Prism adaptation treatment for upper-limb Complex Regional Pain Syndrome: a double-blind randomized controlled trial

Halicka, Monika\textsuperscript{a,b,*}; Vittersø, Axel D.\textsuperscript{a,b,c}; McCullough, Hayley\textsuperscript{d}; Goebel, Andreas\textsuperscript{d,e}; Heelas, Leila\textsuperscript{f}; Proulx, Michael J.\textsuperscript{b,g}; Bultitude, Janet H.\textsuperscript{a,b}

\textsuperscript{a}Centre for Pain Research, University of Bath, Bath, United Kingdom
\textsuperscript{b}Department of Psychology, University of Bath, Bath, United Kingdom
\textsuperscript{c}Department of Sport and Health Sciences, University of Exeter, Exeter, United Kingdom
\textsuperscript{d}Pain Research Institute, Department of Translational Medicine, University of Liverpool, Liverpool, United Kingdom
\textsuperscript{e}Department of Pain Medicine, Walton Centre NHS Foundation Trust, Liverpool, United Kingdom
\textsuperscript{f}Optimise Pain Rehabilitation Unit, Oxford University Hospitals NHS Trust, Oxford, United Kingdom
\textsuperscript{g}Centre for Real & Virtual Environments Augmentation Labs, Department of Computer Science, University of Bath, Bath, United Kingdom

*Corresponding author

Email: mon.halicka@gmail.com
Phone: +44 1225 386226
Address: Department of Psychological Sciences, University of Liverpool, Eleanor Rathbone Building, Bedford Street South, Liverpool, L69 7ZA, United Kingdom

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Abstract

Initial evidence suggested that people with Complex Regional Pain Syndrome (CRPS) have reduced attention to the affected side of their body and the surrounding space, which might be related to pain and other clinical symptoms. Three previous unblinded, uncontrolled studies showed pain relief following treatment with prism adaptation, an intervention that has been used to counter laterised attention bias in brain-lesioned patients. To provide a robust test of its effectiveness for CRPS, we conducted a double-blind randomized controlled trial of prism adaptation for unilateral upper-limb CRPS-I. Forty-nine eligible adults with CRPS were randomized to undergo two-weeks of twice-daily home-based prism adaptation treatment (n = 23) or sham treatment (n = 26). Outcomes were assessed in person four weeks prior to and immediately before treatment, and immediately after and four weeks post-treatment. Long-term postal follow-ups were conducted three and six months after treatment. We examined the effects of prism adaptation versus sham treatment on current pain intensity and CRPS symptom severity score (primary outcomes); as well as sensory, motor, and autonomic functions, self-reported psychological functioning, and experimentally tested neuropsychological functions (secondary outcomes). Primary and secondary outcomes did not differ between the prism adaptation and sham treatment groups when tested at either time point following treatment. Overall, CRPS severity significantly decreased over time for both groups, but we found no benefits of prism adaptation beyond sham treatment. Our findings do not support the efficacy of prism adaptation treatment for relieving upper-limb CRPS-I. This trial was prospectively registered (ISRCTN46828292).
1. Introduction

Complex Regional Pain Syndrome (CRPS) is associated with continuous pain in one or more limbs accompanied by sensory, motor, and autonomic disturbances that are disproportionate to any inciting injury [32]. Individuals with CRPS can also show neuropsychological symptoms reminiscent of hemispatial neglect after brain injury [30]. These can present as distorted cognitive representations of the CRPS-affected limb(s) [42,48,70,85,94], reduced attention to the affected limb(s) and corresponding side of external space [10,19,22,24,74,84], poorer mental representation of the affected side of space [99], and spatially-defined motor deficits [84]. The extent of these neuropsychological changes has been associated with the severity of clinical signs of CRPS [22,43,48,73,74,84,85,106] and could pertain to its central mechanisms [86].

Prism adaptation (PA) is a sensorimotor training technique used to reduce lateralised biases in attention, spatial representations, and (ocular)motor performance in hemispatial neglect after brain injury [53,67,90]. Considering similar neuropsychological deficits in CRPS, three previous studies tested the efficacy of PA in a total of 13 patients with this condition. They reported significant relief of pain and other CRPS symptoms following eight to 20 PA sessions performed with the affected arm when participants adapted towards their affected side [8,11,100]. The reduction in pain lasted up to two weeks. Thus, PA has the potential to durably relieve pain and other symptoms of CRPS. Because PA is quick (5-10 minutes a day), inexpensive, and self-administered, it is an appealing intervention compared to more intensive neurocognitive treatments like graded motor imagery [71]. However, the strength of available evidence for PA is limited, because it was only tested in small samples, without any control treatments or blinding.

The mechanisms through which PA could relieve pain are unclear. One possibility is that it increases attention to the CRPS-affected side relative to the unaffected side. Indeed, when one patient underwent adaptation in the opposite direction such that the theoretical attention bias away from the affected side would be exacerbated, their pain increased [100]. More severe self-reported
“neglect-like” symptoms and spatial attention and motor biases have been related to greater pain intensity and worse long-term pain outcomes [22,84,85,106]. A potential second mechanism is that PA restores normal sensorimotor integration, the disruption of which is thought to contribute to pathological pain, including CRPS [7,35,61,100]. This is consistent with findings that individuals without spatial biases can also benefit from PA [11].

We conducted a double-blind, randomized, sham-controlled trial of PA for upper-limb CRPS-I. We hypothesised that two weeks of twice-daily PA treatment would reduce the primary outcomes of pain intensity and CRPS symptom severity more than sham treatment of the same intensity. We also predicted greater reductions in the secondary outcomes of neuropsychological symptoms (i.e. biases in spatial cognition, motor control, and body representation), clinical signs of CRPS, and self-reported CRPS-related and psychological disturbances following PA compared to sham treatment. The outcomes were assessed at six time points: to establish a one-month pre-treatment baseline, and to examine any immediate effects of PA and their retention at one, three, and six months post-treatment.

2. Methods

2.1. Study design and participants

The study was a two-arm parallel group RCT. It was prospectively registered (ISRCTN46828292) and the full details of the study are reported in the study protocol and analysis plan [31]. Any protocol deviations are specified in Text S1, Supplemental Digital Content 1. The study was approved by the UK National Health Service (NHS) Oxfordshire Research Ethics Committee A and Health Research Authority (REC reference 12/SC/0557).

Recruitment was conducted via post through the National CRPS-UK Registry, internal registries of the Royal United Hospitals and Walton Centre NHS Foundation Trusts, and clinicians’ referrals
through the Oxford University Hospitals NHS Foundation Trust and other NHS pain clinics in the UK. Word of mouth, print and online advertisements, as well as social media were further used to disseminate information about the study. Participants were recruited between March 2017 and December 2018, and the final long-term follow-up took place in July 2019.

Following provisional assessment of eligibility through a phone interview, recruited participants took part in four research sessions (RS) at the University of Bath (n = 33), University of Liverpool (n = 9), or in the participant’s home (for participants who were unable to travel; n = 7). Participants gave written informed consent at the beginning of RS1, prior to any study-related procedures. The research sessions involved in-person assessment of eligibility criteria and of the primary and secondary outcomes, including self-report questionnaires, clinical assessments, and tests of neuropsychological functions. Each RS lasted from two to four hours, including breaks between the assessments. The data collection schedule is presented in Figure 1. The baseline was measured over two research sessions (RS1 and RS2) separated by four weeks. Immediately after RS2, participants commenced a two-week home-based treatment period. Treatment outcomes were measured over two research sessions, one immediately (RS3) and one four weeks (RS4) after completing the treatment. Two long-term follow-ups were conducted via post – one at 12 weeks (LTFU1) and one at 24 weeks (LTFU2) after completing the treatment. The flow of participants through each stage of the study is displayed in a CONSORT diagram (Figure 2).

[Figure 1]

[Figure 2]

Participant inclusion criteria were: being aged 18-80 years; having a diagnosis of CRPS-I primarily affecting one upper limb based on the Budapest research criteria [32]; having a CRPS diagnosis for ≥3 months at the time of RS1; and having a current pain intensity ≥2 on a 0-10 Numeric Rating Scale. Exclusion criteria were: lacking sufficient English language ability to provide informed consent; being classified as legally blind; reporting a history of neurological disorder (e.g. stroke, neurodegenerative
disease, or traumatic brain injury); having CRPS in the opposite limb meeting the Budapest clinical or research criteria; reporting confirmed nerve damage (CRPS-II); reporting or showing dystonia or other physical impairment that would prevent satisfactory execution of PA/sham treatment; or reporting severe psychiatric comorbidity (e.g. schizophrenia [103]) that could be associated with perceptual changes. Inclusion and exclusion criteria were assessed in RS1 and RS2.

Participants with CRPS were primarily recruited for the current RCT of PA treatment, but we also collected measures of spatial cognition, motor control, and body representation at baseline (RS1) for comparison with pain-free controls (data reported elsewhere [29]).

2.2. Interventions

Both groups were instructed to continue any usual treatments (including medications), but were asked not to change their treatment regimens throughout the duration of the trial if possible.

Current treatments and any changes are reported in Table S1, Supplemental Digital Content 2.

2.2.1. Prism adaptation treatment

Participants randomised to the PA treatment used welding goggles fitted with 35-diopter Fresnel lenses that induced approximately 19° lateral optical deviation (visual shift) away from the CRPS-affected side. In each treatment session, participants were seated approximately 50 cm from a wall or other vertical surface (distance was adjusted individually to correspond to the participant’s almost fully extended arm). An A4 sheet was positioned on the wall in a landscape orientation at eye-level and in line with their body midline. There were two targets (2 cm-diameter red circles) on the pointing sheet, located 12.5 cm to the left and 12.5 cm to the right of participant’s body midline.

While wearing the prism goggles, participants used their CRPS-affected arm to perform 50 pointing movements, as fast as possible, alternating between the left and right target.

An example of prism adaptation is illustrated in Figure 3. Prismatic shifts were directed away from the CRPS-affected side, thus participants with left-CRPS would use rightward-shifting prism goggles.
as illustrated in the figure. Due to the rightward visual shift, pointing would initially err to the right. However, with repeated movement execution and motor learning, the pointing would become increasingly accurate, as the movements would adjust in the opposite direction (to the left). This adaptive realignment of sensorimotor reference frames [82,102] would produce movement after-effects towards the left (affected) side. That is, once the goggles were removed, pointing would temporarily err to the left. Conversely, participants with right-CRPS would use leftward-shifting prismatic goggles to induce adaptive realignment (movement after-effects) towards their affected side. Studies from neurologically healthy individuals and stroke patients show that these short-term movement after-effects are accompanied by a longer-lasting realignment of attention, spatial representations, and lateralised (ocular) motor performance in the same direction as the after-effect [3,13,21,40,44,51–53,63,64,67,89,90,95,96,98,105].

[Figure 3]

The chosen direction of PA, inducing a visual shift away from the affected side and thereby an after-effect towards the affected side, is consistent with previous PA studies in CRPS [8,11,100] and the technique’s application in rehabilitation of hemispatial neglect after brain injury [53,90]. To enhance the effects of PA, welding goggles occluded the first half of the arm movement and participants were encouraged to point as quickly as possible. Both of these measures are thought to reduce any deliberate mis-aiming on behalf of the participants and encourage greater adaptive realignment (i.e. “true” sensorimotor adaptation) [17,82,83].

Immediately after RS2, participants were trained in person in how to carry out the treatment by a research psychologist JHB or ADV (neither of whom were involved in any data collection) according to a standardised protocol (see training script in Text S2, Supplemental Digital Content 1). Once the researcher was satisfied that the participant understood the treatment procedure, they performed the first treatment during this training session under the guidance of the researcher. At the end of the training session participants received a pair of prism goggles in a sealed opaque bag, a pointing
sheet, written instructions, and a link to a video tutorial (see Video, Supplemental Digital Content 3) to take home. In addition to the treatment that they underwent during training, participants were instructed to perform twice-daily self-guided treatment sessions at home for two weeks, resulting in 29 treatment sessions in total. Participants were instructed to commence the home-based treatment on the day following RS2, perform one session in the morning and on in the evening, and record the start and end time of each session in a provided logbook.

2.2.2. Sham treatment

Participants randomized to the sham treatment carried out exactly the same procedure as described above, except they used welding goggles fitted with neutral lenses that did not induce any lateral visual shift [9,67]. The neutral lenses distorted the acuity and clarity of vision to a similar extent as prism lenses (only without any lateral shift), therefore the two treatment arms were similar aside from the sensorimotor adaptation.

2.3. Randomisation and blinding

Participant randomization was performed 1-5 days before RS2 by JHB, who was not involved in any data collection. Participants were randomly assigned to either PA or sham treatment group with equal allocation ratio, using MINIM [66] software to minimize baseline (RS1) group differences in current pain intensity, CRPS severity score, primarily affected arm, pre-CRPS dominant hand, sex, age, presence of CRPS in other body parts, presence of other non-CRPS pain, and CRPS duration. The primary outcome measures (current pain intensity and CRPS severity score) were given double weighting compared to the other minimisation characteristics as we considered matching the two groups for these factors to be a higher priority. Note that participants excluded between treatment allocation and RS3 (Figure 2) were removed from the minimization procedure so that subsequently recruited participants could be allocated independent of these exclusions and according to the current pool of participants remaining in each arm.
The only researchers who were aware of individual treatment allocations were those who randomised the participants and/or trained them in carrying out PA or sham treatments and provided them with prism or neutral goggles (JHB and/or ADV). These researchers were not involved in the assessments of any outcomes at any point in the trial. In RS3, the participants returned the goggles in a sealed opaque bag to MH, which she handed unopened to JHB. The researcher responsible for enrolment and all data collection (MH) remained blinded to participants’ treatment allocation until the last participant completed their RS4. Following RS4, there were no further in-person assessments as the long-term follow-up was conducted via postal questionnaires and scored by blinded research assistants. The participants were blinded to their treatment allocations throughout the entire duration of the trial. They were informed that they might receive real or sham treatment, and that both involved reaching out to touch visual targets with their affected arm while wearing goggles that distort vision. However, participants were not made aware of the specific nature of the intervention nor the differences between the types of goggles used in the two treatment arms. All documentation and instructions referred to the treatment arm as “sensorimotor training”.

2.4. Measures

2.4.1. Demographics

In RS1, participants reported on demographic characteristics, including age, sex and handedness prior to CRPS onset. They were asked to complete two versions of Edinburgh Handedness Inventory (EHI) [76]: once rating their recalled hand preference prior to CRPS onset, and once rating their current hand preference. Total scores can range from -100 (extreme left-handedness) to 100 (extreme right-handedness). To approximate the functional impact of CRPS, we calculated an absolute difference between current and recalled EHI scores, that is, change in handedness. We also interviewed the participants regarding their clinical history, including the date and type of any
inciting injury, CRPS duration (time since diagnosis), any co-morbidities, and any ongoing treatments for CRPS.

2.4.2. Primary outcomes

A change between RS2 and RS3 in current pain intensity and CRPS symptom severity score were the primary outcomes. In RS1-RS4 and LTFU1-LTFU2, participants rated their current pain intensity in the CRPS-affected limb on a Numerical Rating Scale (NRS) from 0 (no pain) to 10 (pain as bad as you can imagine). This measure was taken from the Brief Pain Inventory (BPI; item 6) [12], and has been recommended as a core outcome for chronic pain trials [15,28]. CRPS severity was assessed in RS1-RS4 according to a standardised protocol [34]. Eight self-reported symptoms and eight signs evaluated upon clinical examination were scored as 0 (absent) or 1 (present) based on sensory testing, and visual and manual examination (see section 2.4.3.2. for details). The summed CRPS severity score can range from 0 (no CRPS symptoms) to 16 (most severe CRPS symptoms). The CRPS severity score has good discrimination abilities, concurrent validity, and adequate sensitivity to change [33,34], and was recommended as the core outcome measure for CRPS clinical studies [28].

2.4.3. Secondary outcomes

2.4.3.1. Self-report measures

Self-reported secondary outcomes measured in RS1-RS4 and LTFU1-LTFU2 included questionnaires about pain, body representation, and emotional functioning. We measured pain intensity and interference, using the BPI (0-10 scale for each subscale; higher scores indicate greater intensity/interference [12]), and neuropathic features of experienced pain, using Pain Detect Questionnaire (PDQ; -1-38 scale; higher scores indicate greater neuropathic component of pain [23]). Body representation was measured using the Bath CRPS Body Perception Disturbance Scale (BPDS; 0-57 scale; higher scores indicate greater distortions of body perception [47]). For emotional functioning, we measured pain-related fear of movement and re-injury, using Tampa Scale for
Kinesiophobia (TSK; 17-68 scale; higher scores indicate more severe kinesiophobia [65]) and mood disturbance, using Profile of Mood States (POMS; 17-229 scale; higher scores indicate greater mood disturbance [62]). In RS1, participants also rated their levels of optimism and pessimism, using Revised Life Orientation Test (LOTR; 0-24 scale; higher scores indicate higher optimism level [93]), and their expectations and criteria for success in chronic pain treatment, using Patient Centred Outcomes Questionnaire (PCOQ; each item scored on 0-10 scale; higher scores indicate higher usual, desired, expected, and considered successful (in terms of the treatment outcome) levels of pain, fatigue, emotional distress, and interference, and higher importance of improvement in each of these areas [87]). In post-treatment RS3-4 and LTFU1-LTFU2, participants rated their impression of how much their activity limitations, symptoms, emotions, and overall quality of life related to CRPS changed due to treatment, using the Patient Global Impression of Change questionnaire (PGIC; 1-7 scale; 1 indicates no change or worsening of symptoms; higher scores indicate greater improvement [37]). We chose the abovementioned self-report questionnaires based on recommendations for core outcome measures for chronic pain trials [15] and the existing literature on CRPS implicating other relevant measures (e.g. [27]). The LOTR and PCOQ were included to assess whether two treatment groups were matched on their average optimism and expectations of outcomes, because these factors can affect the success of novel treatments [4,49,104].

Throughout the first 10 weeks of the trial (RS1-RS4), participants rated their average level (over the past 24 hours) of pain intensity, the degree to which their symptoms interfered with their daily life, and range of movement in the affected limb, using daily logbooks (0-10 NRS scale; higher scores indicate greater pain intensity, symptoms interference, and better range of movement).

2.4.3.2. Clinical assessments

We assessed participants’ CRPS signs and symptoms, and sensory, autonomic, and motor functions in RS1-RS4. Each assessment started with the unaffected side. Sensory tests were performed on the
most painful site on the CRPS-affected limb and the corresponding site on the unaffected limb, unless specified otherwise.

The Budapest research criteria were assessed in RS1 and RS2 to confirm CRPS diagnosis, and in RS3 and RS4 to determine whether participants still met the diagnostic criteria post-treatment. The same assessments were used to calculate the CRPS severity score in each research session. Specifically, participants reported whether they experienced: (1) continuous, disproportionate pain in their affected limb; (2) allodynia and/or hyperpathia in their affected limb; (3) temperature, (4) colour, and (5) sweating asymmetries between the affected and unaffected limbs; (6) oedema, (7) dystrophic changes, and (8) motor abnormalities in their affected limb. During each research session, we also tested for presence of the same CRPS signs: (9) hyperalgesia, using a single pinprick; (10) allodynia, using a single brush stroke, touch of a 128 Hz tuning fork, and of a cold metal pen; (11) temperature asymmetry, using an infrared thermometer with thermal resolution of 0.1°C (arithmetic mean of three recordings from each limb; asymmetry was present if absolute difference between two limbs was >1°C); (12) colour asymmetry, using visual examination; (13) asymmetric oedema, using a figure-of-eight hand size measure [78] (arithmetic mean of three measurements of each hand; oedema was present if size of the affected hand was >0.56cm larger than size of the unaffected hand [45]); (14) sweating asymmetry, using visual and tactile examination; (15) dystrophic changes, using visual examination; and (16) motor abnormalities, using an electronic hand dynamometer (arithmetic mean of three maximum force grips with each hand; weakness was present if affected/unaffected hand grip force ratio was <0.95 [left-handed participants] or <0.85 [right-handed participants] [39,79]); delta finger-to-palm distance [101] (∆FTP; decreased range of movement was present if affected/unaffected ratio was <0.9); and visual examination (tremor, muscle spasms, dystonia, range of movement).
The reported symptoms, and the signs of CRPS rated as present upon in-person examination were summed to obtain the CRPS severity score. We additionally took photographs of both limbs and videos of fist closure and opening, wrist flexion, extension, and radial and ulnar deviation. These were double-scored for the presence of colour asymmetry, dystrophic changes, and motor abnormalities by a trained research assistant who was blind to treatment allocation, affected limb, and time point of assessment. Cohen’s kappa statistics for inter-rater agreement were significantly different from zero, indicating fair agreement for colour asymmetry ($\kappa = .21, p = .004$) and dystrophic changes ($\kappa = .23, p < .001$), and borderline slight/fair agreement for motor impairment ($\kappa = .20, p < .001$).

Secondary outcomes of sensory function of the affected relative to unaffected limb assessed in RS1-RS4 included elements of quantitative sensory testing, administered according to the standardised protocol [88]. Specifically, we measured Mechanical Detection Thresholds (MDT) using von Frey filaments. A positive threshold ratio $[(\text{MDT}_{\text{affected}}-\text{MDT}_{\text{unaffected}})/\text{MDT}_{\text{affected}}]$ indicates increased tactile detection threshold (hypoesthesia) on the affected side. We further measured Mechanical Pain Thresholds (MPT) using pinprick stimulators. A positive threshold ratio $[(\text{MPT}_{\text{unaffected}}-\text{MPT}_{\text{affected}})/\text{MPT}_{\text{unaffected}}]$ indicates decreased pain threshold (hyperalgesia) on the affected side. A procedure to measure allodynia was adapted from the dynamic mechanical allodynia test [88], in which a cotton ball, a Q-tip, and a brush were applied to the skin five times each, in a random order. An arithmetic mean of participants’ ratings for each sensation from 0 (no sharp, pricking, stinging, or burning sensation) to 100 (most intense pain sensation imaginable) was used to quantify the severity of allodynia on the affected limb. We also measured Two-Point Discrimination thresholds (TPD) using a disk with one and two plastic tips separated by 2-15mm distance, which were applied to participants’ index fingertips. Participants reported whether they perceived touch on one point or two points on their finger. Starting from 7mm distance, we increased or decreased (down to a single
tip) the distance according to a staircase procedure (analogous to that used for MDT and MPT), until we obtained five subthreshold (perceived touch on one point) and five suprathreshold (perceived touch on two points) values. A geometric mean of these 10 values was taken as a TPD threshold for each hand. A positive threshold ratio \(\frac{(TPD_{\text{affected}} - TPD_{\text{unaffected}})}{TPD_{\text{affected}}}/TPD_{\text{affected}}\) indicates higher tactile discrimination threshold, that is, less precise discrimination ability of the affected hand.

In addition to contributing to the CRPS severity score, the following measures were used as secondary outcomes of autonomic and motor function of the affected relative to unaffected limb: temperature difference (affected–unaffected; a negative score indicates that the affected limb was colder; absolute values were also analysed); oedema (affected–unaffected; higher scores indicate greater swelling of the affected limb); grip strength (affected/unaffected; scores <1 indicate weaker strength of the affected hand); and ΔFTP distance (affected/unaffected; scores <1 indicate lower range of movement of the affected hand).

2.4.3.3. Tests of neuropsychological functions

In RS1-RS4, the participants completed six experimental tests of the following neuropsychological functions: visuospatial attention (Temporal Order Judgement, Landmark, and Greyscales tasks); mental representation of space (Mental Number Line Bisection task, MNLB); spatially-defined motor function; and body representation (Hand Laterality Recognition task). Detailed descriptions of the experimental materials and methods can be found in the trial protocol [31]. Below we summarise the key details of the administered tasks that are necessary to interpret the results.

All experimental tasks were programmed and administered using PsychoPy software [77]. For the tasks involving presentation of visual stimuli on a computer screen, a touch-screen (34.5cm x 19.4cm size, 1920 x 1080 pixels resolution) was positioned at 50cm viewing distance. In all tasks (except the MNLB), participant’s head was stabilised by a chinrest and they were instructed to focus their gaze on a fixation cross that was aligned with their body midline. When a manual response was required, participant used their unaffected hand to press the buttons, which were aligned orthogonally to the
required response format (i.e. for left/right responses, participant pressed colour-coded bottom/top buttons). A short practice session was completed before each task to familiarise the participant with the procedures and ensure that they could follow the instructions. Data for stimuli/responses in the left and right sides of space for all tasks were recoded after collection in terms of affected and unaffected space relative to each participant’s CRPS-affected side.

The Temporal Order Judgement (TOJ) task measures covert spatial attention. On each trial, participant saw a pair of brief (10ms), identical, red light flashes, presented with different offsets onto a white table surface, one on each side of space (approximately 18° to the left and 18° to the right of a fixation point, located approximately 28cm away from their torso). Participant reported which of the two lights they perceived first (in one response block) or second (in another response block) by saying “left” or “right”. The stimulus locations and responses were expressed relative to each participant’s CRPS-affected side (i.e. as affected and unaffected). There were 10 temporal offsets between the lights (±10, ±30, ±60, ±120 and ±240ms; negative values indicate that the light on the affected side appeared first). Each temporal offset was presented 15 times in pseudorandom order, resulting in 150 trials per response block. The participant’s responses to different temporal offsets were fitted with a cumulative Gaussian using a criterion of maximum likelihood to derive the Point of Subjective Simultaneity (PSS) for each block of the task. The PSSs from two response blocks were then averaged to account for any response bias [20]. The PSS expresses by how many milliseconds the light in the affected side of space had to precede (negative PSS) or follow (positive PSS) the light in the unaffected side of space for both lights to be perceived as simultaneous.

Information that receives greater attention is perceived earlier than information that receives lesser attention [97]. Thus, a negative PSS value indicates reduced attention to the affected side of near space relative to the unaffected side.
The Landmark task [55] measures visual representation of relative horizontal distance in near space. On each trial, participants saw a fixation cross on constant display in the centre of the computer screen. After 500ms, a pair of landmarks (white 1.1° diameter circles) was presented simultaneously, one landmark to the left and one landmark to the right of the fixation cross. The landmarks were displayed for 300ms and were followed by a 200ms mask. While the distance between both landmarks was 15° across all trials, their relative distance from the fixation cross varied from ±8.1° to ±6.9° away from fixation in the horizontal plane by 0.1° increments (negative values represent the location of the left landmark, and positive values represent the location of the right landmark, relative to central fixation at 0°). Participants pressed a button to indicate whether the left or the right landmark appeared closer to (in one response block) or further from (in another response block) the fixation cross, which initiated the next trial. The stimulus locations and responses were expressed relative to each participant’s CRPS-affected side (i.e. as affected and unaffected). Each of the 13 pairs of landmarks (six pairs in which the landmark on the affected side was further from fixation, six pairs in which the landmark on the unaffected side was further from fixation, and one pair in which both landmarks were equidistant) was presented 15 times in pseudorandom order, resulting in 195 trials per block. The participant’s responses to different relative landmark locations were fitted with a cumulative Gaussian using a criterion of maximum likelihood to derive the Point of Subjective Equality (PSE) for each block of the task. The PSEs from two response blocks were averaged to account for any potential response bias. The PSE expresses the relative distance (°) at which the landmark on the affected side of space had to be further from (negative PSE) or closer to (positive PSE) the fixation cross in order to perceive the two landmarks to be equidistant. A negative PSE value indicates underestimation of the distance on the affected relative to the unaffected side, and thus underrepresentation of the affected side of near space.

The Greyscales task [75] measures overt spatial attention. On each trial, participants saw a pair of horizontal bars (9.95° or 12° x 1.95°) presented in the centre of a computer screen on constant display, one above the other. The two bars were filled with greyscales (i.e. a gradient of shading with
one horizontal end darker than the other) and were mirror images of each other so that one bar was
darker on the left side and the other bar was darker on the right side (expressed relative to each
participant’s CRPS-affected side, i.e. as affected and unaffected side). Participants pressed a button
to indicate whether the top or the bottom bar appeared to be darker overall, which initiated a
150ms mask followed by the next trail. There were 40 trials in which the bars were presented in
different vertical alignments. We calculated an index of spatial bias by subtracting the number of
“unaffected” responses (choosing a bar darker on the unaffected side, regardless of its vertical
alignment) from the number of “affected” responses, and dividing the difference by the total
number of trials. A negative value indicates that a higher proportion of overall darkness judgements
was made based on the unaffected sides of the stimuli, consistent with reduced attention to the
affected relative to unaffected side.

The Mental Number Line Bisection (MNLB) task [99] measures mental representation of space,
based on an implicit representation of numbers in a left-to-right linear arrangement [14]. On each
trial, the experimenter read aloud a pair of numbers (from 2-98 number range) that were separated
by an interval of 9, 16, 25, 36, 49, or 64 digits. Participants were instructed to verbally report the
subjective midpoint between the given pair of numbers, without making any calculations. Each pair
of numbers was presented once in ascending and once in descending order to account for any
response bias, and each of the six intervals was repeated seven times, resulting in 84 trials presented
in pseudorandom order. We calculated an index of spatial bias by subtracting participant’s subjective
midpoint from the objective midpoint number on each trial, and averaging the scores across all
trials. A negative index is consistent with overestimating the subjective midpoint towards larger
numbers (i.e. a rightward bias). The results were expressed relative to each participant’s CRPS-
affected side, thus a negative index indicates a bias away from the affected side of the mental
representation of space, or underrepresentation of the affected side of mental space.
The spatially-defined motor function task [57] measures directional hypokinesia and directional bradykinesia, that is slowing of initiation and execution of movements directed towards the affected relative to unaffected side. On each trial, participants focused on a fixation cross in the centre of a computer screen, and held down a button with their index finger. After a 1500ms-3000ms interval, a black target (1.4° high “X”) appeared 12° to the left or 12° to the right of fixation (i.e. in the left or right visual field, hereafter VF), in pseudorandom order, for 2000ms. Once the target appeared, participants were required to release the button, touch the screen, and return their index finger to the button as soon as possible, which initiated the next trial. There were 30 trials per block. We recorded the times elapsed between the target onset and button release (movement initiation time), and between the button release and touch on the computer screen (movement execution time). There were three hand starting positions, in which the button was aligned with the participant’s body midline (central), located 25cm to the left from body midline (left), and located 25cm to the right from body midline (right). Hand starting positions and target locations (VFs) were expressed relative to each participant’s CRPS-affected side, that is, as affected, central, and unaffected starting positions, and affected and unaffected VFs. Participants completed the task from each starting position twice, once with their unaffected hand, and once with their affected hand, resulting in six blocks in total. The order of the blocks was counterbalanced between participants, and they alternated between the affected and unaffected hand.

Participants’ average movement initiation and execution times for each combination of hand starting position and VF were used to calculate indices of directional hypokinesia and bradykinesia towards the affected side [92], separately for each hand used to complete the task. Index A quantifies the speed of initiating movements towards the affected side (from central starting position) relative to the unaffected side (from affected starting position). This index was calculated as: [central starting position (affected VF – unaffected VF) – affected starting position (affected VF –
unaffected VF)]. Index A allows to dissociate motor and perceptual neglect (i.e. effect of VF), however, it involves movement trajectories of different length. Thus, we also derived Index B that directly quantifies the speed of initiating movements of the same physical length towards the affected side (from central starting position) relative to the unaffected side (from affected starting position). Index B was calculated as: [central starting position (affected VF) – affected starting position (affected VF)]. Positive values of indices A and B indicate slowing of initiation of movements directed towards the affected relative to unaffected side, suggestive of directional hypokinesia towards the affected side. The same indices A and B were calculated for movement execution times. Here, positive values suggest directional bradykinesia towards the affected side.

The Hand Laterality Recognition task [94] measures body representation. On each trial, participants focused on a fixation cross in the centre of a computer screen. After 1000ms, an image of a hand (12.9° x 12.9°) appeared for 180ms, 8° to the left or 8° to the right of fixation (i.e. in the left or right VF). Participants were required to indicate as fast and as accurately as possible whether the image depicted a left or a right hand by pressing a button, which initiated the next trial. We measured accuracy and reaction times. There were 25 images of left hands in different postures and rotations from upright (0°, 90°, 180°, or 270°). The same images were mirror-reversed to create images of right hands in the same postures and rotations. Each image was presented once in the left and one in the right VF in pseudorandom order, resulting in 100 trials. The depicted hand was expressed relative to individual participant’s CRPS-affected side, that is, as affected and unaffected hand.

Participants’ accuracy rates and average reaction times to correctly responded-to trials for each task condition were averaged across two VFs, because the visual field effects were not the primary interest of this trial, and will be reported elsewhere. We calculated the differences in accuracy rates and reaction times between depicted hands to obtain two indices of hand laterality recognition: accuracy index (unaffected hand – affected hand) and RT index (affected hand – unaffected hand).
Positive values of each index indicate less accurate and slower recognition of depicted hands corresponding to participant’s affected hand, relative to depicted hands corresponding to their unaffected hand. Thus, positive accuracy and RT indices suggest distorted representation of the CRPS-affected limb.

2.5. Statistical analyses

2.5.1. Sample size calculation

The study was powered to evaluate the effects of PA treatment on a change in the primary outcome of pain intensity between RS2 and RS3. We estimated [16] that a sample of 21 participants per treatment group would provide 90% power to detect a minimal clinically significant reduction of 2 on the primary outcome of pain intensity (0-10 NRS; [18]), with a SD of 1.98 (based on our previous research [10]), and a 2-tailed alpha of 0.05.

2.5.2. Incomplete outcome data

Our primary analysis involved the intention-to-treat (ITT) population, that is, participants who received their allocated intervention, regardless of their treatment adherence or completion of the outcome assessments. Note that three participants who were allocated to PA treatment did not attend RS2 (n = 2) or did not meet the eligibility criteria in RS2 (n = 1), thus they were not trained and did not receive any treatment (Figure 2). Therefore, the total ITT sample consisted of 49 participants. Eight participants dropped out of the study after having been trained in their allocated intervention (PA treatment n = 2, sham treatment n = 6), and four more participants were lost to long-term follow-up (n = 2 in each treatment group). We report a supportive per-protocol analysis of those participants who completed their allocated treatment (missed no more than six treatment sessions) and provided complete outcome data in Text S3, Supplemental Digital Content 1. The results of the per-protocol analysis are broadly consistent with the ITT analysis. To account for any missing data in the primary ITT analysis, we carried forward the baseline post-randomisation
observation (RS2; the PGIC questionnaire data was only collected post-treatment, thus RS3 observation was carried forward).

Any missing questionnaire items were estimated using the individual participant’s mean for the relevant subscale (0.08% of items across all sessions and participants). Any missing data from the self-report questionnaires, clinical assessments, and computer-based tasks within each research session were replaced by a mean score of the relevant treatment group on the same measure (0.08% of data points across all measures and sessions). Note that six participants completed the test of spatially-defined motor function only with their unaffected hand (due to exacerbation of pain, limited range of movement, or weakness of the affected hand), but their affected hand data was not replaced because data for each hand was analysed separately.

2.5.3. Analyses

We used IBM SPSS Statistics 25 [38], R 3.5.3 [81], and MATLAB 2018b [56] software to process and analyse the data. Data preparation procedures are reported in Text S4, Supplemental Digital Content 1. Throughout, we reported bootstrapped bias-corrected and accelerated 95% confidence intervals (BCa 95% CIs) around all mean and median values. We used bootstrapped χ² tests, bootstrapped t-tests (or their non-parametric alternatives in case of violation of parametric assumptions), and ANOVAs to compare mean values between treatment groups and between data collection time points. ANOVA is robust to moderate violations of normality and homogeneity of variance [5,6], and we used Greenhouse-Geisser corrections if the sphericity assumption was violated. However, where severe (i.e. more than borderline significant and in multiple conditions) violations of the assumptions of normality, homogeneity of variance, and sphericity were found, we used linear mixed models analyses with non-parametric bootstrapping procedures (n = 1000). For linear mixed models analyses, a model term made a significant contribution to predicting an outcome when the 95% CI around the coefficient estimate (B) did not include zero. For the remaining analyses, statistical significance was defined as p < .05. We used one-tailed tests for comparisons for which we had
directional hypotheses (i.e. RS2 vs. RS3 comparisons, as we predicted greater reductions on the outcome measures in PA than sham treatment group), and two-tailed tests for the remaining comparisons. We controlled for type I errors in the primary (but not exploratory) analyses by using Holm-Bonferroni correction for multiple comparisons within analysis of each outcome and reported adjusted p values ($p_{adj}$).

2.5.3.1. Descriptive characteristics and group matching

We performed a series of bootstrapped contrasts (t-tests or Mann-Whitney U tests for continuous variables, and χ² tests for categorical variables) to determine whether the two treatment groups were successfully equated on the minimisation factors, as well as on the average POMS, LOTR, and PCOQ scores, and the extent of exposure (i.e. average number of logged treatment sessions).

2.5.3.2. Effects of PA treatment on the primary outcomes

To evaluate the effects of PA treatment on the first primary outcome of pain intensity and the time course of any changes, we conducted a 2 (Group: PA treatment, sham treatment) x 6 (Time: RS1, RS2, RS3, RS4, LTFU1, LTFU2) ANOVA. We planned sixteen a-priori contrasts to compare RS1 vs RS2, RS2 vs RS3, RS3 vs RS4, RS2 vs RS4, RS2 vs LTFU1, RS4 vs LTFU1, LTFU1 vs LTFU2, and RS2 vs LTFU2 within each treatment group.

To evaluate the effects of PA treatment on the second primary outcome of the CRPS severity score and the time course of any changes, we conducted a 2 (Group: PA treatment, sham treatment) x 4 (Time: RS1, RS2, RS3, RS4) ANOVA. We planned eight a-priori contrasts to compare RS1 vs RS2, RS2 vs RS3, RS3 vs RS4, and RS2 vs RS4 within each treatment group.

2.5.3.3. Effects of PA treatment on the secondary outcomes

To evaluate the effects of PA treatment on self-reported pain and psychological functioning, sensory, motor, and autonomic function, and neuropsychological functions, and the time course of any
changes, we conducted 2x6 and 2x4 ANOVAs and planned the same contrasts as described for the analyses of the primary outcomes.

2.5.3.4. Predictors of the CRPS progression over time

To investigate whether any baseline factors could predict CRPS progression over time, independent of the treatment, we used the data from the total sample (N = 49) to perform exploratory best subsets regression analyses on the overall change in pain intensity and CRPS severity score throughout the course of the study. Change on these outcomes was quantified as individual regression slopes fitted to each participant’s ratings of current pain intensity across RS1-LTFU2 and to each participant’s CRPS severity scores across RS1-RS4. Negative slopes indicate greater improvement over time (i.e. reduction in pain and CRPS severity). Potential explanatory variables included participants’ demographic characteristics, self-reported pain and psychological functioning, sensory, motor, and autonomic function, and neuropsychological functions, as measured in RS1. We restricted the pool of potential predictors by excluding factors that lacked linear relationships with each outcome or were collinear with other predictors (see Text S5, Supplemental Digital Content 1). Best subsets regression is an automated approach that performs an exhaustive search for the best subset of factors for predicting the outcome and returns the best model of each size (up to a specified number of predictors) [54]. Considering our sample size (N = 49), we compared best subsets models that included one up to five predictors of each outcome. From the five models, the one with the lowest Akaike Information Criterion (AIC) was preferred as best fit. To address a potential issue of overfitting, we also performed a five-fold cross-validation [46] of each of the five models suggested by best subsets regression analyses. This approach randomly splits the data set into five folds (subsets of observations). Each model is trained using the 80% of the data (four folds) and then tested on the remaining 20% of the data (one fold). This process is repeated until each fold has served as a test subset. The average of five recorded errors is a cross-validation (CV) error. The lowest CV error indicates best model performance.
3. Results

3.1. Participant characteristics

Table 1 presents baseline characteristics and comparisons between PA and sham treatment groups. On average, participants reported moderate pain intensity (6/10), comparable with previous studies on prism adaptation (5.8-6/10; [11,100]) and other neurocognitive treatments (5.3-7/10; [42,59,71]) for CRPS. Median CRPS severity score in our sample was higher than the average severity reported for individuals with stable CRPS in the validation study of this tool (13 vs. 11.2/16; [34]), possibly because we used stricter inclusion criteria (Budapest research diagnostic criteria; [32]). Our participants on average had longer CRPS duration compared to other studies of neurocognitive treatments for CRPS (58 vs. 5-24 months; [8,11,42,59,71,100]). The proportion of participants with CRPS affecting their right side of the body was consistent with a large population study [68], although it was lower than in small-sample studies on prism adaptation (41% vs. 71-80%; [11,100]). Both the mean age and proportion of females were consistent with those previously reported in CRPS [11,34,68,91,100]. The most common comorbidities in our participants were depression (37%), anxiety (22%), migraines (16%), fibromyalgia (14%), and asthma (14%). These conditions were found to be prevalent in CRPS in previous population studies [50,69]. The most common treatments in the current sample included weak or strong opioids (57%), anticonvulsants (47%), paracetamol (45%), antidepressants (45%), physio-, hydro-, or occupational therapy (39%), and nonsteroidal anti-inflammatory drugs (35%; see Table S1, Supplemental Digital Content 2). Overall, demographic and clinical characteristics of our sample appear to be representative of general population of people with CRPS [2,34,68,91] and comparable to those reported in previous research investigating neurocognitive treatments for CRPS [8,11,42,59,71,100], except for the longer average disease duration in our study.
The randomization procedure successfully equated the two treatment groups on the minimization factors (Table 1). The two groups were also matched on baseline mean levels of optimism, mood disturbance, fear of movement, and expectations and criteria for success of the treatment (there were no significant differences between PA and sham treatment groups on any of the PCOQ items, $U_s \geq 212.00, p_{adj} \geq .27, ds \leq 0.51$).

Eight participants (16%) withdrew from the study following treatment allocation. They were excluded from per-protocol analysis (Text S3, Supplemental Digital Content 1), but their RS2 data was carried forward for the purpose of the primary intention-to-treat analysis. We compared their baseline (RS1) pain intensity and CRPS severity against confidence intervals around the mean pain intensity and CRPS severity score of participants who remained in the trial. Out of those who dropped out, five participants had greater pain intensity and four participants had greater CRPS severity compared to those who remained. However, the same or lower pain intensity and CRPS severity scores were found in another three and four participants who dropped out, respectively.

### 3.2. Treatment adherence and participant blinding

Twenty-one out of 23 participants (91%) in the PA treatment group and 20 out of 26 participants (77%) in the sham treatment group missed no more than six treatment sessions according to their logbooks (see Table S1, Supplemental Digital Content 2). Two participants in the PA and six participants in the sham treatment group missed more than six treatment sessions and/or did not provide post-treatment outcome data. The extent of exposure to treatment (i.e. average number of logged treatment sessions) was not significantly different between the two treatment groups (Table 1). The median recorded durations of the treatment sessions according to the participants’ logbook entries were 2min 25s in the PA group and 2min in the sham treatment group.

At the end of RS4, we asked each participant ($N = 41$) which treatment they thought they received. They could respond “real [PA]”, “sham”, or “no idea”. Similar proportions of participants in each
group made correct (real: 12.2%; sham: 12.2%) or wrong (real: 12.2%; sham: 7.3%) guesses as to their actual treatment allocation, or responded that they had no idea (real: 26.8%; sham: 29.3%), \( \chi^2(2) = .52, p = .771, \text{Cramer's } V = 0.11 \). Only 12% of participants in each group correctly guessed their treatment allocation, therefore participant blinding was successful.

### 3.3. Effects of PA treatment on the primary outcomes

Despite the PA group showing some reduction in the current pain intensity scores immediately after treatment (RS3; Figure 4a), the ANOVA did not reveal any significant main effects of Time, \( F(4.04, 189.81) = 1.82, p = 0.126, \eta^2_p = 0.04 \), or Group, \( F(1, 47) = 0.26, p = 0.615, \eta^2_p = 0.01 \), nor did it show any significant interaction between these factors \( F(4.04, 189.81) = 0.66, p = 0.624, \eta^2_p = 0.01 \). This indicates that there were no significant changes in pain intensity over time in either treatment group. Thus, contrary to our hypothesis, PA treatment did not reduce pain intensity more than sham treatment.

Analysis of the CRPS severity scores (Figure 4b) showed a large significant main effect of Time, \( F(2.28, 107.08) = 17.57, p < .001, \eta^2_p = 0.27 \), indicating that regardless of treatment, CRPS severity decreased over time (Figure 4b). Contrasts revealed a significant reduction in CRPS severity immediately after treatment (RS3; \( Mdn = 11.00, \text{BCa 95% CI [11.00, 11.00]} \)) compared to immediately before treatment (RS2; \( Mdn = 12.00, \text{BCa 95% CI [12.00, 12.00]} \)), \( Z = -3.91, p_{\text{adj}} = .002, d = 0.86 \). This reduction relative to RS2 was maintained four weeks after completing the treatment (RS4; \( Mdn = 11.00, \text{BCa 95% CI [11.00, 11.00]} \)), \( Z = -3.70, p_{\text{adj}} = .002, d = 0.81 \), but without further significant change from RS3, \( Z = -0.81, p_{\text{adj}} = .433, d = 0.16 \). CRPS severity did not change significantly between the first (RS1; \( Mdn = 13.00, \text{BCa 95% CI [13.00, 13.00]} \)) and the second baseline session, \( Z = -1.71, p_{\text{adj}} = .170, d = 0.35 \). There was no significant interaction effect, \( F(2.28, 107.08) = 0.17, p = .886, \eta^2_p < 0.01 \), nor was there any significant effect of Group, \( F(1, 47) = 0.17, p = .685, \eta^2_p < 0.01 \), on the CRPS severity scores. Thus, contrary to our hypothesis, CRPS severity did not decrease more following PA compared to sham treatment, but both groups improved over the treatment period.
We compared mean changes in pain intensity and CRPS severity over the treatment period (RS3 – RS2) between PA and sham treatment groups. Effect sizes of these differences might be important for planning future studies. For current pain intensity, the effect size was small, $d = 0.37$, 95% CI [-0.20, 0.94]. Mean pain reduction in the PA treatment group was -0.78 points on 0-10 NRS scale, BCa 95% CI [-1.55, -0.15]. In the sham treatment group, mean pain reduction was -0.19 points, BCa 95% CI [-0.68, 0.28]. For CRPS severity score, the effect size was negligible, $d = -0.13$, 95% CI [-0.69, 0.43]. Mean CRPS severity reduction in the PA treatment group was -0.78 points on 0-16 scale, BCa 95% CI [-1.19, -0.38]. In the sham treatment group, the mean CRPS severity reduction was -0.96 points, BCa 95% CI [-1.54, -0.38]. Individual pain and CRPS severity reduction scores over the treatment period are illustrated in Figure S1, Supplemental Digital Content 4. On an individual level, five participants in the PA group and four in the sham group achieved clinically significant reductions in pain (i.e. at least two-point decrease on 0-10 NRS scale [18]). None of the participants achieved clinically significant reduction in CRPS severity (i.e. at least 4.9 points decrease on 0-16 scale, although this threshold is quite conservative) [34].

### 3.4. Effects of PA treatment on the secondary outcomes

#### 3.4.1. Self-reported pain, body representation, and emotional functioning

A series of 2x6 ANOVAs was conducted on the self-report questionnaire scores to test the effects of PA on pain-related outcomes, body representation, and emotional functioning (see Table 2 for group average values across six time points; see Table 3 for ANOVA results).

| Table 2 |
| --- |

| Table 3 |
| --- |

A significant main effect of Time on pain interference (BPI) indicated that participants reported less interference from RS2 ($Mdn = 6.00$, BCa 95% CI [5.57, 6.71]) to RS4 ($Mdn = 5.57$, BCa 95% CI [4.86,
5.86]), regardless of treatment, $Z = -2.56$, $p_{\text{adj}} = .040$, $d = 0.54$. There were no significant changes in pain interference between other time points, $Zs \leq 1.86$, $p_{\text{adj}} \geq .273$, $ds \leq 0.38$. A significant main effect of Time for neuropathic features of pain (PDQ) suggested that participants’ scores decreased over time, regardless of treatment group. However, follow-up analyses revealed no significant differences between any of the time points of interest $Zs \leq 1.76$, $p_{\text{adj}} \geq .576$, $ds \leq 0.36$. An ANOVA on body perception disturbance (BPDS) revealed a significant interaction between Time and Group. While there were no changes in the sham treatment group, PA group showed reductions in body perception disturbance over time, yet these effects did not withstand correction for multiple comparisons, $ts \leq 2.86$, $p_{\text{adj}} \geq .336$, $ds \leq 0.54$. An ANOVA on fear of movement also revealed a significant interaction between Time and Group. While there were no changes in the PA group, the sham treatment group showed reductions in fear of movement over time; however, these effects did not withstand correction for multiple comparisons, $ts \leq 2.63$, $p_{\text{adj}} \geq .312$, $ds \leq 0.26$. There were no other significant main effects or interactions (see Table 3). Participants’ global impression of change due to treatment (PGIC) also did not differ between PA and sham treatment group at any of the post-treatment time points and indicated that on average participants in both groups perceived their symptoms to be either “almost the same”, or “a little better” (2-3 out of 7). Overall, contrary to our hypothesis, we found no evidence of significantly greater reductions in self-reported pain-related and psychological disturbances following PA compared to sham treatment.

Average daily logbook ratings of pain intensity, symptoms interference, and range of movement for each group are illustrated in Figure S2, Supplemental Digital Content 4. The PA and sham treatment groups did not differ on any of these measures at any time point [pain intensity: $ts(45) \leq 1.75$, $p \geq .093$, $ds \leq 0.51$; symptom interference: $ts(45) \leq 1.24$, $p \geq .240$, $ds \leq 0.36$; range of movement: $ts(45) \leq 1.81$, $p \geq .062$, $ds \leq 0.53$]. The median number of days from the beginning of treatment to reach peak improvement and from peak improvement to return to baseline on each of these measures were similar in the PA and sham treatment groups (see Text S6, Supplemental Digital Content 1).
3.4.2. Sensory, motor, and autonomic functions

A series of 2x4 ANOVAs was conducted on the scores from clinical assessments to test the effects of PA on sensory, autonomic, and motor functions. We reported group average values for these measures across four time points in Table 4. For the alldynia on the affected limb, absolute temperature difference, and oedema difference data, the ANOVA results are reported in Table 3. The MDT, MPT, and TPD threshold ratios data, as well as grip strength and ΔFTP ratios data were analysed using linear mixed models due to severe violations of the assumptions of normality, homogeneity of variance, and/or sphericity. The results of these analyses are reported in Table 5.

[Table 4]

[Table 5]

A significant main effect of Time on the MPT ratios indicated that participants experienced less hyperalgesia on the affected relative to unaffected limb over the treatment period, regardless of treatment. However, this effect did not withstand correction for multiple comparisons, and there were no significant differences between other time points, Zs ≤ 1.60, p_adj ≥ .208, d ≤ 0.33. We also found a significant interaction between Time and Group on the MPT ratios. Despite the PA group showing a reduction in hyperalgesia over the treatment period, this effect did not withstand correction for multiple comparisons, and there were no other changes on MPT ratios in either group, Zs ≤ 1.68, p_adj ≥ .440, d ≤ 0.51.

Our analyses did not reveal any other significant main effects or interactions (see Tables 3 and 5). Overall, contrary to our hypothesis, we found no evidence of significantly greater improvements in sensory, autonomic, or motor functions following PA compared to sham treatment, except for the trend towards predicted reduction in hyperalgesia (MPT ratio) in the PA group over the treatment period.
3.4.3. Neuropsychological functions

A series of 2x4 ANOVAs was performed on the scores from experimental neuropsychological tasks to test the effects of PA on visuospatial attention, mental representation of space, spatially-defined motor function, and body representation. Table 6 includes group average scores for participants’ performance on these measures across four time points. Negative scores on the tests of visuospatial attention and mental representation of space would indicate a bias away from the affected side. However, confidence intervals around the baseline scores on these tests include zero, suggesting that participants did not show significant spatial biases. Positive values of directional hypokinesia and bradykinesia indices would indicate slowing of movements directed towards the affected side. Yet participants’ median indices were both positive and negative depending on the specific condition, suggesting that there were no systematic spatially-defined motor deficits at baseline. Positive accuracy and reaction time indices on the test of body representation would suggest less accurate and slower laterality recognition for the images of affected hands. However, participants’ scores were mostly negative at baseline. Furthermore, most of the confidence intervals included zero, indicating that there were no differences in recognition of the affected relative to unaffected hands. The ANOVA results for the TOJ, Greyscales, MNLB, and Hand Laterality Recognition tasks are reported in Table 3. Due to severe violations of the assumptions of normality, homogeneity of variance, and/or sphericity, the data for the Landmark task and spatially-defined motor function were analysed using linear mixed models (see Tables 5 and 7, respectively).

[Table 6]

[Table 7]

There were no significant main effects or interactions on any of the measures of visuospatial attention, mental representation of space, or body representation. Linear mixed model analyses revealed a significant main effect of group on Index B of directional bradykinesia when using the unaffected hand. This effect indicates that participants in PA group (\(Mdn = 42.39\), BCa 95% CI [20.42,
showed greater directional bradykinesia on this index (i.e. they were slower to execute movements directed towards the affected relative to unaffected side) compared to participants in sham treatment group (\(Mdn = 12.07, \text{BCa 95\% CI }[-26.41, 40.93]\)), regardless of time point of the study, \(U = 136.00, p = .022, d = 1.06\). No significant effects or interactions were found on any other indices of spatially-defined motor function. Overall, contrary to our hypothesis, there was no evidence of greater improvements in spatial cognition, motor control, or body representation following PA compared to sham treatment.

3.5. Predictors of CRPS progression over time

We explored which baseline factors (RS1) could predict overall change in pain intensity (across RS1-RS4 and LTFU1-LTFU2) and CRPS severity (across RS1-RS4). The identified best subsets regression models with respective values of model selection criteria are summarised in Table S2, Supplemental Digital Content 2. A one-factor model for predicting overall change in pain intensity had the lowest AIC and CV criteria, \(F(1, 46) = 5.46, p = .024, \text{adj. } R^2 = .09, \text{AIC} = -132.24, \text{CV} = 0.28\). In this model, greater reduction in pain intensity was best predicted by smaller change in hand preference since CRPS onset (absolute \(\Delta\text{EHI}; t = 2.34, p = .024, \beta = 0.33\)). For predicting overall change in CRPS severity, a three-factor model had the lowest AIC and CV criteria, \(F(3, 45) = 6.23, p = .001, \text{adj. } R^2 = .25, \text{AIC} = -55.52, \text{CV} = 0.55\). In this model, greater reduction in CRPS severity was best predicted by lower pain intensity \((t = 3.69, p < .001, \beta = 0.52)\), less swelling of the affected limb \((t = 2.52, p = .015, \beta = 0.37)\), and more accurate recognition of images of the affected hand (i.e. smaller Hand laterality recognition accuracy index; \(t = 2.43, p = .019, \beta = 0.32\)), as measured at baseline (RS1).

4. Discussion

The results from this double-blind, randomized, sham-controlled trial of PA for upper-limb CRPS-I do not support the hypothesis that the effects of PA and sham treatment differed. First, two weeks of
twice-daily PA treatment performed with the affected arm did not reduce the primary outcomes of current pain intensity or CRPS symptom severity more than sham treatment of the same intensity and duration. Second, PA did not affect the secondary outcomes of self-reported CRPS-related and psychological functioning; sensory, motor, and autonomic signs of CRPS; or spatial cognition, motor function, and body representation.

Our findings contradict the conclusion of previous preliminary studies that PA could relieve pain and other CRPS symptoms. In the first study of PA treatment for CRPS, two weeks of once-daily training resulted in 50% pain relief, and reduced oedema and skin discoloration in five patients [100]. In the second study, three weeks of daily PA effectively resolved one patient’s pain, reduced autonomic symptoms, and improved motor function [8]. In the third study, four days of twice-daily PA resulted in 36% reduction of pain in seven CRPS patients [11]. In the two latter studies, its effects on pain were maintained for up to two weeks after discontinuing the treatment. While addressing the limitations of these previous small-sample, uncontrolled, unblinded studies, our robust trial showed no benefits of PA for CRPS beyond those of a control treatment. A small reduction in pain intensity immediately following PA (13% reduction) was not significantly greater than after sham treatment (3%). Similarly, there was an overall reduction in CRPS severity immediately after treatment that persisted for four weeks, but it was present in both PA (7%) and sham (8%) treatment groups. Consistent across per-protocol and intention-to-treat analyses, these findings suggest that PA does not incur any greater benefit than sham treatment, and thus is not effective for treating CRPS.

The decrease in CRPS severity across both treatment groups could be explained by a placebo effect and/or general benefits of moving the affected limb. Meta-analyses of clinical trials found that placebo response can correspond to 1.84 point immediate post-treatment reduction in CRPS pain [58], or 0.65 reduction in chronic pain more generally (on a 0-10 scale) [36]. This effect might also be responsible for the reduction in CRPS severity in our trial. Increased movement of the affected limb
is a likely alternative explanation, because all participants performed the pointing task with their affected hand, regardless of which treatment they received. Physical exercise is one of the core pillars of CRPS management [25], and this additional daily activity might have been sufficient to reduce CRPS severity. It is unlikely that the observed changes were due to natural recovery, which might occur within the first year from diagnosis [1], as participants were on average diagnosed with CRPS for five years. Disease duration was also unrelated to changes in pain intensity or CRPS severity (see Figure S3, Supplemental Digital Content 4). Regression to the mean cannot fully account for the decrease in CRPS severity, as no changes occurred over the baseline period. Overall, our findings reinforce the importance of including control treatment arms in pain rehabilitation studies, and the role of active movement in managing long-standing CRPS.

The absence of any effects of PA on clinical outcomes could be driven by the absence of any effects on spatial cognition and/or body representation. One hypothesised mechanism of the apparent benefits of PA treatment in previous studies of CRPS is that it reduces pain by correcting “neglect-like” spatial bias away from the affected side (although why such a bias would contribute to CRPS pain is unclear). A potential second mechanism for the apparent benefits of PA treatment for CRPS is restoring normal sensorimotor integration [8,100]. This is based on the proposal that distorted body representation gives rise to discrepancies between anticipated and actual consequences of movement, which cause or exacerbate pain in conditions such as CRPS [7,35,59,60]. The visual shift during PA induces transient sensorimotor incongruence, providing an error signal that triggers normalisation of body representation. In the present study, PA did not change participants’ performance on experimental measures of spatial cognition and motor control, or body representation. This might explain why there were no therapeutic effects of PA.

It is possible that PA did not affect these neuropsychological functions because, in contrast to previous findings [10,19,22,24,74,84,85,94,99], our participants with CRPS did not have any systematic neuropsychological deficits. On average, they showed balanced distributions of spatial
attention and spatial representations, no systematic slowing of movements directed towards the affected side, and unimpaired laterality recognition of images of affected hands at baseline (see Table 6 and [29]). In healthy individuals, cognitive after-effects depend on baseline spatial bias [13,26,41]. Therefore, absence of pre-existing spatial bias might account for why PA had no effects on spatial cognition or motor control in the present study. Furthermore, if altering spatial cognition and/or body representation were integral mechanisms through which PA reduces CRPS symptoms, the lack of effect of PA on the primary clinical outcomes could be because of the absence of baseline neuropsychological deficits. However, below we discuss three reasons that do not support this explanation.

First, we found no relationships between the extent of baseline spatial and body representation deficits and changes in primary outcomes over the treatment period. Furthermore, sub-group analyses revealed no evidence that PA benefitted individuals who did present with “neglect-like” symptoms or distorted representation of the affected limb. These exploratory results are presented in Figures S4 and S5 and Text S7, Supplemental Digital Content 1 and 4. Second, Christophe et al. [11] reported reduced CRPS pain after PA in the absence of any baseline spatial deficits, and without any effect on spatial cognition or motor control. Finally, Sumitani et al. [100] found a significant reduction in pain post-treatment, and a simultaneous shift in the coding of external spatial information relative to the body away from the affected side (i.e. direction opposite to the expected PA spatial after-effects). Therefore, response to PA treatment appears unrelated to “neglect-like” spatial bias or body representation distortion. However, both of these previous studies [11,100] had no control treatment arms, thus the apparent benefits of PA could be due to other non-specific factors. Nonetheless, we dismiss the explanation that the reason why PA did not reduce pain or CRPS severity was because our participants showed no baseline neuropsychological deficits, and thus PA could not normalise these cognitive functions. Rather, our findings suggest that PA is not an effective treatment for CRPS.
A potential limitation of our study is that we cannot rule out compliance violations. We tested PA as a self-administered, home-based treatment that could realistically be integrated into CRPS management. Although participants received in-person training, written and video instructions, and both groups logged the same number of treatment sessions, we solely relied upon self-reported adherence. Lack of apparent difference between the effects of PA and sham treatment could potentially be due to deviations from the instructed treatment protocol. However, previous CRPS studies reported symptom improvement following less frequent [100], shorter [11], and home-based [8] PA. Although our participants took less time to complete each treatment session compared to post-stroke patients (20-30min), PA protocols similar to ours using sufficiently strong prisms (10-20°) and 10 or more treatment sessions found generalizable, long-lasting effects on hemispatial neglect [21,95]. Finally, it was not feasible to confirm adaptation by measuring pointing after-affects in this trial, yet 50 movements were sufficient in previous studies [90]. Nonetheless, a trial of supervised PA with longer exposure and evidenced adaptation might find a significant benefit for CRPS.

This longitudinal study allowed us to explore potential baseline predictors of CRPS progression over 10-30 weeks, regardless of treatment. Smaller change in hand preference since CRPS onset was related to greater reduction in pain intensity. Consistent with the learned non-use hypothesis [80], underutilization of CRPS-affected limb and compensatory use of the unaffected extremity might maintain CRPS symptoms and hinder recovery. Overall reduction in CRPS severity was predicted by smaller pain intensity and oedema of the affected limb, suggesting that people with milder symptoms are likely to improve more. Individuals who were better at recognising images of affected relative to unaffected hands also achieved greater reduction in CRPS severity. Body perception disturbance was previously linked to longer CRPS duration and more severe sensory and motor signs of CRPS [43,48,106]. Our findings that less distorted representation and maintained use of the affected limb predict greater symptom improvement support multidisciplinary pain management approaches and graded motor imagery, which aim to normalise body representation and foster active movement [25,71,72]. These interpretations are, however, tentative, as the analyses were
exploratory and the abovementioned factors explained only 9% and 25% of variance in the overall changes in pain intensity and CRPS severity, respectively.

We conclude that PA does not reduce pain and other CRPS symptoms more than sham treatment. The benefits of PA for CRPS reported in previous studies are likely due to the placebo effect, greater movement of the affected limb, regression to the mean, or natural recovery.

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Supplemental Digital Content

Supplemental Digital Content 1. Text describing any deviations from the original trial protocol (Text S1), instructions for training CRPS participants in treatment (Text S2), results of outcome analyses in PP sample (Text S3), data preparation procedures (Text S4), factors excluded from exploratory best
subsets regression analyses in ITT sample (Text S5), supplementary daily logbook analyses in ITT sample (Text S6), and exploratory subgroup analyses in ITT sample (Text S7).

**Supplemental Digital Content 2.** Tables illustrating individual participant characteristics (Table S1) and best subsets regression models with model selection criteria in ITT sample (Table S2). Text S3 also refers to tables illustrating baseline characteristics of PA and sham treatment groups in PP sample (Table S3), group average scores on secondary outcome measures across all time points in PP sample (Table S4), results of ANOVAs on secondary outcome measures in PP sample (Table S5), and results of linear mixed models analyses for secondary outcome measures in PP sample (Table S6).

**Supplemental Digital Content 3.** Video tutorial demonstrating the treatment procedure.

**Supplemental Digital Content 4.** Figures illustrating individual pain and CRPS severity reduction scores over the treatment period in ITT sample (Figure S1), average daily logbook ratings of pain intensity, symptoms interference, and range of movement in ITT sample (Figure S2), scatterplots of changes on the primary outcomes vs. CRPS duration in ITT sample (Figure S3), scatterplots of changes on the primary outcomes vs. baseline performance on tests of spatial cognition in ITT sample (Figure S4), scatterplots of changes on the primary outcomes vs. baseline scores on tests of body representation in ITT sample (Figure S5). Text S3 also refers to figures illustrating primary outcomes in PP sample (Figure S6), and individual pain and CRPS severity reduction scores over the treatment period in PP sample (Figure S7).
References

[1] Bean DJ, Johnson MH, Kydd RR. The Outcome of Complex Regional Pain Syndrome Type 1: A Systematic Review. J Pain 2014;15:677–690.

[2] Beertuizen A, Stronks DL, van’t Spijker A, Yaksh A, Hanraets BM, Klein J, Huygen FJPM. Demographic and medical parameters in the development of complex regional pain syndrome type 1 (CRPS1): Prospective study on 596 patients with a fracture: Pain 2012;153:1187–1192.

[3] Berberovic N, Pisella L, Morris AP, Mattingley JB. Prismatic adaptation reduces biased temporal order judgements in spatial neglect. Neuroreport 2004;15:1199–1204.

[4] Bingel U, Wanigasekera V, Wieck K, Mhuircheartaigh RN, Lee MC, Ploner M, Tracey I. The Effect of Treatment Expectation on Drug Efficacy: Imaging the Analgesic Benefit of the Opioid Remifentanil. Sci Transl Med 2011;3:70ra14.

[5] Blanca MJ, Alarcón R, Arnau J. Non-normal data: Is ANOVA still a valid option? Psicothema 2017:552–557.

[6] Blanca MJ, Alarcón R, Arnau J, Bono R, Bendayan R. Effect of variance ratio on ANOVA robustness: Might 1.5 be the limit? Behav Res Methods 2018;50:937–962.

[7] Brun C, Mercier C, Grieve S, Palmer S, Bailey J, McCabe CS. Sensory disturbances induced by sensorimotor conflicts are higher in complex regional pain syndrome and fibromyalgia compared to arthritis and healthy people, and positively relate to pain intensity. Eur J Pain 2019;23:483–494.

[8] 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 2010;204:409–418.

[9] Bultitude JH, Rafal RD, Tinker C. Moving Forward with Prisms: Sensory-Motor Adaptation Improves Gait Initiation in Parkinson’s Disease. Front Neurol 2012;3. doi:10.3389/fneur.2012.00132.
[10] Bultitude JH, Walker I, Spence C. Space-based bias of covert visual attention in complex regional pain syndrome. Brain 2017;140:2306–2321.

[11] Christophe L, Chabanat E, Delporte L, Revol P, Volckmann P, Jacquin-Courtois S, Rossetti Y. Prisms to shift pain away: Pathophysiologival and therapeutic exploration of CRPS with prism adaptation. Neural Plast 2016;2016:1–21.

[12] Cleeland CS. The Brief Pain Inventory. In: McDowell I, Newell C, editors. Measuring health outcomes. New York: Oxford University Press, 1996. pp. 352–7.

[13] Colent C, Pisella L, Bernieri C, Rode G, Rossetti Y. Cognitive bias induced by visuo-motor adaptation to prisms: a simulation of unilateral neglect in normal individuals? Neuroreport 2000;11:1899–1902.

[14] Dehaene S, Bossini S, Giraux P. The mental representation of parity and number magnitude. J Exp Psychol Gen 1993;122:371–396.

[15] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations: Pain 2005;113:9–19.

[16] Estimating Sample Size for Comparison of Two Means – Plant Breeding and Genomics. n.d. Available: https://plant-breeding-genomics.extension.org/estimating-sample-size-for-comparison-of-two-means/. Accessed 14 Mar 2020.

[17] Facchin A, Daini R, Toraldo A. Prismatic Adaptation in the Rehabilitation of Neglect Patients: Does the Specific Procedure Matter? Front Hum Neurosci 2013;7. doi:10.3389/fnhum.2013.00137.
Farrar JT, Young JP, La Moreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–158.

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 2017;7:9712.

Filbrich L, Torta DM, Vanderclausen C, Azañón E, Legrain V. Using temporal order judgments to investigate attention bias toward pain and threat-related information. Methodological and theoretical issues. Conscious Cogn 2016;41:135–138.

Frassinetti F, Angeli V, Meneghello F, Avanzi S, Lädavas E. Long-lasting amelioration of visuospatial neglect by prism adaptation. Brain 2002;125:608–623.

Frettloh J, Hüppe 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 2006;124:184–189.

Freynhagen R, Baron R, Gockel U, Tölle TR. Pain DETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911–1920.

Galer BS, Butler S, Jensen MP. Case reports and hypothesis: A neglect-like syndrome may be responsible for the motor disturbance in reflex sympathetic dystrophy (complex regional pain syndrome-1). J Pain Symptom Manage 1995;10:385–391.

Goebel A, Barker CH, Turner-Stokes L. Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care. Lond RCP 2018.

Goedert KM, Leblanc A, Tsai S-W, Barrett AM. Asymmetrical Effects of Adaptation to Left- and Right-Shifting Prisms Depends on Pre-existing Attentional Biases. J Int Neuropsychol Soc 2010;16:795–804.
[27] Grieve S, Jones L, Walsh N, McCabe CS. What outcome measures are commonly used for Complex Regional Pain Syndrome clinical trials? A systematic review of the literature. Eur J Pain 2016;20:331–340.

[28] Grieve S, Perez RS, Birklein F, Brunner F, Bruehl S, Harden R N, Packham T, Gobeil F, Haigh R, Holly J, Terkelsen A, Davies L, Lewis J, Thomassen I, Connett R, Worth T, Vatine J-J, McCabe CS. Recommendations for a first Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudieS (COMPACT). Pain 2017;158:1083–1090.

[29] Halicka M, Vittersø AD, McCullough H, Goebel A, Heelas L, Proulx MJ, Bultitude JH. Disputing space-based biases in unilateral complex regional pain syndrome. Cortex 2020. doi:10.1016/j.cortex.2020.02.018.

[30] Halicka M, Vittersø AD, Proulx MJ, Bultitude JH. Neuropsychological Changes in Complex Regional Pain Syndrome (CRPS). Behav Neurol 2020;2020:1–30.

[31] Halicka M, Vittersø AD, Proulx MJ, Bultitude JH. Pain reduction by inducing sensory-motor adaptation in Complex Regional Pain Syndrome (CRPS PRISMA): protocol for a double-blind randomized controlled trial. BMC Neurol 2020;20:62.

[32] 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 J-J.

Validation of proposed diagnostic criteria (the “Budapest Criteria”) for Complex Regional Pain Syndrome: Pain 2010;150:268–274.

[33] Harden RN, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Schlereth T, Chont M, Vatine J-J. Development of a severity score for CRPS: Pain 2010;151:870–876.

[34] Harden RN, Maihofner C, Abousaad E, Vatine J-J, Kirsling A, Perez RSGM, Kuroda M, Brunner F, Stanton-Hicks M, Marinus J, van Hilten JJ, Mackey S, Birklein F, Schlereth T, Mailis-Gagnon A, Graciosa J, Connoly SB, Dayanim D, Massey M, Frank H, Livshitz A, Bruehl S. A prospective,
multisite, international validation of the Complex Regional Pain Syndrome Severity Score:
PAIN 2017;158:1430–1436.

[35] Harris AJ. Cortical origin of pathological pain. The Lancet 1999;354:1464–1466.

[36] Hróbjartsson A, Gøtzsche PC. Is the Placebo Powerless? N Engl J Med 2001;344:1594–1602.

[37] Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;27:26–35.

[38] IBM SPSS Statistic. SPSS 23.0 for windows. Chic IL 2015.

[39] Incel NA, Ceceli E, Durukan PB, Erdem HR, Yorgancioglu ZR. Grip strength: effect of hand dominance. Singapore Med J 2002;43:234–237.

[40] Jacquin-Courtois S, O’Shea J, Luauté J, Pisella L, Revol P, Mizuno K, Rode G, Rossetti Y. Rehabilitation of spatial neglect by prism adaptation. Neurosci Biobehav Rev 2013;37:594–609.

[41] Jewell G, McCourt ME. Pseudoneglect: a review and meta-analysis of performance factors in line bisection tasks. Neuropsychologia 2000;38:93–110.

[42] Johnson S, Hall J, Barnett S, Draper M, Derbyshire G, Haynes L, Rooney C, Cameron H, Moseley GL, C. Williams AC, McCabe CS, Goebel A. Using graded motor imagery for complex regional pain syndrome in clinical practice: Failure to improve pain: GMI in CRPS. Eur J Pain 2012;16:550–561.

[43] Kolb L, Lang C, Seifert F, Maihöfner C. Cognitive correlates of “neglect-like syndrome” in patients with complex regional pain syndrome: Pain 2012;153:1063–1073.

[44] Làdavas E, Bonifazi S, Catena L, Serino A. Neglect rehabilitation by prism adaptation: different procedures have different impacts. Neuropsychologia 2011;49:1136–1145.

[45] Leard JS, Breglio L, Fraga L, Ellrod N, Nadler L, Yasso M, Fay E, Ryan K, Pellecchia GL. Reliability and concurrent validity of the figure-of-eight method of measuring hand size in patients with hand pathology. J Orthop Sports Phys Ther 2004;34:335–340.
[46] Lever J, Krzywinski M, Altman N. Model selection and overfitting. Nat Methods 2016;703–704.

[47] Lewis J, McCabe CS. Body perception disturbance (BPD) in CRPS. Pract Pain Manag 2010;10:60–66.

[48] Lewis J, Schweinhartd P. Perceptions of the painful body: The relationship between body perception disturbance, pain and tactile discrimination in complex regional pain syndrome: Perceptions of the painful body in complex regional pain syndrome. Eur J Pain 2012;16:1320–1330.

[49] Linde K, Witt CM, Streng A, Weidenhammer W, Wagenpfeil S, Brinkhaus B, Willich SN, Melchart D. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. PAIN 2007;128:264–271.

[50] Lipman MD, Hess DE, Werner BC, Deal DN. Fibromyalgia as a Predictor of Complex Regional Pain Syndrome After Distal Radius Fracture. HAND 2019;14:516–522.

[51] Loftus AM, Nicholls MER, Mattingley JB, Bradshaw JL. Left to right: Representational biases for numbers and the effect of visuomotor adaptation. Cognition 2008;107:1048–1058.

[52] Loftus AM, Vijayakumar N, Nicholls MER. Prism adaptation overcomes pseudoneglect for the greyscales task. Cortex 2009;45:537–543.

[53] Luauté J, Halligan P, Rode G, Jacquin-Courtois S, Boisson D. Prism adaptation first among equals in alleviating left neglect: a review. Restor Neurol Neurosci 2006;24:409–418.

[54] Lumley T. leaps: Regression subset selection. R package version 3.0 (based on Fortran code by Alan Miller). 2017 p. Available: https://cran.r-project.org/package=leaps.

[55] Makin TR, Wilf M, Schwartz I, Zohary E. Amputees “neglect” the space near their missing hand. Psychol Sci 2010;21:55–57.

[56] MATLAB and Statistics Toolbox. Natick, Massachusetts, United States: The MathWorks, Inc., n.d. p.
[57] Mattingley JB, Bradshaw JL, Phillips JG. Impairments of movement initiation and execution in unilateral neglect: directional hypokinesia and bradykinesia. Brain 1992;115:1849–1874.

[58] Mbizvo GK, Nolan SJ, Nurmikko TJ, Goebel A. Placebo Responses in Long-Standing Complex Regional Pain Syndrome: A Systematic Review and Meta-Analysis. J Pain 2015;16:99–115.

[59] McCabe CS. A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). Rheumatology 2002;42:97–101.

[60] McCabe CS, Blake DR. An embarrassment of pain perceptions? Towards an understanding of and explanation for the clinical presentation of CRPS type 1. Rheumatology 2008;47:1612–1616.

[61] McCabe CS, Blake DR. Evidence for a mismatch between the brain’s movement control system and sensory system as an explanation for some pain-related disorders. Curr Pain Headache Rep 2007;11:104–108.

[62] McNair DM, Lorr M, Droppleman LF. Manual for the POMS. San Diego Educ Ind Test Serv 1971.

[63] Michel C. Beyond the Sensorimotor Plasticity: Cognitive Expansion of Prism Adaptation in Healthy Individuals. Front Psychol 2016;6. doi:10.3389/fpsyg.2015.01979.

[64] Michel C, Pisella L, Halligan PW, Luauté J, Rode G, Boisson D, Rossetti Y. Simulating unilateral neglect in normals using prism adaptation: implications for theory. Neuropsychologia 2003;41:25–39.

[65] Miller RP, Kori SH, Todd DD. The Tampa Scale: a Measure of Kinisophobia. Clin J Pain 1991;7:51.

[66] Minim: allocation by minimisation in clinical trials. n.d. Available: https://www-users.york.ac.uk/~mb55/guide/minim.htm. Accessed 26 Jul 2017.

[67] Mizuno K, Tsuji T, Takebayashi T, Fujiwara T, Hase K, Liu M. Prism adaptation therapy enhances rehabilitation of stroke patients with unilateral spatial neglect: a randomized, controlled trial. Neurorehabil Neural Repair 2011;25:711–720.
[68] de Mos M, de Bruijn AGJ, Huygen FJPM, Dieleman JP, Stricker ChBH, Sturkenboom MCJM. The incidence of complex regional pain syndrome: A population-based study. Pain 2007;129:12–20.

[69] de Mos M, Huygen FJPM, Dieleman JP, Koopman JSHA, Stricker ChBH, Sturkenboom MCJM. Medical history and the onset of complex regional pain syndrome (CRPS): Pain 2008;139:458–466.

[70] Moseley GL. Distorted body image in complex regional pain syndrome. Neurology 2005;65:773–773.

[71] Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. Pain 2004;108:192–198.

[72] Moseley GL. Is successful rehabilitation of complex regional pain syndrome due to sustained attention to the affected limb? A randomised clinical trial. Pain 2005;114:54–61.

[73] 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 2012;135:3676–3686.

[74] 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 2009;132:3142–3151.

[75] Nicholls ME, Bradshaw JL, Mattingley JB. Free-viewing perceptual asymmetries for the judgement of brightness, numerosity and size. Neuropsychologia 1999;37:307–314.

[76] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.

[77] Peirce JW. PsychoPy—psychophysics software in Python. J Neurosci Methods 2007;162:8–13.

[78] Pellecchia GL. Figure-of-eight method of measuring hand size: J Hand Ther 2003;16:300–304.

[79] Petersen P, Petrick M, Connor H, Conklin D. Grip strength and hand dominance: challenging the 10% rule. Am J Occup Ther 1989;43:444–447.
[80] Punt DT, Cooper L, Hey M, Johnson MI. Neglect-like symptoms in complex regional pain syndrome: Learned nonuse by another name?: Pain 2013;154:200–203.

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

[82] Redding GM, Rossetti Y, Wallace B. Applications of prism adaptation: a tutorial in theory and method. Neurosci Biobehav Rev 2005;29:431–444.

[83] Redding GM, Wallace B. Adaptive spatial alignment and strategic perceptual-motor control. J Exp Psychol Hum Percept Perform 1996;22:379.

[84] Reid E, Wallwork SB, Harvie D, Chalmers KJ, Braithwaite FA, Spence C, Gallace A, Moseley GL. Spatially-defined motor deficits in people with unilateral complex regional pain syndrome. Cortex 2018;104:154–162.

[85] 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?: Somatospatial Inattention in Pain. Ann Neurol 2016;79:701–704.

[86] Reinersmann A, Maier C, Schwenkreis P, Lenz M. Complex regional pain syndrome: more than a peripheral disease. Pain Manag 2013;3:495–502.

[87] Robinson ME, Brown JL, George SZ, Edwards PS, Atchison JW, Hirsh AT, Waxenberg LB, Wittmer V, Fillingim RB. Multidimensional success criteria and expectations for treatment of chronic pain: the patient perspective. Pain Med 2005;6:336–345.

[88] Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede R-D. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10:77–77.

[89] Rossetti Y, Jacquin-Courtois S, Rode G, Ota H, Michel C, Boisson D. Does action make the link between number and space representation?: Visuo-manual adaptation improves number bisection in unilateral neglect. Psychol Sci 2004;15:426–430.

[90] Rossetti Y, Rode G, Pisella L, Farné A, Li L, Boisson D, Perenin M-T. Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. Nature 1998;395:166–169.
[91] Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. PAIN® 2003;103:199–207.

[92] Sapir A, Kaplan JB, He BJ, Corbetta M. Anatomical Correlates of Directional Hypokinesia in Patients with Hemispatial Neglect. J Neurosci 2007;27:4045–4051.

[93] Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994;67:1063–1078.

[94] Schwobel J, Friedman R, Duda N, Coslett HB. Pain and the body schema. Brain 2001;124:2098–2104.

[95] Serino A, Barbiani M, Rinaldesi ML, Làdavas E. Effectiveness of prism adaptation in neglect rehabilitation. Stroke 2009;40:1392–1398.

[96] Serino A, Bonifazi S, Pierfederici L, Làdavas E. Neglect treatment by prism adaptation: What recovers and for how long. Neuropsychol Rehabil 2007;17:657–687.

[97] Spence C, Parise C. Prior-entry: A review. Conscious Cogn 2010;19:364–379.

[98] Striemer CL, Borza CA. Prism adaptation speeds reach initiation in the direction of the prism after-effect. Exp Brain Res 2017;235:3193–3206.

[99] 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 2014;90:151–156.

[100] Sumitani M, Rossetti Y, Shibata M, Matsuda Y, Sakaue G, Inoue T, Mashimo T, Miyauchi S. Prism adaptation to optical deviation alleviates pathologic pain. Neurology 2007;68:128–133.

[101] Torok KS, Baker NA, Lucas M, Domsic RT, Boudreau R, Medsger Jr TA. Reliability and validity of the delta finger-to-palm (FTP), a new measure of finger range of motion in systemic sclerosis. Clin Exp Rheumatol 2010;28:S28.

[102] Torta DM, Legrain V, Rossetti Y, Mouraux A. Prisms for pain. Can visuo-motor rehabilitation strategies alleviate chronic pain? Eur J Pain 2016;20:64–69.
[103] Tseng H-H, Bossong MG, Modinos G, Chen K-M, McGuire P, Allen P. A systematic review of multisensory cognitive–affective integration in schizophrenia. Neurosci Biobehav Rev 2015;55:444–452.

[104] Turner JA, Deyo RA, Loeser JD, Korff MV, Fordyce WE. The Importance of Placebo Effects in Pain Treatment and Research. JAMA 1994;271:1609–1614.

[105] Vangkilde S, Habekost T. Finding Wally: prism adaptation improves visual search in chronic neglect. Neuropsychologia 2010;48:1994–2004.

[106] Wittayer M, Dimova V, Birklein F, Schlereth T. Correlates and importance of neglect-like symptoms in complex regional pain syndrome: PAIN 2018;159:978–986.
Figure legends

**Figure 1.** Schedule of data collection and interventions.

**Figure 2.** CONSORT diagram. Flow of participants through the study. RS1, research session 1; RS2, research session 2; RS3, research session 3; RS4, research session 4; LTFU1, long-term follow-up 1; LTFU2, long-term follow-up 2; ITT, intention-to-treat analysis (received allocated intervention); PP, per-protocol analysis (completed allocated intervention, RS3-4 [CRPS severity], and LTFU1-2 [Pain intensity]).

**Figure 3.** Prism adaptation procedure. In this example, participant with left-CRPS is using rightward-shifting prisms (A-C), which induce adaptation towards the left (affected) side. For clarity of illustration, only one target (red circle) is represented in the figure. However, the treatment procedure involved two targets presented in the left and right side of space, and participants’ pointing movements alternated between the left and right targets. (A) Prism goggles shift visual image to the right. Blue triangle represents a shift of visual perspective and perceived target location (pale red circle), relative to real location of the target (light grey triangle, dark red circle). (B) Pointing movements initially err to the right. (C) Adaptive realignment results in correct pointing movements. (D) Goggles are removed and pointing movements err to the left (after-effect).

**Figure 4.** Primary outcomes (intention-to-treat analysis). Mean [BCa 95% CI] current pain intensity (A) and CRPS severity scores (B) in prism adaptation (PA; orange circles) and sham treatment (blue diamonds) groups in each time point. RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; LTFU1 and LTFU2, long-term follow-up 1 and 2. Grey arrows indicate the treatment period. **Significant decrease in CRPS severity between RS2 and RS3, maintained at RS4, regardless of treatment, ps < .01.**
Figure 1. Schedule of data collection and interventions.
319 invited to take part
173 excluded (no response)
143 assessed for eligibility
80 excluded
- 23 primarily lower limb CRPS
- 19 multiple limbs affected
- 7 CRPS type II
- 7 neurological history
- 6 CRPS diagnostic criteria not met
- 11 declined
- 8 unable to contact
63 enrolled
0 excluded
- 7 cancelled
- 1 not eligible (multiple limbs affected)
- 1 not eligible (no pain)
54 completed RS1
2 excluded
- 1 lost contact
- 1 withdrew (CRPS flare-up)
52 randomised
26 allocated to **Prism**
Adaptation treatment
3 excluded
- 1 lost contact
- 1 withdrew (no time)
- 1 not eligible (pain <2 at RS2)
23 completed RS2
23 received allocated intervention
2 excluded
- 1 withdrew (unrelated illness)
- 1 lost contact
21 completed RS3
21 completed RS4
21 completed LTFU1
19 completed LTFU2
**ITT analysis**
- 23 Pain intensity
- 23 CRPS severity
**PP analysis**
- 19 Pain intensity
- 21 CRPS severity
26 allocated to **Sham**
treatment
6 excluded
- 1 discontinued (CRPS symptoms exacerbation)
- 1 withdrawn by researchers (unrelated illness)
- 2 withdrew (unrelated illness)
- 1 withdrew (no time)
26 completed RS2
26 received allocated intervention
18 completed LTFU1
19 completed LTFU2
**ITT analysis**
- 26 Pain intensity
- 26 CRPS severity
**PP analysis**
- 18 Pain intensity
- 20 CRPS severity
Figure 2. CONSORT diagram. Flow of participants through the study. RS1, research session 1; RS2, research session 2; RS3, research session 3; RS4, research session 4; LTFU1, long-term follow-up 1; LTFU2, long-term follow-up 2; ITT, intention-to-treat analysis (received allocated intervention); PP, per-protocol analysis (completed allocated intervention, RS3-4 [CRPS severity], and LTFU1-2 [Pain intensity]).
**Figure 3.** Prism adaptation procedure. In this example, participant with left-CRPS is using rightward-shifting prisms (A-C), which induce adaptation towards the left (affected) side. For clarity of illustration, only one target (red circle) is represented in the figure. However, the treatment procedure involved two targets presented in the left and right side of space, and participants’ pointing movements alternated between the left and right targets. (A) Prism goggles shift visual image to the right. Blue triangle represents a shift of visual perspective and perceived target location (pale red circle), relative to real location of the target (light grey triangle, dark red circle). (B) Pointing movements initially err to the right. (C) Adaptive realignment results in correct pointing movements. (D) Goggles are removed and pointing movements err to the left (after-effect).
Figure 4. Primary outcomes (intention-to-treat analysis). Mean [BCa 95% CI] current pain intensity (A) and CRPS severity scores (B) in prism adaptation (PA; orange circles) and sham treatment (blue diamonds) groups in each time point. RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; LTFU1 and LTFU2, long-term follow-up 1 and 2. Grey arrows indicate the treatment period. **Significant decrease in CRPS severity between RS2 and RS3, maintained at RS4, regardless of treatment, $p_{adj} < .01$. 

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Table 1

Baseline (RS1) participant characteristics by treatment group (intention-to-treat analysis)

| Measure                                      | Prism adaptation treatment (n = 23) | Sham treatment (n = 26) | Contrast |
|----------------------------------------------|------------------------------------|-------------------------|----------|
| **Minimisation factors**                     |                                    |                         |          |
| Current pain intensity (/10) M               | 5.96 [5.02, 6.80]                  | 6.15 [5.26, 7.00]       | t(47) = -0.33, p = .741, d = 0.10 |
| CRPS severity score (/16) Mdn                | 13.00 [12.07, 13.93]               | 12.50 [11.00, 13.00]    | U = 287.50, p = .809, d = 0.07 |
| Primarily affected arm (% right)             | 48%                                | 35%                     | χ²(1) = .88, p = .348, ϕ = -0.13 |
| Pre-CRPS dominant hand (% right)             | 91%                                | 92%                     | χ²(1) = .16, p = .898, ϕ = 0.02 |
| Sex (% female)                               | 83%                                | 85%                     | χ²(1) = .04, p = .850, ϕ = -0.03 |
| Age (years) M                                | 47.35 [43.20, 51.95]               | 45.31 [39.85, 50.85]    | t(47) = 0.53, p = .601, d = -0.15 |
| CRPS in other body parts (%) present         | 13%                                | 8%                      | χ²(1) = .38, p = .537, ϕ = -0.09 |
| Other non-CRPS pain (%) present              | 44%                                | 39%                     | χ²(1) = .13, p = .721, ϕ = -0.05 |
| CRPS duration (months since diagnosis) M     | 61.26 [47.15, 75.12]               | 52.31 [39.49, 66.35]    | t(47) = 0.84, p = .388, d = -0.24 |
| **Other control measures**                   |                                    |                         |          |
| Optimism (LOTR; /24) M                       | 13.00 [10.97, 15.07]               | 12.31 [11.00, 13.61]    | t(47) = 0.59, p = .560, d = -0.17 |
| Mood disturbance (POMS; /229) M              | 94.81 [79.96, 109.93]              | 84.22 [70.94, 98.08]    | t(47) = 0.97, p = .349, d = -0.28 |
| Measure                                      | Prism adaptation treatment (n = 23) | Sham treatment (n = 26) | Contrast          |
|----------------------------------------------|------------------------------------|-------------------------|-------------------|
| Fear of movement (TSK; /68) $M$              | 38.79 [35.45, 41.95]               | 40.38 [37.17, 43.35]    | $t(47) = -0.65, p = .502, d = 0.19$ |
| Number of logged treatment sessions (/29) $Mdn$ | 29.00 [28.54, 29.46]               | 29.00 [28.55, 29.45]    | $U = 297.00, p = .977, d = 0.01$ |

LOTR, Revised Life Orientation Test; POMS, Profile of Mood States; TSK, Tampa Scale for Kinesiophobia.

Bootstrapped bias-corrected and accelerated 95% confidence intervals are reported in square brackets, [BCa 95% CI].

There were no significant differences between groups on any measures.
Table 2

Mean or median values [BCa 95% CI] of self-reported secondary outcome measures at each time point (intention-to-treat analysis)

| Measure | Treatment group | Time point |
|---------|----------------|------------|
|         |                | RS1        | RS2        | RS3        | RS4        | LTFU1      | LTFU2      |
| Pain    |                |            |            |            |            |            |            |
| Pain severity (BPI; /10) | PA | 5.91 [5.17, 6.58] | 6.02 [5.28, 6.71] | 5.41 [4.50, 6.26] | 5.43 [4.55, 6.24] | 5.62 [4.69, 6.48] | 5.59 [4.69, 6.41] |
|         | Sham           | 5.81 [5.02, 6.50] | 5.95 [5.12, 6.78] | 5.85 [5.04, 6.65] | 5.84 [4.82, 6.74] | 6.04 [5.12, 6.80] | 5.95 [5.07, 6.73] |
| Pain interference (BPI; /10) | PA | 6.71 [6.29, 6.71] | 6.43 [5.00, 7.08] | 5.29 [3.57, 6.43] | 5.57 [4.71, 6.29] | 6.00 [5.22, 6.14] | 5.86 [4.57, 6.86] |
| Mdn     | Sham           | 5.79 [5.00, 7.14] | 5.86 [5.72, 5.86] | 5.57 [5.43, 5.57] | 5.64 [4.00, 6.14] | 5.50 [3.71, 6.57] | 5.72 [4.14, 6.57] |
| Neuropathic features of pain (PDQ; /38) | PA | 26.00 [26.00, 26.00] | 25.00 [20.00, 26.00] | 24.00 [21.00, 27.00] | 24.00 [20.00, 26.00] | 26.00 [25.00, 26.00] | 26.00 [21.46, 28.00] |
|         | Sham           | 23.50 [21.50, 27.00] | 24.00 [23.00, 24.00] | 23.50 [20.00, 26.00] | 22.50 [17.06, 28.00] | 23.00 [20.00, 25.00] | 22.50 [18.00, 26.00] |
| Body representation |            |            |            |            |            |            |            |
| Body perception disturbance (BPDS; /57) | PA | 27.65 [22.83, 32.34] | 27.78 [24.00, 31.22] | 22.13 [17.88, 26.44] | 24.39 [20.48, 28.57] | 25.52 [21.78, 29.30] | 24.57 [20.91, 28.44] |
|         | Sham           | 28.96 [23.96, 33.76] | 27.73 [21.98, 33.92] | 29.00 [23.00, 35.36] | 26.81 [20.92, 33.61] | 26.77 [21.48, 32.68] | 27.65 [22.53, 33.28] |
| Emotional functioning |            |            |            |            |            |            |            |
| Fear of movement (TSK; /68) | PA | 38.79 [35.45, 41.95] | 38.52 [35.02, 41.73] | 37.43 [34.26, 40.50] | 37.91 [34.70, 41.17] | 38.74 [35.33, 41.95] | 40.05 [36.22, 43.71] |
| Mood disturbance (POMS; /229) | PA | 94.81 [79.96, 109.93] | 98.25 [82.66, 113.93] | 86.52 [71.16, 100.10] | 86.21 [73.85, 99.00] | 88.80 [74.42, 103.51] | 95.54 [73.56, 117.95] |
|         | Sham           | 84.22 [70.94, 98.08] | 91.27 [76.05, 106.01] | 83.21 [68.95, 96.96] | 83.35 [68.76, 97.56] | 82.42 [68.05, 96.53] | 89.13 [70.81, 106.31] |
| Measure                                      | Treatment group | Time point | RS1     | RS2     | RS3     | RS4     | LTFU1   | LTFU2   |
|---------------------------------------------|-----------------|------------|---------|---------|---------|---------|---------|---------|
| Perceived improvement due to treatment      |                 |            |         |         |         |         |         |         |
| Patient’s global impression of change (PGIC; Mdn) | PA              |            | -       | -       | 2.00 [2.00, 4.00] | 3.00 [3.00, 3.00] | 2.00 [2.00, 4.00] | 3.00 [2.00, 3.00] |
|                                             | Sham            |            | -       | -       | 3.00 [1.00, 4.00] | 4.00 [3.00, 4.00] | 2.00 [2.00, 3.00] | 2.00 [1.00, 4.00] |

BPI, Brief Pain Inventory; PDQ, Pain Detect Questionnaire; BPDS, Bath CRPS Body Perception Disturbance Scale; TSK, Tampa Scale for Kinesiophobia; POMS, Profile of Mood States; TSK, Tampa Scale for Kinesiophobia; PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; LTFU1 and LTFU2, long-term follow-ups 1 and 2.
Table 3

**Analysis of variance results for secondary outcome measures (intention-to-treat analysis)**

| Measure                               | Effect       | df†      | F   | p    | η²p  |
|---------------------------------------|--------------|----------|-----|------|------|
| **Self-report questionnaires**        |              |          |     |      |      |
| Pain severity (BPI)                   | Time         | 4.12, 193.81 | 1.24 | 0.295 | 0.03 |
|                                       | Group        | 1, 47    | 0.19 | 0.664 | < 0.01 |
|                                       | Time x Group | 4.12, 193.81 | 1.06 | 0.379 | 0.02 |
| Pain interference (BPI)               | Time*        | 2.88, 135.32 | 2.84 | 0.043 | 0.06 |
|                                       | Group        | 1, 47    | 0.04 | 0.838 | < 0.01 |
|                                       | Time x Group | 2.88, 135.32 | 0.74 | 0.526 | 0.02 |
| Neuropathic features of pain (PDQ)    | Time*        | 3.29, 154.50 | 3.32 | 0.018 | 0.07 |
|                                       | Group        | 1, 47    | 0.32 | 0.574 | 0.01 |
|                                       | Time x Group | 3.29, 154.50 | 0.61 | 0.625 | 0.01 |
| Body perception                       | Time         | 3.41, 160.11 | 2.43 | 0.059 | 0.05 |
| Body perception disturbance (BPDS)    | Group        | 1, 47    | 0.57 | 0.455 | 0.01 |
|                                       | Time x Group*| 3.41, 160.11 | 2.60 | 0.047 | 0.05 |
| Fear of movement (TSK)                | Time         | 3.86, 181.61 | 2.41 | 0.053 | 0.05 |
|                                       | Group        | 1, 47    | < 0.01 | 0.993 | < 0.01 |
|                                       | Time x Group*| 3.86, 181.61 | 2.89 | 0.025 | 0.06 |
| Mood disturbance (POMS)               | Time         | 3.60, 169.21 | 2.29 | 0.069 | 0.05 |
|                                       | Group        | 1, 47    | 0.36 | 0.554 | 0.01 |
|                                       | Time x Group | 3.60, 169.21 | 0.25 | 0.894 | 0.01 |
| Patient’s global impression of change (PGIC) | Time      | 3, 120  | 0.96 | 0.414 | 0.02 |
|                                       | Group        | 1, 40    | 0.02 | 0.890 | < 0.01 |
|                                       | Time x Group | 3, 120  | 0.56 | 0.644 | 0.01 |
| **Clinical assessments**              |              |          |     |      |      |
| Allodynia (affected limb)             | Time         | 2.23, 104.67 | 1.03 | 0.367 | 0.02 |
|                                       | Group        | 1, 47    | 0.25 | 0.616 | 0.01 |
| Measure           | Effect               | df†               | F     | p       | η²p   |
|-------------------|----------------------|-------------------|-------|---------|-------|
|                   | Time x Group         | 2.23, 104.67      | 0.35  | 0.730   | 0.01  |
|                   | Absolut temperature  |                   |       |         |       |
|                   | difference           |                   |       |         |       |
|                   | Group                | 3, 141            | 0.43  | 0.731   | 0.01  |
|                   | Time x Group         | 3, 141            | 0.63  | 0.595   | 0.01  |
|                   | Oedema difference    |                   |       |         |       |
|                   | Time                | 2.41, 113.08      | 0.99  | 0.387   | 0.02  |
|                   | Group              | 1, 47             | 0.06  | 0.805   | < 0.01|
|                   | Time x Group        | 2.41, 113.08      | 1.86  | 0.153   | 0.04  |

**Experimental tests of neuropsychological functions**

| Measure           | Effect               | df†               | F     | p       | η²p   |
|-------------------|----------------------|-------------------|-------|---------|-------|
| Temporal Order    | Time                | 1.70, 79.69       | 1.08  | 0.335   | 0.02  |
| Judgement task (PSS) | Group          | 1, 47             | 0.16  | 0.692   | < 0.01|
|                   | Time x Group        | 1.70, 79.69       | 0.63  | 0.512   | 0.01  |
| Greyscales task   | Time                | 2.17, 101.82      | 0.57  | 0.581   | 0.01  |
|                   | Group               | 1, 47             | 0.02  | 0.899   | < 0.01|
|                   | Time x Group        | 2.17, 101.82      | 0.52  | 0.609   | 0.01  |
| Mental Number Line| Time               | 2.39, 112.17      | 0.48  | 0.656   | 0.01  |
| Bisection task    | Group              | 1, 47             | 0.50  | 0.481   | 0.01  |
|                   | Time x Group        | 2.39, 112.17      | 0.14  | 0.899   | < 0.01|
| Hand laterality recognition | Time               | 3, 141            | 2.39  | 0.072   | 0.05  |
| Accuracy Index    | Group              | 1, 47             | 1.54  | 0.221   | 0.03  |
|                   | Time x Group        | 3, 141            | 0.44  | 0.723   | 0.01  |
| Hand laterality recognition | Time               | 3, 141            | 1.32  | 0.269   | 0.03  |
| Reaction Time Index | Group            | 1, 47             | 0.05  | 0.826   | < 0.01|
|                   | Time x Group        | 3, 141            | 1.48  | 0.224   | 0.03  |

* Statistically significant effect (p < .05).
† Greenhouse-Geisser adjusted degrees of freedom are reported where sphericity assumption was violated.

BPI, Brief Pain Inventory; PDQ, Pain Detect Questionnaire; BPDS, Bath CRPS Body Perception Disturbance Scale; TSK, Tampa Scale for Kinesiophobia; POMS, Profile of Mood States; TSK, Tampa Scale for Kinesiophobia.

PSS, Point of Subjective Simultaneity.
Table 4

Mean or median values [BCa 95% CI] of sensory, autonomic, and motor secondary outcome measures at each time point (intention-to-treat analysis)

| Measure                                      | Treatment group | Time point | RS1 | RS2 | RS3 | RS4 |
|----------------------------------------------|-----------------|------------|-----|-----|-----|-----|
| **Sensory functions**                        |                 |            |     |     |     |     |
| Mechanical Detection Threshold ratio [(affected – unaffected) / affected] Mdn | PA              |            | -0.04 [-0.43, 0.38] | -0.35 [-1.12, 0.17] | -0.44 [-0.84, -0.06] | -0.54 [-1.51, -0.10] |
|                                              | Sham            |            | -0.30 [-1.37, 0.24] | -0.05 [-0.25, 0.17] | -0.14 [-0.91, 0.30] | -0.22 [-0.76, 0.28] |
| Mechanical Pain Threshold ratio [(unaffected – affected) / unaffected] Mdn | PA              |            | 0.62 [0.06, 0.69] | 0.50 [0.43, 0.56] | 0.07 [-0.32, 0.66] | 0.50 [0.06, 0.69] |
|                                              | Sham            |            | 0.57 [0.24, 0.67] | 0.56 [0.38, 0.73] | 0.50 [0.32, 0.71] | 0.43 [0.24, 0.78] |
| Allodynia (affected; /100) Mdn               | PA              |            | 14.00 [5.76, 26.67] | 18.87 [4.67, 30.89] | 16.90 [6.00, 26.17] | 10.73 [2.87, 18.26] |
|                                              | Sham            |            | 20.50 [9.00, 33.83] | 14.37 [6.47, 25.03] | 13.87 [6.47, 46.47] | 18.03 [7.33, 33.33] |
| Two-Point Discrimination Threshold ratio [(affected – unaffected) / affected] Mdn | PA              |            | -0.06 [-0.16, 0.11] | 0.00 [-0.08, 0.13] | -0.08 [-0.20, 0.00] | -0.04 [-0.21, 0.03] |
|                                              | Sham            |            | 0.15 [-0.07, 0.31] | -0.13 [-0.25, 0.10] | -0.09 [-0.17, 0.00] | 0.05 [-0.30, 0.22] |
| **Autonomic functions**                      |                 |            |     |     |     |     |
| Absolute temperature difference (affected – unaffected; °C) Mdn | PA              |            | 0.47 [0.27, 1.40] | 0.30 [0.14, 0.68] | 0.35 [0.20, 0.73] | 0.50 [0.17, 1.17] |
|                                              | Sham            |            | 0.47 [0.30, 0.78] | 0.82 [0.53, 1.07] | 0.77 [0.43, 1.05] | 0.67 [0.40, 1.00] |
| Oedema difference (affected – unaffected; cm) M | PA              |            | -0.01 [-0.42, 0.43] | -0.04 [-0.36, 0.28] | -0.19 [-0.58, 0.21] | -0.23 [-0.64, 0.20] |
|                                              | Sham            |            | -0.11 [-0.51, 0.34] | -0.02 [-0.40, 0.38] | -0.12 [-0.52, 0.30] | 0.04 [-0.33, 0.43] |
| Measure                                         | Treatment group | RS1       | RS2       | RS3       | RS4       |
|------------------------------------------------|-----------------|-----------|-----------|-----------|-----------|
| Grip strength ratio (affected / unaffected)    | PA              | 0.35 [0.17, 0.39] | 0.31 [0.25, 0.44] | 0.35 [0.30, 0.46] | 0.39 [0.30, 0.46] |
| Mdn                                            | Sham            | 0.32 [0.20, 0.65] | 0.33 [0.18, 0.58] | 0.44 [0.26, 0.60] | 0.42 [0.23, 0.60] |
| Finger-to-palm distance ratio (affected /      | PA              | 0.70 [0.60, 0.88] | 0.67 [0.61, 0.87] | 0.73 [0.63, 0.84] | 0.79 [0.70, 0.82] |
| unaffected) Mdn                                 | Sham            | 0.69 [0.55, 0.90] | 0.72 [0.53, 0.88] | 0.79 [0.53, 0.89] | 0.77 [0.60, 0.93] |

PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4.
Table 5

The results of the bootstrapped linear mixed models regressions of scores for the tests of sensory and motor function, and a test of visuospatial attention (intention-to-treat analysis)

| Model term | Sensory functions | Motor functions | Visuospatial attention |
|------------|------------------|----------------|-----------------------|
| | | | | Mechanical Detection Threshold ratio | | | | Mechanical Pain Threshold ratio | | | | Two-Point Discrimination Threshold ratio | | | | Grip ratio | | | | Delta finger-to-palm ratio | | | | Landmark task (PSE) |
| Intercept | -1.26 [-2.22, -0.37]* | 0.19 [-0.10, 0.46] | -0.02 [-0.14, 0.11] | 0.38 [0.33, 0.44]* | 0.60 [0.51, 0.70]* | 0.07 [-0.05, 0.19] |
| Time (RS2 = 0) | | | | | | |
| RS1 | -0.44 [-2.03, 1.01] | -0.43 [-0.99, 0.07] | -0.02 [-0.20, 0.15] | -0.03 [-0.08, 0.01] | -0.04 [-0.12, 0.04] | 0.08 [-0.18, 0.38] |
| RS3 | -0.24 [-1.21, 0.65] | -0.49 [-0.99, -0.06]* | -0.14 [-0.32, 0.03] | 0.01 [-0.05, 0.06] | -0.02 [-0.11, 0.05] | 0.06 [-0.09, 0.21] |
| RS4 | -0.56 [-1.69, 0.50] | -0.14 [-0.52, 0.24] | -0.04 [-0.21, 0.13] | 0.03 [-0.03, 0.09] | 0.03 [-0.04, 0.11] | -0.02 [-0.16, 0.14] |
| Group (PA = 0) | | | | | | |
| Sham | 0.93 [-0.64, 2.54] | 0.06 [-0.35, 0.45] | -0.20 [-0.43, 0.03] | 0.04 [-0.06, 0.12] | 0.14 [-0.05, 0.30] | 0.01 [-0.17, 0.20] |
| Time x Group (RS2, PA = 0) | | | | | | |
| RS1, Sham | -0.01 [-1.63, 1.79] | 0.34 [-0.33, 1.03] | 0.27 [-0.08, 0.64] | 0.01 [-0.05, 0.08] | 0.03 [-0.07, 0.13] | 0.04 [-0.29, 0.34] |
| Model term | Coefficient estimate [95% CI] | Motor functions | Visuospatial attention |
|------------|-------------------------------|-----------------|-----------------------|
|             | Sensory functions              |                 |                       |
|             | Mechanical Detection Threshold | 0.65 [0.08, 1.32]* | 0.16 [-0.11, 0.44] | 0.05 [-0.03, 0.12] | 0.05 [-0.04, 0.16] | -0.05 [-0.24, 0.15] |
|             | Mechanical Pain Threshold ratio | 0.05 [-0.03, 0.12] | 0.05 [-0.04, 0.16] | -0.05 [-0.24, 0.15] |
|             |                  Two-Point Discrimination Threshold ratio | 0.01 [-0.09, 0.09] | 0.00 [-0.09, 0.10] | 0.01 [-0.18, 0.21] |
| RS3, Sham  | -0.77 [-2.52, 0.95]           | 0.16 [-0.11, 0.44] | 0.05 [-0.03, 0.12] | 0.05 [-0.04, 0.16] | -0.05 [-0.24, 0.15] |
| RS4, Sham  | 0.45 [-1.08, 1.91]            | 0.16 [-0.41, 0.72] | -0.08 [-0.53, 0.30] | 0.01 [-0.09, 0.09] | 0.00 [-0.09, 0.10] | 0.01 [-0.18, 0.21] |

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

The reference condition for dummy variable coding is indicated within parentheses for each term.

PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; PSE, Point of Subjective Equality.
| Measure                                      | Treatment group | Time point \( \text{RS}_1 \)  | Time point \( \text{RS}_2 \)  | Time point \( \text{RS}_3 \)  | Time point \( \text{RS}_4 \)  |
|----------------------------------------------|-----------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Temporal Order Judgement task (PSS; ms)**  | PA              | 0.16 [-13.82, 9.02]             | -3.26 [-14.51, 8.35]            | -1.00 [-8.65, 9.71]             | 5.18 [-1.74, 10.87]             |
|                                              | Sham            | -0.05 [-7.40, 7.06]             | -0.75 [-8.55, 6.65]             | 1.17 [-6.16, 7.33]             | -2.12 [-10.48, 6.07]             |
| **Landmark task (PSE; °)** \( \text{Mdn} \) | PA              | 0.04 [-0.20, 0.28]             | 0.09 [-0.01, 0.19]             | 0.03 [-0.09, 0.40]             | -0.02 [-0.13, 0.19]             |
|                                              | Sham            | 0.06 [-0.07, 0.21]             | 0.06 [-0.12, 0.17]             | -0.05 [-0.09, 0.10]            | 0.05 [-0.04, 0.10]              |
| **Greyscales task \( M \)**                 | PA              | 0.17 [-0.07, 0.41]             | 0.12 [-0.11, 0.34]             | 0.08 [-0.13, 0.30]             | 0.11 [-0.12, 0.34]              |
|                                              | Sham            | 0.09 [-0.08, 0.26]             | 0.12 [-0.08, 0.32]             | 0.07 [-0.10, 0.25]             | 0.14 [-0.06, 0.31]              |
| **Mental Number Line Bisection task \( M \)**| PA              | -0.06 [-0.76, 0.67]            | -0.10 [-0.73, 0.54]            | 0.04 [-0.58, 0.63]             | -0.06 [-0.55, 0.42]             |
|                                              | Sham            | 0.12 [-0.51, 0.77]             | 0.24 [-0.50, 0.99]             | 0.39 [-0.36, 1.21]             | 0.31 [-0.34, 0.99]              |
| **Directional hypokinesia, affected hand, \( \text{Index A (MIT; ms)} \) \( \text{Mdn} \)** | PA              | -4.88 [-41.02, 29.55]          | -2.23 [-40.87, 16.76]          | -15.41 [-58.35, -9.44]         | -21.93 [-40.85, -9.44]          |
|                                              | Sham            | -15.65 [-79.21, 26.94]         | 21.51 [-21.38, 56.06]          | -24.31 [-61.88, -12.51]        | -12.26 [-47.44, 16.73]          |
| **Directional hypokinesia, affected hand, \( \text{Index B (MIT; ms)} \) \( \text{Mdn} \)** | PA              | -37.53 [-90.19, 16.61]         | -25.46 [-84.04, 13.63]         | -48.49 [-80.33, -22.88]        | 4.10 [-40.19, 10.67]            |
|                                              | Sham            | -40.43 [-48.52, -21.96]        | -0.40 [-61.60, 15.61]          | -8.19 [-48.87, 13.72]          | 3.32 [-43.06, 20.37]            |
| Measure                              | Treatment group | Time point | RS1            | RS2            | RS3            | RS4            |
|-------------------------------------|-----------------|------------|----------------|----------------|----------------|----------------|
| Directional hypokinesia, unaffected hand, Index A (MIT; ms) | PA              | 0.14 [-15.93, 19.88] | 10.28 [1.15, 22.22] | -6.76 [-19.29, 13.43] | -2.78 [-45.45, 13.43] |
|                                     | Sham            | 5.57 [-24.54, 26.03] | -7.88 [-20.59, 14.27] | 6.88 [-15.63, 18.92] | 2.51 [-13.48, 23.38] |
| Directional hypokinesia, unaffected hand, Index B (MIT; ms) | PA              | 4.84 [-6.43, 11.89] | 9.41 [-17.73, 25.19] | -3.40 [-21.35, 33.52] | 7.43 [-26.43, 38.21] |
|                                     | Sham            | -23.63 [-48.34, 12.93] | 9.18 [-12.92, 28.54] | 11.01 [-10.84, 28.46] | 16.47 [-2.91, 26.35] |
| Directional bradykinesia, affected hand, Index A (MET; ms) | PA              | 97.95 [23.29, 216.69] | 64.71 [22.36, 123.85] | 46.11 [14.19, 72.77] | 52.74 [22.18, 66.01] |
|                                     | Sham            | 3.73 [-32.67, 67.35] | 50.72 [-5.50, 64.21] | 31.79 [3.63, 87.48] | 41.09 [11.92, 64.21] |
| Directional bradykinesia, affected hand, Index B (MET; ms) | PA              | -49.68 [-125.50, -8.16] | -180.86 [-235.79, -16.96] | -124.70 [-129.09, -122.32] | -78.67 [-115.85, -42.31] |
|                                     | Sham            | -63.53 [-149.00, -57.28] | -103.18 [-170.48, -54.09] | -77.46 [-97.96, -17.51] | -75.60 [-99.62, -48.41] |
| Directional bradykinesia, unaffected hand, Index A (MET; ms) | PA              | 48.80 [35.53, 64.67] | 69.36 [35.74, 103.71] | 79.01 [45.24, 99.85] | 79.78 [59.27, 116.99] |
|                                     | Sham            | 86.46 [54.45, 127.39] | 69.84 [24.68, 113.96] | 84.79 [76.26, 86.26] | 48.80 [35.53, 64.67] |
| Directional bradykinesia, unaffected hand, Index B (MET; ms) | PA              | 31.39 [-13.35, 64.92] | 69.35 [25.05, 98.88] | 36.70 [21.07, 63.50] | 20.37 [-13.72, 66.72] |
|                                     | Sham            | -28.35 [-71.98, 41.21] | 3.34 [-39.16, 44.61] | 28.60 [6.71, 53.45] | 3.38 [-22.98, 12.57] |

**Body representation**

| Measure                              | Treatment group | Time point | RS1            | RS2            | RS3            | RS4            |
|-------------------------------------|-----------------|------------|----------------|----------------|----------------|----------------|
| Hand laterality recognition Accuracy Index (%) | PA              | -1.65 [-5.66, 2.34] | -2.26 [-5.68, 1.43] | 1.30 [-2.23, 4.37] | 1.57 [-2.70, 6.00] |
|                                    | Sham            | 2.77 [-1.32, 7.37] | -1.77 [-5.83, 2.21] | 3.92 [0.19, 7.72] | 2.54 [-2.00, 6.83] |
| Hand laterality recognition Reaction Time (ms) | PA              | -97.74 [-268.99, 70.43] | -57.20 [-187.91, 70.02] | -37.44 [-155.06, 78.98] | -130.05 [-240.98, -27.84] |
|                                    | Sham            | -236.04 [-448.24, -65.14] | -129.37 [-263.61, 21.19] | -28.65 [-173.14, 95.70] | 19.77 [-112.95, 161.67] |
PSS, Point of Subjective Simultaneity; PSE, Point of Subjective Equality; MIT, movement initiation time; MET, movement execution time; PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4
Table 7

The results of the bootstrapped linear mixed models regressions of indices of directional hypokinesia and bradykinesia for the spatially-defined motor function task (intention-to-treat analysis)

| Model term                  | Coefficient estimate [95% CI] |
|-----------------------------|-------------------------------|
|                             | Directional hypokinesia (MIT) | Directional bradykinesia (MET) |
|                             | Affected hand                 | Unaffected hand                | Affected hand | Unaffected hand |
|                             | Index A | Index B | Index A | Index B | Index A | Index B | Index A | Index B |
| Intercept                   | -11.95  | -23.14  | 8.63    | 0.94    | 6.56   | -93.90 | 84.07   | 65.60   |
|                             | [-40.94, 19.61]               | [-52.63, 7.40]                 | [-6.39, 24.24] | [-21.21, 20.64] | [-61.92, 68.33] | [-175.79, 3.94] | [62.32, 106.44]* | [34.96, 95.76]* |
| Time (RS2 = 0)              | 8.39    | -20.72  | -4.96   | 2.44    | 101.53 | 41.98  | 15.05   | -25.10 |
|                             | [-31.73, 49.37]               | [-67.93, 25.85]                | [-35.64, 29.32] | [-25.43, 30.40] | [-0.10, 209.18] | [-57.89, 149.11] | [-21.41, 49.03] | [-76.04, 24.74] |
| RS3                         | -31.21  | -45.39  | -9.90   | 0.68    | 7.81   | -40.25 | 5.55    | -22.18 |
|                             | [-83.79, 13.52]               | [-111.04, 7.52]                | [-38.46, 15.04] | [-25.73, 28.63] | [-79.00, 93.41] | [-142.74, 53.50] | [-23.80, 37.85] | [-59.45, 12.77] |
| RS4                         | -15.50  | 25.65   | -24.33  | -6.41   | 20.26  | 53.08  | -6.30   | -32.55 |
|                             | [-62.46, 33.97]               | [-25.47, 75.22]                | [-52.94, 2.60] | [-49.64, 34.72] | [-57.47, 110.05] | [-41.08, 155.80] | [-34.26, 22.32] | [-73.00, 7.92]  |
| Group (PA = 0)              | Sham                            | 34.27                          | 20.52               | -3.65  | 14.98  | 55.82  | -57.61  | -4.43    | -67.00  |
|                             | [-22.36, 87.39]               | [-24.27, 64.73]                | [-26.22, 21.47]    | [-15.77, 50.03] | [-17.47, 135.08] | [-197.35, 65.94] | [-39.74, 29.20] | [-109.25, -24.86]* |
| Model term                                    | Coefficient estimate [95% CI] |
|----------------------------------------------|-------------------------------|
| Directional hypokinesia (MIT)                |                               |
| Affected hand                                | Unaffected hand               |
| Index A                                      | Index B                       |
| RS1, Sham                                    | -45.16 [-125.14, 38.62]      |
|                                              | 18.55 [-61.15, 97.28]        |
|                                              | 2.02 [-43.86, 42.90]         |
|                                              | -21.72 [-63.89, 21.18]       |
|                                              | -110.69 [-233.29, 13.49]     |
|                                              | -27.37 [-171.51, 103.83]     |
|                                              | -7.62 [-59.42, 42.81]        |
|                                              | 13.68 [-57.81, 81.17]        |
| RS3, Sham                                    | -26.61 [-99.16, 46.45]       |
|                                              | 12.83 [-71.22, 102.89]       |
|                                              | 10.74 [-25.81, 45.99]        |
|                                              | -0.99 [-41.65, 39.36]        |
|                                              | 0.85 [-111.67, 107.19]       |
|                                              | 70.90 [-70.74, 203.15]       |
|                                              | -11.42 [-56.67, 30.87]       |
|                                              | 43.84 [-2.70, 93.38]         |
| RS4, Sham                                    | -29.67 [-115.20, 54.26]      |
|                                              | -13.56 [-99.10, 70.45]       |
|                                              | 25.33 [-10.84, 61.39]        |
|                                              | 20.53 [-31.38, 77.00]        |
|                                              | -11.91 [-106.35, 81.27]      |
|                                              | -8.74 [-142.49, 124.83]      |
|                                              | -19.00 [-61.68, 28.21]       |
|                                              | 26.31 [-24.08, 75.24]        |

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

The reference condition for dummy variable coding is indicated within parentheses for each term.

PA, prism adaptation treatment; Sham, sham treatment; RS1, RS2, RS3, and RS4, research sessions 1, 2, 3, and 4; MIT, movement initiation time; MET, movement execution time.