Motor dysfunction in complex regional pain syndrome : the role of sensory processing and sensory-motor integration

Bank, P.J.M.

Chapter 6

Evaluation of mirrored muscle activity in patients with Complex Regional Pain Syndrome

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Motor dysfunction in Complex Regional Pain Syndrome (CRPS) has been associated with bilateral changes in central motor processing, suggesting abnormal coupling between the affected and unaffected limb. We evaluated the occurrence of involuntary muscle activity in a limb during voluntary movements of the contralateral limb (i.e., mirror activity) in unilaterally affected patients to examine disinhibition of contralateral motor activity in CRPS. Mirror activity was examined during unimanual rhythmic flexion-extension movements of the wrist through in-depth analysis of electromyography recordings from the passive arm in 20 CRPS patients and 40 controls. The number of mirror-epochs was comparable for both arms in both CRPS patients and controls. Mirror-epochs in the affected arm of patients were comparable to those in controls. Mirror-epochs in the unaffected arm were shorter and showed less resemblance (in terms of rhythm and timing) to activity of the homologous muscle in the moving arm compared to mirror-epochs in controls. In conclusion, no evidence for disinhibition of contralateral motor activity was found during unimanual movement. Although motor dysfunction in CRPS has been associated with bilateral changes in cortical motor processing, the present findings argue against disinhibition of interhemispheric projections to homologous muscles in the contralateral limb during unimanual movement.

Introduction

Complex Regional Pain Syndrome (CRPS) is characterized by pain and accompanied by sensory, autonomic, trophic, and motor abnormalities (Marinus et al., 2011). Reported motor impairments include weakness, restricted active range of motion (AROM), problems with movement initiation and execution, and prominent abnormal posturing (Birklein et al., 2000; Goris et al., 1990; Huge et al., 2011; Marinus et al., 2011; Schilder et al., 2012; Schwartzman and Kerrigan, 1990; Veldman et al., 1993). Several pathophysiological mechanisms have been postulated to underlie the motor abnormalities in CRPS, ranging from structural and functional alterations in skeletal muscle tissue (Hulsman et al., 2009; Tan et al., 2011; van der Laan et al., 1998; Vas et al., 2013) to psychological factors (Hawley and Weiner, 2011; Reedijk et al., 2008; Schrag et al., 2004).

A growing number of studies provided evidence for maladaptive neuronal plasticity at various levels of the central nervous system (Marinus et al., 2011; Schwenkreis et al., 2009; Swart et al., 2009; van Hilten, 2010; van Hilten et al., 2005) underpinning chronification of pain (central sensitization, Seifert and Maihöfner, 2009; Woolf, 2011) and disinhibition of the somatosensory (Lenz et al., 2011) and motor system in CRPS (Eisenberg et al., 2005; Juottonen et al., 2002; Kirveskari et al., 2010; Krause et al., 2004; Schouten et al., 2003; Schwenkreis et al., 2003; van de Beek et al., 2002). In line with these findings, spontaneous spreading of CRPS to other limbs, often in a mirror-like pattern (Schwartzman and Kerrigan, 1990; van Rijn et al., 2011) and impaired sensory and motor function contralateral to the affected side (Chapter 4; Huge et al., 2011; Schilder et al., 2012; van Rooijen et al., 2013b) have been reported for CRPS. Moreover, voluntary movement of the affected hand has been associated with bilateral activation of cerebral circuits involved in sensory-motor processing (Maihöfner et al., 2007), suggesting abnormal coupling between the affected and unaffected limb in CRPS.

Collectively, these findings point at a significant role of maladaptive neuronal plasticity in CRPS-related motor dysfunction in general and disinhibition of the motor system in particular. Associated reductions of selectivity of motor output may manifest in the occurrence of mirror activity, which refers to involuntary activity in or movements of a limb that accompany voluntary movements of the contralateral limb and indicate neural

crosstalk from the intentionally moving limb to the homologous muscle groups in the contralateral limb (Carson, 2005; Cincotta and Ziemann, 2008). In order to advance our understanding of CRPS-related motor dysfunction and the alleged role of disinhibition of the motor system in this condition, we evaluated mirror activity in the affected and unaffected arm of CRPS patients during voluntary rhythmic wrist flexion and extension of the contralateral arm and compared the findings to those obtained from healthy controls.

Methods

Subjects

Twenty patients diagnosed with CRPS type 1 of the upper extremity and 40 healthy subjects participated in the experiment (see Table 6.1 for characteristics). All patients fulfilled the diagnostic criteria for CRPS established at the 1993 consensus conference ('Orlando criteria'), which were the criteria formally endorsed by the International Association for the Study of Pain (IASP) at the time the present study was initiated (Merskey and Bogduk 1994). All patients had some degree of impaired motor function, evidenced predominantly by muscle weakness and limitations in AROM of fingers and/or wrist. In 13 patients the inflicted body part preferably adopted an abnormal posture, which was mainly characterized by flexion of the fingers and wrist. Patients were excluded if they *(1)* had a clinically detectable injury to a major nerve in the extremity (i.e., CRPS type 2); *(2)* suffered a known genetic form of dystonia (e.g., DYT1-DYT11 or Wilson's disease), mobile dystonia, or conditions affecting the central nervous system; *(3)* had an implanted drug-delivery pump for intrathecal baclofen; *(4)* had a wrist AROM <30°; or *(5)* were unable to perform flexion-extension movements of the wrist at a frequency ≥0.5Hz. Healthy control subjects, who had normal function of both arms and did not suffer from known diseases of the central nervous system, were matched individually with respect to age (within 5 years) and gender to the CRPS patients in a 2-to-1 ratio.

Table 6.1 Participant characteristics

	CRPS patients		Healthy controls	
N	20		40	
Sex (male/female)	4/16		8/32	
Age (mean, SD) in years	51.3	(13.3)	51.4	(13.3)
Disease duration (mean, SD) in years	8.9	(8.6)	-	
Affected side (dominant/non-dominant)	14/6		-	
CRPS severity score (median, IQR)	10.0	(8.3-11.0)	-	
Medication score (median, IQR)	7.2	(0-17.8)	-	
$Pain_{week}$ (median, IQR)	7.0	(5.3-8.0)	-	
MPQ-PRI (mean, SD)	27.6	(10.6)	-	
RSQ (mean, SD)	3.0	(0.8)	-	

Abbreviations: SD, standard deviation; IQR, interquartile range; $Pain_{week}$, average pain experienced during the week preceding the experiment as scored on a numeric rating scale (NRS, 0-10); MPQ-PRI, Pain Rating Index of the McGill Pain Questionnaire; RSQ, Radboud Skills Questionnaire.

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 procedure

The severity of CRPS was rated by means of the CRPS severity score (maximum score = 17, with higher scores reflecting higher CRPS severity; Harden et al., 2010). Pain was evaluated using the Pain Rating Index of the McGill Pain Questionnaire (MPQ-PRI, maximum score = 63; Melzack, 1975) and a numeric rating scale (0 = no pain, 10 = unbearable pain) for average pain experienced during the week preceding the experiment ($Pain_{week}$) and during the experimental task ($Pain_{task}$). Disability due to limitations in arm function was evaluated using the Radboud Skills Questionnaire (RSQ, range = 0-5, with higher scores reflecting more limitations; Oerlemans et al., 2000a). Medication was quantified according to the Medication Quantification Scale Version III (Harden et al., 2005). Hand dominance was assessed in patients and controls using a Dutch version of the Edinburgh Handedness Questionnaire (Oldfield, 1971).

Subjects sat comfortably in a chair with their elbows slightly flexed and feet supported. On two stands, positioned on both sides of the chair, vertically oriented manipulanda were mounted that registered wrist flexion-extension movements in the horizontal plane. Both forearms were placed in the apparatus with the palms facing inward and their positions restrained by foam-padded supports. Adjustable handgrips (diameter 32 mm) on the manipulanda fell in the crease between thumb and index finger. The rotation axes of the manipulanda were aligned with those of the wrists. An opaque screen precluded vision of the hands. Electromyography (EMG) recordings were obtained from the flexor (FCR) and extensor carpi radialis (ECR) muscles of both arms. After preparation of the skin, rectangular (20x30 mm) non-disposable differential surface electrodes (DE-2.1, Delsys) were positioned in the center of the muscle belly on the line from origin to insertion as determined by palpation. EMG signals were amplified (1,000-10,000 times; Bagnoli™ 4-channel desktop amplifier with 20-450 Hz band-pass filter; Delsys Inc., Boston, MA, USA) and recorded (sampling rate: 1000 Hz; 16 bit A/D conversion).

Subjects performed unimanual rhythmic flexion-extension movements of the wrist. Movement frequency (f_m = 0.7 Hz in all participants, except for one patient in whom f_m = 0.6 Hz) was indicated by an auditory metronome specifying the moments of peak flexion (pitch: 800 Hz) and peak extension (400 Hz). All subjects completed three trials per side (duration: 30 cycles per trial), with the order of voluntarily moving 'side' (i.e., affected vs. unaffected side in patients, and non-dominant vs. dominant side in controls) being randomized over participants. Mirror activity was evaluated in the contralateral, passive arm.

Data analysis

Prior to the analysis, the first five and the last cycle of each trial were removed to eliminate possible transient effects. The angular position data of the manipulandum were low-pass filtered (second-order bi-directional Butterworth filter, cut-off frequency = 10 Hz). All EMG signals were band-pass filtered (second-order bidirectional Butterworth filter, 10-400 Hz) and full-wave rectified. The amplitude of active wrist movements was calculated from the angular position data as half the peak-to-peak flexion-extension

excursion and the muscle activity associated with these active wrist movements was quantified by means of the EMG area (i.e., integrated EMG) per movement cycle.

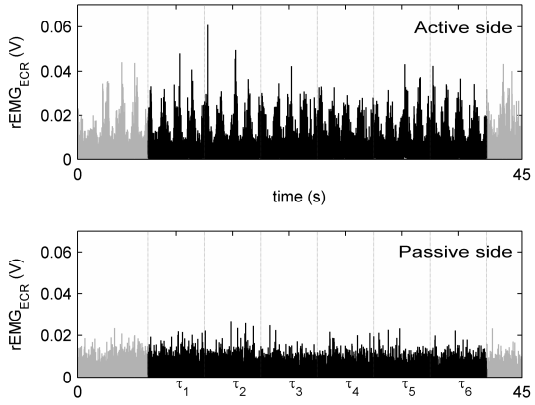
Mirror activity, which refers to involuntary activity in (or movements of) a limb that resembles activity in the intentionally moved contralateral limb (Carson, 2005), was evaluated in the passive arm. Due to its irregularity and smallness of amplitude it is difficult to reliably detect and quantify mirror activity on the basis of kinematic data or conventional EMG analysis. Therefore, we applied a sensitive analysis to our EMG recordings that allowed quantification of the degree to which the predominant rhythm and relative timing of involuntary muscle activity in the passive arm resembled that of the homologous muscle in the moving arm (cf. Ridderikhoff et al., 2005a). These EMG signals were expected to have identical dominant frequencies ("frequency locking") and a stable relative timing ("phase locking") in case mirror activity was present. In short, the analysis involved two steps: *(1)* detection of brief periods (epochs) with mirror activity; and *(2)* evaluation of those mirror-epochs in terms of frequency and phase locking. An overview of this method is provided in Figure 6.1.

To detect brief periods with mirror activity (Step 1 in Figure 6.1), the frequency content of the rectified EMG (rEMG) signals of the passive arm was evaluated. In the present study we used a modified version of the Fourier transform, i.e., the Gabor transform, which is given by

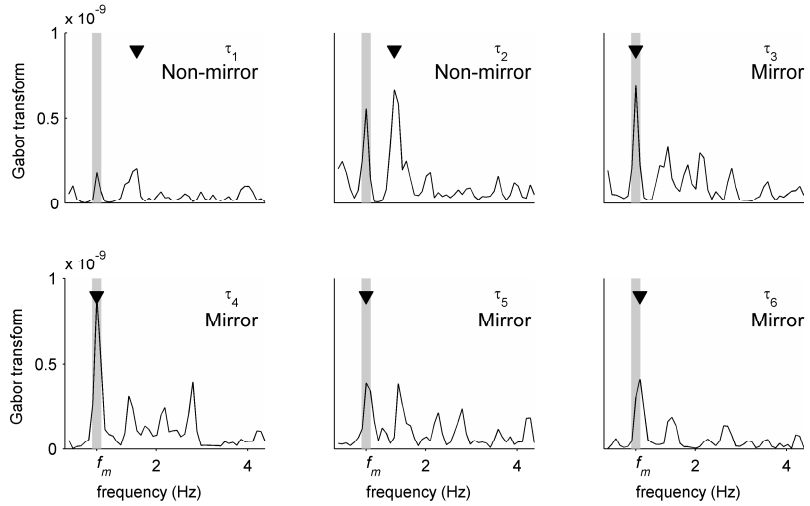
$$G_a(\tau,\omega) = \int g_a(t-\tau)\, x(t)\, e^{-i\omega t}\, dt$$

where $g_a(t-\tau)$ is a Gaussian function that serves to window the time series by defining a sliding time-window with midpoint τ and width $2a$ (see Ridderikhoff et al., 2005a for full details and parameter settings). The Gabor transform of a time series thus depends on both frequency (ω) and time (τ), and allows identification of brief periods of mirror activity within the noisy EMG signals of the passive arm. We aimed to identify time-windows (duration: four cycles) for which the dominant frequency in the rEMG of the passive arm approximated the movement frequency of the active hand. To this end, the Gabor transform was used to determine the power spectral density of the rEMG signal (frequency range: $f_m/8$ to $50*f_m/8$) for each trial at six different values of τ (with $\Delta\tau$ equal to four cycles).

Step 0 **Rectified EMG data**



Step 1 **Detection of mirror activity in rEMG of the passive side using the Gabor transform**



Step 2 **Analysis of mirror epochs**

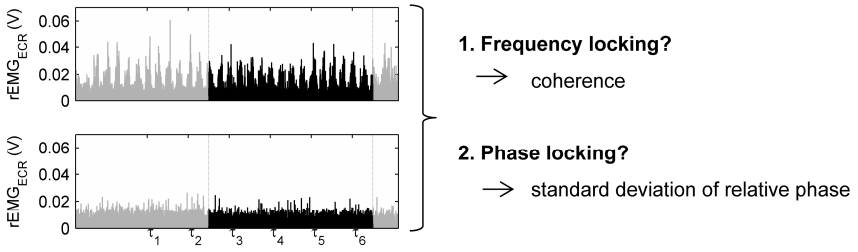


Figure 6.1 Schematic overview of the method. **Step 0:** EMG data (filtered and rectified) as obtained from the extensor carpi radialis muscle (ECR) of a healthy participant during unimanual rhythmic wrist flexion-extension movements (1 trial, 30 cycles). The first five and last two cycles were excluded from analysis. **Step 1:** The Gabor transform was used to determine the power spectral density of the rEMG signal for each trial at six different values of τ (with $\Delta\tau$ equal to four cycles). At each time step τ it was determined whether the maximum of the power spectral density curve (indicated by the black arrow) occurred at the movement frequency of the active hand as prescribed by the metronome (indicated by the grey area) to identify time-windows (duration: four cycles) for which the dominant frequency in the rEMG of the passive arm approximated the movement frequency of the active hand. Whenever this occurred, the time-window of four cycles around the instance τ was selected for further analysis. **Step 2:** Adjacent time windows with mirror activity were collated into mirror-epochs (in this example, τ_3 - τ_6 constituted a mirror epoch; here indicated in black), which were subsequently evaluated in terms of frequency and phase locking.

At each time step τ it was subsequently determined whether the maximum of the power spectral density curve occurred at the movement frequency of the active hand as prescribed by the metronome (tolerance range: f_m ± 0.0875 Hz), which would reflect potential mirror activity in the passive arm. Whenever this occurred, the time-window of four cycles around the instance τ was selected for further analysis (note that selected time-windows were non-overlapping).

Since 50 frequency bins were used for evaluation of the time-resolved power spectral density, at each time step there was a 2% probability p_d of detecting a maximum at the movement frequency by chance alone. The probability P_M of detecting a given number of potential 'mirror activity epochs' by chance alone could be calculated for each combination of muscle (ECR, FCR), side (affected/unaffected in patients, non-dominant/dominant in controls) and group (patient, control) using the formula

$$P_M\,(k \mid N) = (N \text{ over } k)\; {p_d}^k\; (1\text{-}p_d)^{N-k}$$

where k is the number of time steps at which potential mirror activity was detected and N is the total number of time steps evaluated (i.e., 720 per side in controls and, due to the exclusion of data from one CRPS patient [see Results], 342 per side in CRPS patients, which was further reduced to 330 for the non-affected hand due to the exclusion of two additional trials). The number of detections was significant for ECR in all side-group combinations (P_M<.001), whereas for FCR the number of detections was significant in the

dominant arm of controls only (P_M=.003). Further analyses were therefore limited to ECR.

For ECR, adjacent time-windows with mirror activity were collated into 'mirror-epochs', which were evaluated further in terms of frequency and phase locking between rEMGs of homologous muscles (Step 2 in Figure 6.1).

Frequency locking was indexed by the coherence between the rEMGs of homologous muscles (tolerance range: f_m ± 0.0875 Hz) using Welch's modified periodogram method with window length equal to 2 cycles. Stronger coherence reflected stronger frequency locking between muscle activity in the passive and moving arm. Phase locking was evaluated in terms of the continuous relative phase between filtered rEMGs of homologous muscles (second-order bidirectional Butterworth band-pass filter, f_m ± 0.0875 Hz). A relative phase of 0° reflected simultaneous activation of the muscles, whereas negative (positive) phase relations indicated that activity in the passive arm was lagging (leading) activity in the moving arm. To determine whether a predominant phase relation existed, the mean relative phase was calculated for each (metronome) cycle using circular statistics (Fisher, 1993; Ridderikhoff et al., 2005a) and the relative phase distribution as obtained for the mirror-epochs of each side-group combination was tested for uniformity using Kuiper's test (Fisher, 1993). The variability (i.e., circular standard deviation) of the relative phase within each mirror-epoch provided an index of the stability of the obtained relative phasing (Schöner et al., 1986). For comparison, coherence and relative phase between rEMGs of homologous muscles were also calculated for all data segments not included in mirror-epochs.

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics 20.0 (IBM Corp., Armonk, NY, USA). For each participant, the amplitude of active wrist movements (in °) and the associated muscle activity (EMG area, in RR per cycle) were averaged over the three measurements per side. Movement amplitude and ^{10}log-transformed EMG area were submitted to a mixed analysis of variance (ANOVA) with group (patients, controls) as between-subjects factor and side (affected/unaffected in patients, non-dominant/dominant in controls) as within-subject factor. Because no significant effects of hand dominance were detected for any outcome measure, the non-dominant and

dominant side of controls were arbitrarily allocated to the factor 'side', which implied that the non-dominant and dominant side of controls were equated to the affected and unaffected side of patients, respectively. (Note that the dissociation between the non-dominant and dominant side of controls was immaterial to our research question).

The proportion of subjects with mirror-epochs was compared between groups using chi-square tests for the two sides separately. To explore whether the presence of mirror activity in the patient's affected or unaffected side was related to clinical characteristics (i.e., disease duration, CRPS severity, medication use, $Pain_{week}$, $Pain_{task}$, MPQ-PRI and RSQ) or characteristics of the active wrist movements of the contralateral side (movement amplitude and EMG area), comparisons were performed between CRPS patients with mirror activity and CRPS patients without mirror activity (cf. Table 6.2). Independent *t*-tests were used for normally distributed data (i.e., RSQ, MPQ-PRI and movement amplitude) and Mann-Whitney *U*-tests were used for all other data.

Only in four patients and nine controls, mirror-epochs were detected in both arms. This implied that, within groups, mirror-epochs detected in the affected/unaffected arm (in patients) or the non-dominant/dominant arm (in controls) were not necessarily observed in the same subjects. For the purpose of statistical analyses, the detected mirror-epochs were therefore treated as independent observations. Accordingly, the median (and interquartile range) of mirror-epoch duration and the mean (and SD) of within-epoch variability of the relative phase and coherence were calculated across all mirror-epochs per side-group combination. Values of coherence were first transformed to normally distributed values using the Fischer transform and subsequently weighted by mirror-epoch duration, such that long mirror-epochs contributed more to the group average than short mirror-epochs. As for statistical purposes the detected mirror-epochs were treated as independent observations, it was not possible to use a mixed ANOVA. Instead, comparisons across side-group combinations were performed, using Mann-Whitney *U*-tests for mirror-epoch duration and using independent *t*-tests for coherence and relative phase variability (two-tailed; $p<.05$).

Results

One patient was excluded from analysis, as severe edema in the affected arm precluded EMG recordings, and two additional trials (in two different patients) were excluded because the affected hand did not move at the prescribed movement frequency.

The amplitude of voluntary wrist flexion-extension movements of the patients' affected side was smaller than that of their unaffected side and the dominant and non-dominant side of controls (see Table 6.2), as was evidenced by post hoc analysis of the significant interaction effect between side and group ($F_{1,57}$=47.24,p<.001, η_p^2=.45) that complemented the significant main effects of side ($F_{1,57}$=29.99, p<.001, η_p^2=.35) and group ($F_{1,57}$=6.76, p=.012, η_p^2=.11). For the EMG area, a significant main effect of side ($F_{1,57}$=4.15, p=.046, η_p^2=.07) and a significant interaction effect between side and group ($F_{1,57}$=9.24,p=.004, η_p^2=.14) were obtained. Post hoc analysis revealed that active movements of the affected side in patients were associated with a smaller EMG area than active movements of the unaffected side.

Mirror-epochs in ECR were observed in 9 patients (47%) and 25 controls (63%). Specifically, mirror epochs were observed in the affected arm of 7 patients, the unaffected arm of 6 patients, the non-dominant arm of 14 controls and the dominant arm of 20 controls, with 4 patients and 9 controls showing mirror-epochs in both arms. No mirror-epochs were observed in 10 patients (53%) and 15 controls (37%). The proportion of subjects in whom mirror-epochs were detected did not differ between groups (affected/non-dominant side: χ^2_1=1.77, p=.263; unaffected/dominant side: χ^2_1=0.02, p=1.00). No significant differences in terms of disease duration, severity of CRPS, level of pain (i.e., $Pain_{week}$, $Pain_{task}$ and MPQ-PRI), disability (i.e., RSQ), and characteristics of the voluntarily moving side (i.e., amplitude and EMG area) were observed between subgroups of patients with and without mirror activity in the affected and/or unaffected arm (see Table 6.2). Only the medication score of patients with mirror activity in the unaffected arm was significantly higher than that of patients without mirror activity in the unaffected arm.

Table 6.2 Comparison of clinical characteristics and task performance between CRPS patients with and without mirror activity

	PT–A				*p*	PT–UA				*p*
Mirror activity?	No		Yes			No		Yes		
N	13		6			12		7		
Clinical characteristics										
Disease duration (in years) [a]	10.7	(1.8-14.7)	4.7	(1.4-10.3)	.323	9.8	(2.3-12.5)	4.5	(1.5-13.5)	.902
CRPS severity score [b]	10	(7-11)	10.5	(9.5-12.3)	.296	10	(8-10.8)	11	(9-13)	.242
Medication score [b]	4.6	(0-9.1)	15.7	(1.7-33.1)	.152	3.4	(0-7.8)	14.1	(4.4-36)	.034*
$Pain_{week}$ [b]	7	(5.5-8)	7	(5.3-9)	.781	7	(4.3-7.8)	7	(6-9)	.204
$Pain_{task}$ [b]	7	(5-8)	8	(6.3-9)	.258	7	(4-8)	8	(7-9)	.146
MPQ-PRI [a]	27.2	(11.5)	28.5	(10.2)	.820	26.7	(10.9)	29.3	(10.4)	.625
RSQ [a]	3.0	(0.9)	3.2	(0.7)	.627	2.8	(0.7)	3.4	(0.8)	.119
Characteristics active movement contralateral side										
Movement amplitude (in °) [a]	47.0	(14.5)	53.3	(11.3)	.360	31.6	(15.1)	24.0	(11.2)	.262
EMG area (in RR) [b]	6.1	(3.6-8.4)	5.1	(2.4-10.1)	.898	3.0	(2.3-7.9)	2.5	(1.8-4.3)	.536

Abbreviations: PT-A, CRPS patients, affected side; PT-UA, CRPS patients, unaffected side; MPQ-PRI, Pain Rating Index of the McGill Pain Questionnaire; $Pain_{week,}$ average pain experienced during the week preceding the experiment as scored on a numeric rating scale (NRS, 0-10); $Pain_{task}$, average pain experienced during the experimental task as scored on an NRS (0-10); RSQ, score on the Radboud Skills Questionnaire; EMG area,, average area under the EMG curve (per cycle); RR, Ratio to Rest, normalization of EMG to resting value; [a] measures are presented as mean (standard deviation); Per side, independent *t*-tests were used for comparing the patients with and without mirror activity. [b] measures are presented as median (interquartile range); Per side, Mann Whitney *U*-tests were used for comparing the patients with and without mirror activity.

* $p<.05$

Results with respect to detection and analysis of mirror epochs in ECR of the passive side are presented in Table 6.3. The number of mirror epochs was comparable between groups (if the unequal sample size is taken into account; see Table 6.3). Duration of the mirror-epochs in ECR varied from 17-83% of the trial duration (i.e., 1-5 adjacent epochs of 4 cycles). Mirror-epochs in the unaffected arm of CRPS patients were significantly shorter than mirror-epochs in controls (vs. dominant arm: U=134.5, Z=-2.20, p=.026; vs. non-dominant arm: U=196.0, Z=-1.92, p=.055;) and showed lower values of coherence between rEMGs of the ECR muscles (indicating less prominent frequency locking) than mirror-epochs in controls (vs. dominant arm: t_{44}=2.12, p=.040; vs. non-dominant arm: t_{36}=2.50, p=.017). The side-group comparisons revealed no other significant differences in

Table 6.3 Summary of the results for the ECR muscle

Group	CRPS (*n*=19)		Control (*n*=40)	
Active side	***Unaffected***	***Affected***	***Dominant***	***Non-dominant***
Movement amplitude (in °; mean, SD)	49.0 (13.6)	28.8 (14.0) $^{\#\,\dagger}$	47.0 (14.4)	49.3 (14.1)
EMG area (in RR per cycle; mean, SD)	7.0 (5.0)	5.2 (5.1) ‡	6.0 (5.1)	6.6 (4.8)
Passive side	***Affected***	***Unaffected***	***Non-dominant***	***Dominant***
Detection of epochs				
Number of detected time-windows with mirror activity	27*	21*	63*	82*
Number of mirror-epochs	17	12	26	34
Number (%) of subjects	7 (36.8)	6 (31.6)	14 (35)	20 (50)
Analysis of selected mirror epochs				
Epoch duration (in cycles; median, IQR)	4 (4-8)	4 (4-8) $^{\#}$	8 (4-16)	8 (4-20)
Coherence (mean, SD)	0.73 (0.38)	0.55 (0.30) $^{\#\,\dagger}$	0.83 (0.33)	0.83 (0.42)
Within-epoch circular SD of relative phase (in °; mean, SD)	28.9 (18.5)	30.5 (21.6)	19.6 (16.3)	26.9 (19.0)

NOTE: Reported movement amplitude and EMG area values were used to characterize performance of the voluntarily moving limb ('active side'), while mirror activity was evaluated in the contralateral limb ('passive side'). Abbreviations: EMG area, average area under the EMG curve, integrated EMG (per cycle); RR, Ratio to Rest, normalization of EMG to resting value; SD, standard deviation; IQR, interquartile range; FCR, flexor carpi radialis muscle; ECR, extensor carpi radialis muscle. * $p<.01$, indicating significant number of detections. $^{\#}$ $p<.05$, indicating significant differences compared to the dominant side of controls. † $p<.05$, indicating significant differences compared to the non-dominant side of controls. ‡ $p<.05$, indicating a significant difference compared to the unaffected side.

mirror-epoch duration and coherence. As expected, the coherence in mirror-epochs (see Table 6.3) was significantly higher than in the data segments not included in mirror-epochs (patients, affected side: 0.13±0.28, unaffected side: 0.11±0.13; controls, non-dominant side: 0.12±0.26, dominant side: 0.18±0.30; $p<.001$ in all cases).

The predominant phase relations between the ECR muscles during the mirror-epochs (bold dashed lines in Figure 6.2; Kuiper's test indicated a significant deviation from uniformity in all side-group combinations, $p<.001$) indicated that activity of this muscle in the passive arm was roughly in phase with activity of the homologous muscle in the contralateral, moving arm (i.e., relative phase close to 0°). This phase relation was less distinct in the unaffected arm of CRPS patients, indicating less pronounced mirror activity. As anticipated, no markedly predominant phase relation was observed for data

segments not included in mirror-epochs (cf. solid grey lines in Figure 6.2; only for ECR of controls a small but significant deviation from uniformity was observed). No significant differences were found for within-epoch variability of the relative phase, indicating that within-epoch stability of the phase relation was comparable over side-group combinations.

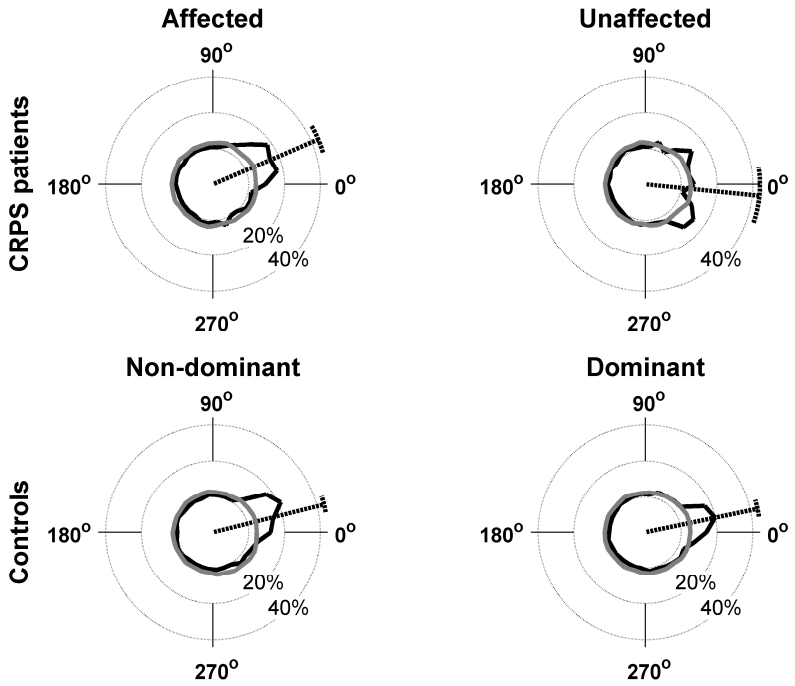


Figure 6.2 Circular histograms of the average relative phase between the rEMGs of the ECR muscles of the passive arm and the contralateral (moving) arm, as obtained for the individual cycles during the mirror-epochs (solid black line) and the segments that were not included in mirror-epochs (solid grey line). Bold dashed lines indicate the predominant phase relation between the two arms during the mirror-epochs (i.e., the mean relative phase across cycles and the corresponding 95% confidence interval, indicated by the perpendicular line segment).

Discussion

We examined mirrored muscle activity during rhythmic unimanual wrist movements to evaluate whether CRPS-related motor dysfunction is associated with disinhibition of contralateral motor activity.

In approximately 50-60% of CRPS patients and controls, occasional brief periods of mirror activity were observed in the ECR of the passive arm. The number of detected mirror-epochs was comparable for CRPS patients and controls. Mirror-epochs in the *affected* arm of CRPS patients were comparable to those of controls in terms of duration, coherence, relative phase distribution and within-epoch relative phase stability. Interestingly, however, mirror-epochs in the *unaffected* arm were shorter and showed less pronounced frequency and phase locking compared to those in controls. In contrast with the anticipated disinhibition of contralateral motor activity in patients with CRPS-related motor dysfunction, the current analysis thus revealed "normal" mirror activity in the affected arm and less pronounced mirror activity in the unaffected arm.

Mirror activity is commonly observed in children up to 10 years of age and in patients with various congenital or acquired neurological disorders, e.g., Parkinson's disease, corticobasal syndrome and hemiplegic stroke (for reviews see Cincotta and Ziemann, 2008; Cox et al., 2012). It may also be observed in reduced form in healthy adults when appropriate detection methods are used (Ridderikhoff et al., 2005a). Two not mutually exclusive mechanisms have been proposed to underlie mirror activity. Congenital mirror activity appears to originate primarily from the same hemisphere as the contralateral voluntary movements through direct corticospinal projections along ipsilateral (uncrossed) pathways or along abnormal branches of contralateral (crossed) pathways. Acquired mirror activity, by contrast, appears to originate primarily from activation of both hemispheres during intended unimanual movement, when the (transcallosal) inhibition of interhemispheric facilitation is insufficient (Cincotta and Ziemann, 2008; Cox et al., 2012; Daffertshofer et al., 1999). For example, 'mirror dystonia' that occurs in the affected hand of patients with focal hand dystonia while performing a specific task with their unaffected hand, has been associated with

dysfunctional interhemispheric inhibitory connections (Beck et al., 2009; Nelson et al., 2010).

The affected arm of patients with CRPS-related motor dysfunction did not exhibit increased levels of mirrored muscle activity during rhythmic movements of the unaffected side. This finding was in contrast with the anticipated disinhibition of contralateral motor activity, which was expected to result in enhanced mirror activity. As such, this finding corroborated recent empirical indications that deviant joint postures and motor dysfunction in CRPS do not exhibit the characteristics of dystonia (Chapter 3).

Mirrored muscle activity in the unaffected side of CRPS patients during voluntary movement of the affected side was less pronounced than the mirrored muscle activity that was observed in healthy subjects. Figure 6.3 (based on Cox et al., 2012) illustrates the four mechanisms that may be proposed to explain the observed reduction of mirrored muscle activity in the unaffected arm of CRPS patients: *(1)* lower intensity of motor commands generated in the primary motor cortex of the hemisphere responsible for controlling the voluntarily moving limb; *(2)* enhanced interhemispheric inhibition or attenuated interhemispheric facilitation from the hemisphere responsible for controlling the voluntarily moving limb towards the 'mirror hemisphere'; *(3)* stronger suppression of activity by inhibitory neural networks within the mirror hemisphere; and *(4)* peripheral factors related to transmission of low-intensity motor commands and subsequent low-level activation of muscles.

Given these possibilities, a direct effect of impaired voluntary control of the affected limb (i.e., mechanism 1 in Figure 6.3) is the most likely explanation for the weaker mirror activity in the unaffected arm of CRPS patients. Specifically, movement amplitude of the affected side was smaller than that of the unaffected side or controls, while all movements were performed at the same frequency f_m. These smaller movements of the affected arm were also associated with lower levels of EMG activity, which in turn may have a peripheral or central origin. With regard to the potential role of peripheral mechanisms, it can be argued that the mere presence of mirror activity in the affected arm is indicative of unimpeded transmission of low-intensity motor commands and subsequent low-level activation of muscles in the affected arm of CRPS patients. Moreover, CRPS patients with a clinically detectable nerve lesion (i.e., CRPS type 2) were excluded from the current

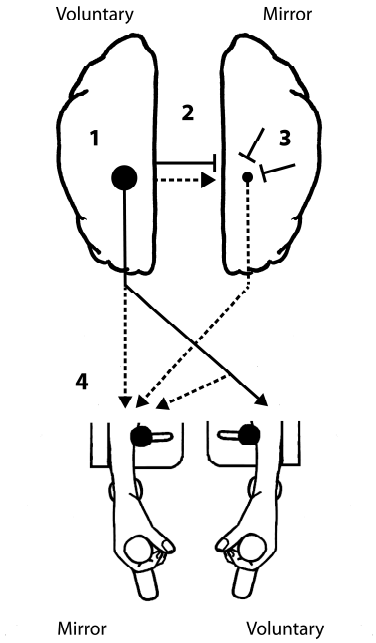


Figure 6.3 Proposed mechanisms involved in the modulation of mirrored muscle activity (dotted lines) during unimanual voluntary movement (solid line), based on Cox et al., 2012. The intensity of mirrored muscle activity depends on: **(1)** intensity of motor commands generated in the primary motor cortex of the hemisphere responsible for controlling the voluntarily moving limb; **(2)** strength of interhemispheric inhibition and facilitation from the hemisphere responsible for controlling the voluntarily moving limb towards the 'mirror hemisphere'; **(3)** suppression of mirrored activity by inhibitory neural networks within the mirror hemisphere; and **(4)** peripheral factors related to transmission of low-intensity motor commands and subsequent low-level activation of muscles.

study. Hence, the smaller movements and reduced EMG activity of the affected arm more likely reflected a lower intensity of motor commands (cf. Chapter 3). This in turn probably invoked less neuronal cross-talk to the contralateral (unaffected) side (Hinder et al., 2010) via interhemispheric interactions and/or direct corticospinal projections that may otherwise be normal.

The current findings suggest that central mechanisms involved in the generation of motor commands play a role in the motor dysfunction of the affected limb in CRPS. Because mirror activity in the affected arm was not reduced, it seems unlikely that the hemisphere responsible for controlling the affected limb is subjected to excessive

inhibitory influences exerted by the unaffected hemisphere, which has been reported in stroke patients (Murase et al., 2004). Taken together, our findings thus suggest that CRPS-related motor impairments emerge from dysfunction of neural networks within the hemisphere responsible for controlling the affected limb. Possibly pain-related processes play a significant role in this regard, e.g., due to pain-induced changes at various levels of the motor system (Chapter 2; Hodges and Tucker, 2011) or patients being reluctant to exert full effort because of increasing pain. Because all patients reported moderate to severe pain, limited variability in this regard may have obscured a potential relation between pain intensity and measures of motor function in the present study.

Prior to drawing further conclusions, the following aspects should be considered as well. Firstly, the appearance of mirrored muscle activity in CRPS-related motor dysfunction may be affected by multiple processes along the neuraxis. Although the current analysis provided some insights into the potential role of these underlying mechanisms, other techniques (e.g., using transcranial magnetic stimulation) are needed for direct evaluation of the separate aspects of the motor system, e.g., the excitability of corticospinal projections and the functional integrity of excitatory and inhibitory neural circuits. Secondly, epochs of mirror activity could reliably be detected in ECR, but not in FCR (cf. Ridderikhoff et al., 2005a). This might reflect stronger inhibition of unwanted activity in FCR (in line with more precise control of the flexion phase of the movement cycle; Carson, 2005; de Boer et al., 2011), or, alternatively, it might be due to the location of the recording electrode relative to the muscle (i.e., FCR is situated less superficial than ECR, rendering registration of small fluctuations in activity difficult). Thirdly, it should be noted that epochs of mirror activity were detected in approximately 50-60% of the CRPS patients and controls, and that mirror epochs from the two sides of the body (affected/unaffected, non-dominant/dominant) were not necessarily obtained from the same individuals. Although the current results may thus provide insight into mechanisms at the group level, they do not allow statements regarding individual cases, especially for those in whom no epochs of mirror activity were detected. Fourthly, our findings were not confounded by the arbitrary allocation of the dominant and non-dominant arm of controls to the factor 'side' in the mixed ANOVA, since similar results were obtained if the analyses were repeated with the dominant side of controls being compared to the affected

hand of patients and the non-dominant side of controls being compared to unaffected hand of patients. Finally, patients were tested while on their regular medication, which in seven patients comprised oral muscle relaxants or other centrally acting drugs that might affect the motor system (Ziemann, 2004). Exploratory analysis revealed that the observed reduction of mirror activity in the unaffected arm is not likely due to effects of medication, given that the medication score of patients with mirror activity in the unaffected arm was comparable to that of patients with mirror activity in the affected arm, and that there were no marked differences regarding the type of drugs used by patients with and without mirror activity. Moreover, no significant differences in terms of disease duration, severity of CRPS, disability and level of pain were observed between subgroups of patients with and without mirror activity in the affected and/or unaffected arm (see Table 6.3).

In conclusion, no evidence for disinhibition of contralateral motor activity was found during unimanual voluntary movement in patients with CRPS-related motor dysfunction. Mirror activity in the unaffected arm of CRPS patients was less pronounced than in controls, which was probably related to impaired motor processing within the affected hemisphere during voluntary movement of the affected arm. Such a reduction of mirror activity has not previously been demonstrated in CRPS, possibly due to difficulties in detection and quantification of these subtle manifestations of mirror activity.

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