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Visual illusions modulate body perception disturbance and pain in Complex Regional Pain Syndrome: A randomized trial

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Abstract

Background: Effective treatment of longstanding Complex Regional Pain Syndrome (CRPS) is a challenge, as causal mechanisms remain elusive. People with CRPS frequently report distorted subjective perceptions of their affected limb. Evidence of pain reduction when the affected limb is visually altered in size suggests that visual illusions used to target central processing could restore coherence of this disrupted limb representation. We hypothesized that using virtual reality that alters hand image to match the patient's desired hand appearance would improve body perception disturbance and pain. Also, repeated exposure would maintain any therapeutic effect.

Methods: A blinded randomized controlled trial of 45 participants with refractory upper-limb CRPS and body perception disturbance (BPD) viewed a digital image of their affected hand for 1 min. The image was digitally altered according to the patient's description of how they desired their hand to look in the experimental group and unaltered in the control group. BPD and pain were measured pre- and post-intervention. A subgroup was followed up 2 weeks after a course of repeated interventions.

Results: BPD (mean-6, $\pm SD$ 7.9, $p = 0.036$, effect size [ES] = 0.6) and pain intensity (mean-0.43, $\pm SD$ 1.3, $p = 0.047$, ES = 0.5) reduced in 23 participants after single exposure compared to controls ($n = 22$). At follow-up, the subgroup (experimental $n = 21$; control $n = 18$) showed sustained pain reduction only ($p = 0.037$, $\pm SD$ 1.9, ES = 0.7), with an overall 1.2 decrease on an 11-point scale.

Conclusions: Visually changing the CRPS hand to a desired appearance modulates BPD and pain suggesting therapeutic potential for those with refractory CRPS. Further research to optimize this therapeutic effect is required.

Significance: Visual bodily illusions that change the shape and appearance of the painful CRPS hand to that desired by the patient result in a rapid amelioration of pain and body perception disturbance in people with longstanding CRPS. These findings highlight the future potential of this drug-free approach in the treatment of refractory CRPS.

1 | INTRODUCTION

The recalcitrance of longstanding Complex Regional Pain Syndrome (CRPS) to treatment is a challenge for the international pain community. Whilst most CRPS cases recover within the first 12 months, 27% of patients suffer from persistent symptoms that develop into a long-term condition (Bean et al., 2016a). In these cases, CRPS symptomatology considerably impacts on function, emotional and social well-being and poses an economic burden on society (Bean et al., 2016a, 2016b; Goebel, 2011; de Mos et al., 2007).

Successful treatment of longstanding CRPS remains problematic as therapeutic responses to conventional pharmacological options are limited (Harden et al., 2006). Since the underlying mechanisms of CRPS remain still unknown, therapeutic targets remain elusive (Bruehl, 2015). There is little evidence to support the gold standard treatment of multidisciplinary rehabilitation which is costly and resource intensive (Harden et al., 2013; McCormick et al., 2015; Perez et al., 2010; Singh et al., 2004; Smart et al., 2016; Turner-Stokes et al., 2011). To address this challenge, it is crucial to develop approaches that are both clinically and cost effective.

People with CRPS frequently report distorted subjective perceptions of their affected limb. These can manifest as perceptual changes in affected limb size and shape, a dislike in appearance and a loss of ownership of their painful limb (Lewis et al., 2007; Lewis & McCabe, 2010; Moseley, 2005). Body perception disturbances comprise both alterations in sensorimotor representation, e.g., perceived changes in size and shape (body schema) and a perceptual awareness of the limb, e.g., dislike of appearance and disownership of the limb (body image) (Paillard, 1999). There is some evidence that these body perception disturbances may be associated with maladaptive cortical representation of the limb (Echalier et al., 2020; Maihöfner et al., 2003; Peltz et al., 2011); however, it remains an open question as others have found no somatosensory cortical change on the affected side (Mancini et al., 2019). Body perception disturbance has been shown to positively correlate with CRPS pain intensity (Lewis & Schweinhardt, 2012).

Novel drug-free technologies such as virtual reality have revealed analgesic effects in acute and chronic pain states (Chan et al., 2018; Indovina et al., 2018; Pourmand et al., 2018). Specifically, the use of body illusions to relieve clinical pain shows therapeutic promise (Boesch et al., 2016). Body representation is highly adaptive, as various illusions that change the shape of the painful body have shown (Diers et al., 2013; Moseley et al., 2008; Preston & Newport, 2011; Stanton et al., 2018). These illusions alter central body representation– multiple dynamic multisensory maps of the body that are constantly updated by somatosensory, visual, proprioceptive, vestibular inputs and motor feedback (Longo & Haggard, 2012). That this sense of the bodily self-persists even when the limb has been amputated, emphasizes the robustness of our body representation (Melzack, 1989).

Given that central mechanisms are a driver in persistent pain (Tracey & Mantyh, 2007), manipulating central systems as a potential target in the treatment of pain seems a logical route for exploration (Moseley & Flor, 2012; Moseley, Gallance, & Iannetti, 2012). Therefore, we propose using body illusions in CRPS to address body perception disturbance which may influence centrally mediated maladaptive body representations, which may, in turn, reduce pain.

Using Mediated Virtual Reality (MVR) in longstanding CRPS, we aim to alter the appearance of the affected hand based on how those with CRPS would like their hand to look. We postulate that a match between the visual appearance and desired representation of the CRPS hand would normalize the maladapted central representation of the hand. We hypothesize that a visual illusion to improve the subjective appearance of the affected hand would (1) normalize body perception, ownership and liking of the hand, which would lead to (2), a reduction of pain and (3) sustain a therapeutic effect with repeated exposure for those with longstanding CRPS.

2 | METHODS

2.1 | Participant recruitment and group assignment

Potential participants were identified from the CRPS UK network registry (crpsnetworkuk.org/Registry.php) and clinics at The Royal National Hospital for Rheumatic Diseases, Royal United Hospitals Bath NHS Foundation Trust, Bath and The Walton Centre NHS Foundation Trust, Liverpool, UK. Those who met the following study inclusion criteria were recruited from June 2013 to February 2016; met the Budapest clinical diagnostic criteria (Harden et al., 2010) for CRPS affecting one upper limb; aged 18 and over and had no co-morbidity that might influence CRPS symptoms, i.e., stroke, diabetes and fibromyalgia.

The sample size for this study was based on MIRAGE illusion within-subject pilot data in 14 CRPS participants. A total sample size of 88 participants (44 per group) was calculated as sufficient for a mean (*SD*) reduction in the pain numerical rating scale (primary outcome) of 1.733 (2.89) points, on a 0–10 scale with a power of 80% and a 0.05 two-sided significance.

Participants gave written informed consent prior to participation in procedures approved by local hospital and University ethics committees in accordance with the Declaration of Helsinki. The registered ISRCTN trial number is ISRCTN64093359 (www.isrctn.com/ISRCTN64093359). Following informed consent and to avoid selection

bias, participants were randomly allocated to either the manipulation (experimental) or non-manipulation (control) group. In advance of testing, a person independent of data collection used a computer-generated random sequence to produce information regarding group allocation that was placed in sealed and numbered envelopes. Envelopes were sequentially opened by the MIRAGE operator after consent and prior to testing. To minimize performance bias, participants were blinded to group allocation. Participants were not informed of the study hypothesis to minimize responder bias.

2.2 | Experimental procedure

Participants attended up to five sessions comprising 4 weekly intervention sessions and a final follow-up session 2 weeks later. A detailed schematic of the study procedure is illustrated in Figure 1. Data were collected within laboratory-controlled conditions. The primary outcome measures collected were metrics directly related to our hypotheses (Body perception disturbance, pain intensity, perceptual ratings).

Intervention sessions (sessions 1–4) consisted of three parts: (A) pre-intervention, (B) intervention and (C) post-intervention. The intervention using the MIRAGE system (Preston & Newport, 2011), a non-invasive MVR device, consisted of either visual illusions involving the digital manipulation of the appearance of participants' hands for the manipulation group (MG) or non-manipulation for the non-manipulation group (NG). Baseline primary and secondary outcome measures were collected prior to the initial intervention within the first session (see Figure 1).

2.2.1 | Baseline (conducted outside the MIRAGE system)

In a seated position, participants directly viewed their actual hands positioned palm down on a table at waist height in front of them and outside of the MIRAGE system. Primary and secondary baseline measures were collected.

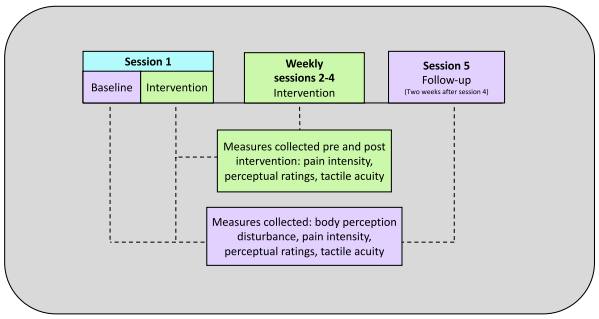

FIGURE 1 Study procedure

For purposes of describing pain characteristics participants also completed The Neuropathic Pain Symptom Inventory (NPSI) (Bouhassira et al., 2004). The NPSI is a validated measure for the severity of neuropathic pain. The questionnaire determines subjective intensities (for the preceding 24 hr) of spontaneous superficial, spontaneous deep, paroxysmal and evoked pain, as well as paraesthesia. These different neuropathic symptoms are rated on an 11-point numerical rating scale. A total score is calculated by summing the five categories. Higher scores denote greater intensity.

Pre-intervention (conducted within the MIRAGE system)

In a similar seated position to that at baseline, participants sat with each arm placed into one of the two apertures of the MIRAGE system so that both hands rested palm down on a flat surface within the system. Participants viewed a real-time digital video image of their hands through a horizontal 'window-like' surface above and perpendicular to these apertures. The image of their hands was displayed via this surface in such a way that their hand image appeared to be in the same physical and spatial location as their actual hands. For the purposes of embodiment, the participant viewed their affected hand image and moved their hand within the device prior to the intervention. In healthy participants, a period of less than 20 s is sufficient to induce ownership of the seen limb (Newport et al., 2010). Primary outcome measures were collected as described below.

Intervention (conducted within the MIRAGE system)

Manipulation. As the participant viewed their affected hand within the device, the MIRAGE system operator digitally altered the appearance of the painful hand using specifically designed software via a laptop (MacBook Pro 15" Model ME664B/A using Windows 7 running LabView 2012 (National Instruments), as part of the MIRAGE system. In response to the specific description given by each participant, changes were made in real time to aspects of shape, size and/or colour of the hand, based on how they wished their hand to look, i.e., their desired hand appearance. Participants rated their satisfaction of hand appearance whilst looking at the hand image by answering the question "*How satisfied are you with the hand as you see it?"* on a 7-point Likert scale ranging from −3 (strongly dissatisfied) to +3 (strongly satisfied). If participants rated <+1, the image was further altered to reach a rating of +1 in order to better match the participant's desired hand appearance. Requests were specific to the individual; therefore, resulting hand images were unique on each occasion and took up to a minute to complete.

Once they were satisfied, participants viewed the resultant image for 1 min. No visual changes were made to the unaffected hand. Post-intervention measures were collected following this procedure.

Non-manipulation. The procedure and duration (approx. 1 min) for non-manipulation was exactly the same as that described in i) manipulated condition by the operator appearing to click the computer keys with the exception that the image was not actually visually altered, although the participant believed it to have been. A satisfaction level of ≥+1 was not required in the control group in order to proceed with the intervention. The hand image was viewed for 1 min and followed by post-intervention data collection.

Post-intervention (conducted within the MIRAGE system)
The same measures taken at pre-intervention were repeated post-intervention.

2.2.2 | Primary outcome measures

Primary outcomes were measured at baseline, pre-intervention and post-intervention as follows:

The Bath body perception disturbance (BPD) scale
The BPD scale was used to measure changes in body perception of the affected limb (Lewis & McCabe, 2010). This scale demonstrates good internal consistency (Cronbach's alpha = 0.66) (Streiner & Norman, 2008) and adequate interrater reliability (Cohen's kappa = 0.87) (Nunnally & Bernstein, 1994) in a CRPS sample (Lewis & Schweinhardt, 2012). A higher score indicates a greater degree of disturbance (see Lewis and McCabe [2010] for a description of the scale).

Pain intensity numerical rating scale (NRS)
To assess current pain, participants verbally rated their affected hand pain intensity on an 11-point NRS anchored at 0 (no pain) and 10 (worst pain imaginable).

Perceptual statement ratings
Perceptual statement ratings were adapted from Schaefer et al. (2007). These were used to assess subjective perceptual changes associated with the affected hand. Whilst viewing their hand, participants provided a verbal rating to the following statements on a 7-point Likert scale ranging from −3 (strongly disagree) to +3 (strongly agree): *(1) It feels like the hand that I am looking at is my hand; (2) I like the appearance of my hand as I see it; (3) I feel my hand is lighter; (4) I feel my hand is heavier; (5) I feel my hand is different in sensation*.

2.3 | Statistical analyses

To test our hypotheses that a visual illusion to improve the subjective appearance of the affected hand would (1) normalize body perception, ownership and liking of the hand, and (2) reduce pain, we calculated post-intervention changes in these measures at session 1 by subtracting the respective pre-intervention score from the post-intervention score. Parametric tests (independent *t* tests) were performed on group mean change scores to compare pre–post-intervention change in outcome measures between the two groups (MG and NG) ($n = 45$).

Our third hypothesis, that repeated exposure would sustain a therapeutic effect, was tested with a repeated measures ANOVA with a Greenhouse–Geisser correction, on the repeated exposure subgroup ($n = 39$) over the four sessions and between the two groups (MG and NG). An independent *t* test was performed to explore changes in pain at baseline (session 1) when compared to follow-up (session 5) between these two groups. Statistical significance levels were set at $p = 0.05$. Effect sizes for each comparison were calculated by dividing the mean difference between groups by the pooled standard deviation. Confidence intervals were calculated at 95%. All analyses were undertaken using IBM SPSS Statistics v.23 (IBM corp.).

3 | RESULTS

A total of 46 participants were assessed for eligibility (Figure 2). One patient did not meet the Budapest clinical criteria for CRPS (Harden et al., 2010) of one arm on examination and was excluded. Forty-five participants (29 women, aged [mean ± *SD*] 52 ± 13 years, mean disease duration 56 ± 54 months [4.7 years]) were randomized to either the manipulation (experimental) group ($n = 23$) or the non-manipulation (control) group ($n = 22$) and completed session 1. Individual participant characteristics are presented in Table 1. The total sample did not reach the expected sample

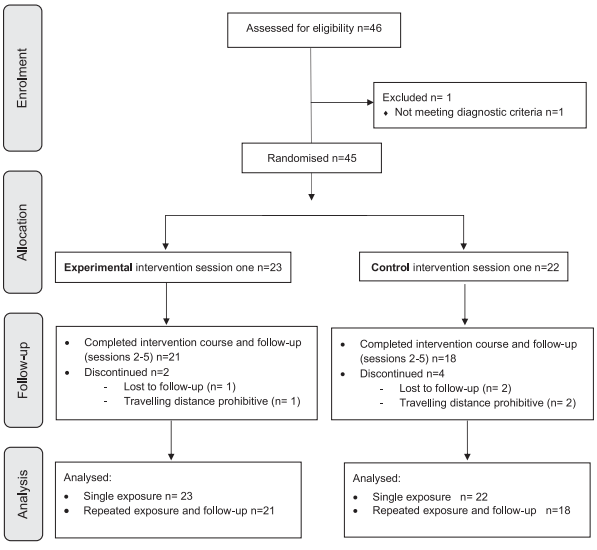

FIGURE 2 CONSORT flow diagram Moher et al. (2010)

TABLE 1 Patient characteristics

ID	Age(years)/ gender	Reported inciting incident	Affected upper limb	Dur. (months)	Reported pain medications	Meets Budapest research diagnostic criteria (Bruehl et al. 1999)	Experimental group	Repeated exposure and follow-up
01	78/F	PS	L	14	Lidocaine patch	✓	✓	✓
02	57/F	STI	R[a]	96	Tramadol, paracetamol	✓	✓	✓
03	60/F	Fr	L[a]	31	Pregabalin, paracetamol	✓	✓	✓
04	73/M	SP	R[a]	96	None	✓		✓
05	32/M	STI	R[a]	18	Lidocaine patch, amitriptyline	✓	✓	✓
06	69/F	PS	L	36	Lidocaine patch, paracetamol	✓	✓	✓
07	49/M	STI	R[a]	8	Pregabalin, amitriptyline	✓	✓	✓
08	66/F	PS	R[a]	24	Co-codamol paracetamol			✓
09	20/F	STI	R[a]	24	Pregabalin, paracetamol, tramadol, duloxetine	✓		✓
10	33/M	Fr	L[a]	156	Pregabalin, amitriptyline, paracetamol, MST, duloxetine	✓		✓
11	61/M	Fr	R[a]	6	Tramadol	✓		✓
12	67/F	Fr	L	60	None			✓
13	55/F	Fr	R[a]	7	pregabalin	✓		✓
14	71/F	PS	R[a]	84	None			✓
15	48/M	SP	R[a]	24	Pregabalin	✓	✓	✓
16	60/F	P	L	84	Paracetamol, oxycontin, meloxicam	✓	✓	✓
17	38/M	STI	R[a]	36	Pregabalin	✓	✓	✓
18	25/F	STI	L	52	Ibuprofen	✓		✓
19	58/F	STI	L	18	None	✓	✓	✓
20	44/F	STI	L	47	Ibutrans patch, duloxetine, naproxen			
21	39/M	Fr	L	11	Pregabalin, amitriptyline, zolpadine	✓	✓	✓
22	42/M	SP	R[a]	72	Nefopam	✓		
23	52/M	STI	R[a]	57	Sertraline	✓	✓	✓
24	44/F	SP	L	96	Pregabalin, tramadol, paracetamol	✓		
25	47/F	Fr	R[a]	24	Lidocaine patch	✓	✓	✓
26	60/F	Fr	R[a]	132	Gabapentin, naproxen, dihydrocodeine, diazepam, nortriptyline, zomorph, sertraline	✓	✓	✓
27	42/F	PS	L	29	None	✓		✓

(Continues)

TABLE 1 (Continued)

ID	Age(years)/ gender	Reported inciting incident	Affected upper limb	Dur. (months)	Reported pain medications	Meets Budapest research diagnostic criteria (Bruehl et al. 1999)	Experimental group	Repeated exposure and follow-up
28	55/M	Fr	R[a]	60	Tramadol, amitriptyline, paracetamol	✓		✓
29	43/F	STI	R[a]	17	Tramadol, paracetamol	✓	✓	✓
30	48/M	Fr	R[a]	4	Lidocaine patch	✓	✓	
31	49/F	Fr	R	93	None	✓	✓	✓
32	39/F	Fr	L	57	Pregabalin, MST, oramorph	✓	✓	✓
33	66/F	PS	R[a]	53	Tramadol	✓		✓
34	40/M	PS	R[a]	48	Zopiclone	✓		✓
35	46/M	Fr	R[a]	216	Clonazepam	✓	✓	
36	44/M	Fr	L	84	Gabapentin, naproxen	✓		
37	57/F	Fr	L	17	Pregabalin	✓	✓	✓
38	54/M	Fr	R[a]	264	Amitriptyline, codeine phosphate, codydramol, ibuprofen	✓		✓
39	56/F	Fr	R[a]	48	None	✓		✓
40	59/F	Fr	R	30	Gabapentin, ibuprofen	✓		✓
41	45/F	STI	R[a]	15	None	✓	✓	✓
42	45/F	STI	L	19	Tramadol, paracetamol, duloxetine	✓	✓	✓
43	64/F	Fr	L	96	Co-codamol, duloxetine	✓	✓	✓
44	53/F	PS	L	12	Lidocaine patch	✓		✓
45	62/F	STI	R	29	Co-codamol, temazepam	✓		✓

Abbreviations: F, female; M, male; STI, soft tissue injury; Fr, fracture; PS, post-surgery; SP, spontaneous; P, post-infection; L, left; R, right; Dur. (months), duration in months since symptom onset.

[a]Dominant hand is affected.

size as Registry administrators fed back that potential participants felt unable to tolerate travelling to multiple sessions due to persistent painThe usage "fed back" is not clear. Please check.

Twenty-one of the Manipulation Group (MG) completed a course of four intervention sessions and a follow-up, whilst 18 of the Non-Manipulation (NG) group completed the intervention course and follow-up. Analysis of data was conducted in 45 participants for single exposure and in 39 participants for repeated exposure and follow-up (Figure 2). There were no significant differences in demographic and clinical characteristics between the two groups at baseline (Table 2) or between the repeated intervention subgroup and those that were lost to follow-up (Table 3).

Participants were very specific about how and the degree to which changes to hand appearance were made (i.e. lengthening fingers or narrowing the dorsum of the hand). Reshaping (enlarging or reducing) of precise areas such as individual digits was considered important by the participant to achieve their desired appearance. These hand images were individual to the participant and unique to each study session. An example is shown in Figure 3.

3.1 | Single exposure (Hypotheses 1&2)

Body perception disturbance: A significantly greater reduction in the Bath BPD scale total score ($t = 2.16$, $df = 43$, $p = 0.036$) for pre–post-intervention differences in MG (mean, $\pm SD$) (−6, 7.9) was found when compared to NG (−1.3, 6.5). See Figure 4a. Effect size (ES) = 0.64 (0.042,1.25).

Perceptual ratings: A significant difference ($t = 3.81$, $df = 43$, $p < .00001$) in pre–post-intervention changes between MG (2.1, 2.1) and NG (−0.6, 2.6) for perceived liking of the affected hand represented an improvement in liking of hand appearance, ES = 1.135 (−1.73, −0.53). Sense of heaviness was significantly reduced ($t = 2.67$, $df = 43$, $p = 0.011$) post-intervention for MG (−1.5, 2) compared to NG (0.23, 2), ES = 0.8 (0.193, 1.39). A significant difference ($t = 2.27$, $df = 43$, $p = 0.03$) in pre–post-intervention changes for perceived lightness was found between MG (1.24, 1.8) and NG (−0.05, 1.7), ES= −0.7 (−1.28, −0.07). Taking the change in rating of perceived lightness and heaviness together demonstrates an overall perception that the hand felt lighter post-intervention. No pre–post-intervention differences were found between the groups for ownership ($t = 1.49$, $df = 43$, $p = 0.14$), ES = −0.45 (−1.05, 0.16) and sensation ($t = 1.09$, $df = 43$, $p = 0.28$), ES = 0.32 (−0.28, 0.93). Perceptual rating results are presented in Figure 4bi-v (see Supplementary Data Table S1 for mean perceptual rating scores pre/post-intervention).

Current pain intensity: A significant reduction in current pain ($t = 2.03$, $df = 43$, $p = 0.047$) was found between pre–post-intervention pain differences for MG (−0.43, 1.3) compared with NG (0.23, 0.8) (Figure 4ci 3ci), ES = 0.46 (0.003, 0.92).

In summary, we found that a single 1 min exposure to an illusion that visually altered affected hand appearance to a desired look significantly reduced body perception disturbance, improved liking and increased perceived lightness of the affected hand. There was also a significant decrease in pain.

3.2 | Repeated exposure (Hypothesis 3)

3.2.1 | Pain

A repeated measures ANOVA of mean pre–post-intervention changes in pain (sessions 1–4) revealed a significant

TABLE 2 Participant characteristics between the manipulation and the non-manipulation group

Characteristics	Manipulation group (MG)	Non-manipulation group (NG)	Parametric testing Indep *t* test
N	23	22	
Age (years)	52(11; 32–78)	52 (14.5; 20–71)	0.96
Gender (female)	15 (65%)	14 (64%)	0.9
Gender (male)	8 (35%)	8 (36%)	
Disease duration (months)	49 (51; 4–216)	63 (56; 6–264)	0.4
Dominant affected limb	13 (56%)	14 (64%)	0.6
Non-dominant affected limb	10 (44%)	8 (36%)	
Baseline NPI score	59 (21)	53 (30)	0.8
Baseline hand pain	5.7 (3)	5.45 (3)	0.8
Pre-intervention hand pain inside MIRAGE	5.6 (3)	5.7 (3)	0.99

TABLE 3 Participant characteristics between the repeated exposure and the lost to follow-up groups

Characteristics	Repeated exposure subgroup	Lost to follow-up	Parametric testing Indep *t* test
N	39	6	
Age (years)	53 (13; 32–78)	44 (1;44–46)	0.14
Gender (female)	26 (67%)	3 (50%)	0.23
Gender (male)	13 (33%)	3 (50%)	
Disease duration (months)	51 (50; 4–264)	86.5 (71; 47–216)	0.48
Dominant affected limb	24 (61.5%)	3 (50%)	0.3
Non-dominant affected limb	15 (38.5%)	3 (50%)	
Baseline NPI score	54 (26)	74 (16)	0.14
Baseline hand pain	5.4 (3)	7 (4)	0.61
Pre-intervention hand pain inside MIRAGE	6 (3)	7 (4)	0.67

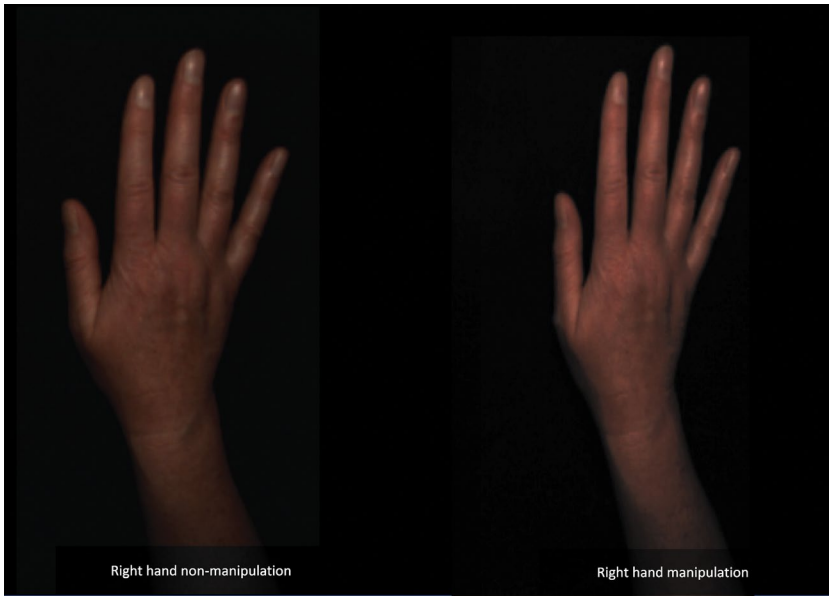

FIGURE 3 Example of illusory hand manipulation (CRPS 02)

effect of repeated illusory exposure on pain reduction in MG $F(3,105) = 1.89$, $p = 0.014$) when compared to NG.

Furthermore, to establish whether the effects of illusory exposure were sustained for 2 weeks after repeated exposure, the mean pain intensity change at session 1 and follow-up (session 5) was compared between the two groups. This revealed a significant reduction in pain intensity in MG ($t = 2.18$, $df = 36$, $p = 0.037$) when compared to NG showing an overall mean pain reduction in MG of 1.2 on an 11-point scale at follow-up (MG mean = −1.19, NG mean = 0) (Figure 4cii 3cii), ES = 0.7 (0.05, 1.38). See Figure S1 in supplementary data for mean pain scores pre- and post-intervention by group at each session.

3.2.2 | Body perception disturbance and perceptual ratings

Measures at baseline (session 1) when compared to follow-up (session 5) between MG and NG revealed no statistical differences between the two groups in the Bath BPD scale ($t = -0.03$, $df = 37$, $p = 0.98$), ES = −8.8 (−0.65, 0.63) perceptual ratings of ownership ($t = 0.495$, $df = 37.8$, $p = 0.62$), ES = 0.16 (−0.49, 0.8) liking of appearance ($t = 0.62$,$df = 37$,$p = 0.53$), ES = 0.2 (−4.7, 8.9) lightness ($t = 1.8$, $df = 38$, $p = 0.08$), ES = 0.6 (−1.4, 2.8) heaviness ($t = 0.7$, $df = 34$, $p = 0.5$), ES=0.22 (−3.6, 7.3) or difference in sensation ($t = 0.6$, $df = 39$, $p = 0.6$), ES = 0.12 (−4.05, 7.5).

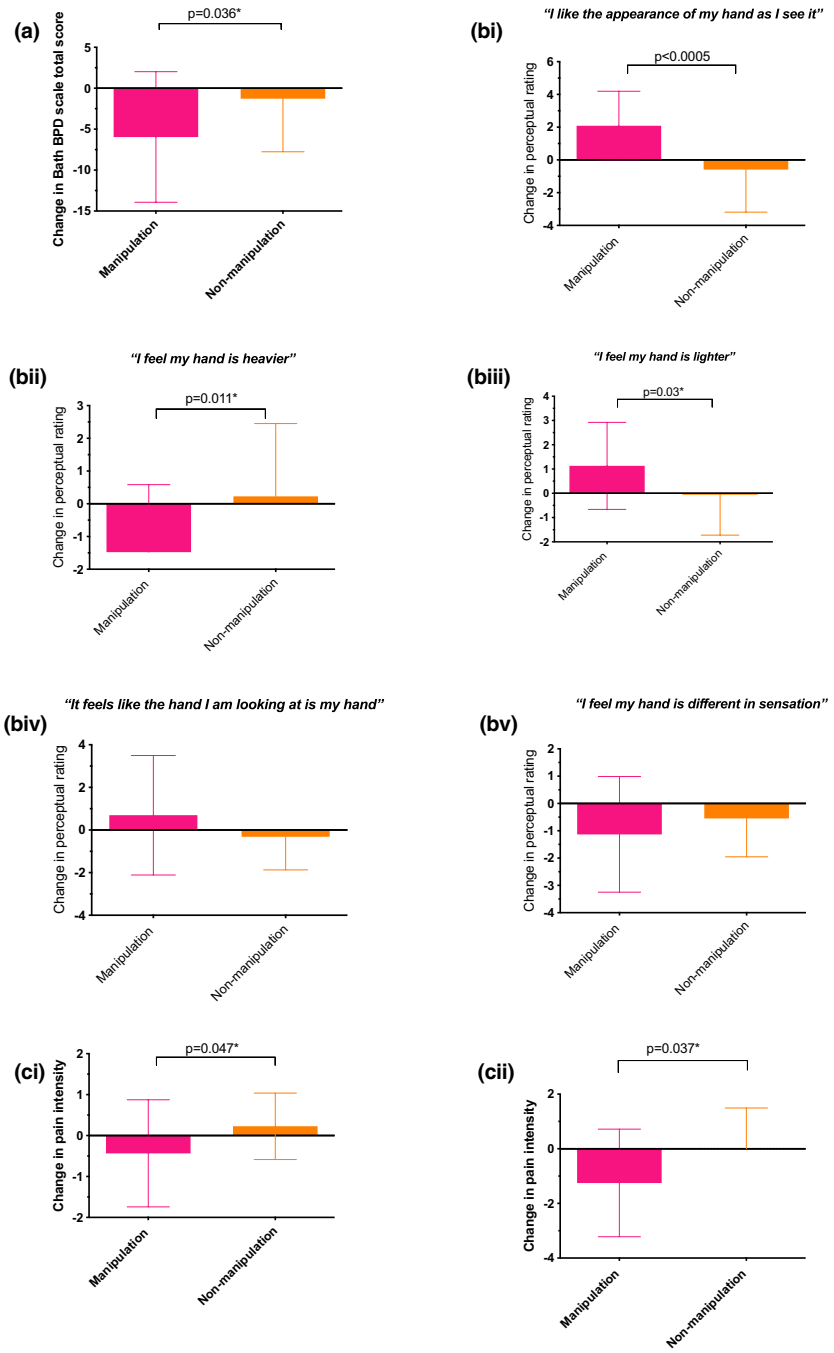

FIGURE 4 (a) Body perception disturbance: single exposure. (b) i-v Perceptual ratings:single exposure. (c) Pain: (i) single exposure (ii) repeated exposure

4 | DISCUSSION

Findings confirm our hypotheses that short exposure to a visual illusion which matches the desired appearance of the painful hand in longstanding CRPS, (1) normalizes body perception disturbance, (2) reduces pain and (3) sustains a therapeutic effect with repeated illusory exposure. However, there was no effect on perceived ownership of the hand. To aid interpretation, we present these findings within the context of a conceptual model.

We suggest that our findings are applicable to Pitron et al.'s (2018) model of body representation (see Figures 4,5). This '*serial co-construction*' model enhances previous conceptual models of body representation in clinical conditions by presenting body schema and body image as two distinct yet interacting concepts (Mölbert et al., 2017; Moseley, Gallance, & Iannetti, 2012; Moseley, Gallace, & Spence, 2012). Responses to the illusion were rapid and resulted in changes to a range of sensory–perceptual and cognitive experiences. This suggests that illusory exposure rapidly modifies the more malleable body image by visually presenting a perceptually more appealing affected hand that triggers these changes.

How the more enduring configuration of body schema interacts within this conceptual model is of particular interest (Longo, 2015; Pitron et al., 2018). That participants were specific about how and to what degree they wished their hand

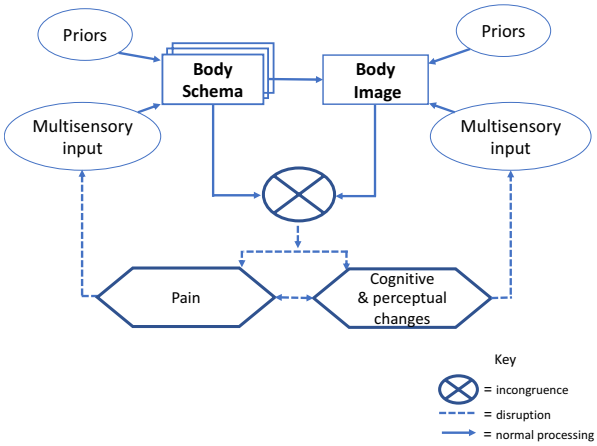

FIGURE 5 Body representation co-construction model modified from Pitron et al. (2018)

appearance to change, indicates that different body representations co-exist and can be accessed in the brain. We suggest that participants spontaneously accessed their longstanding body schema. The concept of an inherent body schema is reminiscent of children with congenital aplasia who experience a phantom limb suggesting the presence of an innate cortical limb representation (Melzack, 1989).

Reshaping of specific areas was considered important by the participant to achieve the desired appearance reflecting their unique body schema map. Individualized virtual reshaping offers potential for an advanced approach to treatment from that of uniformly resizing the whole hand as previous CRPS studies have done (Peltz et al., 2011; Ramachandran, 2009).

The interplay between the desired hand image and perceptual responses reflects the interaction between body image and changes in perceived weight that are indicative of body schema (Paillard, 1999). That CRPS presents with simultaneous deficits in body schema and image is similar to eating disorders where evidence of distortions in these two distinct types of body representation have been shown (Gadsby, 2017; Mölbert et al., 2017).

So how might viewing the desired appearance of the painful hand ameliorate pain? We propose that the visually desired hand stimulus matches that of the innate body schema triggering a congruence to be restored. Short illusory exposure rapidly reduced pain in people with longstanding CRPS, representative of the 27% with treatment resistant chronic disease (Bean et al., 2016a). Reconfiguration between cognitive and perceptual representations of body image with the innate body schema may resume congruent multisensory processing and could explain why participants express a restorative change in hand perception. Pain may result from an incongruence between body image and body schema; hence, once congruence is restored pain rapidly ameliorates. Indirectly modulating pain by directly targeting body perception disturbance supports a relationship between body perception disturbance and pain (Lewis & Schweinhardt, 2012).

In CRPS the innate body schema may be suppressed by pain such that the altered hand representation which CRPS patients describe becomes dominant. Pain-related body perception disturbances may be caused by maladaptive cortical plasticity that is continually maintained by this incongruence so preventing the innate body schema from being restored to the 'working' schema. Perhaps this explains why it is a challenge to therapeutically correct (Lewis et al., 2011). Based on our interpretation, we propose an updated conceptual body perception disturbance model to that of Pitron et al. (2018) (Figure 4).

Neuroimaging studies of body representation processing show activation in the posterior parietal cortex (Buccino et al., 2001; Felician et al., 2009). Furthermore, our results support previous findings that visual manipulation triggers alterations in body self-perception demonstrating that visual inputs involving the occipital cortex influence higher order multisensory processing associated with body representation (Schaefer et al., 2007). The lateral (extrastriate body area) and medial (fusiform body area) occipitotemporal cortices may also be involved given associations with visual representation of body shape (Calvo-Merino, 2010; Costantini et al., 2011; Downing, 2011). Future brain imaging studies of real-time exposure to body reshaping illusions would add valuable insight into neural mechanisms.

Interestingly, pain relief was maintained for up to 2 weeks after repeated illusory exposure providing a sustained therapeutic effect for those with refractory CRPS. Unlike pain, however, changes in body perception disturbance were not sustained at follow-up. The frequency of these short illusions over a month was perhaps insufficiently powerful to maintain an effect.

Ownership, considered part of body image (Longo et al., 2009), remained unchanged following either single or repeated exposure. This is contrary to our conceptual model (Figure 5) and previous results where experimental manipulation of the upper limb produced changes in ownership (Moseley, Gallance, & Iannetti, 2012; Moseley, Gallace, & Spence, 2012). Perhaps the illusion was of insufficient strength and/or duration to restore ownership.

4.1 | Limitations

The sample size is smaller than expected which reflects the difficulty in undertaking complex intervention studies within a chronic pain population. Although the illusion reduced pain, we note that our results do not meet the clinical significance threshold of a two-point reduction in NRS (Farrar et al., 2001). Furthermore, due to the nature of the intervention it was not possible to blind the assessor so a double-blinded study was not feasible. However, these results are encouraging and suggest that further work is required to maximize the effect and

reach clinical significance. Also, the period between repeated exposure and follow-up was short; therefore, how long the therapeutic effect might last remains unknown.

Further to previous pain-relieving treatments that evoke a virtual limb (Johnson et al., 2012; Moseley, 2004), our findings suggest the treatment potential of a 'desired-appearance illusion' for patients previously considered to have refractory disease. Future work is required to explore the optimum duration and frequency of the illusion for best therapeutic effect. In addition, how the intervention can be adapted for suitable delivery in a clinical setting could be established.

In summary, we found in patients with refractory disease that single exposure to a visual image of the CRPS hand digitally manipulated to match the subjective desired hand appearance, reduces body perception disturbance and pain. Repeated illusory exposure sustained this effect in pain. A reduction in body perception disturbance and pain in patients with refractory disease suggests exciting treatment potential for CRPS and other chronic pain conditions where body perception disturbances arise. Future studies are required to determine dosage and clinical suitability in order to achieve sustained relief for those with longstanding CRPS.

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CONFLICT OF INTEREST

No conflicts of interest are declared for all the authors. JS Lewis's salary and costs of the project were funded by a National Institute for Health Research Post-Doctoral Fellowship (grant number CAT-CL-03–2012–019).

AUTHOR CONTRIBUTIONS

Dr Jennifer Lewis is responsible for the integrity of the work from inception to the published article. Dr Roger Newport provided substantial contributions to the conception and design. Professor Gordon Taylor significantly contributed to analysis and interpretation of data. All authors discussed the results and contributed to and have given final approval for the final version of manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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