Space-based bias of covert visual attention
in Complex Regional Pain Syndrome

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Word count: 8073

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Running title: Biased covert visual attention in CRPS
Abstract

Some patients with Complex Regional Pain Syndrome (CRPS) report that movements of the affected limb are slow, more effortful, and lack automaticity. These symptoms have been likened to the syndrome called hemispatial neglect that sometimes follows brain injury in which patients exhibit attentional impairments and problems with movements affecting the contralesional side of the body and space. Psychophysical testing of CRPS patients has found evidence for spatial biases when judging visual targets distanced at two metres, 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 arms’ reach, CRPS patients exhibited a bias away from the affected side. What is not yet known is whether CRPS patients only have biased attention for bodily-specific information in the space within arms’ 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 (TOJ) task we found that CRPS patients 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 CRPS 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 CRPS may arise in parallel with a distorted body perception.

Keywords: Complex Regional Pain Syndrome, spatial attention, pain, body representation
Abbreviations

CI: Confidence Interval
CRPS: Complex Regional Pain Syndrome
CRPS BPDS: Bath Complex Regional Pain Syndrome Body Perception Disturbance Scale
JND: Just Noticeable Difference
PPC: Posterior Parietal Cortex
PSS: Point of Subjective Simultaneity
RT: Reaction Time
SEM: Standard Error of the Mean
TOJ: Temporal Order Judgement
TMS: Transcranial Magnetic Stimulation
TSK: Tampa Scale for Kinesiophobia
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 (Förderreuther et al., 2004; Robinson et al., 2011; Schwoebel et al., 2001). They also report that movements of the affected limb are slow, effortful, and lack automaticity (Galer et al., 1995; Galer and Jensen, 1999). These symptoms have been likened to the syndrome of hemispatial neglect (“neglect”) that may follow brain injury. Brain-lesioned patients with neglect show attention and motor impairments affecting the contralesional side of the body and space (Bisiach and Vallar, 2000; Parton et al., 2004). Notably, pain and other symptoms might be alleviated in CRPS patients treated with prism adaptation (Bultitude and Rafal, 2010; Christophe et al., 2016; Sumitani, Rossetti, et al., 2007), a promising behavioural treatment for neglect following brain injury (Làdavas et al., 2015; Luauté et al., 2006; Mizuno et al., 2011; Rode et al., 2014; Rossetti et al., 1998; Saevarsson et al., 2012; Serino et al., 2006, 2009, Shiraishi et al., 2008, 2010). Finding that a treatment for neglect also helps CRPS patients 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 (see Torta et al., 2016, for a recent review). Indeed, Punt and his colleagues (2013) have argued that the motor impairments that first prompted the use of the term “neglect-like” with regards to CRPS could be better categorised as learned non-use. Testing sensory processing, rather than motor function, in CRPS could be more informative.

1 Slowed movements and feelings of estrangement from the affected limb(s) in CRPS patients were first referred to as “neglect-like” symptoms by Bradley Galer and his colleagues (1995) and this term has since been used widely by both researchers and clinicians. However, as the same authors later emphasized (Galer et al., 2013), there are also many differences between the unusual experiences and lateralized motor and sensory deficits of CRPS patients, 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 CRPS patients.
provide more certain information about whether altered spatial perception plays a role in physical CRPS symptoms.

Several studies have examined the performance of CRPS patients 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, CRPS patients show none of the omissions or displacements that would indicate problems with directing attention to the affected side of space (Förderreuther et al., 2004; Kolb et al., 2012; Reinersmann et al., 2012; Robinson et al., 2011; although 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 CRPS patients 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 and his colleagues reported that when judging when a point of light was positioned straight ahead of their body midline in a darkened room CRPS patients were biased toward the affected side of space (Sumitani et al., 2014; Sumitani, Shibata, et al., 2007; Uematsu et al., 2009). 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 CRPS patients 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 (Christophe et al., 2016; Kolb et al., 2012). 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 CRPS patients, these might not always manifest themselves as a bias away from the affected limb. Significantly deviated visual straight ahead judgements were only observed when CRPS patients 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 CRPS patients 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; Karnath et al., 1994; Roll et al., 1991; Taylor and McCloskey, 1991).

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 and his colleagues (2009) provided the first objective evidence that CRPS patients have an attentional bias away from the affected side. CRPS patients 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 CRPS patients 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, CRPS patients 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 arms’ reach of the head and torso, or in the region of space that is outside of arms’ reach, Legrain et al., 2012). The pattern of responses to evoked stimuli in near space\(^2\) 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). 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 CRPS patients 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 CRPS patients would require the stimuli to appear earlier on the affected as compared to the unaffected side of space for their 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 (e.g., 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 CRPS patients would be larger than for controls.

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

\(^2\) 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.
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, in order to evaluate whether any body-based bias in visual attention was specific to the affected limb, we recruited both upper- and lower-limb CRPS patients.

The second aim of the present study was to test which clinical or cognitive factors predict PSS values in CRPS patients. 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 attention bias might arise in CRPS (they need not be considered to be 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 (D’Amour et al., 2015; Farnè et al., 2000; van der Hoort et al., 2011; Tamè et al., 2013). 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 (Fogassi and Luppino, 2005; Graziano, 1999; Graziano et al., 1994; Makin et al., 2007, 2009). If this is the
case, then a tendency to favour the unaffected limb by CRPS patients (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, since 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 CRPS patients is driven by action asymmetries in near space, it should only be manifested in upper-limb CRPS patients, 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 CRPS patients 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 (Corbetta & Shulman, 2002; Nobre et al., 1997; Shulman et al., 2010), the higher frequency of hemispatial neglect following right- than left-hemisphere lesions (Becker and Karnath, 2007; Beis et al., 2004; Ringman et al., 2004; Stone et al., 1993), and asymmetries in the performance of healthy participants in some spatial tasks (e.g. 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 reorganisation. 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 hypothesised 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 CRPS patients, 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 people 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 (see Table 1). Patients were excluded if they were diagnosed less than three 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 CRPS patients 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 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, \(SEM = 3.8\); 1 male) and twelve had predominantly lower-limb CRPS (mean age = 36 years, \(SEM = 3.6\); 4 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.

[Insert Table 1 here]

Twenty-four age- and sex-matched pain-free control participants were recruited through community advertisements (mean age = 46 years, \(SEM = 3.0\); 5 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 CRPS patients 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 CRPS patients 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.

CRPS patients 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, CRPS patients 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 one hundred 14.5 cm wide x 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, thirty pictures depicted “medial” hand postures, ten pictures depicted “anterior” hand postures, and ten 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 x 3.1 cm high for the least expansive posture to 6.0 cm wide x 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 who was depicted in the photographs. The pictures were presented at a viewing distance of approximately 50 cm for 500 msec each in the centre of a laptop computer screen (30 cm wide x 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. CRPS patients 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 sec.

Visual TOJ
For the visual TOJ task, a white board (45.6 cm wide x 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 pipette 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 approximately 28 cm.

The TOJ task was identical for each condition. The experimenter initiated each trial. After a pause that varied randomly between 500 and 1000 msec, the lights flashed for 10 msec each. There were 15 repetitions for each of 10 temporal offsets: -120, -60, -30, -15, -5, 5, 15, 30, 60 and 120 msec. Negative values represent those conditions in which the first light appeared on the affected side of space for the CRPS patients, 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 CRPS patients, 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 RTs and percentage accuracy were calculated separately for the affected and unaffected (CRPS patients) or non-dominant and dominant (controls) Hand Picture conditions. Two CRPS patients 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 (CRPS patients) 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 (CRPS patients) 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 materials.

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 RTs (msec) and Accuracy (%), along with the interaction term Group × Hand Picture.

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 CRPS patients 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 RTs 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 RTs and Accuracy, respectively. Group significantly predicted RTs on the hand laterality judgement task, with the CRPS patients ($M = 1414$ msec, $SEM = 119$) an average of 163 msec slower than the controls ($M = 1251$ msec, $SEM = 70$). 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 ($M = 76.7\%$, $SEM = 2.4$, pooled across patients and controls). Reinersmann and her colleagues (2010) reported a similar generalized delay in the RTs of CRPS patients to pictures of hands (i.e., slower RTs 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 RTs by Group in the present study could reflect a deficit in

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3 Analyses were repeated with percentage scores subjected to an arcsine transformation. No qualitative change appeared and so we report the untransformed analyses for clarity.
body representation that generalises to representations of both hands (as was concluded by Reinersmann et al., 2010). We therefore decided to enter the mean RT 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.

Table 2
The results of the bootstrapped ($N = 1000$) regression of RTs on Group and Hand Picture for the hand laterality judgement task.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Coefficient estimate</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept*</td>
<td>1246.9</td>
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<tr>
<td>Group (controls = 0)</td>
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<td></td>
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<tr>
<td>Patients*</td>
<td>163.5</td>
<td>26.0</td>
<td>300.6</td>
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<tr>
<td>Hand Picture (affected/non-dominant = 0)</td>
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<td></td>
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<tr>
<td>Unaffected/dominant</td>
<td>12.6</td>
<td>-91.7</td>
<td>146.4</td>
</tr>
<tr>
<td>Group x Hand Picture (patients-controls, affected/non-dominant = 0)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients-controls, unaffected/dominant</td>
<td>-7.8</td>
<td>-164.0</td>
<td>124.4</td>
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</tbody>
</table>

Notes: 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)

Visual TOJ task

Fig. 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 CRPS patients’ PSS values were, numerically speaking, 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 CRPS patients 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 CRPS patients were significantly different from 0 in the no hands condition [t(23) = 3.4, P = .003; CI_{0.95} = [-43.5, -12.6]]. The PSS values for the CRPS patients in the uncrossed condition [t(23) = 1.8, P = .081, CI_{0.95} = [-32.2, 1.77]] and crossed condition [t(21) = 0.17, P = .87, CI_{0.95} = [-16.3, 15.7]] were not significantly different to 0. The PSS values for the control participants were not significantly different to 0 in the no hands condition [t(23) = 0.62, P = .54, CI_{0.95} = [-17.0, 7.4]], the uncrossed condition [t(23) = 1.5, P = .15, CI_{0.95} = [-14.3, 2.1]], or the crossed condition [t(23) = 1.06, P = .30, CI_{0.95} = [-19.0, 4.4]].

Table 3

<table>
<thead>
<tr>
<th>Effect</th>
<th>Coefficient estimate</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept*</td>
<td>78.3</td>
<td>74.7</td>
<td>81.8</td>
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</table>

* Group (controls = 0)

**Patients**

Hand Picture (affected/non-dominant = 0)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Coefficient estimate</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected/dominant</td>
<td>2.3</td>
<td>-1.3</td>
<td>6.8</td>
</tr>
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</table>

* Group x Hand Picture (patients-controls, affected/non-dominant = 0)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Coefficient estimate</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients-controls, unaffected/dominant</td>
<td>-1.9</td>
<td>-10.5</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Notes: 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)
Fig. 1. Cumulative data for the visual temporal order judgement (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 Points of Subjective Simultaneity (PSSs).

**PSS analysis**

Comparison of the CRPS and control groups. Group (control vs patient) was a significant predictor of the PSS (see Table 4). The PSSs for the patients ($M = -15.0$ msec, $SEM = 8.2$) were an average of 9 msec further towards the affected/non-dominant side of space relative to the control group ($M = -5.9$ msec, $SEM = 6.0$). In the no hands condition, the patients had a 22 msec bias relative to the controls. The coefficient estimate for the first Group x Hand Arrangement interaction term indicates that the performance difference between the patients and the controls in the uncrossed condition was an average of 13 msec 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 ($P > .05$). This means, statistically speaking, 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 x 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 msec. 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 [$t(44) = 0.58, P = .58, CI_{0.95} = [-13.9, 27.5]$]. This confirms that the patients’ performance in this condition was not significantly biased compared to the...
controls’. We consider the between-group performance difference to be most important for ascertaining whether the CRPS patients showed a bias in any given condition. However, it should be noted that a second post-hoc t-tests with bootstrapping ($N = 1000$ samples) that compared the PSS values of the patient group in the no hands and crossed conditions was also not significant [$t(21) = 2.17, P = .08, CI_{0.95} = [-53.0, -1.7]$].

Table 4
The results of the bootstrapped ($N = 1000$) regression of PSS on Group and Hand Arrangement.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Coefficient estimate</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-4.2</td>
<td>-14.0</td>
<td>5.1</td>
</tr>
<tr>
<td><em>Group (controls = 0)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients*</td>
<td>-22.4</td>
<td>-42.0</td>
<td>-4.0</td>
</tr>
<tr>
<td><em>Hand Arrangement (no hands = 0)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncrossed</td>
<td>-1.6</td>
<td>-13.1</td>
<td>9.5</td>
</tr>
<tr>
<td>Crossed</td>
<td>-3.1</td>
<td>-18.2</td>
<td>10.4</td>
</tr>
<tr>
<td><em>Group x Hand Arrangement (patients-controls, no hands = 0)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients-controls, uncrossed</td>
<td>13.0</td>
<td>-9.0</td>
<td>36.2</td>
</tr>
<tr>
<td>Patients-controls, crossed*</td>
<td>27.2</td>
<td>0.7</td>
<td>53.9</td>
</tr>
</tbody>
</table>

Notes: 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)

Neither of the Hand Arrangement terms (uncrossed vs no hands and crossed vs 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 explanatory variables for variation in PSS values for the CRPS patients. The only term that significantly predicted PSS was CRPS BPDS score, with PSS
shifting towards the affected side by 1.7 msec for every one point increase in body perception
disturbance score (see Table 5).

Table 5
The results of the bootstrapped ($N = 1000$) regression of PSS on the possible explanatory
variables for the CRPS patients’ data only.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Coefficient estimate</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>15.3</td>
<td>-51.5</td>
<td>83.1</td>
</tr>
<tr>
<td>Pain intensity</td>
<td>6.0</td>
<td>-1.0</td>
<td>12.7</td>
</tr>
<tr>
<td>CRPS BPDS*</td>
<td>-1.7</td>
<td>-2.6</td>
<td>-0.7</td>
</tr>
<tr>
<td>$Z_{Hand}$ laterality RT</td>
<td>-0.002</td>
<td>-0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Limb</td>
<td>-2.8</td>
<td>-30.4</td>
<td>26.6</td>
</tr>
<tr>
<td>$Z_{Handedness}$</td>
<td>4.4</td>
<td>-14.0</td>
<td>28.7</td>
</tr>
<tr>
<td>$Z_{Handedness}$ change</td>
<td>-0.02</td>
<td>-14.3</td>
<td>12.4</td>
</tr>
<tr>
<td>TSK</td>
<td>-0.8</td>
<td>-2.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Body-side</td>
<td>-1.9</td>
<td>-42.7</td>
<td>38.8</td>
</tr>
<tr>
<td>Weeks since diagnosis</td>
<td>0.03</td>
<td>-0.002</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Notes: CRPS BPDS = Bath CRPS Body Perception Disturbance Scale, TSK = Tampa Scale for Kinesiophobia, * = Significant predictor of PSS (95% CI around the coefficient estimate does not include 0)

Inspection of individual patterns in PSS 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 the upper- and lower-limb CRPS participants are represented in Supplementary Figs. 1 and 2.

Individual upper-limb CRPS patients 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 \([N = 8/35; \chi^2(1) = 8.6, P = .009; \text{ Bonferroni corrected}]\). Upper-limb CRPS patients were less likely \((N=6/35)\) to have PSS values indicating no significant bias in attention compared to lower-limb CRPS participants \([N = 17/35; \chi^2(1) = 7.8, P = .015]\). The incidence of PSS values that reflected a bias of attention towards the affected side was similar for the upper limb CRPS participants \((N = 9/35)\) and the lower limb CRPS participants \([N = 10/35; \chi^2(1) = 0.07, P = .788]\). Individual differences are further discussed in the Supplementary materials.

**JND data**

**Comparison of CRPS and control group data.** Group (control vs patients) was a significant predictor of JNDs (see Table 6). The JNDs were an average of 20 msec larger for patients \((M = 94.2 \text{ msec}, SEM = 11.1)\) than for the control group \((M = 74.9 \text{ msec}, SEM = 9.9)\). The second of the two Hand Arrangement terms (crossed vs no hands) was also a significant predictor of JNDs, with JNDs an average of 16 msec larger for the crossed condition \((M = 94.2 \text{ msec}, SEM = 10.0)\) than for the no hands condition \((M = 77.8 \text{ msec}, SEM = 6.5)\) when considered across both Groups. Neither term for the Group x Hand Arrangement interaction contributed significantly to the model, indicating that the difference in JNDs for CRPS patients compared to controls did not significantly vary as a function of the Hand Arrangement.

**Analysis of possible explanatory variables for variation in JND values for the CRPS patients.** Pain intensity and Weeks since diagnosis were significant predictors (see Table 7), with JNDs increasing by 14.9 msec for every one point increase in pain and decreasing by 0.05 msec for every Week since diagnosis (2.6 msec reduction per year).
Table 6
The results of the bootstrapped \((N = 1000)\) regression of JND on Group and Hand Arrangement.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Coefficient estimate</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept*</td>
<td>66.1</td>
<td>54.0</td>
<td>78.6</td>
</tr>
</tbody>
</table>

*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 x 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     |

Notes: 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)

Inspection of individual patterns in JND values. The individual JND values of the upper- and lower-limb CRPS patients are represented 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 upper- and lower-limb CRPS patients (See Supplementary materials).
Table 7
The results of the bootstrapped ($N = 1000$) regression of JND on the possible explanatory variables for the CRPS patients only.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Coefficient estimate</th>
<th>Lower $CI$</th>
<th>Upper $CI$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>5.8</td>
<td>-78.3</td>
<td>114.1</td>
</tr>
<tr>
<td>Pain intensity*</td>
<td>14.9</td>
<td>3.9</td>
<td>27.1</td>
</tr>
<tr>
<td>CRPS BPDS</td>
<td>-1.4</td>
<td>-3.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Hand laterality RT</td>
<td>-0.01</td>
<td>-0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Limb</td>
<td>-28.8</td>
<td>-63.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Handedness</td>
<td>14.6</td>
<td>-11.2</td>
<td>44.4</td>
</tr>
<tr>
<td>Handedness change</td>
<td>8.7</td>
<td>-4.3</td>
<td>19.6</td>
</tr>
<tr>
<td>TSK</td>
<td>1.3</td>
<td>-0.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Body-side</td>
<td>44.3</td>
<td>-8.6</td>
<td>100.8</td>
</tr>
<tr>
<td>Weeks since diagnosis*</td>
<td>-0.05</td>
<td>-0.1</td>
<td>-0.005</td>
</tr>
</tbody>
</table>

Notes: CRPS BBPS = Bath CRPS Body Perception Disturbance Scale, TSK = Tampa Scale for Kinesiophobia, * = Significant predictor of JND (95% $CI$ around the coefficient estimate does not include 0).

Discussion
We measured covert attention in CRPS patients 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, CRPS patients 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 (Berberovic et al., 2004; Rorden et al., 1997; 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 CRPS patients’ bias relative to controls when the hands are crossed.

In further analyses we examined which factors predicted attention bias in CRPS patients. 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 (D’Amour et al., 2015; Farnè et al., 2000; van der Hoort et al., 2011; Tamè et al., 2013). However, such an explanation for the relationship between body representation distortion and attention bias is negated by the fact that the CRPS patients 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 CRPS patients, 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 characterised 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 CRPS patients.

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 CRPS patients 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.

CRPS patients 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 (Attridge et al., 2015; Hart et al., 2000). It could be noted that the mean JNDs for the patients of 94 msec 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 msec; 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 (e.g., Van Damme et al., 2009; Shore et al., 2002). Nonetheless, we re-performed our main group analyses on a reduced dataset that excluded those conditions for which the JNDs had exceeded 120 msec (excluding 20% of the total data). The analysis of the reduced dataset replicated our main finding, of significantly leftward PSS values for CRPS patients compared to controls, but this bias did not vary between the three Hand Arrangement conditions. Future researchers who test CRPS patients 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 (e.g., De Paepe et al., 2014), or using a procedure that adjusts temporal offsets adaptively based on the participants’ responses (Berberovic et al., 2004; Filbrich et al., 2017; Stelmach and Herdman, 1991; Sternberg et al., 1971).

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 RTs on the hand laterality judgement task, an objective measure of body representation. Like Reinersmann and her colleagues (2010) we found that CRPS patients were significantly slower than controls in recognising pictures of upper limbs and that there were no differences in their RTs for pictures that corresponded to the affected vs. unaffected side of the body. Like the larger JNDs compared to controls, the slower RTs of CRPS patients 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 CRPS patients in the study by Reinersmann and colleagues (2010) showed no deficits in alertness or working memory. However, we conducted a follow-up analysis comparing RTs for upper- and lower-limb CRPS patients in the present study and found no difference between these groups,
whereas if the task measured limb representation we would expect slower RTs for the upper-limb patients. The differences in RTs between CRPS patients 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 CRPS patients 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 (Bultitude and Rafal, 2010; Christophe et al., 2016; Sumitani, Rossetti, et al., 2007) 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 (two metre) visual targets have not found evidence for a bias in attention away from the affected side, but towards the affected side (Sumitani et al., 2014; Sumitani, Shibata, et al., 2007; 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 leads 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 CRPS
patients 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 (TMS; Dambeck et al., 2006; Walsh et al., 1999). 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 (Lebel et al., 2008; Maihöfner et al., 2006, 2007), 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 (Cohen et al., 2013; Förderreuther et al., 2004; Lewis et al., 2010; Robinson et al.,
2011), and supports the existence of a relationship between spatial attention bias and
distortion of body perception in patients with this condition.
Acknowledgements

We would like to thank Annika Reinersmann and Christoph Maier for providing stimuli for the hand laterality judgement task; Nick Davis for providing suggestions on the manuscript; Leila Heelas, Tudor Phillips, and Candida McCabe for assistance with patient recruitment; and the participants for volunteering their time.

Funding

This study was supported by a grant from the Oxford University Press John Fell Fund to JHB (Grant number 121/461).
Supplementary Materials

Supplementary Methods

Data preparation for the TOJ task

The responses of one upper-limb CRPS patient (UL11) showed insufficient variability to fit the cumulative Gaussian for the uncrossed condition because she indicated that the light on the unaffected side preceded the light on her affected side in 95% of the trials. Nearest neighbour replacement was used to fill this empty datapoint: since this patient’s responses reflected a strong bias to state that the light on the unaffected side appeared first, the next-closest PSS value was taken as a conservative estimate of her PSS value for this condition. However, no JND was entered for this patient for the uncrossed condition since there was no way of estimating how small or large this would be. The same patient (UL11) had no discernible pattern to her responses across the different temporal offsets for the crossed condition and the cumulative Gaussian could not be fitted to these data. These patterns suggest possible difficulties in performing the task during this condition, which may be because of the cognitive difficulty associated with the incongruence between the side of space and the hand that the lights appeared on. Furthermore, one patient (LL07) declined to complete the crossed condition due to shoulder pain caused by holding her arms crossed over her body midline. No PSS or JND values were entered for these participants for these conditions because there was no way of estimating these from the available data.

Supplementary Results and Discussion

Individual patterns in PSS values

Separate bootstrapped (N=1000) 95% CIs were calculated around the control group’s PSS values for the no hands (CI_{0.95} = [-17.0, 7.4]), uncrossed (CI_{0.95} = [-14.3, 2.1]), and crossed (CI_{0.95} = [-19.0, 4.4]) conditions. The individual PSS values of the upper- and lower-limb CRPS participants were compared to these CIs and are represented in Supplementary Figs. 1 and 2, respectively. For visualization purposes, the figures include the 95% CI around the control data for the crossed condition, which was the widest CI for the controls out of the three Hand Arrangement conditions.
Supplementary Fig. 1. Individual PSS data for the upper-limb CRPS participants. X axes show PSS (in milliseconds), with negative values indicating that the light needed to appear earlier on the affected side of space in order for the two lights to be perceived as simultaneous. Light blue shading indicates the 95% CI around the mean PSS for control group responses in the crossed condition, which was the condition with the widest CI. UL = upper limb, NH = no hands, UN = uncrossed, C = crossed, ◊ = PSS is near to zero and therefore not visible in the figure, † = No PSS was obtained from this participant for this condition.

On an individual level, five patients (UL01, UL02, UL04, UL06, and LL05) showed some degree of inattention to the affected side in all three Hand Arrangement conditions, consistent with an attentional bias when processing general spatial information in near space. Four of the patients showed no significant bias in attention compared to controls for any of the three Hand Arrangement conditions (UL07, UL10, LL03, and LL08). The PSS values for two patients (UL12 and LL10) are consistent with a bias of attention towards the affected side of space in all Hand Arrangement conditions. We can thus infer that there may be different behavioural phenotypes of CRPS according to the nature of attention bias that is present.
Supplementary Fig. 2. Individual PSS data for the lower-limb CRPS participants. X axes show PSS (in milliseconds), with negative values indicating that the light needed to appear earlier on the affected side of space in order for the two lights to be perceived as simultaneous. Light blue shading indicates the 95% CI around the mean PSS for control group responses in the crossed condition, which was the condition with the widest CI. LL = lower limb, NH = no hands, UN = uncrossed, C = crossed, ◇ = PSS is near to zero and therefore not visible in the figure, † = No PSS was obtained from this participant for this condition.

Three patients showed patterns of PSS values that differed substantially across Hand Arrangement conditions. Patient UL09 showed a pattern of PSS values that is consistent with inattention to whichever side of space her affected limb is positioned in. Specifically, her results indicate inattention to the affected side in the no hands and uncrossed condition, but a bias of attention toward the affected side when her affected arm was placed in the unaffected side of space. Patient LL01 showed a somewhat similar pattern of results, with the exception that there was no bias of attention when her arms were crossed rather than a complete reversal.
of the attentional bias. These patterns indicate that in CRPS patients there may be individual differences in the extent to which inattention is anchored to the affected side of space or the hand of the affected side of the body. Finally, UL05 showed a bias of attention away from the affected side of space in the no hands condition, towards the affected side of space in the uncrossed and crossed condition. This pattern of results is consistent with inattention to general visual information on the affected side of near space but attentional capture to bodily information for whichever hand is placed within the affected side of near space. Although we observed this pattern in only one patient, it demonstrates a proof of concept that, somewhat paradoxically, a patient might experience inattention to general visual information in the side of near space that is normally occupied by their affected limb, and also hypervigilance to bodily-specific visual information located within the affected side of space. The individual differences, both with regards to the presence or absence of attention bias and its manifestation for different types of information, may be relevant for the implementation of therapies that target attention, such as prism adaptation.

Individual patterns in JND values

Separate bootstrapped (N=1000) 95% CIs were calculated around the control group’s JND values for the no hands (CI_{0.95} = [53.5, 80.7]), uncrossed (CI_{0.95} = [51.8, 85.3]), and crossed (CI_{0.95} = [66.3, 121.8]) conditions. The individual JND values of the upper- and lower-limb CRPS participants are represented in Supplementary Figs. 3 and 4, respectively, along with the 95% CI around the control data for the crossed condition (i.e., the widest CI for the controls out of the three Hand Arrangement conditions).

There was no difference between the proportion of responses from upper-limb (N = 14/34) compared to lower-limb CRPS patients (N = 14/35) that indicated JNDs that were higher than the higher bound of the control group’s 95% CI ($\chi^2(1) = .01, P = 1.0$). There was also no difference between the proportion of responses from upper-limb (N = 13/34) compared to lower-limb CRPS patients (N = 12/35) that indicated JNDs that were within the control group’s 95% CI ($\chi^2(1) = 0.12, P = .81$). Similarly, there was no difference between the proportion of responses from upper-limb (N = 7/34) compared to lower-limb CRPS patients (N = 9/35) that indicated JNDs that were lower than the lower bound of the control group’s 95% CI ($\chi^2(1) = 0.25, P = .78$).
Supplementary Fig. 3. Individual JND data for the upper-limb CRPS participants. Y axes show JND (in milliseconds). Light blue shading indicates the 95% CI around the mean JND for control group responses in the crossed condition, which was the condition with the widest CI. UL = upper limb, NH = no hands, UN = uncrossed, C = crossed, † = No JND was obtained from this participant for this condition.
Supplementary Fig. 4. Individual JND data for the lower-limb CRPS participants. Y axes show JND (in milliseconds). Light blue shading indicates the 95% CI around the mean PSS for control group responses in the crossed condition, which was the condition with the widest CI. LL = lower limb, NH = no hands, UN = uncrossed, C = crossed, † = No JND was obtained from this participant for this condition.
References


Cohen HS, McCabe CS, Harris N, Hall J, Lewis JS, Blake DR. Clinical evidence of parietal
17: 527–538.

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain.


Interhemispheric imbalance during visuospatial attention investigated by unilateral and

Van Damme S, Gallace A, Spence C, Crombez G, Moseley GL. Does the sight of physical
threat induce a tactile processing bias? Modality-specific attentional facilitation induced by

Eccleston C. Chronic pain and distraction: An experimental investigation into the role of
sustained and shifting attention in the processing of chronic persistent pain. Behav. Res. Ther.

Farnè A, Pavani F, Meneghello F, Làdavas E. Left tactile extinction following visual

Filbrich L, Alamia A, Burns S, Legrain V. Orienting attention in visual space by nociceptive
stimuli: investigation with a temporal order judgment task based on the adaptive PSI method.
Exp. Brain Res. in press.

Filippopulos FM, Grafenstein J, Straube A, Eggert T. Complex regional pain syndrome
(CRPS) or continuous unilateral distal experimental pain stimulation in healthy subjects does
not bias visual attention towards one hemifield. Exp. Brain Res. 2015; 233: 3291–3299.


Longo MR, Azañón E, Haggard P. More than skin deep: Body representation beyond primary


12 Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory.


R Core Team. R: A language and environment for statistical computing. 2015


Shiraishi H, Muraki T, Sampei Y, Itou A, Hirayama K. Prism intervention helped sustainability of effects and ADL performances in chronic hemispatial neglect: A follow-up


Tamè L, Farnè A, Pavani F. Vision of the body and the differentiation of perceived body side


7 Walsh V, Ellison A, Cowey A, Ashbridge E. The role of the parietal cortex in visual attention - hemispheric asymmetries and the effects of learning: a magnetic stimulation study.