeed limited to bodily information would be to compare responses to visual information presented on the body surface versus responses to visual information presented in the same region in space without vision of the body.

Taken together, the evidence discussed thus far suggests that CRPS may be accompanied by complex and contrasting changes in perception across different sensory modalities (i.e. vision and touch), and for information presented in different regions of space (i.e. on the body, within arm's reach of the head and torso, or in the region of space that is outside of arm's reach, Legrain *et al.*, 2012). The pattern of responses to evoked stimuli in near space is consistent with reduced attention to the affected as compared to the unaffected side of space, and this reduction is so far limited to tasks that involve some form of bodily information (i.e. touch, or implied or real vision of a limb). Near space is here defined as the region of space surrounding the torso and head that is within the furthest possible extent of arms reach of the participant, including but not limited to the space that is occupied by the arms and hands at any given moment. There is, as yet, no evidence for a bias in general sensory processing in near space (i.e. a bias that is not limited to information about a limb), but a sufficiently sensitive test might reveal such a bias. The primary aim of the present study was therefore to measure the distribution of covert attention of patients with CRPS to visual information presented in near space without vision of the hands, and on the surface of the hands.

To achieve this goal, we measured visual attention using a temporal order judgement (TOJ) task. Two visual stimuli were briefly presented, one on either side of space, separated by different amounts of time. Two measures can thus be derived. First, the 'point of subjective simultaneity' (PSS) can be derived to assess the spatial (left versus right) bias in attention. The prediction was that patients with CRPS would require the stimuli to appear earlier on the affected as compared to the unaffected side of space for them to be perceived as simultaneous, consistent with a bias of attention away from the affected side. Second, the 'just noticeable difference' (JND) provides a measure of the smallest interval needed to reliably indicate the temporal order in which the two stimuli were presented, giving a measure of temporal acuity. There is evidence to suggest that patients with neglect following brain injury have decreased temporal acuity on both TOJ tasks (Barrett *et al.*, 2010) and attentional blink paradigms (Husain *et al.*, 1997). Chronic pain also reduces cognitive resources (Eccleston, 1995), and healthy volunteers who completed a TOJ task under high cognitive load had larger JNDs (Pérez *et al.*, 2008). We therefore predicted that the JND values of patients with CRPS would be larger than for control participants.

Participants completed the TOJ task under three separate conditions. In the first condition, the participants sat with their hands and arms positioned out of sight next to their torso and the stimuli appeared on a white board placed on the table in front of them. Through this condition we aimed to examine whether CRPS is associated with a bias in attention to visual information. In the second condition, the participants placed their hands on the board such that the stimuli appeared on their uncrossed hands, thus enabling us to examine whether any bias in visual attention is limited to, or stronger for, information that appears on the surface of the hands (consistent with a body-based bias in attention as opposed to a bias that was independent of bodily information). In the third condition, the stimuli appeared on the participants' crossed hands, thus enabling us to examine whether any body-based bias in visual attention was specific to the hand on the affected side of the body or whichever hand that was positioned within the affected side of space. Finally, to evaluate whether any body-based bias in visual attention was specific to the affected limb, we recruited both patients with upper-limb CRPS and patients with lower-limb CRPS.

The second aim of the present study was to test which clinical or cognitive factors predict PSS values in patients with CRPS. Knowing the markers that most strongly relate to any attentional bias could provide insights into how it might arise. We examined four possible explanations for how an attentional bias might arise in CRPS (they need not be considered as mutually exclusive). First, attention may be diverted away from the affected side as an implicit mechanism to lessen the impact of stimuli that may provoke pain. Such a tendency could be proportional to the severity of pain. We therefore included pain intensity as a possible predictor of attentional bias. Second, patients with CRPS report changes in the perceived size and shape of the affected limb, as well as the impression that their limb is alien to them and not part of their body. These reports are consistent with altered perceptual and cognitive representations of the affected limb (i.e. changes in what the affected limb is felt to be like and what the body is believed to be like; Longo *et al.*, 2010). Altered body representation may interfere with the ability to process information coming from the limb and the space that surrounds it (Farnè *et al.*, 2000; van der Hoort *et al.*, 2011; Tamè *et al.*, 2013; D'Amour *et al.*, 2015). To explore this possibility, we included one subjective (Lewis and McCabe, 2010) and one objective (Reinersmann *et al.*, 2012) measure of limb representation as possible predictors of any attentional bias.

A third possible attention-biasing mechanism in CRPS relates to the proposal that perception and action in reaching space share a common hand-centred frame of reference (Graziano *et al.*, 1994; Graziano, 1999; Fogassi and Luppino, 2005; Makin *et al.*, 2007, 2009). If this is the case, then a tendency to favour the unaffected limb by patients with CRPS (e.g. through learned non-use; Punt *et al.*, 2013) might well lead to an asymmetrical representation of near space. This proposal is supported by evidence that attention in upper-limb amputees is biased away from the residual limb in near space, but not in far space (Makin *et al.*, 2010). An asymmetry in the representation of space that is driven by uneven use of the limbs on the two sides of the body would only be expected to manifest in upper-limb patients, as lower-limb CRPS should not significantly alter the distribution of movements within arm-reaching space. We also administered self-report measures of the extent of possible motor asymmetries, specifically handedness and pain-related fear of movement. Action-driven changes in spatial representations are likely to be greatest when there has been a marked change in the hand that is used for daily tasks, therefore we also measured any change in the participants' handedness at the time of testing relative to before the development of CRPS. Change in handedness is most likely to occur when CRPS of the dominant hand leads to a reduction in its use, but could also occur when CRPS of the non-dominant hand leads to a greater favouring of the dominant hand. This measure is similar to recording whether or not the person's affected limb was their dominant or non-dominant hand, but had the added advantage of allowing us to quantify the extent of any increase or decrease in handedness rather than being limited to categorical coding. If the attention bias of patients with CRPS is driven by action asymmetries in near space, it should only be manifested in patients with upper-limb CRPS, and should be predicted by affected limb and other measures of motor asymmetries.

Finally, the fourth possibility that we wished to explore here was whether any attentional bias would be more pronounced in patients with CRPS in whom the left side of the body was affected as compared to those with CRPS affecting the right side. The greater role of the right cerebral hemisphere in some aspects of spatial attention is evidenced by neuroimaging studies (Chen and Spence, 1997; Nobre *et al.*, 1997; Corbetta and Shulman, 2002; Shulman *et al.*, 2010), the higher frequency of hemispatial neglect following right- than left-hemisphere lesions (Stone *et al.*, 1993; Beis *et al.*, 2004; Ringman *et al.*, 2004; Becker and Karnath, 2007), and asymmetries in the performance of healthy participants in some spatial tasks (Jewell and McCourt, 2000). Thus, inattention in CRPS could be more pronounced in those patients in whom the left side of the body is most affected, because this would presumably lead to greater right-hemisphere reorganization. We therefore examined whether the magnitude of any attentional bias could be predicted by which side of the body was affected.

For all four possible drivers of attention bias—pain, distortions in limb representation, asymmetries in movement distribution in near space, and side of the body—it could be expected that the magnitude of the bias would increase over time. We therefore included time since diagnosis as a final possible predictor of attention bias. Finally, we also tested which of the same factors predicted JNDs. Although temporal acuity was not the primary focus of the present study, examining which factors predict JNDs could provide insights into whether any differences between patients and controls for this measure can be attributed to changes to cognitive function that resemble those that are seen in neglect following brain injury, or are instead related to the generalized decrement in cognitive function that is associated with chronic pain.

In summary, we hypothesized that patients with CRPS would show a bias in covert visual attention away from their affected side in the TOJ task. The extent to which this bias is related to bodily information could be informed by any differences in the performance of upper- and lower-limb patients with CRPS, and by any differences when stimuli are presented on a blank board, on the patient's uncrossed hands, or on their crossed hands. We also tested which of several factors could predict spatial attention and temporal acuity in CRPS to identify possible mechanisms through which any abnormalities in these measures might arise.

Materials and methods

Participants

Twenty-four patients with CRPS exclusively or predominantly affecting one limb on one side of the body were recruited from the Oxford University and Royal United Hospitals Bath NHS Trusts (Table 1). Patients were excluded if they were diagnosed <3 months prior to the study date, if they were diagnosed with any neurological injury/disorder or any severe psychiatric illness, or if their English language comprehension was not sufficient for them to understand the information sheet and task instructions. The current 'Budapest' diagnostic criteria are more conservative for diagnosing patients with CRPS for research purposes than when making a clinical diagnosis (Harden *et al.*, 2007). However, we decided to retain all patients to enable measurement of visual attention across a broad

Table 1 Clinical and demographic information for CRPS patient participants

Patient	Diagnosis	Age, years	Sex	Limb	Side	Inciting injury	Duration, weeks	Pain (/10)	Handedness	Δ Handedness	CRPS BPDS (/57)	TSK (/68)	Medication	Other pain
UL01	CRPS-R	27	F	UL	L	Finger fracture	27	6.5	100	30.8	35	23	None	
UL02	CRPS-R	43	F	UL	R	Wrist fracture	52	3	45.5	42	18	58	Pregabalin, noratryptyline, Versatis® medicated plaster	
UL03	CRPS-R	61	F	UL	R	Surgery for Dupuytren's contracture	24	3	60	40	15	33	Codeine, paracetamol, ibuprofen, amitriptyline	
UL04	CRPS-R	35	F	UL	R	Minor thumb injury	78	3	−100	200	36	43	None	Pain in joints throughout body associated with hypermobility, including L UL and L LL.
UL05	CRPS-NOS	53	F	UL	L	Multiple wrist fractures and dislocation of elbow, with corrective surgery	34	3	100	0	8	44	Ibuprofen, codeine phosphate	History of pain in L lower back
UL06	CRPS-NOS	55	F	UL	R	Wrist fracture	54	2	−6	85	15	40	None	
UL07	CRPS-R	60	F	UL	L	Arm fracture	122	6	−44	56	10	34	Paracetamol	CRPS 'Starting to spread' to R hand, but no pain in R hand at time of testing
UL08	CRPS-R-II	45	F	UL	L	Multiple fractures to arm and damage to radial nerve	392	5	100	0	23	45	Gabapentin, amitryptaline	'Starting to spread' to L LL and R LL.
UL09	CRPS-R	60	F	UL	R	Wrist fracture and ligament injuries	335	7	−33	122	49	22	Morphine sulphate, lidocaine patches, Matrifen® patches, EMLA 5% cream	CRPS spread to R LL
UL10	CRPS-R	74	M	UL	R	Wrist fracture (+MRSA)	371	0	0	100	25	27	None	
UL11	CRPS-R	63	F	UL	L	Multiple fractures and dislocations to wrist and arm	386	8	100	0	55	45	Omeprazole, oxybutynin, senna, tramadol	Some spread of CRPS to the R shoulder
UL12	CRPS-R-II	58	F	UL	R	Nerve damage from needle	423	7	71	29	11	31	Tramadol	Some pain in joints throughout body including L LL and R LL (non-CRPS)
LL01	CRPS-R	23	F	LL	R	Medial collateral ligament tear	48	8.5	9	0	44	28	Pregabalin and lidocaine plasters	
LL02	CRPS-C	33	F	LL	L	Arthroscopic surgery	484	7	100	0	18	42	None	History of headaches. Aches and tightness in L LL and R LL (non-CRPS)
LL03	CRPS-R	22	F	LL	L	No injury	285	8.5	100	0	35	31	None	CRPS spread to L UL
LL04	CRPS-R	62	F	LL	L	Foot fracture	82	7.5	26	0	21	25	Amitryptaline, gabapentin, tramadol, oromorth, ibuprofen, paracetamol	Pain in joints throughout body due to osteoarthritis and rheumatoid arthritis since age of 19

(continued)

Table 1 Continued

Patient	Diagnosis	Age, years	Sex	Limb	Side	Inciting injury	Duration, weeks	Pain (/10)	Hand-edness	Δ Hand-edness	CRPS BPDS (/57)	TSK (/68)	Medication	Other pain
LL05	CRPS-R	29	F	LL	L	Partial rupture of posterior cruciate ligament	99	5	100	0	29	38	Codeine phosphate, cocodamol, paracetamol	
LL06	CRPS-R	30	M	LL	L	Arthroscopic surgery	82	7	100	0	8	42	Pregabalin, tramadol, amatriptaline	Lower back pain
LL07	CRPS-R	44	F	LL	L	No injury	135	5.5	100	0	15	42	Amatryptaline, codeine, duloxetine, lactulose, pregabalin, simvastin, naproxen	CRPS spread to upper arms bilaterally
LL08	CRPS-R	57	M	LL	R	Spinal surgery	129	6	−90	0	26	47	Morphine sulphate	
LL09	CRPS-R	29	M	LL	L	Talar dome lesion	20	7	100	0	34	46	Gabapentin, amatryptaline	
LL10	CRPS-R	38	F	LL	L	No injury	81	6	100	0	17	29	None	
LL11	CRPS-R	30	F	LL	R	Foot surgery	41	8	100	0	8	43	Cocodamole, codeine, paracetamol	
LL12	CRPS-R	35	M	LL	L	Infection	694	7	50	0	27	31	None	

Δ Handedness = change in handedness (expressed here as an absolute value); CRPS-C = CRPS type I clinical diagnosis; CRPS-NOS = CRPS type I not otherwise specified diagnosis; CRPS-R = CRPS type I research diagnosis; CRPS-R-II = CRPS type II research diagnosis; Handedness = scored from − 100 (extreme left-handedness) to + 100 (extreme right-handedness); L = left; LL = lower limb; R = right; UL = upper limb.

spectrum of severity of CRPS. Twenty-one patients met the research diagnostic criteria, one met the clinical diagnostic criteria, and two were diagnosed with CRPS not otherwise specified. Twelve patients had predominantly upper-limb CRPS [mean age = 53 years, standard error of the mean (SEM) = 3.8; one male] and 12 had predominantly lower-limb CRPS (mean age = 36 years, SEM = 3.6; four males). Two patients were diagnosed with CRPS II as they reported that nerve injuries were associated with the onset of their symptoms. The remaining patients were diagnosed with CRPS I.

Twenty-four age- and sex-matched pain-free control participants were recruited through community advertisements (mean age = 46 years, SEM = 3.0; five males). All of the participants had normal or corrected-to-normal vision and gave written informed consent to participate in a research protocol approved by hospital and university ethics committees according to the Declaration of Helsinki.

Stimuli and procedure

Self-report measures

All participants completed the Edinburgh Handedness Inventory (Oldfield, 1971), which is typically scored from −100 (indicating extreme left-handedness) to 100 (indicating extreme right-handedness). According to this scoring, two control participants and five patients with CRPS were left-handed. The remaining participants were right-handed. To express handedness scores in terms of the degree to which the hand on the affected side of the body was used for everyday tasks, handedness scores for the patients with CRPS were re-expressed such that negative and positive numbers indicated preferences for using the hand on the affected and unaffected side of their body, respectively.

Patients with CRPS completed four additional self-report measures that were not completed by the controls. The first was a second version of the Edinburgh Handedness Inventory to indicate their memory of hand preference prior to the onset of CRPS. From this, a Handedness Change score was calculated as the difference between the handedness quotients before CRPS onset and at the time of testing. Second, patients rated current pain intensity on a numerical rating scale ranging from 0 (‘no pain’) to 10 (‘worst possible pain’). Third, to measure the extent of their disturbance in body representation, patients with CRPS completed the 7-item Bath CRPS Body Perception Disturbance Scale (CRPS BPDS; Lewis and McCabe, 2010), which is scored on a scale of 0 (no body perception disturbance) to 57 (highest possible body perception disturbance). Fourth, to measure pain-related fear of movement and re-injury, patients completed the 17-item Tampa Scale of Kinesiophobia (TSK; Miller *et al.*, 1991), scored from 17 (no kinesiophobia) to 68 (highest possible kinesiophobia).

Hand laterality judgement

A hand laterality judgement task was used as an objective measure of body representation (Viswanathan *et al.*, 2012). The stimuli and procedure were similar to those described elsewhere (Reinersmann *et al.*, 2010). The stimuli consisted of 100 14.5 cm wide × 9.5 cm high pictures of hands photographed in different postures and orientations. The pictures included other parts of the body ranging from a minimum of the distal half of the forearm to a maximum of the entire arm and shoulder, and part of the torso. The hand was positioned in the centre of every picture. Each posture was photographed for both the left and right hand such that the stimuli consisted of 50 left-hand and 50 right-hand images that depicted identical postures. For each hand, 30 pictures depicted 'medial' hand postures, 10 pictures depicted 'anterior' hand postures, and 10 depicted 'uncommon' hand postures. The total surface area of the picture that contained the hand varied depending on which posture was being depicted, and ranged from 2.0 cm wide × 3.1 cm high for the least expansive posture to 6.0 cm wide × 6.0 cm high for the most expansive posture. The same Caucasian adult was depicted in all the photographs. They wore a loose-fitting black t-shirt and stood in front of a neutral background. There was insufficient information to judge the sex of the person depicted in the photographs. The pictures were presented at a viewing distance of ~50 cm for 500 ms each in the centre of a laptop computer screen (30 cm wide × 19 cm high) using Presentation 17.0 software (Neurobehavioral Systems, Inc., USA; www.neurobs.com) in Windows 7. Participants indicated the laterality (left or right) of the hand by pressing the left or right button on a custom-built button box. Patients with CRPS responded using the index and middle fingers of the hand on the unaffected side of their body. Half of the control participants responded using their left hand and half responded using their right hand. The participants were informed that both speed and accuracy were important. The trial timed-out after 10 s.

Visual temporal order judgement

For the visual TOJ task, a white board (45.6 cm wide × 35.5 cm deep) with a 3 mm-diameter fixation point drawn at its centre was placed on a table. Two identical red laser pointers were mounted above the board using a burette stand, projecting light stimuli (3 mm diameter) 9 cm to the left and right of the fixation point. The left–right arrangement of the laser pointers was swapped for half the participants to compensate for any possible difference in their brightness. The laser pointers were controlled via the parallel port by Eprime 2.0 software running on a Windows 7 operating system.

Participants sat at the table with their head resting on a chin-rest and their legs uncrossed. Both laser pointers were turned on before the beginning of each block while the participant positioned their hands. During the 'no hands' condition, the participants held their hands folded together immediately in front of the base of the chin-rest such that they were occluded from view. During the 'uncrossed' condition, the participants positioned their hands palms-down on the white board such that the left and right light appeared on the centre of the dorsal surface of their left and right hand, respectively. In the 'crossed' condition, the participants crossed their hands such that the left and right light appeared on the centre of the dorsal surface of the right and left hand, respectively. To accommodate these hand arrangements, the distance of the board (and therefore the locations of the fixation cross and targets) from the body varied between participants such that they could comfortably hold their hands in the uncrossed and crossed positions while they also rested their head on the chin-rest. The horizontal distance between the fixation point and each participant's torso was ~28 cm.

The TOJ task was identical for each condition and the experimenter initiated each trial. After a pause that varied randomly between 500 and 1000 ms, the lights flashed for 10 ms each. There were 15 repetitions for each of 10 temporal offsets: −120, −60, −30, −15, −5, 5, 15, 30, 60 and 120 ms. Negative values represent those conditions in which the first light appeared on the affected side of space for the patients with CRPS, and on the side of the non-dominant hand for the control participants. Positive numbers represent those trials in which the light first appeared on the unaffected side of space for the patients with CRPS, and on the side of the dominant hand for the control participants. The trials were presented in a pseudorandomized order whereby each temporal offset occurred once within each set of 10 trials. The participants indicated the light that appeared first (left or right, two-alternate forced-choice) with a vocal response. The experimenter keyed the response into the computer, which initiated the next trial.

Data preparation

For the hand laterality judgement task, mean reaction times and percentage accuracy were calculated separately for the affected and unaffected (patients with CRPS) or non-dominant and dominant (controls) Hand Picture conditions. Two patients with CRPS did not complete the hand laterality judgement task due to computer failure on the day of testing.

The TOJ data were expressed in terms of the proportion of trials in which the participant reported that the light had appeared first on the unaffected (patients with CRPS) or dominant (controls) side. For each participant, and each condition, these data were fitted with a cumulative Gaussian using a maximum-likelihood criterion. The PSS was calculated as the temporal offset at which participants responded that the two responses ('unaffected first' / 'affected first' or 'dominant first' / 'non-dominant first') were equiprobable. Negative values indicated that the light needed to appear earlier on the affected (patients with CRPS) or non-dominant (controls) side of space for the two stimuli to be perceived as simultaneous. As per convention, the JND was defined as the difference between the 75% and 25% points of the cumulative Gaussian. There were three instances in which data were not available for particular conditions for individual patients. Details of how these were managed are provided in the Supplementary material.

Statistical analyses

Analyses were performed with R software (R Core Team, 2015) using linear mixed models regression with bootstrapping procedures wherein 1000 bootstrap samples were generated for each analysis. The combination of linear mixed models and bootstrapping addressed potential problems that could arise due to missing data and differences in the variances for the patients and the control groups. A variable made a significant contribution to predicting the outcome variable when the 95% confidence interval (CI) around the regression coefficient (*B*) did not include zero.

The analyses for the hand laterality judgement task was as follows: Group (controls, patients) and Hand Picture (affected/non-dominant, unaffected/dominant) were entered using dummy variable coding into the analyses of reaction times (ms) and accuracy (%), along with the interaction term Group × Hand picture. Analyses were repeated with percentage scores subjected to an arcsine transformation; no qualitative change appeared and so we report the untransformed analyses for clarity.

For the visual TOJ task, Group (controls, patients) and Hand arrangement (no hands, uncrossed, and crossed) were entered using dummy variable coding into the analyses of the PSS and JND data, along with the interaction term Group × Hand arrangement. Presuming that these analyses revealed that the patients with CRPS differed significantly from controls, further analyses were planned to determine the contribution of possible explanatory variables to PSSs and JNDs within the CRPS group. The possible explanatory variables identified prior to the study were: current pain intensity; CRPS BPDS score; a measure of performance on the hand laterality judgement task (to be chosen based on the outcome of the analysis of reaction times and percentage accuracy for this task); affected limb; *Z*-scores of handedness, *Z*-scores of handedness change; TSK score; affected body-side; and weeks since diagnosis.

Results

Hand laterality judgement task

Tables 2 and 3 show the coefficient estimates and their 95% CIs for the analyses of reaction times and accuracy, respectively. Group significantly predicted reaction times on the hand laterality judgement task, with the patients with CRPS (mean = 1414 ms, SEM = 119) an average of 163 ms slower than the controls (mean = 1251 ms, SEM = 70). Neither the laterality of the Hand Picture, nor the interaction of Group × Hand Picture, significantly contributed to the model. None of the entered variables contributed to the prediction of Accuracy on the hand laterality judgement task (mean = 76.7%, SEM = 2.4, pooled across patients and controls). Reinersmann *et al.* (2010) reported a similar generalized delay in the reaction times of patients with CRPS to pictures of hands (i.e. slower reaction times to pictures of any hands, regardless of laterality), but the same patients showed normal performance on tests of alertness and working memory. This suggests that the significant prediction of reaction times by Group in the present study could reflect a deficit in body representation that generalizes to representations of both hands (as was concluded by Reinersmann *et al.*, 2010). We therefore decided to enter the mean reaction time of each CRPS patient on the hand laterality judgement task (converted to *Z*-scores) as the objective measure of body representation for the prediction of PSSs and JNDs.

Visual temporal order judgement task

Figure 1 shows psychometric functions fitted to the cumulative data for the CRPS and control groups for each condition of Hand arrangement. Visual inspection of Fig. 1 reveals that the PSS values of patients with CRPS were, numerically, more negative than those for the controls in the no hands and uncrossed conditions. In the crossed hands condition, the PSS value for the cumulative CRPS and control group data were numerically similar and close to zero. Compared to controls, the slopes of the psychometric functions for the patients with CRPS in all three Hand arrangement conditions are qualitatively less steep, giving rise to numerically larger JNDs. Bootstrapped ($n = 1000$) one sample *t*-tests of the group data revealed that PSS values for the patients with CRPS were significantly different from 0 in the no hands condition [$t(23) = 3.4$, $P = 0.003$; 95% CI = −43.5 to −12.6]. The PSS values for the patients with CRPS in the uncrossed condition [$t(23) = 1.8$, $P = 0.081$, 95% CI = −32.2 to 1.77] and crossed condition [$t(21) = 0.17$, $P = 0.87$, 95% CI = −16.3 to 15.7] were not significantly different from 0. The PSS values for the control participants were not significantly different to 0 in the no hands condition [$t(23) = 0.62$, $P = 0.54$, 95% CI = −17.0 to 7.4], the uncrossed condition [$t(23) = 1.5$, $P = 0.15$, 95% CI = −14.3 to 2.1], or the crossed condition [$t(23) = 1.06$, $P = 0.30$, 95% CI = −19.0 to 4.4].

Point of subjective simultaneity analysis

Comparison of patients with complex regional pain syndrome and control

Group (control versus patient) was a significant predictor of the PSS (Table 4). The PSSs for the patients (mean = −15.0 ms, SEM = 8.2) were an average of 9 ms further towards the affected/non-dominant side of space relative to the control group (mean = −5.9 ms, SEM = 6.0). In the no hands condition, the patients had a 22 ms bias relative to the controls. The coefficient estimate for the first Group × Hand arrangement interaction term indicates that the performance difference between the patients and the controls in the uncrossed condition was an average of 13 ms smaller than the performance difference between the two groups in the no hands condition; however, the confidence interval for the coefficient estimate indicates that this difference was not significant ($P > 0.05$). This means, statistically, that the patients' PSS values were similarly biased in the no hands and uncrossed conditions. By contrast, the coefficient estimate and confidence interval for the second Group × Hand arrangement interaction term indicate that the performance difference between the patients and the controls in the crossed condition was significantly smaller than the performance difference in the no hands condition by an average of 27 ms. As is apparent in Fig. 1, this change left the two groups showing similar PSS values in the crossed condition. A *post hoc t*-test with bootstrapping ($n = 1000$ samples) to compare the PSS values for the patient and control groups in the crossed condition was not significant [$t(44) = 0.58$, $P = 0.58$, 95% CI = −13.9 to 27.5]. This confirms that the patients' performance in this condition was not significantly biased compared to controls. We consider the between-group performance difference to be most important for ascertaining whether the patients with CRPS showed a bias in any given condition.

Table 2 The results of the bootstrapped (n = 1000) regression of reaction times on Group and Hand picture for the hand laterality judgement task

Effect	Coefficient estimate	Lower CI	Upper CI
Intercept*	1246.9	1166.1	1329.2
Group (controls = 0)			
Patients*	163.5	26.0	300.6
Hand picture (affected/non-dominant = 0)			
Unaffected/dominant	12.6	−91.7	146.4
Group × Hand picture (patients-controls, affected/non-dominant = 0)			
Patients-controls, unaffected/dominant	−7.8	−164.0	124.4

The reference condition for dummy variable coding is indicated within parentheses for each term.
*Significant predictor of PSS (95% CI around the coefficient estimate does not include 0).

Table 3 The results of the bootstrapped (n = 1000) regression of accuracy (%) on Group and Hand picture for the hand laterality judgement task

Effect	Coefficient estimate	Lower CI	Upper CI
Intercept*	78.3	74.7	81.8
Group (controls = 0)			
Patients	−4.7	−11.2	1.5
Hand picture (affected/non-dominant = 0)			
Unaffected/dominant	2.3	−1.3	6.8
Group × Hand picture (patients-controls, affected/non-dominant = 0)			
Patients-controls, unaffected/dominant	−1.9	−10.5	5.7

The reference condition for dummy variable coding is indicated within parentheses for each term.
*Significant predictors of accuracy (95% CI around the coefficient estimate does not include 0).

However, it should be noted that a second *post hoc t*-tests with bootstrapping ($n = 1000$ samples), which compared the PSS values of the patient group in the no hands and crossed conditions, was also not significant [$t(21) = 2.17$, $P = 0.08$, 95% CI = −53.0 to −1.7].

Neither of the Hand arrangement terms (uncrossed versus no hands and crossed versus no hands) were significant, indicating that this variable did not contribute significantly to the prediction of PSS when considered independently of Group.

Analysis of possible predictors of patients' point of subjective simultaneity values

The only term that significantly predicted PSS was CRPS BPDS score, with PSS shifting towards the affected side by 1.7 ms for every one point increase in body perception disturbance score (Table 5).

Inspection of individual patterns in point of subjective simultaneity values

Inspection of individual data revealed patterns of potential interest concerning differences in the incidence of spatial attention biases between upper- and lower-limb patients.

For each Hand arrangement, the PSS of each CRPS patient was compared to the bootstrapped ($n = 1000$) 95% CI around the mean for the controls. Each PSS was classified as reflecting a bias of attention away from the affected side if it was less than the lower bound of the control group's 95% CI. If the PSS was greater than the upper bound of the control group's 95% CI it was classified as reflecting a bias of attention towards the affected side. If it was within the bounds of the controls group's 95% CI the PSS was classified as reflecting no bias of attention. The individual PSS values of patients with upper- and lower-limb CRPS are represented in Supplementary Figs 1 and 2.

Individual patients with upper-limb CRPS were more likely than lower-limb patients to show an attentional bias away from the affected side. Summed across Hand arrangement, a higher proportion of upper-limb patients ($n = 20/35$) showed PSS values consistent with a significant bias of attention away from the affected side when compared to lower-limb patients [$n = 8/35$; $\chi^2(1) = 8.6$, $P = 0.009$; Bonferroni corrected]. Patients with upper-limb CRPS were less likely ($n = 6/35$) to have PSS values indicating no significant bias in attention compared to patients with lower-limb CRPS [$n = 17/35$; $\chi^2(1) = 7.8$, $P = 0.015$]. The incidence of PSS values that reflected a bias of attention towards the affected side was similar for patients with upper-limb CRPS ($n = 9/35$) and the patients with lower-limb CRPS [$n = 10/35$; $\chi^2(1) = 0.07$, $P = 0.788$]. Individual differences are further discussed in the Supplementary material.

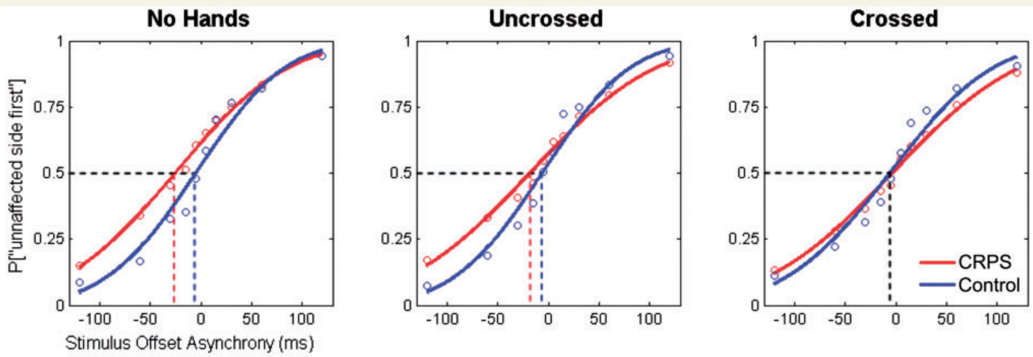

Figure 1 Cumulative data for the visual TOJ task under the different Hand arrangements. Separate psychometric curves are fitted to the summed responses from the CRPS (red) and control (blue) groups. Negative scores indicate attentional bias away from the affected side (in patients) or non-dominant side (in controls). Dashed lines indicate the PSSs.

Table 4 The results of the bootstrapped (n = 1000) regression of PSS on Group and Hand arrangement

Effect	Coefficient estimate	Lower CI	Upper CI
Intercept	−4.2	−14.0	5.1
Group (controls = 0)			
Patients*	−22.4	−42.0	−4.0
Hand arrangement (no hands = 0)			
Uncrossed	−1.6	−13.1	9.5
Crossed	−3.1	−18.2	10.4
Group × Hand arrangement (patients-controls, no hands = 0)			
Patients-controls, uncrossed	13.0	−9.0	36.2
Patients-controls, crossed*	27.2	0.7	53.9

The reference condition for dummy variable coding is indicated within parentheses for each term.
*Significant predictor of PSS (95% CI around the coefficient estimate does not include 0).

Just noticeable difference analysis

Comparison of patients with complex regional pain syndrome and controls

Group (control versus patients) was a significant predictor of JNDs (Table 6). The JNDs were an average of 20 ms larger for patients (mean = 94.2 ms, SEM = 11.1) than for controls (mean = 74.9 ms, SEM = 9.9). The second of the two Hand arrangement terms (crossed versus no hands) was also a significant predictor of JNDs, with JNDs an average of 16 ms larger for the crossed condition (mean = 94.2 ms, SEM = 10.0) than for the no hands condition (mean = 77.8 ms, SEM = 6.5) when considered across both Groups. Neither term for the Group × Hand arrangement interaction contributed significantly to the model, indicating that the difference in JNDs for patients with CRPS compared to controls did not significantly vary as a function of the Hand arrangement.

Analysis of possible predictors of patients' just noticeable difference values

Pain intensity and weeks since diagnosis were significant predictors (Table 7), with JNDs increasing by 14.9 ms for every one point increase in pain and decreasing by 0.05 ms for every week since diagnosis (2.6 ms reduction per year).

Inspection of individual patterns in just noticeable difference values

The individual JND values of patients with upper- and lower-limb CRPS are presented in Supplementary Figs 3 and 4. The JND for each CRPS patient for each Hand arrangement condition was compared to the bootstrapped (n = 1000) 95% CI around the mean for controls. There were no differences between the patterns of deviations of JNDs from normal between the patients with upper- and lower-limb CRPS (Supplementary material).

Discussion

We measured covert attention in patients with CRPS to visual information that appeared in near space without vision of the hands, and to visual information that appeared in the same spatial locations but on the surface of the hands. The main finding was that, as a group and compared to control participants, patients with CRPS

Table 5 **The results of the bootstrapped (*n* = 1000) regression of PSS on the possible explanatory variables for data for patients with CRPS only**

Effect	Coefficient estimate	Lower CI	Upper CI
Intercept	15.3	−51.5	83.1
Pain intensity	6.0	−1.0	12.7
CRPS BPDS*	−1.7	−2.6	−0.7
$Z_{\text{Hand laterality reaction time}}$	−0.002	−0.01	0.01
Limb	−2.8	−30.4	26.6
$Z_{\text{handedness}}$	4.4	−14.0	28.7
$Z_{\text{handedness change}}$	−0.02	−14.3	12.4
TSK	−0.8	−2.0	0.2
Body side	−1.9	−42.7	38.8
Weeks since diagnosis	0.03	−0.002	0.07

*Significant predictor of PSS (95% CI around the coefficient estimate does not include 0).

Table 6 **The results of the bootstrapped (*n* = 1000) regression of JND on Group and Hand arrangement**

Effect	Coefficient estimate	Lower CI	Upper CI
Intercept*	66.1	54.0	78.6
Group (controls = 0)			
Patients*	23.5	4.9	41.1
Hand arrangement (no hands = 0)			
Uncrossed	1.8	−14.4	19.7
Crossed*	25.2	3.8	48.6
Group × Hand arrangement (patients-controls, no hands = 0)			
Patients-controls, uncrossed	8.4	−17.5	33.2
Patients-controls, crossed	−15.9	−49.2	13.9

The reference condition for dummy variable coding is indicated within parentheses for each term.
*Significant predictor of JND (95% CI around the coefficient estimate does not include 0).

Table 7 **The results of the bootstrapped (*n* = 1000) regression of JND on the possible explanatory variables for the patients with CRPS only**

Effect	Coefficient estimate	Lower CI	Upper CI
Intercept	5.8	−78.3	114.1
Pain intensity*	14.9	3.9	27.1
CRPS BPDS	−1.4	−3.2	0.2
$Z_{\text{Hand laterality reaction time}}$	−0.01	−0.03	0.01
Limb	−28.8	−63.3	5.2
$Z_{\text{handedness}}$	14.6	−11.2	44.4
$Z_{\text{handedness change}}$	8.7	−4.3	19.6
TSK	1.3	−0.5	2.7
Body side	44.3	−8.6	100.8
Weeks since diagnosis*	−0.05	−0.1	−0.005

*Significant predictor of JND (95% CI around the coefficient estimate does not include 0).

showed a bias in covert visual attention away from the affected side. Importantly, this bias was observed when participants made TOJs concerning lights appearing on a blank board. Such delayed processing of visual information on one side of space is similar to that seen in patients with neglect following brain injury on visual TOJ tasks (Rorden *et al.*, 1997; Berberovic *et al.*, 2004; Sinnett *et al.*, 2007). To the best of our knowledge, this is the first evidence that patients with CRPS have diminished attention to the affected compared to the unaffected side of space in terms of their general sensory processing (i.e. independent of visual or tactile bodily information).

This bias was not significantly altered when the same TOJ task was performed with the visual information appearing on the surface of the uncrossed hands. However, crossing the hands over to the opposite side of space significantly reduced the patients' bias such that it was no longer significantly different to that of the controls. This bias reduction (what some might term a reversal) cannot be explained solely by a bias away from the hand on the affected side of the body, since that would also have resulted in a significant group difference, but this time with PSS values for the patients that would be more positive than those for the controls. Rather, the similarity of performance between patients and controls when the arms were crossed suggests that patients' attention is biased both away from the affected side of space and away from the hand of the affected side of the body. When the hands are crossed, the tendency for attention to be biased away from the affected side of space and the tendency for attention to be biased away from the hand of the affected side of the body cancel out (i.e. they sum to zero). Although we believe this is the best interpretation of our results, it should be acknowledged that a *post hoc t*-test that directly compared the PSS values of the patients in the no hands and crossed conditions failed to reach statistical significance. We therefore conclude that an avenue for further research is to investigate the reliability of the change that we have observed in patients bias relative to controls when the hands are crossed.

In further analyses we examined which factors predicted attention bias in patients with CRPS. We found that the extent to which attention was directed away from the affected side was predicted by scores on the CRPS BPDS (Lewis and McCabe, 2010), a subjective measure of distortions in the representation of the affected limb. One possibility is that altered body representation may interfere with the ability to process information coming from the limb and the space that surrounds it (Farnè *et al.*, 2000; van der Hoort *et al.*, 2011; Tamè *et al.*, 2013; D'Amour *et al.*, 2015). However, such an explanation for the relationship between body representation distortion and attention bias is negated by the fact that the patients with CRPS showed biased attention during the no hands condition, when the targets did not appear on or near the hands. Some of the unusual perceptions reported by patients with CRPS, such as feelings of disownership of, or aversion towards, their affected limb, resemble neurological delusions of body representation that can follow brain injury. For example, asomatagnosia is the denial of ownership of a limb and misoplegia is characterized by feelings of dislike towards a limb (Vallar and Ronchi, 2009). Such delusions often co-occur with neglect following brain injury (Bisiach and Berti, 1987; Heilman *et al.*, 2000; Loetscher *et al.*, 2006), which suggests that there may be overlapping cognitive and neural bases for deficits in body representation and spatial attention. The significant relationship between covert visual attention and body representation in our study is consistent with the possibility that these cognitive symptoms could also be driven by related cortical changes in patients with CRPS.

The attentional bias of the patients was not predicted by pain intensity or time since diagnosis, consistent with previous studies that measured spatial attention using tactile TOJ tasks (Moseley *et al.*, 2009; Reid *et al.*, 2016). Interestingly, studies that have tested attention to explicit visual information about the affected limb found that pain intensity and duration of symptoms significantly related to the degree of attention bias (Reid *et al.*, 2016). We speculate that tasks that use explicit visual information about the limb could be more closely related to pain due to the greater emphasis that they place on the affected body part.

Our group-level analysis also found the magnitude of attentional bias was not predicted by affected limb, handedness, change in handedness, or TSK scores. Nonetheless, we do not yet eliminate the possibility that a generalized bias in attention might be driven by an asymmetrical representation of near space due to a tendency to favour the unaffected limb when performing actions (e.g. due to learned non-use; Punt *et al.*, 2013). Our sample may have been too small and heterogeneous to elucidate statistical relationships between the extent of limb use and magnitude of attention bias in the group analysis, since some patients had both upper- and lower-limb involvement. Indeed, when the performance of the patients was examined on an individual basis relative to the control group, significant inattention to the affected side was more frequent in those patients with predominantly upper-limb CRPS than those with predominantly lower-limb CRPS. Furthermore, self-report measures of current hand preference, remembered hand preference, and fear of movement may be poor indicators of asymmetries of actual hand movements in daily life. It may yet be beneficial to further investigate whether the covert attention bias in patients with CRPS is driven by an asymmetrical distribution of movements. This could be achieved through research on patients with CRPS that exclusively affects one upper or one lower limb, using accelerometers to gain a more precise and objective measure of the spatial distribution of actions.

Patients with CRPS had significantly larger JNDs than control participants, indicating reduced temporal acuity. Since these were positively predicted by pain intensity, but not by body perception distortion or any of our other markers of cognitive change, these could reflect general cognitive impairments (e.g. to sustained attention and processing speed) that are known to accompany chronic pain (Hart *et al.*, 2000; Attridge *et al.*, 2015). It could be noted that the mean JNDs for the patients of 94 ms could be considered large, and some of the participants had JNDs for some conditions that were larger than the largest temporal offset (i.e. 120 ms; see Supplementary Figs 3 and 4). This indicates that in order for the participant to be able to reliably judge the temporal order of the stimuli in these instances, the stimuli would need to have been presented at temporal offsets larger than the maximum offset that was actually used in the study. In our experience it is not unusual to observe large JNDs, particularly for crossed hands conditions in tactile TOJ tasks, and when studying non-expert community participants and clinical populations who have not had a lot of training in such experimental tasks. Previous studies using TOJ tasks have reported mean JNDs that were similarly large relative to the maximum temporal offset (Shore *et al.*, 2002; Van Damme *et al.*, 2009). Nonetheless, we reperformed our main group analyses on a reduced dataset that excluded those conditions for which the JNDs had exceeded 120 ms (excluding 20% of the total data). The analysis of the reduced dataset replicated our main finding, of significantly leftward PSS values for patients with CRPS compared to controls, but this bias did not vary between the three Hand arrangement conditions. Future researchers who test patients with CRPS on TOJ tasks and who are concerned about high JNDs might consider using a broader range of temporal offsets, forming *a priori* exclusion rules based on the JND magnitudes (De Paepe *et al.*, 2014), or using a procedure that adjusts temporal offsets adaptively based on the participants' responses (Sternberg *et al.*, 1971; Stelmach and Herdman, 1991; Berberovic *et al.*, 2004; Filbrich *et al.*, 2017).

Considering that attention bias was predicted by scores on the questionnaire measure of body perception distortion, it is perhaps curious that it was not also predicted by reaction times on the hand laterality judgement task, an objective measure of body representation. Like Reinersmann *et al.* (2010) we found that patients with CRPS were significantly slower than controls in recognizing pictures of upper limbs and that there were no differences in their reaction times for pictures that corresponded to the affected versus unaffected side of the body. Like the larger JNDs compared to controls, the slower reaction times of patients with CRPS on this hand laterality judgement task might reflect non-specific factors such as impaired sustained attention rather than a deficit in body representation. In contradiction of this possibility, the patients with CRPS in the study by Reinersmann *et al.* (2010) showed no deficits in alertness or working memory. However, we conducted a follow-up analysis comparing reaction times for patients with upper- and lower-limb CRPS in the present study and found no difference between these groups, whereas if the task measured limb representation we would expect slower reaction times for the upper-limb patients. The differences in reaction times between patients with CRPS and controls on the hand laterality judgement task in the present study could therefore reflect non-specific cognitive deficits rather than body representation, which would explain why this measure did not predict attention bias even though the scores on the CRPS BPDS did.

Overall, the present study provides the first evidence demonstrating a bias in attention away from the affected side in patients with CRPS that is seen in the absence of explicit or implied information about the limbs. Although the attention bias was not predicted by pain in the present study, the alleviation of pain by addressing spatial attention bias using prism adaptation (Sumitani *et al.*, 2007*a*; Bultitude and Rafal, 2010; Christophe *et al.*, 2016) suggests an indirect relationship between the two. Harris (1999) proposed that conditions such as CRPS in which symptoms cannot be completely explained by damage to the affected limb might arise as a result of discrepancies between sensory input, movement output and movement intention. Biased spatial attention could contribute to such discrepancies by distorting or degrading the spatial and temporal alignment of information that occurs in the affected side of space.

In light of our and others' findings for reduced attention to the affected side of the body and near space, it is curious that several studies using judgements of visual straight-ahead based on far (2 m) visual targets have not found evidence for a bias in attention away from the affected side, but towards the affected side (Sumitani *et al.*, 2007*b*, 2014; Uematsu *et al.*, 2009), or else towards the right side of space regardless of which side of the body was affected by CRPS (Reinersmann *et al.*, 2012). Understanding the contrasting ways in which spatial biases present in different spatial reference frames in CRPS could be critical to understanding how pain arises in this condition, or indeed in the normal experience of pain (Legrain *et al.*, 2012). The contrasting findings in near and far space also lead to the critical question of which attention bias should be targeted for treatment. It seems highly relevant that the spatial realignment that occurs during prism adaptation can be observed as opposing but additive shifts in two reference frames (Redding and Wallace, 2006). After adapting by pointing at visual targets that are viewed through lenses that shift the visual image to one side, the felt position of the pointing arm relative to the body shifts in the opposite direction to the prismatic shift, whereas judgements of visual straight ahead shift in the same direction as the prismatic shift. This means that prism adaptation that is designed to reorient arm movements towards the affected side of near space will also shift visual straight-ahead judgements away from the affected side. Thus, it is possible that prism adaptation alleviates symptoms of CRPS by reducing both of the conflicting visual biases that have been reported for these patients.

Since the attention bias exhibited by our patients was not predicted by which side of the body (left or right) was most affected, our result could indicate that biased spatial attention in CRPS arises due to changes in the dorsal attention network. This network is present in both hemispheres and directs attention to features on the contralateral side of space (Corbetta and Shulman, 2002). Subtle visuospatial impairments, such as those demonstrated by patients with CRPS in the current study, can occur when the dorsal attention network in either hemisphere is disrupted by a lesion (List *et al.*, 2008; Schendel *et al.*, 2016) or using transcranial magnetic stimulation (Walsh *et al.*, 1999; Dambeck *et al.*, 2006). In contrast, the marked deficits that constitute neglect, and that are seen with greater frequency following right-hemisphere lesions, are thought to arise due to disruption of both the dorsal attention network and the ventral network for detecting behaviourally-relevant stimuli, which is mainly lateralized to the right hemisphere (Corbetta and Shulman, 2002). Within the dorsal attention network, the posterior parietal cortex (PPC) has been associated with allodynia and motor impairments in CRPS (Maihöfner *et al.*, 2006, 2007; Lebel *et al.*, 2008), and is also part of the network of brain regions implicated in the multisensory representation of the space near to the body (the 'body matrix'; Longo *et al.*, 2010; Moseley *et al.*, 2011). Our study adds to previous evidence of neuropsychological symptoms that suggest altered PPC function in CRPS (Förderreuther *et al.*, 2004; Lewis *et al.*, 2010; Robinson *et al.*, 2011; Cohen *et al.*, 2013), and supports the existence of a relationship between spatial attention bias and distortion of body perception in patients with this condition.

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Supplementary material

Supplementary material is available at *Brain* online.

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