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## **Sensory and motor dysfunction in Complex Regional Pain Syndrome**

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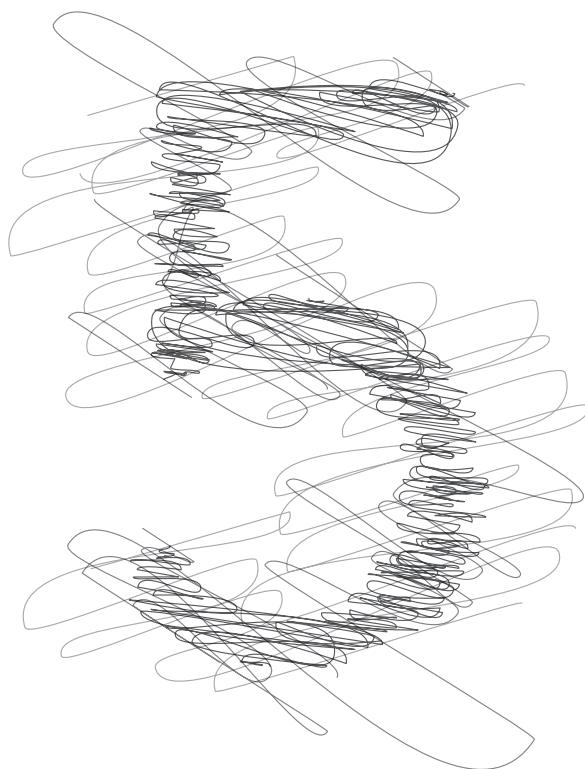


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## CHAPTER 5: Force modulation deficits in Complex Regional Pain Syndrome: A potential role for impaired sense of force production

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## **ABSTRACT**

Compelling evidence points at both impaired proprioception and disturbed force control in patients with chronic Complex Regional Pain Syndrome (CRPS). Because force modulation at least partly relies on proprioception, we evaluated if an impaired sense of force production contributes to disturbances of force control in patients with CRPS. Characteristics of voluntary force modulation were examined in the affected upper extremity in 28 CRPS patients with abnormal postures, in 12 CRPS patients without abnormal postures, and in 32 healthy controls. Isometric grip force matching was compared between conditions with and without visual feedback to identify potential deficits in the sense of force production in terms of force reproduction errors. Results showed that voluntary force modulation was impaired in CRPS patients, but more so in patients with abnormal postures. In particular CRPS patients with abnormal postures were characterized by reduced maximum force, reduced ability to increase force output according to task instructions, higher variability of force output, and less adequate correction of deviations from the target force. Although effects of visual feedback removal appeared largely similar for the two patient groups and controls, our findings with respect to force reproduction errors suggested that an impaired sense of force production may contribute to the motor dysfunction in CRPS. In conclusion, CRPS patients, in particular those with abnormal postures, showed impaired voluntary force control and an impaired sense of force production. This suggests that therapeutic strategies aimed at restoration of proprioceptive impairments, possibly using on-line visual feedback, may promote the recovery of motor function in CRPS.

## INTRODUCTION

Motor disturbances are frequently reported in Complex Regional Pain Syndrome (CRPS) and may involve weakness, abnormal postures, and problems with initiation and execution of movements.<sup>1-6</sup> The prominent loss of voluntary control is associated with significant disability.<sup>3, 7-11</sup> Several pathophysiological mechanisms have been postulated to underpin the CRPS-related motor impairments, ranging from structural and functional alterations in skeletal muscle tissue,<sup>12, 13</sup> to maladaptive neuroplasticity at various levels of the central nervous system.<sup>9, 14</sup> The latter may have profound consequences for motor control, presumably through impaired processing of afferent input and abnormal integration of sensory signals during motor control.<sup>15</sup>

Successful performance of motor tasks requires adequate modulation of force output. Accordingly, information from various sources (including tendon organs, muscle spindles, and pressure-sensitive skin receptors) has to be properly integrated with centrally generated motor commands (for a review see Proske and Gandevia, 2012).<sup>16</sup> In CRPS, several sensory impairments have been reported that may interfere with force control, including altered sensitivity of cutaneous and muscular afferents<sup>17-23</sup> and disturbances in sensory-motor integration.<sup>24-26</sup> One study using computational modeling found that aberrant force feedback from Golgi tendon organs may contribute to abnormal postures in CRPS.<sup>27, 28</sup> Additionally, some CRPS patients need to watch their affected limb to control movements,<sup>29</sup> which may implicate an increased reliance on the visual system to compensate for disturbed proprioception (i.e., the senses of position and movement of our body parts, and the senses of effort, force, and heaviness).<sup>16</sup> Collectively, these findings suggest that proprioceptive impairment might play a significant role in the motor dysfunction of CRPS. So far, however, the putative contribution of proprioceptive deficits has not been investigated during functional motor tasks.

The present study aims to advance our understanding of motor dysfunction in CRPS and the potential role of deficits in the sense of force production. To this end, we evaluated characteristics of voluntary force modulation during an isometric force matching task in CRPS patients with and without abnormal postures of the upper extremity, and compared the findings with those obtained from healthy controls. We compared task performance with and without on-line visual feedback to evaluate po-

tential deficits in the sense of force production, i.e., to assess whether proprioceptive and tactile input could adequately be used for control of force.

## **METHODS**

The experiment presented in this paper was performed for the upper extremity and for the lower extremity. In view of the length and legibility of the article, the procedure and results for the lower extremity are presented in the supplementary material (Methods S1, Results S1, Discussion S1).

### *Participants*

Force control was evaluated in 40 patients diagnosed with CRPS of the upper limb and 32 age- and sex-matched healthy controls (Table 5.1). All patients fulfilled the diagnostic criteria for CRPS adopted at the 1993 consensus conference ('Orlando criteria'), which were the criteria formally endorsed by the International Association for the Study of Pain (Merskey and Bogduk, 1994) at the time this study was initiated. In 28 patients, the inflicted body part preferably adopted an abnormal posture from which return to a neutral position was not possible, or only with great difficulty. To further our insight into these abnormal postures, 12 CRPS patients without abnormal postures were included that served to control for the effects of CRPS. Patients were excluded if they suffered a known genetic form of dystonia (e.g. DYT11/DYT11 or Wilson's disease), mobile dystonia, or conditions affecting the central nervous system, or if they had an implanted drug-delivery pump for intrathecal baclofen. Healthy controls had no history of lesions or diseases of the central or peripheral nervous system, or other conditions associated with pain and/or limited function of the extremities. Informed consent was obtained according to the Declaration of Helsinki. The ethical committee of the Leiden University Medical Center approved of the study's protocol before the study was conducted.

## **MEASUREMENT INSTRUMENTS AND DATA COLLECTION**

### *Scales and questionnaires*

In patients, pain was evaluated using a numeric rating scale (NRS, 0: no pain, 10: unbearable pain) and the Pain Rating Index of the McGill Pain Questionnaire (MPQ-PRI;

maximum score: 63).<sup>30</sup> The Burke Fahn Marsden scale was used to indicate the presence and functional impairment of abnormal postures (maximum score: 120).<sup>31</sup> Disability due to limitations in arm function was evaluated using the Radboud Skills Questionnaire (RSQ; range: 0-5).<sup>32</sup> The occurrence and extent of neglect-like symptoms was evaluated using a 5-item scale (range: 1-6).<sup>33</sup> Higher scores on these questionnaires reflected higher levels of pain, disability, and neglect, respectively. In controls, hand dominance was assessed using a Dutch version of the Edinburgh Handedness Questionnaire.<sup>34</sup>

**Table 5.1:** Demographic and clinical information of participants

	CRPS <sub>AP</sub> (n=28)	CRPS <sub>noAP</sub> (n=12)	HC (n=32)	p
Sex (male/female) <sup>a</sup>	5/23	4/8	5/27	.402
Age (years) <sup>b</sup>	49.0 (12.1)	48.5 (8.9)	48.8 (13.6)	.990
Disease duration (years) <sup>c</sup>	10.5 (5-14)	10.5 (8-22)		.360
BFM score <sup>c</sup>	19.5 (9.4-37.3)	-		
MPQ-PRI <sup>b,d</sup>	30.6 (10.8)	30.4 (10.7)		.970
Sensory symptoms (%) <sup>a,e</sup>				
Allodynia	29	17		.693
Hyperesthesia	21	75		.003*
Hypesthesia	43	17		.157
Pain <sup>b</sup>	6.4 (2.2)	6.0 (1.9)		.626
RSQ <sup>b,d</sup>	3.4 (0.9)	3.1 (0.8)		.317
Neglect-like symptoms <sup>b</sup>	3.2 (1.3)	2.3 (0.7)		.023*

Abbreviations: CRPS<sub>AP</sub>, CRPS patients with abnormal posture; CRPS<sub>noAP</sub>, CRPS patients without abnormal posture; HC, healthy controls; BFM score, total score on the Burke Fahn Marsden scale; MPQ-PRI, Pain Rating Index of the McGill Pain Questionnaire; Pain, rating on a numeric rating scale (NRS, 0-10); RSQ, score on the Radboud Skills Questionnaire. <sup>a</sup> Chi-square test was used for comparing the groups. <sup>b</sup> Measures are presented as mean (standard deviation); ANOVA was used for comparison of age between the three groups, independent t-tests were used for comparing the two CRPS groups. <sup>c</sup> Measures are presented as median (interquartile range); Mann Whitney U-tests were used for comparing the two CRPS groups. <sup>d</sup> Due to incomplete questionnaires, measures were based on n=27 CRPS<sub>AP</sub> (MPQ-PRI), and n=26 CRPS<sub>AP</sub> vs. n=12 CRPS<sub>noAP</sub> (RSQ). <sup>e</sup> The total number of sensory symptoms exceeded 100% because of the coexistence of different symptoms in some patients. \* p<.05.

### Pressure pain threshold

Prior to force measurements, the pressure pain threshold (PPT, in kgf) was measured over the m. abductor pollicis brevis with an electronic algometer (FPX50, Wagner instruments, Greenwich, USA) in order to quantify muscle hyperalgesia, which has been

found associated with motor dysfunction of CRPS.<sup>35</sup> Each test was repeated three times per hand, alternating between the hands (left, right; order randomized across participants).

#### *Force measurements*

Throughout the experiment, participants were seated in a comfortable chair. Force control was evaluated using a precision grip task (i.e., with the thumb opposing the index finger) while the forearm was held horizontally in the sagittal plane and the wrist was held in a neutral position. Five patients (of which four with abnormal posture) were unable to sufficiently extend their index finger to perform a precision grip and used a key grip instead.

#### *Maximum voluntary force*

Maximum force during isometric maximum voluntary contraction (MVC in N) was recorded using a handheld dynamometer (Citec CT3001, C.I.T. Technics, Haren, The Netherlands) that was held stationary by the experimenter. Participants were verbally encouraged to gradually build up strength and sustain force until a plateau in peak force was reached. Two MVC measurements were performed per arm, in similar order as the measurements of PPT.

#### *Force matching*

The modulation of force output was evaluated using a force transducer with a diameter of 40mm (Nano-40, ATI Industrial Automation, Apex, NC, USA; 0.025N resolution) that was attached to a grip instrument mounted on a table top to measure thumb force during precision grip (modified from the “Q-Motor” grip-force task [“manumotography”]<sup>36,37</sup> – see Fig. 1). Table height was adjusted if required. Force signals were captured at a sampling rate of 400Hz using the data acquisition program WINSC (Umea University, Sweden).





**Figure 5.1:** Overview of the experimental setup. Thumb force was measured during precision grip using the ‘Q-Motor’ grip instrument (Reilmann et al., 2010). Target force and real-time visual feedback of the participant’s force output were presented on a computer screen during the VF phase.

A two-phase isometric force-matching protocol was used to evaluate the adequacy of force output modulation and to assess the influence of visual feedback. Each trial consisted of a 20s ‘visual feedback’ (VF) phase and a 20s ‘no visual feedback’ (NF) phase, separated by a 10s pause period. During the VF phase, real-time visual feedback of the participant’s force output was provided on a computer screen, and participants were instructed to match their force output to the target force that was presented as a horizontal line. During the subsequent NF phase, no visual feedback on the participant’s force output was provided. Participants were instructed to accurately reproduce the level of force that they had exerted during the previous VF phase, and to maintain this level of force as stable as possible during the entire NF phase. The start and end of each phase were indicated by an acoustic signal. Prior to each trial, the hand was placed in a standardized position, in which the force sensor was not touched. At the end of each phase, the sensor was released and the hand was returned to its initial position.

For each side (left, right), three target force levels were tested (low, medium, and high: 1, 3, and 5N). Each ‘force level’ block comprised four identical trials, the first of which was considered as a practice trial that was not included in the analysis. Between

trials, at least 30s pause was held, or more if required. Participants received no feedback on their performance during the NF phase. The order of force level blocks was randomized within each arm and the order of limbs was randomized over participants.

### *Data analysis*

Only data obtained from the affected side were included in the analysis, because in 23% of the patients both sides were affected and 71% of the patients with one side affected suffered from pain and/or motor complaints related to CRPS or a variety of other conditions in the 'unaffected extremity'. If both sides (left, right) were affected, the most severely affected side – based on the presence of CRPS, the severity of abnormal posturing and the pain score – was selected for the analysis. Severe abnormal postures precluded measurements of force control of the affected side in 4 patients. Due to worsening of complaints during the experiment, 6 trials (in 2 CRPS patients with abnormal posture, low: 1 trial; medium: 3 trials; high: 2 trials) could not be performed. One trial (3N) was excluded from analysis because the sensor was intermittently released.

### *Force modulation*

Data from the force sensor were low-pass filtered (4th-order bi-directional Butterworth filter, cut-off frequency: 40Hz). To evaluate the characteristics of force output modulation, several outcome parameters were extracted from the two phases of each trial (i.e., VF and NF). For the final 15s of each phase, the mean isometric force ( $F_{\text{mean}}$ ) and variability of force output (expressed as coefficient-of-variation;  $F_{\text{CV}} = \text{standard deviation} / F_{\text{mean}} * 100\%$ ) were calculated. Matching performance was indexed by  $F_{\text{error}}$ , which was calculated as the average absolute discrepancy between actual force and target force. For the two phases of each trial, the force build-up rate was calculated as  $F_{\text{mean}} / T_{\text{mean1}}$  (in  $\text{Ns}^{-1}$ ), where  $T_{\text{mean1}}$  denotes the time (in s) from the first contact with the sensor to the first moment that force output exceeded  $F_{\text{mean}}$ .

### *Force reproduction errors*

As an index of the sense of force production, the 'force reproduction error' (in N) was calculated as the difference in force output between the two subsequent phases of

each individual trial (i.e.,  $F_{\text{mean}}$  in VF vs. NF), with a positive error meaning that force output was higher during the NF phase than during the VF phase of the trial in question. The sense of force production was quantified by means of the mean absolute error, the constant error (i.e., mean error, in which the sign of the error [i.e., under- or over-estimation] is taken into account) as a measure of accuracy or 'bias', and the variable error (i.e., the range of force reproduction errors per target level) as a measure of precision or 'reproducibility'. These parameters were calculated on the basis of a 5s-window (selected by means of a running window analysis) during which the force output was most stable (i.e., characterized by minimum variability and minimum systematic drift). This 'most stable' window reflected a minimum adjustment of force output (indicating that the participant was most confident of producing the correct amount of force) and was therefore considered the most accurate estimate of an individual's sense of force production.

#### *Statistical analysis*

For each participant, the median value of PPT (in kgf) per hand was used, to reduce the influence of outliers. The higher of the two MVC values (in N) per hand was selected for the analysis. All other dependent variables were averaged per phase (VF, NF) per target level (low, medium, high) for the selected extremity of each participant in question. Statistical analysis was performed using IBM® SPSS® Statistics 20.0 (IBM Corp., Armonk, NY, USA). Normality curves were inspected and Kolmogorov-Smirnov tests were used to assess whether the data were normally distributed within each group.<sup>38</sup> Except for MVC, which was normally distributed in all groups, substantial deviations from normality were observed for all parameters. Inspection of the data revealed that some deviations from normality (i.e.,  $F_{\text{mean}}$ , constant error, absolute error and variable error) could not be resolved by transformations due to outliers in the dataset (e.g., two CRPS patients with abnormal postures produced an excessive grip force). To avoid that such participants would have a disproportionate impact on the statistical analyses of these variables, outliers were replaced by the mean plus or minus two standard deviations of the remainder of the group (i.e., after removal of outliers).<sup>38</sup> After  $^{10}\log$  transformation of PPT,  $F_{\text{CV}}$ ,  $F_{\text{error}}$ , force build-up rate, absolute error, and square root transformation of

$F_{\text{mean}}$  and variable error, data were normally distributed in circa 90% of all combinations of phase, target and group. Although transformed data were used for statistical analysis of these parameters, for reasons of clarity the untransformed data are presented in the Results (after correction of outliers, if applicable). Because no relevant significant differences were detected between the dominant and non-dominant side of control subjects, data from the non-dominant side were used for comparison with the CRPS patients.

PPT and MVC were each submitted to an analysis of variance (ANOVA) with group (CRPS patients with abnormal postures [CRPS<sub>AP</sub>] vs. CRPS without abnormal postures [CRPS<sub>noAP</sub>] vs. healthy controls [HC]) as between-subjects factor. To compare force control of CRPS patients with and without abnormal postures to that of controls, measures of force modulation (i.e.,  $F_{\text{mean}}$ ,  $F_{\text{CV}}$ ,  $F_{\text{error}}$  and force build-up rate) were each submitted to an ANOVA with group (CRPS<sub>AP</sub> vs. CRPS<sub>noAP</sub> vs. HC) as between-subjects factor and with phase (VF vs. NF) and target level (low vs. medium vs. high) as within-subject factors. Per combination of group and target, a one-sample Wilcoxon signed rank test was used to determine whether the slope of the best linear fit to the force output over the final 15s of each phase was significantly different from 0 (i.e., the value reflecting no systematic trend in force output), using Bonferroni correction for multiple comparisons. To evaluate the sense of force production, the measures reflecting errors in force reproduction (i.e., constant error, absolute error, and variable error) were each submitted to an ANOVA with group as between-subject factor and target level as within-subject factor. To minimize any potentially confounding effect of motor impairment on group comparisons of force reproduction errors, data obtained from the lowest target force were submitted to a separate one-way ANOVA with group (CRPS<sub>AP</sub> vs. CRPS<sub>noAP</sub> vs. HC) as between-subjects factor. For all ANOVAs, degrees of freedom were adjusted if the sphericity assumption was violated<sup>38</sup> and effect sizes were quantified as partial eta squared ( $\eta_p^2$ ). Significant interaction effects ( $p < .05$ ) were analyzed step-by-step using simple effects analyses, which yielded the effect of one independent variable at individual levels of the other independent variable. Post-hoc analyses of significant main effects ( $p < .05$ ) were performed using two-tailed t-tests with Bonferroni correction. All values are presented as mean  $\pm$  standard deviation. To evaluate whether maximum

voluntary force (i.e., MVC), sub-maximal force modulation (during VF, averaged over all target forces), or the sense of force production (force reproduction errors at the lowest target force) was related to muscle hyperalgesia (i.e., PPT), pairwise correlations were calculated for the untransformed data using Spearman's rho.

## RESULTS

Table 5.2 presents the significant (interaction) effects obtained from the ANOVAs. Results with respect to the lower extremity are presented in Supplement 5.1.

### *Pressure pain threshold*

In both patient groups, the affected side showed increased levels of muscle hyperalgesia compared to controls, as was evidenced by significantly lower values of PPT (CRPS<sub>AP</sub>: 2.47±2.33 kgf and CRPS<sub>noAP</sub>: 2.42±3.03 kgf, lower than HC: 5.28±1.79 kgf).

### *Maximum voluntary force*

Maximum voluntary grip force (i.e., MVC) was significantly lower in CRPS<sub>AP</sub> (20.0±9.7N) than in CRPS<sub>noAP</sub> (35.7±24.3N) and HC (44.6±10.9N).

### *Force modulation*

$F_{\text{mean}}$  increased significantly with increasing target force in all groups, albeit slightly less pronounced for CRPS<sub>AP</sub>, who showed significantly lower  $F_{\text{mean}}$  than controls at the medium and high target force (Figure 5.2A), as was indicated by post-hoc analysis of the interaction between group and target. The main effect of phase indicated that  $F_{\text{mean}}$  was higher during NF compared with VF, regardless of group and target force. For  $F_{\text{CV}}$  post-hoc analysis of the interaction between group and phase revealed that in CRPS<sub>AP</sub> and HC, but not in CRPS<sub>noAP</sub>, variability of force output increased when visual feedback was removed (i.e., during NF; Figure 5.2B). In the VF phase,  $F_{\text{CV}}$  was larger in the two patient groups compared with controls, whereas in the NF phase  $F_{\text{CV}}$  in CRPS<sub>AP</sub> was larger compared with CRPS<sub>noAP</sub> and HC. Post-hoc analysis of the interaction between phase and target indicated that, irrespective of group, the effect of feedback removal on  $F_{\text{CV}}$  was least pronounced at the lowest target force, and that higher target forces were

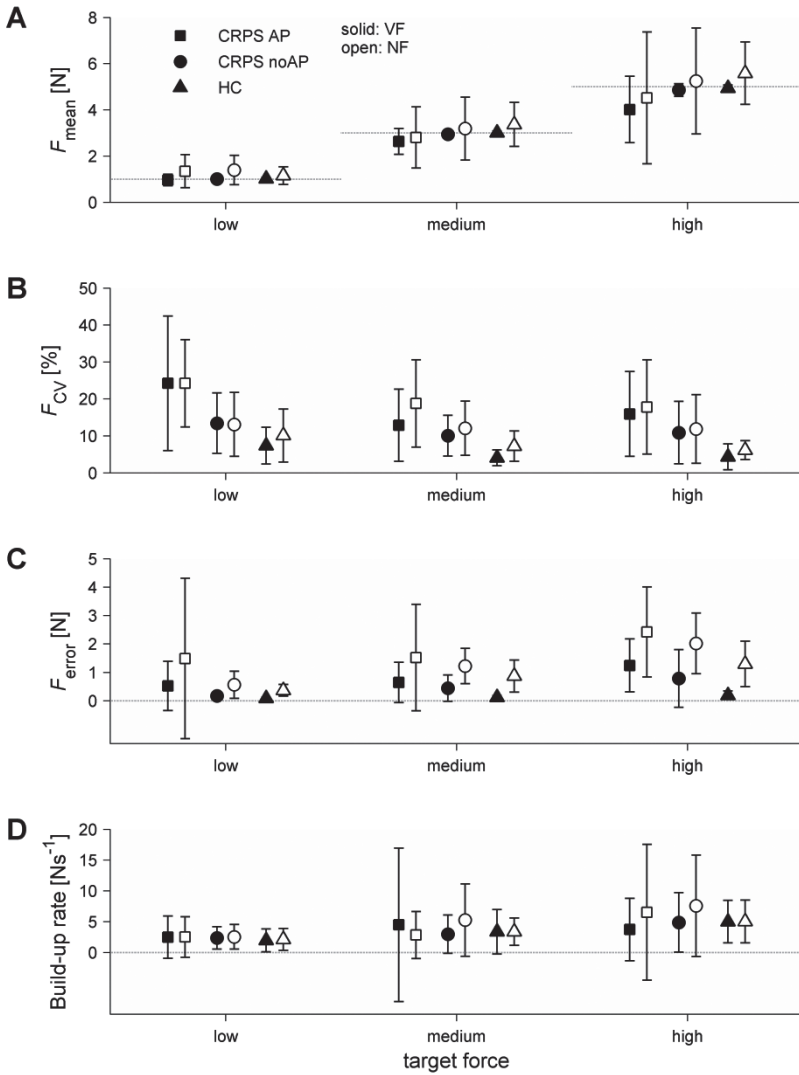
characterized by smaller  $F_{CV}$  (VF:  $F_{CV}$  at medium and high target force smaller than  $F_{CV}$  at low target force; NF: significant differences between all target forces). For  $F_{error}$  post-hoc analysis of the three-way interaction between group, phase, and target showed that, in all groups, matching performance was better (i.e.,  $F_{error}$  was lower) when visual feedback was provided (Fig. 5.2C).  $F_{error}$  was larger in CRPS<sub>AP</sub> compared to HC (for all combinations of phase and target) and CRPS<sub>noAP</sub> (in all combinations except VF-medium and NF-high), and in CRPS<sub>noAP</sub> compared with HC (in all combinations except NF-low and NF-medium). For both patient groups,  $F_{error}$  increased with increasing target force, regardless the presence of visual feedback. For HC, in contrast, the amplification of  $F_{error}$  with increasing target force predominantly occurred in the NF phase, with the deterioration associated with removal of visual feedback being greater at medium and high target force than at low target force.

With respect to the force build-up rate (Fig. 5.D), a significant interaction between group, phase, and target was observed. Post-hoc analysis of this three-way interaction revealed that, in general, force build-up occurred more rapidly at a higher target level and when visual feedback was removed. Only during VF at the highest target force, a significant effect of group was observed, with slower force build-up in CRPS<sub>AP</sub> compared with CRPS<sub>noAP</sub> and HC. There was no systematic trend in force output for any combination of group, phase, and target (i.e., slope of the linear fit was not significantly different from 0).

**Table 5.2:** Significant results of the ANOVAs

Outcome	Effect	<i>F</i> -value		<i>p</i>	$\eta_p^2$
<i>Pressure pain threshold</i>					
PPT	group	$F_{2,68} =$	21.31	<.001	.41
<i>Maximum voluntary force</i>					
MVC	group	$F_{2,66} =$	188.22	<.001	.39
<i>Force modulation</i>					
$F_{\text{mean}}$	group	$F_{2,65} =$	3.22	.046	.09
	phase	$F_{1,65} =$	5.29	.025	.08
	target	$F_{1,6,105.8} =$	963.4	<.001	.94
	group x target	$F_{3,3,105.8} =$	7.91	<.001	.20
$F_{\text{CV}}$	group	$F_{2,65} =$	25.36	<.001	.44
	phase	$F_{1,65} =$	19.72	<.001	.23
	target	$F_{2,130} =$	29.61	<.001	.31
	group x phase	$F_{2,65} =$	6.31	.003	.16
$F_{\text{error}}$	phase x target	$F_{2,130} =$	5.58	.005	.08
	group	$F_{1,65} =$	27.79	<.001	.46
	phase	$F_{1,65} =$	233.59	<.001	.78
	target	$F_{1,5,100.3} =$	85.69	<.001	.57
	group x phase	$F_{2,65} =$	13.71	<.001	.30
	phase x target	$F_{2,130} =$	4.26	.016	.06
	group x phase x target group	$F_{4,130} =$	3.00	.021	.08
Build-up rate	phase	$F_{1,65} =$	7.84	.007	.11
	target	$F_{2,130} =$	34.47	<.001	.35
	group x phase x target	$F_{4,130} =$	3.24	.014	.09
<i>Force reproduction errors</i>					
Absolute error	group <sup>a</sup>	$F_{2,65} =$	3.17	.049	.30
	target	$F_{2,130} =$	70.73	<.001	.52
Constant error	group <sup>a</sup>	$F_{2,65} =$	3.70	.030	.32
Variable error	group <sup>a</sup>	$F_{2,65} =$	8.17	.008	.45
	target	$F_{1,9,121.5} =$	55.03	<.001	.46

Effect size of the significant ( $p < .05$ ) main effects and interaction effects (indicated by 'x') was quantified as partial eta squared ( $\eta_p^2$ ). Between-subjects factor: group (CRPS patients with abnormal posture [CRPS<sub>AP</sub>] vs. CRPS patients without abnormal posture [CRPS<sub>noAP</sub>] vs. healthy controls [HC]). Within-subject factors: phase (visual feedback [VF] vs. no visual feedback [NF]); target (3 levels: 1, 3, 5 N). Comparisons were based on  $n=24$  CRPS<sub>AP</sub>,  $n=12$  CRPS<sub>noAP</sub>, and  $n=32$  HC (except for PPT:  $n=27$  CRPS<sub>AP</sub>; MVC:  $n=25$  CRPS<sub>AP</sub>; variable error:  $n=23$  CRPS<sub>AP</sub>).<sup>a</sup> significant effect if analysis was restricted to the lowest target level to minimize any confounding effects of motor impairment.

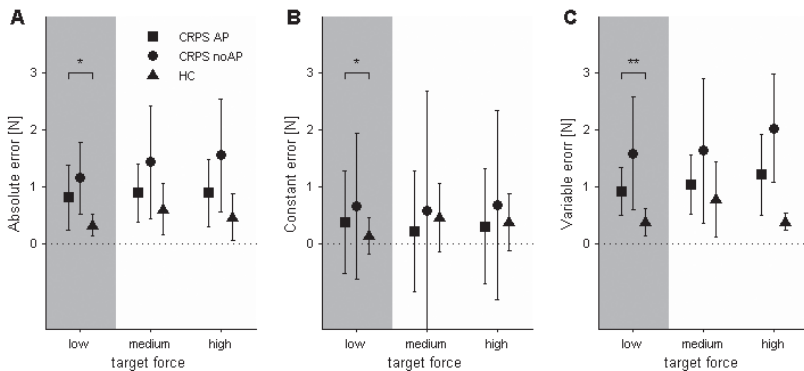


**Figure 5.2:** Results for grip force modulation with visual feedback (VF) and without visual feedback (NF) at three levels of target force (1, 3 and 5 N). (A) mean isometric force,  $F_{mean}$ . Target forces are indicated by dotted lines; (B) variability of force output,  $F_{CV}$ ; (C) matching performance, average absolute discrepancy between actual force and target force,  $F_{error}$ ; (D) force build-up rate. Abbreviations: CRPS<sub>AP</sub>, CRPS patients with abnormal posture (n=24); CRPS<sub>noAP</sub>, CRPS patients without abnormal posture (n=12); HC, healthy controls (n=32).



### Force reproduction errors

For all groups, absolute error increased with target force (Fig 5.3A), as was evidenced by a significant main effect of target. For constant error (Fig. 5.3B), no significant (interaction) effects of group and target were observed. A one-sample t-test revealed that the overall constant error ( $0.4 \pm 0.9\text{N}$ , averaged over all groups and target forces) was significantly different from 0 ( $t(67)=3.78$ ,  $p<.001$ ), indicating a small systematic error in force reproduction (i.e., force output was slightly higher during the NF reproduction phase). A significant main effect of target indicated that variable error increased with target force, irrespective of group (Fig. 5.3C). When any potentially confounding effect of motor impairment was minimized by restricting the analysis to the lowest target force, a significant main effect of group was observed for absolute error, constant error, and variable error, with post-hoc analyses indicating larger errors in CRPS<sub>AP</sub> compared to HC.



**Figure 5.3:** Results for force reproduction errors at three levels of target force (1, 3 and 5 N). (A) absolute error; (B) constant error; (C) variable error. Asterisks indicate significant differences between groups (\* $p<.05$ , \*\* $p<.01$ ) for analyses that were restricted to the lowest target level (shaded area) to minimize any confounding effects of motor impairment. Abbreviations: CRPS<sub>AP</sub>, CRPS patients with abnormal posture ( $n=24$ , for variable error  $n=23$ ); CRPS<sub>noAP</sub>, CRPS patients without abnormal posture ( $n=12$ ); HC, healthy controls ( $n=32$ ).

## DISCUSSION

Although there are indications of disturbed regulation of force output in chronic CRPS patients, the potential role of proprioceptive deficits in this motor impairment is still poorly understood. Therefore, we examined characteristics of grip force in chronic CRPS

patients with and without abnormal postures of the affected limb, and compared performance with and without on-line visual feedback of force output to evaluate whether proprioceptive and tactile input could adequately be used for control of force (i.e., to identify potential deficits in the sense of force production). In line with findings from previous studies, voluntary force modulation was impaired in CRPS patients, but more so in cases with an abnormal posture. In particular CRPS<sub>AP</sub> patients were characterized by reduced MVC (in line with previous studies),<sup>3,7</sup> reduced ability to increase force output according to task instructions, higher variability of force output, and less adequate correction of deviations from the target force. Compared with controls, the impaired force control in patients was already evident at low target forces, with differences between groups being more pronounced at (slightly) higher target forces. Findings with regard to force control of the lower extremity largely supported our findings for the upper extremity, albeit that force control appears more prominently impaired in CRPS patients with an affected lower limb (see Discussion S1).

As expected, controls were able to produce a stable force output after removal of visual feedback,<sup>39,40</sup> which points at adequate use of tactile and proprioceptive input for precise control of force. Given that CRPS has been associated with altered processing of cutaneous input,<sup>17-20</sup> impaired proprioception,<sup>22,41</sup> and disturbances in sensory-motor integration,<sup>24-26</sup> it was anticipated that removal of visual feedback would have a profound adverse effect on force control in these patients. In contrast to our expectations, the effect of visual feedback removal appeared largely similar for the two patient groups and controls. Only at the low target force, removal of visual feedback resulted in a more prominent increase of  $F_{\text{error}}$  in CRPS<sub>AP</sub> patients compared with controls. Overall, evaluation of the force reproduction errors revealed no differences between CRPS patients and controls in terms of constant error, absolute error, and variable error. However, when potential confounding effects of motor impairment were minimized by restricting the analysis of force reproduction errors to the low target force, marked deficits in force production sense were observed in CRPS<sub>AP</sub> (see results, section force production errors). The apparent increase of force reproduction errors in CRPS<sub>noAP</sub> compared with HC failed to reach significance, possibly due to the relatively small number of participants in the CRPS<sub>noAP</sub> group. These

findings suggest that motor dysfunction in CRPS is associated with an impaired sense of force production.

The potential sources of impaired voluntary force modulation are diverse and comprise various aspects of (interactions between) the sensory and motor system. Evidence has been provided that the following factors may contribute to the observed deficits in voluntary force modulation in CRPS patients (c.f.<sup>6</sup>): (1) structural and functional alterations in muscular tissue;<sup>12, 13, 42, 43</sup> (2) altered processing of information from cutaneous or muscle afferents (e.g. <sup>17-19 20 21, 35</sup>); (3) defective regulation of muscle tone due to aberrant force feedback regulation;<sup>27, 28</sup> (4) inappropriate motor programming in higher-order centers of motor control,<sup>25, 44</sup> which may arise from a mismatch between predicted and actual sensory outcomes of a given motor command<sup>45</sup> and be due to disturbances in the body scheme;<sup>33, 46-48</sup> and (5) psychological factors,<sup>2, 49</sup> which may be substantiated by the resemblance of symptoms in CRPS<sub>AP</sub> and functional movement disorders, e.g. the relation with peripheral trauma, the presence of pain, and the type of postures.<sup>2, 49</sup>

Based on the current findings, it is difficult to disentangle the exact mechanisms underlying impaired force control. Since the CRPS patients reported high levels of pain, it might be tempting to simply attribute the observed motor impairments to pain-related processes (e.g., pain interfering with the processing of afferent information and competing with other attention-demanding stimuli for limited cognitive resources, or patients being reluctant to exert full effort because of increasing pain). Indeed, muscle hyperalgesia was associated with a reduction of maximum grip force and sensory disturbances were present in the majority of patients (see Table 5.1). However, PPT was not correlated with other measures of force control. Moreover, pain ratings, muscle hyperalgesia, and sensory disturbances were largely similar for the two patient groups, which suggests that other factors involved with sensory-motor processing account for the more prominent deficits in CRPS<sub>AP</sub> patients. A contribution of attention deficits towards the affected limb seems plausible in this regard, given that CRPS<sub>AP</sub> patients showed more neglect-like symptoms with respect to their affected limb than CRPS<sub>noAP</sub> patients. Interestingly, a significant role of attentional modulation has also been postulated in functional movement disorders.<sup>50, 51</sup> since patients with functional tremor per-

formed better on a motor task that involved less explicit (i.e., more automatic) voluntary control.<sup>51</sup> This warrants further research aimed at identification of potentially shared pathophysiological aspects between CRPS<sub>AP</sub> and functional movement disorders.

Prior to drawing conclusions from the current results, the following aspects should be considered as well. Firstly, the experimental tasks were considered feasible for as many patients as possible because thumb and index finger often seem relatively spared.<sup>1, 52</sup> Nonetheless, severe abnormal postures precluded the force measurements in four patients (see Data analysis). In all probability, the current results therefore provide an underestimation of deficits in CRPS<sub>AP</sub>. Secondly, although the experiment appeared more strenuous for patients than for controls, no systematic decrease in force output was observed over the final 15s of each phase (not even at high target force in patients), indicating that sufficient rest was provided to minimize potential effects of fatigue. Thirdly, because sensory disturbances (reported in Table 5.1) were qualitatively assessed and tested at the hand dorsum, only tentative statements can be made on the contribution of altered cutaneous sensitivity to pressure sensation at the fingertips. Fourthly, a comparison of patients with CRPS to patients with other causes of chronic or neuropathic pain would have been valuable, as this may reveal to which extent the observed impairments are specific to CRPS, or are associated with chronic pain in general. Lastly, only data obtained from the affected extremities could be included in the analysis (see Data analysis). A comparison between the affected and unaffected side may prove valuable in discriminating between the respective contributions of peripheral and central factors.

In conclusion, our results show impaired voluntary modulation of (maximal and submaximal) force output of the affected upper extremity in CRPS patients, which was more pronounced in patients with abnormal postures. In contrast to our expectations, the effect of visual feedback removal appeared largely similar for the two patient groups and controls. When potential confounding effects of motor impairment were minimized by restricting the analysis to the lowest force level, however, our results with regard to force reproduction errors suggest that impaired sense of force production may contribute to the motor dysfunction of CRPS. This indicates that therapeutic strategies aimed at restoration of proprioceptive impairments, possibly using on-line visual feedback, may promote the recovery of motor function in CRPS.

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## SUPPLEMENT 5.1: FORCE MODULATION IN THE LOWER EXTREMITY

### METHODS

Because the experimental procedure was identical to that for the upper extremity, the description of the methods for the lower extremity is limited to deviations from the methods for the upper extremity that are described in the main part of this chapter.

#### *Participants*

Force control was evaluated in 26 patients diagnosed with CRPS of the lower limb and 32 age- and sex-matched healthy controls (Table S5.1). In 15 patients, the inflicted body part preferably adopted an abnormal posture from which return to a neutral position was not possible, or only with great difficulty. Note that 12 CRPS patients with abnormal postures and 4 CRPS patients without abnormal postures presented with both an affected upper and lower extremity.

#### *Measurement instruments and data collection*

##### *Scales and questionnaires*

Disability was evaluated using the questionnaires on Walking (maximum score inside = 17, outside = 23)<sup>53</sup> and Rising (maximum score = 19)<sup>54</sup> in patients with one or both lower limbs affected. Higher scores reflected higher levels of disability.

##### *Pressure pain threshold*

Prior to force measurements, the pressure pain threshold (PPT, in kgf) was measured over the m. abductor hallucis. Each test was repeated three times per foot, alternating between the feet (left, right; order randomized across participants).



**Table S5.1:** Demographic and clinical information of participants

	CRPS <sub>AP</sub> (n=15)	CRPS <sub>noAP</sub> (n=11)	HC (n=32)	p
Sex (male/female) <sup>a</sup>	1/14	1/10	5/27	.642
Age (years) <sup>b</sup>	46.9 (12.8)	39.7 (12.4)	48.8 (13.6)	.155
Disease duration (years) <sup>c</sup>	10 (5-14)	13 (7-15)		.599
BFM score <sup>c</sup>	30 (22-43)	-		
MPQ-PRI <sup>b,d</sup>	32.4 (13.0)	25.1 (8.5)		.123
Sensory symptoms (%) <sup>a,e</sup>				
Allodynia	40	27		.683
Hyperesthesia	20	36		.407
Hypesthesia	33	36		1.000
Pain <sup>b</sup>	6.9 (2.6)	5.9 (1.5)		.293
Walking – in home <sup>b,d</sup>	10.6 (6.0)	7.0 (3.0)		.092
Walking – outside <sup>b,d</sup>	16.8 (7.4)	14.5 (5.9)		.434
Rising <sup>b</sup>	14.1 (5.3)	11.2 (4.3)		.165
Neglect-like symptoms <sup>b</sup>	3.0 (0.9)	2.8 (1.3)		.608

Abbreviations: CRPS<sub>AP</sub>, CRPS patients with abnormal posture; CRPS<sub>noAP</sub>, CRPS patients without abnormal posture; HC, healthy controls; BFM score, total score on the Burke Fahn Marsden scale; MPQ-PRI, Pain Rating Index of the McGill Pain Questionnaire; Pain, rating on a numeric rating scale (NRS, 0-10); RSQ, score on the Radboud Skills Questionnaire. <sup>a</sup> Chi-square test was used for comparing the groups. <sup>b</sup> Measures are presented as mean (standard deviation); ANOVA was used for comparison of age between the three groups, independent t-tests were used for comparing the two CRPS groups. <sup>c</sup> Measures are presented as median (interquartile range); Mann Whitney U-tests were used for comparing the two CRPS groups. <sup>d</sup> Due to incomplete questionnaires, measures were based on n=14 CRPS<sub>AP</sub> vs. n=11 CRPS<sub>noAP</sub> (MPQ-PRI), n=12 CRPS<sub>AP</sub> vs. n=10 CRPS<sub>noAP</sub> (Walking), and n=13 CRPS<sub>AP</sub> vs. n=10 CRPS<sub>noAP</sub> (Rising). <sup>e</sup> Different symptoms may coexist in some patients

### Force measurements

Throughout the experiment, participants were seated in a comfortable chair. Force control of the lower extremity was evaluated by means of a plantar flexion task of the first toe, while the knee flexion angle was approximately 90° and the foot rested on a support surface (Figure S5.1). In three patients with abnormal posture of the foot, the foot support was slightly inverted to allow force measurements.



Figure S5.1: Device used for measuring toe plantar flexion force.

### *Maximum voluntary force*

Maximum toe flexion force during isometric maximum voluntary contraction (MVC in N) was recorded using a handheld dynamometer (Citec CT3001, C.I.T. Technics, Haren, The Netherlands) that was held stationary by the experimenter. Participants were verbally encouraged to gradually build up strength and sustain force until a plateau in peak force was reached. During MVC measurements of toe plantar flexion, the ankle was restrained by the experimenter to minimize a possible contribution of ankle plantar flexors. Two MVC measurements were performed per limb, in similar order as the measurements of PPT.

### *Force matching*

The experimental protocol was identical to the protocol as described for the upper extremity. In brief, a two-phase isometric force-matching protocol was used to evaluate the adequacy of force output modulation and to assess the influence of visual feedback, with each trial consisting of a 20-s 'visual feedback' (VF) phase and a 20-s 'no visual feedback' (NF) phase, separated by a 10-s pause period. The force transducer was mounted on a footrest (18° inclination angle, with adjustable heel support) to measure toe plantar flexion force (Figure S5.1). Footrest height was adjusted if required. For each limb, three target force levels were tested (low, medium, and high: 5, 10, and 15 N). Each 'force level' block comprised four identical trials, the first of which was considered as a

practice trial that was not included in the analysis. Between trials, at least 30 s pause was held, or more if required. Participants received no feedback on their performance during the NF phase. The order of force level blocks was randomized within each limb and the order of limbs was randomized over participants.

## DATA ANALYSIS

Only data obtained from affected extremities were included in the analysis. If both sides (left, right) were affected, the most severely affected side – based on the presence of CRPS, the severity of abnormal posturing and the pain score – was selected for the analysis. Severe abnormal postures precluded measurements of force control of the affected foot in four patients. Due to worsening of complaints during the experiment, 21 trials could not be performed (in 5 CRPS patients with abnormal postures, medium: 5 trials, high: 12 trials; and in 2 CRPS patients without abnormal postures, low: 1 trial, medium: 1 trial, high: 2 trials). This resulted in eight empty cells in three patients with abnormal posture of the lower limb.

### *Force modulation*

Outcome parameters for the lower extremity were calculated in a similar way as for the upper extremity (see description on p. 127): mean isometric force ( $F_{\text{mean}}$ ), variability of force output ( $F_{\text{CV}}$ ) and average absolute discrepancy between actual force and target force ( $F_{\text{error}}$ ) were calculated on the basis of the final 15 s for the two phases (VF, NF) of each trial. Also the force build-up rate (in  $\text{Ns}^{-1}$ ) was calculated for the two phases (VF, NF) of each trial.

### *Force reproduction errors*

The sense of force production was quantified by means of the ‘force reproduction error’ in terms of the mean absolute error, the constant error (i.e., mean error, in which the sign of the error [i.e., under- or overestimation] is taken into account) as a measure of accuracy or ‘bias’, and the variable error (i.e., the range of force reproduction errors per target level) as a measure of precision or ‘reproducibility’.

### *Statistical analysis*

Statistical analysis was similar to that for the upper extremity (see p. 128), except for slight differences in the data pre-processing. Inspection of the data revealed that for  $F_{\text{mean}}$  and constant error deviations from normality could not be resolved by transformations due to outliers in the dataset (e.g., two patients without abnormal posture of the foot produced far too little toe flexion force). These outliers were replaced by the mean plus or minus two standard deviations of the remainder of the group (i.e., after removal of outliers). After  $^{10}\log$  transformation of PPT,  $F_{\text{CV}}$ ,  $F_{\text{error}}$ , force build-up rate and absolute error, and square root transformation of variable error, data were normally distributed in circa 90% of all combinations of phase, target and group. Although transformed data were used for statistical analysis of these parameters, for reasons of clarity the untransformed data are presented in the Results (after correction of outliers, if applicable).

## **RESULTS**

Table S5.2 presents the significant (interaction) effects obtained from the ANOVAs.

### *Pressure pain threshold*

In both patient groups, the affected limb showed increased levels of muscle hyperalgesia compared to controls, as was evidenced by significantly lower values of PPT (CRPS<sub>AP</sub>:  $2.56 \pm 2.30$  kgf and CRPS<sub>noAP</sub>:  $1.88 \pm 1.60$  kgf, lower than HC:  $5.76 \pm 1.86$  kgf).

### *Maximum voluntary force*

Maximum voluntary toe flexion force (i.e., MVC) differed significantly between all groups (CRPS<sub>AP</sub>:  $16.2 \pm 10.5$  N, CRPS<sub>noAP</sub>:  $40.4 \pm 23.8$  N, HC:  $92.0 \pm 26.6$  N).

### *Force modulation*

As can be appreciated from Figure S5.2A,  $F_{\text{mean}}$  increased with target force in HC and CRPS<sub>noAP</sub>, but not in CRPS<sub>AP</sub>. Post hoc analysis of this interaction between group and target further indicated that CRPS<sub>AP</sub> patients were unable to increase force output in accordance with the task instructions, which resulted in significantly lower  $F_{\text{mean}}$  than HC

and CRPS<sub>noAP</sub> at medium and high target levels. The main effect of phase indicated that  $F_{\text{mean}}$  was higher during NF compared with VF, irrespective of group and target force.

**Table S5.2:** Significant results of the ANOVAs

Outcome	Effect	F-value	p	$\eta_p^2$	
<i>Pressure pain threshold</i>					
PPT	group	$F_{2,54} =$	25.28	<.001	.48
<i>Maximum voluntary force</i>					
MVC	group	$F_{2,53} =$	55.94	<.001	.68
<i>Force modulation</i>					
$F_{\text{mean}}$	group	$F_{2,48} =$	30.83	<.001	.56
	phase	$F_{1,48} =$	11.90	.001	.20
	target	$F_{1,6,76.4} =$	174.25	<.001	.78
	group x target	$F_{3,2,76.4} =$	22.09	<.001	.48
$F_{\text{CV}}$	group	$F_{2,48} =$	38.89	<.001	.62
	phase	$F_{1,48} =$	8.99	.004	.16
	target	$F_{1,8,86.9} =$	12.06	<.001	.20
$F_{\text{error}}$	group	$F_{2,48} =$	36.96	<.001	.61
	phase	$F_{1,48} =$	77.18	<.001	.62
	target	$F_{2,96} =$	117.19	<.001	.71
	group x phase	$F_{2,48} =$	12.87	<.001	.35
	group x target	$F_{4,96} =$	5.36	.001	.18
	Build-up rate	group	$F_{2,48} =$	7.84	.001
	phase	$F_{1,48} =$	17.00	<.001	.26
	target	$F_{2,96} =$	6.42	.002	.12
	group x phase	$F_{2,48} =$	4.24	.020	.15
	group x target	$F_{4,96} =$	5.36	.001	.18
<i>Force reproduction errors</i>					
Absolute error	target	$F_{2,96} =$	13.13	<.001	.22
Constant error	.	.	.	.	.
Variable error	target	$F_{2,94} =$	9.29	<.001	.17

Effect size of the significant ( $p < .05$ ) main effects and interaction effects (indicated by 'x') was quantified as partial eta squared ( $\eta_p^2$ ). Between-subjects factor: group (CRPS patients with abnormal posture [CRPS<sub>AP</sub>] vs. CRPS patients without abnormal posture [CRPS<sub>noAP</sub>] vs. healthy controls [HC]). Within-subject factors: phase (visual feedback [VF] vs. no visual feedback [NF]); target (3 levels: 5, 10, 15 N). Comparisons were based on  $n=8$  CRPS<sub>AP</sub>,  $n=11$  CRPS<sub>noAP</sub> and  $n=32$  HC (except for PPT:  $n=14$  CRPS<sub>AP</sub>; MVC:  $n=13$  CRPS<sub>AP</sub>; variable error:  $n=7$  CRPS<sub>AP</sub>).

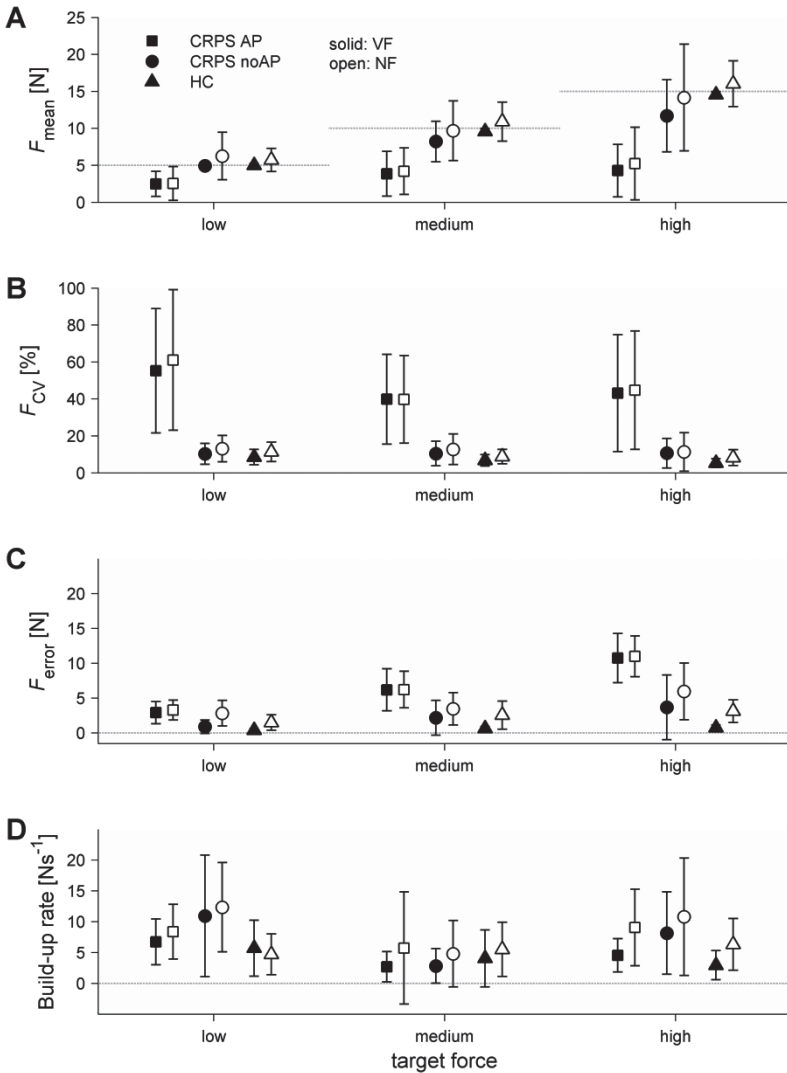
Variability of force output ( $F_{\text{CV}}$ ) was larger in CRPS<sub>AP</sub> compared with CRPS<sub>noAP</sub> and HC (Figure S5.2B) and, irrespective of these groups,  $F_{\text{CV}}$  was larger when visual feedback was removed and it was smaller at higher levels of target force, as was evidenced by

significant main effects of group, phase and target. For  $F_{\text{error}}$ , post hoc analysis of the interaction between group and phase indicated that for HC and CRPS<sub>noAP</sub> matching performance was better (i.e.,  $F_{\text{error}}$  was lower) during VF, whereas for CRPS<sub>AP</sub> no such effect of phase was observed (Figure S5.2C). When visual feedback was provided (i.e., during VF),  $F_{\text{error}}$  was larger in CRPS<sub>AP</sub> compared with CRPS<sub>noAP</sub>, which in turn showed larger  $F_{\text{error}}$  than HC. After removal of the visual feedback (i.e., during NF), both patient groups, irrespective of the presence of abnormal postures, showed larger  $F_{\text{error}}$  than controls. Post hoc analysis of the interaction between group and target indicated that  $F_{\text{error}}$  increased with target force in all groups, with this increase being less pronounced for medium vs. high target force in HC.

Force build-up was slower in CRPS<sub>AP</sub> compared with HC, with this effect of group being less pronounced (but still significant) for NF compared with VF (Figure S5.2D). Post hoc analysis of this interaction between group and phase further revealed that the removal of visual feedback resulted in a higher rate of force build-up in CRPS<sub>noAP</sub> (VF vs. NF:  $5.2 \pm 8.7 \text{ N s}^{-1}$  vs.  $8.7 \pm 6.1 \text{ N s}^{-1}$ ), whereas the effect of feedback was non-significant for HC ( $7.8 \pm 4.8 \text{ N s}^{-1}$  vs.  $8.5 \pm 4.2 \text{ N s}^{-1}$ ) and CRPS<sub>AP</sub> ( $3.2 \pm 3.2 \text{ N s}^{-1}$  vs.  $5.4 \pm 6.0 \text{ N s}^{-1}$ ). Post hoc analysis of the interaction between group and target showed no group differences in force build-up at the low target force, whereas force build-up in CRPS<sub>AP</sub> was slower compared with CRPS<sub>noAP</sub> and HC at medium and high target forces. In contrast to the increasing rate of force build-up with increasing target force that was observed in HC (low:  $5.2 \pm 3.1 \text{ N s}^{-1}$ , medium:  $7.6 \pm 3.1 \text{ N s}^{-1}$ , high:  $11.7 \pm 7.6 \text{ N s}^{-1}$ ; all differences significant), and CRPS<sub>noAP</sub> (low:  $4.6 \pm 2.7 \text{ N s}^{-1}$ , medium:  $6.8 \pm 4.1 \text{ N s}^{-1}$ , high:  $9.5 \pm 7.4 \text{ N s}^{-1}$ ; all differences non-significant), the rate of force build-up in CRPS<sub>AP</sub> decreased with increasing target force (low:  $4.8 \pm 4.0 \text{ N s}^{-1}$ , medium,  $4.2 \pm 5.7 \text{ N s}^{-1}$ , high:  $3.8 \pm 4.1 \text{ N s}^{-1}$ ; all differences non-significant). A small but significant trend in force output was observed for the final 15 s of the VF phase in HC, i.e., the slope of the linear fit deviated significantly from 0 at low and medium target force (median [interquartile range]:  $0.016 [-0.000, 0.028]$  and  $0.028 [0.012, 0.065]$ , respectively). There was no systematic trend in force output for all other combinations of group, phase and target.

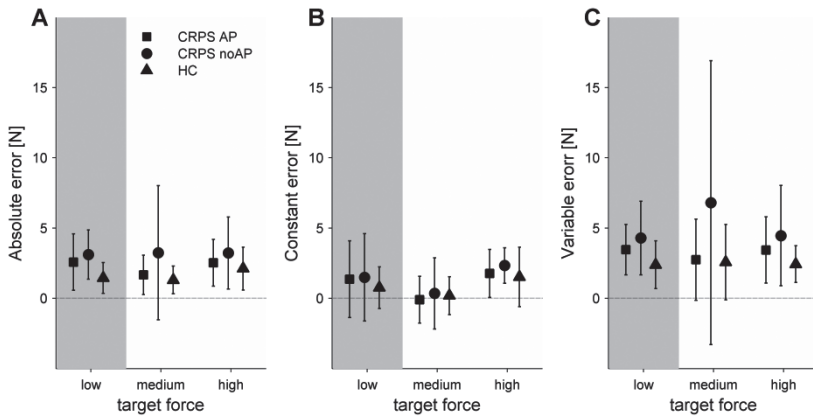
*Force reproduction errors*

For all groups, absolute error increased with target force (Figure S5.3A), as was evidenced by a significant main effect of target. For constant error, no significant (interaction) effects of group and/or target were observed (Figure S5.3B). A one-sample t-test revealed that the overall constant error ( $1.2 \pm 1.9$  N, averaged over all groups and target forces) was significantly different from 0 ( $t_{50}=4.34$ ,  $p<.001$ ), indicating a small systematic error in force reproduction (i.e., force output was slightly higher during the NF reproduction phase). Variable error increased with target force (Figure S5.3C), as was indicated by a main effect of target. No significant (interaction) effect of group was observed. Also when analysis was restricted to the lowest target force, no significant effect of group was observed for absolute error, constant error and variable error.



**Figure S5.2:** Results for toe flexion force modulation with visual feedback (VF) and without visual feedback (NF) at three levels of target force (5, 10 and 15 N). (A) mean isometric force,  $F_{\text{mean}}$ . Target forces are indicated by dotted lines; (B) variability of force output,  $F_{\text{CV}}$ ; (C) matching performance, average absolute discrepancy between actual force and target force,  $F_{\text{error}}$ ; (D) force build-up rate. Abbreviations: CRPS<sub>AP</sub>, CRPS patients with abnormal posture (n=24), CRPS<sub>noAP</sub>= CRPS patients without abnormal posture (n=12), HC=healthy controls (n=32).





**Figure S5.3:** Results for force reproduction errors at three levels of target force (5, 10 and 15 N). (A) absolute error; (B) constant error; (C) variable error. Abbreviations: CRPS<sub>AP</sub>, CRPS patients with abnormal posture (n=8, for variable error n=7); CRPS<sub>noAP</sub>, CRPS patients without abnormal posture (n=11); HC, healthy controls (n=32).

## DISCUSSION

Voluntary force modulation of the lower extremity was impaired in CRPS patients, more so in cases with an abnormal posture. In particular CRPS<sub>AP</sub> patients were characterized by reduced MVC, slower build-up of force, reduced ability to increase force output according to task instructions, higher variability of force output and less adequate correction of deviations from the target force. Compared with low controls, the impaired force control in patients was already evident at low target forces, with differences between groups being more pronounced at higher target forces. These findings are in line with those obtained from the upper extremity, albeit that force control appeared more prominently impaired in CRPS patients with an affected lower limb.

Like for the upper extremity, it was anticipated that removal of visual feedback would have a profound adverse effect on force control in CRPS patients. In contrast to our expectations, the effect of visual feedback removal appeared largely similar for the two patient groups and controls, and evaluation of the force reproduction errors revealed no differences between CRPS patients and controls. Even when analysis was restricted to the lowest target force to minimize any potential confounding effects of impaired motor function, no differences between the CRPS patients and controls were observed in terms of force reproduction errors (in contrast to the deficits in force pro-

duction sense in CRPS<sub>AP</sub> that were found for the upper extremity). However, it should be noted that in particular CRPS<sub>AP</sub> patients with an affected lower extremity appeared unable to achieve the low target force, even when visual feedback was provided (see Results, Figure S5.2A). As a consequence, little room was left for further deterioration of force control after removal of visual feedback. The absence of a significant increase of  $F_{\text{error}}$  after removal of visual feedback, as well as the absence of a significant increase of force reproduction errors in this condition therefore do not necessarily imply adequate (integration of) sensory information in these CRPS<sub>AP</sub> patients. Rather, it appears that even the lowest target force was too high for CRPS<sub>AP</sub> patients with an affected lower extremity, which might have precluded the detection of proprioceptive deficits.