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Patients with complex regional pain syndrome overestimate applied force in observed hand actions

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Abstract

Background: Movement accuracy is ensured by interaction between motor, somatosensory, and visual systems. In complex regional pain syndrome (CRPS), this interaction is disturbed. To explore CRPS patients' visual perception of actions, we investigated how these patients evaluate the applied force in observed hand actions of another person.
Methods: Nineteen patients suffering from unilateral upper-limb CRPS and 19 healthy control subjects viewed six different videos of left- and right-hand actions. They were asked to evaluate the applied force in each hand action, as well as their subjective sensations of unpleasantness and pain during the observation.
Results: The patients overestimated the force applied in the videos: the ratings were two times as large as in the control subjects for actions performed with the hand corresponding to the patients' affected hand, and 1.5 times as large for actions corresponding to their healthy hand. The control subjects considered the stimuli neutral and painless, whereas the patients rated them unpleasant. Moreover, the patients felt increased pain during viewing actions performed with the hand corresponding to their affected side. The overestimation of force was related to the elicited unpleasantness and pain, but not to the patients' muscle strength.
Conclusions: We propose that the overestimation of force is explained both by the pain elicited by the observation and by the abnormal sensorimotor integration that is associated with perception of increased effort. This visually elicited unpleasantness and painfulness may promote avoidance of viewing own actions, further impairing the patients' motor performance.

1. Introduction

Complex regional pain syndrome (CRPS) is a chronic pain condition predominantly affecting one limb. According to diagnostic criteria (Harden et al., 2010), CRPS comprises – in addition to pain – sensory, vasomotor, sudomotor and motor symptoms in the affected limb. CRPS is often preceded by minor trauma, but the symptoms are too severe, long-lasting and wide-spread to be explained by the injury itself. CRPS type I exists without evidence of a major peripheral nerve injury, whereas CRPS type II includes this.

In CRPS patients, motor action, or sometimes even imagined motor action, of the affected limb aggravates pain (Veldman et al., 1993; Moseley et al., 2008), which might further promote the disuse of

What's already known about this topic?

- Complex regional pain syndrome (CRPS) includes motor symptoms, such as weakness and clumsiness. Motor action often aggravates the patients' pain, promoting disuse of the affected limb, which leads to impairment of motor skills and to muscle atrophy.
- CRPS patients make errors in judging the posture and shape of the affected limb. Although visual feedback corrects these misconceptions, the patients often keep the affected limb out of sight.

What does this study add?

- CRPS patients overestimate the applied force in observed hand actions. The disease-driven changes in the central nervous system thus likely include visual interpretation of motor actions.
- Patients experience observation of others' motor actions painful and unpleasant. Overestimation of the force relates to the increase in experienced pain and unpleasantness.

the limb (Punt et al., 2013). Moreover, the disuse itself can cause movement-induced pain (Terkelsen et al., 2008). This vicious circle easily leads to muscle atrophy and impaired motor skills. Accordingly, weakness and muscular incoordination are common in the affected limbs of CRPS patients (Veldman et al., 1993).

Prior studies have shown that CRPS patients, when not receiving visual feedback, are not able to evaluate their affected limb's position and shape accurately (McCabe et al., 2005; Lewis et al., 2007, 2010), which likely further impairs their motor skills. Visual feedback can remediate these misevaluations (McCabe et al., 2005; Lewis et al., 2010) and could thus have an important role in the patients' motor control. However, the patients often keep the affected limb away from their field of vision (Lewis et al., 2007). This avoidance of visual feedback might be explained by the distress and confusion elicited by the conflict between visual information and aberrant non-visual conception of the limb (Lewis et al., 2007). Even visual input not related to the body may feel uncomfortable, e.g. the ambiguous visual image of a Necker cube can elicit pain in CRPS patients (Hall et al., 2011).

Observation and execution of motor actions are known to rely on overlapping brain activations (for a review, see Rizzolatti et al., 2009). Thus, studying interpretation and experiences related to action observation could inform about the functioning of the viewer's own motor system.

Chronic pain patients have recently been shown to be impaired in estimating weights that others lift provided that the lifting includes movements that would be painful for the patients (De Lussanet et al., 2012). The altered interaction between visual information, motor action and experienced pain may impair the patients' motor skills, and the study of this interaction is thus clinically relevant. Here, we investigated how upper limb CPRS patients evaluate the applied force in observed hand actions of others, and how these evaluations are related to patients' motor symptoms, and to the pain and unpleasantness elicited by the observation.

2. Materials and methods

Nineteen patients suffering from chronic unilateral upper limb CRPS type I (18 females; ages 24–62 years, mean 44.6; 17 right- and two left-handed) and 19 sex- and age-matched (within 2 years) healthy control subjects (18 females; ages 24–60, mean 44.8; all right-handed by report) participated in the study. Patients were recruited primarily from the Pain Clinic at the Helsinki University Central Hospital, where the patient records from year 2007 to 2013 were searched for CRPS diagnosis, resulting in 96 patients. Then, all 18–65-year-old chronic upper limb CRPS type I patients with severe rest or movement pain and with no record of other major neurological or psychiatric diagnosis or alcohol or drug addiction were contacted for recruitment (46 patients). Other clinics, mainly in Uusimaa District, known to treat CRPS patients, were informed of our study and asked for eligible subjects. Finally, 36 patients were clinically examined and of those, 19 fulfilled the research criteria. The control subjects were recruited primarily by email advertisements.

All patients had earlier been diagnosed with CRPS. At the time of the inclusion, all but two patients fulfilled the current diagnostic criteria of CRPS for research purposes, and the other two the clinical diagnostic criteria (Harden et al., 2010).

Table 1 lists clinical information of the patients. Eight (42%) patients had left-sided and 11 (58%) right-sided symptoms; in 11 (58%) patients, the symptoms were on the dominant side. Symptoms

Table 1 Patients' clinical information.

	Gender	Age	Dominant hand	Affected hand	Symptom duration [years]	Rest pain[a]	Movement pain[a]
p01	F	24	R	L	1.5	8	9
p02	F	31	R	L	3.5	9	9
p03	M	34	R	L	4.5	4	8
p04	F	35	L	R	0.9	8	8
p05	F	35	R	R	3.3	8	8
p06	F	38	R	R	1.5	7	10
p07	F	43	R	R	8.2	6	7
p08	F	44	R	R	8.3	10	10
p09	F	44	R	R	7.5	8	7
p10	F	44	R	L	4.2	10	9
p11	F	46	R	R	1.4	5	7
p12	F	47	R	R	15.5	4	5
p13	F	48	R	R	2.0	9	5
p14	F	49	R	L	3.5	7	7
p15	F	50	R	R	2.1	6	9
p16	F	53	L	L	28.5	6	8
p17	F	56	R	L	2.9	8	9
p18	F	57	R	R	5.0	7	7
p19	F	62	R	L	2.3	1	6

[a] Maximum pain intensity [NRS-11] during previous week.

had lasted for 0.9–28.5 years (median 3.5 years, mean ± SD 5.6 ± 6.6 years).

The patients and the control subjects had no other neurological or psychiatric diagnoses, except that three patients also suffered from migraine. The control subjects did not report long-lasting or ongoing pain. None of the subjects had alcohol or drug addiction. Informed written consent was obtained from all subjects according to the Declaration of Helsinki. The Ethics Committee of the Helsinki and Uusimaa Hospital District had approved the study protocol.

2.1 Clinical examination and motor assessment

The patients were examined at inclusion by an experienced neurologist with a subspecialty in pain (HH) at the Pain Clinic of the Helsinki University Central Hospital. In the clinical examination, pain, sensory, vasomotor, sudomotor/oedema and motor/trophic symptoms and signs were evaluated. Sensory assessment included testing of tactile, pinprick, cold and warm sensations, as well as dynamic and static allodynia. Ranges of motion and motor function were examined by inspection and testing the motor ranges of hand and wrist against resistance.

To further assess the motor abilities of the upper extremities, a trained physiotherapist tested grip strength using a dynamometer (Saehan®), active range of motion of the wrist joints by measuring the angles with a goniometer and hand dexterity with a nine-hole peg test (9-HPT) (Mathiowetz et al., 1985).

The clinical examination and motor assessment were conducted on days separate from the actual experiment for all except five patients in whom the motor assessment was performed right before the actual experiment. Separate analysis indicated that timing of the clinical testing did not have any effect on the results reported in this paper.

2.2 Questionnaires

Before the experiment, the patients marked a number on an 11-point numeric rating scale (NRS-11; 0 = no pain, 10 = worst pain imaginable) to evaluate the maximum pain intensity they had experienced during the previous week at rest and during motor action. They also ranked the most important aggravating and relieving factors for their pain. Six examples were given for aggravating factors (motor action, posture, weather, mood, stress, time of the day) and two for relieving factors (rest, medication).

Patients completed the Finnish version of the Disabilities of the Arm, Shoulder and Hand questionnaire (DASH, Institute for Work & Health; http://www.dash.iwh.on.ca/home; Hudak et al., 1996), which is a 30-item self-report questionnaire designed to measure physical function and symptoms in patients with disabilities of the upper limb.

2.3 Experimental design

The subjects were first asked to rate, on NRS-11, their pre-experiment pain while their hands were still ('What is your pain experience at the moment while your hand is still?'). To provide a controlled prior experience with the hand movements shown on the forthcoming videos and to evaluate the actual painfulness of similar actions, the subjects performed two tasks separately with both hands: (1) opening and closing of the hand (FIST), and (2) squeezing four given objects with maximum force (SQUEEZE; for objects, see Supplementary Fig. S1). After each task, the subjects rated the maximum pain intensity (NRS-11) in their acting hand during the task (FIST: 'How painful was the hand movement?'; SQUEEZE: 'How painful was the squeezing at its worst?').

After performing the motor tasks, the subjects viewed series of videos in which an actress held her hand still in an upright position (STATIC), and performed the same tasks as the subjects had performed (FIST and SQUEEZE). Only the hand and about 10 cm of antebrachium were visible on the screen (see Fig. 1). The actress performed the tasks with her right hand; left-hand stimuli were created by mirroring the videos vertically. Videos were shown on a laptop computer with a 13.3-inch widescreen display, and the subjects were advised not to perform any movements themselves when observing the stimuli. The subjects were seated comfortably in front of the display that was approximately on the subject's midline. The subjects typically kept their hands on their lap, although the hand position was not specifically controlled. The tests were conducted in a quiet room. The instructions were given in written form and clarified verbally when needed.

Fig. 1 demonstrates the stimulation sequence comprising altogether six blocks of video stimuli: one 32.6-s block for each left- and right-hand task. Each block contained eight 3.2-s hand action videos of that particular task, separated by a 1-s blank screen, and each video showed that action from a different first-person view. All 3.2-s FIST and SQUEEZE videos contained one cycle of closing and opening of the hand. Blocks presented the tasks always in the same order: (1) STATIC, (2) FIST and (3) SQUEEZE. For each task, the patients were always first shown the block presenting their healthy hand, followed by the block presenting their affected hand; for control subjects, left-hand stimuli were presented first and right-hand stimuli then. After each block, the subjects marked on a questionnaire (1) whether the left or the right hand had been presented; (2) the NRS-11 estimate of the force applied on the video ('How much force was

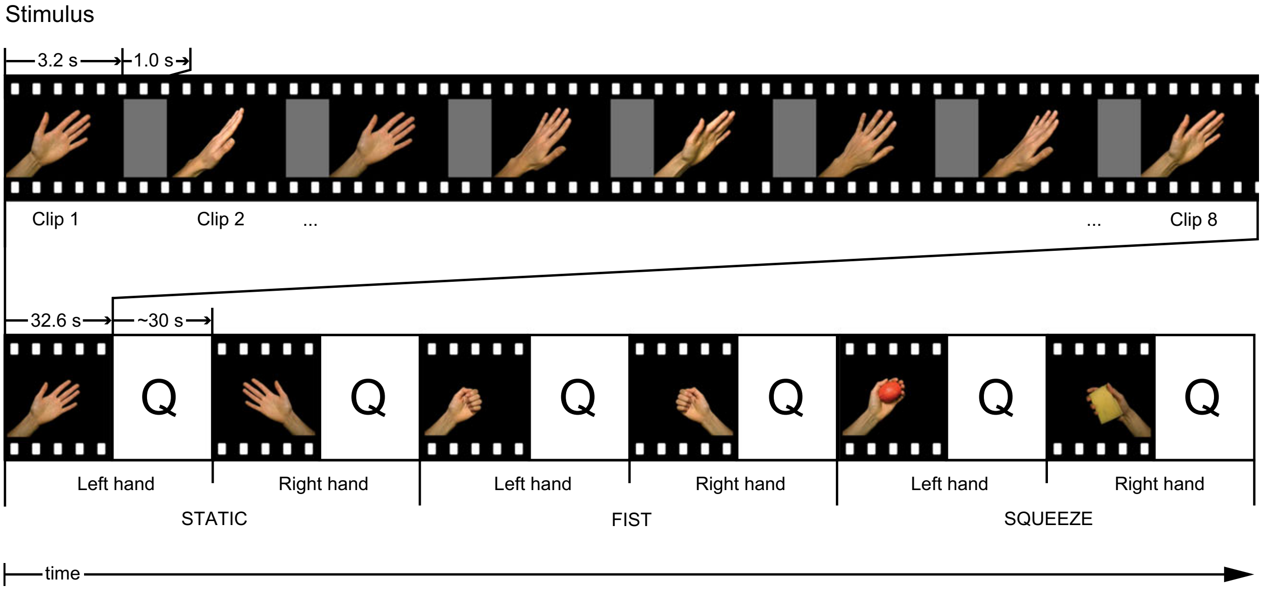

Figure 1 Experimental protocol for the patients with the affected right hand and all control subjects; hand sidedness was in reversed order for patients with the affected left hand. Each stimulation block lasted 32.6 s and depicted either left or right hand performing one of the three tasks: hand still in upright position (STATIC), hand making a fist (FIST), and hand squeezing an object (SQUEEZE). Each block contained eight consecutive 3.2-s video clips separated by 1-s breaks. After each stimulation block, subjects answered questions (Q) concerning previously presented stimulus: (1) which hand had been presented, (2) how much force was used on the video, (3) how pleasant or unpleasant was it to observe the video, and (4) how much pain did you experience during the video. Time to answer was unlimited but usually lasted ca. 30 s per stimulus.

used on the video?'; 0 = no force, 10 = very much force); (3) the NRS-11 estimate of the valence of observing the video ('How pleasant or unpleasant was it to observe the video?'; 0 = very pleasant, 5 = neutral, 10 = very unpleasant); and (4) the NRS-11 estimate of experienced pain intensity while observing the video ('How much pain did you experience during the video?'; 0 = no pain, 10 = worst pain imaginable).

2.4 Statistical analysis

Statistical testing was performed using IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA). Alpha level of $p < 0.05$ was used in all evaluations, with Bonferroni corrections.

For the questionnaires and motor assessment data, as well as for the comparison between pre-experiment and video stimuli pain ratings, two-tailed *t*-tests were applied whenever the results met normality hypothesis in the Shapiro–Wilk test. Otherwise corresponding non-parametric tests were applied. All significance values refer to Student's *t*-test unless otherwise stated.

All the three NRS-11 parameters of the hand-action-stimulus-rating experiment (force, valence and pain) were analysed with ANOVAs with no alpha-correction for multiple ANOVAs. Initially, a 2 (GROUP: patient, control) × 2 (HAND: affected, healthy) × 3 (CONDITION: Static, Fist, Squeeze) mixed-design ANOVA was conducted. GROUP was a between-subjects factor, whereas HAND and CONDITION were within-subjects factors. Because the control subjects had two healthy hands with similar pain, force and valence ratings (see Results), their right hand was arbitrarily labelled as 'affected' in the ANOVAs. Greenhouse–Geisser correction was applied if sphericity was not met in Mauchly's test. Statistically significant effects were further tested with simple effects tests or planned contrasts. Correlations were estimated using Pearson's *r* with two-tailed significance testing.

In the following, the results are presented as mean ± SD values if not stated otherwise.

3. Results

3.1 Symptoms, signs and clinical data

The patients' estimates for previous week's maximum pain intensity indicated severe pain, both during motor action (7.8 ± 1.5) and rest (6.9 ± 2.3), see Table 1. The most commonly reported aggravating factors for pain were movement (in 89% of the patients) and posture (84%). The most often reported relieving factors were rest (95%) and medication (74%). Compared with normative values (Hunsaker et al., 2002), the patients' DASH score was significantly increased (51.9 ± 15.0 vs. 10.1 ± 14.7; $t = 11.9$, $p < 0.0001$, $n = 18$).

In clinical examination, all 19 patients reported motor symptoms, and motor signs were observed in 17 patients. Grip force was weaker in the affected than in the healthy hand (16.3 ± 8.9 vs. 24.2 ± 8.0; $t = 3.9$, $p < 0.01$). The joints' active ranges of motion were smaller in the affected than the healthy hand for wrist flexion (69.7 ± 12.0 deg vs. 80.9 ± 6.2 deg; $t = 4.0$, $p < 0.005$) and extension (61.6 ± 12.2 deg vs. 76.7 ± 8.2 deg; $t = 5.9$, $p < 0.0001$). The times needed to perform the 9-HPT were significantly prolonged in patients compared with age-, hand- and sex-matched normative values (Mathiowetz et al., 1985) for both affected (22.3 ± 6.9 s; Wilcoxon Signed Rank Test, $p < 0.05$) and healthy (19.7 ± 2.5 s; Wilcoxon Signed Rank Test, $p < 0.05$) hands.

In sum, our patients suffered from severe movement-related pain and disability associated with extensive motor deficits. These features are common sequels of CRPS.

3.2 Pain intensity, force and valence rating

Fig. 2A shows the patients' mean (± SEM) pain ratings during (1) the pre-experiment state, (2) the motor tasks with the affected hand, and (3) the video stimuli. The patients reported severe pre-experiment pain (5.5 ± 2.3). Observing the actions of the hand corresponding to the healthy hand did not significantly alter the reported pain level; specifically, the pain was at the pre-experiment level during the first video stimuli (STATIC). Observing the motor tasks of the hand corresponding to the affected hand, however, increased the pain intensity by 16 ± 18% in FIST and 19 ± 24% in SQUEEZE condition compared with the pre-experiment level (pain scores 6.4 ± 2.2 during FIST and 6.5 ± 2.3 during SQUEEZE; both were higher than the pre-experiment level at $p < 0.05$, $t = 4.2$, and 3.6, respectively). The patients reported 15 ± 27% stronger pain when they were observing the hand corresponding to the affected compared with the healthy hand ($F_{1,18} = 6.3$, $p < 0.05$, $\eta_p^2 = 0.26$). There was a linear trend of pain increase in the patients in the order of STATIC – FIST – SQUEEZE conditions ($F_{1,18} = 5.1$, $p < 0.05$, $\eta_p^2 = 0.22$). The control

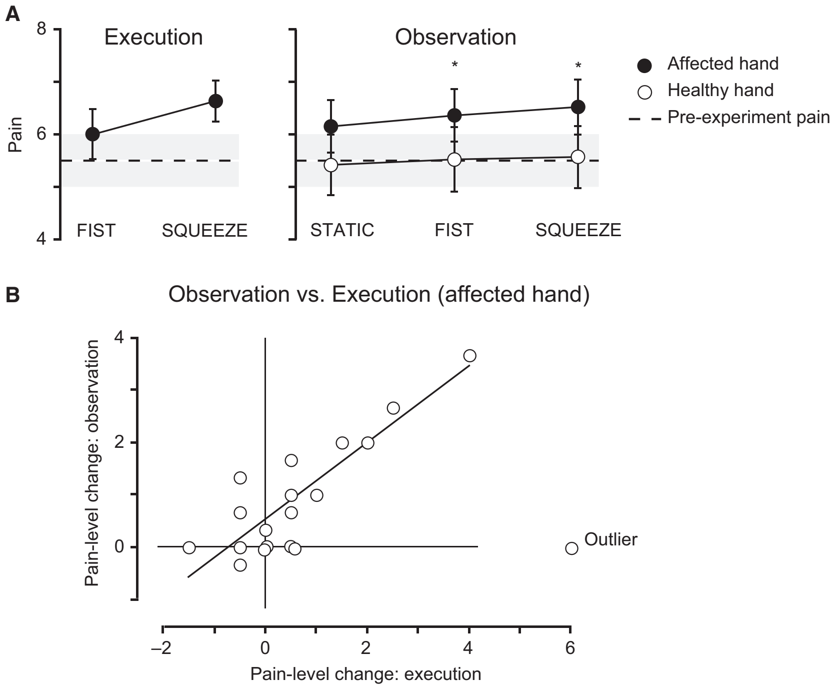

Figure 2 (A) Mean ± SEM experienced pain (0 = no pain, 10 = worst pain imaginable) in patients, separately for action execution with the affected hand (left panel) and for observation of the hand actions corresponding to the affected and healthy hand (right panel; filled and open symbols, respectively). Results are presented separately for STATIC, FIST, and SQUEEZE conditions. Shaded bands show mean ± 1 SEM (5.5 ± 0.5) of the pre-experiment pain ratings. Asterisks denote statistically significant differences ($p < 0.05$) between pain ratings for the hand corresponding to the affected hand versus pre-experimental state. (B) Patient-wise mean pain-level change relative to the pre-experiment pain during observation of the hand corresponding to the affected hand as a function of the pain-level change during action execution with the affected hand. The black line presents linear fit when excluding the denoted outlier.

subjects did not report any pain during action observation.

Fig. 2B shows patient-wise mean pain-level changes for the hand corresponding to the affected hand (relative to the pre-experiment level) in action observation as a function of that for the affected hand in action execution. For the affected hand, the pain-level change in action observation and execution correlated significantly ($r = 0.46$, $p < 0.05$, $n = 19$). One patient was considered as an outlier (Cook's distance 6.3) and a *post hoc* analysis excluding this patient strengthened the correlation substantially ($r = 0.86$, $p < 0.0001$, $n = 18$).

Fig. 3A shows the mean (± SEM) force evaluations during the three stimulus types in patients and control subjects. For all stimuli, the patients overestimated the force applied in the videos: their scores were 99 ± 93% higher than those of the control subjects for the hand corresponding to the affected hand ($F_{1,36} = 17.3$, $p < 0.0005$, $\eta_p^2 = 0.33$) and 52 ± 80% higher for the hand corresponding to the healthy hand ($F_{1,36} = 6.4$, $p < 0.05$, $\eta_p^2 = 0.15$). Further, the patients felt that the actress was applying 34 ± 35% more force when the hand corresponded to the patient's affected compared with the healthy hand ($F_{1,18} = 18.8$, $p < 0.0005$, $\eta_p^2 = 0.51$). In the control subjects, the scores for the applied force were similar for both hands (see Supplementary Table S1).

Fig. 3B shows the mean (± SEM) valence ratings. The control subjects rated all stimuli as neutral (5.0 ± 0.5), whereas, compared with the control subjects, the patients experienced all stimuli unpleasant, especially those corresponding to the affected hand ($F_{1,36} = 17.3$, $p < 0.0005$, $\eta_p^2 = 0.33$ and $F_{1,36} = 4.1$, $p = 0.05$, $\eta_p^2 = 0.10$ for the hand corresponding to the healthy hand). The patients consistently considered observing the hand corresponding to the affected hand more unpleasant than observing the hand corresponding to the healthy hand ($F_{1,18} = 28.3$, $p < 0.00005$, $\eta_p^2 = 0.61$). Observing the SQUEEZE was more unpleasant than the STATIC ($F_{1,18} = 10.1$, $p < 0.05$, $\eta_p^2 = 0.36$) or FIST ($F_{1,18} = 8.1$, $p < 0.05$, $\eta_p^2 = 0.31$).

In patients, the subject-wise ratings of pain intensity, valence and force for the observed hand

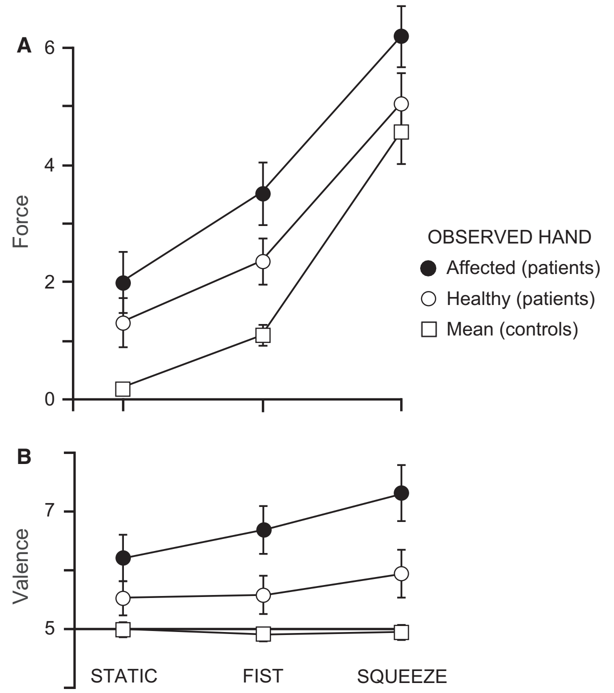

Figure 3 Mean ± SEM ratings of (A) applied force (0 = no force, 10 = very much force) and (B) experienced valence (0 = very pleasant, 5 = neutral, 10 = very unpleasant). Results are presented separately for STATIC, FIST, and SQUEEZE conditions. For the patients, the results for both observed hands are displayed, and for the control subjects, the means of right and left hands are displayed.

corresponding to the affected hand did not correlate. However, when we correlated the difference between the ratings for the hands corresponding to the healthy and affected hand, the mean difference in pain and force estimates as well as the mean difference in valence and force estimates correlated statistically significantly ($r = 0.637$, $p < 0.05$ and $r = 0.761$, $p < 0.001$, respectively). Fig. 4 illustrates these between-hands force-score differences as a function of the corresponding pain (1) and valence (2) score differences.

3.3 Correlations between symptoms, signs and clinical and behavioural data

The patients' pain intensity, valence and force ratings for observed hand corresponding to the affected or healthy hand did not correlate statistically significantly with the grip strength, active joint ranges of motion, 9-HPT and DASH results, or symptom duration. Moreover, the valence and force scores did not correlate with the reports of the previous weeks' maximum motor action or rest pain.

4. Discussion and conclusions

We found that CRPS patients overestimate the force applied by another person in hand actions that the patients view from first-person's perspective. The overestimation was most pronounced for actions corresponding to the patients' affected hand but also occurred for the healthy hand. Observation of hand actions was unpleasant, and observation of the hands corresponding to the affected side increased the patients' pain. When the ratings for the hand corresponding to the healthy hand were used as reference, force overestimations correlated with the increase in pain and unpleasantness.

The simplest explanation for the overestimation of the observed force would be that the patients compared the observed action and their own force that they, in principle, could apply in a similar action. Critically, however, the patient-wise force estimates

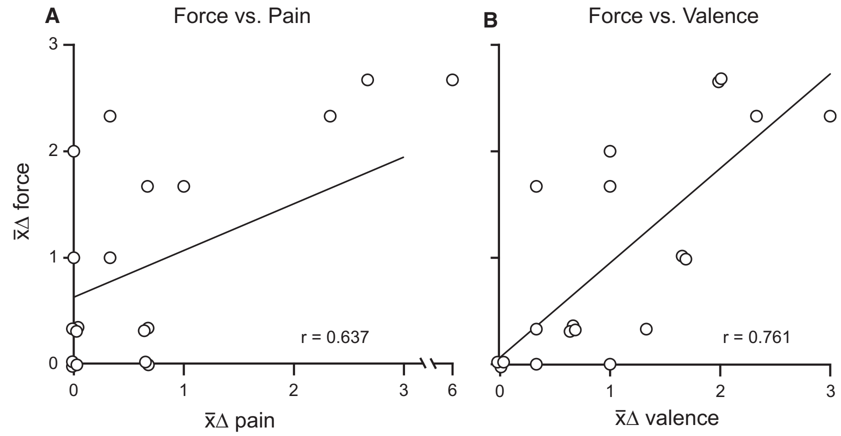

Figure 4 The mean between-hands force-score differences as a function of the corresponding between-hands (A) pain and (B) valence score differences; individual mean values for all stimuli ($\bar{x}\Delta$) are shown for each of the 19 patients.

did not correlate with the measured grip strength or other measures of motor function that were separately tested for the patients' affected and healthy hands. The overestimation of force could thus relate to misjudgement of the patient's own force or have other explanations, e.g. the interference of pain with force estimation or altered sense of effort.

The association between force overestimation and increased pain and unpleasantness could imply that the perceived pain as such impairs the force estimation of others' actions. Experimentally produced muscle soreness and cutaneous pain can result in overestimation of own applied force (Weerakkody et al., 2003). However, we are not aware of previous results that would show that chronic pain (such as in CRPS) could distort the estimation of own force and that such misestimation would extend to observed actions performed by other people. Two recent studies demonstrated the pronounced effect of the removal of visual cues on force reproduction error in two subgroups of upper limb CRPS: patients suffering from dystonia (Mugge et al., 2013) or of abnormal postures of the affected limb (Bank et al., 2014). These patients first learnt to produce target forces with the help of visual cues presented on a screen, and they then had to reproduce equal forces without the cues. Compared with healthy control subjects, the patients overproduced (i.e. underestimated) their affected limb's force in the no-cue setting. Unfortunately, neither study addressed specifically the effect of direct visual feedback or of pain during the task on the performance.

A recent behavioural study (De Lussanet et al., 2012) demonstrated that chronic pain impairs the ability to discriminate weights that a point-light actor manipulates. Importantly, the impairment was body-part-specific, manifesting only for movements of the painful body part. The impairment was not related to visual recognition of the actions, suggesting that chronic pain interferes with sensorimotor but not visual judgments. The same research team replicated these results for chronic low-back-pain patients (De Lussanet et al., 2013) and further suggested the impairment not to be related to attentional or general cognitive deficits in chronic pain; in an additional complex visual task, only acute, and not chronic, pain interfered with the task-performance. Whether acute and chronic pain would affect differentially the estimation of another person's force was not addressed; however, chronic low-back-pain patients, compared with healthy control subjects, did overestimate the applied force. Our results are consistent with this finding.

In the present study, viewing hand actions that were not painful for healthy persons increased the pain of the CRPS patients so that the increase correlated with the painfulness of own similar actions. This effect could result from the activation of the viewer's central representation of own actions during observation of others' actions involving, e.g. the primary motor cortex M1 (Hari et al., 1998). In CRPS, movements are associated with pain to the extent that the patients typically avoid moving the affected limb, and thus activation of the central motor circuitry could automatically increase the associated pain. This idea is consistent with earlier studies showing that also imagined movements – known to activate the motor circuitry (for a recent review, see Hétu et al., 2013) – can increase CRPS patients' pain and even swelling of the affected limb (Moseley, 2004a; Moseley et al., 2008). The pain induced by action observation could worsen motor control by promoting avoidance of visual feedback during own motor actions.

In a recent transcranial magnetic stimulation study with healthy subjects, action observation recruited the M1 cortex and the corticomuscular system in a force-dependent manner so that M1 activation was the stronger, the heavier was the weight that the subjects were observing another person to lift (Alaerts et al., 2010). If M1 activation was to account for the overestimation of the applied force in an observed action, we could expect that the observed action would activate the M1 cortex more strongly in CRPS patients than in control subjects. Such an increase in activation level could result from the decreased inhibition of M1 cortex manifested in CRPS (for a recent review, see Di Pietro et al., 2013a). Whether M1 activation is increased during action observation remains to be shown in future experiments, although it is already known that CRPS patients recruit the M1 cortex during their own motor actions more intensively than do healthy control subjects (Maihöfner et al., 2007).

Altered sensorimotor integration belongs to the core of CRPS, as is evident from the multitude of sensory and motor symptoms, and functional changes in the somatosensory and motor cortices (Juottonen et al., 2002; Di Pietro et al., 2013a,b). CRPS patients also often have misconceptions of their affected limb's size and orientation in space (McCabe et al., 2005; Moseley, 2005; Lewis et al., 2010; Peltz et al., 2011), which could further account for difficulties in the planning and control of motor actions.

CRPS patients are slower than control subjects in determining the laterality of hands that are presented from different orientations on a monitor screen (Reinersmann et al., 2010), and the response times are specifically prolonged for hands corresponding to their own affected hand when the required mental rotation is large (Schwoebel et al., 2001). Such slowed processing has been attributed to pain-induced abnormalities in the body schema (Schwoebel et al., 2001; Moseley, 2004b).

Many of the factors discussed above could affect the sense of motor effort that is considered to reflect a combination of both central motor commands and peripheral reafference that facilitates the action. As one sign of increased motor effort, CRPS patients often report the need for increased attention to perform movements (Galer et al., 1995; Frettlöh et al., 2006; Lewis et al., 2007). Increased motor effort is common also in stroke patients, deafferented subjects (due to a large-fibre sensory neuropathy), patients with multiple sclerosis, as well as subjects whose peripheral afferents have been anaesthetized (for a review, see Proske and Gandevia, 2012). Any distortion of the sensorimotor integration could thus increase the feeling of effort related to own actions, but possibly also to actions performed by others. The increased effort and the overestimation of required force in seen actions could together lead to physical inactivity, thereby devastating motor skills.

Intriguingly, the patients overestimated the observed force and felt unpleasant also when observing hands corresponding to their healthy hand, although the effects were weaker than for the affected hand. It thus seems likely that just seeing a hand, without laterality recognition (which takes considerably more time), is enough to evoke the unpleasant associations with one's own painful hand. On the other hand, this finding could be related to the bilaterality of the CRPS pathology, shown previously as decreased inhibition of M1 cortex in both hemispheres in patients with unilateral symptoms (Schwenkreis et al., 2003) and as a spread of unilateral symptoms and brain abnormalities in S1 cortex during the disease duration also to the other side (Forss et al., 2005). Consistent with the latter consideration, our patients' hand function was clinically impaired also on the healthy side.

One major limitation of the present study is the small group size. The prevalence of CRPS is low (20/100,000; Sandroni et al., 2003), and our patients thus comprise over 5% of the CRPS patients in Uusimaa district (population of approx. 1.5 million). Another limitation, affecting the interpretation, is the lack of grip strength and other measures from our control subjects. As we presented the conditions in a similar order to all subjects, some order effects are likely; however, they should not affect the comparison between the two subject groups. Performing the motor tasks before observation (to ensure that each participant was fully aware of the presented actions) may have affected the perception of the videos so that own experience served as a basis for, e.g. force estimation. Moreover, although we instructed the subjects to stay immobile during the measurement, we did not directly control unintentional hand movements.

Overall, our findings provide insight into one major problem in CRPS rehabilitation – the coupling of motor action with pain. Specifically, we suggest that this coupling may corrupt interpretation of visuomotor information and promote avoidance of visual control in motor actions. The results call for future studies that should clarify how CRPS patients estimate their own force, how their varying pain level affects this estimation, how these findings generalize to observation of other persons' actions and how the central motor circuitry is activated during action observation.

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Author contributions

All authors of the manuscript fulfil the criteria for authorship. J.H. has contributed in the conception and design of the work, the acquisition of data, in the analysis and interpretation of data and in drafting the article, and takes responsibility for the integrity of the work as a whole. H.H. has contributed in the acquisition and interpretation of data. L.N. has contributed in the analysis and interpretation of data. E.K. has contributed in the conception and design of the work and in the interpretation of data. N.F. and R.H. have contributed in the conception and design of the work, in the analysis and interpretation of data and drafting the article. In addition, all authors have contributed in critical revision of important intellectual content in the article and read and approved the article.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Sample shots of the SQUEEZE video stimuli presenting the four squeezed objects.

Table S1. Mean ± SEM ratings of applied force in healthy subjects. The results are presented separately for STATIC, FIST, and SQUEEZE conditions for the observed left- and right-hand actions.