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Highlights

- The relative weighting of bimanual and unimanual brain processing in CRPS is unknown.
- We used a novel perceptual illusion to explore this issue.
- The illusion was weaker in people with CRPS than it was in controls.
- Adding tactile data normalised the response, suggesting clinical implications.

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A novel finger illusion reveals reduced weighting of bimanual hand cortical representations in people with complex regional pain syndrome.

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Abstract

Complex regional pain syndrome (CRPS) is associated with deficits in sensorimotor control. Here we used a novel finger illusion to investigate whether CRPS is associated with reduced weighting of bimanual hand representations. The illusion normally induces a compelling feeling that the hands are close together when in fact they are 12cm apart. People with CRPS and age, gender and dominant hand-matched controls tested the illusion in the midline then on either side of the midline. The illusion had two variants; the passive pincer-grip position, without contact ('No Grasp'), and with contact ('Grasp'), of the artificial finger. The primary outcome was the perceived vertical distance between the index fingers. Twenty CRPS and 20 controls participated (mean (SD) age 44.4±11.7 years). During No Grasp, CRPS participants perceived the vertical distance significantly closer to the actual 12cm (mean [95% CI] = 8.0cm [6.5 - 9.5cm]), than controls did (6.4cm [5.5 – 7.2cm]). That is, the illusion was weaker in people with CRPS than in controls during No Grasp. There was no such difference during Grasp – that is, both groups showed the predicted illusion response. There was no effect of hand placement relative to midline or relative to the opposite hand. We conclude that people with unilateral CRPS have lower weighting of bimanual hand representation than controls have, independent of hand location. However, adding additional cutaneous input returns those with CRPS to the expected performance. We suggest the results have clear clinical and research implications.

Perspective: An abnormal weighting of bilateral hand representation may reflect a vulnerability for chronic CRPS, an adaptation to the disease, and/or a potential therapeutic target. That addition of cutaneous input immediately normalises the problem points to the possible role of bimanual tasks in prevention or rehabilitation.

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Introduction

Complex regional pain syndrome (CRPS) is characterised by excessive pain, usually in a peripheral limb such as the hand, and affects sensation, movement and function [32]. Quantified deficits include higher thresholds for two-point discrimination in the index finger [45], impaired hand size estimation [35, 44], finger misidentification [14, 33], tactile processing disturbances [28]; errors in bilateral limb positioning [30], fine motor [26] and motor imagery performance [34, 49, 50]. These deficits implicate distortions in body representation [53] and are corroborated by evidence of cortical re-organisation in CRPS [9, 10], although much remains unclear [29].

Several known sensorimotor deficits in CRPS are also associated with both the affected limb and the side of space in which the affected limb usually resides. These problems include spatially-defined prioritisation of tactile stimuli [38], midline-dependent changes in thermoregulation [36], spatial judgement performance [47], motor imagery [47] and spontaneous pain and the sense of ownership over the limb [37]. These disruptions were conceptualised in terms of the cortical body matrix [39] - an integrative model involving a dynamic neural representation of the body and the space around it. The available literature including case reports on CRPS [6, 16, 17], suggest a causal link between disrupted body representation in CRPS and pain [19].

During a bimanual task, the reliability of a given sensory channel determines its influence on proprioception, such that the least reliable input is sometimes discarded completely [5, 24, 25, 51, 56]. The weighting of proprioceptive information from each hand also depends on the relative reliability of each input [56] and performance of each hand depends on the relative influence of interhemispheric inhibition and coordination [54]. These various contributors to performance are all critical for optimal motor and sensory function [8, 42]. That people with unilateral upper limb CRPS show poor bilateral motor and sensory function raises these processes as unexplored potential contributing mechanisms.

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We aimed to determine whether people with unilateral CRPS of the upper limb have reduced weighting of bimanual hand representations. Our secondary aims were to determine whether there are differential effects according to where, in space, the limbs are located. To test these predictions, we used two versions of a novel finger illusion [23]. In one version, with the two hands aligned on the body midline but 12 cm apart vertically, healthy people feel their hands to be closer together than they really [8] and the magnitude of this effect is thought to reflect the relative weighting of bimanual ('pulling' the perceived location of the hands towards each other) and unimanual (accurately reflecting each hand's location) representations. In the other version, tactile input is added and the illusion is strengthened. This version integrates input from a single class of cutaneous receptors and has been shown to influence both perceived body position and the sense of ownership [22]. Our primary hypotheses were that people with CRPS would show a weaker finger illusion and a lower sense of ownership over the artificial finger, both indicative of reduced weighting of bimanual representations.

Methods

Recruitment and Ethics

Recruitment of participants to this observational study was by convenience sampling. Participants were recruited into the study through advertising from the Australian states of Victoria, Queensland, South Australia, New South Wales, and included a concurrent Sydney-based study investigating recovery following wrist and hand fractures [43]. Participant consent and all experimental procedures were carried out in accordance with the Declaration of Helsinki (2008). The University of New South Wales Human Research Ethics Committee (HC13214) and South Eastern Local Health District Ethics Committee (HREC 10/051) approved the study.

Participants

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Telephone screening, consent and assessment procedures were separated. Responders to the advertisement, aged 18 to 89 years with sufficient command of the English language for the study, were included for preliminary telephone screening, which involved exclusion criteria (pregnancy; any other areas of significant pain (for participants with CRPS); and any significant medical disorders that the experimenters felt, *a priori*, would impact on their participation) and symptomatic criteria for CRPS [20]. Suitable participants were invited for an assessment of CRPS diagnostic criteria [20] at the investigational site or at their home by another researcher. Each assessment result was re-checked against the study criteria by a different researcher who was also blinded to any previous clinical diagnosis of CRPS in the participants. As participants with CRPS had one affected hand or upper limb, their other hand or upper limb was regarded as their "unaffected" hand or side. Healthy pain-free participants were included if they had no previous history of a chronic pain disorder, excessive medication or drug usage and were currently pain-free. Healthy pain-free participants were matched with CRPS participants for potential confounders : age, gender and hand dominance as evaluated by the Edinburgh Handedness Inventory Questionnaire [41].

Experimental procedure

Equipment

A custom made box (length 50 cm, width 30 cm, height 15 cm), with two platforms: an upper and lower platform, each covered with memory foam (1 cm thick) on which to place the forearms and hands, was placed on a table in front of a height adjustable chair but concealed with drapery. Inside the box was a rigid metal shaft with an artificial finger attached perpendicular to the shaft at its top. This artificial finger was made from silicone with a narrow rigid plastic cylinder (diameter 0.5 cm, length 3 cm) running down the inside of the finger like a bone. The distance from the artificial finger to the mid-point of the pipe was 12 cm. A small pipe (2.5 cm diameter, length 5 cm) was attached perpendicular to the shaft at its bottom.

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A chart holder was placed at eye-level, in front of the participant. Each chart had 21 randomly ordered distance markers ranging in height from 0 to 21 cm (Fig. 1). A different chart was used for every assessment.

Assessment variables and conditions

There were two primary outcomes. First, an estimate made by the participant, of the vertical distance between their two index fingers. This estimate was made by matching what the distance *felt* like, with one of the distance markers shown on the chart holder. Second, participants rated their sense of finger ownership using a 7-point Likert scale chart (Fig. 5).

Workspace

We defined three ‘workspaces’: centre (on the body midline), unaffected side (or matched unaffected side for controls), and affected side (or matched affected side for controls). For example, for a participant with CRPS of their right hand, the space to the right of the body midline was defined as the Affected Workspace; for the matched control participant, the space to the right of body midline was defined as the matched Affected Workspace.

Hand

Conditions were labelled according to whether the affected or unaffected hand was placed on the top platform.

No Grasp and Grasp condition

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The No Grasp condition involved the researcher's hand guiding the fingers of the participant's top hand, to be adjacent to, but not grasping the artificial finger (Figure 1B). The Grasp condition was similar except that the researcher guided the participant's fingers to passively grasp the artificial finger in a pincer grip (Figure 1C).

Procedure

Each participant sat in front of the table in a human systems research laboratory at Neuroscience Research Australia, Sydney. The researcher sat directly opposite the participant, obscured from view by a dark partition (Figure 1A). This position allowed the researcher to manipulate the participant's hand posture under the screen. Both hands of the participant were passively placed in a box, with one arm on the lower platform and the other 12 cm above on the upper platform. A screen and drapery over the box concealed their hands and the experimental apparatus.

All assessments were tested in the Centre Workspace first. Testing was then randomised to either the Affected or Unaffected Workspace (Fig. 1). Hand placement (upper and lower) was randomised for each workspace.

Figure 1 about here

The protocol is described here using an example of the 'right hand of the participant within the centre workspace': the right forearm and hand rested semi-pronated on the lower platform inside the box. The distal and middle segments of the right index finger (referred to as the fixed index finger) were then wrapped in a piece of neoprene and placed snugly in the pipe attached to the bottom of the shaft. The shaft was aligned with the approximate axis of the proximal interphalangeal joint of both the artificial finger and the participant's finger in the pipe. The researcher ensured that there was adequate padding below each hand and that there was no skin touching the steel shaft or the box at any time.

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During testing, the researcher estimated the mid-point tip of the top index finger to ensure adequate positioning and ensured their own limbs (e.g. elbow) were supported to reduce the effect of intermittent vibrations or tremors for feedback. The distance from the artificial finger to the mid-point of the pipe in which the participant's index finger was placed was 12 cm.

Finger illusion and Assessment Order

The *finger illusion* was assessed first in the No Grasp condition, and then in the Grasp condition. The rating of the artificial finger ownership was obtained only during the Grasp condition

No Grasp condition

First, the researcher placed the participants finger and thumb in the No Grasp position (Figure 1, bottom left). The researcher instructed the participant to look at the chart (Figure 1B) and to estimate the perceived vertical distance as follows: *"Looking at this chart, which line represents the vertical distance between the tip of your left index finger and the tip of your right index finger?"* The participant was asked to estimate the vertical distance between their index fingers immediately by choosing a line on the chart.

Grasp condition

The researcher placed the participant's index finger and thumb in a passive pincer grip over the artificial finger (Figure 1C). Again, the participant was asked to estimate the vertical distance between their index fingers immediately by choosing a distance marker on the chart.

Rating of artificial finger ownership

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Embodiment of the artificial finger during the Grasp condition was interrogated with finger ownership statements. The researcher read out either one of the two statements depending on which 'finger' was held: *"Looking at this chart how strongly do you agree or disagree with this statement:* I feel that I am holding my right index finger with my left hand" or *"Looking at this chart how strongly do you agree or disagree to this statement*: I feel that I am holding my left index finger with my right hand". Participants rated their level of agreement using a 7-point Likert scale.

The participant's hands were removed from the box after the assessments were completed. They were reminded to look at their hands during the 2 minute break. Assessments were repeated so that data were collected in each of six conditions, which involved the two hand positions (upper platform and lower platform) and the three workspaces (Unaffected, Centre and Affected). The order of the remaining five conditions was randomised.

Data and Statistical Analysis

Data management

Pairs (participant and control) were matched for dominance, rather than matching the dominant hand of controls to the unaffected hand of CRPS participants. The independent variables were: *Pain* grouping (CRPS or healthy control), *Workspace* (Unaffected, Centre or Affected) and top *Hand* location (unaffected or affected). The dependent variables were: the perceived vertical distance between the fingertips, called 'Distance', and finger ownership rating.

Statistics

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Our *a priori* plan was to undertake mixed model analyses. However, statistical advice after data collection (but before initial analysis) was to change this approach. As such, each dependent variable was subjected to a repeated measures analysis of variance (ANOVA), the repeated measures being the scores of the two members of each matched pair in each experimental condition. This analysis yields a Between-Pairs component, not bearing on the effects of the test conditions, and a Within-Pairs component testing the effects of Group (2 levels - CRPS vs control), Workspace (3 levels - Centre, Affected and Unaffected), Hand (2 levels - affected and unaffected), and No Grasp or Grasp, and the interactions of these four factors. The effects of chief interest were the interactions with the effect of Group for the hypotheses.

The analysis used the SPSS computational procedure called multivariate analysis of variance (MANOVA), to test the differences across dependent variables simultaneously. If the Mauchley test was significant, non-sphericity was corrected with a Greenhouse-Geisser estimate used to adjust to the degrees of freedom of the F-ratio in the repeated measures ANOVA.

We investigated (1); the accuracy of the perceived location in the No Grasp condition (Group x No Grasp) and (2) the Grasp condition (Group x Grasp) using the reported vertical distance between the index fingers in CRPS and controls. Then, we tested if the weakness of the illusion (Group x Workspace x Hand) between CRPS and controls, in each condition (No Grasp and Grasp) was influenced by an interaction between the affected Hand and side of Workspace. For the second hypothesis, we tested if people with CRPS would have a weaker sense of ownership over the artificial finger, than that reported by controls (Group x Workspace x Hand).

Any significant interactions found with the repeated measures factorial ANOVA were followed up with post-hoc simple contrasts. Statistical power and effects sizes, using partial ETA-squared (η^2_ρ), were calculated. Data are presented as means with 95% CI where appropriate. All tests were carried out using SPSS (version 22: SPSS Inc., Chicago, IL, USA) with $\alpha = 0.05$.

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Results:

Twenty-one age, gender and dominance-matched pairs consented for the study (36 female, 6 male, mean (SD) age 44.4±11.7 years). Data from the 20 of the original 21 matched pairs were included for the final analysis of all experimental conditions. One CRPS participant did not complete the side workspaces assessments. There were 10 left hand affected CRPS participants and 10 right hand affected CRPS participants. Among them, there were nine participants with non-dominant affected upper limb CRPS and 10 participants with dominant affected upper limb CRPS and one participant who reported they were ambidextrous and scored borderline right-handedness on the Edinburgh Handedness Questionnaire.

Analysis confirmed that the data were normally distributed. The results are presented in the order of the hypotheses tested.

(1) First hypothesis – No Grasp condition

For No Grasp, all participants perceived the distance between their index fingers to be less than the actual distance of 12 cm (Fig. 2). CRPS participants perceived their index fingers to be further apart at a mean (95% CI) of 8.0cm (6.5 - 9.5cm), than the controls did at 6.4cm (5. 5 - 7.2cm) regardless of the Workspace used (main effect of Pain - $F(1,19) = 4.82$, $p = 0.041$, $\eta^2_\rho = 0.202$, power= 0.550).

FIG 2 ABOUT HERE

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The post-hoc contrast on CRPS data only, comparing affected and unaffected hands in the Affected and Unaffected Workspace, revealed the perceived vertical distance between index fingers at 'No Grasp' was significant, ($F(1,19) = 6.13$, $p = 0.023$, $\eta^2_\rho = 0.244$, *power* = 0.651). This result was modulated by the orientation of the hands and the Workspace in which the task was conducted – specifically, which hand was on the top platform in which workspace (Fig. 3). The perceived vertical distance with the CRPS-affected hand on the top platform in the Affected Workspace was 8.10 cm (6.13, 10.07) and 6.68 cm (5.08, 8.27) in the Unaffected Workspace. In contrast, the CRPS-unaffected hand on the top platform in the Affected Workspace had a perceived distance of 6.65cm (4.67, 8.63) and 8.58cm (6.54, 10.61) in Unaffected Workspace. Hence, the perceived vertical distance at 'No Grasp' appeared to be dependent on both the hand placement at the top platform and which type of side workspace (Fig. 3). However, individual post hoc t-tests failed to detect which factor(s) were mediating the interaction.

FIG 3 ABOUT HERE

(2) First hypothesis- Grasp condition

The perceived vertical distance at Grasp finger position for CRPS participants was similar at 5.2cm (3.9 - 6.4cm) to that found in controls at 4.9cm (4.1 – 5.7cm) (Fig. 4). There were no significant differences between CRPS participants and controls, $F(1,19) = 0.15$, $p = 0.699$, $\eta^2_\rho = 0.008$, *power* = 0.059.

(3) First hypothesis- Weakness of finger illusion and the influence of side workspace and hand

Although we previously investigated whether this illusion is weaker in people with CRPS than in matched healthy controls, we also wanted to determine if there was an influence of Workspace and Hand type. However, we did not find enough evidence to suggest the illusion was weaker in CRPS due to an influence of side Workspace or Hand type in perceived vertical distance in either No Grasp or Grasp condition.

For No Grasp condition, Mauchly's test assumption showed that the assumption of sphericity was violated for the interaction effect of Pain by Workspace by Hand ($X^2(2) = 7.87$, p = .020). Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.739$) was used to adjust for the degrees of freedom The influence of side Workspace or Hand type on the effect of No Grasp condition were not significantly different between the groups; No Grasp- Group x Workspace x Hand interaction , F (2,38) =0.51, $p = 0.603$, $\eta^2_\rho = 0.033$, power= 0.197). For Grasp condition, Mauchly's test assumption of sphericity was met. The same interaction was also not significant between groups in the Grasp condition; Grasp- Group x Workspace x Hand interaction, F (2,38) =0.72, p = 0.495, $\eta^2_\rho = 0.013$, power = 0.112).

FIG 4 ABOUT HERE

In summary, our analysis of the first hypothesis found the only difference between CRPS and controls was for perceived vertical distance of the 'finger' illusion during the initial condition of No Grasp. Both CRPS and controls experienced a reduction in perceived vertical distance from the actual distance, indicating a strong finger illusion effect in both groups for Grasp. There were no significant group interaction effects for Workspace and Hand position on perceived vertical distance in either condition.

Second hypothesis

Our secondary hypothesis was a lower sense of ownership over the artificial finger in CRPS participants than in controls. Mauchly's test assumption of sphericity was violated for the interaction effect of Pain by Workspace ($X^2(2) = 7.97$, $p < 0.05$). Greenhouse-Geisser estimates of sphericity (ε = 0.734) was used to adjust for the degrees of freedom. There was no significant difference between CRPS participants and controls on subjective ratings of finger ownership, F (1,19)= 1.96, p= 0.177 , η^2_ρ= .094, *power* = 0.265, and no significant interactions (Pain by Workspace F (1, 19) = 0.000, p=

1.00, η^2_ρ = 0.031 and Pain by Hand F (1,19)= 1.66, p= 0.214, η^2_ρ= 0.080). The pooled mean rating for finger ownership in CRPS was 5.4 (*95 % CI*: 4.8 - 6.0) and in controls was 5.8 (*95 % CI:* 5.3 - 6.3) shown in Figure 5.

Fig 5 about here

Discussion

We hypothesised that people with CRPS would show a weaker illusion than controls, indicative of lower weighting of bimanual representations. The results are in part supportive; those with CRPS perceived their fingers to be further apart than the controls did during the No Grasp condition of the illusion. The second main hypothesis – that CRPS patients would have a weaker sense of ownership over the artificial finger, was not supported. Our results suggest that people with unilateral CRPS have reduced weighting of bimanual representations but the deficit can be quickly overcome by adding cutaneous input that is consistent with bimanual activity, as reflected in the Grasp condition. We did not detect a difference between those with left or right sided CRPS, but our secondary analyses for 'No Grasp' did suggest an interesting effect of which hand was where and on which side of the body midline the task was undertaken. We were not powered to quantify this effect further, but that interactions between spatial deficits and side-to-side imbalances might be at play seems consistent with recent discoveries in this population [47, 48] (although the full picture of spatial processing in CRPS is unclear [7, 52 13]) and worthy of further investigation.

Our results in controls are consistent with previous observations of this artificial finger illusion [21, 23]. People with CRPS demonstrated a deficit in the expected systematic bias for the illusion for the No grasp condition but not for the Grasp condition. We suggest this difference between conditions is because the Grasp condition adds cutaneous input – the top index finger holds an artificial finger while the bottom index finger is held in a tube. The degree of synchrony between stimuli, rather than the number of sensory modalities involved, is thought to be important in such illusions [55]. That perceived distance between fingers is reduced, but ownership ratings not affected is also consistent with the original 'finger' illusion [23]. That is, participants do not agree that they own the artificial finger (Fig. 5). This might be explained thus: illusions that use synchronous multimodal input, such as the rubber hand illusion, [4] exploit the brain's predilection to associate two simultaneous stimuli with the same sensory event. The artificial finger illusion used here rather exploits the brain's predilection to associate both hands to the same task or location if they are positioned in a manner consistent with that. In other words, we are exploiting the normal heavy weighting of bimanual representations.

That the weighting of bimanual representations is reduced in CRPS supports previous assertions that cortical processes contribute to the syndrome of multiple system dysfunction [9, 10]. There is a large literature on the role of collaboration and competition between cortical hand representations when the hands are used together or singularly[40]. That is, during two-handed tasks, which usually occur around the body midline, the side-specific representations collaborate; during single-handed tasks, the active hand representation inhibits its contralateral counterpart - working in competition - in order to prevent the other hand from interfering with the task[40]. This ongoing balance between representations is critical for optimal function. Relevant here is the cortical body matrix model, which integrates spatial processing as well such that cortical representations of peripersonal space relative to the body midline, interact with regulatory, sensory and motor representations and have measurable impacts on bodily awareness, blood flow and histamine reactivity[39]. Neuroanatomical characteristics of complex cortical representations such as those representing bimanual versus unimanual tasks, or spatial processing, have been proposed[39] but remain to clearly demonstrated.

Disrupted relative weighting of bimanual and unimanual representations might be intuitively sensible when one considers that people with CRPS can drastically limit use of their affected limb. However, abnormal primary sensory cortex (S1) responses to tactile stimuli in CRPS – broadly captured by alterations in the size of the affected and/or unaffected hand's representation in S1 [10, 11] (although available data rely on Euclidean distances between digits, which leaves some doubt over this issue) – are not immediately explained by self-reported changes in use [12]. That S1 abnormalities

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might resolve when CRPS symptoms resolve [31, 46] seems consistent with use-dependence, but other mechanisms could contribute to the problem. The use-dependent theory is also consistent with abnormalities in primary motor cortex representation of the hands in CRPS [9]. Longitudinal data are required to verify these possibilities.

This 'finger' illusion may have clinical utility. The illusion was easily induced passively (within seconds), and was tolerable for CRPS participants despite their allodynia. The illusion avoids repeated tactile stimulation (e.g. brushing). Patients with CRPS can find such stimuli intolerable and they run the risk of inducing 'wind up' and thus augment allodynia and hyperalgesia. We used a bespoke system but development of a patient-friendly version of our paradigm is possible. Whether the extent of the illusion during the No Grasp condition relates to symptoms or has clinical utility remains to be determined, but certainly seems worth investigating.

How should we interpret the differences in the two conditions of the finger illusion and possible effects on the weighting of bimanual hand representations? The most likely explanation is that grasping might provide proprioceptive input that is additionally synchronous and congruent. This may be enough to enhance the weighting of the bimanual hand representations and overcome the deficit that is present in CRPS. This, too, may have clinical implications; perhaps the addition of bimanual tasks in which the fingers of both hands work against each other will facilitate re-weighting of bimanual representations; perhaps the anecdotal observation that some people find great functional benefit in compression garments even when they are not swollen reflects an enhancing effect of added tactile input.

Limitations and future directions

We encountered minor difficulties with matching and completion of all conditions: one CRPS participant agreed to participate in the centre workspace trials but not the trials in the two other

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workspaces, so this participant and their matched pair could not be included in the final repeated measures ANOVA for matched pairs in the side workspaces. A procedural error meant that we had one pair in which the CRPS patient was much older (72 years) than the control (46 years), but visual inspection indicated this did not influence the main results.

Our paradigm required us to undertake the No Grasp condition first. This may have introduced an order effect. We tested whether two consecutive trials would systematically effect distance judgments and found that there was no effect of assessing distance twice (see Supplementary Information). That the effect was observed across workspaces also argues against an order effect, but randomising the order of conditions could fully exclude this possibility. Post-experiment interviews revealed interesting considerations for future work. Two participants reported feeling that their fingers had drifted apart horizontally. We did not formally assess perceived horizontal distance drift during the experiment. We also acknowledge that the order of workspace always begun with the centre workspace, although Affected and Unaffected workspace was randomised. We made this decision *a priori* because of extensive evidence that working in one side of space could induce temporary perceptual changes in healthy controls [2, 3], and that hands crossing over the midline can change nociceptive processing in healthy controls [18] and induce changes in tactile processing [38], temperature regulation [36] and sense of ownership [37] in people with unilateral CRPS.

We did not account for attention and memory effects on the outcome measures during the experiments, although we did not see a systematic effect of time on our results. For example, the timing of the artificial finger ownership rating immediately after asking the perceived vertical distance at Grasp condition might explain our lack of differences between groups due to attentional modulation for rapid task switching. We are unable to entirely exclude the possibility of other mechanisms – perhaps the No Grasp condition was influenced by attentional effects associated with pain which resolved for the Grasp condition. Further studies could verify this. Further studies could also verify whether the effects we have observe are idiosyncratic to CRPS, or are also present in neuropathic or non-neuropathic hand pain. That dysynchiria is observed in CRPS [1] but not neuropathic hand pain [27]

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raises the possibility of an idiosyncratic phenomenon, but further studies are clearly required. Finally, although we had an *a priori* protocol and analysis plan, we did not publish it, which is now a standard for transparency in science [15]. We have noted deviations from our original protocol but we acknowledge that the failure to publish the protocol *a priori* is an important oversight.

Conclusion:

This study supported the hypothesis that people with CRPS would show a weaker illusion, but not the hypothesis that they would have a lower sense of ownership over the fake finger. Participants with CRPS performed in a similar fashion to healthy controls when additional cutaneous input was introduced during the Grasp condition, suggesting that the deficit could be compensated for in CRPS. We suggest that bimanual hand representation is impaired in unilateral upper limb CRPS. We also suggest that further interrogation of the finger illusion used here may lead to possible clinical therapeutic benefit.

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References

1. Acerra NE, Moseley GL. Dysynchiria: watching the mirror image of the unaffected limb elicits pain on the affected side. *Neurology.* 65:751-753, 2005

2. Azanon E, Longo MR, Haggard P, Soto-Faraco S. Disrupting tactile spatial transformations with TMSE. *Perception.* 38:143-144, 2009

3. Azanon E, Longo MR, Soto-Faraco S, Haggard P. The Posterior Parietal Cortex Remaps Touch into External Space. *Curr. Biol.* 20:1304-1309, 2010

4. Botvinick M, Cohen J. Rubber hands 'feel' touch that eyes see. *Nature.* 391:756, 1998

5. Buckingham G, Binsted G, Carey DP. Bimanual reaching across the hemispace: which hand is yoked to which? *Brain Cogn.* 74:341-346, 2010

6. Bultitude JH, Rafal RD. Derangement of body representation in complex regional pain syndrome: report of a case treated with mirror and prisms. *Exp. Brain Res.* 204:409-418, 2010

7. Bultitude JH, Walker I, Spence C. Space-based bias of covert visual attention in complex regional pain syndrome. *Brain.* 140:2306-2321, 2017

8. Butler AA, Heroux ME, Gandevia SC. Body ownership and a new proprioceptive role for muscle spindles. *Acta Physiol (Oxf).* 220:19-27, 2017

9. Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, Stanton TR. Primary motor cortex function in complex regional pain syndrome: a systematic review and meta-analysis. *J. Pain.* 14:1270-1288, 2013

10. Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, Stanton TR. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. *J. Pain.* 14:1001-1018, 2013

11. Di Pietro F, Stanton TR, Moseley GL, Lotze M, McAuley JH. Interhemispheric somatosensory differences in chronic pain reflect abnormality of the Healthy side. *Hum. Brain Mapp.* 36:508-518, 2015

ACCEPTED MANUSCRIPT

12. Di Pietro F, Stanton TR, Moseley GL, Lotze M, McAuley JH. An exploration into the cortical reorganisation of the healthy hand in upper-limb complex regional pain syndrome. *Scand J Pain.* 13:18-24, 2016

13. Filbrich L, Alamia A, Verfaille C, Berquin A, Barbier O, Libouton X, Fraselle V, Mouraux D, Legrain V. Biased visuospatial perception in complex regional pain syndrome. *Sci Rep.* 7:9712, 2017

14. Forderreuther S, Sailer U, Straube A. Impaired self-perception of the hand in complex regional pain syndrome (CRPS). *Pain.* 110:756-761, 2004

15. Foster ED, Deardorff A. Open Science Framework (OSF). *J. Med. Libr. Assoc.* 105:203-206, 2017

16. Frettloh J, Huppe M, Maier C. Severity and specificity of neglect-like symptoms in patients with complex regional pain syndrome (CRPS) compared to chronic limb pain of other origins. *Pain.* 124:184-189, 2006

17. Galer BS, Jensen M. Neglect-like symptoms in complex regional pain syndrome: results of a self-administered survey. *J. Pain Symptom Manage.* 18:213-217, 1999

18. Gallace A, Torta DM, Moseley GL, Iannetti GD. The analgesic effect of crossing the arms. *Pain.* 152:1418-1423, 2011

19. Haggard P, Iannetti GD, Longo MR. Spatial sensory organization and body representation in pain perception. *Curr. Biol.* 23:R164-176, 2013

20. Harden RN, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine JJ. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. *Pain.* 150:268-274, 2010

21. Heroux ME, Bayle N, Butler AA, Gandevia SC. Time, touch and temperature affect perceived finger position and ownership in the grasp illusion. *J. Physiol.*, 2017

ACCEPTED MANUSCRIPT

22. Heroux ME, Bayle N, Butler AA, Gandevia SC. Time, touch and temperature affect perceived finger position and ownership in the grasp illusion. *J. Physiol.* 596:267-280, 2018

23. Heroux ME, Walsh LD, Butler AA, Gandevia SC. Is this my finger? Proprioceptive illusions of body ownership and representation. *J. Physiol.* 591:5661-5670, 2013

24. Iandolo R, Squeri V, De Santis D, Giannoni P, Morasso P, Casadio M. Proprioceptive bimanual test in intrinsic and extrinsic coordinates. *Front Hum Neurosci.* 9:72, 2015

25. Kelso JA, Southard DL, Goodman D. On the coordination of two-handed movements. *J. Exp. Psychol. Hum. Percept. Perform.* 5:229-238, 1979

26. Kolb L, Lang C, Seifert F, Maihoefner C. Cognitive correlates of neglect-like syndrome in patients with complex regional pain syndrome. *Pain.* 153:1063-1073, 2012

27. Kramer HH, Seddigh S, Lorimer Moseley G, Birklein F. Dysynchiria is not a common feature of neuropathic pain. *Eur. J. Pain.* 12:128-131, 2008

28. Kuttikat A, Noreika V, Chennu S, Shenker N, Bekinschtein T, Brown CA. Altered Neurocognitive Processing of Tactile Stimuli in Patients with Complex Regional Pain Syndrome (CRPS). *The Journal of Pain.*

29. Legrain Vr, Bultitude JH, De Paepe AL, Rossetti Y. Pain, body, and space: What do patients with complex regional pain syndrome really neglect? *Pain.* 153:948-951, 2012

30. Lewis JS, Kersten P, McPherson KM, Taylor GJ, Harris N, McCabe CS, Blake DR. Wherever is my arm? Impaired upper limb position accuracy in complex regional pain syndrome. *Pain.* 149:463-469, 2010

31. Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Cortical reorganization during recovery from complex regional pain syndrome. *Neurology.* 63:693-701, 2004

32. Marinus J, Moseley GL, Birklein F, Baron R, Maihofner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol.* 10:637-648, 2011

ACCEPTED MANUSCRIPT

33. McCabe CS, Shenker N, Lewis J, Blake DR. Impaired self-perception of the hand in complex regional pain syndrome (CRPS) [S. Forderreuther, U. Sailer, A. Straube, Pain 2004; 110:756-761]. *Pain.* 114:518; author reply 519, 2005

34. Moseley GL. Why do people with complex regional pain syndrome take longer to recognize their affected hand? *Neurology.* 62:2182-2186, 2004

35. Moseley GL. Distorted body image in complex regional pain syndrome. *Neurology.* 65:773-773, 2005

36. Moseley GL, Gallace A, Di Pietro F, Spence C, Iannetti GD. Limb-specific autonomic dysfunction in complex regional pain syndrome modulated by wearing prism glasses. *Pain.* 154:2463-2468, 2013

37. Moseley GL, Gallace A, Iannetti GD. Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome. *Brain.* 135:3676-3686, 2012

38. Moseley GL, Gallace A, Spence C. Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb. *Brain : a journal of neurology.* 132:3142-3151, 2009

39. Moseley GL, Gallace A, Spence C. Bodily illusions in health and disease: physiological and clinical perspectives and the concept of a cortical 'body matrix'. *Neurosci. Biobehav. Rev.* 36:34-46, 2012

40. Mountcastle V: The sensory hand. Neural mechanisms of somatic sensation., Harvard University Press, London, UK, 2005.

41. Oldfield R. The assessment and analysis of handedness: the Edinburgh inventory. *Pneuropsychologica.* 9:97-113, 1971

42. Ostry DJ, Darainy M, Mattar AA, Wong J, Gribble PL. Somatosensory plasticity and motor learning. *J. Neurosci.* 30:5384-5393, 2010

ACCEPTED MANUSCRIPT

43. Parkitny L, McAuley JH, Kelly PJ, Di Pietro F, Cameron B, Moseley GL. Multiplex cytokine concentration measurement: how much do the medium and handling matter? *Mediators Inflamm.* 2013:890706, 2013

44. Peltz E, Seifert F, Lanz S, Muller R, Maihofner C. Impaired hand size estimation in CRPS. *J. Pain.* 12:1095-1101, 2011

45. Pleger B, Ragert P, Schwenkreis P, Forster AF, Wilimzig C, Dinse H, Nicolas V, Maier C, Tegenthoff M. Patterns of cortical reorganization parallel impaired tactile discrimination and pain intensity in complex regional pain syndrome. *Neuroimage.* 32:503-510, 2006

46. Pleger B, Tegenthoff M, Ragert P, Forster AF, Dinse HR, Schwenkreis P, Nicolas V, Maier C. Sensorimotor returning in complex regional pain syndrome parallels pain reduction. *Ann. Neurol.* 57:425-429, 2005

47. Reid E, Wallwork SB, Harvie D, Chalmers KJ, Gallace A, Spence C, Moseley GL. A New Kind of Spatial Inattention Associated With Chronic Limb Pain? *Ann. Neurol.* 79:701-704, 2016

48. Reid EJ, Braithwaite FA, Wallwork SB, Harvie D, Chalmers KJ, Spence C, Gallace A, Moseley GL. Spatially-defined motor deficits in people with unilateral complex regional pain syndrome. *Cortex.* 2017

49. Schwoebel J, Coslett HB, Bradt J, Friedman R, Dileo C. Pain and the body schema: Effects of pain severity on mental representations of movement. *Neurology.* Vol 59:775-777, 2002

50. Schwoebel J, Friedman R, Duda N, Coslett HB. Pain and the body schema: evidence for peripheral effects on mental representations of movement. *Brain.* 124:2098-2104, 2001

51. Squeri V, Sciutti A, Gori M, Masia L, Sandini G, Konczak J. Two hands, one perception: how bimanual haptic information is combined by the brain. *J. Neurophysiol.* 107:544-550, 2012

52. Sumitani M, Misaki M, Kumagaya S, Ogata T, Yamada Y, Miyauchi S. Dissociation in accessing space and number representations in pathologic pain patients. *Brain Cogn.* 90:151-156, 2014

53. Tsay A, Allen TJ, Proske U, Giummarra MJ. Sensing the body in chronic pain: a review of psychophysical studies implicating altered body representation. *Neurosci. Biobehav. Rev.* 52:221-232, 2015

54. Vercauteren K, Pleysier T, Van Belle L, Swinnen SP, Wenderoth N. Unimanual muscle activation increases interhemispheric inhibition from the active to the resting hemisphere. *Neurosci. Lett.* 445:209-213, 2008

55. Walsh LD, Moseley GL, Taylor JL, Gandevia SC. Proprioceptive signals contribute to the sense of body ownership. *The Journal of physiology.* 589:3009-3021, 2011

56. Wong JD, Wilson ET, Kistemaker DA, Gribble PL. Bimanual proprioception: are two hands better than one? *J. Neurophysiol.* 111:1362-1368, 2014

ACCEPTED MANUSCRIPT

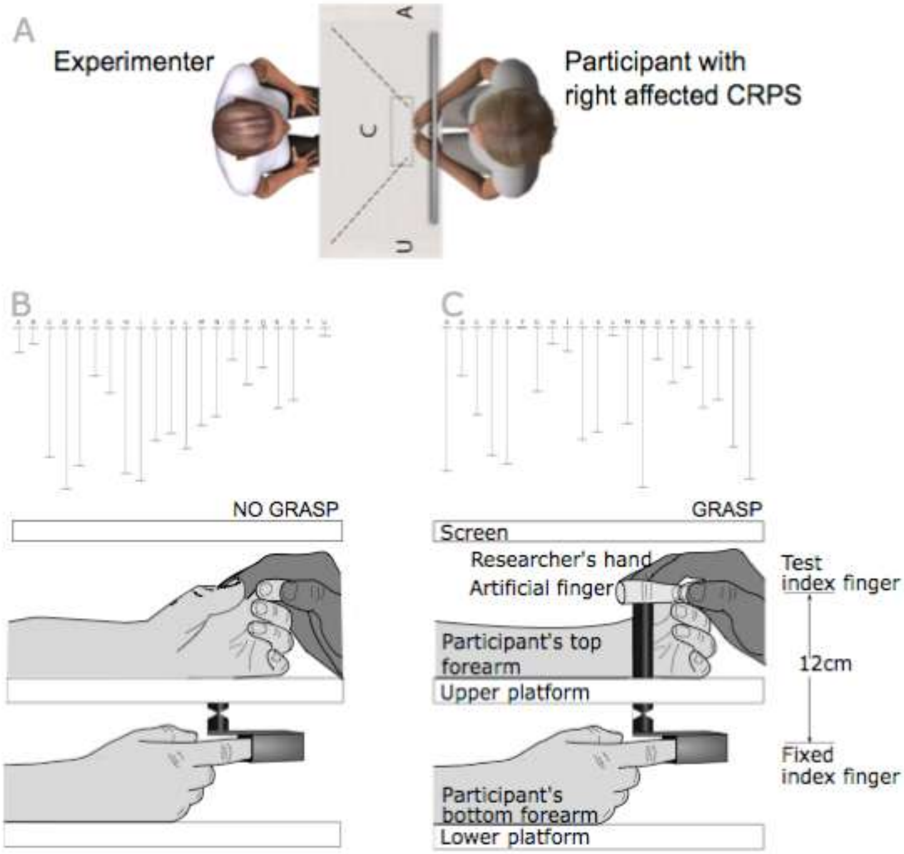

Figure 1: The finger illusion experimental set-up.

A. An illustration of the experimental set-up, showing the unaffected, centre and affected workspace for a participant with CRPS of the right hand (Workspaces are defined as A = Affected, C = Centre, U = Unaffected). Exemplar distance markers used for distance estimates are also shown. B. Set-up for the No Grasp condition. The hands were out of view of the participant. Note the artificial finger and the pipe either end of the shaft. Here, the researcher's hand is shown guiding the participant's fingers, on their top hand, to be adjacent to, but not grasping the artificial finger. C. A view of the set-up for the Grasp condition. This was an identical set-up except that the researcher is guiding the participant's fingers to passively grasp the artificial finger.

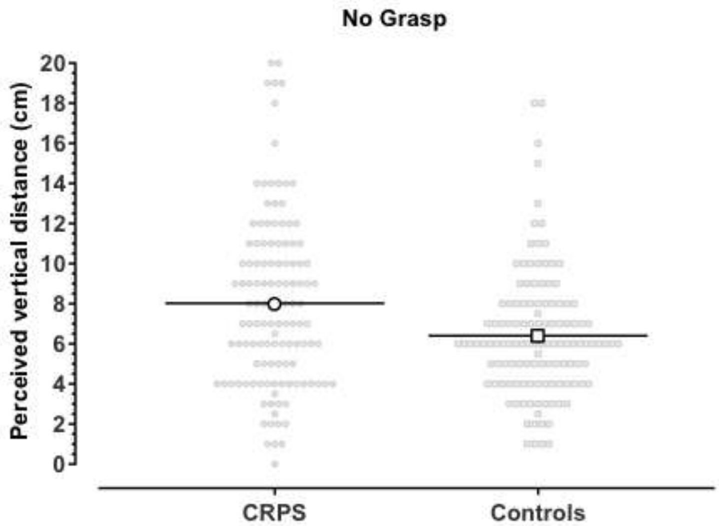

Figure 2: The No Grasp condition of the finger illusion.

CRPS participants perceived their index fingers to be further apart than controls did, F (1,19) = 4.82, p = 0.041, η^2_ρ = 0.202, *power* = 0.550). Raw data from individual perceived vertical distances during No Grasp from all conditions with the multivariate estimated mean for CRPS (7.96 cm) and controls (6.35 cm) are illustrated (circle = CRPS; square = Controls). The horizontal dotted line indicates the actual distance of 12 cm. The unseen posture of the participant's top hand (left hand) at No Grasp relative to the artificial finger during the experiment is shown under the graph.

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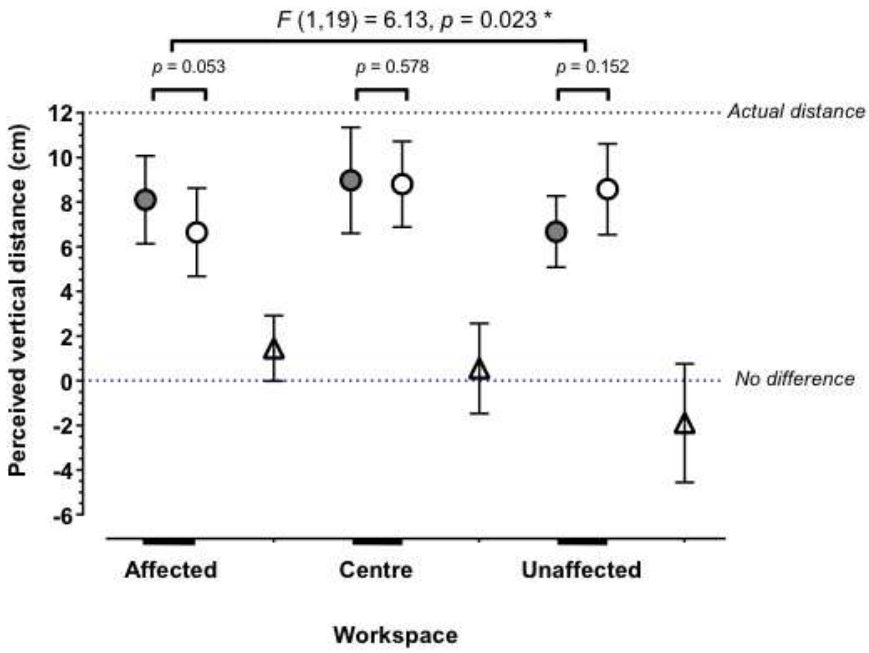

Figure 3: The effect of hand placement on the upper platform by workspace in the 'No Grasp' condition in CRPS.

The perceived vertical distance between index fingers for CRPS participants: circles (closed circle = affected hand; open circle = unaffected hand; triangle = the difference in mean perceived vertical distance between the affected and the unaffected hand within each workspace) represent the means and error bars represent 95% CI around each mean. The top dotted line indicates the actual distance of 12 cm and the bottom dotted line at 0 cm indicates no difference between hands in each workspace.

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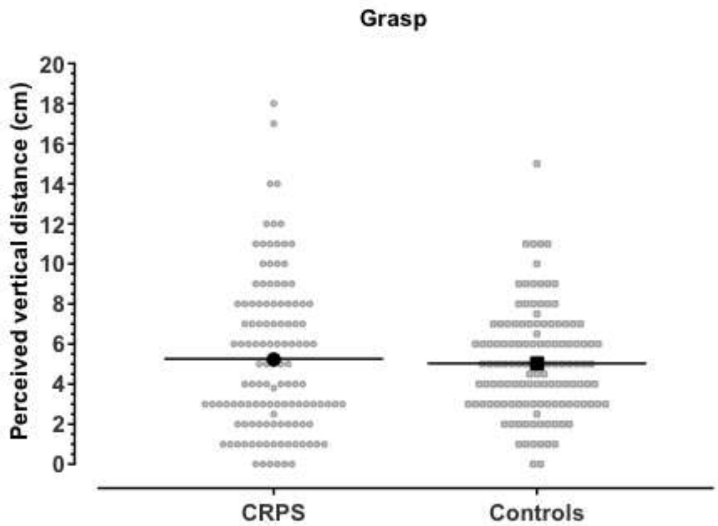

Figure 4: The Grasp condition of the finger illusion.

Raw data from individual perceived vertical distances during Grasp are represented. There were no significant differences between CRPS participants and controls, $F(1,19) = 0.15$, $p = 0.699$, $\eta^2_\rho = 0.008$, *power* = 0.059 Raw data from repeated measures across all conditions with the multivariate estimated mean illustrated for CRPS (5.18 cm) and controls (4.92 cm) ; circles = CRPS, squares = Controls .

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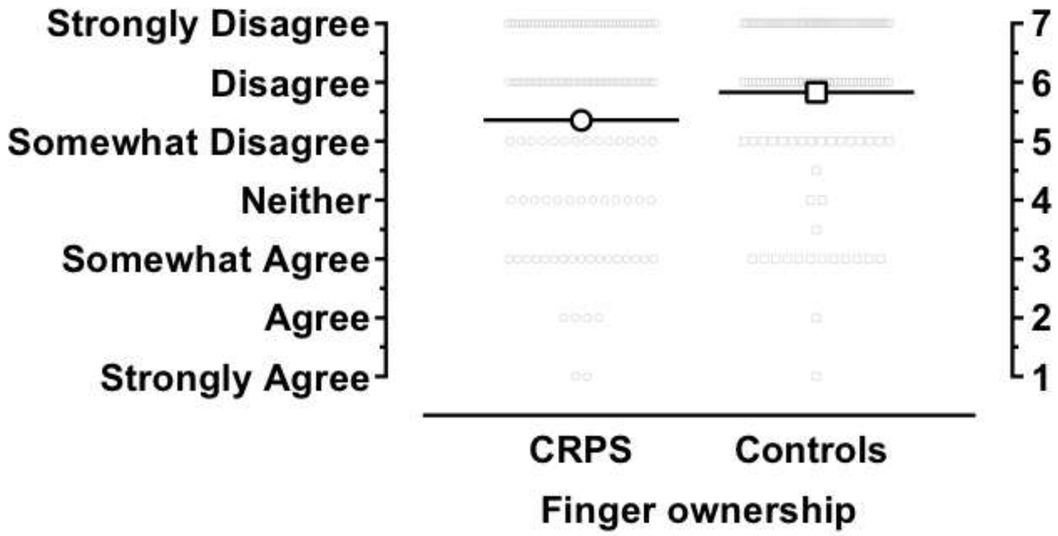

Figure 5: Artificial finger ownership during grasp condition of the finger illusion. CRPS and healthy control participants were not significantly different on their ratings when asked either "I feel that I am holding my left index finger with my right" or "I feel that I am holding my right index finger with my left hand", when presented with the 7-point Likert-scale artificial finger ownership chart, F (1,19) = 1.96, p = 0.177, η^2_ρ = .094, *power* = 0.26. Raw data from repeated measures ownership ratings are illustrated from all conditions; squares from controls and circles from CRPS with the multivariate estimated mean from CRPS participants (5.39) and controls (5.79).