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

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HIGHLIGHTS

- Complex Regional Pain Syndrome (CRPS) has been associated with disinhibition of the motor system.
- Mirror activity was examined to assess potential disinhibition of contralateral motor activity during intended unimanual movement.
- Mirror activity in the affected arm of CRPS patients was comparable to that in healthy subjects.

ABSTRACT

Objective: 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.
Methods: 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.
Results: 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.
Conclusions: No evidence for disinhibition of contralateral motor activity was found during unimanual movement.
Significance: 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.

1. 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)

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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 (Bank et al., 2013b; Huge et al., 2011; Schilder et al., 2012; van Rooijen et al., 2013) 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 be 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.

2. Methods

2.1. Subjects

Twenty patients diagnosed with CRPS type 1 of the upper extremity and 40 healthy subjects participated in the experiment (see Table 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 $\geqslant$0.5 Hz. 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. 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.

Table 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)	–

SD = standard deviation; IQR = interquartile range; Severity of CRPS was indexed by the CRPS severity score (maximum score: 17; Harden et al., 2010). Medication was quantified according to the Medication Quantification Scale Version III (Harden et al., 2005). Pain was evaluated using a numeric rating scale for average pain experienced during the week preceding the experiment ($Pain_{week}$; 0: no pain, 10: unbearable pain) and the Pain Rating Index of the McGill Pain Questionnaire (MPQ-PRI; maximum score: 63; Melzack, 1975). Disability was evaluated using the Radboud Skills Questionnaire (RSQ; maximum score: 5; Oerlemans et al., 2000).

2.2. 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., 2000). 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 (20 × 30 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 (1000–10,000 times; Bagnoli™ 4-channel desktop amplifier with 20–450 Hz bandpass 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