PAIN® 154 (2013) 1519–1527

PAIN®

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# The rubber hand illusion in complex regional pain syndrome: Preserved ability to integrate a rubber hand indicates intact multisensory integration ☆

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*Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.*

ARTICLE INFO

*Article history:*
Received 6 October 2012
Received in revised form 9 March 2013
Accepted 29 March 2013

*Keywords:*
Body image
Complex regional pain syndrome
Cortical reorganization
Rubber hand illusion
Sense of ownership

ABSTRACT

In patients with complex regional pain syndrome (CRPS) type 1, processing of static tactile stimuli is impaired, whereas more complex sensory integration functions appear preserved. This study investigated higher order multisensory integration of body-relevant stimuli using the rubber hand illusion in CRPS patients. Subjective self-reports and skin conductance responses to watching the rubber hand being harmed were compared among CRPS patients (N = 24), patients with upper limb pain of other origin (N = 21, clinical control group), and healthy subjects (N = 24). Additionally, the influence of body representation (body plasticity [Trinity Assessment of Body Plasticity], neglect-like severity symptoms), and clinical signs of illusion strength were investigated. For statistical analysis, 1-way analysis of variance, *t* test, Pearson correlation, with $\alpha = 0.05$ were used. CRPS patients did not differ from healthy subjects and the control group with regard to their illusion strength as assessed by subjective reports or skin conductance response values. Stronger left-sided rubber hand illusions were reported by healthy subjects and left-side-affected CRPS patients. Moreover, for this subgroup, illness duration and illusion strength were negatively correlated. Overall, severity of neglect-like symptoms and clinical signs were not related to illusion strength. However, patients with CRPS of the right hand reported significantly stronger neglect-like symptoms and significantly lower illusion strength of the affected hand than patients with CRPS of the left hand. The weaker illusion of CRPS patients with strong neglect-like symptoms on the affected hand supports the role of top-down processes modulating body ownership. Moreover, the intact ability to perceive illusory ownership confirms the notion that, despite impaired processing of proprioceptive or tactile input, higher order multisensory integration is unaffected in CRPS.


## 1. Introduction

In patients with complex regional pain syndrome (CRPS) type 1, there is a well-known relationship between sensory disturbances and cortical reorganization phenomena associated with this syndrome [46,47,53,54]. Several studies linked decreased tactile acuity with the reduced size of cortical hand representation and altered excitability in the somatosensory cortex of CRPS patients [27,34,46,47]. At the same time, recent findings indicate that despite dysfunctional sensory processing, integration of body-related multisensory perceptions is intact in CRPS [40,51,64]. For example, despite decreased tactile spatial acuity, CRPS patients present intact 2-dimensional form-recognition abilities, provided that the form is above the spatial resolution performance [51]. Moreover, visuotactile integration was shown to be unaffected when CRPS patients underwent tactile training while simultaneously watching their healthy hand [40]. These findings imply that brain regions associated with multisensory integration may be preserved in CRPS. Multisensory integration of body signals underlies coherent body representation, which can be distorted in CRPS patients [15–17,28,29,38,39,45,49,50]. Unfortunately, there are no studies that directly investigate multisensory integration related to body representation in CRPS. However, a better understanding of

☆ This work is part of the doctoral thesis of Julia Landwehrt.

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0304-3959/$36.00 
http://dx.doi.org/10.1016/j.pain.2013.03.039

body-related sensory integration could provide information on the precise localization of those somatosensory functions that are impaired and add to the understanding of distorted body representations in CPRS.

A useful paradigm to investigate multisensory integration related to body representation is the rubber hand illusion (RHI) in which covert stroking of a participant's hand, synchronous with overt stroking of a rubber hand, elicits a sense of body ownership over the rubber hand [1,4,48,58,60]. The sense of body ownership (the perception that bodily sensations arise from oneself) is argued to arise in a process in which congruent visuotactile stimulation is integrated in prefrontal and parietocerebellar regions and matched with preexisting mental body representations [1,4,7,10,12,48,60–63]. Various studies have used the RHI to explore the sense of body ownership showing that compared with healthy subjects, patients with fragile body representation (eg, patients with eating disorders) are more susceptible to the illusion [4,10–12,14,25,32,41,48,60,67]. In contrast, amputees with centrally disrupted sensory processing experience a reduced RHI, whereas poststroke patients may even fail to experience it at all [10–12,25,41,48,60,67]. In the current study, the RHI was used for the first time in CRPS patients to explore body ownership and the underlying multisensory integration in CRPS for which (bilateral) cortical reorganization phenomena, sensory disturbances, and distorted body representations are reported [33,34,46,47,53]. The illusion strengths in CRPS patients were compared with healthy subjects and patients with upper limb pain of other origin (clinical control group), for whom cortical reorganization is confined to the unaffected hemisphere and body representation is presumed to be unimpaired [27,55–57]. Additionally, the influence of pain intensity, motor impairment, body plasticity, and neglect-like severity symptoms on illusion strength was investigated [15,16,18,32]. Based on previous RHI findings in patients with centrally disrupted sensory processing, chronic pain, or distorted body representation [11,41,48,67], we hypothesized that CRPS patients with chronic pain, dysfunctional sensory processing, and disrupted body representations would experience reduced illusion strengths compared with a clinical control group and healthy subjects.

## 2. Methods

### 2.1. Participants

This study included 24 patients (12 women) with CRPS type 1 of the upper extremity (mean age, 53.4 years; range, 34–78 years), 21 patients (12 women) with pain of the upper extremity of other origin (clinical control group) (mean age, 51.8 years; range, 32–71 years), and 24 healthy subjects (mean age, 52.8 years; range, 29–76 years), age and sex matched to CRPS patients. Except for 2 patients in the clinical control group, all participants were right-handed. Details on recruitment of all participants and detailed clinical characteristics of both patient groups were previously reported [50] and can in part be found in Table 1. Note that the experiment conducted in this study was independent of the previously published study [50] and that the testing was performed by a different investigator. The study was approved by the Ethics Committee of the Ruhr-University Bochum, Germany (no. 3412-09, July 2010; Clinical Trials: NCT01618578), and all subjects gave written informed consent before participation. CRPS type 1 was diagnosed based on the recently modified diagnostic research criteria [22] and additionally confirmed by typical enhancement in the late phase of the 99m-technetium triple-phase bone skeleton scintigraphy [66].

### 2.2. Questionnaires

Before testing, patients rated their average and current pain intensity during the past 7 days on an 11-point numerical rating scale, ranging from 0 (= no pain) to 10 (= worst pain imaginable).

The severity of neglect-like symptoms, indicating body image distortion in CRPS, was assessed in both patient groups using a standardized questionnaire by Frettlöh et al. [15]. This is a German

**Table 1**
Summary of patient characteristics and frequency of sensory, sudomotor, vasomotor, trophic, and motor signs in CRPS patients and patients with upper limb pain of other origin (clinical control group).

| | CRPS type 1 | | | Clinical control group | | |
|---|---|---|---|---|---|---|
| | Left affected (n = 12) | Right affected (n = 12) | Total (N = 24) | Left affected (n = 9) | Right affected (n = 12) | Total (N = 21) |
| Initiating event | | | | | | |
| Fracture | 6 | 7 | 13 | 6 | 2 | 8 |
| After surgery | 2 | 1 | 3 | – | 2 | 2 |
| Other kind of surgery | 4 | 4 | 8 | 3 | 8 | 11 |
| Illness duration, mo (mean ± SD) | 23.6 ± 2.7 | 14.1 ± 3.4 | 18.9 ± 8.8[a] | 51.8 ± 0.3 | 53.5 ± 4.9 | 52.8 ± 50.1[a] |
| Current medications | | | | | | |
| NSAIDs | 2 | 3 | 5 | 3 | 3 | 6 |
| Antidepressants | 2 | 4 | 6 | 3 | 3 | 6 |
| Anticonvulsants | 2 | 2 | 4 | 2 | 1 | 3 |
| Opioids | 1 | 2 | 3 | 2 | 4 | 6 |
| Other | 3 | 7 | 10 | 4 | 1 | 5 |
| Sensory abnormalities | | | | | | |
| Tactile hypesthesia | 7 | 11 | 18[a] | 6 | 2 | 8 |
| Sudomotor dysregulation | | | | | | |
| Edema/sweetening | 6 | 6 | 12[a] | 1 | 1 | 2 |
| Vasomotor dysregulation | | | | | | |
| Skin changes and/or temperature difference | 5 | 5 | 10[a] | 0 | 0 | 0 |
| Trophic dysregulation | | | | | | |
| Impaired hair and/or nail growth | 9 | 8 | 17[a] | 1 | 0 | 1 |
| Motor impairment | | | | | | |
| ROM wrist (quotient of affected side to nonaffected side) | 0.6 ± 0.3 | 0.3 ± 0.3 | 0.5 ± 0.3[a] | 0.8 ± 0.3 | 0.7 ± 0.3 | 0.8 ± 0.3 |
| Finger to palm distance, cm (mean ± SD) | 4.2 ± 3.1 | 4.2 ± 4.0 | 4.2 ± 3.5[a] | 1.6 ± 3.7 | 0.6 ± 1.3 | 1.0 ± 2.4 |

CRPS, complex regional pain syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; ROM, range of motion.

translation of a questionnaire originally developed by Galer and Jensen [16] and was previously used in a large case-control study investigating the sensitivity and specificity of the instrument as well as in other clinical studies investigating neglect-like symptoms in CRPS [15,16,26,28,50]. The mean of the questionnaire comprising 5 items such as "My painful limb feels as though it is not part of the rest of my body" and " I need to focus all of my attention on my painful limb to make it move the way I want it to" indicates the total score.

The Edinburgh Handedness Inventory is a well-established questionnaire to assess handedness [44]. The validated German version was used to assess handedness in all participants [5,44]. The questionnaire indicates handedness by means of a laterality quotient (LQ), ranging from −100 to +100. Negative values indicate left-handedness, whereas positive values indicate right-handedness. Almost all participants were right-handed (CRPS subjects LQ: 67.3 ± 36.2; control group LQ: 80.5 ± 23.1; healthy subjects LQ: 92.1 ± 21.9) except for 2 patients in the control group who were determined to be left-handed (LQ = −77.7 ± 22.2).

To assess the extent to which participants identify with the outer appearance of their somatic body, we used the translated, but not yet validated, Trinity Assessment of Body Plasticity questionnaire, which includes items such as "How easy or uneasy would you feel if you were to receive a lung transplant" or "Sometimes I feel that I am more part of my surroundings than a discreet human being" [9,32]. The total sum score ranges from 0 to 115, with low scores indicating a strong self- identification with the physical appearance of the own body and high scores expressing the belief that self-identification with the own body must not be limited to its physical appearance but can be modified [32]. Function of the affected limb in daily activities was assessed using the Disabilities of the Arm, Shoulder, and Hand (DASH) instrument, which is widely established and validated in Germany [18]. The final mean score of this validated questionnaire ranges from 0 to 100, with low scores indicating a high function of the limb, whereas high scores indicate a severe disability [18].

Finally, the parameters pain, ranging from 0 (= no pain) to 100 (= worst pain imaginable) and sensory abnormalities such as paresthesia, alterations of skin temperature, and swelling were assessed by means of an in-house questionnaire for both patient groups after each trial. This questionnaire relied on self-reports to assess whether experiencing illusory ownership over a rubber hand influences subjective perception of the affected hand. Paresthesia was assessed on a 4-point scale (0 = no paresthesia, 1 = paresthesia unchanged, 2 = paresthesia less severe than before; 3 = paresthesia stronger than before). Alterations of skin temperature were assessed on a nonparametric scale (0 = no alterations, 1 = hand feels colder, 2 = hand feels warmer), and alterations in the perception of swelling on the affected hand was assessed using a dichotomous response scale (0 = no swelling, 1 = the hand felt swollen after the experiment).

### 2.3. Procedure

Participants sat upright at a table on which 2 identical white occluder screens (40 × 60 cm) were placed ∼18 cm from the table's edge. The subject's hands were positioned palm down behind each occluder and a life-sized hand, and forearm prosthesis was then placed in an anatomically plausible position in full view. Depending on the condition, either a left or a right prosthetic limb was used. Importantly, positioning of the prosthesis was in alignment to the real hand behind the occluder (Fig. 1). The distance between the real hand and the prosthesis was ∼17.5 cm, which has been reported to be the most effective distance to elicit the illusion [30]. A gray hairdresser's cape was placed over the subject's shoulders to cover both the end of the prosthesis and the real hand so that the prosthesis seemed to be connected to the participant's body. A syringe was placed in full sight on the table next to the rubber hand. The rationale behind this was that previous studies have shown CRPS patients to often report increased pain or swelling when thinking about movement or imagining the affected hand to be touched [39]. Therefore, we hypothesized that habituation to the sight of a syringe during the stroking process could minimize anxious responses and subsequent autonomic nervous system reactions. Before the experiment, 2 electrodes were placed on the thenar and hypothenar eminence on the nonstimulated hand to measure skin conductance response (SCR). The participants were then instructed to focus on the artificial limb and to verbally indicate ("now") when they experienced a sensation of ownership toward the prosthesis during the stimulation. Fig. 1 shows the setup of the RHI in the synchronous experimental trial (ET) on the left hand (Fig. 1A). The participant and the experimenter sat opposite of each other at a white table (80 × 80 cm), and the participant's occluded own hand and the rubber hand were placed in full view and synchronously stroked according to a pre-established schema (Fig. 1B).

Each participant experienced 3 consecutive RHI trials, beginning with the control trial (CT) in which brushstrokes of the rubber hand and the participant's (analogous) hand were asynchronously applied for 3 minutes. For stimulation, the trained experimenter used 2 soft paintbrushes ∼25 mm in size. Subsequently, 2 ETs on the left and the right hand, respectively, were conducted. In these trials, the rubber hand and the participant's hand were synchronously stimulated according to a modified, pre-established schema (Fig. 1B), based on Ocklenburg et al. [43]. After 3 minutes of synchronous stimulation, participants watched the index finger of the prosthesis being stabbed with a syringe equipped with a needle for 20 seconds. After each trial, participants completed a questionnaire assessing perception and intensity of the illusion. Additionally, patients indicated changes in pain perception or any other sensory abnormalities. To reduce artifacts in the SCR data possibly caused by the transfer of the electrodes from 1 hand to the other, the first 2 trials were conducted on 1 hand.

### 2.4. Measurement of the illusion strength

The vividness of the illusion experience was evaluated after each RHI trial using a questionnaire. The questionnaire contained 5 items (items 1–5) of the German-translated version of Ocklenburg et al. [43], which is based on the original questionnaire by Botvinick and Cohen [4]. In view of reports by CRPS patients who experienced pain or swelling on imagining painful movements [21,39], 3 additional items (items 6–8), interrogating perception of the needle threat (eg, "the penetration of the needle into the prosthesis frightened me") were taken up in the questionnaire (Table 3). All items were answered using a 7-point Likert scale, ranging from 1 (= disagree strongly) to 7 (= agree strongly), with values >4 indicating a subjective perception of the RHI.

Because self-reports inherently contain limitations and subjective phenomena such as perceptual illusions underlie high interindividual variability, we additionally acquired an objective measure of identification with the prosthesis by measuring the SCR, which is an indicator of autonomic nervous system arousal in anticipation of pain [1,13,43]. SCR has previously been used to assess illusion strength in a number of studies [1,11,43]. Several studies [1,43] demonstrated a greater SCR amplitude in the experimental RHI trials than the asynchronously stimulated CTs, indicating that measurement of SCR values is a valid and objective instrument with which to assess illusion strength. On every trial, the SCR was recorded with 2 Ag-AgCl electrodes from the thenar and hypothenar eminence on the nonstimulated hand. Conductivity was measured in microsiemens (μS) (1/Ω). Data were recorded through Varioport

Portable Recorder System (Apparatus MP150, Biopac Systems München, Germany) and analyzed using Excel 2007. The protocol and analysis of SCR data were based on Ocklenburg et al. [43], following Armel and Ramachandran [1]. The amplitude of the largest SCR >0.03 μS occurring 1 to 5 seconds after onset of the threat was defined as peak amplitude and scored as a response [1]. Thus, participants with amplitudes <0.03 μS in both ETs were defined as nonresponders and excluded from analysis. Additionally, a baseline was determined by calculating the mean values of the SCR data for 2 seconds before the onset of the needle threat. Finally, baseline-corrected amplitudes were determined to avoid possible differences between recordings from the left and right hand.

### 2.5. Statistics

Statistics were performed using SPSS 15.0 software (SPSS Inc, Chicago, IL). Significance levels for all analyses were set at $\alpha = .05$. Group differences with respect to illusion strength on each trial were analyzed using 1-way analysis of variance (ANOVA) with post hoc Bonferroni correction. To investigate the influence of the affected side on illusion strength as well as a possible effect on the side on which the RHI was first elicited during the experiment, ANOVA with the affected hand and the side started as an independent variable was used. Furthermore, to explore subjective identification with the rubber hand, repeated- measures ANOVA with the trial as the within-subjects factor and group as the between-subjects factor was conducted. Additionally, a paired-sample $t$ test was calculated to explore differences regarding illusion strength between the affected and nonaffected side in both patient groups and between the dominant and nondominant hand in healthy subjects. In the overall sample, Neyman-Pearson correlation coefficients were calculated between illusion strength and the outcome measures body plasticity and handedness (LQ). In both patient groups, Neyman-Pearson correlation coefficients were additionally calculated for illusion strength and neglect-like severity score, illness duration, motor impairment (DASH), and pain intensity on every trial. Finally, to detect alterations of the parameters pain, paresthesia, change of skin temperature, and swelling in the course of every trial, Friedman's nonparametric repeated-measures comparisons were used.

## 3. Results

### 3.1. Study sample

Both patient groups did not differ with respect to body plasticity ($P = 0.23$), neglect-like severity score ($P = 0.07$), or average ($P = 0.86$) and current pain intensity ($P = 0.55$). Furthermore, pain after the CT ($P = 0.95$) and after each ET (affected side: $P = 0.54$; nonaffected side: $P = 0.59$) did not differ between both patient groups (Table 2). Detailed results on the frequency of clinical signs and motor impairment can be found in Table 1.

Compared with CRPS patients, the clinical control group presented with significantly longer illness duration and less pronounced motor symptoms, as evident in a higher range of wrist motion, a lower DASH score, and a smaller finger-to-palm distance than CRPS patients (all $P$ values > 0.01) (Tables 1 and 2). CRPS patients not only presented with greater motor impairment, but clinical investigation also revealed more signs of sensory abnormalities and SUDOMOTOR dysfunction (all $P$ values > 0.01) (Tables 1 and 2) [50]. Furthermore, right-affected CRPS patients showed significantly greater neglect-like symptoms than left-affected patients ($P = 0.02$) or right-affected patients in the control group.

Friedman's nonparametric repeated-measures comparisons revealed no changes in pain intensity (CRPS: $P = 0.89$; clinical control group: $P = 0.41$), paresthesia (CRPS: $P = 0.51$; clinical control group: $P = 0.\ 50$), skin temperature (CRPS: $P = 0.46$; control group: $P = 0.78$), or swelling (CRPS: $P = 0.61$; clinical control group: $P = 0.07$) in any of the patients during application of the RHI.

#### 3.1.1. Subjective illusion strength

In 2 CRPS patients, the RHI was conducted only on the nonaffected hand because of intolerable pain on touching the affected limb. Analyses of mean values of each questionnaire item revealed that only items 1, 2, and 3 yielded scores >4, thus indicating subjective perception of the illusion. Hence, the mean sum score of the first 3 items was used for further analyses with values >12 indicating vivid perception of the illusion (Table 3).

Across all groups, a significantly stronger identification with the rubber hand was shown on both ETs compared with the CT ($P = 0.00$). There were no group differences regarding illusion strength in each of the 3 conducted trials (CT: $P = 0.16$; ET on the affected/dominant side: $P = 0.90$; ET on the nonaffected/nondominant side: $P = 0.\ 45$) (Fig. 2).

There was no influence of the side on which the trials were started in either CRPS patients (ET affected side: $P = 0.27$; ET nonaffected side: $P = 0.42$) or patients with pain of another origin (ET affected side: $P = 0.40$; ET nonaffected side: $P = 0.72$). Vividness of the illusion did not differ between the affected and nonaffected hand in patients with CRPS (mean ± SEM affected side: 15.2 ± 1.3; nonaffected side: 17.1 ± 1.3) ($P = 0.12$) or in the clinical control group (mean ± SEM, affected side: 14.3 ± 1.5; nonaffected side: 15.0 ± 1.4) ($P = 0.69$). Healthy subjects experienced a significantly stronger illusion on the left, nondominant hand (15.9 ± 1.3)

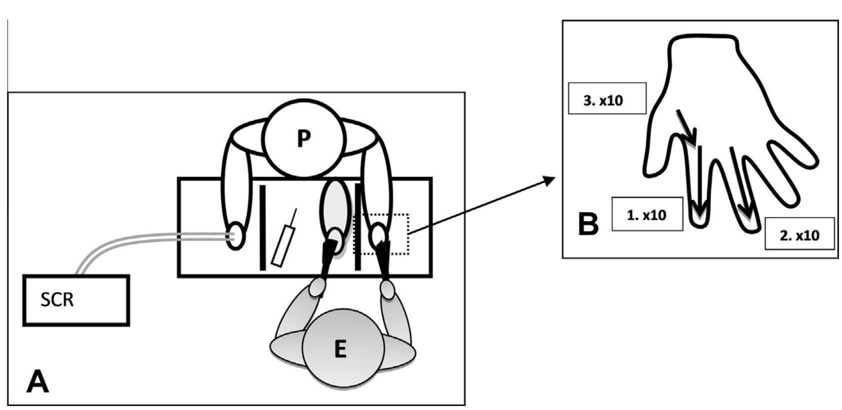


**Fig. 1.** Setup of the rubber hand illusion in the synchronous experimental trial on the left hand (E, experimenter; P, participant) (A). The participant and the experimenter sat opposite of each other at a white table (80 × 80 cm) while the participant's occluded own hand and the rubber hand placed in full view were synchronously stroked according to a modified, pre-established schema (B). During the stimulation, skin conductance response (SCR) was measured on the nonstimulated hand.

compared with the right, dominant hand (14.5 ± 1.4) ($P$ = 0.018) (Fig. 2). Correspondingly, left-affected CRPS patients experienced a significantly stronger illusion on the affected side (mean ± SEM: 18.0 ± 1.3) compared with right-affected CRPS patients (mean ± SEM: 12.4 ± 2.0; $P$ = 0.027) (Fig. 3).

Furthermore, left-affected CRPS patients showed a tendency toward a stronger illusion on the nonaffected side (mean ± SEM: 19.6 ± 0.4) compared with right-affected CRPS patients (mean ± SEM: 15.0 ± 2.1), but this failed to reach significance ($P$ = 0.055). This laterality effect was not found in the clinical control group (ET affected side: $P$ = 0.95; ET nonaffected side: $P$ = 0.16).

The amount with which subjects identify with their somatic body, indicated by the Trinity Assessment of Body Plasticity, did not relate to the intensity with which the RHI was experienced in any of the 3 groups (all $P$ > 0.15). All correlation coefficients between illusion strength, pain intensity, neglect-like severity symptoms score, motor impairment, or handedness did not reach significance in CRPS (all $P$ values > 0.13) or in patients with pain of other origin (all $P$ values > 0.29), showing that these factors are not associated with illusory body ownership. The overall correlation between LQ and illusion strength of the affected hand was significant for CRPS patients ($r$ = 0.42, $P$ = 0.047), but further investigation of this relationship in left- or right-affected CRPS patients did not reveal significant correlations. For left-affected CRPS patients, but not for right-affected CRPS patients or patients in the clinical control group, illness duration and illusion strength were strongly related only for the affected hand (left-affected CRPS patients: $r$ = −0.6, $P$ = 0.036).

### 3.1.2. Skin conductance response (SCR)

Overall, 10 of the 69 participants (4 CRPS patients, 3 clinical control group patients, 3 healthy subjects) were excluded from analysis of SCR. Seven subjects were excluded due to technical reasons (4 CRPS patients, 2 clinical control group subjects, 1 healthy subject). The remaining 3 subjects (1 clinical control group patient, 2 healthy subjects) showed amplitudes <0.03 μS on both ETs and were therefore defined as nonresponders. As for subjective illusion strength, the main factor group did not influence SCR (CRPS, mean ± SEM: affected side, 1.4 ± 0.4; nonaffected side, 2.6 ± 1.2; clinical control group, mean ± SEM: affected side, 1.2 ± 0.4; nonaffected side, 1.5 ± 0.4; and healthy subjects: mean ± SEM dominant side, 1.8 ± 0.6; nondominant side, 0.9 ± 0.2) on any of the ETs (ET affected/dominant side: $P$ = 0.65; ET nonaffected/nondominant side: $P$ = 0.31). SCR did not differ between the dominant and nondominant hand in healthy subjects ($P$ = 0.06) and between the affected and nonaffected hand in CRPS patients ($P$ = 0.34), or the clinical control group ($P$ = 0.55) (Fig. 4).

Moreover, across both patient groups, SCRs were comparable between the side on which the illusion had been elicited first (CRPS patients: ET affected side, $P$ = 0.70; ET nonaffected side, $P$ = 0.34; clinical control group: ET affected side, $P$ = 0.30; ET nonaffected side, $P$ = 0.18) and between left- and right-affected patients in either ET (CRPS patients: ET affected side, $P$ = 0.46; ET nonaffected side, $P$ = 0.62; clinical control group, ET affected side, $P$ = 0.76; ET nonaffected side, $P$ = 0.39). Baseline-corrected amplitudes showed no differences across groups in both ETs (ET affected/dominant side, $P$ = 0.59; ET nonaffected/nondominant side, $P$ = 0.34).

## 4. Discussion

The present study used the RHI to investigate the process of multimodal integration relevant to body representation in (1) patients with disrupted body representation and bilateral cortical reorganization phenomena (CRPS), (2) patients with intact body representation but chronic pain and unilateral cortical reorganization (clinical control group), and (3) in healthy subjects [33,34,46,47,53]. To our knowledge, this is the first study investigating the RHI in CRPS patients in whom touch of the affected limb or visual input can increase pain or swelling [21,39]. The present results show that eliciting the RHI in CRPS patients is feasible and that CRPS patients are just as able to perceive bilateral illusory ownership over an artificial hand as healthy subjects or patients with upper limb pain, as confirmed by both subjective and objective illusion strength measurements (self-reports and SCR measures). Across all groups, perception of ownership of the artificial hand was stronger on ET compared with CT. Moreover, the reported illusion strength and SCRs to watching the rubber hand being harmed confirm results obtained in previous studies [1,4,13,43]. Furthermore, the results support the hypothesis of right-hemisphere dominance for the sense of body ownership, with healthy subjects and left-affected CRPS patients reporting a stronger illusion on the left compared with the right hand [1,7,10,12,13,42,43,59,60,63,67]. Overall, illusion strength was not influenced by pain or motor impairment, suggesting that other mechanisms may account for the intact ability to perceive illusory ownership in CRPS.

### 4.1. Intact ability to perceive illusory ownership

Several studies have investigated the conditions necessary to elicit a sense of ownership and the underlying brain processes. A sense of ownership during the RHI relies on (1) so-called bottom-up processes wherein concurrent visuotactile stimuli are integrated and formed into a perceptual experience that is (2) matched

**Table 2**
Mean scores (± SD) of the body plasticity, neglect-like severity score, DASH, and pain after each trial (CT and ET on the affected side, ET on the nonaffected side) in CRPS patients and patients with upper limb pain of other origin (clinical control group).

| | CRPS type 1 patients | | | Clinical control group | | |
|---|---|---|---|---|---|---|
| | Left affected | Right affected | Total | Left affected | Right affected | Total |
| Body image assessment | | | | | | |
| TABP | 4.8 ± 0.5 | 4.5 ± 0.2 | 4.7 ± 0.4 | 4.6 ± 0.6 | 4.3 ± 0.6 | 4.5 ± 0.6 |
| Neglect-like severity score[a] | 1.0 ± 1.1 | 2.3 ± 1.2[b] | 1.7 ± 1.3 | 1.4 ± 1.1 | 0.8 ± 0.7 | 1.0 ± 0.9 |
| Motor impairment | | | | | | |
| DASH[a] | 46.6 ± 20.1 | 60.5 ± 9.1 | 53.5 ± 16.8[c] | 43.0 ± 14.7 | 40.7 ± 20.4 | 41.6 ± 17.8 |
| Pain after each trial | | | | | | |
| CT | 32.5 ± 21.4 | 38.3 ± 27.2 | 35.4 ± 24.1 | 37.2 ± 26.5 | 33.2 ± 28.1 | 34.9 ± 26.8 |
| ET, affected side | 36.4 ± 21.1 | 29.9 ± 28.6 | 33.1 ± 24.8 | 46.7 ± 33.6 | 32.3 ± 28.7 | 38.5 ± 31.0 |
| ET, nonaffected side | 33.6 ± 21.1 | 32.4 ± 26.7 | 33.0 ± 23.6 | 40.6 ± 29.3 | 34.8 ± 29.5 | 37.3 ± 28.8 |

CRPS, complex regional pain syndrome; CT, control trial, DASH, Disabilities of the Arm, Shoulder, and Hand instrument; ET, experimental trial; TABP, Trinity Assessment of Body Plasticity.
[a] Previously reported by Reinersmann et al. [50].
[b] Significant difference between left-affected and right-affected CRPS patients (significance level: $\alpha$ = .05)
[c] Significant difference between CRPS type 1 and upper limb pain of other origin.

**Table 3**
Mean questionnaire scores (± SD) in both experimental trials on the affected/dominant side and the nonaffected/nondominant side for all 8 items in each group.

| Items | CRPS type 1 (N = 24) | | Clinical control group (N = 21) | | Healthy (N = 24) | |
|---|---|---|---|---|---|---|
| | Affected side (n = 22) | Nonaffected side (N = 24) | Affected side (N = 21) | Nonaffected side (N = 21) | Dominant side (N = 24) | Nondominant side (N = 24) |
| 1. It seemed as if I were feeling the touch of the paintbrush in the location where I saw the rubber hand touched[a] | 5.6 ± 2.0 | 6.0 ± 1.7 | 5.1 ± 2.4 | 5.0 ± 2.3 | 5.5 ± 2.3 | 5.9 ± 2.1 |
| 2. It seemed as though the touch I felt was caused by the paintbrush touching the rubber hand[a] | 4.9 ± 2.4 | 5.7 ± 2.1 | 5.0 ± 2.4 | 5.1 ± 2.5 | 4.3 ± 2.7 | 5. 0 ± 2.7 |
| 3. I felt as if the rubber hand were my hand[a] | 4.7 ± 2.7 | 5.5 ± 2.2 | 4.2 ± 2.8 | 4.8 ± 2.6 | 4.6 ± 2.5 | 5.0 ± 2.7 |
| 4. It felt as if my (real) hand were turning rubbery | 2.1 ± 1.9 | 1.5 ± 1.4 | 1.4 ± 1.2 | 1.4 ± 1.1 | 1.9 ± 1.8 | 2.2 ± 2.1 |
| 5. The rubber hand began to resemble my own (real) hand, in terms of shape, skin tone, freckles, or some other visual feature | 3.6 ± 2.6 | 4.0 ± 2.7 | 3.5 ± 2.8 | 3.7 ± 2.5 | 2.7 ± 2.2 | 3.0 ± 2.6 |
| 6. The penetration of the needle on the prosthesis frightened me | 3.6 ± 2.6[b] | 2.8 ± 2.4 | 3.0 ± 2.3 | 2.6 ± 2.3 | 1.8 ± 1.6 | 2.0 ± 1.9 |
| 7. It seemed, as though I felt the penetration of the needle on my (real) hand | 2.4 ± 2.4 | 1.7 ± 1.7 | 2.7 ± 2.4 | 2.6 ± 2.4 | 1.8 ± 1.5 | 1.8 ± 1.8 |
| 8. The penetration of the needle in the prosthesis was painful for me. Please specify the pain intensity on a scale, ranging from 0 to 100 (0 = no pain, 100 = worst pain imaginable) | 2.0 ± 1.9 | 1.5 ± 1.2 | 2.1 ± 2.1 | 1.9 ± 1.9 | 1.2 ± 0.8 | 1.4 ± 1.3 |

CRPS, complex regional pain syndrome.
[a] Only the items 1, 2, and 3 yielded values >4, indicating a subjective perception toward the rubber hand. The mean sum score of these items was used for further analysis.
[b] Significant difference between CRPS type 1 (affected side) and healthy (dominant side) subjects (significance level: $\alpha = .05$).

with preexisting higher order cognitive body representations in so-called top-down processes [20,35,58–60,62,63]. A neural network comprising the right temporoparietal junction, ventral premotor cortex, posterior parietal regions, right posterior insula, cerebellum, and frontal operculum was shown to be involved in the processing of multisensory stimuli related to body representation [10,12,48,60,63]. Correspondingly, in stroke patients who failed to perceive the RHI, lesion voxels were located subcortically adjacent to the insula and basal ganglia and within the periventricular white matter [67]. Moreover, upper limb amputees, for whom reorganization of somatosensory regions similar to that observed in CRPS has been reported, experienced reduced illusion strength [11,49]. In view of these findings and the disrupted somatotopy-based sensory processing in CRPS, the retained illusion strength reported by these patients was unexpected [15,27,29,33,34,47,49,50,53].

What might have accounted for the intact ability to perceive illusory ownership in CRPS? Body ownership is not reduced to mere registration of peripheral input in the primary and secondary somatosensory cortex (SI and SII) but involves processing and integration of multisensory stimuli in regions beyond those concerned with static tactile processing alone [60,61]. Although our data have yet to be supported by imaging results and interpretation should hence be made tentatively, it may be hypothesized that the integration of multimodal percepts in association areas such as the ventral premotor cortex or posterior parietal region is unaffected in CRPS, the retained illusion strength suggesting similar functionality to that of healthy subjects and patients with upper limb pain of other origin. In line with this notion, Reiswich et al. [51] reported preserved 2-dimensional form recognition abilities in CRPS patients, indicating intact higher order sensory integration, despite impaired tactile acuity (corresponding to S1 and SII function). Moreover, Moseley and Wiech [40] also observed intact visuotactile integration despite impaired tactile discrimination in CRPS patients. Finally, patients with focal hand dystonia, a painless motor disorder associated with (bilateral) cortical reorganization phenomena similar to those demonstrated in CRPS, also report full sense of ownership of a rubber hand despite signs of impaired proprioceptive processing [14].

Although confirmatory imaging research clearly is required, it may be hypothesized that despite disrupted somatotopy-based sensory processing, higher order sensory functions concerned with the integration of body-relevant stimuli and associated with activity in premotor and posterior parietal areas are preserved in CRPS. Clinical findings of distinct neurocognitive impairments that would suggest parietal dysfunction in CRPS appear in contrast to this conclusion [6,37,52]. However, the parietal lobe consists of various specialized subregions and is associated with different functions related to both higher order cognitive abilities and multimodal integration to generate coherent body representation [2,3,61]. Thus, different parietal functions may have been assessed in the present study. Also, it should be noted that before the RHI, the current sample of subjects had participated in an experiment investigating spatial body representation [19,50]. Results revealed a CRPS-specific leftward bias when locating the body midline, suggesting an accentuated involvement of right-hemisphere-dominated spatial processes [23,50,65]. The comparison of body midline shift and subjective illusion strength, however, revealed that these were not related (unpublished data), and thus the shifted body midline did not compromise the ability to perceive illusory ownership. In conclusion, the present results indicate that despite deficient processing of tactile stimuli, multimodal integration of body-related input in association areas linked to multisensory integration is not affected by CRPS pathophysiology. Additionally, top-down cognitive processes may have facilitated the induction of illusory ownership in CRPS patients.

### 4.2. Top-down processes modulate sense of ownership

Several studies have demonstrated the influence of preexisting body representations containing structural and semantic aspects of body representation (the body image) on the sense of body ownership [17,60,63]. For example, patients with feeble body representation such as patients with eating disorders or with unilateral neglect experience the RHI differently [41,48,67]. In the current sample, neither patients of the control group nor CRPS patients reported fragile body plasticity. Moreover, with the exception of right-affected CRPS patients, neglect-like symptoms were less pronounced than in other CRPS samples and, in line with a recent study, not specific to CRPS patients [15,16,26,28]. These results suggest overall unaffected mental hand representation in the current sample. Although the assessment relied on self-administered surveys, which inherently contain limitations, the induction of ownership may have been mediated by top-down modulation of an intact general body part representation (here, what a healthy hand looks like) [60]. This notion is corroborated by the

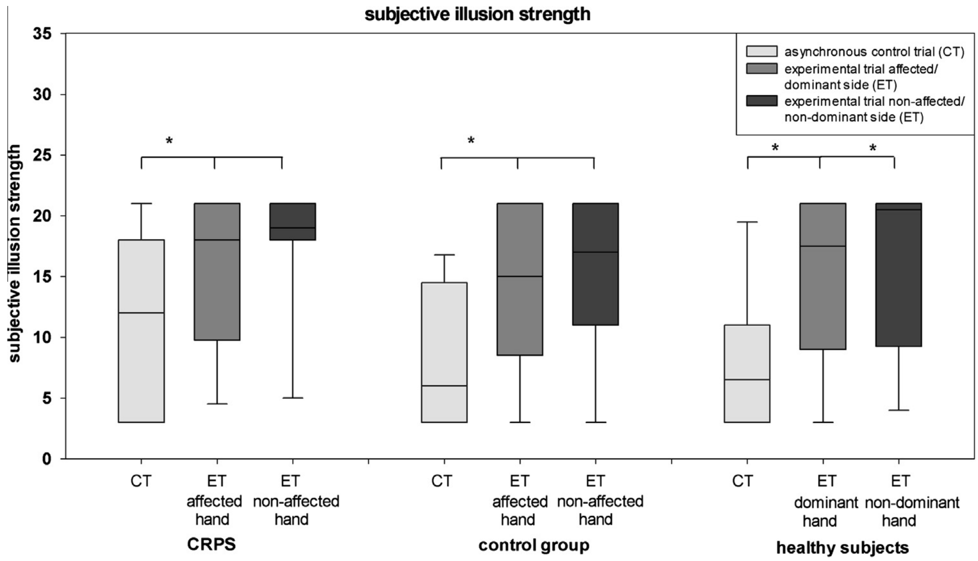


**Fig. 2.** Subjective illusion strength in every trial: control (asynchronous) trial (CT); experimental (synchronous) trial (ET) on the affected/dominant hand and experimental (synchronous) trial on the nonaffected/nondominant hand across all groups. The bottom and the top of the boxes represent the 25th and the 75th percentiles, respectively, the black line within the box marks the 50th percentile (median). The whiskers above and below the boxes indicate the 90th and 10th percentiles. *Significant difference in the subjective illusion strength between trial types. CRPS, complex regional pain syndrome.

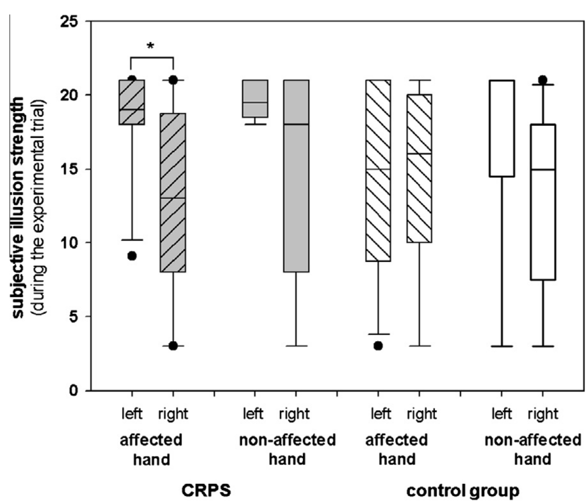


**Fig. 3.** Significant higher subjective illusion strength on the affected hand in left-affected compared with right-affected complex regional pain syndrome (CRPS) patients but not in patients in the clinical control group. The bottom and top of the boxes represent the 25th and 75th percentiles, respectively, the black line within the box is marking the 50th percentile (median). The whiskers above and below the boxes indicate the 90th and 10th percentiles. *Significant difference in the subjective illusion strength between trial types.

observation that right-affected CRPS patients who experience strong neglect-like symptoms, indicating an altered body image, report a weaker illusion [58–60,62,63]. Moreover, top-down conceptual modulation of tactile percepts was shown to affect the RHI for anticipated visual input more than factual tactile sensations alone, a mechanism that is also evident in the so-called visual enhancement of touch effect reflected in enhanced tactile acuity when watching the own body [8,20,31,60].

### 4.3. Laterality and RHI

The right hemisphere was recently suggested to not only be dominant for spatial attention but also for body representation and sense of body ownership, as indicated by more vivid illusions when the RHI is elicited at the left hand [10,12,19,24,42,43,62]. Healthy subjects in the present study also experienced a stronger illusion on the left compared with the right hand in accordance with previous data [42,43]. A laterality effect was also observable in left-affected CRPS patients who reported a stronger illusion on the affected hand than right-affected CRPS patients. Moreover, left-affected CRPS patients displayed a trend toward higher illusion scores on the nonaffected hand compared with right-affected CRPS patients. Thus, overall, left-affected CRPS patients reported a more vivid illusion than right-affected CRPS patients who, in turn, experienced strong neglect-like symptoms. Interestingly, in left-affected patients, illness duration was negatively related to illusion strength. Thus, the longer left-affected CRPS patients had been affected, the weaker the illusion experience was in these patients. Little is known about the longitudinal progress of CRPS signs and symptoms, and the current patient sample, similarly to others, is

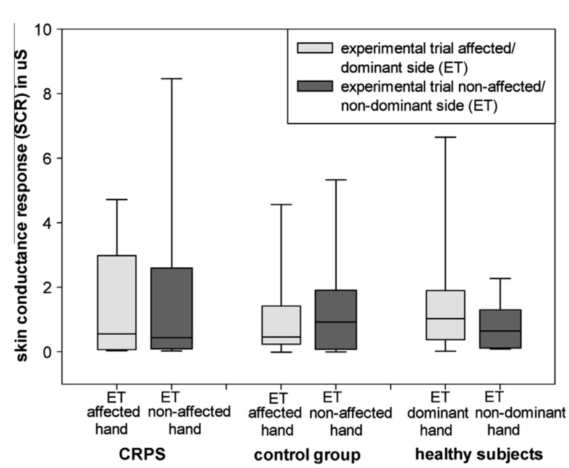


**Fig. 4.** Skin conductance response values in both experimental trials: experimental trial on the affected/dominant side and experimental trial on the nonaffected/nondominant side for all 3 subject groups. The end of the boxes represent the 25th (lower quartile) and the 75th (upper quartile) quartiles, the black line within the box marks the 50th percentile (median). The whiskers above and below the boxes indicate the 90th and 10th percentiles. CRPS, complex regional pain syndrome.

characterized by high interindividual variability [36,50]. Nevertheless, right-hemisphere generation of ownership might be particularly affected in left-affected CRPS patients, as previously suggested [50]. Taken together, these results suggest that in CRPS, lateralized top-down processes mediate the matching of multisensory experiences with body representations even when cortical processing of static tactile input is impaired.

It should be noted that the assessment of illusion strength and body image relied on standardized instruments that are not fully validated [4,15,42,43,50]. Because both concepts entail a highly subjective aspect that inherently is difficult to objectify, we sought to ensure methodical soundness by using SCR to objectify subjective illusion strength and applied widely established instruments to assess the body image.

### 4.4. Conclusions

This study observed intact perception of illusory ownership during RHI in CRPS patients. Although confirmatory imaging evidence is required, the results suggest that higher order multisensory integration functions in cortical association areas such as the premotor cortex and frontoparietal areas are unaffected in CRPS. Moreover, in line with existing neurocognitive models of body ownership, complementary top-down processes of preexisting body models appear to contribute to the illusion perception in CRPS patients [7,58,60,62]. The present results provide a basis for future imaging studies on morphological structures specifically affected in CRPS, showing that multisensory areas, in contrast to somatotopic maps in SI and SII, display functionality similar to that of healthy subjects.

## 5. Conflict of interest

There are no financial or other relationships that might lead to a conflict of interest.

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