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Motor Dysfunction in Complex Regional Pain Syndrome

The Role of Sensory Processing and Sensory-Motor Integration

Paulina J.M. Bank
Motor Dysfunction in Complex Regional Pain Syndrome: The Role of Sensory Processing and Sensory-Motor Integration

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Motor Dysfunction in Complex Regional Pain Syndrome

The Role of Sensory Processing and Sensory-Motor Integration

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Chapter 1

General Introduction

Clinical characteristics of Complex Regional Pain Syndrome

Complex Regional Pain Syndrome (CRPS) is a painful disorder that generally affects distal extremities. The syndrome develops after a minor or moderate tissue injury, such as a fracture, sprain, or operation, in the vast majority (approximately 90%) of patients, but it may also arise without an evident cause (de Mos et al., 2007; de Rooij et al., 2010; Veldman et al., 1993). CRPS is characterized by (severe) pain with various combinations of sensory, autonomic, trophic and motor abnormalities (Marinus et al., 2011), resulting in a substantial heterogeneity in clinical presentation. Sensory abnormalities may include positive sensory phenomena like allodynia (i.e., non-nociceptive stimuli are experienced as painful) and hyperalgesia (i.e., nociceptive stimuli are experienced as extremely painful) and/or negative sensory phenomena like hypoalgesia (i.e., reduced perception of nociceptive stimuli) and hypoesthesia (i.e., reduced perception of subtle touch). Other features include autonomic disturbances (i.e., changes in skin color, temperature and perspiration), trophic disturbances (i.e., abnormal hair and nail growth, changes in skin texture) and oedema. Motor abnormalities may either occur simultaneously with the onset of the condition or evolve later in the course of the disease (Veldman et al., 1993; van Rijn et al., 2007).

The spectrum of motor abnormalities observed in CRPS is broad and includes muscle weakness, loss of voluntary control, restricted range of motion (ROM), problems with movement initiation and execution, tremors, jerks and prominent abnormal posturing (Birklein et al., 2000; Goris et al., 1990; Harden et al., 1999; Huge et al., 2011; Schilder et al., 2012; Schwartzman and Kerrigan, 1990; Veldman et al., 1993). Abnormal posturing occurs in approximately 25% of patients with CRPS, starts distally in the affected limb and may spread more proximally and to other extremities (Munts et al., 2011a; van Rijn et al., 2007, 2011), causing some patients to become severely disabled. Although the abnormal postures in question might originate from various mechanisms, they are often attributed to sustained contractions of flexor muscles (i.e., 'tonic' or 'fixed' dystonia), which in turn may have a central, intramuscular, or psychological cause. More common motor impairments in CRPS do not involve *fixed* postures, but are characterized by milder limitations of the active range of motion (AROM) and increased resistance to passive

movements, with the affected body part preferably adopting an abnormal posture (see Figure 1.1). Although the presentation of these motor impairments may resemble that of dystonia, it is unclear to date if they may indeed be characterized in this manner.

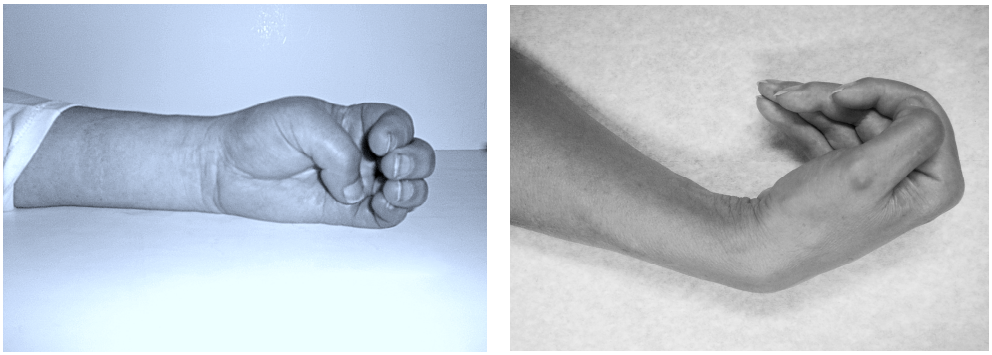


Figure 1.1 Abnormal posturing of the affected hand in two patients with CRPS. The flexion of the fingers and wrist is illustrative of the postures encountered in the studies presented in this thesis.

Pathophysiology of CRPS

CRPS is a multifactorial disorder which is usually brought about by a combination of genetic and environmental factors (i.e., it may be triggered by a traumatic injury in persons with a genetic predisposition for CRPS). The pathophysiology of CRPS has received increasing attention in the scientific literature over the past decades. Several pathophysiological mechanisms underpinning CRPS or parts of its clinical spectrum have been postulated. These mechanisms are briefly highlighted in the following sections.

Aberrant inflammation

Inflammation is a highly complex response of the body to tissue injury, which is essential for wound healing. Similarities between the classical symptoms of inflammation and clinical features of CRPS (i.e., reddening, warming and swelling) have led several investigators to suggest that CRPS is induced by an exaggerated inflammatory response (e.g., Oyen et al., 1993; Sudeck, 1900; Veldman et al., 1993). This view is supported by findings of elevated pro-inflammatory cytokine levels (for a review, see Parkitny et al.,

2013) and neurogenic inflammatory reactions (e.g., Birklein et al., 2001; Birklein and Schmeltz, 2008). However, no correlation was found between levels of pro-inflammatory cytokines and symptoms of inflammation in patients with CRPS (Wesseldijk et al., 2008), which may suggest that other factors play a role in the development and maintenance of inflammation. Possibly the initial inflammatory response is not adequately terminated by anti-inflammatory mediators (Birklein and Kingery, 2009; Leis et al., 2003). Beneficial effects of anti-inflammatory interventions comprising corticosteroids and/or free radical scavengers (e.g., vitamin C) have been reported (for a review, see Fischer et al., 2010). The prevailing view is that inflammatory mechanisms play a significant role in CRPS, in particular during the acute phase (<6 months) of the disease.

Vasomotor dysfunction

CRPS is often characterized by a difference in skin temperature between the affected and unaffected limb (Wasner et al., 2001; Wasner, 2010). In the acute stage of CRPS, the affected limb is usually warmer than the unaffected limbs, whereas at later stages of the disease it is usually colder than the unaffected limbs (Wasner, 2010). Several studies using experimental manipulations (i.e., external heating or cooling) have demonstrated that the affected limb shows marked disturbances in temperature regulation (Niehof, 2006, 2007; Wasner et al., 2001). Collectively, these findings suggest that the mechanisms underpinning vasomotor dysfunction are involved in CRPS. Central disturbances in efferent sympathetic outflow seem to be predominant in the acute stage of CRPS, whereas endothelial changes, disturbed neurovascular transmission and hyperreactivity of blood vessels to circulating catecholamines seem to predominate in the chronic stage of the disease (for reviews, see Marinus et al., 2011; Wasner et al., 2010).

Maladaptive plasticity of the central nervous system

Following peripheral tissue injury or inflammation, nociceptive neurons in the dorsal horn of the spinal cord may undergo maladaptive changes in anatomical and functional connectivity, as a result of which non-noxious stimuli may become painful and pain may become chronic. This so-called 'central sensitization' is associated with increased

sensitivity of the N-methyl-D-aspartic-acid (NMDA) receptor of spinal nociceptive neurons (Latremoliere and Woolf, 2009; Woolf et al., 1991) and a loss of function of interneuronal circuits mediating inhibition (Kuner, 2010). Unlike pain, dystonia-like phenomena in CRPS do not respond to the intravenous NMDA receptor antagonist ketamine (Schwartzman et al., 2009; Sigtermans et al., 2009), which suggests that these motor impairments involve mechanisms that are distinct from those associated with central sensitization. A significant reduction of dystonia was attained by intrathecal administration of the gamma-aminobutyric-acid B ($GABA_B$) receptor agonist baclofen (van Hilten et al., 2000; van Rijn et al., 2009), but not glycine (Munts et al., 2009), suggesting that loss of spinal GABAergic inhibition may contribute to impaired motor function.

In addition to spinal alterations, there is accumulating evidence that supraspinal sensory-motor neural networks are involved in the pathophysiology of CRPS (for reviews, see Marinus et al., 2011; Swart et al., 2009). Changes in the size and organization of the cortical somatosensory map (Juottonen et al., 2002; Maihöfner et al., 2003; Pleger et al., 2004), changes in the motor cortex representation (Maihöfner et al., 2007) and distortions of the mental image of the affected limb (Förderreuther et al., 2004; Frettlöh et al., 2006; Lewis et al., 2007, 2010; Moseley, 2005; Peltz et al., 2011) have frequently been reported in CRPS. In addition, a growing number of studies provided neurophysiological evidence for disinhibition of somatosensory (Lenz et al., 2011) and motor circuits (Eisenberg et al., 2005; Juottonen et al., 2002; Kirveskari et al., 2010; Krause et al., 2004; 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 have been reported (Huge et al., 2011; Schilder et al., 2012; van Rooijen et al., 2013b).

All these findings suggest maladaptive neuronal plasticity at various levels of the central nervous system. Although the exact role of these changes remains to be elucidated, they are likely to contribute to the sensory and motor impairments that are commonly observed in CRPS.

Psychological factors

Since no clear and generally accepted organic cause for CRPS has yet been identified, psychological factors have been put forward as potential predisposing mechanism (e.g., Ochoa and Verdugo, 1995). However, evidence to support this premise is scarce and often based on research of questionable methodological quality (Bruehl et al., 1992). Well-controlled cross-sectional studies showed that the psychological profile of CRPS patients was quite similar to that of patients with other chronic pain conditions (Ciccone et al., 1997) and that CRPS patients with dystonia had a different psychological profile compared to patients with conversion or affective disorders (Reedijk et al., 2008). Prospective studies revealed no unique psychological profile in patients who developed CRPS after a fracture (Beerthuizen et al., 2011) or surgery (Field and Gardner, 1997; Harden et al., 2003; Puchalski and Zyluk, 2005) compared to those who did not. Based on a comparison of the medical history of patients who developed CRPS to that of age- and sex-matched individuals who did not develop CRPS after a similar trauma, De Mos et al. (2008) concluded that psychological factors were not associated with an increased probability to develop CRPS.

To date no evidence has been found for a predisposing role of psychological factors in the onset and maintenance of CRPS (Beerthuizen et al., 2009). However, it remains to be determined whether psychological factors play a role in the development of associated motor impairments (cf. Marinus et al., 2011). Neurologists differ in opinion on whether the motor impairments of CRPS, in particular abnormal postures, are psychogenic or not. It has been argued that the shared characteristics of psychogenic movement disorders and movement disorders that are associated with CRPS may point at a psychogenic origin (Hawley and Weiner, 2011; Schrag et al., 2004). Another interesting phenomenon in this regard is the apparent dissociation between the performance of voluntary and automatic movements in some cases of CRPS. Some patients are unable to perform a movement upon request, whereas a similar movement may be executed without much difficulty in the context of automatic behavior. This discrepancy between voluntary and automatic movements is sometimes taken as evidence of psychogenicity (Edwards et al., 2011; Fahn and Williams, 1988; Pareés et al., 2013). Alternatively, however, it may reflect abnormal sensory-motor integration at specific levels of motor planning and execution.

Motor dysfunction in CRPS: a role for sensory-motor deficits?

The chronic stage of CRPS is characterized predominantly by severe pain and a prominent loss of voluntary control, which is associated with significant disability (Geertzen et al., 1998; Huge et al., 2011; Maihöfner et al., 2003; Marinus et al., 2013; Perez et al., 2002; Savaş et al., 2009) and loss of quality of life (Galer et al., 2000; Savaş et al., 2009). Several of the pathophysiological mechanisms that were described in the preceding sections have been postulated to underpin the CRPS-related motor impairments, including 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), psychological factors (Hawley and Weiner, 2011; Schrag et al., 2004) and maladaptive neuroplasticity at various levels of the central nervous system (Maihöfner et al., 2003; Marinus et al., 2011; Swart et al., 2009). 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 (Abbruzzese and Berardelli, 2003).

Adequate motor control requires intact proprioception (i.e., the sense of position, movement and force) to facilitate movement planning and execution (Hemsdörfer and Nowak, 2009; Park et al., 1999). To this end, information from various peripheral sources (including muscle spindles, joint receptors, tendon organs, pressure-sensitive or stretch-sensitive skin receptors) has to be properly integrated with centrally generated motor commands (for a review, see Proske and Gandevia, 2012) within the context of a mental representation of the limb or 'body schema' (Longo and Haggard, 2010). In CRPS, several abnormalities have been reported that may interfere with proprioception, including altered sensitivity of cutaneous and muscular afferents (Eberle et al., 2009; Huge et al., 2011; Kemler et al., 2000; Maier et al., 2010; van Rooijen et al., 2013a) and distortions of the mental image of the affected limb (Förderreuther et al., 2004; Moseley, 2005; Frettlöh et al., 2006; Lewis et al., 2007, 2010; Peltz et al., 2011). Additionally, some CRPS patients need to closely watch their affected limb in order to control movements (Galer et al., 1995), which may reflect an increased reliance on the visual system to compensate for disturbed proprioception. Together, these findings suggest that proprioceptive impairment might play a significant role in the motor dysfunction of CRPS.

However, it is possible that it is not (only) proprioception itself that is affected, but rather the way in which signals are integrated during motor control (e.g., Juottonen et al., 2002; Maihöfner et al., 2007; Mugge et al., 2013). Abnormal sensory-motor integration may not only affect motor function of the affected limb, but also have consequences for the ability to properly coordinate the movements of two limbs, as is required for many daily-life tasks (e.g., lifting a large box or eating with knife and fork). In this context, abnormalities of sensory-motor integration at specific levels of the motor system (e.g., spinal reflexes vs. higher-order cortical processes) are of special interest, as they may contribute to the apparent dissociation between automatic and voluntary motor control in CRPS.

Aims and outline of this thesis

From the preceding discussion it is evident that motor dysfunction of CRPS is a poorly understood phenomenon that is associated with significant disability. It is characterized predominantly by a decrease or loss of voluntary muscle control that seems to be associated with structural and functional alterations in skeletal muscle tissue as well as decreased inhibition of the motor system, changes in sensory processing and problems in sensory-motor integration. The research presented in this thesis aims to uncover the interrelations among these various aspects of motor control in order to obtain a better understanding of the pathophysiology underpinning the motor dysfunction of CRPS, which ultimately may aid the therapeutic management of these patients. The research in question is reported in six logically ordered chapters followed by an epilogue.

To set the stage, **Chapter 2** provides a systematic review of the extensive literature on the relations between pain and the motor system. Pain, which is a key feature of CRPS, is known to have profound effects on motor behavior. The focus of this review is on the differential effects of various sources of experimental pain (i.e., skin, joint, muscle or tendon) on motor function in healthy humans. The obtained insights into the motor consequences of experimental pain add to our understanding of the potential role of pain-related processes in the sensory and motor disturbances of CRPS that are subsequently addressed in Chapters 3 to 7. **Chapter 3** evaluates whether the AROM limitations and

abnormal postures in chronic CRPS are associated with excessive muscle activity, which is typical of dystonia. To this end, characteristics of surface electromyography (EMG) recordings of the wrist flexor and extensor muscles are evaluated during active maintenance of various wrist positions in the affected and unaffected arm of patients with longstanding CRPS and in healthy controls. The studies reported in Chapters 4 and 5 seek to further our understanding of proprioceptive deficits in CRPS and their potential contributions to impaired motor function of the affected limb. Specifically, in **Chapter 4** the accuracy and precision of joint position sense are examined over a range of wrist positions using passive as well as active displacements in order to gain insight into the extent to which peripheral afferent signals and centrally generated efferent signals contribute to (deficits in) position sense. **Chapter 5** describes whether an impaired sense of force production contributes to disturbances of force control in patients with CRPS. In Chapters 6 and 7, the involuntary and voluntary aspects of (sensory-) motor interactions between the two hands are examined. Specifically, **Chapter 6** focuses on the involuntary 'overflow' of voluntary motor commands associated with movements of one limb towards the passive contralateral limb. Given that CRPS has been associated with decreased inhibition of the motor system, enhanced 'mirror activity' was expected in CRPS patients compared to healthy controls. In **Chapter 7**, a set of unimanual and bimanual rhythmic motor tasks is used to discriminate between the influence of sources of intended and unintended interlimb coupling. Intended interlimb coupling is not only evaluated during active control of both hands, but also during afference-based coordination with passive movements of the contralateral hand. Unintended interlimb coupling is evaluated in terms of reflex-like entrainment of active hand movements to the movement rhythm of to-be-ignored passive movements of the contralateral hand. The results presented in Chapters 6 and 7 shed new light on the apparent dissociation between voluntary and automatic movements, thereby contributing to the ongoing debate regarding the potential causes underlying the decrease of voluntary muscle control in patients with longstanding CRPS. Finally, **Chapter 8** provides a summary of the main conclusions, a general discussion of the results, and suggestions for further research.

Chapter 2

Motor consequences of experimentally induced limb pain: A systematic review

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Compelling evidence exists that pain may affect the motor system, but it is unclear if different sources of peripheral limb pain exert selective effects on motor control. This systematic review evaluates the effects of experimental (sub)cutaneous pain, joint pain, muscle pain and tendon pain on the motor system in healthy humans. The results show that pain affects many components of motor processing at various levels of the nervous system, but that the effects of pain are largely irrespective of its source. Pain is associated with inhibition of muscle activity in the (painful) agonist and its non-painful antagonists and synergists, especially at higher intensities of muscle contraction. Despite the influence of pain on muscle activation, only subtle alterations were found in movement kinetics and kinematics. The performance of various motor tasks mostly remained unimpaired, presumably as a result of a redistribution of muscle activity, both within the (painful) agonist and among muscles involved in the task. At the most basic level of motor control, cutaneous pain caused amplification of the nociceptive withdrawal reflex, whereas insufficient evidence was found for systematic modulation of other spinal reflexes. At higher levels of motor control, pain was associated with decreased corticospinal excitability. Collectively, the findings show that short-lasting experimentally induced limb pain may induce immediate changes at all levels of motor control, irrespective of the source of pain. These changes facilitate protective and compensatory motor behavior, and are discussed with regard to pertinent models on the effects of pain on motor control.

Introduction

Pain may have profound effects on motor behavior that are mediated at various levels of the nervous system, ranging from spinal reflex circuits to (pre)motor cortices. The effects of pain thus may become manifest in a variety of motor parameters such as reflex amplitude, muscle activity, force production, kinematics, movement strategy and activation of cortical areas involved in motor control. Empirical studies typically focus on a single or a limited number of parameters, whereas pertinent descriptive models generally comprise only a selection of the complex interactions between pain and the motor system. Consequently, a coherent view on the consequences of pain on motor behavior has been lacking. Only recently, Hodges and Tucker (2011) proposed a new theory on motor adaptation to pain involving changes at multiple levels of the motor system.

Acute intense pain has been thought to elicit motor responses that serve to protect the painful limb from further damage. Although such behavior serves a clear short-term benefit for the injured part, it may have long-term negative consequences if it does not dwindle with healing of the initial injury. The presence of chronic pain may lead to abnormalities in motor control, either as a direct effect of pain or as a consequence of adopting a movement strategy that compensates for such direct effects (Hodges and Tucker, 2011). Conversely, abnormalities in motor control may lead to the development of (chronic) pain, e.g., when tissues are overloaded (Arendt-Nielsen and Graven-Nielsen, 2008; Sterling et al., 2001). In clinical pain conditions, multiple factors may play a role in the effects of pain on motor behavior, rendering it difficult to disentangle the separate effects of nociceptive input on the motor system. Experimental procedures to induce pain in healthy volunteers allow for establishing clear-cut, reproducible cause-and-effect relations and thus provide invaluable means to isolate motor consequences of acute pain.

The various procedures to induce pain in a controlled manner have specific advantages and methodological limitations (Arendt-Nielsen and Graven-Nielsen, 2008; Graven-Nielsen, 2006; Staahl and Drewes, 2004). Ideally, the effects of pain are studied by selective activation of nociceptive afferents without causing structural tissue damage. In reality, however, experimental procedures cannot exclusively target nociceptive afferents

but also activate non-nociceptive afferents (Graven-Nielsen, 2006; Mense, 1993). Appropriate control conditions that take into account stimulation of these non-nociceptive afferents are required to draw inferences on the effects of pain on motor control.

This systematic review evaluates the effects of experimentally induced pain on the motor system in healthy humans in order to obtain more insight into the empirical evidence for interactions between pain and the motor system. The source of pain (i.e., skin, joint, muscle or tendon) is expected to have differential effects on motor control, considering that these tissues have different roles in the motor system and projections of nociceptive afferents may vary among various tissue types (Almeida et al., 2004; Millan, 1999). This review is limited to pain localized in the extremities and focuses on the effects of controlled external stimuli that lead to localized pain without causing structural damage.

Literature Search Methods

A literature search was performed in three electronic databases (Medline, EMBASE and Web of Knowledge) to identify potentially relevant studies. The search strategy was developed in collaboration with a specialist in information retrieval of the Leiden University Medical Center Library and comprised a combination of MeSH terms and free text terms related to motor function (including proprioception) combined with terms related to experimental pain (see Supplement 2.1). The results were limited to articles in English, German and Dutch. The most recent search was performed on March 7th 2011.

The selection process is presented in Figure 2.1. The identified studies were first screened by title and abstract, after which the full text of potentially relevant articles was studied. Papers were included if all of the following four criteria were met: *(1)* effects of experimentally induced pain on one or more of the following parameters were studied: spinal reflexes, muscle activity, movement characteristics, proprioception and activation in motor-related brain areas; *(2)* experimental pain was induced by a controlled stimulus leading to localized pain without causing structural damage (i.e., thermal, mechanical, electrical or chemical stimulation); *(3)* pain was localized in the upper extremity or lower

extremity; and *(4)* data were obtained from healthy human subjects. Note that papers were excluded if pain was induced by ischemia or eccentric exercise, because effects of ischemia are non-specific and eccentric exercise may lead to inflammatory reactions and structural damage to muscle tissue (Friden and Lieber, 1992). In addition, reference lists of all included publications as well as reviews on this topic were tracked following the procedure described above. In case there was any uncertainty about inclusion or exclusion, a second, independent reviewer was consulted. Discrepancies between the reviewers were to be resolved by consensus agreement. However, no such discrepancies arose during the process.

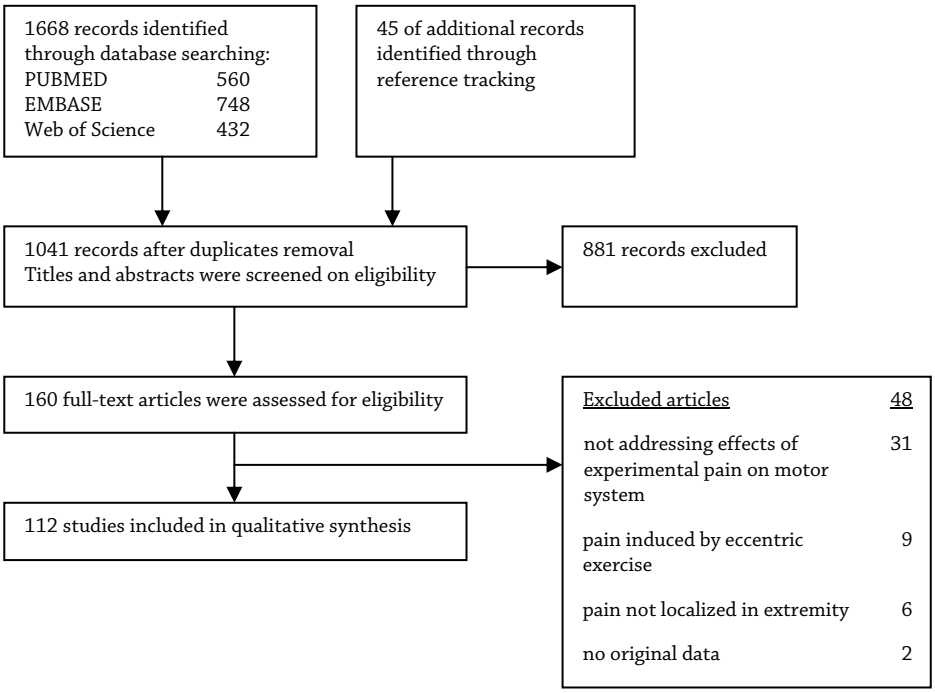


Figure 2.1 Flow chart of study search and selection.

Data regarding the type, intensity and location of pain, the test protocol, outcome parameters and performed motor tasks were extracted using a standard form. Outcome parameters were categorized into one or more of the following aspects of motor function: *(1)* spinal reflexes; *(2)* muscle activity; *(3)* task performance, movement kinetics and kinematics; *(4)* proprioception; and *(5)* brain activation. The systematic review of studies in each category is preceded by a short introduction providing a framework for the topic in question. All studies fulfilling the inclusion criteria are presented in Supplement 2.2 (Tables S2.1-2.8), which summarize the results on the effects of (sub)cutaneous pain, joint pain, muscle pain and tendon pain. If possible, pain intensity is categorized into mild (Visual Analogue Score (VAS) <30mm), moderate (VAS 30-54mm) and severe pain (VAS >54mm) (Collins et al., 1997). Note that some authors did not explicitly report measures of pain intensity, whereas others expressed pain intensity as VAS-peak, VAS-mean or the area under the VAS curve (on the basis of which the average pain level was calculated). Results for each of the aforementioned aspects of motor function are summarized in the text, with *n* indicating the number of studies on which the description of results is based. A more detailed description of the results is provided online (see Supplement 2.3).

Results

The distribution of studies over the various aspects of motor function (Figure 2.2) reveals that research has concentrated on muscle activity and movement characteristics. These aspects of motor function were examined predominantly by means of experimentally induced muscle pain, whereas spinal reflexes and brain activation patterns were mainly examined by means of experimentally induced cutaneous pain. A direct comparison between different pain sources was made in only 9 out of 112 studies. Overall, the effects of (sub)cutaneous pain and muscle pain have received considerable attention, unlike the effects of tendon pain and joint pain.

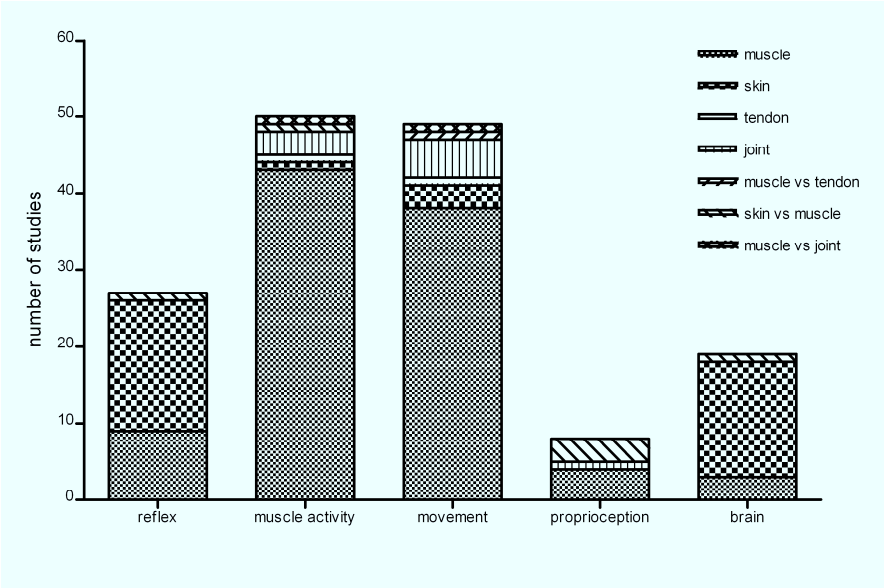


Figure 2.2 Overview of the studies included in this review, grouped by aspects of motor function and sources of pain under study. Several studies addressed more than one aspect of motor function and are thus presented in more than one column. Within a given column, each study can only appear once; the source(s) of pain under study (e.g. 'muscle' or 'muscle vs. skin') are indicated by various patterns.

Spinal reflexes

Spinal reflexes belong to the most basic elements of motor behavior. On this level, the effects of experimentally induced pain have been studied for the nociceptive withdrawal reflex (NWR; *n*=13), the phasic stretch reflex (*n*=2), the H-reflex (*n*=17) and inhibitory spinal circuits (*n*=7; see Table S2.1).

The NWR (for reviews, see Clarke and Harris, 2004; Sandrini et al., 2005) is a spinal reflex elicited by noxious stimulation of cutaneous afferents and has a 'modular organization' in animals (Clarke and Harris, 2004) and humans (Andersen et al., 1999, 2001, 2003; Schmit et al., 2003; Sonnenborg et al., 2001). The evoked motor response represents the most appropriate movement to withdraw the stimulated area from the offending source. Pain stimuli applied to the skin (Andersen et al., 1994; Ellrich and Treede, 1998; Ellrich et al., 2000; Grönroos and Pertovaara, 1993) or muscle (Andersen et al., 2000) consistently caused a modulation of the NWR, which probably served to protect the painful tissue, a finding in line with those obtained from animal research (Clarke and

Harris, 2004). However, effects of phasic muscle pain may depend on the exact timing of the painful intramuscular electrical stimulation (Andersen et al., 2006; Ge et al., 2007). Suppression of the NWR was observed during painful heterotopic stimulation, which was attributed to a 'diffuse noxious inhibitory control' mechanism (Roby-Brami et al., 1987; Serrao et al., 2004; Terkelsen et al., 2001; Willer et al., 1984, 1989).

At the spinal level, motor output is modulated by various excitatory and inhibitory circuits (Pierrot-Deseilligny and Burke, 2005). The most well-known excitatory spinal circuit consists of Ia afferents originating from muscle spindles and projecting to α-motoneurons of the homonymous muscle and synergists, which leads to a reflex contraction of a previously stretched muscle (i.e., the phasic stretch reflex). The H-reflex is evoked by direct stimulation of Ia afferents, thereby bypassing the muscle spindles and fusimotor activity that are involved in the stretch reflex, and is generally assumed to reflect excitability of the motor neuron pool (Knikou, 2008). Inhibitory spinal circuits mediated by Ib interneurons play a role in coordinating the activity of muscles operating at several joints (Jankowska, 1992; Rossi and Decchi, 1997) and protective negative feedback circuits mediated by Renshaw cells inhibit contracting muscles (recurrent inhibition; for a review, see Katz and Pierrot-Deseilligny, 1999). We found insufficient evidence for systematic modulation of the phasic stretch reflex, the H-reflex, or inhibitory circuits by pain stimuli applied to the skin or muscle. The failure to detect systematic modulation of those reflexes does not necessarily imply that pain has no influence on the associated spinal circuits. Findings regarding these spinal reflexes – which are typically prone to methodological issues – were often highly variable and obtained from small samples. Nevertheless, there were some indications that the effects of pain may to some extent be mediated by inhibitory spinal circuits, e.g., through reinforcement of recurrent inhibition during contraction of a painful muscle (Rossi et al., 2003a) or through modulation of the Ib inhibitory pathway (Rossi et al., 1999a, 1999b; Rossi and Decchi, 1995, 1997). As it stands, it is not clear if this modulation depends on the origin of pain.

Muscle activity

The effects of experimentally induced pain on muscle activity have been examined at rest (Table S2.2: n=10), during isometric and dynamic contractions (Tables S2.3: n=23 and

Table S2.4: *n*=14) and during low-load repetitive work (Table S2.5: *n*=5). For isometric and dynamic contractions, the effects of pain on the activity of the (painful) agonist muscle, the non-painful synergists and the non-painful antagonists are presented in separate columns.

Experimentally induced pain generally did not affect resting muscle activity (Birznieks et al., 2008; Cobb et al., 1975; Fernández-Carnero et al., 2010; Ge et al., 2008; Graven-Nielsen et al., 1997a, 1997b; Madeleine and Arendt-Nielsen, 2005; Serrao et al., 2007; Svensson et al., 1998; Xu et al., 2010), but facilitated muscle cramps when latent myofascial trigger points were stimulated (Ge et al., 2008; Serrao et al., 2007; Xu et al., 2010). During both isometric and dynamic contractions, activity of the (painful) agonist (Birch et al., 2000b; Ciubotariu et al., 2004, 2007; del Santo et al., 2007; Ervilha et al., 2004a, 2004b, 2005; Falla et al., 2007, 2008, 2009, 2010; Farina et al., 2005a; Ge et al., 2005; Graven-Nielsen et al., 1997a; Henriksen et al., 2007, 2009a, 200b, 2011; Madeleine et al., 1999a, 1999b, 2006; Martin et al., 2008; Qerama et al., 2005) and its non-painful antagonist (Ervilha et al., 2004a, 2004b; Henriksen et al., 2009b; Madeleine et al., 1999b) generally was reduced by pain arising from the skin, joint, muscle, or tendon. However, parameters derived from the surface electromyography (sEMG) signal of these muscles (i.e., amplitude and median power frequency) often remained unaffected during contractions at a relatively low intensity, i.e., <25% of the maximum voluntary contraction (MVC) for muscles located in the upper or lower limb (Birch et al., 2000a; Farina et al., 2004a, 2005b, 2008; Hirata et al., 2010; Hodges et al., 2008; Madeleine and Arendt-Nielsen, 2005; Tucker and Hodges, 2009) and <15% MVC for muscles located in the shoulder-neck region (Diederichsen et al., 2009; Samani et al., 2010). During dynamic tasks, several findings indicated that inhibition of a muscle was most pronounced when activity was highest (Ervilha et al., 2004a, 2004b; Graven-Nielsen et al., 1997a; Henriksen et al., 2007, 2009a; Hodges et al., 2009). These findings suggest that the likelihood of a muscle being inhibited by pain may depend on its activation level: the stronger the activity, the more likely that its activity will be reduced. However, activity of the painful muscle remained unaffected despite a relatively high intensity of isometric contraction in four out of eight studies (Bandholm et al., 2008; Graven-Nielsen et al., 1997a; Madeleine and Arendt-Nielsen, 2005; Schulte et al., 2004).

Notably, findings at low intensity muscle contractions may depend on the applied EMG technique, since sEMG recordings failed to detect any pain-induced alterations (Birch et al., 2000a; Farina et al., 2004a, 2005b; Hodges et al., 2008; Schulte et al., 2004; Tucker et al., 2009), whereas imEMG recordings showed adaptations in motor unit firing and recruitment (Birch et al., 2000a; Farina et al., 2004a, 2005b, 2008; Hodges et al., 2008; Tucker et al., 2009; Tucker and Hodges, 2009, 2010). Several findings, including unaltered sEMG parameters following electrical stimulation of motor axons (Farina et al., 2005a; Qerama et al., 2005) and unaffected muscle fiber conduction velocity in four out of five studies (Farina et al., 2004a, 2005a, 2005b, 2008; vs. Schulte et al., 2004), indicated that alterations in muscle activation were due to central rather than peripheral effects of pain. Furthermore, several studies revealed signs of redistribution of activity, both within the (painful) agonist (Falla et al., 2008, 2009, 2010; Tucker et al., 2009; Tucker and Hodges, 2009, 2010) and among muscles involved in the task (Bandholm et al., 2008; Ciubotariu et al., 2004; Diederichsen et al., 2009; Ervilha et al., 2004b, 2005; Falla et al., 2007; Graven-Nielsen et al., 1997a; Hodges et al., 2009; Madeleine et al., 1999a, 1999b, 2008; Samani et al., 2009, 2010; Schulte et al., 2004). Reduced activation of painful muscles in some cases was compensated by activation of non-painful synergists (Bandholm et al., 2008; Ciubotariu et al., 2004; Diederichsen et al., 2009; Ervilha et al., 2004b, 2005; Madeleine et al., 1999b; Schulte et al., 2004). However, non-painful synergists often remained unaffected (Birch et al., 2000b; Henriksen et al., 2009a; Hodges et al., 2008; Schulte et al., 2004) or were inhibited just like the (painful) agonist (Ciubotariu et al., 2004, 2007; Ervilha et al., 2004a, 2004b, 2005; Henriksen et al., 2007, 2009b, 2011).

Task performance, movement kinetics and kinematics

The effects of experimentally induced pain on characteristics of motor control have been examined in terms of kinetics, kinematics and other indices of task performance during isometric contractions (Table S2.3: n=22), dynamic contractions (Table S2.6: n=23) and low-load repetitive work (Table S2.5: n=7).

The performance of various motor tasks mostly remained unimpaired by pain arising from skin, joint, muscle, or tendon. Subjects were able to produce a given submaximal

force level (Bandholm et al., 2008; del Santo et al., 2007; Farina et al., 2004a, 2005a, 2005b, 2008; Hodges et al., 2008; Madeleine and Arendt-Nielsen, 2005; Martin et al., 2008; Schulte et al., 2004; Tucker et al., 2009; Tucker and Hodges, 2009, 2010), which was often associated with reduced sEMG activity level of the (painful) agonist muscle (see *Muscle activity*). Maximum voluntary force production was reduced in four out of five studies (Graven-Nielsen et al., 1997a, 2002; Henriksen et al., 2010b; Slater et al., 2003; vs. Slater et al., 2005). In dynamic motor tasks, effects of pain were mostly reflected in the movement kinetics, e.g., in a reduction of peak moments around the joint upon which a painful muscle acted (Bonifazi et al., 2004; Henriksen et al., 2007, 2009a, 2009b, 2010a, 2010b), although impact force just after heel strike was unaffected by pain in a knee extensor muscle (Henriksen et al., 2008). Despite observed alterations in kinetics, changes in movement kinematics were absent (Diederichsen et al., 2009; Henriksen et al., 2007, 2008, 2009b; Maihöfner et al., 2007) or rather subtle (Bonifazi et al., 2004; Ervilha et al., 2004a, 2004b, 2005; Henriksen et al., 2009a, 2011; Jaberzadeh et al., 2003; Madeleine et al., 1998, 1999a, 1999b, 2008). The performance of computer work (Birch et al., 2000b, 2001; Samani et al., 2009, 2010) or manual dexterity tasks (Smith et al., 2006) was not deteriorated by experimentally induced muscle pain. During quiet standing, pain applied to the lower leg muscles led to weight shifting to the non-painful leg (Hirata et al., 2010). Postural stability was slightly reduced by severe pain induced in the bilateral upper trapezius muscles (Vuillerme and Pinsault, 2009) and by pain applied to cutaneous or muscular tissue of the lower leg (Blouin et al., 2003; Corbeil et al., 2004; Hirata et al., 2010; Madeleine et al., 1998, 1999b), but it remained unaffected by pain arising from other sources (Bennell and Hinman, 2005; Corbeil et al., 2004; Madeleine et al., 1999a, 2004).

Proprioception

The sense of positions and movements of one's body parts, as well as the perception of forces produced by muscles, are basic requirements for adequate motor control. Proprioception not only provides information about the internal state of a limb to facilitate movement planning, it also allows for more flexible movement control (Gentilucci et al., 1994; Park et al., 1999) and assists the voluntary control of goal-

directed movements, e.g., by triggering muscle activation sequences (Park et al., 1999) or by timing and coordinating movement sequences (Cordo et al., 1994).

Indications were found of a slight deterioration of proprioception (Table S2.7: *n*=8). Pain stimuli applied to skin or muscle caused a deterioration of movement sense – albeit not in all conditions (Matre et al., 2002; Weerakkody et al., 2008) – and the perception of produced force (Weerakkody et al., 2003). Although it has been reported that pain caused a distortion or loss of position sense (Rossi et al., 1998, 2003b), no quantitative evidence has been presented for impaired joint position sense (Bennell et al., 2005; Matre et al., 2002) or alterations in firing of muscle spindle afferents (Birznieks et al., 2008). Indications were found that muscle pain interfered with processing of other afferent signals from the muscle (Niddam and Hsieh, 2008; Rossi et al., 1998, 2003b). Although most studies did not include a direct comparison between the effects of cutaneous pain, joint pain and muscle pain, it appears that pain arising from muscle tissue may have more pronounced effects on proprioception than pain arising from (sub)cutaneous tissue (Weerakkody et al., 2003).

Brain activation

Since the emergence of functional brain imaging techniques, considerable efforts have been made to identify the cortical and subcortical structures that are activated by pain. Research has concentrated on examining brain activation in response to acute painful stimulation in healthy subjects lying quietly in a scanner. It is well known that pain activates cortical areas involved with perception of intensity and location of the painful stimulus, the regulation of emotional responses accompanying pain, and the distribution of attention (for a review, see Peyron et al., 2000). Although activation of motor-related areas (i.e., primary motor cortex, supplementary motor area, premotor area, cerebellum and/or basal ganglia) has occasionally been reported, this topic has mainly been regarded a side issue. Unfortunately, research has not yet focused on the effects of pain on brain activation patterns during movement planning or execution.

Several studies have addressed the interference between pain and cortical correlates of motor function by examining motor evoked potentials (MEPs) evoked by transcranial magnetic stimulation (TMS) or transcranial electric current stimulation (TECS) over the

primary motor cortex (Table 2.8: *n*=18). In general, MEP amplitude was reduced as a consequence of pain signals originating from skin (Farina et al., 2001; Fierro et al., 2010; Kaneko et al., 1998; Kofler et al., 1998, 2001; Tamburin et al., 2001; Uncini et al., 1991; Urban et al., 2004; Valeriani et al., 1999) or muscle (le Pera et al., 2001; Martin et al., 2008; Svensson et al., 2003), but in some studies it was found to be unaffected (Cheong et al., 2003; Fadiga et al., 2004; le Pera et al., 2001; Martin et al., 2008) or even elevated (Cheong et al., 2003; del Santo et al., 2007; Fadiga et al., 2004). In the case of distally localized pain, inhibition of MEPs evoked in the biceps brachii may be followed by excitation, probably reflecting preparations for hand withdrawal (Kofler et al., 1998, 2001; Urban et al., 2004). Painful stimulation at the hand sometimes caused modulation of corticospinal excitability of a muscle in the contralateral hand (Kofler et al., 2001; Valeriani et al., 1999) or arm (Hoeger Bement et al., 2009).

MEPs provide a measure of corticospinal excitability, which encompasses both cortical and spinal processes. In order to disentangle the effects of pain on cortical processes, assessment of MEPs should therefore be complemented by assessment of cervicomedullary motor evoked potentials (CMEP) or H-reflexes. Unfortunately, such measurements were present in only 5 out of 18 studies, and the results were inconclusive. The reduction of MEP amplitude induced by pain applied at the skin appears not attributable to decreased excitability of spinal motor neurons (Farina et al., 2001; Urban et al., 2004), whereas the reduction of MEP amplitude as a consequence of muscle pain may (partly) reflect decreased excitability of spinal rather than cortical motor neurons (le Pera et al., 2001; Svensson et al., 2003). In contrast, the findings of Martin et al. (2008) suggest that muscle pain may lead to decreased cortical excitability accompanied by opposing alterations at the spinal level.

Furthermore, studies analyzing electroencephalography (EEG) signals in terms of oscillation frequencies (Babiloni et al., 2008) or the exact timing of evoked potentials (Tarkka et al., 1992) provided indications of interference between pain and sensory-motor processes related to the planning and execution of movement (Table S2.8: *n*=2).

Discussion

This systematic review was conducted to obtain a better understanding of how pain affects motor behavior. Since it is unclear if pain from different tissues differentially affects the motor system, we evaluated the various sources of pain separately.

Notably, some motor components (spinal reflexes) were mainly examined by means of experimentally induced cutaneous pain, while others (muscle activity and movement characteristics) were predominantly examined by means of experimentally induced muscle pain (Figure 2.2). Although these differences hamper comparisons across studies, the observed effects on various components of the motor system were largely similar irrespective of the source of pain. Studies on spinal reflexes indicated differential influences of cutaneous pain and muscle pain, but due to the limited amount of available data and the heterogeneity of results it is not possible to draw firm conclusions in this regard.

Although some findings of this systematic review are congruent with existing models, others are not. In line with earlier reports (Arendt-Nielsen and Graven-Nielsen, 2008; Hodges and Tucker, 2011; Knutson, 2000), regardless of the pain source, we found no evidence of muscle hyperactivity as predicted by the 'vicious cycle model' (Johansson and Sojka, 1991; Travell et al., 1942). This model is based on the assumption that pain leads to muscle spasms, whereas evidence pointed at inhibition of painful muscles. The observed inhibition of the (painful) agonist muscle is consistent with the 'pain-adaptation model' (Lund et al., 1991). However, this model predicts excitation of antagonist muscles, for which no evidence was found in this review. On the contrary, a muscle's susceptibility to inhibition by pain seemed to depend on its activity state, rather than its function within a particular movement. Also the 'neuromuscular adaptation model', which predicts alterations in synergies, does not provide a conclusive explanation for the interaction between pain and motor control (Sterling et al., 2001). In particular, this model cannot account for the finding that the synergist's behavior often paralleled that of the (painful) agonist muscle. However, the theory on motor adaptation to pain recently proposed by Hodges and Tucker (2011) was largely in accord with our findings showing that pain affected many components of motor behavior mediated at multiple levels of the motor

system. Under circumstances of acute pain, the observed redistribution of activity within and among muscles as well as the (subtle) changes in mechanical behavior indeed seem to reflect adaptations leading to protection from further pain or injury. Hodges and Tucker (2011) intended to offer an explanation for the substantial variance observed between individuals and tasks, which resulted in a widely applicable theory. Given the relatively homogenous picture that emerges from the present review, it might be suggested that effects of short-lasting, experimentally induced limb pain can be described with higher specificity (Figure 2.3).

The majority of studies focused on the influence of pain on muscle activation during various types of contraction. Pain generally caused a reduction of activity of the (painful) agonist as well as non-painful synergists and antagonists, especially at higher intensity of contraction. Despite the influence of pain on muscle activation, the performance of various motor tasks mostly remained unimpaired, presumably as a result of redistribution of activity, both within the (painful) agonist and among muscles involved in the task. The finding that a given force level was associated with less sEMG activity in the painful muscle also pointed at compensation by other (not recorded) motor units or muscles. Effects of pain were mainly reflected in movement kinetics as a reduction of maximum force or peak moment, resulting in subtle alterations in movement kinematics. Although there were indications of a slight deterioration of proprioception, no evidence was found of detrimental effects on motor control. Given the observed activation-dependent inhibition of muscle activity, this sensory impairment is unlikely to play a major role in mediating the effects of pain on motor control because, if so, more complex alterations in timing and coordination of movement sequences would have been expected (Cordo et al., 1994).

Because muscle activation and movement characteristics are the result of many processes mediated at various levels of the motor system, their responses to pain do not allow identification of the exact mechanisms that underpin the interaction between pain and the motor system. Given that small diameter afferents have projections both at the spinal and the supraspinal level (Almeida et al., 2004; Millan, 1999), it is not surprising that motor control was found to be affected by pain at its most basic level, i.e., spinal reflexes, as well as its highest level, i.e., cortical processes related to movement planning

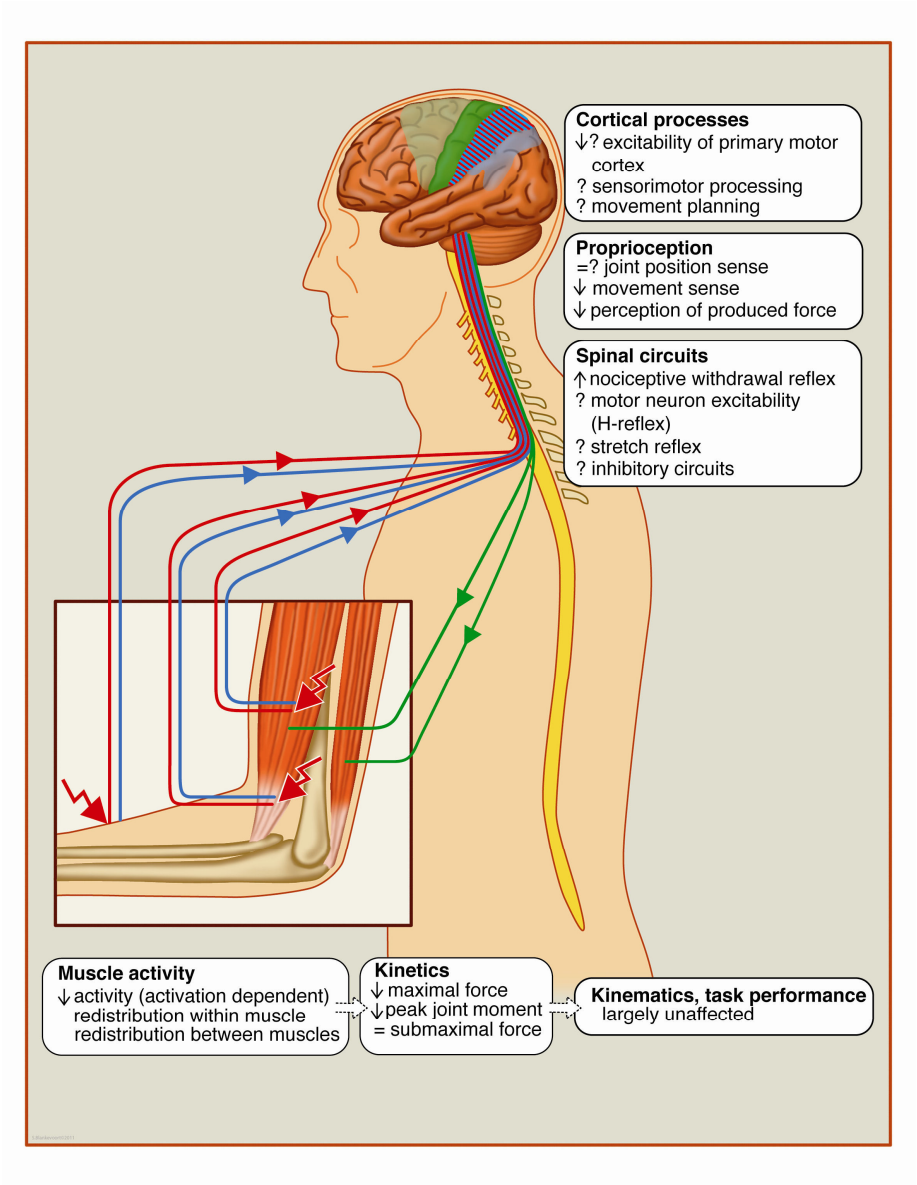


Figure 2.3 Motor consequences of experimental limb pain induced in skin, muscle or tendon. The main findings regarding the effects of nociceptive afferent signals (red) on motor control, which involves interaction between non-nociceptive afferent signals (blue) and motor efferent signals (green), are presented in text boxes. Dotted arrows between the lower three text boxes suggest a causal relationship between the effects of pain on muscle activity, kinetics and kinematics, but the relation between these parameters has not been directly addressed as such.

and execution. Findings regarding spinal reflexes were often highly variable and obtained from small samples. This may partly explain why we found limited evidence for systematic modulation of the H-reflex, the stretch reflex or inhibitory circuits. In contrast, pain caused a consistent modulation of the NWR, as has also been observed in animal research (Clarke and Harris, 2004).

At the highest level of motor control, EEG studies provided indications of pain interfering with cortical sensory-motor processes related to movement planning and execution. Studies using TMS or TECS over the primary motor cortex showed that pain arising from skin or muscle leads to reduced excitability of the corticospinal motor pathway. The question remains, however, if and to what extent these changes are attributable to altered spinal excitability. Attempts to disentangle the cortical and spinal contributions to alterations in corticospinal excitability have been made in a limited number of studies, which provided inconclusive results. Unfortunately, studies using functional brain imaging techniques have focused on brain activation at rest (Peyron et al., 2000), leaving the issue of how pain affects brain activation during movement planning or execution unaddressed.

The research on experimentally induced pain covered in this review delineates the effects of acute and transient pain stimuli on motor control and allowed to disentangle the intricate cause-and-effect relation between pain and movement. However, the findings cannot be translated to clinical pain conditions (Edens and Gil, 1995) which likely are associated with long-term adaptations to pain, a key aspect of the theory proposed by Hodges and Tucker (2011). Additionally, clinical pain conditions are commonly associated with structural damage that may induce additional effects on movement. Moreover, emotional and cognitive responses to (chronic) pain may greatly affect motor control, e.g., movement strategies may be altered by fear of pain (Vlaeyen and Linton, 2000). Such responses, if present, are probably different in experimental conditions as participants are aware that the pain will quickly resolve. Also, in some studies, participants were made familiar with the nociceptive stimulus prior to the experimental session in order to minimize a potential emotional component of the pain.

Many other factors affect the impact of pain on motor function as well, e.g., the severity, duration and location of pain, additional activation of non-nociceptive afferents,

and the state of the motor system (i.e., at rest or during planning or execution of movement). Unraveling the impact of pain on motor function thus requires diligent experimental control of many factors, which represents a major methodological challenge. Moreover, similar to gender differences in perception and tolerance of pain (Fillingim et al., 2009; Racine et al., 2012), the results of several studies suggest that gender-specific factors may influence the motor responses to pain (Falla et al., 2008, 2010; Ge et al., 2005; Madeleine et al., 2006). However, only two studies explicitly assessed potential gender-specific differences in motor consequences of pain. Surprisingly, the potential influence of this factor on the results was not addressed in the majority of studies (e.g., gender distribution was not reported in 23% of studies).

As regards the overall picture emerging from the studies included in this review, several limitations have to be acknowledged. Firstly, sample size was typically small (ranging from 1 to 36 subjects, with only 48% of the studies including more than 10 subjects). Secondly, 63% of the studies lacked an appropriate condition to control for possible non-nociceptive effects of pain stimuli. Thirdly, research has concentrated on relatively easily accessible aspects of motor function (i.e., muscle activity and movement characteristics; Figure 2.1), culminating in a limited number of coherent parameters. Several findings indicated that the observed changes result from central rather than peripheral effects of pain. Due to methodological issues and heterogeneity regarding outcome parameters, however, findings remained largely inconclusive for parameters that may provide insight into processes mediating the effects of pain at different levels of the central nervous system (i.e., spinal reflexes and cortical correlates of motor function). This motivates future examination of the impact of pain on spinal reflexes and cortical correlates of motor function, taking special care of methodological considerations. In this context, it should be noted that research on the effects of pain on spinal reflexes and brain activation has mainly focused on the motor system at rest. For a full appreciation of the interaction between pain and motor control, it is essential to examine the effects of pain on spinal reflexes and brain activation not only at rest, but also during movement planning and execution.

Acknowledgment

The authors thank Jan Schoones of the Walaeus Library for his help with the literature search.

Supplement 2.1: Search strategy

The search strategy was optimized for each of the consulted databases, taking into account the database-specific technical variations. The search terms used for Pubmed are presented below. The search terms used for the other databases are published online at http://onlinelibrary.wiley.com/doi/10.1002/j.1532-2149.2012.00186.x/suppinfo

Pubmed search terms

("motor system"[tw] OR "motor neurons"[mesh] OR "motor neuron"[tw] OR "motor neurons"[tw] OR "motoneuron"[tw] OR "motoneurons"[tw] OR "Motor Cortex"[mesh] OR "Motor Cortex"[tw] OR "Motor area" [tw] OR "premotor cortex"[tw]OR "premotor area"[tw] OR "cerebellum"[mesh] OR "cerebellum"[tw] OR "supplementary motor area"[tw] OR "basal ganglia"[mesh] OR "basal ganglia"[tw] OR "Evoked Potentials, Motor"[mesh] OR "motor evoked potentials"[tw] OR "motor evoked potential"[tw] OR "muscle tonus"[mesh] OR "muscle tone"[tw] OR "muscle activity"[tw] OR "muscle activation"[tw] OR "muscular activity"[tw] OR "muscular activation"[tw] OR "motor unit"[tw] OR "motor units"[tw] OR "muscle contraction"[tw] OR "muscle contractions"[tw] OR "Muscle Contraction"[mesh:noexp] OR "Excitation Contraction Coupling"[mesh] OR "Isometric Contraction"[mesh] OR "Isotonic Contraction"[mesh] OR "Muscular Contractions"[tw] OR "Muscular Contraction"[tw] OR "Muscle Strength"[mesh] OR "Muscle Strength"[tw] OR "maximal voluntary contraction"[tw] OR "maximal voluntary contractions"[tw] OR (("motor function"[tw] OR "motor task"[tw] OR "motor tasks"[tw] OR "movement"[tw] OR gait[tw])

AND ("kinetics"[tw] OR "kinetic analysis"[tw] OR "kinetic parameters"[tw] OR "kinematics"[tw] OR "kinematic analysis"[tw] OR "kinematic parameters"[tw] OR "EMG"[tw] OR "electromyography"[tw])) OR (excitability[tw] AND motor[tw]) OR "EMG-activity"[tw] OR "motor control"[tw] OR "neuromuscular control"[tw] OR "activation pattern"[tw] OR "activation patterns"[tw] OR "motor pattern"[tw] OR "motor

patterns"[tw] OR ((coordination[tw] OR "co-ordination"[tw] OR timing[tw] OR strategy[tw]) AND (muscle[tw] OR movement[tw] OR motor[tw])) OR "Neuromuscular adaptation"[tw] OR "proprioceptive sense"[tw] OR "proprioceptive senses"[tw] OR propriocepsis[tw] OR "proprioception"[mesh] OR proprioception OR kinesthesia[tw] OR kinaesthesia[tw] OR proprioreceptor[tw] OR proprioreceptors[tw] OR "muscle spindle"[tw] OR "muscle spindles"[tw] OR "stretch reflex"[tw] OR "stretch reflexes"[tw] OR "golgi tendon organ"[tw] OR "golgi tendon organs"[tw] OR "movement sense"[tw] OR "position sense"[tw])

AND ("induced pain"[tw] OR "experimental muscle pain"[tw] OR "experimental pain"[tw] OR (("pain induced" OR "induced pain") AND (experimentally OR "chemical"[tw] OR "chemically"[tw] OR "mechanical"[tw] OR "mechanically"[tw] OR "pinprick"[tw] OR "pressure"[tw] OR "thermal"[tw] OR "thermally" OR "electrical"[tw] OR "electrically"[tw])) OR ((nociceptive[tw] OR noxious[tw]) AND ("cutaneous stimulus"[tw] OR "cutaneous stimuli"[tw] OR "cutaneous stimulation"[tw])) OR ((capsaicin[tw] OR "capsaicin"[mesh] OR "hypertonic saline"[tw] OR "Saline Solution, Hypertonic"[mesh] OR "laser evoked potential"[tw] OR "laser evoked potentials"[tw] OR "intramuscular glutamate"[tw]) AND pain) OR "painful stimuli"[tw] OR "painful stimuli"[tw] OR "chemical pain" OR "mechanical pain" OR "electrical pain" OR "thermal pain" OR "pressure pain"[tw] OR "heat pain"[tw])

NOT (animal NOT human) AND (English[lang] OR French[lang] OR German[lang] OR Dutch[lang])

Supplement 2.2: Overview of included studies

All studies fulfilling the inclusion criteria are presented in Tables S2.1-2.8 on p. 37-60, which summarize the results on the effects of (sub)cutaneous pain, joint pain, muscle pain and tendon pain.

Supplement 2.3: Results

A detailed description of the results can be found online.
(http://onlinelibrary.wiley.com/doi/10.1002/j.1532-2149.2012.00186.x/suppinfo)

Table S2.1 Effects of experimentally induced pain on spinal reflexes

Reference [a]	*N*	(♂/♀)	Pain Method [b]	Intensity [c]	Location [d]	Reflex Location [e]	Results
Nociceptive withdrawal reflex							
(Sub)cutaneous pain							
Andersen et al., 1994	12	(12/0)	TH	● – ●●● [NR]	Foot sole [4]	TA	↑
Andersen et al., 1995	8	(?)	CH+MC/TH	●● [NR]	Foot dorsum [4]	BF/RF	↑
Ellrich and Treede, 1998	11	(6/5)	TH	NR	Foot sole [4]	TA	↑
Ellrich et al., 2000	2	(?)	TH	NR	Foot sole [4] (distal/middle/proximal)	TA	↑ / ↑ / ↑
					Foot sole [4] (distal/middle/proximal)	BF	↑ / ↑ / ↑
	1	(?)	TH	NR	Foot dorsum [4] (standing)	TA / BF	↑ / ↑
Grönroos and Pertovaara, 1993	5	(?)	CH⁺	● [NR]	Foot dorsum [5]	BF	↑ *
			CH	● [NR]	Above medial malleolus [5]	BF	↑ *
	1	(?)	CH	● [NR]	Foot dorsum [C, 5]	BF	↑ *
					Hand dorsum [C, 5]	BF	=
Roby-Brami et al., 1987	5	(4/1)	EL	●●● [NR]	Finger IV+V [C, 4]	BF	↓
Serrao et al., 2004	36	(16/20)	TH	●●● [NR]	Hand [C, 5]	BF	↓
Terkelsen et al., 2001	12	(12/0)	TH	NR	Foot [C, 5]	BF	↓
					Hand [C, 5]	BF	↓
Willer et al., 1984	10	(8/2)	TH	● – ●●● [NR]	Hand [C, 5]	BF	↓ *
Willer et al., 1989	11	(3/8)	TH	● – ●●● [NR]	Hand [C, 5]	BF	↓ *
Muscle pain							
Andersen et al., 2000	12	(12/0)	CH	●● [P]	TA [5]	ST	↑
					SOL [5]	ST	↓
Andersen et al., 2006	18	(?)	EL	● [M]	TA [5]	ST	↑
Ge et al., 2007	12	(10/2)	EL	●●● [M]	TA [5]	ST	↓
	10	(8/2)			TA [C,5]	ST	↓
	10	(8/2)			TZ [5]	ST	↓

Table S2.1 Effects of experimentally induced pain on spinal reflexes *(continued)*

Reference [a]	*N*	(♂/♀)	Pain Method [b]	Intensity [c]	Location [d]	Reflex Location [e]	Results
Phasic stretch reflex							
Muscle pain							
Matre et al., 1998	14	(14/0)	CH [+]	●● [M]	SOL	SOL / active SOL	↑ / ↑
	9	(9/0)	CH [+]	●● [M]	TA	SOL / active SOL	↑ / ↑
Matre et al., 1999	10	(10/0)	CH [+]	●●● [M]	SOL	SOL / active SOL	↑ / =
H-reflex							
(Sub)cutaneous pain							
Andersen et al., 1994 [1]	3	(3/0)	TH	● – ●● [NR]	Foot sole	SOL	=
Andersen et al.,1995 [1,2]	8	(?)	CH	NR	Foot dorsum	SOL	=
Ellrich and Treede, 1998 [2]	1	(?)	TH	NR	Foot sole	TA / SOL	↓ / =
Ellrich et al., 2000 [2]	2	(?)	TH	●●● [NR]	Foot sole (distal/middle/proximal)	SOL	↑ / = / ↓
					Foot sole (distal/middle/proximal)	PM	↑ / = or ↓ / = or ↓
Farina et al., 2001 [1]	6	(4/2)	CH	● [P]	FCR	FCR	=
Grönroos and Pertovaara, 1993 [1,2]	4	(?)	CH	● [M]	Lower leg, posterior-distal	SOL	=
Rossi and Decchi, 1995 [1]	4	(?)	CH	●●● [P]	Foot dorsum	SOL / Q	↑= / ↑=
Rossi et al., 1996 [1]	1	(?)	EL	● [NR]	Foot sole	TA	↑
Rossi and Decchi, 1997 [1]	5	(?)	CH	●●● [P]	Above EDB	SOL	↑
					Above TA	SOL	↑
Urban et al., 2004 [1,3]	10	(5/5)	EL	NR	Finger II	APB / BB	↑ / ↑
Willer et al., 1989 [1,2]	11	(3/8)	TH	● – ●●● [NR]	Hand [C]	SOL	=
Muscle pain							
Ge et al., 2007 [1]	11	(?)	EL	●●● [M]	TA	SOL	=
Le Pera et al., 2001 [1,2]	11	(8/3)	CH [+]	●● [P]	FCR	FCR	↓
Matre et al., 1998 [1,2,3]	7	(7/0)	CH [+]	●● [M]	SOL	SOL / active SOL	= / =
				●● [M]	TA	SOL / active SOL	= / =

H-reflex *(continued)*							
Muscle pain (continued)							
Rossi and Decchi, 1997 [1]	5	(?)	CH	●●● [P]	EDB	SOL	↓
					TA	SOL	↓
Rossi et al., 1999a [1]	3	(?)	CH	●●● [P]	EDB	SOL / Q	↓ / ↑=
Rossi et al., 1999b [1]	5	(3/2)	CH	●●● [P]	EDB	SOL	↓
Rossi et al., 2003a [3]	7	(?)	CH	●●● [P]	SOL	SOL / active SOL	↑ * / ↑ *
Ib inhibitory pathway							
(Sub)cutaneous pain							
Rossi and Decchi, 1995	4	(?)	CH	●●● [P]	Foot dorsum	SOL / Q	↑ * / ↑ *
Rossi and Decchi, 1997	5	(?)	CH	●●● [P]	Foot dorsum (above EDB)	SOL	↑ *
					Above TA	SOL	=
Muscle pain							
Rossi and Decchi, 1997	5	(?)	CH	●●● [P]	EDB	SOL	↓ *
					TA	SOL	↑↓
Rossi et al., 1999a	3	(?)	CH	●●● [P]	EDB	SOL / Q	↓ * / ↓ *
Rossi et al., 1999b	5	(?)	CH	●●● [P]	EDB	SOL	↓ *
Recurrent inhibition							
Muscle pain							
Rossi et al., 2003a	7	(?)	CH	●●● [P]	SOL	SOL / active SOL	↑ * / =
Cutaneous silent period							
(Sub)cutaneous pain							
Inghilleri et al., 1997	6	(?)	EL	NR	Finger IV+V	FDI	=
Uncini et al., 1991	8	(5/3)	EL	NR	Finger II	OP	=
Vibration-induced flexion reflex							
(Sub)cutaneous pain							
Takakura et al., 2004	12	(9/3)	EL	●●● [NR]	Hand dorsum	Finger II	↓

[a] Methodological aspects of studies on the H-reflex are indicated by [1] appropriate stimulus intensity; [2] constant size of the M-wave; [3] low level voluntary muscle activation; [b] Pain was induced chemically (CH), electrically (EL), mechanically (MC) or thermally (TH), with [+] indicating the presence of a non-nociceptive control condition; [c] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; NR = not reported; [d] The nociceptive withdrawal reflex was elicited by painful stimulation of the foot sole or sural nerve ([4]) or by painful stimulation of the foot dorsum or tibial nerve ([5]); [e] Reflexes were studied in passive muscles, unless indicated otherwise.

APB, abductor pollicis brevis; BB, biceps brachii; BF, biceps femoris; ECR, extensor carpi radialis; EDB, extensor digitorum brevis; FCR, flexor carpi radialis; FDI, first dorsal interosseous; OP, opponens pollicis; PM, foot plantar muscles; Q, quadriceps; RF, rectus femoris; SOL, soleus; ST, semitendinosis; TA, tibialis anterior; TZ, trapezius; [C] contralateral; ↑ and ↓ indicate significant ($p<0.05$) facilitation and inhibition of reflexes, '↑=' indicates a transient facilitation, '=' indicates the absence of significant effects, and * indicates that findings correlate with subjective pain sensation.

Table S2.2 Effects of experimentally induced pain on muscle activity at rest

Reference	*N*	(♂/♀)	Pain Method [a]	Intensity [b]	Location	Results Muscle activity	Cramp provocation
(Sub)cutaneous pain							
Birznieks et al., 2008	15	(11/4)	CH	●● ^{P}	Above TA	= ^{S}	No
Muscle pain							
Birzinieks et al., 2008	15	(11/4)	CH	●● ^{P}	TA	= ^{S}	No
Cobb et al., 1975	6	(?)	CH	●● – ●●● ^{P}	ECR	↑ ^{S} *	No
	1	(?)	CH	●● – ●●● ^{P}	ECR	↑ ^{S} *, = ^{IM}	No
Fernández-Carnero et al., 2010	12	(10/2)	CH $^{+}$	●● ^{P}	IS – MTrP	= ^{S,IM}	No
Ge et al., 2008	14	(10/4)	CH $^{+}$	●●● ^{P}	GM – MTrP	↑ ^{S,IM}	Yes
				●● ^{P}	GM – non-MTrP	= ^{S,IM}	No
Graven-Nielsen et al., 1997a	9	(9/0)	CH $^{+}$	●● ^{P}	TA	= ^{S}	No
Graven-Nielsen et al., 1997b	6	(?)	CH $^{+}$	●● ^{P}	TA	= ^{IM}	No
Madeleine and Arendt-Nielsen, 2005	12	(12/0)	CH $^{+}$	●● ^{M,P}	BB	= ^{S}	No
Serrao et al., 2007	13	(6/7)	CH $^{+}$	●● ^{P}	FHB	= $^{S, M}$	Yes
Svensson et al., 1998	10	(10/0)	CH $^{+}$	●● ^{P}	TA	↑= ^{S,IM}	No
Xu et al., 2010	12	(8/4)	MC	●●● ^{P}	EDC – MTrP	↑ ^{S,IM} *	Yes
				●● ^{P}	EDC – non-MTrP	= ^{S,IM}	No

[a] Pain was induced chemically (CH) or by mechanical stimulation (MC), with $^{+}$ indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; ^{M} = mean pain; ^{P} = peak pain;

BB, biceps brachii; ECR, extensor carpi radialis; EDC, extensor digitorum communis; FHB, flexor hallucis brevis; GM, gastrocnemius; IS, infrasupinatus; TA, tibialis anterior; MTrP, (latent) myofascial trigger point; ^{IM} intramuscular EMG recordings; ^{S} surface EMG recordings; ↑ and ↓ indicate significant (p<0.05) increase and decrease, '↑=' indicates a transient increase, '=' indicates the absence of significant effects, and * indicates that findings correlate with subjective pain sensation.

Table S2.3 Effects of experimentally induced pain on muscle activity and performance during isometric contractions

Reference	*N*	(♂/♀)	Pain			Task [c]			Results			
			Method [a]	Intensity [b]	Location	Contraction	Intensity (% MVC)	Duration (s)	Agonist Amplitude / Frequency	Synergist Amplitude	Antagonist Amplitude	Performance [d]
Joint pain												
Henriksen et al., 2010b	17	(9/8)	CH [+]	●● [M]	IFP	FL knee	100	NR				↓[*] torque
						EX knee	100	NR				↓[*] torque
Tucker and Hodges, 2009	8	(4/4)	CH	●●● [M]	IFP	EX knee	"low"	10-20		↓[IM]		= force [#]
Tucker et al., 2009	7	(?)	CH	●●● [M]	IFP	EX knee	≈ 7	30	=[S]	↓[IM]		= force, SD
Tucker and Hodges, 2010	9	(?)	CH	●● [M]	IFP	EX knee	"low"	10		↓[IM]		= force [#]
	6	(?)	CH	●● [M]	IFP	EX knee	"low"	10		↓[IM]		= force [#]
Muscle pain												
Bandholm et al., 2008	9	(?)	CH	●● [M]	SU	AB arm (90°)	20, 27.5, 35	10	=[S]	↑[S] DLa, =[S] IS, =[S] TZl, TZu, =[S] DLm	=[S] LD, SA	↑ SD = CV
Birch et al., 2000a	9	(0/9)	CH	●● [P]	ECU	EX wrist	0→10	10	=[IM]	=[IM]		= force [#]
							10	60	=[IM]	=[IM]	=[S] ECR, =[S] FCR	= force [#]
Ciubotariu et al., 2004	10	(6/4)	CH	●●● [P]	TA	DFL ankle	50, 80	max (≈133, 51)	↓[S]	↓[S]	↓[S] EHL, =[S] GM, GL, =[S] SOL	↓ torque ↓ T_{end}
				●●● [P]	GL	PFL ankle	50, 80	max (≈301, 85)	↓[S]	↓[S]	↓[S] GM, ↑[S] SOL, =[S] TA, EHL	↓ torque ↓ T_{end}
Ciubotariu et al., 2007	10	(6/4)	CH	●–●● [M,P]	TA	DFL ankle	0→80	3	↓[S]		↓[S] EHL	= torque [#]
							100	3	↓[S]		↓[S] EHL	= torque
	10	(6/4)	CH	●–●● [M,P]	GL	PFL ankle	0→80	3	↓[S]		↓[S] GM, =[S] SOL	= torque [#]
							100	3	↓[S]		↓[S] GM	= torque
del Santo et al., 2007	8	(5/3)	CH	●●● [P]	ADM	AB finger V	30	5	↑[S] *			= force ↑CV
				●●● [P]	BB	FL elbow	30	5	↓[S] *			= force ↑CV

Muscle pain (continued)											
Falla et al., 2008	9	(9/0)	CH $^{+}$	●● ^{P}	TZu	AB arm (90°)	≈ 15-20	60	↓^{S}	↓^{S}	
	9	(0/9)	CH $^{+}$	●●● ^{P}	TZu	AB arm (90°)	≈ 15-20	60	↓^{S}	↓^{S}	
Falla et al., 2009	9	(9/0)	CH $^{+}$	●● ^{P}	TZu	AB arm (90°)	≈ 15-20	60	↓^{S}		
Falla et al., 2010	10	(0/10)	CH $^{+}$	●●● ^{P}	TZu	AB arm (90°)	≈ 15-20	60	↓^{S}	=^{S}	
Farina et al., 2004a	12	(5/7)	CH $^{+}$	●–	TA	DFL ankle	10	20	=^{S}	=^{S}	= torque$^{\#}$
				●●● ^{M,P}						↓^{IM} *	= SD
Farina et al., 2005a	12	(6/6)	CH $^{+}$	●–●● ^{M,P}	TA	DFL ankle	30	10	↓^{S} *	=^{S}	= torque$^{\#}$
Farina et al., 2005b	11	(7/4)	CH $^{+}$	●● ^{M,P}	TA	DFL ankle	25	240	=^{S}	=^{S}	= torque$^{\#}$
										↓^{IM}	
Farina et al., 2008	16	(11/5)	CH $^{+}$	●● ^{M,P}	TA	DFL ankle	10	15		↓^{IM} *	= torque$^{\#}$
							≈ 4.4	180	=^{S}	=^{IM} $^{\#}$	= torque
Ge et al., 2005	10	(10/0)	CH $^{+}$	●●● ^{P}	TZu^{B}	AB arm (90°)	≈ 15-20	5	↓^{S}	↓^{S}	
								180	↑^{S}	↑^{S}	
	9	(0/9)	CH $^{+}$	●●● ^{P}	TZu^{B}	AB arm (90°)	≈ 15-20	5	↓^{S}	=^{S}	
								180	=^{S}	=^{S}	
Graven-Nielsen et al., 1997a	19	(19/0)	CH $^{+}$	●● ^{P}	TA	DFL ankle	80	max (≈31)	=^{S}	=^{S}	= torque$^{\#}$
											↓T_{end}
	9	(9/0)	CH $^{+}$	●● ^{P}	TA	DFL ankle	100	4	↓^{S} *	=^{S}	↓* torque$^{\#}$
Graven-Nielsen et al., 2002	8	(5/3)	CH $^{+}$	● ^{A}	RF	EX knee	100	4			↓ torque$^{\#}$
Hodges et al., 2008	10	(10/0)	CH	●● ^{P}	GL	PFL ankle	“low”	20	=^{S}	↓^{IM} (N=1)	=^{S} GM, SOL ↓^{IM} GM, SOL	= force$^{\#}$
Jaberzadeh et al., 2003	12	(7/5)	CH	●● ^{M}	EDC	EX finger III	“low”	120				= tremor
Madeleine and ‘rendt-Nielsen, 2005	12	(12/0)	CH $^{+}$	●● ^{M,P}	BB	FL elbow	10, 30, 50, 70	5	=^{S}	=^{S}		= force$^{\#}$ = SD
							0→50	25	=^{S}	=^{S}		= force$^{\#}$

Table S2.3 Effects of experimentally induced pain on muscle activity and performance during isometric contractions *(continued)*

Reference	*N*	(♂/♀)	Pain			Task			Results			
			Method [a]	Intensity [b]	Location	Contraction [c]	Intensity (% MVC)	Duration (s)	Agonist Amplitude / Frequency	Synergist Amplitude	Antagonist Amplitude	Performance [d]
Muscle pain (continued)												
Madeleine et al., 2006	10	(10/0)	CH +	●● M	TZu	AB arm (90°)	≈ 15-20	90	↓ S	= S		
Martin et al., 2008	7	(?)	CH	●● P	BB	FL elbow	20	20	↓ S			= torque
Qerama et al., 2005	18	(?)	CH	●● P	BB	FL elbow	100	3	↓ IM	↓ IM		
	14	(?)	CH	●● P	BB	FL elbow	100	3	↓ IM	↓ IM		
Schulte et al., 2004	15	(13/2)	CH +	●● P	BB	FL elbow	40	max (≈89)	= S	= S	= S BR, DL, ↑ S TZu	= force # = CV, T_{end}
							40	10	= S	= S	= S BR, DL, ↑ S TZu	= force #
							100	3	= S	= S	= S BR, DL, ↑ S TZu	= force = CV
Slater et al., 2003	12	(6/6)	CH +	●● P	ECR	EX wrist	100	NR				↓ * force
				●●● P	SUP	EX wrist	100	NR				↓ force
	12	(5/7)	CH	●●● P	ECR	EX wrist	100	NR				↓ force
Slater et al., 2005	20	(10/10)	CH	●●● P	ECR	EX wrist	100	NR				= force
						Hand grip	100	NR				= force
Tucker et al., 2009a	7	(6/1)	CH	●● M	FPL	FL thumb	≈ 1.5	10-20		↓ IM	= IM EPL	= torque #
Tendon pain												
Slater et al., 2003	12	(6/6)	CH	●●● P	CEO	EX wrist	100	NR				↓ force

[a] Pain was induced chemically (CH), with [+] indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; [A] = mean pain as calculated from area under the VAS curve; [c] AB, abduction; DFL, dorsal flexion; EX, extension; FL, flexion; MVC, maximum voluntary contraction; PFL, foot plantar flexion; [d] Effects on task performance are described by $T_{end,}$ endurance time; SD, standard deviation; CV, coefficient of variance; [#] used as target value.

ADM, abductor digiti minimi; BB, biceps brachii; BR, brachioradialis; CEO, common extensor origin; DL, deltoideus; DLa, anterior deltoideus; DLm, middle deltoideus; ECR, extensor carpi radialis; ECU, extensor carpi ulnaris; EDC, extensor digitorum communis; EHL, extensor hallucis longus; EPL, m extensor pollicis longis; FCR, flexor carpi radialis; FPL, flexor pollicis longis; GL, lateral gastrocnemius; GM, (medial) gastrocnemius; IS, infraspinatus; IFP, infrapatellar fat pad; LD, latissimus dorsi; RF, rectus femoris; SA, serratus anterior; SOL, soleus; SU, supraspinatus; SUP, supinator; TA, tibialis anterior; TZl, lower trapezius; TZu, upper trapezius; [B] bilateral; [IM] intramuscular EMG recordings; [S] surface EMG recordings; ↑ and ↓ indicate significant ($p<0.05$) increase and decrease, '=' indicates the absence of significant effects, 'NR' denotes 'not reported' and * indicates that findings correlate to subjective pain sensation.

Table S2.4 Effects of experimentally induced pain on muscle activity during dynamic contractions

Reference	*N*	(♂/♀)	Pain Method [a]	Intensity [b]	Location	Task description [c]	Results [d, e] Agonist	Synergist	Antagonist
Joint pain									
Hodges et al., 2009	10	(3/7)	CH	●● – ●●● [P]	IFP	EX knee (stair up)	↓[S] VL, =[S] VM (delayed *)		
						EX knee (stair down), eccentric	=[S] VL , VM		
Muscle pain									
Bandholm et al., 2008	9	(?)	CH	●● [M]	SU	AB arm, 20-35% MVC	=[S] ***SU***	↑[S] IS, TZl ** =[S] DL, TZu	=[S] LD, SA
						AB arm, 20-35% MVC, eccentric	=[S] ***SU***	=[S] IS, TZl, =[S] DL, TZu	=[S] LD, SA
Diederichsen et al., 2009	11	(11/0)	CH	●● [P]	SU	AB arm, 10% MVC	=[IM] ***SU***	↓[S] IS, Dla, Tzu, ↑[S] TZl, =[S] DLm	↑[S] LD, =[S] SA
Ervilha et al., 2004a	15	(11/4)	CH	● [M]	BB	FL elbow	↓[S] ***BB*** **	↓[S] BR, =[S] TZ	↓[S] TB
Ervilha et al., 2004b	10	(7/3)	CH	●● [M]	BB	FL elbow	↓[S] ***BB*** **	↓[S] BR, ↑[S] TZ (before start)	↓[S] TB
					TB		↓[S] ***BB*** **	↓[S] BR, ↑[S] TZ (before start)	↓[S] ***TB***
				● [M]	BB	FL elbow	=[S] ***BB*** **	=[S] BR	=[S] TB
					TB		=[S] BB	=[S] BR	=[S] ***TB***
	15	(13/2)	CH	● [M]	BB	FL elbow	=[S] ***BB*** (low accuracy ↓**)	=[S] BR	=[S] TB
					TB		=[S] BB (low accuracy ↓**)	=[S] BR	=[S] ***TB***
Ervilha et al., 2005	10	(6/4)	CH [+]	●● [M]	BB	FL elbow, repeated (120s)	↓[S] ***BB***	↓[S] BR ** ↑[S] TZu	=[S] TB
				●●● [M]	BB + TB		↓[S] ***BB***	↓[S] BR ** ↑[S] TZu	=[S] ***TB***

Muscle pain (continued)								
Ervilha et al., 2005, *continued*	10	(6/4)	CH $^{+}$	●● ^{M}	BB	EX elbow, repeated (120s)	= ^{S} TB	↑^{S} TZu	↓^{S} BR ** = ^{S} ***BB***
				●●● ^{M}	BB + TB		= ^{S} ***TB***	↑^{S} TZu	= ^{S} BR, ***BB***
Falla et al., 2007	9	(5/4)	CH $^{+}$	●●● ^{P}	TZu	FL shoulder, rhythmic (150s)	↓^{S} ***TZu***	↑^{S} TZl, TZu ^{C} = ^{S} TZm ^{B}, TZl ^{C}	
Graven-Nielsen et al., 1997a	10	(10/0)	CH $^{+}$	●● ^{P}	TA	Walking	= ^{S} ***TA***		↑^{S} GM (stance)
					GM		↑^{S} ***GM*** (after toe-off)		↓^{S} TA (stance)
Henriksen et al., 2009a	15	(9/6)	CH $^{+}$	●●^{M}	GLUTmd	Walking	↓^{S} ***GLUTmd*** **	= ^{S} VM, VL, ST = ^{S} BF, GLUTmx	
Henriksen et al., 2007	20	(10/10)	CH $^{+}$	●● ^{M}	VM	Walking	↓^{S} ***VM*** (before heel strike) ↓^{S} ***VM*** (stance eccentric) = ^{S} ***VM*** (stance concentric)	↓^{S} VL (before heel strike) = ^{S} VL (stance)	= ^{S} BF, ST
Henriksen et al., 2009b	20	(10/9)	CH $^{+}$	● ^{M}	VM	Forward lunge, contact phase	↓^{S} ***VM***	↓^{S} VL	↓^{S} BF, ST
Hirata et al., 2010	9	(5/4)	CH $^{+}$	●● ^{P}	TA	Standing, static or with perturbations	= ^{S} ***TA*** ^{B}		= ^{S} GM ^{B}
				●●● ^{P}	GM		= ^{S} ***GM*** ^{B}		= ^{S} TA ^{B}
				●●● ^{P}	GM + TA		= ^{S} ***GM*** ^{B}***, TA*** ^{B}		
Madeleine et al., 1999b	6	(6/0)	CH	●● ^{P}	TA	Forward stepping (leading leg)	↓^{S} ***TA*** **	↑^{S} TA ^{C} (before start) = ^{S} GM ^{C}, SOL ^{B} = ^{S} VL ^{B}, BF ^{B}	↓^{S} GM **
Tendon pain									
Henriksen et al., 2011	16	(8/8)	CH $^{+}$	● ^{M}	AT	PLF ankle, standing rhythmic	↓^{S} SOL	↓^{S} GL, GM, ↓^{S} PL, PB	↓^{S} TA

Footnote on p. 48

[a] Pain was induced chemically (CH), with [+] indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; [c] AB, abduction; EX, extension; FL, flexion; MVC, maximum voluntary contraction; PLF, foot plantar flexion; [d] Painful muscles are printed in ***bold italics***; [e] Results pertain to muscles ipsilateral to the side of pain, unless indicated otherwise.

AT, Achilles tendon; BB, biceps brachii; BF, biceps femoris; BR, brachioradialis; DL, deltoideus; DLa, anterior deltoideus; DLm, middle deltoideus;GL, lateral gastrocnemius; GLUTmd, gluteus medius; GLUTmx, gluteus maximus; GM, (medial) gastrocnemius; IFP, infrapatellar fat pad; IS, infraspinatus; LD, latissimus dorsi; PB, peroneus brevis; PL, peroneus longus; SA, serratus anterior; SOL, soleus; ST, semitendinosis; SU, supraspinatus; TA, tibialis anterior; TB, triceps brachii; TZl, lower trapezius; TZm, middle trapezius; TZu, upper trapezius; VL, vastus lateralis; VM, vastus medialis; [B] bilateral; [C] contralateral; [S] surface EMG recordings; [IM] intramuscular EMG recordings; ↑ and ↓ indicate significant ($p<0.05$) increases or decreases, '=' indicates the absence of significant effects, * indicates that findings correlate to subjective pain sensation, and ** indicates that findings were more evident during periods of highest activation.

Table S2.5 Effects of experimentally induced pain on muscle activity and movement characteristics during computer work and other types of low load repetitive work

Reference	*N*	(♂/♀)	Pain Method [a]	Intensity [b]	Location	Task description	Results [c] Activity of painful muscle	Activity of other muscles	Kinetics	Kinematics
Muscle pain										
Birch et al., 2000b	13	(13/0)	CH [+]	● [M,P]	ECU	CW - low precision	↓[S] ECU **	= [S] FCR, TZ		= T_{cycle}, performance
						CW - high precision	= [S] ECU	= [S] FCR, TZ		= T_{cycle}, performance
Birch et al., 2001	12	(12/0)	CH	●● [M,P]	TZu	CW - high precision				= T_{cycle}, performance
				● [M,P]	ECU	CW - high precision				↓ T_{cycle}, = performance
Madeleine et al., 1998	13	(13/0)	CH	●●● [P]	SOL	LLRW - standing			↑ ΔCOP_{ML}	= ankle movement
Madeleine et al., 1999a	10	(10/0)	CH	●●● [P]	TZu	LLRW	↓[S] TZu (↑[S] MPF)**	↓[S] DLa (=[S] MPF) =[S] DLm (↑[S] MPF) =[S] IS (↑[S] MPF; altered pattern)	= ΔCOP	↑ T_{cycle} ↑ rotation arm ↑ FL trunk
Madeleine et al., 2008	20	(?)	CH	●● [P]	TZu, IS	LLRW	Cycle-to-cycle variability: =[S] TZu, IS	=[S] DLm, ↓[S] DLa (non-active period)		↑ SD T_{event} ↑ SD arm movements ↑ SD arm start position ↑ SD FL-EX trunk = SD trunk start position
Samani et al., 2009	12	(12/0)	CH	●● [M]	TZu	CW - passive pause	↑[S] TZu	↑[S] TZm, =[S] TZl (↓ RRT)		= performance
						CW - active pause	↑[S] TZu ↓[S] TZm variability	↑[S] TZm, =[S] TZl (↓ RRT)		= performance
Samani et al., 2010	12	(12/0)	CH	●● [M]	TZu	CW	=[S] TZu (= RRT)	↓[S] ECR, =[S] FCU (↓ RRT)		= performance

Footnote on p. 50

[a] Pain was induced chemically (CH), with [+] indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; [c] Results refer to EMG amplitude, unless indicated otherwise; MPF, median power frequency; RRT, relative resting time; Effects on movement kinetics are described by ΔCOP, displacement of center of pressure, with $_{ML}$ medial-lateral. Effects on movement kinematics are described by EX, extension; FL, flexion; SD, standard deviation; T_{cycle}, cycle duration; T_{event}, event duration.

CW, computer work; DLa, anterior deltoideus; DLm, middle deltoideus; ECR, extensor carpi radialis; ECU, extensor carpi ulnaris; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; IS, infraspinatus; LLRW, low-load repetitive work; SOL, soleus; TZl, lower trapezius; TZm, middle trapezius; TZu, upper trapezius; [S] surface EMG recordings. ↑ and ↓ indicate significant (p<0.05) increases and decreases, '=' indicates the absence of significant effects, * indicates that findings correlate to subjective pain sensation, and ** indicates that findings were more evident during periods of highest activation.

Table S2.6. Effects of experimentally induced pain on movement characteristics during dynamic contractions

Reference	*N*	(♂/♀)	Pain			Task description	Results	
			Method [a]	Intensity [b]	Location		Kinetics [c]	Kinematics [d]
(Sub)cutaneous pain								
Blouin et al., 2003	10	(10/0)	TH [+]	●● [M]	Above GM [B]	Standing (static)	↑ $\Delta COP_{AP, ML}$ ↑ $\nu COP_{AP, ML}$ ↑ COP variability	
Corbeil et al., 2004	10	(10/0)	EL	●● [M]	Hand dorsum	Standing (static)	= $\Delta COP_{AP, ML}$ = $\nu COP_{AP, ML}$	
				● –	Foot dorsum	Standing (static)	↑* $\Delta COP_{AP, ML}$	
				●●● [M]			= $\nu COP_{AP, ML}$	
Maihöfner et al., 2007	12	(2/10)	CH	●● [M]	Forearm (dorsal)	Reach-and-grasp		= T_{mov}, path curvature
Joint pain								
Bennel and Hinman, 2005	12	(6/6)	CH	●●● [M]	IFP	Standing (static, stepping, or perturbations)	= $\Delta COP_{AP, ML}$	
Henriksen et al., 2010a	34	(16/18)	CH [+]	● [M]	IFP	Walking	↓M_{peak} AD knee ↓M_{peak} FL-EX knee	= φ FL knee (heelstrike) ↓ φ_{peak} FL knee (early stance) ↓ φ_{peak} EX knee (late stance)
Henriksen et al., 2010b	18	(9/9)	CH [+]	●● [M]	IFP	FL knee (isokinetic, max) EX knee (isokinetic, max)	↓* torque ↓* torque	
Muscle pain								
Bandholm et al., 2008	9	(9/0)	CH	●● [M]	SU	AB arm (20-27.5-35% MVC, concentric) AB arm (20-27.5-35% MVC, eccentric)	= force variability = force variability	

Table S2.6. Effects of experimentally induced pain on movement characteristics during dynamic contractions *(continued)*

Reference	*N*	(♂/♀)	Pain			Task description	Results	
			Method [a]	Intensity [b]	Location		Kinetics [c]	Kinematics [d]
Muscle pain (continued)								
Bonifazi et al., 2004	8	(8/0)	CH	●● [P]	PEM	One-arm bench press (10 kg, 25-40% MVC)	↓[B] force, power	↓* v [B] ↑ $T_{power,peak}$
					TB	One-arm bench press (10 kg, 25-40% MVC)	↓[B] force, = power	= v = $T_{power,peak}$
Diederichsen et al., 2009	11	(11/0)	CH	●● [P]	SU	AB arm (10% MVC)		= v [#]
Ervilha et al., 2004a	15	(11/4)	CH	● [M]	BB	FL elbow (70° amplitude, low accuracy)		↑ $T_{reaction}$, T_{mov} ↓ A, a, v_{peak}
Ervilha et al., 2004b	10	(7/3)	CH	●● [M]	BB or TB	FL elbow (30°amplitude, low accuracy)		↑ $T_{reaction}$, $T_{mov,}$, $T_{v,peak,}$ = A, a
				● [M]	BB or TB	FL elbow (90°amplitude, low accuracy)		↑ $T_{v,peak}$, = $T_{reaction}$, T_{mov} = A, a
	15	(13/2)	CH	● [M]	BB or TB	FL elbow (70°amplitude, low/high accuracy)		↑ $T_{reaction}$, $T_{v,peak,}$ = T_{mov}, = A, a
Ervilha et al., 2005	10	(6/4)	CH [+]	●● [M]	BB, or BB + TB	FL-EX elbow (repeated, 120s)		= T_{mov} = A, a
Henriksen et al., 2007	20	(10/10)	CH [+]	●● [M]	VM	Walking	↓ M EX knee = M AD knee = F_{comp} knee	= φ_{peak} FL knee
Henriksen et al., 2008	20	(10/10)	CH [+]	● [NR]	VM	Walking	= F_{impact} (heelstrike)	= α_{peak} FL knee = φ FL knee (heelstrike)

Muscle pain (continued)								
Henriksen et al., 2009a	15	(6/9)	CH^{+}	●● ^{M}	GLUTmd	Walking	↓ M_{peak} AB hip ↓ M_{peak} AD knee = M_{peak} INV ankle	↓ φ AD hip (midstance) ↓ φ EX hip (end stance) ↓ φ EX knee (midstance) = φ ankle, step length ↑ φ trunk (to side of pain)
Henriksen et al., 2009b	20	(10/9)	CH^{+}	● ^{M}	VM	Forward lunge (contact phase)	↓ M EX knee = M AD knee = M hip, ankle	= φ_{peak} FL knee, hip = φ_{peak} DFL ankle = T_{mov}
Hirata et al., 2010	9	(4/5)	CH^{+}	●● ^{P} ●●● ^{P} ●●● ^{P}	TA GM GM + TA	Standing (static or perturbations)	↑ ΔCOP to foot ^{C} ↑ νCOP_{ML} ↑ ΔCOP_{AP}, νCOP_{ML}, ↑ ΔCOP to foot ^{C}	
Jaberzadeh et al., 2003	12	(7/5)	CH	●● ^{M}	EDL	FL-EX digit III		↑ tremor amplitude = tremor frequency
Madeleine et al., 1999b	6	(6/0)	CH	●● ^{P}	TA (stepping leg)	Forward stepping	↓ M_{peak} knee, ankle = $\Delta COP_{AP, ML}$ ↑ COP area ^{C}	↓ ω knee, = φ ankle, knee ↓ ν step, ↑ $T_{reaction}$ = T_{mov}, step length
Madeleine et al., 2004	11	(4/7)	CH	●● ^{M,P}	TZu	Standing (static)	= $\Delta COP_{AP, ML}$	
Smith et al., 2006	19	(7/12)	CH	●● ^{M} ● ^{M}	FDI	Modified pegboard task Grip-and-lift task		= ^{B} number of sticks = ^{B} grip-lift delay
Vuillerme and Pinsault, 2009	16	(16/0)	EL	●●● ^{M}	TZu^{B}	Standing (static)	↑ $\Delta COP_{AP, ML}$, $\nu COP_{AP, ML}$	
Tendon pain								
Henriksen et al., 2011	16	(8/8)	CH^{+}	● ^{M}	AT	PFL ankle (standing, rhythmic)	= force variability ↑ 10Hz component of force	↓ φ_{peak} DFL ankle = φ_{peak} PFL ankle ↓ ν concentric, = ν eccentric

[a] Pain was induced chemically (CH), thermally (TH) or electrically (EL), with [+] indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; [NR] = 'not reported'; [c] Effects on movement kinetics are described by ΔCOP and vCOP, displacement and velocity of the center of pressure, with [AP] anterior-posterior and [ML] medial-lateral; $M_{(peak),}$ (peak) joint moment calculated from force platform recordings; F_{comp}, compression force; F_{impact}, impact force; [d] Effects on movement kinematics are described by A amplitude, v velocity, and a acceleration of movement; $\varphi_{(peak)}$ (peak) angle, ω angular velocity, and α angular acceleration of a given joint; T_{mov}, movement time; $T_{power,peak}$, time to peak power; $T_{reaction}$, reaction time; $T_{v,peak}$, time to peak velocity; [#] used as target value.

AB, abduction; AD, adduction; AT, Achilles tendon; BB, biceps brachii; DFL, foot dorsal flexion; EDL, extensor digitorum longus; EX, extension; FDI, first dorsal interossei; FL, flexion; GLUTmd, gluteus medius; GM, (medial) gastrocnemius; IFP, infrapatellar fat pad; INV, inversion; MVC, maximum voluntary contraction; PEM, pectoralis major; PFL, foot plantar flexion; SU, supraspinatus; TA, tibialis anterior; TB, triceps brachii; TZu, upper trapezius; VM, vastus medialis; [B] bilateral; [C] contralateral; ↑ and ↓ indicate significant (p<0.05) increases and decreases, '=' indicates the absence of significant effects, and * indicates that findings correlate to subjective pain sensation.

Table S2.7 Effects of experimentally induced pain on measures of proprioception

Reference	*N*	(♂/♀)	Pain			Aspect of proprioception	Location	Results [c]
			Method [a]	Intensity [b]	Location			
(Sub)cutaneous pain								
Birznieks et al., 2008	15	(11/4)	CH	●● [P]	Above TA	Muscle spindle activity	TA (relaxed)	=
Weerakkody et al., 2003	8	(?)	TH	●● [P]	Above BB - indicator	Force matching	Elbow	↓* force indicator
					Above BB - reference	(match force produced		↑* force indicator
					Forearm (medial) - indicator	by reference arm)		=
					Forearm (medial) - reference			=
	3	(?)	TH	●● [P]	Above SOL	Force matching	Elbow	=
Weerakkody et al., 2008	12	(?)	CH	●● [P]	Above FPL	Movement sense (passive)	Finger I	=
	10	(?)	CH	●●● [P]	Finger I	Movement sense (passive)	Finger I	↓
Joint pain								
Bennel et al., 2005	16	(5/11)	CH	●●● [M]	IFP	Joint position sense (active)	Knee	= accuracy
								= precision
Muscle pain								
Birznieks et al., 2008	15	(11/4)	CH	●● [P]	TA	Muscle spindle activity	TA (relaxed)	=
Matre et al., 2002	11	(0/11)	CH [+]	●● [M]	TA + SOL	Joint position sense (passive)	Ankle	= accuracy
						Movement sense (passive)		↓
	12	(0/12)	CH [+]	● [M]	TA	Joint position sense (passive)	Ankle	= accuracy
						Movement sense (passive)		=
	10	(0/10)	CH	●● [M]	TA	Joint position sense (passive)	Ankle	= accuracy
						Movement sense (passive)		=
Niddam and Hsieh, 2008	8	(8/0)	CH	●●● [P]	APB	Perception of APB stimulation	n.a.	↓

Table S2.7 Effects of experimentally induced pain on measures of proprioception *(continued)*

Reference	*N*	(♂/♀)	Pain			Aspect of proprioception	Location	Results [c]
			Method [a]	Intensity [b]	Location			
Muscle pain								
Rossi et al., 1998	7	(5/2)	CH	●●● [P]	EDB	Joint position sense	Ankle	"↓ * "
						Perception of EDB nerve stimulation	n.a.	↓ *
Rossi et al., 2003b	6	(?)	CH	●●● [P]	FDI	Joint position sense	Fingers	"↓ * "
						Perception of FDI stimulation	n.a.	"↓ * "
Weerakkody et al., 2003	5	(?)	CH [+]	●● [P]	BB - indicator	Force matching	Elbow	↓* force indicator
					BB - reference			↑* force indicator
Weerakkody et al., 2008	11	(?)	CH	●● [P]	FPL	Movement sense (passive)	Finger I	↓
	10	(?)	CH	●●● [P]	FCR	Movement sense (passive)	Finger I	=

[a] Pain was induced chemically (CH) or thermally (TH), with [+] indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; [c] Results between " " were not quantified.

APB, abductor pollicis brevis; BB, biceps brachii; EDB, extensor digitorum brevis; FCR, flexor carpi radialis; FDI, first dorsal interossei; FPL, flexor pollicis longus; IFP, infrapatellar fat pad; SOL, soleus; TA, tibialis anterior; ↑ and ↓ indicate significant (p<0.05) increases and decreases, '=' indicates the absence of significant effects, 'n.a.' denotes 'not applicable', and * indicates that findings correlate to subjective pain sensation.

Table S2.8 Effects of experimentally induced pain on cortical correlates of motor function

Reference	*N*	(♂/♀)	Pain			Task description		Results		
			Method [a]	Intensity	Location	Method [c]		MEP amplitude [d]		CMEP/H-reflex amplitude
Transcranial stimulation studies										
(Sub)cutaneous pain										
Cheong et al., 2003	30	(12/18)	CH	●–●● [M]	Over FCR	TMS	Active (10, 30% MVC)	↑* FCR, = ECR, OP		
Fadiga et al., 2004	12	(6/6)	MC	●● [M]	Finger I	TMS	Active (% MVC NR)	↑ OP		
				●●● [M]			Relaxed	= OP		
Farina et al., 2001	11	(6/5)	CH	● [P]	Over FDI	TMS	Relaxed	↓ FDI, = APB, ADM		= FDI [F]
	6	(4/2)	CH	● [P]	Over FCR		Relaxed	↓ FCR, = ECR		= FCR [H]
Fierro et al., 2010	7	(4/3)	CH	●–●● [M,P]	Hand dorsum	TMS	Relaxed	↓ APB		
Hoegher Bement et al., 2009	25	(?)	MC	●–●●● [M,P]	Finger II	TMS	Relaxed	↑* BR[C]		
Kaneko et al., 1998	6	(6/0)	EL	NR	Finger II	TMS	Active (30% MVC)	[SL] = APB	[LL]↓ APB	
Kofler et al., 1998	5	(3/2)	EL	●●● [NR]	Finger II	TMS	Relaxed	[SL] = TE, BB	[LL]↓ TE, ↑ BB	
Kofler et al., 2001	6	(?)	EL	●●● [P]	Finger II	TMS	Relaxed	[SL]↓ TE, TB	[LL]↓ TE	
								[SL] = BB	[LL]↑ TB, BB	
								[SL]↑↓ ADM	[LL]↑↓ ADM	
	7	(?)	EL	●●● [P]	Finger II	TECS	Relaxed		[LL]↓ TE	
	7–11	(?)	EL [+]	●–●●● [P]	Finger II	TMS	Relaxed		[LL]↓ * TE	
									[LL] ↑ TB, BB, ADM	
	6	(?)	EL [+]	●–●● [P]	Finger V	TMS	Relaxed	[SL]↓ TE, TB	[LL]↓ TE, TB	
								[SL]↑ BB, = ADM	[LL]↓ ADM, ↑ BB	

Table S2.8 Effects of experimentally induced pain on cortical correlates of motor function *(continued)*

Reference	*N*	(♂/♀)	Pain Method [a]	Intensity [b]	Location	Task description Method [c]		Results MEP amplitude [d]		CMEP/H-reflex amplitude
Transcranial stimulation studies *(continued)*										
(Sub)cutaneous pain (continued)										
Kofler et al., 2001 *continued*	6	(?)	EL [+]	●–●● [P]	Finger II [C]	TMS	Relaxed	[SL] = TE, TB [SL] = BB, ADM	[LL]↓ TE, = TB [LL]= BB, ADM	
le Pera et al., 2001	12	(10/2)	CH [+]	●● [P]	Over ADM	TMS	Relaxed	[SL] = ADM		
Tamburin et al., 2001	6	(2/4)	EL [+]	NR	Finger II	TMS	Relaxed	[SL]↓ ADM	[LL]↓ ADM	
					Finger V		Relaxed	[SL]↓ ADM	[LL]↓ ADM	
					Finger II+V		Relaxed	[SL]↓ ADM	[LL]↓ ADM	
Uncini et al., 1991	8	(5/3)	EL	NR	Finger II	TECS	Active (50% MVC)	[SL]↓ OP	[LL]↓ OP	
Urban et al., 2004	10	(5/5)	EL	NR	Finger V	TMS	Relaxed	[SL]↓ APB, ADM [SL]↓ BB, DL = ADM [C]	[LL]↓ APB, ADM [LL]↑ BB, DL [LL] = ADM [C]	↑ APB, BB [H]
Valeriani et al., 1999	5	(3/2)	TH [+]	● [NR]	Hand dorsum	TMS	Relaxed	[SL]↓ FDI [B]	[LL]↓ FDI [LL] = FDI [C]	
	4	(?)	TH	● [NR]	Hand dorsum	TECS	Relaxed	[SL]= FDI	[LL] = FDI	
Valeriani et al., 2001	5	(1/4)	TH	● [NR]	Hand dorsum	TMS	Relaxed		[LL]↓ BB	
					Upper arm (lateral)		Relaxed		[LL] ↓ BB [N=3] [LL] = BB [N=2]	
	3	(?)	TH	● [NR]	Hand dorsum	TMS	Active		[LL] = BB	
						TECS	(%MVC NR)		[LL] = BB	

Muscle pain									
del Santo et al., 2007	8	(5/3)	CH	●●● [P]	ADM	TMS	Active	↑ * ADM	
					BB		(30% MVC)	↑ * BB	
le Pera et al., 2001	10	(7/3)	CH [+]	●●● [P]	ADM	TMS	Relaxed	↓ ADM, = ADM [C]	
	10	(7/3)	CH [+]	●● [P]	FDI		Relaxed	↓ FDI	
	11	(8/3)	CH [+]	●● [P]	FCR		Relaxed	↓ FCR	↓ FCR [H]
Martin et al., 2008	6	(?)	CH [+]	●● [P]	BB	TMS	Relaxed	= BB, TB	↑ BB, TB [CMEP]
							Active FL (20% MVC-force)	↓ BB, TB	= BB, TB [CMEP]
	6	(?)	CH [+]	●● [P]	BB		Active FL (20% MVC-EMG)	= BB, TB	↑ BB, TB [CMEP]
							Active EX (20% MVC-EMG)	= BB, ↓ TB	= BB, ↑TB [CMEP]
Svensson et al., 2003	10	(8/2)	CH	●● [M]	FDI	TMS	Relaxed	↓ FDI, = FCU	↓ FDI [CMEP N=2]
EEG studies									
(Sub)cutaneous pain									
Babiloni et al., 2008	18	(?)	EL	●● [NR]	Finger II	EEG	Move finger II [C]	alpha ERD (anticipation to integration of painful and motor information)	
							Move finger II	↓ alpha ERD (interference with sensory-motor processing)	
Tarkka et al., 1992	7	(7/0)	TH	NR	Hand (lateral)	EEG	Reaction time	↑ reaction time, ↑ latency between N2 EEG-potential and EMG activity in FDI (efferent component of central processing time)	

Footnote on p. 60

[a] Pain was induced chemically (CH), electrically (EL), thermally (TH), or mechanically (MC), with [+] indicating the presence of a non-nociceptive control condition;

[b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; NR = not reported; [c] Motor evoked potentials (MEPs) were elicited by Transcranial Magnetic Stimulation (TMS) or Transcranial Electric Current Stimulation (TECS) over the primary motor cortex; EX, extension; FL, flexion; MVC, maximum voluntary contraction. [d] Results pertain to muscles ipsilateral to the side of pain, unless indicated otherwise; [B] bilateral; [C] contralateral; Findings for acute painful stimulation are presented separately for intervals between painful stimulus and MEP eliciting stimulus ≤50ms (short-latency; [SL]) and >50ms (longer-latency; [LL]). Alpha ERD denotes the event-related desynchronization in alpha band (8-12 Hz) of the EEG signal.

ADM, abductor digiti minimi; APB, abductor pollicis brevis; BB, biceps brachii; BR, rachioradialis; DL, deltoideus; ECR, extensor carpi radialis; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDI, first dorsal interossei; OP, opponens pollicis; TB, triceps brachii; TE, thenar eminence; [F] F-wave;

[H] H-reflex; [CMEP] cervicomedullary motor evoked potential; ↑ and ↓ indicate significant ($p<0.05$) increases or decreases, '=' indicates the absence of significant effects, and * indicates that findings correlate to subjective pain sensation.

Chapter 3

Deficient muscle activation in patients with Complex Regional Pain Syndrome and abnormal hand postures: An electromyographic evaluation

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Motor abnormalities in Complex Regional Pain Syndrome (CRPS) are common and often characterized by a restricted active range of motion (AROM) and an increased resistance to passive movements, whereby the affected body part preferably adopts an abnormal posture. The objective of the present study was to obtain a better understanding of the factors that are associated with these abnormal postures and limitations of the AROM, and to investigate whether these motor impairments reflect dystonia. We therefore evaluated characteristics of the surface electromyogram of the flexor carpi radialis and extensor carpi radialis muscles during active maintenance of various flexion-extension postures of the wrist of the affected and unaffected side in 15 chronic CRPS patients and in 15 healthy controls. Collectively, our results showed that deviant joint postures in chronic CRPS – at least in those patients with some range of active movement – were not characterized by sustained muscle contractions, and that limitations of the AROM were not attributable to excessive co-contraction. Rather, the agonistic muscle and its antagonist were activated in normal proportions, albeit over a limited range. This indicates that the AROM limitations and abnormal postures that are often observed in chronic CRPS patients are not associated with excessive muscle activity and hence do not exhibit the characteristics typical of dystonia. This may have important clinical implications, since commonly prescribed treatments are aimed at reducing excessive muscle contraction. We hypothesize that structural alterations in skeletal muscle tissue and pain-induced adaptations of motor function may contribute to the observed motor impairments.

Introduction

Complex Regional Pain Syndrome (CRPS) is characterized by pain, in combination with sensory, autonomic, trophic and motor abnormalities (Marinus et al., 2011). The spectrum of motor abnormalities reported in CRPS is broad and may vary from weakness, loss of voluntary control and slowness of movements to jerks, tremor and abnormal postures (Birklein et al., 2000; Goris et al., 1990; Harden et al., 1999; Huge et al., 2011; Schilder et al., 2012; Schwartzman and Kerrigan, 1990; Veldman et al., 1993). The latter, which occur in approximately 25% of the patients with CRPS, start distally in the affected limb and may spread more proximally and to the other extremities (Munts et al., 2011; van Rijn et al., 2007, 2011), causing some patients to become severely disabled. Although these postures might originate from various mechanisms, they are often attributed to sustained contractions of flexor muscles (i.e., 'tonic' or 'fixed' dystonia), which in turn may have a central, intramuscular, or psychological origin. Motor impairments that are more frequently observed in CRPS do not involve fixed abnormal postures, but are characterized by milder limitations of the range of motion (ROM) and increased resistance to passive movements, with the affected body part preferably adopting an abnormal posture. Although the presentation of these motor impairments resembles that of dystonia, it is unclear to date if they can indeed be characterized in this way.

The pathophysiological mechanisms of impaired motor function in CRPS, and in particular of CRPS-related dystonia, are still poorly understood. In chronic CRPS patients, the central nervous system neurons that are implicated in nociception and pain undergo maladaptive changes in anatomical and functional connectivity (central sensitisation), which are associated with increased sensitivity of the N-methyl-D-aspartic-acid (NMDA) receptor of spinal nociceptive neurons and a loss of function of interneuronal circuits mediating inhibition (Marinus et al., 2011). Unlike pain, dystonia in CRPS does not respond to the intravenous NMDA receptor antagonist ketamine (Schwartzman et al., 2009; Sigtermans et al., 2009). However, a significant reduction of dystonia was attained by intrathecal administration of the gamma-aminobutyric-acid B ($GABA_B$) receptor agonist baclofen (ITB; van Hilten et al., 2000; van Rijn et al., 2009), but not glycine (Munts et al., 2009), suggesting that loss of spinal GABAergic inhibition may contribute to impaired motor function.

In CRPS patients with abnormal postures of the affected limb, treatments have been aimed at reducing the activity of the skeletal muscles assumed to be responsible for the deviant posture, e.g. by intramuscular Botulinum toxin injections (BoNT). Although an immediate (i.e., placebo) response has been reported in some patients with chronic pain and fixed postures (Edwards et al., 2011), the therapeutic yield of BoNT in patients with 'fixed' dystonia is generally unsatisfactory (Jankovic, 1998; van Rooijen et al., 2011). This contrasts with the marked beneficial effect of BoNT in mobile dystonia and spasticity and raises an interesting question concerning the role of excessive muscle contraction in the maintenance of abnormal postures. In a single study on ten chronic CRPS patients diagnosed with dystonia, needle electromyography (EMG) recordings provided little evidence for sustained muscle activation at rest (van de Beek et al., 2002).

These findings suggest that abnormal postures in longstanding CRPS may result from other factors – including alterations of muscular tissue or joint ligaments – that cause a shift of the joint position associated with minimum muscle activity. To maintain a position other than this resting position, a passive joint torque needs to be counteracted by muscular activity. EMG characteristics during active maintenance of various joint positions may thus contribute to our understanding of factors that hinder movements beyond the resting position (e.g., reduced ability to selectively activate muscles) and impose limitations on the active ROM, and factors that contribute to maintenance of abnormal postures of the affected hand in chronic CRPS patients.

Methods

The data were collected as part of the empirical study on proprioception that is presented in Chapter 4.

Participants

Muscular activity was evaluated using EMG in fifteen patients (12 women, 3 men; mean ± SD age: 47.4 ± 14.1 years) diagnosed with CRPS type 1 of one or both upper extremities (see Table 3.1 for patient characteristics). All patients fulfilled the Budapest clinical criteria for CRPS (Harden et al., 2007) and presented with sustained abnormal

postures of the affected fingers and/or wrist, limiting the ability to align the hand dorsum with the forearm. Abnormal postures were mainly characterized by flexion of the fingers and wrist, which typically was more pronounced for the fingers than for the wrist (cf. Munts et al., 2011; van Rijn et al., 2007; see Figure 3.1). Subjects were excluded if *(1)* they suffered from mobile dystonia, or lesions or diseases of the central nervous system; *(2)* they had an implanted drug-delivery pump for ITB; or *(3)* their active wrist flexion-extension ROM was smaller than 30°. The latter criterion implied that only patients with at least some voluntary motor control were enrolled and that completely 'fixed' abnormal postures were not examined in this study. Healthy control subjects, who had normal function of both arms and no lesions or diseases of the central nervous system, were gender- and age-matched to the patients (12 women, 3 men; age: 45.4 ± 13.3years). 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 3.1 Demographic and clinical information of participants.

Patient number	Age (yr)	Sex	Affected upper limb	Duration of CRPS (yr)	$Pain_{week}$	MPQ-PRI	RSQ	Medication score
2	50	F	R	12	6	24	2.4	4.4
4	39	F	R	11	7	40	3.2	12.4
5	46	F	L	25	6	31	2.6	18.8
6	27	F	R	2	8	31	4.3	36.0
7	27	F	R	1	8	15	3.0	7.8
8	47	F	R	10	10	44	4.4	14.6
11	44	M	R	10	4	27	2.7	0.0
12	54	M	L>R	10	7	20	3.5	12.9
14	40	M	L	11	4	17	2.2	0.0
15	20	F	R>L	4	6	32	2.6	6.6
19	64	F	R	5	9	19	3.4	68.2
22	58	F	R	18	7	12	2.5	14.1
23	62	F	L	9	8	30	2.9	19.0
24	58	F	L	1	5	57	4.1	0.0
25	53	F	R	10	5	23	3.1	18.6

Abbreviations: F, female; M, male; L, left; R, right; $Pain_{week}$, average pain experienced during the week prior to 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.

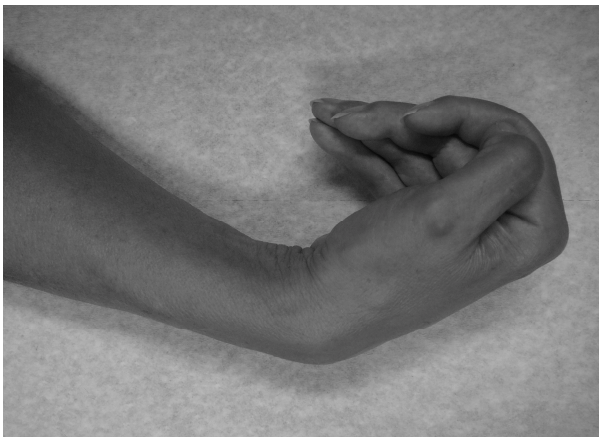


Figure 3.1 Abnormal posturing of the affected hand in a patient with CRPS. The flexion of the fingers and wrist is illustrative of the postures encountered in the present study.

Apparatus

Subjects were seated comfortably in a chair with their elbows slightly flexed and their feet supported. On two stands, positioned on both sides of the chair, vertically oriented manipulanda were mounted that only permitted flexion-extension movements of the wrist in the horizontal plane. The forearm was placed in the apparatus with the thumb up and palm facing inward and its position was restrained by foam-padded support surfaces on the medial and dorsal side, and by two vertical foam-coated supports on the ventral side. The distance of the handgrip (diameter 32 mm) on the manipulandum was adjusted such that the handgrip fell in the crease between thumb and index finger and the rotation axis of the wrist was aligned with that of the manipulandum, which was mounted on a potentiometer (FCP40A, tolerance ± 0.1%, Sakae Tsushin Kogyo Co., Ltd., Nakahara-ku, Kawasaki-city, Japan) to register wrist joint angles (see Figure 3.2). In doing so, it was ensured that the position of the handgrip relative to the participant's hand remained constant over the whole range of wrist positions and that the measurement of wrist joint angles remained unaffected by any finger movements. A white opaque screen precluded visual feedback of the hand movements.

EMG recordings were obtained from the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles of both arms. After careful preparation of the skin, rectangular (20x30mm) 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) by a Bagnoli™ 4-channel desktop amplifier with a 20-450 Hz bandpass filter (Delsys Inc, Boston, MA, USA). All signals were captured at a sampling rate of 1000 Hz with 16 bit A/D conversion.

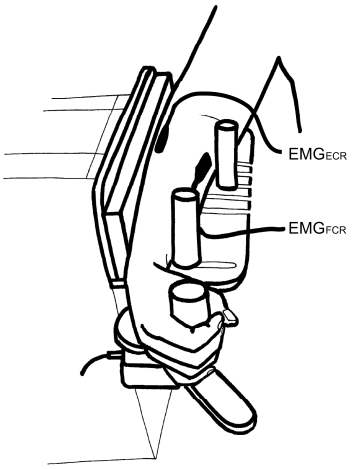


Figure 3.2 Schematic overview of the experimental setup. Manipulandum and supports were adjusted for each participant. Two surface EMG electrodes were used to record activity of the m. flexor carpi radialis and the m. extensor carpi radialis (EMG_{FCR} and EMG_{ECR}, respectively).

Data collection procedure

A numeric rating scale (NRS; 0 = no pain, 10 = unbearable pain) for average pain experienced during the week preceding the experiment ($Pain_{week}$), the McGill Pain Questionnaire (MPQ; Melzack, 1975) and the Radboud Skills Questionnaire (RSQ; Oerlemans et al., 2000) were administered to patients to evaluate pain and disability. The Pain Rating Index (PRI) of the MPQ was used in the analysis. Medication was quantified according to the Medication Quantification Scale Version III (Harden et al., 2005). Hand dominance was assessed in controls only using a Dutch version of the Edinburgh Handedness Questionnaire (Oldfield, 1971). Prior to the start of the experiment, the pressure pain threshold (PPT, in kgf) was measured over the abductor pollicis brevis

muscle (FDN Wagner algometer FPX50, Wagner instruments, Greenwich, USA) to quantify muscle hyperalgesia. Three PPT measurements were performed per hand, alternating between the hands. A numeric rating scale (NRS, 0-10) was administered to patients immediately after completion of each experimental condition in order to evaluate pain and perceived strain ($Pain_{task}$).

For the purpose of normalization of the EMG recordings, the participant's forearm was placed in the apparatus. Two EMG recordings were obtained at rest while the wrist was in a comfortable position. Subsequently, all participants performed maximum voluntary contractions (MVC) by generating an isometric flexion or extension torque with each wrist while the experimenter prevented wrist movements by counteracting the flexion or extension torque that was actively generated by the participant. Each maximum voluntary contraction was performed twice. For each muscle, the lower of the two resting values (EMG_{REST}) and the higher of the two MVC values (EMG_{MVC}) were used for normalization of the EMG (see *Data pre-processing*).

Passive ROM (PROM) was determined by measuring the maximal wrist flexion and extension achieved by applying force at a right angle to the manipulandum until discomfort was reported. Active ROM (AROM) was determined by measuring the actively achieved maximal wrist flexion and extension positions. For PROM and AROM, two measurements were performed per side. Prior to and following the AROM measurements, participants were instructed to adopt the most comfortable wrist position, which was recorded as their preferred wrist orientation.

For each individual patient, five target positions were calculated on the basis of the AROM of the affected side, which was averaged over the two measurements. Target positions were located at the center of this AROM (0%), which was considered the neutral wrist orientation for the participant in question, and at 40% and 80% of the maximum excursion relative to this neutral position (in the direction of both flexion and extension). Target positions for the patient's unaffected hand were located at the same relative positions (i.e., expressed as a percentage of that wrist's AROM; *relative matching*), or at exactly the same positions as they were for the affected hand (*absolute matching)*. Similarly, age- and gender-matched control subjects performed the relative matching as well as the absolute matching condition – the latter implying that target positions were

identical to those of the matched patient's affected hand. For each condition, five blocks of five trials were completed, with each of the target positions being presented in random order once within a block.

Participants actively performed flexion or extension of the wrist in order to reach the predefined target positions. Visual information regarding the target positions was not provided because the measurements were part of a larger study designed for examining proprioception. Instead, acoustic signals were provided via headphones to indicate *(1)* when the actual wrist position fell within the tolerance range around the target position (i.e., ±1.875°; 800 Hz); and *(2)* when the wrist had remained in this target range for 2 s (400 Hz). Subjects were instructed to maintain this stable wrist orientation with minimal effort while recording of position and EMG data was continued for about 5-10 s. Subsequently, the next trial was started and participants were instructed to actively flex or extend the wrist towards the next predefined target position.

Data analysis

Two of the 15 CRPS patients had two affected arms (see Table 3.1). Data from the most affected side were used for analysis. Because data obtained from these two patients could not be included in analyses involving a comparison with the unaffected hand, data from 13 patients remained for those analyses. Technical issues related to safety constraints of the apparatus hampered evaluation of the '80% flexion' position in one of these patients and in the absolute matching condition for the matched control.

Data pre-processing

Angular position data of the manipulandum were low-pass filtered (second-order bi-directional Butterworth filter, cut-off frequency = 10 Hz). Power line noise was removed from EMG recordings using a fourth-order bidirectional Butterworth notch filter (50 Hz and its 100 and 150 Hz harmonics). Subsequently, EMG data were digitally band-pass filtered (second-order bi-directional Butterworth 10-400 Hz) and full-wave rectified. Because EMG signal characteristics depend on the precise location of the sensor relative to the muscle and the conductive properties of tissue located between the muscle and sensor, normalization procedures are required for inter-muscular and inter-individual

comparison of muscular activity (de Luca, 1997). Although normalization of EMG signals to values obtained during MVC is the recommended method for comparing EMG signals in healthy participants (Burden, 2010), it has been recognized that normalization to MVC yields unreliable results in patients with reduced ability to voluntarily activate the muscles (Soderberg and Knutson, 2000). Therefore, various procedures were explored: *(A)* no normalization, EMG_{RAW} (in V); *(B)* normalization by subtraction of the resting value, $EMG–EMG_{REST}$ (in V); *(C)* normalization to the resting value, EMG / EMG_{REST} (in Ratio to Rest; RR); and *(D)* normalization to the MVC value, $(EMG / EMG_{MVC}) *100\%$ (in %MVC). To identify the most suitable procedure, the coefficient of variance (CV = SD/mean) of EMG values was calculated for each muscle separately within each group of participants. In all conditions, CV was lowest when muscular activity was normalized to EMG_{REST} (i.e., using method *C*), which was therefore adopted as the most reliable normalization procedure in the current context. This normalization procedure had one evident drawback: findings could be influenced significantly by the presence or absence of sustained muscle activity at rest, which is one of the interests of the present study. Therefore, all EMG analyses were also performed using the other normalization procedures. Findings obtained using methods *(A)*, *(B)* and *(C)* were more or less similar, which ensured that results and conclusions were not specific to the normalization procedure applied in this study. Normalization of muscle activity to MVC (i.e., method *D*) yielded divergent results, which are presented in Supplement 3.1. For a meaningful interpretation of these results it is essential to take into account that patients suffered from a loss of voluntary control, which was substantiated by reduced values of raw EMG_{FCR} and EMG_{ECR} during MVC (Table S3.1 in Supplement 3.1) and the small ratio of EMG_{MVC} to EMG_{REST} (see Table 3.2). As a consequence, normalization of muscle activity to EMG_{MVC} caused a systematic bias in the results (i.e., reduced EMG_{MVC} values automatically result in high EMG values [in %MVC]). The results obtained from normalization of muscle activity to MVC are presented in Supplement 3.1 to illustrate how normalization procedures that are 'standard procedure' in some instances (i.e., in healthy participants) may provide a misleading impression in other instances (i.e., in patients with limited voluntary control).

Range of motion and voluntary modulation of muscle activity

AROM and PROM were calculated from angular position data obtained during maximum flexion and extension and averaged over the two measurements. Maximum active flexion (F_{max}) and extension (E_{max}), as well as the activity of the agonist and antagonist muscle at these maximum excursions, were averaged over the two measurements. For each muscle the ratio of EMG_{MVC} to EMG_{REST} was calculated to gain further insight into the participant's ability to voluntarily modulate its activity.

Preferred wrist orientation

The preferred wrist orientation and the associated values of EMG_{FCR} and EMG_{ECR} were averaged over the two measurements, with negative values indicating flexion relative to the hand being aligned with the forearm. The deviation between this preferred wrist orientation and the wrist's neutral position (i.e., the center of the participant's AROM) was calculated (Δ_{pref} in °), with negative values indicating that the preferred orientation was located more towards the flexion endpoint.

EMG characteristics over AROM

For a trial to be included in the analysis, hand displacement during the selected episode (i.e., the 3 s immediately following the onset of the acoustic signal indicating that wrist orientation had been within the target range for 2 s) had to be less than 1.5° in order to ensure that a stable wrist orientation was maintained. Based on this criterion, 64 trials were discarded. Data from seven additional trials were excluded due to movement artifacts in EMG recordings. In addition, two patients were unable to reach some of the predefined flexion (P8: 9 trials) or extension (P25: 2 trials) target positions due to aggravation of complaints during the experiment. Altogether 82 out of 2505 trials (3.3%) were excluded from data analysis, resulting in 3 empty cells (P7: non-affected hand, 80% flexion; P8: affected hand, 80% and 40% flexion).

For the remaining trials, EMG_{FCR}, EMG_{ECR} (both in RR) and angular position data (in °) were averaged over the selected 3-s episode to obtain a measure for the muscular effort needed to maintain that specific position. In addition, for trials in which the target was located at 80% flexion or 80% extension, EMG data and angular position data were

averaged over the final 0.5 s of the wrist flexion or extension movement (i.e., the 0.5-s episode prior to the onset of the acoustic signals indicating that the actual wrist position fell within the tolerance range around the target position) to obtain a measure for the muscular effort needed to achieve these positions.

Co-contraction

In literature, various methods have been described for quantifying co-activation during isometric contractions (e.g., Damiano et al., 2000; Malfait and Sanger, 2007; Yao et al., 2004), usually involving either the ratio or the difference between the agonist and antagonist muscles. Because such methods can produce values indicating maximal co-contraction even when both muscles are relaxed – as we frequently observed in our data set – and since a specific value for co-contraction may result from different combinations of overall activity and the ratio between agonist and antagonist activity, these methods were not suitable for our purposes. Instead, we decided to follow Malfait and Sanger (2007) and defined co-contraction as 'any activity in a normally silent muscle'. Hence, for each trial the activity level of the less active muscle (i.e., EMG_{FCR} or EMG_{ECR}) was taken as an index of co-contraction (CCI; in RR) that was independent of the total amount of muscle activity.

Statistical analysis

For each participant, the median value of PPT per hand was used to reduce the influence of outliers. All other dependent variables were averaged per hand for each participant in each condition. Statistical analysis was performed using SPSS (PASW Statistics 18.0, SPSS Inc., Chicago, IL, USA). For all dependent variables, normality curves were inspected and Kolmogorov-Smirnov tests were used to assess whether the data were normally distributed within each group; only preferred position and Δ_{pref} were normally distributed. Because a considerable proportion of the data did not meet the assumptions for parametric testing, it was not possible to use a mixed ANOVA and planned comparisons were performed instead. Preferred position was submitted to a paired *t*-test for within-subject comparisons and to an independent *t*-test for between-subject comparisons. One-sample *t*-tests were conducted to see whether Δ_{pref} differed

significantly from 0 (the value indicating that the preferred orientation coincides with the neutral position). All other dependent variables were submitted to a Wilcoxon signed-rank test for within-subject comparisons (i.e., affected vs. non-affected hand in patients, and dominant vs. non-dominant hand in controls) and to a Mann-Whitney *U*-test for between-subjects comparisons (i.e., affected hand of patients vs. healthy controls, unaffected hand of patients vs. healthy controls). Because no relevant significant differences were detected between the dominant hand and the non-dominant hand of control subjects, data from the dominant hand were used for further analyses. To obtain insight into the level of muscle activity associated with static maintenance of various positions within the AROM, within-subject and between-subjects effects were examined by testing EMG_{FCR} and EMG_{ECR} and CCI (all in RR) for each target position separately (i.e., 80% flexion, 40% flexion, etc.), for relative matching conditions as well as absolute matching conditions. Similarly, tests for within-subject and between-subjects comparisons of EMG_{FCR}, EMG_{ECR} and CCI (all in RR) obtained during the final phase of movement towards target positions at 80% flexion and 80% extension were conducted for relative matching conditions as well as absolute matching conditions. To assess whether motor outcomes of the patients' affected hands were correlated to measures of pain (i.e., $Pain_{week}$, $Pain_{task,}$ PPT and MPQ-PRI) and disability (RSQ), pairwise correlations were calculated using Pearson's correlation coefficient for normally distributed continuous data and using Spearman's rho for all other data. Two-tailed significance was set at $p<.05$. Only for comparisons related to the level of muscle activity over the AROM, a more conservative *p* value was used ($p<.01$) to correct for multiple comparisons. Missing values were excluded per analysis.

Results

Results with respect to the EMG characteristics over the AROM are depicted in Figure 3.3. The other results are summarized in Tables 3.2 and 3.3.

Table 3.2 Comparison of muscle hyperalgesia and motor parameters between the affected hand and unaffected hand of CRPS patients and the dominant hand of healthy controls.

	PT-A (n=15)		PT-UA (n=13)		HC (n=15)	
Pain						
PPT (kgf) [a]	1.22 ** #	(0.66-2.34)	3.88	(2.68-5.91)	3.50	(3.02-4.64)
$Pain_{task}$ (NRS; 0-10) [b]	8.1	(1.5)	-		-	
Range of motion						
PROM (°)[a]	81.3 ** ##	(50.2-94.3)	159.5	(145.4-177.9)	162.9	(157.0-174.8)
AROM (°)[a]	83.6 ** ##	(61.9-96.1)	178.3	(154.7-189.7)	171.5	(168.2-186.4)
Parameters obtained from maximum active flexion						
F_{max} (°) [a]	68.8 ** ##	(46.7-73.5)	104.3	(96.8-109.1)	105.1	(100.2-109.2)
EMG_{FCR} (RR); agonist [a]	5.1 ** ##	(3.4-13.4)	24.2	(16.1-40.8)	16.76	(14.6-24.2)
EMG_{ECR} (RR); antagonist [a]	1.6 * #	(1.2-2.0)	2.4	(1.0-4.6)	2.8	(1.9-3.3)
Parameters obtained from maximum active extension						
E_{max} (°) [a]	20.3 ** ##	(8.2-34.3)	70.4	(59.3-80.8)	68.6	(61.5-77.0)
EMG_{ECR} (RR); agonist [a]	2.7 ** ##	(2.2-12.2)	27.7	(17.1-58.8)	28.8	(18.0-46.6)
EMG_{FCR} (RR); antagonist [a]	1.9 **	(1.3-2.6)	3.3	(2.0-5.4)	3.0	(2.4-5.2)
Preferred wrist orientation						
Preferred position (°) [b]	-28.9	(27.1)	-19.0	(13.8)	-16.7	(18.7)
Δ_{pref} (°) [c]	-7.0 †	(10.8)	-3.9	(14.1)	0.8	(16.7)
EMG_{FCR} (RR) [a]	3.0 ** ##	(2.2-10.6)	12.6	(7.5-18.3)	11.3	(8.3-14.2)
EMG_{ECR} (RR) [a]	3.7 ** ##	(2.8-4.8)	14.9	(9.1-24.1)	9.5	(7.1-15.3)
Voluntary modulation of muscle						
EMG_{FCR} MVC/REST [a]	69.3 ** ##	(34.5-149.3)	434.9	(261.5-917.5)	425.7	(235.1-685.7)
EMG_{ECR} MVC/REST [a]	61.1 ** ##	(27.2-85.9)	294.3	(140.1-358.5)	300.2	(196.7-473.0)

Abbreviations: PT, patients; A, affected side; UA, unaffected side; HC, healthy controls; $Pain_{task}$, average pain experienced during the experimental task; PPT, pressure pain threshold; PROM, passive range of motion; AROM, active range of motion; $F_{max,}$ maximum wrist flexion angle; E_{max}, maximum wrist extension angle; EMG_{FCR}, activity of the flexor carpi radialis muscle expressed as ratio to rest (RR); EMG_{ECR}, activity of the extensor carpi radialis muscle expressed as ratio to rest (RR); $\Delta_{pref,}$ deviation between preferred wrist orientation and neutral position; MVC, maximum voluntary contraction; [a] Measures are presented as median (interquartile range); the Wilcoxon signed-rank test was used for within-subject comparisons (PT-A vs. PT-UA) and the Mann-Whitney *U*-test was used for between-subjects comparisons (PT-A vs. HC, PT-UA vs. HC). [b] Measures are presented as mean (standard deviation); the paired *t*-test was used for within-subject comparisons and the independent *t*-test was used for between-subjects comparisons. [c] One-sample *t*-tests were conducted to assess whether Δ_{pref} differs from 0 († = p<.05, indicating that preferred wrist orientation and neutral position are not similar). Symbols indicate significant differences compared to HC (* = p<.05, ** = p<.01), PT-UA (# = p<.05, ## = p<.01).

Range of motion and voluntary modulation of muscle activity

Both the PROM and the AROM were significantly smaller for the affected hand of CRPS patients compared to their non-affected hand and healthy controls (see Table 3.2). Maximum active flexion (F_{max}) and extension (E_{max}) positions achieved by the patients' affected hand were smaller than those achieved by the unaffected hand and healthy controls, with extension (50.1° reduction compared to the unaffected hand) being more impaired than flexion (35.5° reduction compared to the unaffected hand). The limited movement excursions of the affected hand were characterized by significantly lower levels of activity of the agonist and antagonist muscles compared to the unaffected hand and healthy controls (see Table 3.2; no significant difference between the patients' hands was observed for EMG_{FCR} at maximum extension). The ratio of EMG_{MVC} to EMG_{REST} was smaller for the ECR and FCR muscles from the affected side of patients compared to their unaffected side and healthy controls (Table 3.2). The significant negative correlation between MPQ-PRI and EMG_{FCR} (both at maximum flexion and extension) indicated that higher MPQ-PRI scores were associated with lower levels of FCR activity. All other correlations with measures of pain and disability failed to reach significance (see Table 3.3).

Preferred wrist orientation

The preferred orientation of the affected wrist tended to be more flexed than that of the unaffected side and that of the healthy controls, albeit not significantly so (see Table 3.2). The one-sample *t*-tests revealed that Δ_{pref} differed from 0 for the patients' affected hand only. Thus, the preferred orientation largely coincided with the neutral position for healthy controls and the patients' unaffected hand, whereas the affected wrist preferably adopted a more flexed posture. Importantly, this preferred flexion posture was not characterized by increased levels of muscle activity in FCR and ECR. In contrast, values of EMG_{FCR} and EMG_{ECR} were lower for the patients' affected side compared to their unaffected side and healthy controls (see Table 3.2), and lower values of EMG_{FCR} were associated with higher MPQ-PRI scores (see Table 3.3). Other correlations with measures of pain and disability failed to reach significance (see Table 3.3).

Table 3.3 Correlation coefficients of pain and disability with motor parameters of the affected hand.

	$Pain_{week}$	$Pain_{task}$	PPT	MPQ-PRI	RSQ
Range of motion					
PROM	-.38[a]	-.13[a]	.36[b]	-.11[a]	-.46[a]
AROM	-.48[a]	-.23[a]	.21[b]	-.38[a]	-.34[a]
Parameters obtained from maximum active flexion					
F_{max}	-.02[b]	-.11[b]	-.13[b]	.14[b]	.01[b]
EMG_{FCR}; agonist	.13[b]	.12[b]	-.10[b]	-.53[b] *	-.05[b]
EMG_{ECR}; antagonist	-.21[b]	-.04[b]	-.30[b]	-.21[b]	-.08[b]
Parameters obtained from maximum active extension					
E_{max}	-.46[b]	-.34[b]	.35[b]	-.30[b]	-.29[b]
EMG_{ECR}; agonist	-.09[b]	.09[b]	-.04[b]	-.29[b]	-.18[b]
EMG_{FCR}; antagonist	-.04[b]	.09[b]	-.35[b]	-.64[b] **	-.04[b]
Preferred wrist orientation					
Preferred position	-.22[a]	-.10[a]	.17[b]	-.09[a]	-.35[a]
Δ_{pref}	-.14[a]	.00[a]	.19[b]	-.00[a]	-.03[a]
EMG_{FCR}	.10[b]	.07[b]	-.29[b]	-.57[b] *	-.04[b]
EMG_{ECR}	-.13[b]	.12[b]	.02[b]	-.33[b]	.06[b]
Voluntary modulation of muscle activity					
EMG_{FCR} MVC/REST	-.04[a]	.14[a]	.33[b]	-.34[a]	-.20[a]
EMG_{ECR} MVC/REST	.00[b]	.09[b]	.31[b]	.01[b]	.34[b]

Abbreviations: $Pain_{week}$, average pain experienced during the week prior to the experiment; $Pain_{task}$, average pain experienced during the experimental task; PPT, pressure pain threshold; MPQ-PRI, pain rating index of the McGill Pain Questionnaire; RSQ, Radboud Skills Questionnaire; PROM, passive range of motion; AROM, active range of motion; $F_{max,}$ maximum wrist flexion angle; $E_{max,}$ maximum wrist extension angle; EMG_{FCR}, activity of the flexor carpi radialis muscle; EMG_{ECR}, activity of the extensor carpi radialis muscle; $\Delta_{pref,}$ deviation between preferred wrist orientation and neutral position; MVC, maximum voluntary contraction. Pairwise correlations were calculated using Pearson's correlation coefficient ([a]) or Spearman's rho ([b]). Significant correlations are indicated (* = p<.05, ** = p<.01).

EMG characteristics over AROM

Figure 3.3 shows that differences between the patients' affected hand, their unaffected hand, and healthy controls in terms of EMG_{FCR} and EMG_{ECR} levels associated with static maintenance of various positions were mainly found at positions near the extremes of the individually determined AROM (i.e., in relative matching conditions; Figure 3.3A and 3.3C). For the 80% flexion position, activity of the agonist muscle (EMG_{FCR}) was not only significantly lower compared to the unaffected side during active maintenance of this position (Figure 3.3A), but also during movement towards this position (Figure 3.3A; open symbols). Similarly, lower levels of agonist muscle activity (EMG_{ECR}) were observed for the affected side compared to the unaffected side and healthy controls during static maintenance of the 80% extension position (Figure 3.3C) and during movement towards this position (Figure 3.3C; open symbols). This was accompanied by a slight reduction of antagonist muscle activity in the affected arm during the flexion movement (EMG_{ECR}; relative to the unaffected hand), during the extension movement (EMG_{FCR}; relative to healthy controls), and during static maintenance of the 80% extension position (EMG_{FCR}; relative to the unaffected hand). Group comparisons revealed no significant differences for CCI, apart from a significant reduction for the affected hand compared to the unaffected hand at the 80% extension position in relative matching conditions (Figure 3.3E). In general, the observed CCI values (in RR) were close to 1 – indicating that the antagonist muscle was at rest – over the whole range of positions (Figure 3.3E and 3.3F), which illustrates that there was no abnormal co-contraction between FCR and ECR in the patients' affected arm. The observed lower levels of agonist muscle activity in relative matching conditions were likely attributable to the smaller excursions towards flexion and extension: when positions were identical (in absolute matching conditions), EMG levels recorded from the patients' affected side were no longer significantly different from EMG levels recorded from their unaffected side or from healthy controls, for static maintenance (Figure 3.3B and 3.3D) as well as movement towards these positions (Figure 3.3B and 3.3D; open symbols).

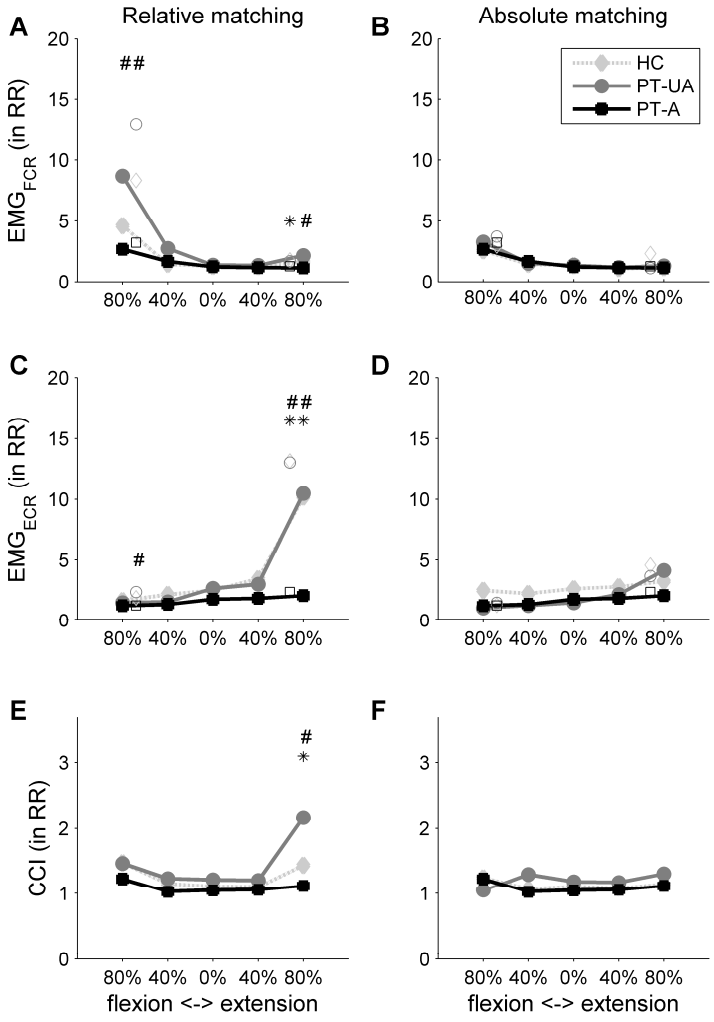


Figure 3.3 Muscle activity during active maintenance of various joint positions. Activity of the wrist flexor muscle (**A-B**; EMG_{FCR}) and extensor muscle (**C-D**; EMG_{ECR}) and co-contraction (**E-F**; CCI) during static maintenance of various positions over the individually determined active range of motion (relative matching; left panels) and at identical positions (absolute matching; right panels). Data points reflect median values per group. Open symbols represent muscle activity during the last 0.5s of movement towards the 80% flexion and 80% extension positions. Significant differences (p<.01) are indicated by symbols (* for PT-A vs. HC, # for PT-A vs. PT-UA). Abbreviations: PT, patients; A, affected side; UA, unaffected side; HC, healthy controls.

Discussion

EMG characteristics were evaluated in chronic CRPS patients during active maintenance of various wrist postures to obtain a better understanding of the factors that limit the AROM and contribute to the maintenance of abnormal joint postures.

The AROM of the affected hand was limited in CRPS patients, with extension being more impaired than flexion. There was a trend of the preferred wrist orientation towards flexion. This trend just failed to reach significance, probably because abnormal postures were more pronounced for the fingers than for the wrist (cf. Munts et al., 2011; van Rijn et al., 2007). For the unaffected hand and healthy controls the preferred orientation coincided with the neutral position (in line with Roerdink, 2008), whereas the affected wrist preferably adopted a more flexed posture (i.e., Δ_{pref} was smaller than 0). The abnormal postures were not associated with sustained muscle activity (in line with van de Beek et al., 2002) and deviations from this posture were not hampered by excessive co-contraction of agonist and antagonist muscles. Rather, the agonistic muscle and its antagonist were activated in normal proportions, albeit over a limited range. Recorded EMG levels were comparable to those of the unaffected side and healthy controls in absolute matching conditions (i.e., at identical positions). Figure 3.4 illustrates that EMG levels recorded from the affected hand generally fell well within the range of 'normal' EMG values associated with specific joint angles, but that higher levels of agonist muscle activity would be required to counteract the increasing passive joint torque associated with larger wrist excursions. The observed AROM limitations may thus originate from a substantial loss of voluntary modulation of muscle activity, which is also supported by the smaller ratios of EMG_{MVC} to EMG_{REST} for the ECR and FCR muscles from the patients' affected side compared to their unaffected side and healthy controls (in line with van de Beek et al., 2002).

The PROM was limited to a similar extent as the AROM, which may suggest a major limiting contribution of passive structures around the joint. However, the EMG recordings indicated that limitations of the AROM were predominantly attributable to a lack of muscle activation.

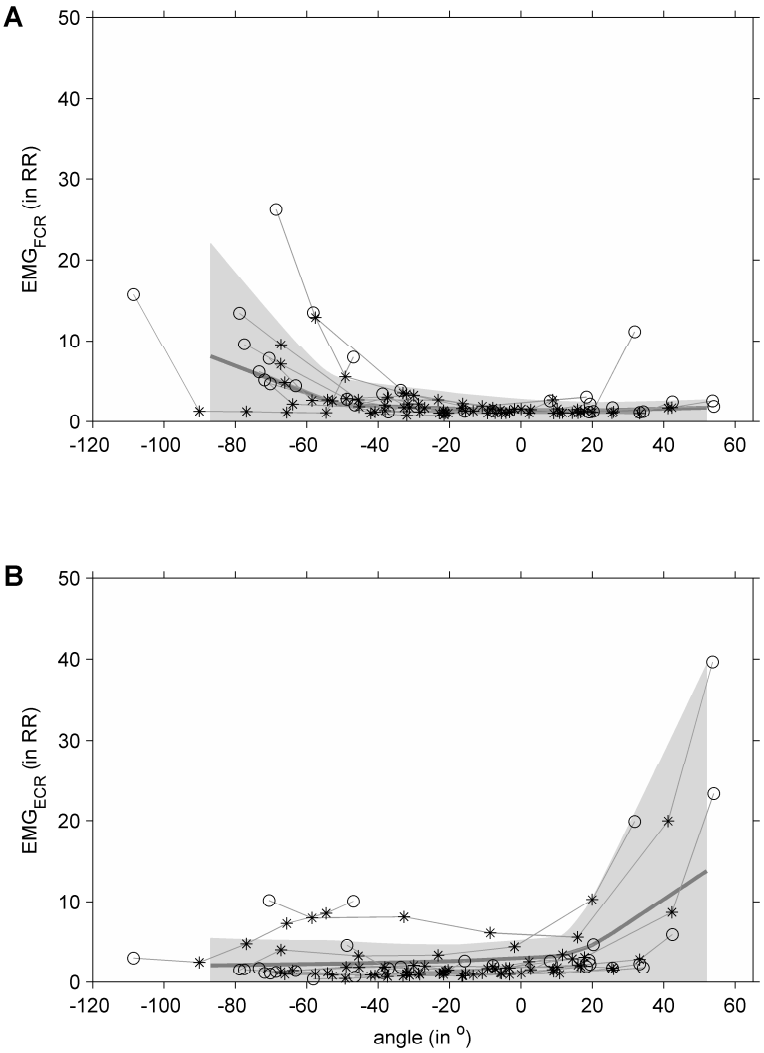


Figure 3.4 Muscle activity of the affected hand versus the 'healthy range' of EMG values. Activity of the wrist flexor (**A**; EMG_{FCR}) and extensor muscle (**B**; EMG_{ECR}) plotted against wrist angle for each patient's affected hand. Asterisks represent EMG values for each patient during maintenance of the various wrist orientations (averaged over five repetitions). Open circles represent EMG values at maximum active flexion and extension (averaged over two repetitions). The shaded area illustrates the 'healthy range of EMG values for each joint angle', which was calculated over the average active range of motion (AROM) of healthy controls as the 95% confidence interval around the group mean EMG level (dark grey curve). Negative angles denote wrist flexion.

Taken together, our findings clearly show that the abnormal postures and AROM limitations observed in patients with chronic CRPS – at least in those patients with wrist AROM>30° – were not characterized by sustained muscle contractions or excessive co-contraction. Hence, although their presentation resembles that of dystonia, these motor impairments do not reflect the characteristics typical of dystonia, which is defined as a syndrome of *sustained muscle contraction*, frequently causing twisting and repetitive movements or abnormal postures (Fahn, 1988). We found no evidence for excessive muscle activity at rest or during attempts to deviate from this resting position. It should be noted that diametrically opposite – but in all likelihood erroneous – conclusions would have been drawn if EMG would have been normalized to MVC (see Supplement 3.1).

Although reductions in maximal voluntary strength of upper limb muscles in CRPS patients have also been reported previously (e.g., Huge et al., 2011; Zyluk, 2001), such findings have not yet been related to development or maintenance of abnormal joint postures. In this respect, it is noteworthy that abnormal postures in children with spastic cerebral palsy have been associated with muscle weakness and decreased muscle fiber diameter, rather than sustained muscle contractions (Barrett and Lichtwark, 2010; Malaiya et al., 2007; Shortland et al., 2002). Attempts have been made to explain the development of abnormal postures – and the predominance of flexion postures in this regard – from a biomechanical perspective. Specifically, a decrease in muscle fiber diameter not only leads to loss of strength, but may also result in a shorter muscle belly (Heslinga and Huijing, 1992), which may cause a slight shift of the joint's resting position. It has been suggested that transmission of force through myofascial tissue may account for gradual aggravation of such postures (Huijing, 2007). Importantly, however, patients with muscular dystrophy suffer from severe muscle weakness due to muscle fiber degeneration, but they do not develop deviant joint postures. This indicates that such peripheral mechanisms are not sufficient for the development of abnormal joint postures and suggests the involvement of a central factor.

The potential sources of impaired voluntary activation and muscle weakness are diverse and range from peripheral alterations to high-level central disturbances of motor control. Evidence has been provided that the following factors may contribute to the development of abnormal postures and AROM limitations in CRPS patients: *(1)* 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); *(2)* defective muscle tone regulation due to disturbances in the stretch reflex (Mugge et al., 2012a, 2012b; Schouten et al., 2003; van de Beek et al., 2002) or aberrant force feedback regulation (Mugge et al., 2012a; Munts et al., 2011); *(3)* muscle hyperalgesia (Huge et al., 2011; Maier et al., 2010), which is presumably attributable to sensitization of nociceptive type III and IV muscle afferents (Graven-Nielsen and Mense, 2001) that have been associated with modulation of inhibitory spinal circuits (Piercey and Goldfarb, 1974; Rossi and Decchi, 1997; Rossi et al., 1999a, 1999b, 2003); *(4)* inappropriate motor programming in higher-order centers of motor control (Maihöfner et al., 2007; Swart et al., 2009), which may arise from a mismatch between the predicted and actual sensory feedback of a given motor command (McCabe and Blake, 2008) and be due to distortions in the mental image of the affected limb (Forderreuther et al., 2004; Frettlöh et al., 2006; Lewis et al., 2007, 2010; Peltz et al., 2011); *(5)* pain-induced adaptations at multiple levels of the motor system, which facilitate protective and compensatory motor behavior (Chapter 2; Hodges and Tucker, 2011) and are probably susceptible to influences of descending factors related to anticipation of pain (Tucker et al., 2012) or perceived harmfulness of activities (de Jong et al., 2011); and *(6)* psychological factors (Hawley and Weiner, 2011; Reedijk et al., 2008; Schrag et al., 2004), which have been shown not to predispose to CRPS (Beerthuizen et al., 2011), but whose contributions to chronification of CRPS or development of associated motor impairments are still unknown (Marinus et al., 2011).

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., patients being reluctant to exert full effort because of increasing pain). However, correlations between motor parameters and measures of pain failed to reach significance (Table 3) and such an approach would disregard the potential role of numerous other factors. A comparison of patients with CRPS to patients with other causes of chronic (neuropathic) pain would be of interest in this regard, as it may reveal to which extent the observed motor impairments are associated with chronic pain in general, or are specific to CRPS. Although the current experimental setup does not allow discriminating between the respective contributions of the aforementioned factors, it warrants further research aimed at

unraveling their potential contributions. In this regard, we want to highlight the putative role of structural alterations in skeletal muscle tissue, as well as alterations in motor unit recruitment and motor behavior that may be a direct consequence of nociceptive input – possibly reinforced by increased sensitivity of muscle nociceptors – or may be mediated by emotional or cognitive responses to pain. Assessment of a possible functional (psychogenic) component, which may be superimposed on an organic fundament, may prove valuable but constitutes a major methodological challenge.

Prior to drawing conclusions from the current results, the following aspects should be considered as well. Firstly, it should be noted that we found no evidence for sustained or excessive muscle contractions in the *chronic* phase of the disease; hence our findings do not allow conclusions on the potential role of involuntary excessive muscle contractions in an earlier stage of the disease. Secondly, we concluded that patients did not show characteristics typical of dystonia, which – after all – is defined as a syndrome of sustained muscle activity and abnormal co-contraction of agonist and antagonist muscles. To substantiate this conclusion, it would be of interest to apply the same protocol to a control group of patients with (secondary) dystonia of the arm and compare patterns of muscle activation across the two patient groups. Thirdly, patients were tested while on their regular medication, which comprised muscle relaxants in 6 out of 15 patients (i.e., oral administration of baclofen (3 patients) or clonazepam (3 patients)), which may have affected our results. However, there was no significant difference in AROM or EMG parameters between patients who did or did not use muscle relaxants. Fourthly, the applied EMG technique did not allow for identification of a potential redistribution of activity among synergistic muscles (e.g., EMG activity of the flexor carpi ulnaris muscle and extensor carpi ulnaris muscle was not recorded), though the possible contribution of other muscles acting around the wrist was reduced by fixating the forearm and allowing only flexion-extension movements of the wrist. Finally, patients were enrolled in the present study only if their AROM was at least 30°. The present findings thus relate to CRPS patients with at least some degree of voluntary motor control. It remains to be investigated whether patients who present with fixed postures and a complete loss of motor control represent a more severe manifestation of symptoms identified in the current study, or form a subgroup with a distinct phenomenology and underlying

pathophysiology. In patients with fixed postures, in-depth analysis of intramuscular EMG recordings based on isolation of motor unit potentials by means of inference analysis and pattern recognition could provide insights into underlying abnormalities of muscular, neuromuscular or central origin (Daube and Rubin, 2009).

In conclusion, our results show that deviant joint postures in chronic CRPS – at least in those patients with some range of active movement – are not characterized by sustained muscle contractions, and that AROM limitations are not attributable to excessive co-contraction. The motor impairments observed in these CRPS patients are not associated with excessive muscle activity and hence do not exhibit the characteristics typical of dystonia. Considering the lack of evidence for excessive muscle activation, it may not be surprising that treatments aimed at reducing excessive muscle contractions have a moderate (but often disappointing) effect at best (van Rooijen et al., 2011). Because further weakening of the muscles might actually lead to further deterioration of motor function, multi-disciplinary treatment (Schrag et al., 2004; Stanton-Hicks et al., 2002) aimed at prevention of muscle atrophy by means of physical therapy and stimulation of using the affected limb may prove more rewarding. Our findings emphasize the importance of thorough evaluation of EMG characteristics prior to deciding on the treatment strategy in patients who present with motor impairments similar to those examined in the present study. In this regard, it should be taken into account that normalization of EMG data to values obtained during MVC is not appropriate for comparing levels of muscle activity in patients with a loss of voluntary control and may lead to erroneous conclusions.

Acknowledgment

The authors thank Dr. Melvyn Roerdink and Prof. Dr. Gert van Dijk for their valuable comments regarding the reported dataset.

Supplement 3.1: Normalization of EMG to MVC

All EMG analyses presented in this Chapter were performed using four different normalization procedures (cf. *Data pre-processing*). The procedure that was adopted as the most reliable normalization procedure in the current context (i.e., normalization to EMG_{REST}) had one evident drawback: findings could be influenced significantly by the presence or absence of sustained muscle activity at rest, which was precisely a point of interest in the present study. However, this was unlikely the case because methods based on raw EMG data yielded similar findings (including the absence of elevated levels of muscle activity at the preferred wrist orientation). In other words, results and conclusions were not specific to the normalization procedure applied in the main sections of this paper. However, normalization of muscle activity to MVC, which is typically recommended for analysis of EMG in a healthy population (Burden, 2010) and is also widely applied in clinical research (e.g., Stearns et al., 2009; Wen et al., 2008; Wing et al., 1990), yielded deviating results that are presented below.

Results

When muscular activity was expressed as %MVC, the preferred posture of the patients' (most) affected hand was characterized by higher levels of EMG_{FCR} than that of healthy controls, and by higher levels of EMG_{ECR} than that of their unaffected hand and healthy controls (see Table S3.1). During static maintenance of various positions over the AROM (Figure S3.1A-D), significantly higher values of EMG_{FCR} and EMG_{ECR} (in %MVC) were observed for the patients' affected hand compared to their unaffected hand and healthy controls, regardless of condition (i.e., relative or absolute matching of positions). Over the whole range of positions, significantly higher values of CCI (in %MVC) were observed for the patients' affected hand (Figure S3.1E and S3.1F), again irrespective of condition. Also during flexion and extension movements, EMG values obtained from the patients' affected hand were generally higher than those obtained from their unaffected hand and healthy controls (see Figure S3.1A-D, open symbols). For the muscle that functioned as agonist during movements of the affected hand, however, activity level was not significantly higher than for the unaffected side. In line with this, EMG_{ECR} obtained

from the affected side was not significantly elevated relative to the unaffected side and healthy controls during the final phase of extension movement in relative matching conditions (Table S3.1) and during static maintenance of extreme extension postures, i.e., 80% extension in the relative matching condition (Figure S3.1C). In addition, agonist activity was not significantly elevated during maximum flexion and extension, whereas antagonist activity was (Table S3.1).

Table S3.1 Comparison of EMG parameters between the affected hand and unaffected hand of CRPS patients and the dominant hand of healthy controls, normalized to MVC or without normalization.

	PT-A (*n*=15)		PT-UA (*n*=13)		HC (*n*=15)	
Range of motion						
Parameters obtained from maximum active flexion						
EMG_{FCR} (%MVC); agonist	8.75	(3.97-16.96)	5.81	(2.07-10.12)	4.49	(2.94-6.43)
EMG_{ECR} (%MVC); antagonist	2.82 **##	(1.05-7.25)	0.83	(0.50-1.53)	0.99	(0.48-2.04)
Parameters obtained from maximum active extension						
EMG_{ECR} (%MVC); agonist	7.94	(4.91-9.78)	11.21	(8.41-16.04)	8.76	(4.79-15.43)
EMG_{FCR} (%MVC); antagonist	2.44 **##	(1.54-5.49)	0.83	(0.59-1.13)	0.86	(0.51-1.28)
Preferred wrist orientation						
EMG_{FCR} (%MVC)	5.52 *	(3.74-9.94)	3.32	(1.35-4.70)	2.68	(1.98-3.99)
EMG_{ECR} (%MVC)	6.39 *#	(2.76-11.39)	2.87	(1.54-6.47)	2.82	(1.52-4.04)
Raw EMG values						
$EMG_{REST,FCR}$ (V)	0.020	(0.013-0.024)	0.015 *	(0.013-0.018)	0.025	(0.013-0.030)
$EMG_{REST,ECR}$ (V)	0.020 #	(0.016-0.054)	0.017	(0.011-0.025)	0.020	(0.017-0.024)
$EMG_{MVC,FCR}$ (V)	1.37 **##	(0.41-2.81)	4.53	(3.57-11.96)	5.59	(4.19-17.47)
$EMG_{MVC,ECR}$ (V)	1.56 **##	(0.55-3.30)	4.48	(2.63-5.58)	5.28	(4.63-9.80)

Abbreviations: PT = patients; A = affected side; UA = unaffected side; HC = healthy controls. EMG_{FCR} = activity of the flexor carpi radialis muscle; EMG_{ECR} = activity of the extensor carpi radialis muscle; MVC = maximum voluntary contraction; All measures are presented as median (interquartile range); the Wilcoxon signed-rank test was used for within-subject comparisons (PT-A vs. PT-UA) and the Mann-Whitney *U*-test was used for between-subjects comparisons (PT-A vs. HC, PT-UA vs. HC). Symbols indicate significant differences compared to HC (* = $p<.05$, ** = $p<.01$), PT-UA (# = $p<.05$, ## = $p<.01$).

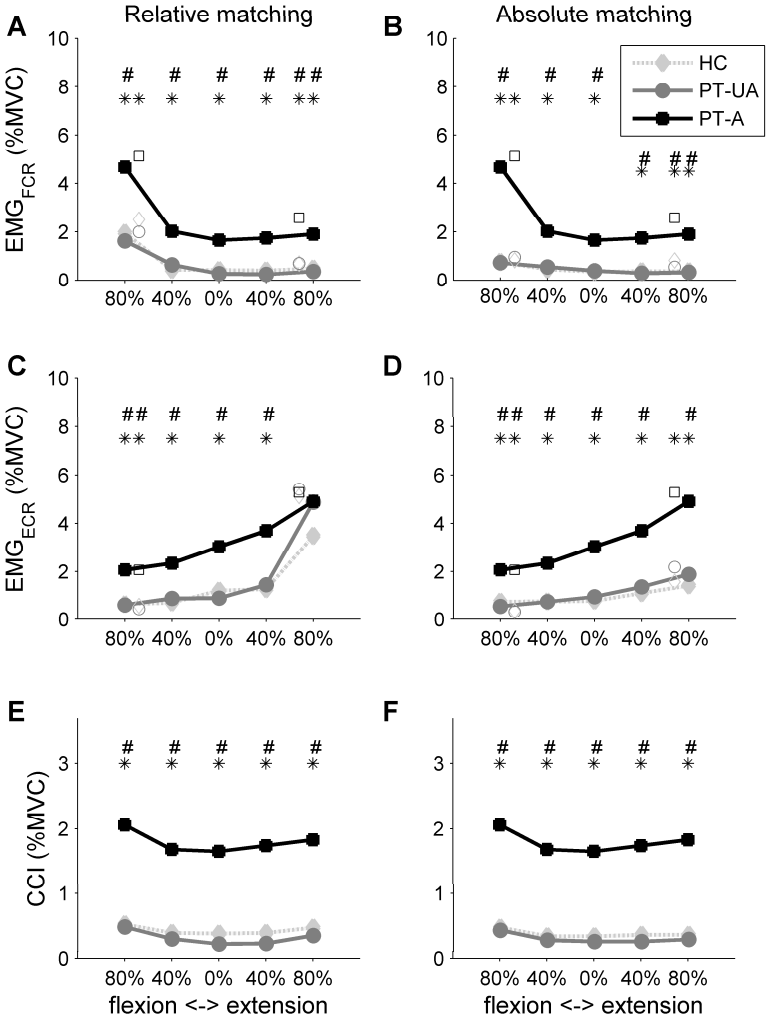


Figure S3.1 Activity of the wrist flexor muscle (**A-B**; EMG_{FCR}) and extensor muscle (**C-D**; EMG_{ECR}) and co-contraction (**E-F**; CCI) during static maintenance of various positions over the individually determined active range of motion (relative matching; left panels) and at identical positions (absolute matching; right panels). All measures are expressed as %MVC. Data points reflect median values per group. Open symbols represent muscle activity during the last 0.5s of movement towards the 80% flexion and 80% extension positions. Significant differences (p<.01) are indicated by symbols (* for PT-A vs. HC, # for PT-A vs. PT-UA). Abbreviations: PT = patients; A = affected side; UA = non-affected side; HC = healthy controls.

Discussion

Based on the results obtained by normalization of EMG levels to MVC values alone, one might conclude that there is excessive muscle activation, with increased levels of activity and co-contraction at rest, during movement, as well as during active maintenance of various postures. This conclusion is orthogonal to that obtained with the other procedures for normalization of EMG (i.e., with normalization to EMG_{REST} [in RR; presented in the main section of this Chapter], by subtraction of EMG_{REST}, or without normalization). For a meaningful interpretation of the present results, however, it is essential to take into account that patients suffered from a loss of voluntary control, which was also reflected in reduced values of raw EMG_{FCR} and EMG_{ECR} during MVC (see Table S3.1). Please recall the formula used for normalization of muscle activity to MVC values (i.e., EMG [in %MVC] = EMG_{RAW} / EMG_{MVC} * 100%), as a consequence of which reduced EMG_{MVC} values automatically resulted in high EMG values (in %MVC) in all conditions. Normalization of muscle activity to EMG_{MVC} thus caused a systematic bias in the results due to the observed loss of voluntary control, leading to erroneous conclusions. In contrast, we are confident that results obtained by normalization to EMG_{REST} (in RR, presented in the main sections of this Chapter) are more valid and reliable, as those results were replicated using other analyses (i.e., without normalization or with normalization by subtraction of the resting value). In addition, comparison of raw EMG levels obtained at rest showed that the patients' affected side did not differ systematically from their unaffected side and healthy controls, apart from a difference in EMG_{ECR} between the patients' affected and unaffected side (see Table S3.1), which turned out to be non-significant after removal of one outlier (P25).

In conclusion, the general elevation of EMG levels when expressed as %MVC provides a misleading impression. Moreover, the absence of a significant elevation of EMG_{ECR} and EMG_{FCR} levels during movement towards extreme extension positions, or maintenance of those positions, indicated a relative reduction of agonist activity, which is consistent with findings presented in the main section of this Chapter (compare Figure S3.1 and Figure 3.3).

Chapter 4

Motor dysfunction of Complex Regional Pain Syndrome is related to impaired central processing of proprioceptive information

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Our understanding of proprioceptive deficits in Complex Regional Pain Syndrome (CRPS) and its potential contribution to impaired motor function is still limited. To gain more insight into these issues, we evaluated accuracy and precision of joint position sense over a range of flexion-extension angles of the wrist of the affected and unaffected side in 25 chronic CRPS patients and in 50 healthy controls. The results revealed proprioceptive impairment at both the patients' affected and unaffected sides, characterized predominantly by overestimation of wrist extension angles. Precision of the position estimates was more prominently reduced at the affected side. Importantly, group differences in proprioceptive performance were not only observed for tests at identical percentages of each individual's range of wrist motion, but also when controls were tested at wrist angles that corresponded to those of the patient's affected side. More severe motor impairment of the affected side was associated with poorer proprioceptive performance. Based on additional sensory tests, variations in proprioceptive performance over the range of wrist angles and comparisons between active and passive displacements, the disturbances of proprioceptive performance most likely resulted from altered processing of afferent (and not efferent) information and its subsequent interpretation in the context of a distorted 'body schema'. The present results point at a significant role for impaired central processing of proprioceptive information in the motor dysfunction of CRPS and suggest that therapeutic strategies aimed at identification of proprioceptive impairments and their restoration may promote the recovery of motor function in CRPS patients.

Introduction

Complex Regional Pain Syndrome (CRPS) is characterized by chronic pain, in combination with sensory, autonomic, trophic and motor abnormalities (Marinus et al., 2011). Reported motor impairments may include weakness, restricted range of motion (ROM), problems with the initiation and execution of movements, and abnormal posturing (Birklein et al., 2000; Goris et al., 1990; Harden et al., 1999; Schilder et al., 2012; Schwartzman and Kerrigan, 1990; Veldman et al., 1993). The pathophysiology of CRPS-related motor impairment, however, is still poorly understood (de Mos et al., 2009). Several pathophysiological mechanisms have been postulated, 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 maladaptive neuronal plasticity at various levels of the central nervous system (Maihöfner et al., 2007; Marinus et al., 2011; Swart et al., 2009; van Hilten et al., 2005). The latter may have profound consequences for motor control, presumably through impaired processing of peripheral afferent input and abnormal integration of sensory signals during motor control (Abbruzzese and Berardelli, 2003).

Adequate motor control requires intact proprioception (i.e., the sense of position and movement) to facilitate planning and execution of movement (Hemsdörfer and Nowak, 2009; Park et al., 1999). To this end, information from various peripheral and central sources (i.e., muscle spindles, joint receptors, skin stretch receptors and centrally generated motor commands; for a review, see Proske and Gandevia, 2012) has to be integrated within the context of a mental representation of the limb or 'body schema' (Longo and Haggard, 2010). The relative contribution of the various signals may vary across joints (Collins et al., 2005) and within their movement range (Burke et al., 1988) and depend on whether a position was achieved by passive displacement or voluntary movement (Cullen, 2004; Erickson and Karduna, 2012; Gritsenko et al., 2007; Lönn et al., 2000; Paillard and Brouchon, 1968).

Given that pain may interfere with the processing of afferent signals contributing to position sense (Niddam and Hsieh, 2008; Rossi et al., 1998, 2003b) and that the mental image of the affected limb is often distorted in CRPS patients (Förderreuther et al., 2004;

Frettlöh et al., 2006; Lewis et al., 2007, 2010; Moseley, 2005; Peltz et al., 2011), a significant role of proprioceptive impairment in CRPS-related motor dysfunction seems plausible. The clinical observation that some CRPS patients need to closely watch their affected limb in order to control movements (Galer et al., 1995) may implicate an increased reliance on the visual system to compensate for disturbed proprioception. Unfortunately, little is known about proprioception in CRPS. Only recently, reported difficulties in limb position sense were supported by experimental data showing a reduced accuracy of upper limb positioning in CRPS patients (Lewis et al., 2010).

The aim of this study was to further our understanding of proprioceptive deficits in CRPS and its potential contribution to impaired motor function. To this end, we assessed accuracy and precision of joint position sense over a range of wrist positions using *passive* as well as *active* displacements. The purpose of including both types of displacement was to gain insight into the extent to which peripheral afferent signals and centrally generated efferent signals contribute to (deficits in) position sense. We also investigated whether proprioceptive performance was related to clinical characteristics and/or the sensory function of the affected limb.

Materials and Methods

Part of the experimental setup and a specific aspect of the data collected during this experiment have been described in Chapter 3, in which we evaluated the electromyographic (EMG) data obtained during active maintenance of various wrist positions in 15 CRPS patients and 15 healthy controls.

Subjects

In the present study, joint position sense was evaluated in 25 patients diagnosed with CRPS type 1 of one or both upper extremities (see Table 4.1 for patient characteristics). All patients fulfilled the International Association for the Study of Pain (IASP) criteria for CRPS (Merskey and Bogduk, 1994) and had some degree of impaired motor function, evidenced predominantly by limitations in the ROM of fingers and/or wrist, and muscle weakness. In more severely affected patients, the inflicted body part

preferably adopted an abnormal posture, impeding the ability to align the hand dorsum with the forearm. Abnormal postures were mainly characterized by flexion of the fingers and wrist, and were typically more pronounced for the fingers than for the wrist (cf. Munts et al., 2011a; van Rijn et al., 2007). Subjects were excluded if they *(1)* suffered from a known genetic form of dystonia (e.g., DYT1-DYT11 or Wilson's disease), mobile dystonia, or lesions or diseases of the central nervous system; *(2)* had an implanted drug-delivery pump for intrathecal baclofen; or *(3)* had an active wrist ROM smaller than 30°. Healthy control subjects, who had normal function of both arms and suffered no 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 (40 women, 10 men; mean ± SD age: 50.1 ± 13.4 years). 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 4.1 Patient characteristics

N	25	
Sex (male/female)	5/20	
Age (mean, SD) in years	50.6	(13.7)
Disease duration (mean, SD) in years	9.0	(8.3)
Medication score (median, IQR)	7.8	(1.1-18.7)
$Pain_{week}$ (mean, SD)	6.4	(1.8)
Pain Rating Index of the		
McGill Pain Questionnaire (mean, SD)	28.2	(11.6)
Radboud Skills Questionnaire (mean, SD)	3.1	(0.7)

Abbreviations: SD, standard deviation; IQR, interquartile range; $Pain_{week}$, average pain experienced during the week prior to the experiment as scored on a numeric rating scale (NRS, 0-10).

Measurement instruments

In patients, pain and disability were evaluated using a numeric rating scale (NRS, 0 = no pain, 10 = unbearable pain) for average pain experienced during the week preceding the experiment ($Pain_{week}$), the Pain Rating Index of the McGill Pain Questionnaire (MPQ-PRI; maximum score = 63; Melzack, 1975) and the Radboud Skills Questionnaire (RSQ;

range = 0-5; Oerlemans et al., 2000a). Medication was quantified according to the Medication Quantification Scale Version III (Harden et al., 2005). In controls, hand dominance was assessed using a Dutch version of the Edinburgh Handedness Questionnaire (Oldfield, 1971).

ROM and proprioception were tested while participants sat comfortably in a chair with their elbows slightly flexed and their feet supported. On two stands, positioned on both sides of the chair, vertically oriented manipulanda were mounted that only permitted flexion-extension movements of the wrist in the horizontal plane (Figure 4.1). One hand (left, right) was measured at a time. The forearm of the tested side was placed in the apparatus in a neutral position (thumbs up and palms facing inward) and its position was restrained by foam-padded supports to prevent movements about the elbow. The distance of the handgrip (diameter 32 mm) on the manipulandum was adjusted such that the handgrip fell in the crease between thumb and index finger and the rotation axis of the wrist was aligned with that of the manipulandum. In *active conditions*, the manipulandum moved with negligible friction as it was mounted on a nearly frictionless potentiometer (FCP40A, tolerance ±0.1%, Sakae Tsushin Kogyo Co., Ltd., Nakahara-ku, Kawasaki-city, Japan) to record wrist joint angles during active movement. In *passive conditions*, the manipulandum was connected to a servo-controlled motor that moved the hand passively towards the target positions along a bell-shaped velocity profile with a maximum speed of $30°s^{-1}$. These passive movements were generated using a servo-motor (Parvex RS440GR1031, SSD Parvex SAS, Dijon Cedex, France) and a precision gearbox (Wittenstein alpha TP010S-MF1-7-0C0-2S, backlash ±0.02°, Wittenstein alpha GmbH, Igersheim, Germany), while a moderate level of white background noise was provided via headphones to eliminate any auditory feedback from the motor's motion. Visual feedback of the hand movements was precluded by an opaque screen on which an indicator was mounted, whose axis of rotation was aligned with the wrist's flexion-extension axis and whose angular position was recorded by means of a potentiometer (FCP40A, tolerance ±0.1%, Sakae Tsushin Kogyo Co., Ltd., Nakahara-ku, Kawasaki-city, Japan). On each trial, the indicator was used to record perceived joint position. To ensure that indication of the perceived joint position was not hampered by motor impairments of the participant, the

experimenter manually operated the indicator based on verbal instructions of the participant.

Surface EMG signals of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) of both arms were recorded using rectangular (20x30 mm) non-disposable differential surface electrodes (DE-2.1, Delsys Inc, Boston, MA, USA). EMG signals were amplified (1,000-10,000 times; Bagnoli™ 4-channel desktop amplifier with 20-450 Hz bandpass filter; Delsys Inc). All signals were captured at a sampling rate of 1000 Hz with 16 bit A/D conversion.



Figure 4.1 Overview of the experimental setup in passive conditions. The manipulandum with adjustable handgrip was connected to a servo-controlled motor that moved the hand passively towards the target positions. The same manipulandum was mounted on a potentiometer to record wrist joint angles in active conditions. The indicator was manually operated by the experimenter based on verbal instructions of the participant to indicate the perceived joint position.

Data collection procedure

Prior to investigating proprioception, the following sensory tests were conducted in random order to evaluate other sensory functions: *(1)* pain threshold for deep somatic pressure exerted on the abductor pollicis brevis muscle to quantify muscle hyperalgesia (pressure pain threshold [PPT] in kgf) using an electronic algometer (FPX50; Wagner Instruments, Greenwich, CT); *(2)* two-point discrimination (TPD) on the hand dorsum (in

mm) to quantify tactile spatial acuity using an aesthesiometer (Baseline; Fabrication Entrprises, White Plains, NY); *(3)* perceptual threshold for 100 Hz vibration applied to the hand dorsum (os metacarpale II) to quantify vibrotactile sensibility (vibration detection threshold [VDT] in μm) using a vibrameter (Type II, Somedic, Stockholm, Sweden; pressure 0.45 kgf). Each test was repeated three times per hand (left, right), alternating between the hands.

For the purpose of normalization of the EMG recordings, the participant's forearm was placed in the apparatus with the wrist in a comfortable position. For each forearm, two EMG recordings were obtained at rest. For each muscle the lower of the two resting values was used for normalization of the EMG (cf. Chapter 3).

Passive ROM (PROM) was determined by measuring the maximal wrist flexion and extension achieved by applying force at a right angle to the manipulandum until discomfort was reported. Active ROM (AROM) was subsequently determined by measuring the actively achieved maximal wrist flexion and extension positions. For PROM and AROM, two measurements were performed per hand (left, right). The initial movement direction (flexion, extension) was counterbalanced across participants. Prior to and following the AROM measurements, participants were instructed to adopt the most comfortable wrist position, which was recorded as their preferred wrist orientation.

For each individual patient, five target positions were calculated on the basis of the AROM of the affected side, which was averaged over the two measurements. Target positions were located at the center of this AROM (0%), which was considered the neutral wrist orientation for the participant in question, and at 40% and 80% of the maximum excursion relative to this neutral position (in both flexion and extension directions). In order to control for differences in proprioceptive performance that might be related to differences in ROM (Fuentes and Bastian, 2010; Janwantanakul et al., 2001; Yang et al., 2008), target positions of the patient's unaffected hand were located at the same relative positions (i.e., expressed as a percentage of that wrist's AROM; *relative matching*), or at exactly the same positions as they were for the affected hand (*absolute matching)*. Similarly, age- and gender-matched control subjects performed the relative matching as well as the absolute matching condition – the latter implying that target positions were identical to those of the matched patient's affected hand (Figure 4.2). For each condition,

five blocks of five trials were completed, with each of the target positions being presented in random order once within a block to ensure that the five target positions were evenly distributed within each condition. There was no extra pause between these blocks of five trials, because evaluation of proprioceptive precision required that subjects remained ignorant of the fact that five standardized positions were repeatedly tested.

For testing passive joint position sense, the wrist was passively flexed or extended towards a target position where it remained until the end of the trial. Participants were instructed to keep their arm muscles as relaxed as possible during the entire trial. As soon as the target position was reached, the experimenter started to rotate the indicator at constant speed until the participant indicated that its orientation matched the perceived joint angle. After completion of a trial, the indicator was alternately positioned in either a 120° flexion or 120° extension orientation upon which the next trial was initiated. The wrist was moved from one target position to the next (i.e., without returning to the neutral position between trials), with an inter-trial interval of approximately 5-10 seconds. The same procedure was followed for testing active joint position sense, except that participants actively performed flexion or extension of the wrist in order to reach the predefined target positions. To guide these movements, acoustic signals were provided via the headphones to indicate *(1)* when the actual wrist position fell within the tolerance range around the target position (i.e., ±1.875°; pitch: 800 Hz); and *(2)* when the wrist had remained within this target range for 2 seconds (pitch: 400 Hz). The procedure of indicating the perceived joint position was initiated after the second acoustic signal to ensure that the wrist orientation was stable.

Hence, the experiment involved eight experimental conditions, comprising all combinations of active and passive displacements of the left and right hand, for both relative and absolute matching (Figure 4.2). However, if relative and absolute matching did not yield sufficiently different target positions (i.e., if both the difference in AROM obtained for an individual participant and the difference in neutral position were smaller than 15% of the AROM of the unaffected hand), then the experimental tasks were only performed for absolute matching, resulting in four instead of eight conditions. To minimize inconvenience for the patients, the order of experimental tasks was pseudo-randomized such that two conditions involving the affected hand were always separated

by at least one condition involving the unaffected hand. The inter-condition interval was approximately 5 minutes, with a longer break (15-20 min) after completing 50% of the conditions. Throughout the experiment, participants were allowed to rest longer if requested. An NRS (0-10) was administered to patients immediately after completion of each condition (i.e., passive and active) with their affected hand in order to evaluate pain experienced during the task ($Pain_{task}$).

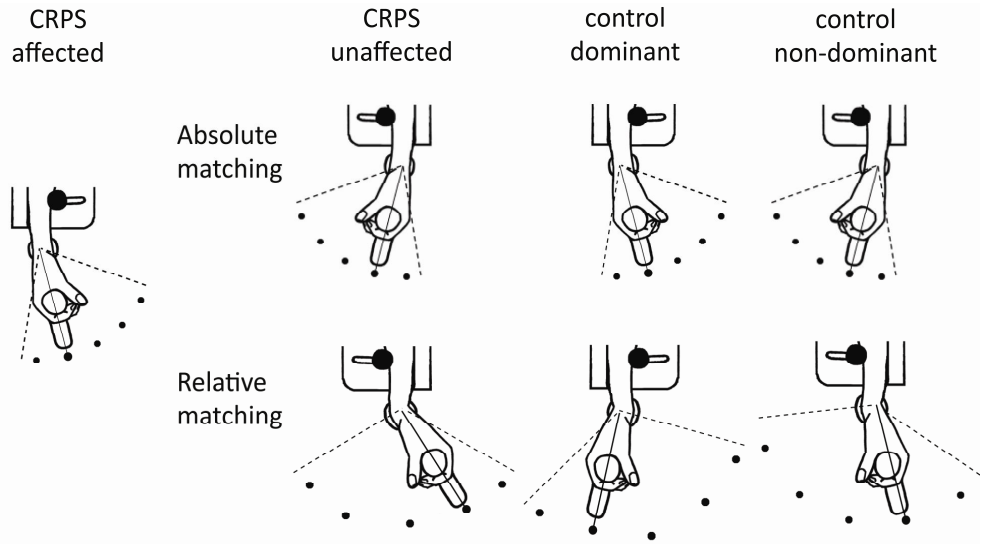


Figure 4.2 Schematic overview of experimental conditions. Target positions of the patient's affected side (indicated by dots) were located at the center of the AROM (0%) and 40% and 80% of the maximum excursion relative to this neutral position (in both flexion and extension directions; maxima indicated by dotted lines). Target positions of the patient's unaffected side and the matched controls were located at exactly the same positions as they were for the patient's affected side (absolute matching), or at the same relative positions (i.e., expressed as a percentage of that wrist's AROM: relative matching; note the variation in locations of target positions between individual hands). All conditions were performed twice (i.e., using active as well as passive displacements).

Data analysis

Two of the 25 CRPS patients had two affected arms. Data from the most affected side were used for analysis. Because data obtained from these two patients could not be included in analyses involving a comparison with the unaffected hand, data from 23

patients remained for those analyses. Technical issues related to safety constraints of the apparatus hampered evaluation of the '80% flexion' position in one patient and in the absolute matching condition for the two matched control subjects. Due to technical problems, no EMG recordings were obtained from four patients and one control subject.

Motor parameters

AROM and PROM were calculated from angular position data of the manipulandum obtained during maximum flexion and extension (low-pass filtered using a second-order bi-directional Butterworth filter, cut-off frequency = 10 Hz). The preferred (i.e., most comfortable) wrist orientation was averaged over the two measurements, with negative values indicating flexion relative to the manipulandum being aligned with the forearm.

Proprioceptive performance

Angular position data of the manipulandum and the indicator were low-pass filtered (second-order bi-directional Butterworth filter, cut-off frequency = 10 Hz). The final, stable orientation of the indicator (averaged over a period of 250 ms) reflected the perceived joint position. To ensure that the indicated joint position reflected a stable wrist orientation, trials from active conditions were excluded from analysis if hand displacement was >0.5° over the 250 ms before the indicator reached its final orientation. Based on this criterion, 50 trials were discarded (patients: 24 trials; controls: 26 trials). Data from nine additional trials were excluded from analysis, because these trials were terminated inadvertently before completion of the indication procedure. Because of aggravation of complaints with active movements of the affected hand, one patient performed only three repetitions per target position, whereas two other patients were unable to reach some of the predefined flexion (P8: 10 trials) or extension (P25: 2 trials) target positions. Altogether 66 out of 12,920 trials (0.5%) were excluded from data analysis.

For the remaining trials, the error (in degrees) was calculated as the difference between the orientation of the indicator and the concurrent orientation of the manipulandum, with a positive error meaning that the wrist was perceived in a more extended position. Proprioceptive performance was quantified by means of the absolute

error (AE; mean absolute error), the constant error (CE; mean error, in which the sign of the error [i.e., direction] is taken into account) as a measure of accuracy or 'directional bias' and the variable error (VE; standard deviation of the error) as a measure of precision or 'reproducibility of estimates'. For each participant, these outcome measures were not only calculated over all included trials per condition (i.e., AE_{total}, CE_{total} and VE_{total}), but also separately for each of the five target positions per condition (i.e., AE_{target}, CE_{target} and VE_{target}) to gain more insight into variations in proprioceptive performance over the range of positions.

Because the initial position of the hand (i.e., the end position in the previous trial) varied over trials, between-trial variations in the direction of (passive or active) movements might have contributed to variations in proprioceptive performance over the range of positions (Fuentes and Bastian, 2010). To evaluate a possible effect of movement direction on proprioceptive performance without any potentially confounding effects of target position, the accuracy of estimates obtained after a flexion movement towards the neutral position ($CE_{0,F}$) was compared with the accuracy of estimates obtained after extension movements to this position ($CE_{0,E}$). Importantly, on average the distribution of flexion and extension movements was comparable between patients and controls given the random sequencing of target positions

Muscle activity

EMG recordings were used to compare muscle activity between active and passive proprioception tests, in order to assess the potential role of efferent signals in position sense (for a detailed analysis of EMG recordings in active conditions see Chapter 3). EMG data from 1.4% of the trials (i.e., 61 trials in patients, 117 trials in controls) were excluded due to movement artifacts. For the remaining trials, power line noise was removed using a fourth-order bidirectional Butterworth band-stop filter (50 Hz and its 100 Hz and 150 Hz harmonics). Subsequently, EMG data were digitally band-pass filtered (second-order bi-directional Butterworth 10-400 Hz) and full-wave rectified. Because many patients to some degree suffered from a loss of voluntary control, the lower of the two resting values per muscle was used for EMG normalization (Chapter 3; Soderberg and Knutson, 2000). Activity of the wrist flexor (EMG_{FCR}) and wrist extensor (EMG_{ECR}) muscles was thus

expressed as ratio-to-rest (RR; see Chapter 3) and quantified for two phases of each trial: *(1)* mean amplitude of EMG during the second half of movement towards the target position (i.e., from the time instant that half of the distance towards the target position had been traversed, characterizing the muscle activity needed to generate the movement towards the target position); and *(2)* mean amplitude of EMG at the target position (characterizing the muscle activity required to maintain the target position). Initial overshoot of the target position and subsequent corrective movements were occasionally observed in active conditions, but were not included in the EMG analysis.

Statistical analysis

For each participant, the median values of sensory tests (PPT in kgf, VDT in μm and TPD in mm) per hand were used, in order to reduce the influence of outliers. AROM, PROM and preferred orientation were averaged over the two measurements per hand. Statistical analysis was performed using IBM® SPSS® Statistics 20.0 (IBM Corp., Armonk, NY, USA). Normality curves were inspected and Kolmogorov-Smirnov tests were performed to assess whether the data in each condition were normally distributed within each group. PROM and preferred orientation were normally distributed in all conditions, whereas slight deviations from normality were observed for AROM, AE_{total}, CE_{total}, VE_{total}, CE_{target}, $CE_{0,F}$ and $CE_{0,E}$ in a small subset (<20%) of conditions. For other parameters (PPT, VDT, TPD, EMG_{FCR}, EMG_{ECR}, AE_{target} and VE_{target}), deviations from normality were observed in circa 50% of the conditions, mainly due to positive skew in the control group. After log-transformation, these parameters were normally distributed in >87.5% of conditions. Although log-transformed data were used for statistical analysis of these parameters, for reasons of clarity the untransformed data are presented in the Results.

To compare proprioceptive performance of the patients' affected hands to that of the unaffected hands and healthy controls, statistical analyses were conducted separately for relative and absolute matching conditions. For the unaffected hand of 4 CRPS patients and the dominant and/or non-dominant hand of 6 controls, data from absolute matching conditions was also used for comparisons involving the relative matching conditions, because proprioception tests had been performed under the absolute matching conditions only (see *Data collection procedure*). Measures of overall proprioceptive performance (i.e.,

AE_{total}, CE_{total} and VE_{total}) were submitted to a mixed analysis of variance (ANOVA) with movement type (active vs. passive) and side (affected/non-dominant vs. unaffected/dominant) as within-subject factors and group (CRPS patients [PT] vs. healthy controls [HC]) as between-subjects factor. Because no significant effect of hand dominance was detected, the non-dominant and dominant hand of controls were arbitrarily allocated to the factor 'side'.

In view of empty cells resulting from the exclusion criteria and technical issues, data of 21 PT and 50 HC (reduced to 48 in the absolute matching conditions) remained for statistical analysis of proprioceptive performance over the entire range of wrist positions. CE_{target} and the log-transformed AE_{target} and VE_{target} were subjected to a mixed ANOVA with movement, side and target position (5 levels: 80% and 40% flexion, neutral position, 40% and 80% extension) as within-subject factors and group as between-subjects factor. Degrees of freedom were adjusted if the sphericity assumption was violated (Field, 2009). Because this analysis was conducted to examine the variations of proprioceptive performance over the range of positions, only effects that involved the factor 'target position' were reported.

To evaluate a potential effect of movement direction on proprioceptive performance, a mixed ANOVA was conducted on CE_0 with direction (flexion vs. extension), side and movement type as within-subject factors, and group as between-subjects factor. As a result of the randomized sequence of target positions, the neutral position was approached from the same direction in all five repetitions of a specific condition for some participants, leaving 21 PT and 36 HC for analysis of CE_0 in relative matching conditions and 21 PT and 46 HC in absolute matching conditions. Because this analysis was designed to gain insight into effects of movement direction on proprioception, only (interaction) effects of direction are reported.

EMG_{FCR} and EMG_{ECR} were submitted to a mixed ANOVA with phase (during movement vs. at target), movement type and side as within-subject factors, and group as between-subjects factor (PT: n=20, HC: n=48). Because this analysis was conducted to compare muscle activity between active and passive conditions, only (interaction) effects of movement type were reported.

Measures of sensory function (i.e., VDT, TPD and PPT) and motor parameters (i.e., AROM, PROM and preferred orientation) were submitted to a mixed ANOVA with side as within-subject factor and group as between-subjects factor. For all ANOVAs, effect sizes were quantified as partial eta squared (η_p^2). For significant effects ($p<.05$), post hoc analyses were performed using two-tailed *t*-tests. Values are presented as mean ± standard deviation.

To explore whether proprioceptive performance (quantified by AE_{total}, CE_{total} and VE_{total}) of the patients' affected and unaffected hands was related to clinical characteristics (i.e., disease duration, medication use, $Pain_{week}$, $Pain_{task}$, MPQ-PRI and RSQ), measures of sensory function (i.e., VDT, TPD and PPT), or motor parameters (i.e., AROM, PROM and preferred orientation), pairwise correlations were calculated separately for the two hands. Pairwise correlations were also used to examine whether proprioceptive performance of the two hands of CRPS patients (affected, unaffected) were correlated. Pearson correlation coefficient was used for normally distributed continuous data. Kendall tau was used for correlations with $Pain_{week}$ and $Pain_{task}$, because for these variables a small range of scores was observed, which resulted in tied ranks (Field, 2009). Spearman rho was used for all other data. Because this was regarded as an exploratory analysis, statistical significance was not adjusted for multiple testing (Bender and Lange, 2001). Instead, only relatively strong (i.e., >.40) and consistent correlations (i.e., observed in both active and passive conditions) were considered to be of interest.

Results

Sensory and motor parameters

For each of the measures of sensory and motor function, a significant interaction between hand and group was observed (see Table 4.2). Post hoc analyses showed that the affected hand of CRPS patients was inclined to adopt a more flexed posture at rest and was characterized by increased levels of muscle hyperalgesia (i.e., lower PPT), a loss of spatial discrimination (i.e., higher TPD) and a limited range of motion (i.e., smaller AROM and PROM) compared with the unaffected hand and controls. The reduction of vibration

sense (i.e., higher VDT) for the affected hand failed to reach significance, whereas for controls the non-dominant hand appeared more sensitive to vibration than the dominant hand. No other significant differences were observed between the unaffected hand of patients and the dominant hand of controls and between the two hands of controls.

Proprioceptive performance

Table 4.3 presents the significant (interaction) effects obtained from the mixed ANOVAs. Results with respect to overall proprioceptive performance are depicted in Figure 4.3, whereas variations in proprioceptive performance over the range of target positions can be appreciated from Figure 4.4 (relative matching conditions) and Figure 4.5 (absolute matching conditions).

Table 4.2 Results of sensory tests and range of motion measurements

	PT-A	PT-UA	HC-ND	HC-D	'Group × side'	
					p-value	η_p^2
PPT (kgf)	1.77 (1.07) #*	3.60 (1.26)	4.25 (1.68)	4.30 (1.61)	<.001	.49
VDT (μm)	0.50 (0.36)	0.43 (0.39)	0.42 (0.25)	0.49 (0.34) *	.006	.50
TPD (mm)	23.1 (7.7) #*	18.2 (7.2)	17.0 (5.7)	18.0 (4.6) *	<.001	.21
Preferred orientation (°)	-27.7 (22.9) #*	-18.8 (13.6)	-17.4 (13.3)	-17.0 (14.6)	.007	.10
AROM (°)	96.4 (32.2) #*	159.0 (28.8)	170.0 (12.3)	168.8 (12.6)	<.001	.54
PROM (°)	95.6 (32.0) #*	152.7 (20.9)	161.8 (13.1)	161.5 (12.3)	<.001	.51

Abbreviations: PT, patients; A, affected side; UA, unaffected side; HC, healthy controls; D, dominant side; ND, non-dominant side; PPT, pressure pain threshold; VDT, vibration detection threshold; TPD, two-point discrimination; AROM, active range of motion; PROM, passive range of motion. Measures are presented as mean (SD) and are based on 23 PT vs. 50 HC, except for PPT: *n*=21 PT; VDT: *n*=21 PT; TPD: *n*=20 PT; Missing values were the result of severe allodynia (*n*=1; all sensory tests) or failure in detecting sensory thresholds (*n*=2); Effect size of the 'group × side' interaction was quantified as partial eta squared (η_p^2). Post hoc analyses of the significant interaction between group and side were performed using paired *t*-tests for within-subject comparisons (PT-A vs. PT-UA, HC-ND vs. HC-D) and independent *t*-tests for between-subjects comparisons (PT-A vs. HC-ND, PT-UA vs. HC-D); Symbols indicate significant differences (p<.05) compared to HC-ND (*) and PT-UA (#).

Table 4.3 Significant results of the mixed ANOVAs

		Relative matching				**Absolute matching**			
Outcome	Effect	*F-value*		*p*	η_p^2	*F-value*		*p*	η_p^2
Absolute error (AE)									
AE_{total}	group	$F_{1,71}$ =	8.75	.004	.11	$F_{1,71}$ =	10.07	.002	.12
	movement type	$F_{1,71}$ =	14.76	<.001	.17	$F_{1,71}$ =	22.24	<.001	.24
AE_{target}	target	$F_{2.6,177.0}$ =	39.12	<.001	.36	$F_{2.4,159.6}$ =	25.74	<.001	.28
	target × group		.	.	.	$F_{2.5,168.3}$ =	7.59	<.001	.10
Accuracy – constant error (CE)									
CE_{total}	group	$F_{1,71}$ =	27.49	<.001	.28	$F_{1,71}$ =	38.36	<.001	.29
	movement type		.	.	.	$F_{1,71}$ =	7.12	.009	.09
CE_{target}	target	$F_{4,131.6}$ =	133.61	<.001	.66	$F_{1.6,108.9}$ =	185.31	<.001	.73
	target × movement type	$F_{4,236.4}$ =	3.94	.006	.05	$F_{3.0,199.4}$ =	3.57	.015	.05
	target × side × group	$F_{4,236.4}$ =	4.04	.019	.06		.	.	.
Precision – variable error (VE)									
VE_{total}	group		.	.	.	$F_{1,71}$ =	4.79	.032	.06
	movement type	$F_{1,71}$ =	8.36	.005	.11	$F_{1,71}$ =	12.39	.001	.15
	side × group	$F_{1,71}$ =	7.69	.007	.10		.	.	.
VE_{target}	target	$F_{4,276}$ =	24.67	<.001	.26	$F_{4,268}$ =	6.38	<.001	.09
	target × group	$F_{4,276}$ =	4.48	<.001	.07		.	.	.
Muscle activity in active vs. passive conditions									
EMG_{FCR}	movement type × phase	$F_{1,67}$ =	28.10	<.001	.30	$F_{1,66}$ =	18.23	<.001	.22
	movement type × phase × group	$F_{1,67}$ =	5.14	.027	.07		.	.	.
EMG_{ECR}	movement type	$F_{1,67}$ =	62.47	<.001	.48	$F_{1,66}$ =	67.00	<.001	.50
	movement type × phase	$F_{1,67}$ =	61.55	<.001	.48	$F_{1,66}$ =	28.25	<.001	.30
	movement type × phase × group	$F_{1,67}$ =	8.03	.006	.11		.	.	.
Effect of movement direction									
CE_0	movement direction	$F_{1,55}$ =	143.02	<.001	.72	$F_{1,65}$ =	134.52	<.001	.67
	movement direction × group	$F_{1,55}$ =	5.90	.018	.10	$F_{1,65}$ =	6.70	.012	.09

Effect size of the significant (p<.05) main effects and interaction effects (indicated by '×') was quantified as partial eta squared (η_p^2). Between-subjects factor: group (CRPS patients vs. controls). Within-subject factors: side (affected/non-dominant vs. unaffected/dominant); movement type (active vs. passive); target (5 levels: 80% and 40% flexion, neutral position, 40% and 80% extension; only for AE_{target}, CE_{target} and VE_{target}); phase (during movement vs. at target; only for muscle activity of flexor carpi radialis [EMG_{FCR}] and extensor carpi radialis [EMG_{ECR}]); movement direction (flexion vs. extension; only for CE_0). Because the analyses were designed to assess the effects of specific factors on proprioception, only effects that involved the factor 'target' are reported for AE_{target}, CE_{target} and VE_{target}, only (interaction) effects of 'movement type' are reported for EMG_{FCR} and EMG_{ECR}, and only (interaction) effects of 'movement direction' are reported for CE_0.

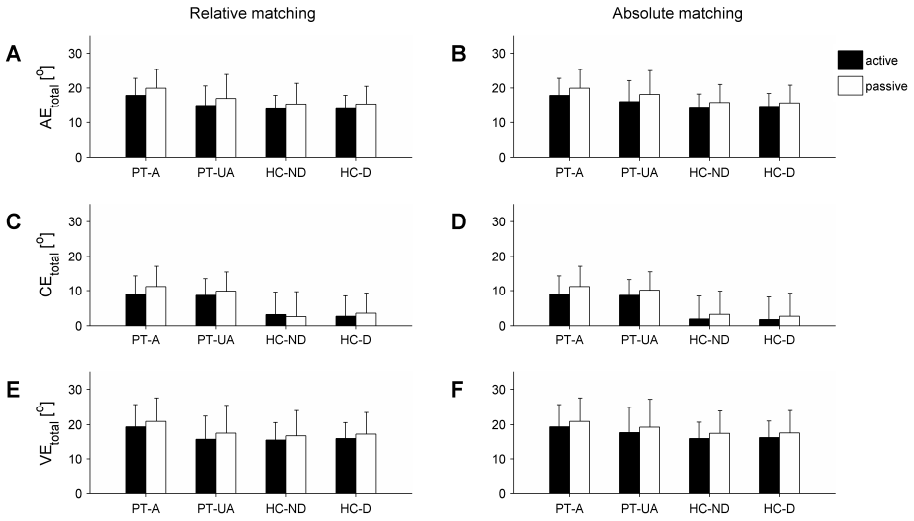


Figure 4.3 Results for overall proprioceptive performance using active and passive displacements under relative and absolute matching conditions. **(A-B)** mean absolute error, AE_{total}; **(C-D)** mean constant error, CE_{total}; **(E-F)** mean variable error, VE_{total}. In all graphs, error bars represent standard deviations. Abbreviations: PT, patients (n=23); HC, healthy controls (n=50); A, affected side; UA, unaffected side; D, dominant side; ND, non-dominant side.

Absolute error

AE_{total} was larger for CRPS patients compared to controls and for passive movements compared to active movements (see Figure 4.3A-B), as was evidenced by significant main effects of group and movement type for both relative and absolute matching. No significant interaction effects between side and group were observed.

Variations of AE over the range of target positions can be appreciated from Figures 4.4A-B and 4.5A-B. For relative matching conditions, AE increased from flexion to extension, with significant differences between all targets, except that AE_{target} at 80% flexion was not significantly different from AE_{target} at 40% flexion and the neutral position (0%). For absolute matching conditions, the main effect of target was complemented by a significant interaction between target and group. Post hoc analysis revealed that patients made larger errors than controls at the neutral position and at the two extension positions, whereas there were no differences between patients and controls at both flexion positions. For patients, AE_{target} increased with larger deviations from the neutral

wrist position, but only in the extension direction (i.e., AE at each of the two flexion positions was not significantly different from that at the neutral position). Such an asymmetry between AE_{target} at flexion and extension positions was absent for controls, in whom values of AE_{target} at the 80% extension and 80% flexion targets were of similar magnitude and both significantly increased relative to AE_{target} at the intermediate positions.

Accuracy – constant error

For relative matching, a significant main effect of group on CE_{total} was observed, whereas the interaction between movement type, side and group just failed to reach significance (p=.064). The main effect indicated that proprioceptive accuracy was reduced in patients, who perceived their hands to be located more towards extension than controls (9.9 ± 4.1° vs. 3.0 ± 5.6°). Also under absolute matching conditions, patients were less accurate than controls (9.9 ± 4.1° vs. 2.4 ± 6.2°) with active movement resulting in more accurate perception of hand orientation than passive movement (4.1 ± 6.7° vs. 5.4 ± 7.1°) in both groups.

As can be appreciated from Figures 4.4C-D and 4.5C-D, proprioceptive accuracy varied considerably over the range of target position in both relative and absolute matching conditions. Post hoc analyses of the interaction effect between target and movement type revealed that CE_{target} was different for all target positions, with lower values at flexion positions and higher values at extension positions, and with passive movements being less accurate than active movements at 80% extension. No meaningful interpretation of the three-way interaction between side, target position and group in relative matching conditions was evident. The most prominent result of the associated post hoc analysis was found at the neutral position, where CE_{target} tended to be lower for the affected side in patients and for the dominant side in controls. Over the entire range of positions, however, no significant differences were observed between the two hands within each group, which suggests that the observed three-way interaction might have resulted from the relatively arbitrary allocation of the dominant and non-dominant hand of controls to the factor 'side' in the mixed ANOVA.

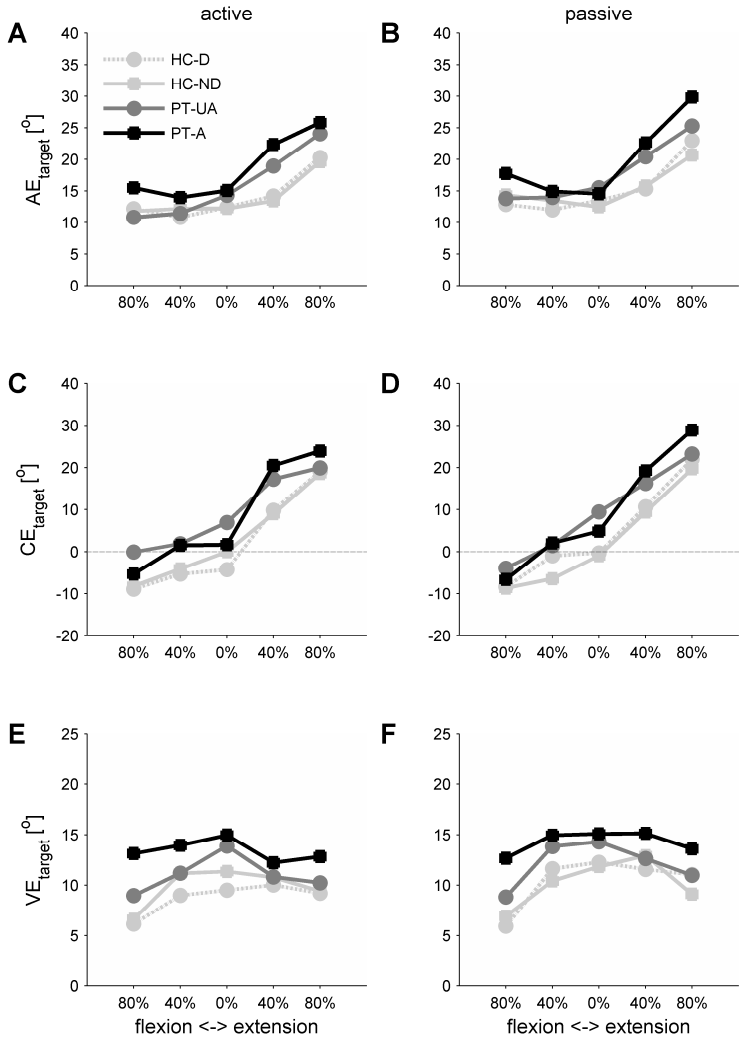


Figure 4.4 Proprioceptive performance over the range of target positions under *relative matching conditions*, using active and passive displacements. **(A-B)** mean absolute error, AE_{target}; **(C-D)** mean constant error, CE_{target}; **(E-F)** mean variable error, VE_{target}. For reasons of clarity, error bars are omitted and untransformed data are presented, although log-transformed AE_{target} and VE_{target} were used in statistical analysis. Abbreviations: PT, patients (n=21); HC, healthy controls (n=50); A, affected side; UA, unaffected side; D, dominant side; ND, non-dominant side.

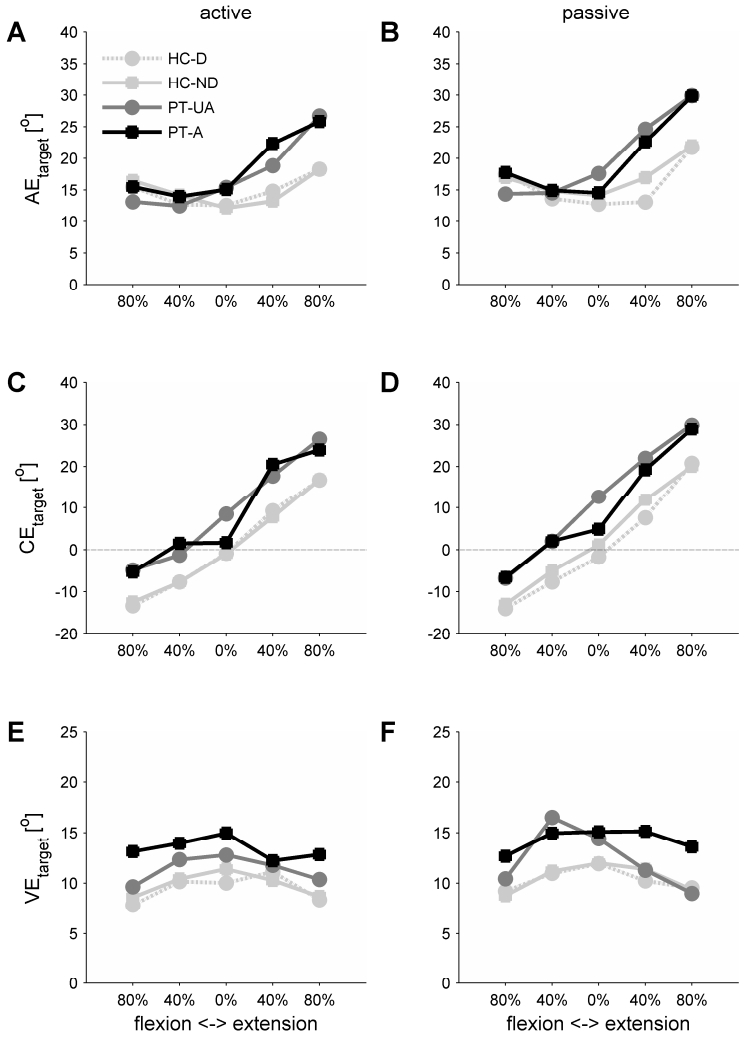


Figure 4.5 Proprioceptive performance over the range of target positions under *absolute matching conditions*, using active and passive displacements. **(A-B)** mean absolute error, AE_{target}; **(C-D)** mean constant error, CE_{target}; **(E-F)** mean variable error, VE_{target}; For reasons of clarity, error bars are omitted and untransformed data are presented, although log-transformed AE_{target} and VE_{target} were used in statistical analysis. Abbreviations: PT, patients (n=21); HC, healthy controls (n=48); A, affected side; UA, unaffected side; D, dominant side; ND, non-dominant side.

Precision – variable error

A significant effect of movement type on VE_{total} indicated higher precision (i.e., smaller VE) for active compared to passive movements (relative matching: 16.6 ± 4.8° vs. 18.0 ± 6.5°; absolute matching: 17.1 ± 5.0° vs. 18.6 ± 6.4°). For relative matching, post hoc analyses of the significant interaction between side and group revealed that patients were less precise than controls, but only for their affected hand. Such a significant interaction was absent for absolute matching, indicating that proprioception was less precise in CRPS patients than in controls (19.9 ± 5.4° vs. 16.9 ± 5.3°), irrespective of the hand involved.

Proprioceptive precision varied over the range of target positions (see Figures 4.4E-F and 4.5E-F; VE_{target}). For relative matching, post hoc analysis of the interaction between target and group showed that patients were less precise than controls at the neutral position and the 80% flexion target position. Both groups were less precise at the neutral position than at positions close to the extremes of the movement range (i.e., at the 80% flexion and 80% extension positions), with the lowest values of VE_{target} being observed for controls at the 80% flexion target. Also for absolute matching, precision was higher at the 80% flexion and 80% extension target positions than at intermediate positions (i.e., 40% flexion and neutral).

Exploratory analyses

Muscle activity in active vs. passive conditions

In relative matching conditions, post hoc analysis of the three-way interactions between movement type, phase and group revealed that EMG_{ECR} (in RR) was lower in passive compared to active conditions for both patients and controls, with the difference between these conditions being larger at the target (PT: 2.3 ± 1.1 vs. 3.7 ± 2.1; HC: 2.8 ± 1.4 vs. 4.7 ± 2.6) than during movement towards the target (PT: 2.6 ± 1.1 vs. 3.6 ± 2.0; HC: 3.3 ± 1.7 vs. 4.1 ± 2.1). Also EMG_{FCR} (in RR) was significantly lower in passive compared to active conditions, but only at the target (PT: 2.9 ± 1.5 vs. 3.3 ± 1.5; HC: 3.2 ± 1.9 vs. 3.8 ± 1.8) and not during movement towards the target (PT: 3.2 ± 2.0 vs. 3.2 ± 1.9; HC: 3.8 ± 2.5 vs. 3.3 ± 1.6). In the control group, relatively high values of EMG_{ECR} and EMG_{FCR} were observed during passive displacements. Findings for absolute matching were

largely similar, although interaction effects with group were no longer significant. Post hoc analysis of the interaction effect between movement type and phase showed that the reduction of muscle activity in passive compared to active conditions was more pronounced for static maintenance at the target position (passive vs. active, EMG_{ECR} [in RR]: 1.7 ± 1.0 vs. 2.9 ± 1.8; EMG_{FCR} [in RR]: 2.1 ± 1.3 vs. 2.3 ± 1.3) than for hand displacements (EMG_{ECR} [in RR]: 2.0 ± 1.1 vs. 3.0 ± 1.9; EMG_{ECR} [in RR]: 2.4 ± 1.9 vs. 2.3 ± 1.3).

Effect of movement direction

Joint angle perception depended on whether the neutral wrist orientation was achieved by means of a flexion or extension movement, as was evidenced by a main effect of movement direction in relative and absolute matching conditions. Specifically, flexion movements introduced a bias towards flexion, whereas extension movements introduced a bias towards extension. Post hoc analysis of the interaction effect between movement direction and group revealed that the effect of movement direction was more pronounced in patients (flexion vs. extension, relative matching: -0.3 ± 5.0° vs. 16.1 ± 9.6°; absolute matching: 1.7 ± 7.3° vs. 18.6 ± 10.4°) than in controls (relative matching: -5.3 ± 8.6° vs. 5.6 ± 9.3°; absolute matching: -4.5 ± 9.7° vs. 6.1 ± 10.0°), and that reductions of proprioceptive accuracy in patients occurred mainly after extension movements. These findings were similar for active and passive movements because interaction effects with movement type were absent.

Correlations

The correlation coefficients of overall proprioceptive performance (quantified by $AE_{total,}$ CE_{total} and VE_{total}) of the patient's affected side with clinical characteristics and measures of sensory and motor function are presented in Table 4.4. Range of motion (AROM as well as PROM) was strongly correlated with precision and absolute error for both active and passive conditions. Specifically, a smaller range of motion was associated with larger spread of the errors (i.e., reduced precision) and larger absolute errors, both of which are indicative of impaired proprioceptive performance. No consistent correlations were observed with measures of pain and disability, other clinical characteristics, or the

outcomes of sensory tests. For the patients' unaffected hands, no consistent correlations were observed between proprioceptive performance and measures of sensory and motor function. Proprioceptive performance of the affected and unaffected sides of CRPS patients were highly correlated (AE_{total}: r=.59 and r=.72, CE_{total}: r=.59 and r=.58, and VE_{total}: r=.65 and r=.79 in active and passive conditions, respectively; all p<.01).

Table 4.4 Correlations with proprioceptive performance for the affected hand of CRPS patients

	Absolute error – AE_{total} (°)		Accuracy – CE_{total} (°)		Precision – VE_{total} (°)	
	Active	Passive	Active	Passive	Active	Passive
Clinical characteristics						
Disease duration (yr) [a]	–.33	–.23	–.08	–.28	–.36	–.17
Medication score [b]	.35	.17	.29	.07	.19	.20
$Pain_{week}$ (NRS 0-10) [c]	.16	.07	.07	–.12	.19	.20
$Pain_{task}$ (NRS 0-10) [c]	.10	–.06	.05	–.17	.14	.19
MPQ-PRI [a]	.09	.32	–.47 *	.01	.17	.48 *
RSQ [a]	.18	.30	–.19	.06	.21	.47 *
Sensory function						
PPT (kgf) [a]	–.20	–.11	–.23	–.02	–.17	–.23
VDT (μm) [b]	–.15	–.02	–.03	–.03	.01	–.15
TPD (mm) [a]	–.08	.15	–.37	–.23	.15	.28
Range of motion						
Preferred orientation (°) [a]	.13	.02	–.04	.09	.16	–.11
AROM (°) [a]	–.45 *	–.57 **	–.02	–.18	–.41 *	–.57 **
PROM (°) [a]	–.63 **	–.70 **	–.09	–.20	–.61 **	–.75 **

Abbreviations: NRS, numeric rating scale; MPQ-PRI, pain rating index of the McGill Pain Questionnaire; RSQ, Radboud Skills Questionnaire; PPT, pressure pain threshold; VDT, vibration detection threshold; TPD, two-point discrimination threshold; AROM, active range of motion; PROM, passive range of motion. $Pain_{week}$ = average pain experienced during the week prior to the experiment; $Pain_{task}$ = average pain experienced during the experimental task; Pairwise correlations were calculated using Pearson's correlation coefficient ([a]), Spearman's rho ([b]) or Kendall's tau ([c]). Significant correlations are indicated by asterisks (* = p<.05; ** = p<.01).

Discussion

In this study we examined proprioception over a range of positions, using active and passive displacements, in chronic CRPS patients with various degrees of motor dysfunction. Our findings showed bilateral proprioceptive impairment in patients, in line with Lewis et al. (2010), and provide new insights into the proprioceptive deficits by differentiating between precision (VE) and accuracy (CE). In particular, patients displayed reduced precision (i.e., higher variability) of the perception of limb postures in combination with a systematic 'misperception' of extension positions (i.e., reduced accuracy), where the perceived hand position was located more towards extension than the actual position. This was also reflected in larger absolute errors (AE). For the patients' affected hands, more severe motor impairment (i.e., smaller AROM and PROM) was associated with poorer proprioceptive performance (in terms of AE and VE), suggesting a close relationship between proprioceptive impairment and CRPS-related motor dysfunction. Because these differences in proprioceptive performance between patients and controls persisted in absolute matching conditions, they cannot simply be attributed to the smaller range and closer spacing of target positions of the patients' affected hands.

Bilateral proprioceptive deficits and unilateral motor impairments?

Bilateral proprioceptive impairments were observed in patients showing unilateral ROM limitations. At first glance, this seems incompatible with the notion of a close relationship between proprioceptive deficits and CRPS-related motor dysfunction. However, previous studies have shown that impaired central motor processing in CRPS is not limited to the affected side but may also manifest itself in the unaffected side, although to a lesser degree and predominantly during relatively complex motor tasks (Ribbers et al., 2002; Schilder et al., 2012). Hence, the AROM may not have been a sensitive enough measure to discern potential motor impairments in the unaffected hand. Alternatively, the motor deficits in the affected hand may be primarily related to the observed reduction of proprioceptive precision (i.e., increased VE), which – in contrast to the bilateral impairment of AE and CE – was more pronounced in the affected hand of CRPS patients. After all, the *precision* of sensory information is crucial for adequate motor

control because in the integration of proprioceptive, tactile and visual input, the highest weight is given to the most precise source of sensory information (sensory weighting; Bays and Wolpert, 2007; Ernst and Bülthoff, 2004). Indeed, motor impairment of the affected hand correlated strongly and consistently with proprioceptive precision (VE_{total}) but not with accuracy (CE_{total}).

Origin of proprioceptive deficits

Adequate proprioception comprises three sequential stages of information processing: *(1)* detection and transmission of afferent information; *(2)* integration of information from various peripheral and central sources; and *(3)* interpretation of this information in relation to a body schema (Proske and Gandevia, 2012). Below, strategic comparisons of proprioceptive parameters between conditions (i.e., active vs. passive; absolute vs. relative matching) and within conditions (i.e., over the range of wrist positions) are addressed, with the aim to identify at which of these stages the observed proprioceptive deficits arise.

Stage 1: Detection and transmission of information

Although vibration sense was not significantly impaired (contrary to Huge et al., 2011), impaired processing of afferent signals in CRPS patients was reflected in the presence of muscle hyperalgesia and reduced tactile discrimination. However, these variables did not correlate with measures of proprioceptive performance. Perhaps the examined aspects of sensory function were not directly involved in proprioception, or the associated tests were too simple in relation to the complexity of proprioception. To obtain more insight into afferent signals that are directly involved in proprioception, we evaluated variations of proprioceptive performance over a range of positions within the wrist's AROM. In contrast to controls, patients showed an asymmetrical distribution of proprioceptive errors, with negligible systematic misperception at flexion positions (i.e., CE close to 0) and large systematic overestimation of wrist extension angles. The largest values of AE were observed at extension positions for both patients and controls, which was less pronounced for controls in absolute matching conditions. This suggests that proprioceptive errors are associated with the processing of afferent input from receptors

(i.e., in muscle, joint and/or skin) that are markedly activated when the limits of one's ROM are approached. Furthermore, our analysis showed that position estimates were biased towards overshooting in the direction of movement (in line with Fuentes and Bastian, 2010; Goble and Brown, 2008; Jones et al., 2010; Laufer et al., 2001; Lönn et al., 2000; Mel'nichouk et al., 2007). Such a bias might be associated with movement-dependent alterations in muscle spindle sensitivity (Mel'nichouk et al., 2007) and may have contributed to the larger spread of errors (i.e., higher VE) and smaller systematic error (i.e., lower CE) at intermediate positions (which were always approached from opposite directions) compared to relatively low VE and high CE at the outermost positions (which were predominantly approached from the same direction). Notably, the patients' estimates of wrist orientation were more susceptible to influences of movement direction than those of controls, again in particular for extension movements.

These findings may imply that proprioceptive deficits in CRPS are associated with altered sensitivity of the receptors involved in proprioception. This may be a consequence of CRPS-related trophic changes, but it may also reflect suboptimal peripheral adaptations to the smaller ROM at the affected side. The encountered proprioceptive impairment of the unaffected hand, however, suggests a central processing deficit.

Stage 2: Integration of information

Given the role of efferent signals in the generation of sensory predictions of motor behavior (Festinger and Canon, 1965), the contribution of efferent signals to proprioceptive performance was examined by comparing active and passive conditions. As intended, higher levels of EMG_{ECR} and EMG_{FCR} were observed in active conditions than in passive conditions, although some muscle activity was detected during passive displacements, with participants tending to move their hand along with the manipulandum. Comparisons of proprioceptive performance in active versus passive conditions yielded similar results for absolute matching, with no significant interaction effects between movement type and group for EMG_{FCR} and EMG_{ECR}.

In line with previous reports on healthy subjects (Cullen, 2004; Erickson and Karduna, 2012; Gritsenko et al., 2007; Laufer et al., 2001; Lönn et al., 2000; Paillard and Brouchon, 1968), active displacements were associated with higher proprioceptive

accuracy and precision than passive displacements. Like controls, CRPS patients benefited from the availability of an 'efference copy' (Branch et al., 2008; Medina et al., 2010) and increased muscle spindle sensitivity (Allen et al., 2008) that are associated with active displacements, which indicates that the observed proprioceptive deficits were likely due to impaired processing of *afferent* (and not efferent) information. Possibly pain plays a significant role in this regard, given its interference with the processing of afferent signals contributing to proprioception (for a review, see Chapter 2) and its competition with other attention-demanding stimuli for limited cognitive resources (Eccleston and Crombez, 1999; Grisart and Van der Linden, 2001). Because all patients reported moderate to severe pain, limited variability in this regard may have obscured a potential relation between pain intensity and proprioceptive performance in the present study. Because in the present study $Pain_{task}$ was not assessed in relation to the various target positions, the potential association between pain and proprioceptive disturbances over the range of wrist angles could not be determined. This warrants further research on the relationship between clinical pain, abnormal pain processing and impaired proprioception in CRPS.

Stage 3: Interpretation of information

The final step in the proprioceptive process involves interpretation of the information within the context of a mental image of the body (Longo and Haggard, 2010). Hypothetically, if in CRPS patients the frame of reference has not correctly been 'updated' to the altered status of the limb (e.g., maximum joint angles are still mapped upon the maximum joint angles before developing CRPS), then the largest proprioceptive errors would be expected where the mismatch between the original and actual movement excursion is largest. Indeed, the largest proprioceptive deficits were observed across the range of extension positions, precisely where the motor impairments were most pronounced (maximum active flexion: 69.1 ± 20.5°; maximum active extension: 25.9 ± 24.1°). Given that distortions of the mental image of the affected limb (Förderreuther et al., 2004; Frettlöh et al., 2006; Lewis et al., 2007, 2010; Moseley, 2005; Peltz et al., 2011) and reorganization of the somatosensory cortex (Juottonen et al., 2002; Maihöfner et al.,

2003; Pleger et al., 2004) have frequently been reported in CRPS, the central interpretation of proprioceptive signals likely constitutes a major source of error.

Study limitations

Compared with other studies on proprioception (Adamo and Martin, 2009; Carey et al., 1996; Gay et al., 2010), the proprioceptive errors made by the healthy subjects that served as controls were relatively large, perhaps as a result of specific task characteristics. Firstly, a round handgrip was used to allow all patients to hold the manipulandum despite their reduced ability to extend the fingers. Secondly, joint angles were recorded using an indicator, because motor dysfunction of the patients' affected hands precluded the use of other common methods. This method required transformation of coordinates from a body-centered frame of reference to a visual frame of reference, which may have constituted an additional source of error (Laufer and Hocherman, 1998).

Conclusion and clinical implications

In conclusion, our results show proprioceptive impairment at both the affected and unaffected side in CRPS patients, characterized predominantly by overestimation of wrist extension angles. Precision of the estimates was more prominently reduced at the affected side. Collectively, our results suggest that these proprioceptive deficits may contribute to the motor dysfunction of CRPS, probably due to altered processing of afferent information and its subsequent interpretation in relation to a 'body schema' that does not accurately match the actual status of the limb. This indicates that therapeutic strategies aimed at identification and restoration of proprioceptive impairments may promote the recovery of motor function in CRPS patients. Although mirror therapy in CRPS did not completely fulfill its initial expectations (Ezendam et al., 2009), it is conceivable that some form of mirror therapy may serve to increase the awareness of the presence of a proprioceptive deficit and may possibly be used as a training tool for reducing the mismatch between the perceived and actual position of the affected limb, with potential benefits for motor function in CRPS patients.

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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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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 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 online 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 (Chapter 3; Gierthmühlen et al., 2012; Huge et al., 2011; Schilder et al., 2012; Schrag et al., 2004; Schwartzman and Kerrigan, 1990). The prominent loss of voluntary control is associated with significant disability (Geertzen et al., 1998; Huge et al., 2011; Maihöfner et al., 2003; Marinus et al., 2013; Perez et al., 2002; Savaş et al., 2009). Several pathophysiological mechanisms have been postulated to underpin the CRPS-related motor impairments, 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 maladaptive neuroplasticity at various levels of the central nervous system (Maihöfner et al., 2003; Marinus et al., 2011; Swart et al., 2009). 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 (Abbruzzese and Berardelli, 2003).

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). In CRPS, several sensory impairments have been reported that may interfere with force control, including altered sensitivity of cutaneous and muscular afferents (Chapter 3; Eberle et al., 2009; Huge et al., 2008; Kemler et al., 2000; Maier et al., 2010; Munts et al., 2011b; van Rooijen et al., 2013a) and disturbances in sensory-motor integration (Juottonen et al., 2002; Maihöfner et al., 2007; Mugge et al., 2013). One study using computational modeling found that aberrant force feedback from Golgi tendon organs may contribute to abnormal postures in CRPS (Mugge et al., 2012a; Munts et al., 2011a). Additionally, some CRPS patients need to watch their affected limb to control movements (Galer et al., 1995), 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; Proske and Gandevia, 2012).

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 aimed 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 online visual feedback to evaluate potential 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 Supplement 5.1.

Subjects

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. DYT1-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.

Table 5.1 Demographic and clinical information of participants

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

Abbreviations: $CRPS_{AP}$, CRPS patients with abnormal posture; $CRPS_{noAP}$, 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. [a] Chi-square test was used for comparing the groups. [b] 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. [c] Measures are presented as median (interquartile range); Mann Whitney *U*-tests were used for comparing the two CRPS groups. [d] Due to incomplete questionnaires, measures were based on *n*=27 $CRPS_{AP}$ (MPQ-PRI), and *n*=26 $CRPS_{AP}$ vs. *n*=12 $CRPS_{noAP}$ (RSQ). [e] The total number of sensory symptoms exceeded 100% because of the coexistence of different symptoms in some patients.* $p<.05$.

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; Melzack, 1975). The Burke Fahn Marsden scale was used to indicate the presence and functional impairment of abnormal postures (maximum score = 120; Burke et al., 1985). Disability due to limitations in arm function was evaluated using the Radboud Skills Questionnaire (RSQ; range = 0-5; Oerlemans et al., 2000a). The occurrence and extent of neglect-like symptoms was evaluated using a 5-item scale (range = 1-6; Frettlöh et al., 2006). 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 (Oldfield, 1971).

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 (van Rooijen et al., 2013a). 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 40 mm (Nano-40, ATI Industrial Automation, Apex, NC, USA; 0.025 N 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'] (Reilmann et al., 2010; Reilmann et al., 2013) – see Figure 5.1). Table height was adjusted if required. Force signals were captured at a sampling rate of 400 Hz 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 20-s 'visual feedback' (VF) phase and a 20-s 'no visual feedback' (NF) phase, separated by a 10-s pause period. During the VF phase, real-time visual feedback of the participant's force output was provided on a computer screen, and the 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 5 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 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 (3 N) was excluded from analysis because the sensor was intermittently released.

Force modulation

Data from the force sensor were low-pass filtered (fourth-order bi-directional Butterworth filter, cut-off frequency = 40 Hz). 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 15 s of each phase, the mean isometric force (F_{mean}) and variability of force output (expressed as coefficient-of-variation; F_{CV} = standard deviation/F_{mean} * 100%) were calculated. Matching performance was indexed by F_{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_{mean}/T_{mean1} (in Ns^{-1}), where T_{mean1} denotes the time (in s) from the first contact with the sensor to the first moment that force output exceeded F_{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_{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 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'. These parameters were calculated on the basis of a 5-s 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 (Field, 2009). 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., $F_{mean,}$ 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; Field, 2009). After ^{10}log transformation of PPT, F_{CV}, F_{error}, force build-up rate and absolute error, and after square root transformation of F_{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 [$CRPS_{AP}$] vs. CRPS without abnormal postures [$CRPS_{noAP}$] 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_{mean}, F_{CV}, F_{error} and force build-up rate) were each submitted to an ANOVA with group ($CRPS_{AP}$ vs. $CRPS_{noAP}$ 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 15 s 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-subjects 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 ($CRPS_{AP}$ vs. $CRPS_{noAP}$ vs. HC) as between-subjects factor. For all ANOVAs, degrees of freedom were adjusted if the sphericity assumption was violated (Field, 2009) and effect sizes were quantified as partial eta squared (η_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 ± 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 ($CRPS_{AP}$: 2.47 ± 2.33 kgf and $CRPS_{noAP}$: 2.42 ± 3.03 kgf, lower than HC: 5.28 ± 1.79 kgf).

Table 5.2 Significant results of the ANOVAs

Outcome	Effect	*F-value*		*p*	η_p^2
Pressure pain threshold					
PPT	group	$F_{2,68}$ =	21.31	<.001	.41
Maximum voluntary force					
MVC	group	$F_{2,66}$ =	188.22	<.001	.39
Force modulation					
F_{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 × target	$F_{3.3,105.8}$ =	7.91	<.001	.20
F_{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 × phase	$F_{2,65}$ =	6.31	.003	.16
	phase × target	$F_{2,130}$ =	5.58	.005	.08
F_{error}	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 × phase	$F_{2,65}$ =	13.71	<.001	.30
	phase × target	$F_{2,130}$ =	4.26	.016	.06
	group × phase × 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 × phase × target	$F_{4,130}$ =	3.24	.014	.09
Force reproduction errors					
Absolute error	group [a]	$F_{2,65}$ =	3.17	.049	.30
	target	$F_{2,130}$ =	70.73	<.001	.52
Constant error	group [a]	$F_{2,65}$ =	3.70	.030	.32
Variable error	group [a]	$F_{2,65}$ =	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 '×') was quantified as partial eta squared (η_p^2). Between-subjects factor: group (CRPS patients with abnormal posture [$CRPS_{AP}$] vs. CRPS patients without abnormal posture [$CRPS_{noAP}$] 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 $CRPS_{AP}$, n=12 $CRPS_{noAP}$, and n=32 HC (except for PPT: n=27 $CRPS_{AP}$; MVC: n=25 $CRPS_{AP}$; variable error: n=23 $CRPS_{AP}$). [a] significant effect if analysis was restricted to the lowest target level to minimize any confounding effects of motor impairment.

Maximum voluntary force

Maximum voluntary grip force (i.e., MVC) was significantly lower in $CRPS_{AP}$ (20.0 ± 9.7 N) than in $CRPS_{noAP}$ (35.7 ± 24.3 N) and HC (44.6 ± 10.9 N).

Force modulation

F_{mean} increased significantly with increasing target force in all groups, albeit slightly less pronounced for $CRPS_{AP}$, who showed significantly lower F_{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_{mean} was higher during NF compared with VF, regardless of group and target force. For F_{CV}, post hoc analysis of the interaction between group and phase revealed that in $CRPS_{AP}$ and HC, but not in $CRPS_{noAP}$, variability of force output increased when visual feedback was removed (i.e., during NF; Figure 5.2B). In the VF phase, F_{CV} was larger in the two patient groups compared with controls, whereas in the NF phase F_{CV} in $CRPS_{AP}$ was larger compared with $CRPS_{noAP}$ and HC. Post hoc analysis of the interaction between phase and target indicated that, irrespective of group, the effect of feedback removal on F_{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 (Figure 5.2C). F_{error} was larger in $CRPS_{AP}$ compared with HC (for all combinations of phase and target) and $CRPS_{noAP}$ (in all combinations except VF-medium and NF-high), and in $CRPS_{noAP}$ compared with HC (in all combinations except NF-low and NF-medium). For both patient groups, F_{error} increased with increasing target force, regardless of 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.

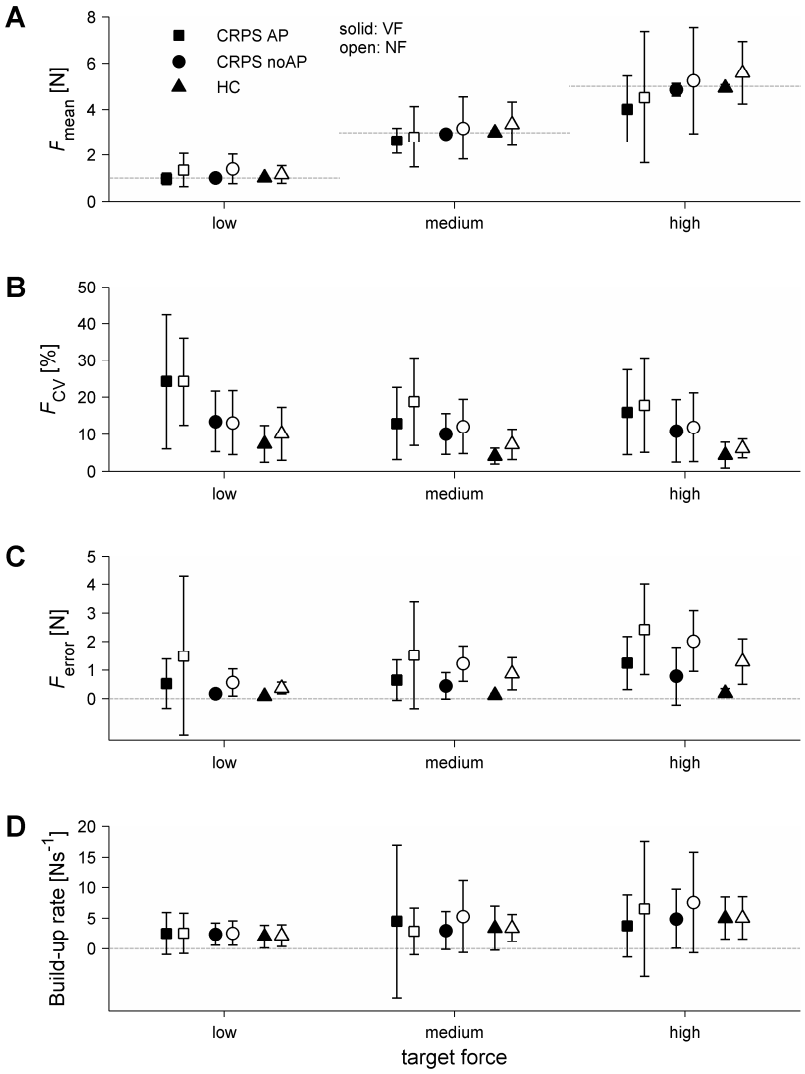


Figure 5.2 Results for grip force modulation with visual feedback (VF) and without visual feedback (NF) at three levels of target force (1, 3 and 5 N). **(A)** mean isometric force, F_{mean}. Target forces are indicated by dotted lines; **(B)** variability of force output, F_{CV}; **(C)** matching performance,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

With respect to the force build-up rate (Figure 5.2D), 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 $CRPS_{AP}$ compared with $CRPS_{noAP}$ 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).

Force reproduction errors

For all groups, absolute error increased with target force (Figure 5.3A), as was evidenced by a significant main effect of target. For constant error (Figure 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 ± 0.9 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 (Figure 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 $CRPS_{AP}$ compared with HC.

Correlation between PPT and force measurements

PPT was correlated with maximum voluntary force in $CRPS_{AP}$ (rho=.482, p=.015) and $CRPS_{noAP}$ (rho=.720, p=.008). Specifically, lower values of PPT (i.e., higher levels of muscle hyperalgesia) were associated with lower values of MVC. No consistent correlations were observed with measures of sub-maximal force modulation or the force reproduction errors.

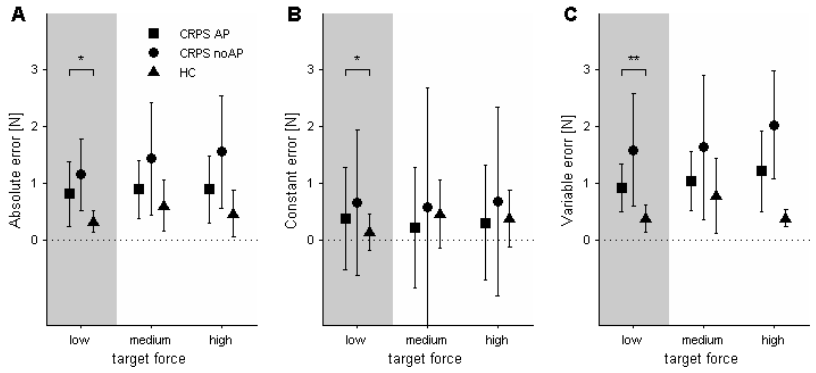


Figure 5.3 Results for force reproduction errors at three levels of target force (1, 3 and 5 N). **(A)** absolute error; **(B)** constant error; **(C)** variable error. Asterisks indicate significant differences between groups (*p<.05, **p<.01) for analyses that were restricted to the lowest target level (shaded area) to minimize any confounding effects of motor impairment. Abbreviations: $CRPS_{AP}$, CRPS patients with abnormal posture (n=24, for variable error n=23); $CRPS_{noAP}$, 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 online 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 $CRPS_{AP}$ patients were characterized by reduced MVC (in line with Geertzen et al., 1998; Huge et al., 2011), 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 appeared more prominently impaired in CRPS patients with an affected lower limb (see Supplement 5.1).

As expected, controls were able to produce a stable force output after removal of visual feedback (Slifkin et al., 2000; Vaillancourt and Russell, 2002), 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 (Eberle et al., 2009; Huge et al., 2008; Kemler et al., 2000; Maier et al., 2010), impaired proprioception (Chapter 4; Lewis et al., 2010) and disturbances in sensory-motor integration (Juottonen et al., 2002; Maihöfner et al., 2007; Mugge et al., 2013), 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_{error} in $CRPS_{AP}$ 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 $CRPS_{AP}$ (see p. 133). The apparent increase of force reproduction errors in $CRPS_{noAP}$ compared with HC failed to reach significance, possibly due to the relatively small number of participants in the $CRPS_{noAP}$ 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 (cf. Chapter 3): *(1)* structural and functional alterations in muscular tissue (Hulsman et al., 2009; Tan et al., 2011; van der Laan et al., 1998; Vas et al., 2013); *(2)* altered processing of information from cutaneous or muscle afferents (e.g., Eberle et al., 2009; Huge et al., 2008; Kemler et al., 2000; Maier et al., 2010; Munts et al., 2011b; van Rooijen et al., 2013a); *(3)* defective regulation of muscle tone due to aberrant force feedback regulation (Mugge et al., 2012a; Munts et al.,

2011a); *(4)* inappropriate motor programming in higher-order centers of motor control (Maihöfner et al., 2007; Swart et al., 2009), which may arise from a mismatch between predicted and actual sensory outcomes of a given motor command (McCabe and Blake, 2008) and be due to disturbances in the body scheme (Förderreuther et al., 2004; Frettlöh et al., 2006; Lewis et al., 2007; Peltz et al., 2011); and *(5)* psychological factors (e.g., Hawley and Weiner, 2011; Schrag et al., 2004), which may be substantiated by the resemblance of symptoms in $CRPS_{AP}$ and functional movement disorders, e.g. the relation with peripheral trauma, the presence of pain and the type of postures (Hawley and Weiner, 2011; Schrag et al., 2004).

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 $CRPS_{AP}$ patients. A contribution of attention deficits towards the affected limb seems plausible in this regard, given that $CRPS_{AP}$ patients showed more neglect-like symptoms with respect to their affected limb than $CRPS_{noAP}$ patients. Interestingly, a significant role of attentional modulation has also been postulated in functional movement disorders (Edwards et al., 2011; Pareés et al., 2013), since patients with functional tremor performed better on a motor task that involved less explicit (i.e., more automatic) voluntary control (Pareés et al., 2013). This warrants further research aimed at identification of potentially shared pathophysiological aspects between $CRPS_{AP}$ 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 (Schwartzman and Kerrigan, 1990; van Hilten et al., 2001). 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 $CRPS_{AP}$. Secondly, although the experiment appeared more strenuous for patients than for controls, no systematic decrease in force output was observed over the final 15 s 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 online visual feedback, may promote the recovery of motor function in CRPS.

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; Roorda et al., 2005b) and Rising (maximum score = 19; Roorda et al., 2005a) 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

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

Abbreviations: $CRPS_{AP}$, CRPS patients with abnormal posture; $CRPS_{noAP}$, 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. [a] Chi-square test was used for comparing the groups. [b] 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. [c] Measures are presented as median (interquartile range); Mann Whitney *U*-tests were used for comparing the two CRPS groups. [d] Due to incomplete questionnaires, measures were based on *n*=14 $CRPS_{AP}$ vs. *n*=11 $CRPS_{noAP}$ (MPQ-PRI), *n*=12 $CRPS_{AP}$ vs. *n*=10 $CRPS_{noAP}$ (Walking), and *n*=13 $CRPS_{AP}$ vs. *n*=10 $CRPS_{noAP}$ (Rising). [e] 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_{mean}), variability of force output (F_{CV}) and average absolute discrepancy between actual force and target force (F_{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 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_{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_{CV}, F_{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 ($CRPS_{AP}$: 2.56 ± 2.30 kgf and $CRPS_{noAP}$: 1.88 ± 1.60 kgf, lower than HC: 5.76 ± 1.86 kgf).

Maximum voluntary force

Maximum voluntary toe flexion force (i.e., MVC) differed significantly between all groups ($CRPS_{AP}$: 16.2 ± 10.5 N, $CRPS_{noAP}$: 40.4 ± 23.8 N, HC: 92.0 ± 26.6 N).

Force modulation

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

and $CRPS_{noAP}$ at medium and high target levels. The main effect of phase indicated that F_{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*	η_p^2
Pressure pain threshold					
PPT	group	$F_{2,54}$ =	25.28	<.001	.48
Maximum voluntary force					
MVC	group	$F_{2,53}$ =	55.94	<.001	.68
Force modulation					
F_{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 × target	$F_{3.2,76.4}$ =	22.09	<.001	.48
F_{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_{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 × phase	$F_{2,48}$ =	12.87	<.001	.35
	group × target	$F_{4,96}$ =	5.36	.001	.18
Build-up rate	group	$F_{2,48}$ =	7.84	.001	.25
	phase	$F_{1,48}$ =	17.00	<.001	.26
	target	$F_{2,96}$ =	6.42	.002	.12
	group × phase	$F_{2,48}$ =	4.24	.020	.15
	group × target	$F_{4,96}$ =	5.36	.001	.18
Force reproduction errors					
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 '×') was quantified as partial eta squared (η_p^2). Between-subjects factor: group (CRPS patients with abnormal posture [$CRPS_{AP}$] vs. CRPS patients without abnormal posture [$CRPS_{noAP}$] 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 $CRPS_{AP}$, n=11 $CRPS_{noAP}$ and n=32 HC (except for PPT: n=14 $CRPS_{AP}$; MVC: n=13 $CRPS_{AP}$; variable error: n=7 $CRPS_{AP}$).

Variability of force output (F_{CV}) was larger in $CRPS_{AP}$ compared with $CRPS_{noAP}$ and HC (Figure S5.2B) and, irrespective of these groups, F_{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_{error}, post hoc analysis of the interaction between group and phase indicated that for HC and $CRPS_{noAP}$ matching performance was better (i.e., F_{error} was lower) during VF, whereas for $CRPS_{AP}$ no such effect of phase was observed (Figure S5.2C). When visual feedback was provided (i.e., during VF), F_{error} was larger in $CRPS_{AP}$ compared with $CRPS_{noAP}$, which in turn showed larger F_{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_{error} than controls. Post hoc analysis of the interaction between group and target indicated that F_{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 $CRPS_{AP}$ 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 $CRPS_{noAP}$ (VF vs. NF: 5.2 ± 8.7 Ns^{-1} vs. 8.7 ± 6.1 Ns^{-1}), whereas the effect of feedback was non-significant for HC (7.8 ± 4.8 Ns^{-1} vs. 8.5 ± 4.2 Ns^{-1}) and $CRPS_{AP}$ (3.2 ± 3.2 Ns^{-1} vs. 5.4 ± 6.0 Ns^{-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 $CRPS_{AP}$ was slower compared with $CRPS_{noAP}$ 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 ± 3.1 Ns^{-1}, medium: 7.6 ± 3.1 Ns^{-1}, high: 11.7 ± 7.6 Ns^{-1}; all differences significant), and $CRPS_{noAP}$ (low: 4.6 ± 2.7 Ns^{-1}, medium: 6.8 ± 4.1 Ns^{-1}, high: 9.5 ± 7.4 Ns^{-1}; all differences non-significant), the rate of force build-up in $CRPS_{AP}$ decreased with increasing target force (low: 4.8 ± 4.0 Ns^{-1}, medium, 4.2 ± 5.7 Ns^{-1}, high: 3.8 ± 4.1 Ns^{-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.

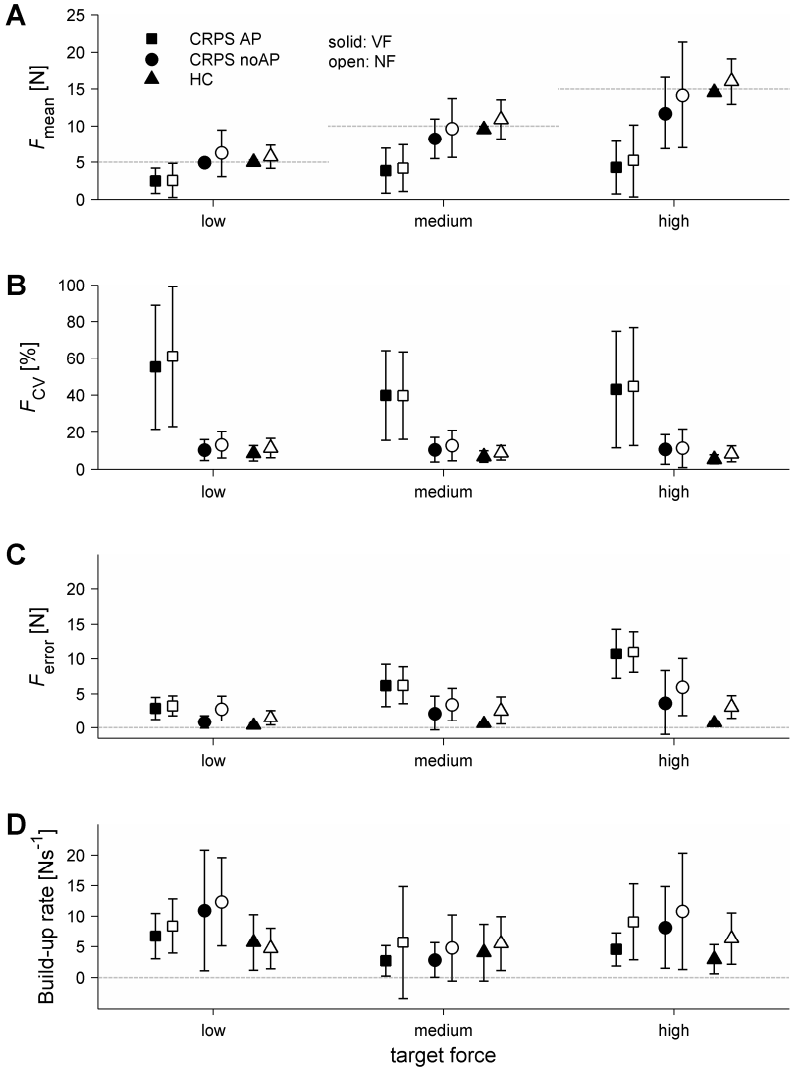


Figure S5.2 Results for toe flexion force modulation with visual feedback (VF) and without visual feedback (NF) at three levels of target force (5, 10 and 15 N). **(A)** mean isometric force, F_{mean}. Target forces are indicated by dotted lines; **(B)** variability of force output, F_{CV}; **(C)** matching performance, average absolute discrepancy between actual force and target force, F_{error}; **(D)** force build-up rate. Abbreviations: $CRPS_{AP}$, CRPS patients with abnormal posture (n=11); $CRPS_{noAP}$, CRPS patients without abnormal posture (n=8); HC, healthy controls (n=32).

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 ± 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.

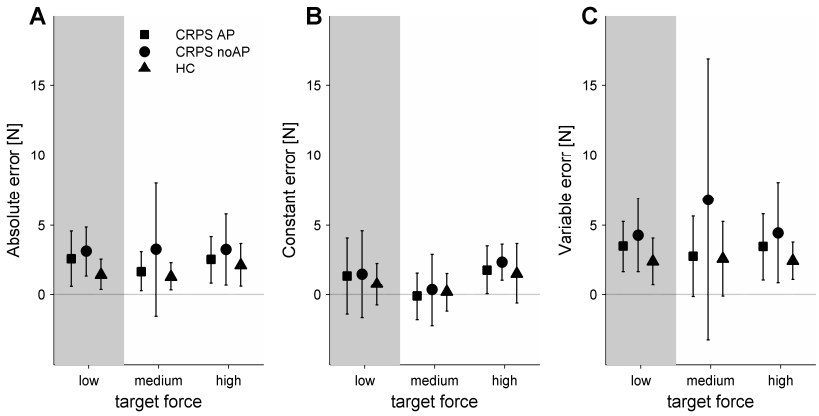


Figure S5.3 Results for force reproduction errors at three levels of target force (5, 10 and 15 N). **(A)** absolute error; **(B)** constant error; **(C)** variable error. Abbreviations: $CRPS_{AP}$, CRPS patients with abnormal posture (n=8, for variable error n=7); $CRPS_{noAP}$, CRPS patients without 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 $CRPS_{AP}$ 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 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 production sense in $CRPS_{AP}$ that were found for the upper extremity). However, it should be noted that in particular $CRPS_{AP}$ 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_{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 $CRPS_{AP}$ patients. Rather, it appears that even the lowest target force was too high for $CRPS_{AP}$ patients with an affected lower extremity, which might have precluded the detection of proprioceptive deficits.

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.

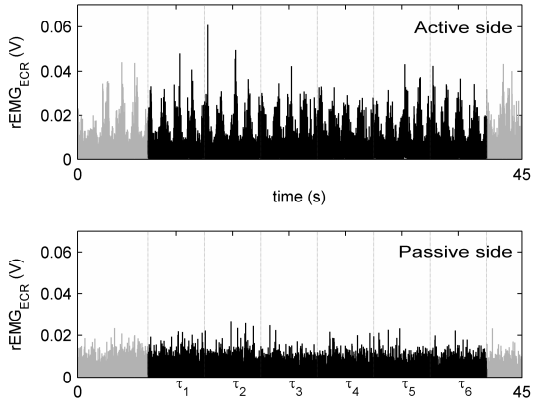
Mirror activity, which refers to involuntary activity in (or movements of) a limb that resembles activity in the intentionally moved contralateral limb (Carson, 2005), was evaluated in the passive arm. Due to its irregularity and smallness of amplitude it is difficult to reliably detect and quantify 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

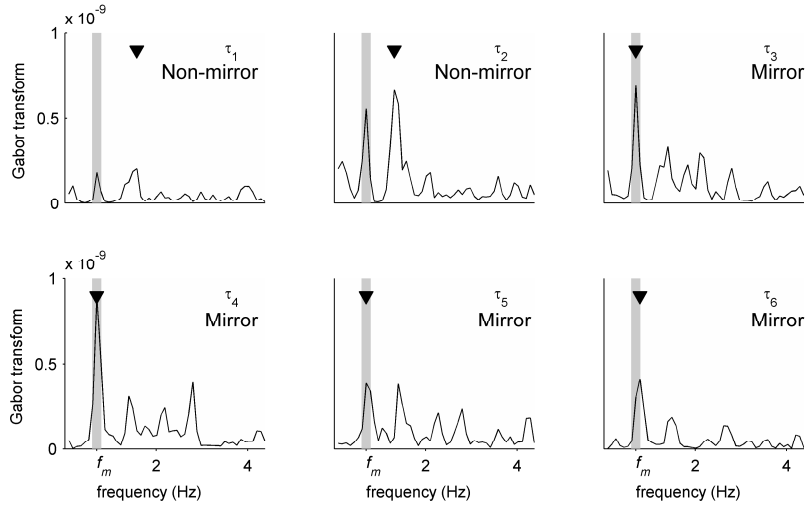
$$G_a(\tau,\omega) = \int g_a(t-\tau)\, x(t)\, e^{-i\omega t}\, dt$$

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**

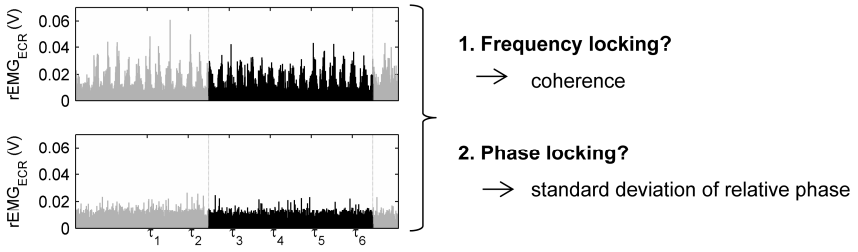


Figure 6.1 Schematic overview of the method. **Step 0:** EMG data (filtered and rectified) as obtained from the extensor carpi radialis muscle (ECR) of a healthy participant during unimanual rhythmic wrist flexion-extension movements (1 trial, 30 cycles). The first five and last two cycles were excluded 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.

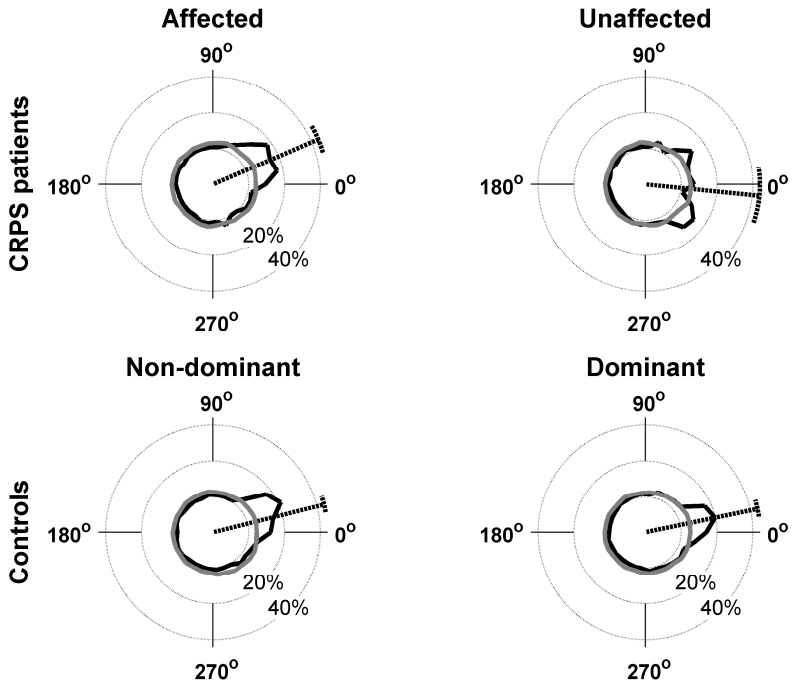


Figure 6.2 Circular histograms of the average relative phase between the rEMGs of the ECR muscles of the passive arm and the contralateral (moving) arm, as obtained for the individual cycles during the mirror-epochs (solid black line) and the segments that were not included in mirror-epochs (solid grey 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

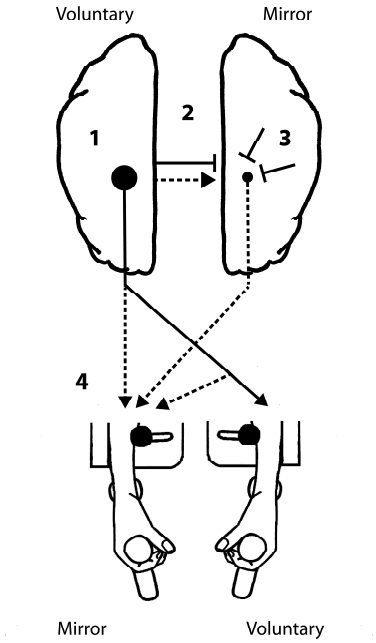


Figure 6.3 Proposed mechanisms involved in the modulation of mirrored muscle activity (dotted lines) during unimanual voluntary movement (solid line), based on Cox et al., 2012. The intensity of mirrored muscle activity depends on: **(1)** intensity of motor commands generated in the primary motor cortex 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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Chapter 7

Intended and unintended coupling between the affected and unaffected upper limb in Complex Regional Pain Syndrome

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Motor dysfunction in Complex Regional Pain Syndrome (CRPS) has been associated with malfunction of sensory and motor circuits. Although there are indications of abnormal coupling between the affected and unaffected limb, the significance of these factors to motor impairments in CRPS is still poorly understood. This study's aim was to discriminate between voluntary and automatic aspects of interlimb coupling by examining the influences of intended bilateral planning, intended afference-based error correction and unintended reflex-like entrainment. To this end, 20 patients with chronic CRPS and 40 healthy controls performed a set of unimanual and bimanual rhythmic motor tasks that differed in the degree to which these sources of intended and unintended interlimb coupling were involved. The results showed that coordination between the hands was less stable in CRPS patients compared to controls, especially for tasks involving active control of the affected side, indicating a prominent impairment of intended rather than unintended coupling between the hands. Collectively, our findings suggest that motor dysfunction of CRPS is largely due to inappropriate functioning of higher-order centers involved in motor control of the affected limb, which in turn is probably associated with impaired central processing of proprioceptive information and pain-related processes. This also has consequences for the temporal and spatial coupling between the affected and unaffected limb, in particular for voluntary (intended) as opposed to automatic (unintended) coupling. Potential implications of these findings for treatment of motor dysfunction in CRPS are discussed.

Introduction

Complex Regional Pain Syndrome (CRPS) is often accompanied by motor disturbances such as muscle weakness, restricted active range of motion (AROM), difficulty 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 associated with 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; Schrag et al., 2004). In recent years, however, a growing number of studies have provided evidence for maladaptive neuronal plasticity at various levels of the central nervous system underlying chronification of pain (central sensitization; Latremoliere and Woolf, 2009; Seifert and Maihöfner, 2009; Woolf, 2011) and prominent malfunction of somatosensory (Lenz et al., 2011) and motor circuits (Eisenberg et al., 2005; Juottonen et al., 2002; Kirveskari et al., 2010; Krause et al., 2004, 2006; Schouten et al., 2003; Schwenkreis et al., 2003; van de Beek et al., 2002) in CRPS. 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 have been reported (Chapter 4; Huge et al., 2011; Schilder et al., 2012; van Rooijen et al., 2013b). 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.

Some CRPS patients are unable to perform a movement upon request, whereas a similar movement may be executed without much difficulty in the context of automatic behavior. This discrepancy between voluntary and automatic movements is sometimes taken as evidence of psychogenicity (Edwards et al., 2011; Fahn and Williams, 1988; Pareés et al., 2013), but may also reflect abnormal sensory-motor integration at specific levels of motor planning and execution. Insight into the pathophysiology underlying the

motor dysfunction of CRPS may have important consequences for the therapeutic management of patients suffering from this syndrome.

Against this background, the current study exploited a set of experimental tasks involving unimanual or bimanual rhythmic wrist flexion-extension movements to discriminate between the influence of sources of intended and unintended interlimb coupling. Intended interlimb coupling was not only evaluated during active control of both hands, but also during afference-based coordination with passive movements of the contralateral hand. Unintended interlimb coupling was evaluated in terms of reflex-like entrainment of active hand movements to the movement rhythm of to-be-ignored passive movements of the contralateral hand (based on Ridderikhoff et al., 2005b; cf. de Boer et al., 2012; van Delden et al., 2009).

Methods

Participants

Interlimb coupling was evaluated in 20 patients diagnosed with unilateral CRPS of the upper extremity (see Table 7.1 for patient characteristics). All patients fulfilled the diagnostic criteria for CRPS type 1 established at the 1993 consensus conference ('Orlando criteria'), which were formally endorsed by the International Association for the Study of Pain 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 the fingers and/or wrist. In 13 patients, the inflicted body part preferably adopted an abnormal posture, mainly characterized by flexion of the fingers and wrist. Patients were excluded if they *(1)* suffered a known genetic form of dystonia (e.g., DYT1-DYT11 or Wilson's disease), mobile dystonia, or lesions or diseases of the central nervous system; *(2)* had an implanted drug-delivery pump for intrathecal baclofen; *(3)* had a wrist AROM smaller than 30°; or *(4)* were unable to perform flexion-extension movements of the wrist at a frequency ≥0.5 Hz. Healthy control participants, who had normal function of both arms and did not suffer from known diseases of the central nervous system, were individually matched with respect to

age (within 5 years) and gender to the CRPS patients in a 2-to-1 ratio (32 women, 8 men; mean ± SD age: 51.4 ± 13.3 years). 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. All participants had previously participated in a study on proprioception (Chapter 4).

Table 7.1 Patient characteristics

N	20	
Sex (male/female)	4/16	
Age (mean, SD) in years	51.3	(13.3)
Disease duration (mean, SD) in years	8.9	(8.6)
CRPS severity score (mean, SD)	10.0	(2.5)
Medication score (median, IQR)	7.2	(0-17.8)
$Pain_{week}$ (median , IQR)	7.0	(5.3-8.0)
Pain Rating Index of the McGill Pain Questionnaire (mean, SD)	27.6	(10.6)
Radboud Skills Questionnaire (mean, SD)	3.0	(0.8)

$Pain_{week}$ = average pain experienced during the week prior to the experiment as scored on a numeric rating scale (0-10). Abbreviations: SD, standard deviation; IQR, interquartile range.

Measurement instruments

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

Interlimb coupling was examined in multiple experimental conditions involving unimanual or bimanual rhythmic flexion-extension movements of the wrist (see *Data collection procedure*), while participants sat comfortably in a chair with their elbows slightly

flexed and their feet supported. On two stands, positioned on both sides of the chair, vertically oriented manipulanda were mounted that only permitted flexion-extension movements of the wrist in the horizontal plane (see Figure 7.1). Both forearms were placed in the apparatus in a neutral position (thumbs up and palms facing inward) and their positions were restrained by foam-padded supports. Adjustable handgrips (diameter 32 mm) on the manipulanda fell in the crease between thumb and index finger, and the rotation axes of the manipulanda were aligned with those of the wrists. An opaque screen precluded vision of the hands.

The manipulanda were either mounted on a potentiometer (FCP40A, tolerance ±0.1%, Sakae Tsushin Kogyo Co., Ltd., Nakahara-ku, Kawasaki-city, Japan) that recorded active wrist movements, or connected to a servo-controlled motor (Parvex RS440GR1031, SSD Parvex SAS, Dijon Cedex, France) with precision gearbox (Wittenstein alpha TP010S-MF1-7-0C0-2S, backlash ±0.02°, Wittenstein alpha GmbH, Igersheim, Germany) that generated passive wrist movements. An auditory metronome indicated the movement frequency (f_m = 0.7 Hz in all participants, except for one patient in whom f_m = 0.6 Hz) by specifying the moments of peak flexion (pitch: 800 Hz) and peak extension (400 Hz), while a moderate level of white background noise was provided via headphones to eliminate any auditory feedback from the motor's motion.

Surface electromyography (EMG) recordings were obtained from the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) of both arms to visualize the average muscle activity within a movement cycle for each task. Methods and results with respect to the EMG recordings are presented in Supplement 7.1.

Data collection procedure

For the purpose of calculating the passive movement trajectories, the AROM was determined by measuring the actively achieved maximal wrist flexion and extension positions. Per movement direction (flexion, extension), two measurements were performed per hand (left, right). The initial movement direction was counterbalanced across participants.

The main part of the experiment consisted of four tasks that involved unimanual or bimanual rhythmic flexion-extension movements of the wrist. In all but one task (i.e., kinesthetic tracking, see below), participants were instructed to ensure that peak flexion and extension of the actively moved hand(s) coincided with the metronome beeps. Participants received no instructions with respect to movement amplitude. All participants performed the following sequence of motor tasks:

1. Active bimanual coordination in the in-phase pattern (peak flexion and extension of both wrists had to be reached simultaneously) and in the antiphase pattern (peak flexion of one wrist had to coincide with peak extension of the contralateral wrist), in order to evaluate interlimb interactions associated with the planning of bimanual coordination patterns (cf. Ridderikhoff et al., 2005b).
2. Active unimanual flexion-extension movements about the wrist, while the contralateral arm did not move. This 'reference situation' involved no evident coupling between the hands.
3. Active unimanual flexion-extension movements about the wrist with simultaneous motor-driven movements of the contralateral hand. Participants were instructed to ignore these passive movements and to let peak flexion and extension of their active hand coincide with the metronome beeps. Two phase relations between the motor-driven movements and the metronome signal pacing the actively moving hand were applied: a phase shift of 0° (implying that peak flexion and extension of the passively moved hand coincided with the metronome beeps) and a phase shift of -30° (implying that passive movements were leading the metronome beeps in time with $1/12^{th}$ of a movement cycle). These to-be-ignored passive movements of the contralateral hand served to induce unintended afference-based interactions. Such interactions result in reflex-like synchronization (entrainment) of the active hand's movements towards the phase-shifted movement rhythm of the passive movements (de Boer et al., 2013; Ridderikhoff et al., 2005b, 2006). Hence, the phasing of the active hand with respect to the metronome was expected to differ between the imposed phase shift of 0° and -30°, and the comparison between these two conditions provided information regarding the unintended coupling between the hands (Ridderikhoff et al., 2005b, 2006).

4. Active unimanual flexion-extension movements about the wrist with simultaneous motor-driven movements of the contralateral hand. No auditory metronome was present and participants were instructed to move their active hand so as to track the rhythm of their passively moving hand (kinesthetic tracking, in-phase coordination), in order to evaluate the intended coupling between the hands on the basis of afferent signals.



Figure 7.1 Overview of the experimental setup for tasks involving motor-driven movements (tasks 3 and 4). A manipulandum with adjustable handgrip was mounted on a potentiometer to record active wrist movements of one hand, while a similar manipulandum was connected to a servo-controlled motor that moved the contralateral hand passively. Depending on the experimental condition, the position of the potentiometer and the motor could be interchanged. Tasks 1 and 2 did not involve motor-driven movements. During these tasks, the two manipulanda (left, right) were each mounted on a potentiometer to record active wrist movements. During all tasks, opaque screens precluded vision of the hands.

For each individual patient, passive movement trajectories were calculated on the basis of the AROM of the affected side, which was averaged over the two measurements. The motor movements were based on sinusoidal trajectories (f_m = 0.7 Hz in all participants, except for one patient in whom f_m = 0.6 Hz) around the center of this AROM, with an amplitude corresponding to 75% of the maximum excursion (both in flexion and extension direction). To reduce predictability of passive movements, the amplitudes of the cycles were randomly varied (SD = 2.5% of the AROM). The trajectories were

multiplied with a windowing function to increase and decrease the amplitude of passive movements in the first and last two trials, respectively. In order to control for differences in bimanual coordination that might be related to an asymmetry in movement amplitude between the hands (Buchanan and Ryu, 2006, 2012; de Boer et al., 2013; de Poel et al., 2009; Peper et al., 2008), the amplitude of passive movements for the patient's unaffected hand was calculated on the basis of that wrist's AROM (*relative matching*), or was exactly the same as for the affected hand (*absolute matching)*. Similarly, age- and gender-matched control participants performed the relative matching as well as the absolute matching condition – the latter implying that the amplitude of passive movements was identical to that of the matched patient's affected hand. However, if relative and absolute matching did not yield sufficiently different movement trajectories (i.e., if both the difference in AROM obtained for an individual participant and the difference in the AROM's center were smaller than 15% of the AROM of the unaffected hand), then the experimental tasks were only performed for absolute matching.

Each condition comprised three trials (duration: 30 cycles) that were preceded by one practice trial (duration: 15 cycles). Tasks involving unilateral voluntary movement (viz. tasks 2–4) comprised separate conditions for each voluntarily moving side (affected vs. unaffected side in patients, non-dominant vs. dominant side in controls), the order of which was randomized over participants. To minimize inconvenience for the patients, the order of conditions within tasks that involved motor-driven movements (i.e., tasks 3 and 4) was pseudo-randomized such that two conditions involving voluntary movement of the affected hand were always separated by at least one condition in which this hand was moved by the motor. A numeric rating scale (NRS, 0-10) was administered to patients directly after completion of each condition in order to evaluate pain ($Pain_{task}$).

Data analysis

The first five and last two cycles of each trial were removed to eliminate possible transitory effects. More cycles were removed if the relative phase between the hands or between the hand and the beeps (Φ and Ψ, respectively; see below) increased or decreased progressively over several consecutive cycles (i.e., in case of phase wrapping). If less than 10 consecutive cycles remained for analysis, a trial was excluded from further analysis. For the remaining trials, the longest epoch of stationary behavior in the appropriate phase relation (i.e., in-phase or antiphase, dependent on task instruction) was retained for the subsequent analyses.

Angular position data of the manipulandum were low-pass filtered (second-order bi-directional Butterworth filter, cut-off frequency = 10 Hz) and a peak-detection algorithm was used to calculate point estimates of the relative phase between the hands (Φ in °; for tasks 1 and 4) or between the voluntarily moving hand and the metronome beeps (Ψ in °; for tasks 2 and 3), for peak flexion and extension separately (cf. Carson et al., 1995; de Boer et al., 2011). The relative phase is an established measure of coordination (Schöner et al., 1986), which captures the phase difference between the hands (or between the hand and metronome), being 0° for in-phase and 180° for antiphase coordination. For each trial, the average values of Φ and Ψ were calculated using circular statistics (Mardia, 1972). A positive phase relation indicated that the voluntarily moving hand was lagging the reference signal (passively moved hand or metronome) in time. The variability (i.e., circular standard deviation; CSD_{Φ} and CSD_{Ψ}) of the relative phase within each trial provided an index of the stability of the obtained relative phasing (Schöner et al., 1986). For adequate performance on the kinesthetic tracking task, perceived errors in the relative phasing between the hands had to be corrected by shortening or lengthening the subsequent half-cycle of the actively moved hand. Therefore, the correlation R_{EC} between the signed error in the relative phasing at peak flexion or extension and the duration of the subsequent half-cycle (Ridderikhoff et al., 2007) was used to characterize error correction in this task. Larger negative values of R_{EC} indicated more error correction. For all tasks, the amplitude of active wrist movements was calculated as half the peak-to-peak flexion-extension excursion.

Statistical analysis

For each participant, dependent variables were averaged per condition, whereby values obtained for flexion and extension, if applicable, were averaged. Statistical analysis was performed using IBM® SPSS® Statistics 20.0 (IBM Corp., Armonk NY). Normality curves were inspected and Kolmogorov-Smirnov tests were used to assess whether the data were normally distributed within each group. Ψ and amplitude were normally distributed in >90% of conditions, whereas deviations from normality were observed for CSD_{Φ} and CSD_{Ψ} in approximately 45% of conditions. After ^{10}log transformation, these parameters were normally distributed in approximately 90% of conditions. R_{EC} was transformed to normally distributed values using the Fisher transform (Fisher, 1915). Although transformed data were used for statistical analysis of CSD_{Φ}, CSD_{Ψ} and R_{EC}, for reasons of clarity the untransformed data are presented in the Results.

The main statistical analysis comprised two parts, with a focus on temporal and spatial coupling between the hands. First, each of the four tasks was evaluated in terms of the relative phasing and its variability to discern the influence of sources of intended and unintended interlimb coupling. The corresponding dependent variables (Φ and CSD_{Φ} for tasks 1 and 4; Ψ and CSD_{Ψ} for tasks 2 and 3) were each submitted to a mixed analysis of variance (ANOVA) with group (CRPS patients vs. healthy controls) as between-subjects factor, and with side (affected/non-dominant vs. unaffected/dominant) and, if applicable, coordination pattern (in-phase vs. antiphase during active bimanual coordination [task 1]) and shift (0° vs. -30° phase shift of to-be-ignored motor-driven movements of the contralateral side [task 3]) as within-subject factors. To determine the influence of intended bimanual planning on temporal coupling between the hands, performance was compared between active bimanual coordination and kinesthetic tracking (as in kinesthetic tracking the coordination pattern depended on afference-based adjustments in one hand only, without active planning of the bimanual temporal pattern itself). To this end, the differences between these tasks were calculated (i.e., $\Delta\Phi_{ActBi\text{-}Kin}$ and $\Delta CSD_{\Phi,\ ActBi\text{-}Kin}$) for each participant in each condition (de Boer et al., 2011; Ridderikhoff et al., 2005b). Per group, these differences were submitted to one-sample *t*-tests to determine for each condition whether they differed significantly from zero. Subsequently, $\Delta\Phi_{ActBi\text{-}Kin}$

and $\Delta CSD_{\Phi,\ ActBi\text{-}Kin}$ were each submitted to a mixed ANOVA with factors side and group. To examine intended error correction based on afferent signals during kinesthetic tracking, R_{EC} was submitted to a mixed ANOVA with factors side and group. To examine unintended reflex-like synchronization (entrainment) based on afferent signals, Ψ was compared between the two phase shift conditions (0° or -30°) of task 3, involving the to-be-ignored motor-driven movements. Such unintended entrainment effects were addressed based on the factor 'shift' in the mixed ANOVA on Ψ. Second, spatial coupling between the hands was examined. To this end, a mixed ANOVA with task (4 levels: unimanual coordination, unimanual coordination while motor-driven movements had to be ignored (0° phase shift only), kinesthetic tracking and active bimanual in-phase coordination) and side as within-subject factors and group as between-subjects factor was performed on movement amplitude to determine whether movement amplitude of a voluntarily moving hand was influenced by passive or active movements of the contralateral hand.

Statistical analyses that involved tasks with passive movements were conducted separately for relative and absolute matching conditions. For 5 CRPS patients and 9 controls, data from absolute matching conditions were also used for comparisons involving the relative matching conditions because the tasks had been performed under the absolute matching conditions only (see *Data collection procedure*). For all ANOVAs, degrees of freedom were adjusted if the sphericity assumption was violated (Field, 2009) and effect sizes were quantified as partial eta squared (η_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 paired samples *t*-tests for within-group comparisons and independent samples *t*-tests for between-group comparisons. All values are presented as mean ± between-subjects standard deviation.

For patients, the non-parametric Friedman test was used to evaluate whether $Pain_{task}$ differed between tasks (for both relative and absolute matching conditions). To explore the potential relation between pain intensity and task performance, Spearman's rho was used to calculate the correlations between $Pain_{task}$ and stability of coordination (i.e., CSD_{Φ}

[tasks 1 and 4] or CSD_{Ψ} [tasks 2 and 3]) and movement amplitude, separately for each task (i.e., active bimanual in-phase coordination, unimanual coordination, unimanual coordination while motor-driven movements had to be ignored [0° phase shift only] and kinesthetic tracking). Pairwise correlations were also used to examine whether $Pain_{task}$ was correlated to intended and unintended sources of interlimb coupling, i.e., intended bimanual planning ($\Delta\Phi_{ActBi\text{-}Kin}$), intended error correction based on contralateral afference (R_{EC}) and unintended entrainment (based on $\Delta\Psi_{0\text{-}30°}$, i.e., the difference in Ψ between the two phase shift conditions [0° or -30°] of task 3, involving the to-be-ignored motor-driven movements). Because this was regarded as an exploratory analysis, statistical significance was not adjusted for multiple testing (Bender and Lange, 2001).

Results

One patient was unable to endure passive movements of the affected side and only performed tasks 1 and 2. In total, 19 trials (0.7%) were excluded from analysis, 14 in patients (11 trials involving voluntary movement of the affected side and 3 trials *not* involving voluntary movement of the affected side) and 5 in controls. Because this resulted in an empty cell (active bimanual coordination, antiphase pattern) in one patient, data from 19 patients remained for analyses involving comparisons with this condition. In addition, one or more cycles were removed from 69 out of 699 trials in patients (9.9%) and from 56 out of 1776 trials (3.1%) in controls; see Table 7.2 for the distribution over experimental conditions.

Table 7.2 Percentage of trials per condition with one or more excluded cycles

		CRPS patients		Controls		**Total**
Affected / non-dominant side active?		Yes	No	Yes	No	
Active bimanual (in-phase)		8.3	-	1.7	-	**3.9**
Active bimanual (antiphase)		5	-	3.3	-	**3.9**
Unimanual		3.3	1.7	0	0	**0.8**
Unimanual with motor	Relative	20.5	0	1.0	3.1	**3.0**
(to be ignored; 0° phase shift) [a]	Absolute	12.3	-	0.8	0.8	**4.2**
Unimanual with motor	Relative	20.5	10.5	7.3	8.3	**10.1**
(to be ignored; -30° phase shift) [a]	Absolute	31.6	-	5	5	**10.1**
Kinesthetic tracking [a]	Relative	12.8	1.8	3.1	2.1	**5.7**
	Absolute	8.8	-	6.7	3.3	**3.8**
Total		**13.0**	**3.5**	**3.2**	**3.1**	**5.1**

[a] For tasks involving motor-driven movements of the contralateral hand, values are presented separately for relative and absolute matching conditions.

Temporal coupling

Table 7.3 presents the significant effects obtained from the mixed ANOVAs for each of the four tasks. Results of the associated post hoc analyses and analyses involving a comparison between tasks (active bimanual in-phase coordination vs. kinesthetic tracking) are presented in the following sections.

Intended coupling – planning of bimanual coordination patterns

CRPS patients and controls were well able to perform the required coordination patterns of task 1: Φ was close to 0° for active bimanual in-phase coordination (1.9 ± 3.7°) and close to 180° for antiphase coordination (181.9 ± 5.5°). No significant main or interaction effects on Φ were observed. However, post hoc analysis of the interaction between group and pattern on CSD_{Φ} revealed that active bimanual coordination was less stable (i.e., CSD_{Φ} was significantly higher) for CRPS patients compared to controls and for in-phase compared to antiphase coordination, with the difference between patients and controls being more pronounced for in-phase coordination (12.5 ± 5.9° vs. 7.9 ± 2.8°, p=.001) than for antiphase coordination (16.1 ± 4.4° vs. 12.7 ± 2.7°, p=.002).

To determine the influence of intended bimanual planning on temporal coupling between the hands, performance was compared between active bimanual coordination and kinesthetic tracking using the differences between these tasks (i.e., $\Delta\Phi_{ActBi\text{-}Kin}$ and $\Delta CSD_{\Phi,ActBi\text{-}Kin}$). For both patients and controls, $\Delta\Phi_{ActBi\text{-}Kin}$ was significantly different from zero in all conditions (all $p<.01$). Movement reversals coincided with the metronome beeps during active bimanual coordination (Φ = 1.9 ± 3.7°, see above), whereas movement reversals of the voluntarily moving hand were slightly leading those of the passively moved hand in time during kinesthetic tracking (see p. 186). The significant main effect of group in relative matching conditions ($F_{1,57}$=9.06, p=.004, η_p^2=.14) indicated that $\Delta\Phi_{ActBi\text{-}Kin}$ was smaller in patients (12.3 ± 7.2°) compared to controls (18.3 ± 7.2°). Such an effect of group was absent for absolute matching conditions (overall mean: 14.0 ± 8.4°). Only for controls, $\Delta CSD_{\Phi,ActBi\text{-}Kin}$ was significantly different from zero ($p<.001$), indicating that relative phasing between the hands was more stable (i.e., CSD_Φ was lower) during active bimanual in-phase coordination than during kinesthetic tracking. The mixed ANOVAs on $\Delta CSD_{\Phi,ActBi\text{-}Kin}$ yielded significant main effects of side (for relative matching, $F_{1,57}$=6.32, p=.015, η_p^2=.10) and group (for absolute matching, $F_{1,57}$=7.95, p=.007, η_p^2=.12) that were complemented by a significant interaction effect between side and group for both relative and absolute matching conditions ($F_{1,57}$=6.74, p=.012, η_p^2=.11 and $F_{1,57}$=6.88, p=.011, η_p^2=.11, respectively). Post hoc analysis indicated smaller values of $\Delta CSD_{\Phi,AB\text{-}KT}$ for the patients' unaffected side compared to their affected side and controls (for relative matching p=.055 and p=.005, and for absolute matching p=.016 and $p<.001$, respectively). Collectively, these analyses revealed that any stabilizing effects of planning were less pronounced in patients compared to controls (see Figure 7.2).

Table 7.3 Significant results of the mixed ANOVAs for measures of temporal coupling (per task) and spatial coupling (comparison between tasks)

		Relative matching				Absolute matching			
Outcome	Effect	*F*-value		*p*	η_p^2	*F*-value		*p*	η_p^2
Temporal coupling									
Active bimanual coordination									
Φ	.		.	.	.		.	.	.
CSD_Φ	group	$F_{1,57}$ =	12.90	.001	.19		.	.	.
	pattern	$F_{1,57}$ =	119.02	<.001	.68		.	.	.
	group × pattern	$F_{1,57}$ =	5.31	.025	.09		.	.	.
Kinesthetic tracking									
Φ	group	$F_{1,57}$ =	6.36	.014	.10		.	.	.
CSD_Φ	group	$F_{1,57}$ =	7.16	.010	.11		.	.	.
	group × side	$F_{1,57}$ =	4.47	.039	.07	$F_{1,57}$ =	7.76	.007	.12
R_{EC}	group × side	$F_{1,57}$ =	5.02	.029	.08	$F_{1,57}$ =	6.90	.011	.11
Unimanual coordination with motor (to be ignored)									
Ψ	group	$F_{1,57}$ =	6.69	.012	.11		.	.	.
	side		.	.	.	$F_{1,57}$ =	6.21	.016	.10
	shift	$F_{1,57}$ =	42.45	<.001	.43	$F_{1,57}$ =	41.76	<.001	.42
	group × shift	$F_{1,57}$ =	5.45	.022	.09		.	.	.
CSD_Ψ	group	$F_{1,57}$ =	6.10	.017	.10	$F_{1,57}$ =	6.43	.014	.10
	side	$F_{1,57}$ =	8.01	.006	.12	$F_{1,57}$ =	12.98	.001	.19
	shift	$F_{1,57}$ =	21.20	<.001	.27	$F_{1,57}$ =	16.34	<.001	.22
Unimanual coordination									
Ψ	side	$F_{1,58}$ =	15.46	<.001	.21		.	.	.
	group × side	$F_{1,58}$ =	8.71	.005	.13		.	.	.
CSD_Ψ	side	$F_{1,58}$ =	16.90	<.001	.23		.	.	.
	group × side	$F_{1,58}$ =	3.92	.052	.06		.	.	.
Spatial coupling									
Amplitude	group	$F_{1,57}$ =	17.11	<.001	.23	$F_{1,57}$ =	6.46	.014	.10
	side	$F_{1,57}$ =	32.77	<.001	.37	$F_{1,57}$ =	44.51	<.001	.44
	task	$F_{1.9,107.6}$ =	15.62	<.001	.22	$F_{1.9,116.1}$ =	22.21	<.001	.28
	group × side	$F_{1,57}$ =	59.38	<.001	.51	$F_{1,57}$ =	72.92	<.001	.56
	group × task		.	.	.	$F_{1.9,116.1}$ =	7.506	.001	.12
	side × task	$F_{3,171}$ =	7.76	<.001	.12	$F_{3,171}$ =	5.36	.001	.09
	group × side× task	$F_{3,171}$ =	9.86	<.001	.15	$F_{3,171}$ =	6.93	<.001	.11

Footnote see p. 185.

Analyses of the mean relative phase (Φ and Ψ), circular standard deviation of the relative phase (CSD_{Φ} and CSD_{Ψ}) and error correction correlation (R_{EC}) were performed separately for relative and absolute matching conditions. Effect size of the significant ($p<.05$) main effects and interaction effects (indicated by '×') was quantified as partial eta squared (η_p^2). Between-subjects factor: group (CRPS patients vs. controls). Within-subject factors: side (affected/non-dominant vs. unaffected/dominant; not for active bimanual coordination), shift (0° vs. 30°; only for unimanual coordination with to-be-ignored passive movements), pattern (in-phase vs. antiphase; only for active bimanual coordination) and task (unimanual coordination vs. unimanual coordination with motor (to-be-ignored; 0° phase shift) vs. kinesthetic tracking vs. active bimanual in-phase coordination; only for amplitude). Measures are based on n=20 patients and n=40 controls, except for active bimanual coordination (n=19 patients, due to exclusion of all three antiphase trials in one patient) and for the tasks that involved motor-driven movements (n=19 patients, because one patient was unable to endure passive movements of the affected side).

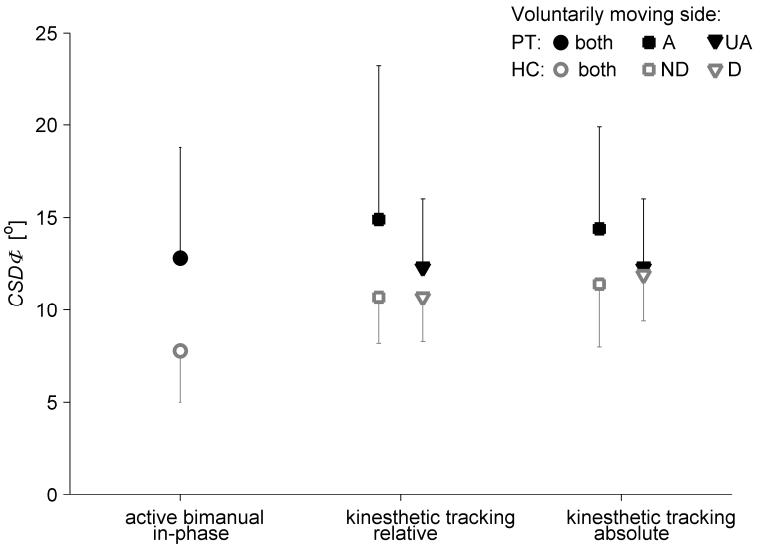


Figure 7.2 Mean variability of the relative phasing between the hands (CSDφ) for tasks that involved intended coupling between the two hands, i.e., during active bimanual in-phase coordination and during afference-based tracking of passive movements of the contralateral hand (kinesthetic tracking) under relative and absolute matching conditions. For reasons of clarity, untransformed data are presented although log-transformed CSDφ was used in statistical analysis. Error bars represent standard deviations. Abbreviations: PT, patients (n=19); HC, healthy controls (n=40); A, affected side; UA, unaffected side; D, dominant side; ND, non-dominant side.

Intended coupling – error corrections based on afferent signals

During kinesthetic tracking (i.e., task 4), movement reversals of the active hand tended to lead those of the passively moved hand in time, an effect that was less pronounced in patients than controls (-10.2 ± 7.6° vs. -15.6 ± 7.6°, p=.014), as was indicated by the main effect of group on Φ in relative matching conditions. No significant effects were observed in absolute matching conditions.

Variability of the phase relation between the hands (CSD_{Φ}) was higher if voluntary movement of the patients' affected side had to be attuned to passive movements of their unaffected side than vice versa, for both relative and absolute matching conditions (p=.051 and p=.016; see Figure 7.2). Post hoc analysis of the interaction effect between side and group also revealed that CSD_{Φ} was significantly higher in patients compared to controls for conditions involving voluntary movements of their affected side (for relative as well as absolute matching, p=.029 and p=.013, respectively). For both relative and absolute matching conditions, the affected side of patients exhibited less error correction (i.e., smaller negative values of R_{EC}) than the non-dominant side of controls (relative matching: -0.58 ± 0.08 vs. -0.64 ± 0.07, p=.003, absolute matching: -0.60 ± 0.07 vs. -0.65 ± 0.06, p=.002), as was demonstrated by post hoc analysis of the significant interaction effects between group and side. In absolute matching conditions, the non-dominant side of controls showed slightly more error correction than their dominant side (-0.65 ± 0.06 vs. -0.62 ± 0.08, p=.008).

Unintended coupling – reflex-like entraining influences

Analysis of Ψ in task 3 revealed that, in general, voluntary hand movements were unintentionally attracted to passive movements of the contralateral side that were -30° phase-shifted relative to the metronome (i.e., leading the metronome in time) for both relative and absolute matching (see Figure 7.3B-C). The significant interaction between group and shift in relative matching conditions, however, indicated that this entraining influence was less pronounced in patients compared to controls. Although in particular the affected side of patients seemed less prominently attracted to passive movements of their unaffected side (Figure 7.3B), the three-way interaction between group, side and shift just failed to reach significance (p=.055). For absolute matching, the main effect of

'side' indicated a slight difference in phasing relative to the metronome between the affected/non-dominant and unaffected/dominant side (-4.0 ± 19.1° vs. -7.9 ± 17.6°, p=.016), but there was no significant interaction with 'shift'.

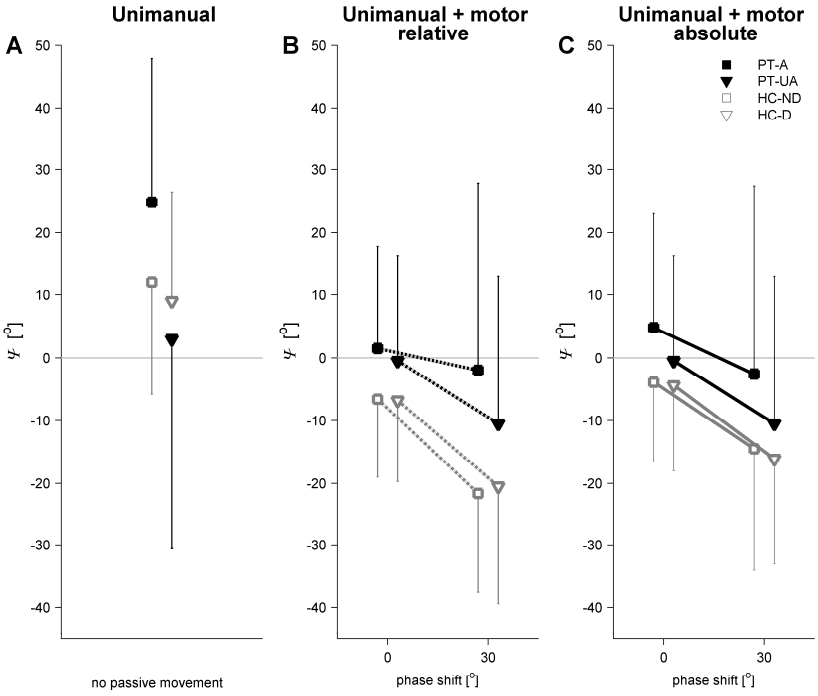


Figure 7.3 Unintended phase entrainment by contralateral passive movements. **(A)** Relative phasing between movement reversals of the voluntary moving hand and the metronome beeps during the unimanual movement task (i.e., without passive movements of the contralateral hand); **(B)** effects of the 'to-be-ignored' passive movements, relative matching condition; **(C)** effects of the 'to-be-ignored' passive movements, absolute matching condition. Error bars represent standard deviations. Abbreviations: PT, patients (n=19); HC, healthy controls (n=40); A, affected side; UA, unaffected side; D, dominant side; ND, non-dominant side.

CSD_{Ψ} was higher(i.e., coordination was less stable) for CRPS patients compared to controls (relative matching: 15.4 ± 4.3° vs. 12.8 ± 4.2°, p=.017; absolute matching: 18.2 ± 8.0° vs. 13.1 ± 2.8°, p=.014), and for the voluntarily moving affected/non-dominant side compared to the unaffected/dominant side (relative matching: 14.5 ± 6.0° vs. 12.7 ± 4.0°, p=.006; absolute matching: 15.0 ± 5.5° vs. 13.0 ± 3.5°, p=.001), as was evidenced by significant main effects of group and side. The main effect of 'shift' indicated that stability was reduced when passive movements were -30° phase-shifted relative to the metronome beeps (0 vs. 30° phase shift, relative matching: 12.1 ± 3.1° vs. 15.1 ± 6.4°, p<.001; absolute matching: 14.0 ± 6.8° vs. 15.4 ± 5.6, p<.001), irrespective of group and side. No significant interaction effects were observed; for absolute matching, the interaction between side and group just failed to reach significance (p=.071).

No coupling – unimanual coordination

During unimanual flexion-extension of the wrist (i.e., task 2), movement reversals of the patients' affected side lagged the beeps more than those of their unaffected side and controls (p=.015 and p=.022; see Figure 7.3A), as was indicated by post hoc analysis of the significant interaction effect between group and side on Ψ. For CSD_{Ψ}, post hoc analysis of the marginally significant interaction effect between side and group (p=.052) suggested that stability of unimanual coordination was reduced for the patients' affected side, but CSD_{Ψ} (17.9 ± 8.5°) appeared not significantly higher than for their unaffected side (13.6 ± 3.7°) and for the non-dominant and dominant side of controls (14.7 ± 4.7° and 13.5 ± 3.7°, respectively).

Spatial coupling

Results with respect to movement amplitude are presented in Table 7.3 and Figure 7.4. Post hoc analysis of the three-way interaction between group, side and task, which was observed for relative as well as absolute matching conditions (see Table 7.3), revealed that for all tasks and conditions the movement amplitude of the patients' affected hand was smaller than that of their unaffected hand and the non-dominant hand of controls (all p<.02; see Figure 7.4). Movement amplitude of the patient's unaffected side was comparable to that of controls, except for the kinesthetic tracking task where controls

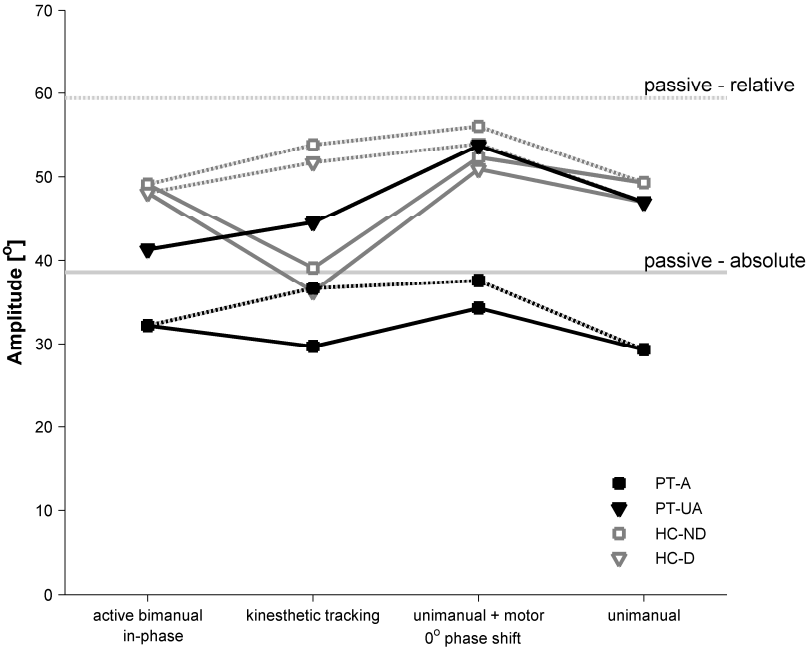


Figure 7.4 Movement amplitude of the actively moving hand per task under absolute (solid lines) and relative (dotted lines) matching conditions. Horizontal grey lines indicate the overall mean amplitude of passive movements of the contralateral side. For reasons of clarity, error bars are omitted. Abbreviations: PT, patients (n=19); HC, healthy controls (n=40); A, affected side; UA, unaffected side; D, dominant side; ND, non-dominant side.

moved with greater amplitude in relative matching conditions (p=.021) and smaller amplitude in the absolute matching conditions (p=.014). Within the patient group, the amplitude difference between the two hands was smaller for tasks involving intended coupling between the hands (viz. active bimanual in-phase coordination and kinesthetic tracking) than for tasks involving no intended coupling between the hands (i.e., unimanual synchronization with the metronome, with or without to-be ignored motor driven movements of the contralateral side). Movement amplitude of the affected hand was greater for tasks involving simultaneous active or passive movements of the unaffected hand than for the strictly unimanual task (all p<.05, except for the absolute matching condition of the kinesthetic tracking task). In contrast, movement amplitude of

the unaffected hand was smaller for active bimanual in-phase coordination than for unimanual wrist flexion-extension movements (p<.001). For both relative and absolute matching conditions, movement amplitude of the unaffected hand was larger in the presence of to-be-ignored passive movements of the affected hand compared to that observed during kinesthetic tracking (p=.001 and p=.005) and during strictly unimanual movements (p=.006 and p=.001). Within the control group, movement amplitude of the non-dominant hand was slightly larger than that of the dominant hand, with the effect of task being similar for the two hands: movement amplitudes during strictly unimanual and active bimanual coordination were larger than those of the voluntarily moving hand in the absolute matching condition of the kinesthetic tracking task, and smaller than those in other conditions involving motor-driven movements (all p<.05).

Potential role of pain-related processes

There were no significant differences in the patients' pain ratings between tasks for both relative and absolute matching conditions ($\chi^2_{4,19}$=3.96, p=.41 and $\chi^2_{4,19}$=4.84, p=.30, respectively). High levels of pain were reported in all conditions (overall median [interquartile range] $Pain_{task}$: 7 [6-8]).

Table 7.4 Correlations between $Pain_{task}$ and motor outcomes per task.

		$CSD_{\Phi/\Psi}$		Amplitude	
Voluntarily moving side		A	UA	A	UA
Active bimanual (in-phase)		.48 *	.48 *	–.44	.01
Unimanual		.52 *	.33	–.31	.24
Unimanual with motor	Relative	.07	.58 **	–.40	.01
(to be ignored; 0° phase shift) [a]	Absolute	.01	.	–.25	.
Kinesthetic tracking [a]	Relative	.59 **	.13	–.41	–.04
	Absolute	.43	.	–.43	.

Correlations were calculated using Spearman's rho (* p<.05, ** p<.01). [a] For tasks involving motor-driven movements of the contralateral hand, values are presented separately for relative and absolute matching conditions. Abbreviations: A, affected side; UA, unaffected side; $CSD_{\Phi/\Psi}$, circular standard deviation of the relative phasing between the hands (Φ) or between the hand and the metronome (Ψ).

The correlation coefficients of $Pain_{task}$ with measures of task performance are presented in Table 7.4. Higher levels of pain were associated with lower stability of coordination for tasks involving voluntary movement of the affected side (viz. unimanual coordination, active bimanual coordination and the relative matching condition of the kinesthetic tracking task), and for the task in which passive movements of the affected side had to be ignored. Although higher levels of $Pain_{task}$ tended to be associated with smaller movement amplitude of the affected side, these correlations failed to reach significance. Higher levels of pain were associated with a less pronounced stabilizing effect of bimanual planning if active bimanual coordination was compared to the kinesthetic tracking task in which movements of the unaffected side had to be attuned to passive movements of the affected side. This was reflected by a significant correlation between $\Delta CSD_{\Phi,ActBi\text{-}Kin}$ and pain during kinesthetic tracking (rho=-.78, p<.01) and pain during active bimanual coordination (rho=-.51, p<.05). No significant correlations were observed between $Pain_{task}$ and error correction (reflected by R_{EC}) or unintended entrainment induced by the phase-shifted passive movements of the contralateral side (reflected by $\Delta\Psi_{0\text{-}30°}$).

Discussion

Although pertinent studies contain indications of abnormal coupling between the affected and unaffected limb in CRPS (Maihöfner et al., 2007), which may be associated with malfunction of sensory (Lenz et al., 2011) and motor circuits (Eisenberg et al., 2005; Krause et al., 2004; Schwenkreis et al., 2003), the significance of these factors to motor impairments in CRPS is still poorly understood. To further our insight into the pathophysiology underlying the motor dysfunction of CRPS, this study aimed to discriminate between voluntary and automatic aspects of interlimb coupling by examining the influences of intended bilateral planning, intended afference-based error correction and unintended reflex-like entrainment.

Our findings showed that bimanual coordination was less stable (i.e., more variable) in CRPS patients compared to controls, especially for tasks involving active control of the affected side. Specifically, the stabilizing effect of intended bilateral planning was less

pronounced in patients compared to controls. Moreover, during kinesthetic tracking the patient's affected side exhibited a lower level of afference-based intended error correction compared to controls. As a consequence, the coordination between the hands was less stable if voluntary movements of the affected side had to be attuned to passive movements of the unaffected side than vice versa and compared to controls. Unintended reflex-like entrainment seemed less prominent in patients than in controls. The latter finding was likely mediated by the disparity in movement amplitude (Buchanan and Ryu, 2006, 2012; de Boer et al., 2013; de Poel et al., 2009; Peper et al., 2008), as differences between groups and sides were no longer significant if the amplitude of passive movements was matched to that of the patients affected side (i.e., for absolute matching). With regard to the potential role of unintended coupling based on efferent signals, it is noteworthy that the stability of active bimanual coordination in CRPS patients was more markedly reduced for in-phase than for antiphase coordination. Given that the opposite would have been expected if CRPS would be characterized by disinhibition of contralateral motor activity, the present findings corroborate the results obtained from an evaluation of mirrored muscle activity during unimanual voluntary wrist movements, which also yielded no evidence for disinhibition of contralateral motor activity (Chapter 6).

Whereas the presence of strong involuntary interlimb interactions would have advocated an organic origin of the motor disturbances in CRPS, our findings collectively thus suggest a prominent impairment of *intended* coupling between the hands. Although the impairment of intended interlimb interactions does not necessarily imply a psychogenic origin of the motor dysfunction of CRPS, this finding corroborates previous suggestions that motor dysfunction in CRPS is related to inappropriate functioning of higher-order centers involved in the motor control of the affected limb (Maihöfner et al., 2007; Swart et al., 2009). In line with this conclusion, several CRPS patients reported that 'the affected hand does not do what the mind wants it to do, like it is 'deaf' for the signals that are sent towards it' (cf. Galer et al., 1995; Lewis et al., 2007; Schwartzman and Kerrigan, 1990).

Analysis of spatial interlimb coupling revealed that movement amplitude of the patients' affected hand was smaller than that of their unaffected hand and the non-dominant hand of controls for all tasks and conditions. Although participants received no

instructions with respect to movement amplitude, the amplitude of the voluntarily moving hand was attracted to that of passive or active movements of the contralateral hand, reflecting amplitude assimilation (Buchanan and Ryu, 2006; Heuer and Klein, 2005; Spijkers and Heuer, 1995). Specifically, movement amplitude of the patients' affected hand was slightly increased by active or passive movements of the unaffected hand, particularly in relative matching conditions, regardless of whether these movements were involved in intended coordination or not. Movement amplitude of the patients' unaffected hand was reduced during intended coordination with the (typically smaller) movements of the affected hand.

Because the CRPS patients reported high levels of pain, it might be tempting to simply attribute the observed motor impairments to pain-related processes, which are known to interfere with motor function (see Chapter 2 for a review) and compete with other attention-demanding processes for limited cognitive resources (Eccleston and Crombez, 1999; Grisart and van der Linden, 2001). In spite of the fact that some CRPS patients reported that pain hampered ignoring movements of the affected side, our findings indicated that patients were reasonably well able to do so. Nevertheless, the to-be-ignored motor-driven movements of the affected side induced a slight reduction of coordinative stability compared to controls, in particular for patients with higher pain scores. However, those motor-driven movements did not induce marked detrimental effects on motor control of the unaffected side (i.e., in terms of amplitude reduction or the number of excluded trials or cycles due to loss of stable coordination) and were not associated with abnormal reflex-like entrainment. Although pain ratings were similar for all tasks and conditions, several results indicated that the active coordination of the affected hand was compromised by pain-related factors. Higher pain ratings were associated with reduced stability of tasks involving active movements of the affected hand and with a less pronounced stabilizing effect of bimanual planning. Moreover, higher pain ratings tended to be associated with smaller movement amplitude of the affected side (but not significantly so).

In CRPS, several sensory impairments have been reported that may interfere with motor control, including altered sensitivity of muscular afferents (Chapter 4; Huge et al., 2011; Maier et al., 2010; van Rooijen et al., 2013a) and disturbances in sensory-motor

integration (Juottonen et al., 2002; Maihöfner et al., 2007; Mugge et al., 2013). Collectively, these findings suggest that impaired processing of proprioceptive information might play a significant role in the motor impairments accompanying CRPS. Also in the present study, some patients spontaneously reported difficulties in precisely sensing the motor-driven or actively controlled movements of the affected side. During the kinesthetic tracking task, however, CRPS patients appeared quite able to attune movements of their unaffected side to passive movements of their affected side. Although the relatively predictable timing of movement reversals might have facilitated anticipatory behavior, this finding suggests that disturbed processing of afferent signals from the affected side is not the essential problem. Rather, the observed impairments seem to be due primarily to inappropriate functioning of higher-order centers involved in the motor control of the affected limb (Maihöfner et al., 2007; Swart et al., 2009), which may arise from a mismatch between predicted and actual sensory outcomes of a given motor command (McCabe and Blake, 2008) and may be related to functional and structural alterations of muscle tissue (Hulsman et al., 2009; Tan et al., 2011; van der Laan et al., 1998; Vas et al., 2013), altered processing of information from cutaneous or muscle afferents (e.g., Eberle et al., 2009; Huge et al., 2011; Kemler et al., 2000; Maier et al., 2010; van Rooijen et al., 2013b) and distortions of the mental image of the affected limb (Förderreuther et al., 2004; Frettlöh et al., 2006; Lewis et al., 2007; Peltz et al., 2011).

Before drawing general conclusions from the current results, the following aspects should be considered. Firstly, the movement frequency was set as low as possible (i.e., 0.7 Hz, which approaches the lower limit for cyclic movements to be rhythmical [Fraisse, 1982]) such that the experimental tasks would be feasible for as many patients as possible. However, several patients were excluded after preliminary testing because they were unable to perform flexion-extension movements of the wrist at a frequency ≥0.5 Hz and/or had a wrist AROM smaller than 30° (see exclusion criteria on p. 172). In addition, the present analyses were based on windows of stationary behavior, while short periods (or complete trials) of unstable performance had to be excluded (which was the case more often in patients, see Table 7.2). In all likelihood, the current results therefore provide an underestimation of motor impairments in CRPS. Secondly, the movement frequency was

relatively low compared to that in previous studies on rhythmic bimanual coordination (de Boer et al., 2011; Ridderikhoff et al., 2005b). As a consequence, participants may have noticed the -30° phase shift of to-be-ignored motor-driven movements. Apparently substantial effort was required to deliberately ignore the phase-shifted passive movements (e.g., see Table 7.2), which might have interfered with the evaluation of unintended entraining influences. Lastly, although the experiment appeared more strenuous for patients than for controls, no systematic increase of pain scores or decrease of movement amplitude was observed over the course of the experimental session, indicating that sufficient rest was provided to minimize potential effects of fatigue.

In conclusion, our results showed reduced stability of bimanual coordination in CRPS patients compared to controls, especially for tasks involving active control of the affected side. Collectively our results suggest that the motor dysfunction in CRPS is probably predominantly due to inappropriate functioning of higher-order centers involved in motor control of the affected limb. This in turn is probably associated with impaired central processing of proprioceptive information and pain-related processes. Our results further show that this prominent motor dysfunction of the affected limb has consequences for the coupling between the affected and unaffected limb, in particular for voluntary (intended) as opposed to automatic (unintended) coupling. In addition, the current results suggest that motor function of the affected side (in terms of movement amplitude and stability) may benefit from intended synchronization with active or passive movements of the unaffected side. This suggests that bilateral rhythmic arm training, whose positive effects have been reported in stroke patients (van Delden et al., 2013; Whitall et al., 2000), may provide a useful complement to conventional therapeutic strategies aimed at improving motor function of the affected limb in patients with unilateral CRPS. One should however be aware that the unaffected side is also inclined to adapt to functioning of the affected side (viz. the smaller amplitude and reduced stability during active bimanual coordination compared to unimanual movement of the unaffected side; in line with Steenbergen et al., 1996, 2008).

Supplement 7.1: Muscle activation patterns

Methods

Measurement instruments

Electromyography (EMG) recordings were obtained from the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) of both arms using rectangular (20x30 mm) non-disposable differential surface electrodes (DE-2.1, Delsys). EMG signals were amplified (1,000-10,000 times; BagnoliTM 4-channel desktop amplifier with 20-450 Hz bandpass filter; Delsys Inc, Boston, MA, USA). All signals were captured at a sampling rate of 1000 Hz with 16 bit A/D conversion.

Data collection procedure

First, two EMG recordings were obtained at rest while the participant's forearms were placed in the apparatus and the wrists were in a comfortable position. For each muscle the lower of the two resting values was used for normalization of the EMG (cf. Chapter 3). Subsequently, EMG recordings were obtained during the four experimental tasks that are described on p. 175-176:

1. Active bimanual coordination in an in-phase pattern and in an anti-phase pattern.
2. Active unimanual wrist flexion-extension, while the contralateral arm remained passive.
3. Active unimanual flexion-extension movements about the wrist, with simultaneous motor-driven movements of the contralateral hand (with a phase shift of 0° or -30° relative to the metronome beeps). Participants were instructed to ignore these passive movements.
4. Active unimanual flexion-extension movements about the wrist with simultaneous motor-driven movements of the contralateral hand. No auditory metronome was present and participants were instructed to move their active hand so as to track the rhythm of their passively moving hand (kinesthetic tracking, in-phase coordination).

Data analysis

EMG analyses were performed for active bimanual in-phase coordination, kinesthetic tracking and unimanual movements with (0° phase shift) or without simultaneous motor-driven movements of the contralateral hand, on the same trials and cycles that were included in the analyses of the kinematics. Activity of the wrist flexor (EMG_{FCR}) and wrist extensor (EMG_{ECR}) muscles was expressed as Ratio to Rest (RR; cf. Chapter 3). To visualize the average muscle activity within a cycle, eight bins were defined which represented an equal part of the movement cycle (cf. Ridderikhoff et al., 2005b). The first bin was centered on peak flexion and the fifth bin was centered on peak extension. For each bin, the normalized root mean square of the EMG was averaged over all cycles within a trial.

Results

One patient was unable to endure passive movements of the affected side and only performed tasks 1 and 2. In one patient, severe edema in the affected arm precluded EMG recordings. EMG data from 14 additional trials (6 in patients and 8 in controls) were excluded due to movement artifacts.

The average amplitudes of the EMG (in RR) during the movement cycle are presented in Figure S7.1, which exposes five noteworthy characteristics of the EMG data. Firstly, the timing of muscle activation was largely similar across groups and sides for all tasks, with the FCR muscle being active during the flexion phase of the movement cycle and the ECR muscle being active the during the extension phase of het movement cycle. Secondly, active movements of the patients' affected hand were characterized by smaller EMG amplitudes compared to the unaffected hand and both hands of healthy controls. Thirdly, the EMG amplitudes of the active hand were slightly lower in absolute compared to relative matching for patients as well as controls. Fourth, no activation of the passive arm was evident during unimanual rhythmic movement. Fifth, in the tasks that involved motor-driven movements the passively moved hand showed EMG activity similar to that observed during active movement, albeit more pronounced for the kinesthetic tracking task than for the task in which these passive movements had to be ignored.

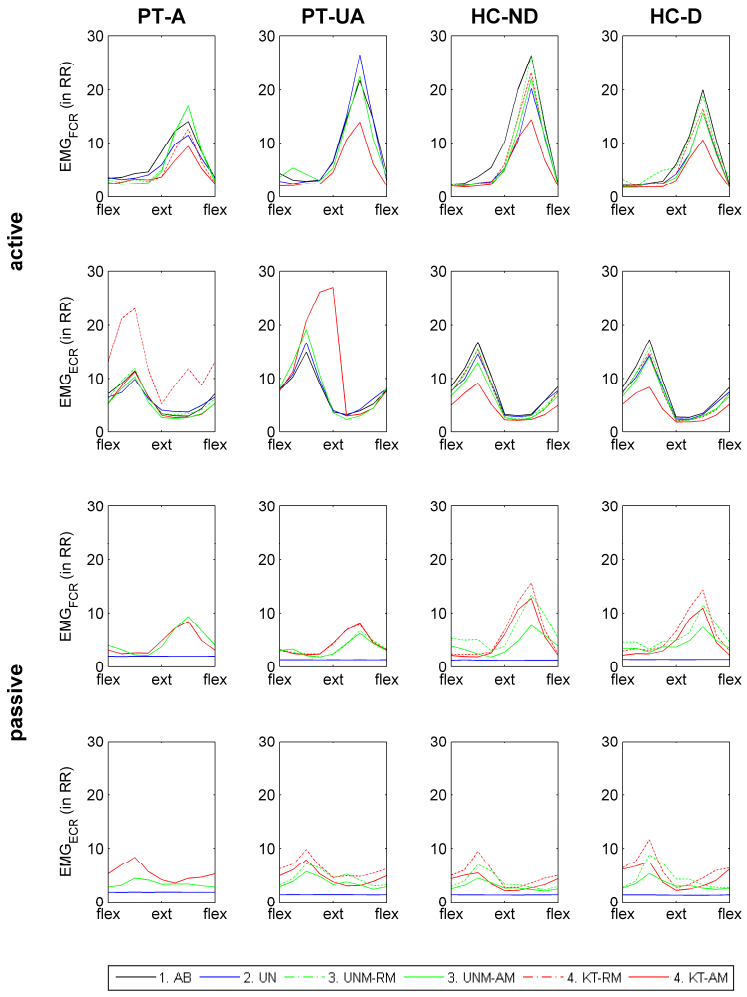


Figure S7.1 Average normalized EMG amplitudes of FCR and ECR at eight phases of the movement cycle during active bimanual coordination (task 1, in-phase), unimanual coordination (task 2), unimanual coordination, with to-be-ignored motor-driven movements of the contralateral side (task 3, 0° phase shift), and kinesthetic tracking (task 4) under absolute (solid lines) and relative (dotted lines) matching conditions. **(A)** FCR of the active limb; **(B)** ECR of the active limb; **(C)** FCR of the passive limb; **(D)** ECR of the passive limb. For reasons of clarity, error bars are omitted. Abbreviations: AB, active bimanual coordination; UN, unimanual coordination; UNM, unimanual coordination with 'to-be-ignored' motor-driven movements of the contralateral side; KT, kinesthetic tracking; ECR, extensor carpi radialis; FCR, flexor carpi radialis; AM, absolute matching; RM, relative matching; PT, patients (task 1 and 2: *n*=19; task 3 and 4: *n*=18), HC, healthy controls (*n*=40); A, affected side; UA, unaffected side; D, dominant side; ND, non-dominant side.

Discussion

Figure S7.1 shows that the temporal aspect of muscle activation was largely similar for CRPS patients and controls. The EMG amplitudes obtained from the affected side of patients, however, were smaller compared to those of their unaffected side and healthy controls. This corresponds to the marked reduction of movement amplitude of the affected side in patients (cf. p. 188-190). Similarly, the finding that EMG amplitude was slightly reduced in absolute compared to relative matching conditions is in line with the differences in the movement amplitude between these conditions.

For both patients and controls, the passively moved hand showed EMG activity similar to that observed during active movement, albeit more pronounced for the kinesthetic tracking task than for the unimanual task in which the motor-driven movements were to be ignored. Hence, especially during tracking of the passively moved hand, participants were 'moving along' by activating the muscles in the passively moved hand as if they were generating the movements themselves, which may have helped to improve performance in the tracking task (cf. de Boer et al., 2011; Ridderikhoff et al., 2005b, 2007). However, given the strength of the motor, this muscle activation did not have any effect on the actual passive movements.

In the strictly unimanual task that did not involve motor-driven movements of the passive arm, no evident muscle activity was detected in the passive arm. Figure S7.1 provides no evidence for unintended overflow or neuronal crosstalk of efferent signals from the voluntarily moving side to homologous muscles in the contralateral passive limb. Also a more sensitive, in-depth analysis of EMG recordings in this condition revealed no evidence of enhanced levels of mirrored muscle activity (Chapter 6). These findings point at normal inhibition of contralateral motor activity in CRPS and provide no indications of abnormal unintended coupling between the affected and unaffected limb on the basis of efferent signals.

Collectively, the muscle activation patterns presented in Figure S7.1 were largely similar to those reported for healthy participants (de Boer et al., 2011; Ridderikhoff et al., 2005b), revealing no differences between patients and controls that may have interfered with our conclusions based on the kinematic analyses that are presented in this Chapter.

Chapter 8

Summary, conclusions and future perspectives

Summary

In the chronic stage of Complex Regional Pain Syndrome (CRPS), motor disturbances are common and cause significant disability. Motor dysfunction of CRPS is characterized first and foremost by a decrease or loss of voluntary muscle control. In addition to structural and functional alterations in skeletal muscle tissue, the motor impairment of CRPS appears to be associated with decreased inhibition of the motor system, changes in sensory processing and problems in sensory-motor integration. The overarching aim of the present thesis is to uncover the interrelations among these aspects so as to obtain a better understanding of the pathophysiology underpinning the motor dysfunction of CRPS, and thus to help create a better foundation for therapeutic interventions.

Pain is a key feature of CRPS and may have profound effects on motor behavior. To first obtain a coherent view on the relations between pain and the motor system, we conducted a systematic review of the literature in which the motor consequences of various sources of experimental pain were evaluated in healthy humans (Chapter 2). Next, the characteristics of muscle activity recordings were scrutinized (Chapters 3 and 6) in order to determine whether the loss of voluntary motor control and abnormal postures in CRPS exhibit characteristics of dystonia that are associated with reduced inhibition of the motor system (i.e., excessive muscle activation [Chapter 3] and enhanced mirror activity [Chapter 6]). Subsequently, we examined the potential role of impaired processing of proprioceptive information related to wrist orientation and force production (Chapters 4 and 5). Finally, we assessed the involuntary and voluntary (sensory-)motor interactions between the affected and unaffected hand (Chapters 6 and 7). In this final chapter, the results are summarized and discussed, and possible directions for future research are suggested.

Motor behavior in clinical pain conditions is the result of a complex interplay between multiple factors, rendering it difficult to separate the various effects of nociceptive input on the motor system. The systematic review presented in **Chapter 2** therefore sought to delineate the effects of experimental (sub)cutaneous pain, joint pain, muscle pain and tendon pain on the motor system in healthy humans and, in so doing, to disentangle the intricate cause-and-effect relation between pain and movement. The

results showed that pain affects many components of motor processing at various levels of the nervous system, but also that the effects of pain are largely irrespective of its source. Pain is associated with inhibition of muscle activity in the (painful) agonist and its non-painful antagonists and synergists, especially at higher intensities of muscle contraction. Despite the influence of pain on muscle activation, the movement kinetics and kinematics were only subtly affected. The performance of various motor tasks remained mostly unimpaired, presumably as a result of a redistribution of muscle activity – both within the (painful) agonist and among the other muscles involved in the task. Collectively, the findings show that, irrespective of the source of pain, short-lasting experimentally-induced limb pain invokes immediate changes at all levels of motor control, possibly to facilitate protective and compensatory motor behavior. In clinical pain conditions, however, motor behavior is likely shaped by a multifaceted interplay between the pain-induced changes described in this chapter and other factors such as structural tissue damage, long-term adaptations to pain, and emotional and cognitive responses to (chronic) pain.

Motor abnormalities in CRPS that are frequently observed include a restricted active range of motion (AROM), increased resistance to passive movements, and abnormal postures. The objective of the experiment presented in **Chapter 3** was to obtain a better understanding of the factors that are associated with these specific motor impairments and to investigate whether they reflect dystonia. To this end, we evaluated the characteristics of surface electromyography (EMG) of the flexor carpi radialis and extensor carpi radialis muscles during active maintenance of various flexion-extension postures of the wrist of the affected and unaffected side in 15 chronic CRPS patients and in 15 healthy controls. The results showed that deviant joint postures in chronic CRPS – at least in patients with some range of active movement – were not characterized by sustained muscle contractions, and that limitations of the AROM were not attributable to excessive co-contraction. Rather, the agonistic muscle and its antagonist were activated in normal proportions, albeit over a limited range. Hence, the AROM limitations and abnormal postures in patients with longstanding CRPS did not exhibit the characteristics typical of dystonia, which – after all – is defined as a syndrome of sustained muscle activity and abnormal co-contraction of agonist and antagonist muscles. This may have

important clinical implications, since in CRPS patients with abnormal postures of the affected limb treatments have been aimed at reducing the activity of the skeletal muscles assumed to be responsible for the deviant posture, e.g., by intramuscular Botulinum toxin injections or oral administration of muscle relaxants. The present findings emphasize the importance of thorough evaluation of EMG characteristics prior to deciding on the treatment strategy and suggest that treatment aimed at prevention of muscle atrophy by means of physical therapy and stimulation of using the affected limb may prove more rewarding.

Pertinent studies contain various hints that impaired processing of proprioceptive information might play a significant role in the motor dysfunction of CRPS. Unfortunately, little is known about proprioception in CRPS. The work presented in Chapters 4 and 5 therefore focused on proprioceptive deficits and their putative contribution to impaired motor function in CRPS.

Chapter 4 described the accuracy and precision of joint position sense over a range of flexion-extension angles of the wrist of the affected and unaffected side in 25 chronic CRPS patients and in 50 healthy controls. The results revealed proprioceptive impairment at both the affected and unaffected side of patients, characterized predominantly by overestimation of wrist extension angles. Precision of the position estimates was more prominently reduced at the affected side. Importantly, group differences in proprioceptive performance were not only observed for tests at identical percentages of each individual's range of wrist motion, but also when controls were tested at wrist angles that corresponded to those of the patient's affected side. More severe motor impairment of the affected side was associated with poorer proprioceptive performance. Results of additional sensory tests, comparisons of active and passive displacements, and variations in proprioceptive performance over the range of wrist angles were examined with the aim to identify at which stage of information processing the observed proprioceptive deficits arise. Together, this led to the conclusion that the disturbances of proprioceptive performance most likely resulted from altered processing of afferent (rather than efferent) information and its subsequent interpretation in the context of a distorted 'body schema'.

The research question addressed in **Chapter 5** was if disturbances in the sense of force production contribute to impaired 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 was compared between conditions with and without 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). The results showed that voluntary force modulation was impaired in CRPS patients. In particular the performance of CRPS patients with abnormal postures was 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. At first sight the effects of the removal of visual feedback appeared largely similar for the two patient groups and controls. However, marked deficits in force production sense were observed in CRPS patients with abnormal postures if the analysis of force reproduction errors was restricted to the lowest target force so as to minimize potential confounding effects of motor impairment. The experiment presented in Chapter 5 was also performed for the affected lower extremity in 15 CRPS patients with abnormal postures, in 11 CRPS patients without abnormal postures and in 32 healthy controls. Importantly, the findings largely supported those obtained from the upper extremity, albeit that force control of the lower limb appeared more prominently impaired in CRPS. This might have precluded the detection of proprioceptive deficits in this extremity.

Disturbances in the processing of proprioceptive information, such as those described in Chapters 4 and 5, and problems with sensory-motor integration may not only affect motor function of the affected limb, but also have consequences for the ability to properly coordinate the movements between two limbs. Although there are indications of abnormal coupling between the affected and unaffected limb in CRPS, the significance of these factors to motor impairments in CRPS is still poorly understood. The (sensory-) motor interactions between the affected and unaffected arm were therefore examined in Chapters 6 and 7. To further our insight into the apparent discrepancy between the performance of automatic and voluntary movements in some cases of CRPS, which is

sometimes taken as evidence of psychogenicity, these chapters sought to discriminate between involuntary and voluntary aspects of interlimb coupling.

The work presented in **Chapter 6** focused on the potential role of involuntary overflow or neuronal crosstalk of efferent signals from a voluntarily moving arm towards homologous muscles in the contralateral passive arm. This study aimed to ascertain if the loss of voluntary control and abnormal posturing of the affected limb in CRPS is associated with disinhibition of contralateral motor activity, which is a common finding in dystonia. To this end, mirrored muscle activity was evaluated during unimanual rhythmic flexion-extension movements of the wrist of the affected and unaffected side in 20 chronic CRPS patients and of the non-dominant and dominant side in 40 healthy controls. A sensitive analysis was applied to EMG recordings from the passive arm in order to detect epochs of mirror activity and quantify 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. The number of detected mirror-epochs was comparable for both arms of CRPS patients and controls. Mirror-epochs in the affected arm of CRPS patients were comparable to those of controls. Mirror-epochs in the unaffected arm, however, were shorter and showed less resemblance (in terms of the predominant rhythm and relative timing) to the activity of the homologous muscle in the moving arm than mirror-epochs in controls. This might have been a secondary effect of impaired voluntary control of the affected arm because the smaller movements of the affected arm required a lower intensity of motor commands, probably invoking less neuronal cross-talk to the contralateral (unaffected) side. No evidence for disinhibition of circuits involved in contralateral motor activity was found, suggesting that the mechanisms underlying CRPS-related motor dysfunction are different from those underpinning dystonia (in line with the results of Chapter 3).

The study described in **Chapter 7** aimed to discriminate between voluntary and automatic aspects of interlimb coupling by examining the influences of intended bilateral planning, intended afference-based error correction and unintended reflex-like entrainment. To this end, 20 chronic CRPS patients and 40 healthy controls performed a set of unimanual and bimanual rhythmic motor tasks that differed in the degree to which these sources of intended and unintended interlimb coupling were involved. Specifically,

intended interlimb coupling was not only evaluated during active control of both hands to examine the influence of bilateral planning, but also during afference-based coordination with passive movements of the contralateral hand to examine the influence of afference-based error correction. Unintended interlimb coupling was evaluated in terms of reflex-like entrainment of active hand movements to the movement rhythm of to-be-ignored passive movements of the contralateral hand. Analysis of temporal interlimb coupling showed that coordination between the two hands was less stable in CRPS patients compared to controls, especially for tasks involving active control of the affected side, and indicated a prominent impairment of intended rather than unintended coupling between the hands. In particular the stabilizing effects of bilateral planning were less pronounced in patients than controls, and the patients' affected side exhibited a lower level of afference-based error correction. No evidence of abnormal reflex-like entrainment was found. Analysis of spatial interlimb coupling revealed that the relatively small movement amplitude of the patients' affected hand was slightly increased by active or passive movements of the unaffected hand, whereas movement amplitude of their unaffected side was reduced during intentional coordination with the (typically smaller) movements of the affected hand. Taken together, the work presented in Chapters 6 and 7 suggests that motor dysfunction of CRPS is largely due to inappropriate functioning of higher-order centers involved in voluntary motor control of the affected limb. This also has consequences for the temporal and spatial coupling between the affected and unaffected limb, in particular for voluntary (intended) as opposed to automatic (unintended) coupling.

Concluding remarks

This thesis aimed to obtain a better understanding of the pathophysiology underpinning the motor dysfunction of CRPS by examining the potential roles of decreased inhibition of the motor system, changes in sensory processing and problems in sensory-motor integration. In the following sections, the insights obtained into these aspects, the potential role of pain-related processes and the potential implications for therapy are discussed in brief.

Decreased inhibition of the motor system?

The research presented in this thesis provided no evidence for abnormal reflex-like entrainment (Chapter 7). Evaluation of mirrored muscle activity yielded no indications of disinhibition of neural circuits mediating contralateral activity (Chapter 6). This was corroborated by the finding that the stability of active bimanual coordination was more markedly reduced for in-phase than for antiphase coordination (Chapter 7), given that the opposite result would be expected if CRPS would have been characterized by disinhibition of contralateral motor activity.

These findings seem incompatible with results of previous studies suggesting that the motor system in CRPS is associated with reduced inhibition. Thus far, however, studies have mainly focused on the putative role of (dis)inhibition while the motor system was at rest, e.g., using a vibratory stimulus to examine the inhibition of the H-reflex (van de Beek et al. 2002), using transcranial magnetic stimulation to measure (modulation of) excitability of the corticospinal tract (Eisenberg et al., 2005; Krause et al., 2004; Schwenkreis et al., 2003), or using magnetoencephalography to examine alterations in rhythmic brain activity in response to nociceptive stimulation (Juottonen et al., 2002; Kirveskari et al., 2010). In contrast, the present findings were obtained when the motor system was actively engaged in manual motor tasks.

Other indications of disinhibition of the motor system were provided by studies reporting a significant reduction of CRPS-related dystonia by intrathecal administration of the gamma-aminobutyric-acid B ($GABA_B$) receptor agonist baclofen (van Hilten et al., 2000; van Rijn et al., 2009). Although these findings suggest that loss of spinal GABAergic inhibition may contribute to impaired motor function, the mechanisms of action of baclofen are still largely unknown. For example, it cannot be ruled out that part of the effect is mediated at a supraspinal level because baclofen may diffuse more rostrally.

As mentioned in Chapter 1, it has remained unclear to date if the commonly observed motor impairments in CRPS that were examined in this thesis (i.e., loss of voluntary control, limited AROM, increased resistance to passive movements, and abnormal postures) are associated with dystonia. Collectively, our findings showed that these motor impairments in chronic CRPS did not exhibit the characteristics typical of dystonia. Firstly, deviant joint postures – at least in those patients with some range of

active movement – were not characterized by sustained muscle contractions and AROM limitations were not attributable to excessive co-contraction (Chapter 3; in line with van de Beek et al., 2002). Secondly, the affected limb did not display increased levels of mirrored muscle activity during rhythmic movement of the unaffected hand (Chapter 6). This contrasts with the 'mirror dystonia' occurring in the affected hand of patients with focal hand dystonia while performing a task with their unaffected hand, which has been associated with dysfunctional interhemispheric inhibitory connections (Beck et al., 2009; Nelson et al., 2010). Hence, despite the substantial resemblance in their clinical presentation, the mechanisms responsible for these CRPS-related motor impairments appear different from those underpinning dystonia.

The present findings relate to CRPS patients with at least some degree of voluntary motor control (i.e., AROM >30°). Consequently, it cannot be ruled out that patients with fixed postures and a complete loss of motor control – who may benefit from intrathecal administration of baclofen (van Hilten et al., 2000; van Rijn et al., 2009) – do exhibit characteristics of dystonia.

Changes in sensory processing

Sensory impairments in CRPS, including altered sensitivity of cutaneous and muscular afferents (Chapters 3, 4 and 5; Eberle et al., 2009; Huge et al., 2008; Kemler et al., 2000; Maier et al., 2010; van Rooijen et al., 2013a), may interfere with motor control. The research presented in this thesis provided direct evidence of impaired processing of proprioceptive information related to joint position (Chapter 4; in line with Lewis et al., 2010) and force production (Chapter 5), and attests to the relationship between proprioceptive impairment and CRPS-related motor dysfunction. In particular, patients displayed a systematic 'misperception' of extension positions (i.e., reduced accuracy), with the hand position being perceived more towards extension than the actual position. Interestingly, the largest proprioceptive deficits were observed in extension positions, exactly where the motor impairment was most pronounced. In addition, more severe motor impairment of the affected hand was associated with poorer precision (i.e., higher variability) of hand position estimates. Evidence for impaired sense of force production also pointed at reduced proprioceptive precision (i.e., increased variable error). The

precision of sensory information is of crucial importance because accurate motor control requires precise knowledge of the state of the body. To this end, proprioceptive, tactile and visual input are integrated within the central nervous system, with the highest weight being given to the most precise source of sensory information (sensory weighting; Bays and Wolpert, 2007; Ernst and Bülthoff, 2004).

Adequate proprioception comprises three sequential stages of information processing: *(1)* detection and transmission of afferent information; *(2)* integration of information from various peripheral and central sources; and *(3)* interpretation of this information in relation to a body schema (Proske and Gandevia, 2012). The comprehensive evaluation of proprioceptive performance presented in Chapter 4 sought to establish at which of these stages the proprioceptive deficits in CRPS arise. Possibly the sensitivity of the receptors involved in proprioception (i.e., in muscle, joint and/or skin) is altered due to CRPS-related trophic changes or suboptimal peripheral adaptations to the smaller ROM at the affected side. However, given that pain may interfere with the processing of afferent signals contributing to position sense (see Chapter 2) and the mental image of the affected limb is often distorted in CRPS patients (Förderreuther et al., 2004; Frettlöh et al., 2006; Lewis et al., 2007, 2010; Moseley, 2005; Peltz et al., 2011), a central processing deficit seems more plausible. Indeed, findings presented in Chapter 4 suggest a significant role for altered processing of afferent information and its subsequent interpretation in relation to a 'body schema' that does not accurately match the actual status of the limb.

Problems with sensory-motor integration

The correct execution of a voluntary movement depends crucially on the ability to use peripheral sensory feedback properly for assisting motor execution. During movement, the actual sensory feedback (i.e., proprioceptive, tactile and visual input) is compared to sensory outcomes predicted on the basis of forward models that collate copies of motor commands and input from initial limb configurations (Festinger and Canon, 1965). Discrepancies between actual and predicted sensory outcomes are corrected online on the basis of feedback modules generating corrective signals that lead to adjustments of motor output (Bays and Wolpert, 2007; Wolpert and Ghahramani,

2000). In CRPS, the actual sensory outcomes of a given motor command may be distorted by functional and structural alterations of muscle tissue (Hulsman et al., 2009; Tan et al., 2011; van der Laan et al., 1998; Vas et al., 2013) and altered processing of information from cutaneous or muscle afferents (e.g., Eberle et al., 2009; Huge et al., 2011; Kemler et al., 2000; Maier et al., 2010; van Rooijen et al., 2013a). At the same time, distortions of the mental image of the affected limb (Förderreuther et al., 2004; Frettlöh et al., 2006; Lewis et al., 2007; Peltz et al., 2011) may contribute to erroneous predictions of the sensory outcome of a given motor command. This implies that the proprioceptive deficits in CRPS (as described in Chapters 4 and 5) may have an immediate adverse effect on motor control via online adaptations of motor output based on erroneous actual and predicted sensory outcomes. Importantly, the forward model that predicts the consequences of planned actions is subject to adaptation, learning and preservation. The cerebellum likely plays a significant role in these processes (Ito, 1970; Miall et al., 1993; Wolpert and Kawato, 1998). This implies that the proprioceptive deficits in CRPS (as described in Chapters 4 and 5) may contribute to maladaptive motor control in the long term through alterations in the forward model.

The close link between impaired proprioception and motor control was aptly illustrated in Chapter 7, where the patients' affected hand exhibited lower levels of intentional error correction during kinesthetic tracking. This indicated that the control of the affected limb's movements was compromised by inadequate integration of afferent and efferent signals of the voluntarily moving affected hand with proprioceptive information arising from the passively moving unaffected hand. However, CRPS patients appeared quite able to attune movements of their unaffected hand to passive movements of their affected hand, which suggests that the proprioceptive information from the affected limb per se is not the essential problem. Based on these findings, it may be hypothesized that impaired bimanual coordination is primarily due to inappropriate integration of afferent and efferent signals in higher-order centers involved in the motor control of the affected limb.

In accordance with this hypothesis, CRPS patients particularly showed a reduced stability of bimanual coordination for tasks involving *active control of their affected limb*. Perhaps changes in skeletal muscle tissue (Hulsman et al., 2009; Tan et al., 2011; van der

Laan et al., 1998; Vas et al., 2013) contributed to the limitations in voluntary force modulation and movement amplitude that were observed in patients with longstanding CRPS. However, the work presented in Chapters 6 and 7 suggests that motor dysfunction of CRPS is largely due to dysfunction of neural networks within the hemisphere responsible for controlling the affected limb. This in turn appears to be associated with impaired processing of proprioceptive information (Chapters 4 and 5). Importantly, no evidence was found for abnormal reflex-like entrainment (Chapter 7) or disinhibition of circuits involved in contralateral motor activity (Chapter 6). Our findings thus corroborate previous suggestions that motor dysfunction in CRPS is related to inappropriate functioning of higher-order centers involved in the motor control of the affected limb (Maihöfner et al., 2007; Swart et al., 2009).

Potential role of pain-related processes

Since all CRPS patients reported moderate to severe pain, it is tempting to simply attribute the observed sensory and motor impairments to pain-related processes, e.g., pain competing with other attention-demanding stimuli for limited cognitive resources (Eccleston and Crombez, 1999; Grisart and van der Linden, 2001), or patients being reluctant to exert full effort because of increasing pain. However, such an interpretation would disregard numerous indications of involvement of other factors. For example, the marked deficits of force control in CRPS patients with abnormal postures (Chapter 5) and the between-task variations in coordinative stability and movement amplitude (Chapter 7) are likely attributable to other factors than pain, because pain ratings were largely similar in the CRPS patients with and without abnormal postures examined in Chapter 5, and across all tasks and conditions of the experiment described in Chapter 7.

A significant role of pain in the motor dysfunction of CRPS, however, seems undeniable. In a recent study, it was demonstrated that pain reduction – regardless of whether it was achieved by administration of intravenous ketamine or placebo – was associated with improvement of motor function in CRPS (Schilder et al., 2013). Such a relation between pain and impaired motor function in CRPS is also evident from several cross-sectional studies (e.g., Huge et al., 2011; van Rooijen et al., 2013a). In this thesis, a significant association between muscle hyperalgesia and reduced maximum grip force was

found (Chapter 5) and higher levels of pain were associated with lower stability of coordination for tasks involving voluntary movement of the affected hand (Chapter 7). In particular for patients with higher pain scores, the stabilizing effect of bimanual planning was less pronounced and a slight reduction of coordinative stability was induced by to-be-ignored motor-driven movements of the affected hand. Possibly, limited variability in the measures of pain obscured a potential relation with other measures of sensory and motor function that were examined in Chapters 3, 4, 5 and 6.

Chapter 2 revealed that, irrespective of its source, short-lasting experimentally induced limb pain induces immediate changes at all levels of the motor system, probably to facilitate protective and compensatory motor behavior. In clinical pain conditions such as CRPS, however, motor behavior is likely shaped by a multifaceted interplay between the pain-induced changes outlined in Chapter 2 and other factors such as structural tissue damage, long-term adaptations to pain, and psychological aspects of chronic pain (Hodges and Tucker, 2011).

Emotional and cognitive responses to (chronic) pain may greatly affect motor behavior, e.g., fear of pain typically is manifested in altered movement strategies (Vlaeyen and Linton, 2000) and the belief that activity will harm a painful limb often leads to avoidance of physical activity and disuse of the limb in question (e.g., Rainville et al., 2011; Zale et al., 2013). It is therefore not surprising that scientists have been particularly intrigued by these psychological factors in their search for determinants of physical disability (for a review, see Zale et al., 2013) and predictors of the transition from acute to chronic pain (e.g., Gatchel et al., 1995; Hinrichs-Rocker et al., 2009; Pincus et al., 2002; Theunissen et al., 2012). Based on the premise that pain-related disuse may interact with other pathophysiological mechanisms of CRPS to prevent the ending of a viscious cycle (Bruehl, 2001), it has been advocated that treatment of CRPS should comprise a psychological pain management component (Bruehl and Chung, 2006). Whereas the benefit of psychological interventions for the management of pain and disability has been established in other chronic pain conditions (Williams et al., 2012), randomized controlled studies of psychological interventions for CRPS, alone or in a multidisciplinary context, are still scarce. In two studies, a multidisciplinary intervention combining physical therapy and training techniques aimed at increasing the control of pain and

optimizing pain coping resulted in significantly improved pain and active range of motion and lower levels of impairment compared with a control group counseled by a social worker (Oerlemans et al., 1999, 2000b). Recently, promising results of 'pain exposure' physical therapy have been reported with respect to pain reduction and motor function (de Jong et al., 2005; Ek et al., 2009; van de Meent et al., 2011). In the absence of a proper control condition, however, no firm statements can be made regarding the effectiveness of this therapy, which consists of progressive-loading exercises beyond the patient's pain limits and management of pain-avoidance behavior.

In conclusion, although pain most likely plays a role in the motor dysfunction of CRPS, the exact manifestation of its effects remains to be investigated. The studies presented in this thesis corroborated pertinent studies providing evidence for involvement of factors related to (central processes of) sensory and motor function (e.g., Bailey et al., 2013; Maihöfner et al., 2007). A comparison of patients with CRPS to patients with other causes of chronic (neuropathic) pain would be of interest in order to determine the extent to which the observed sensory and motor impairments are associated with chronic pain in general, or are specific to CRPS.

Implications for therapy

In CRPS patients with abnormal postures of the affected limb, treatments have been aimed at reducing the activity of the skeletal muscles assumed to be responsible for the deviant posture, e.g., by intramuscular Botulinum toxin injections or oral administration of muscle relaxants. In Chapters 3 and 6 of this thesis, however, thorough evaluation of EMG characteristics provided no evidence for excessive muscle activation in the affected limb of patients with longstanding CRPS with at least some degree of voluntary motor control (i.e., AROM >30°). In fact, the motor dysfunction of CRPS was associated with deficient muscle activation (Chapter 3). In view of these findings, it may not be surprising that treatments aimed at reducing excessive muscle contractions usually have a disappointing effect (van Rooijen et al., 2011). As a matter of fact, further weakening of already weak muscles might lead to further deterioration of motor function in these patients. Although the present research does not allow conclusions on the potential role of excessive muscle activity in patients who present with fixed postures and a complete

loss of motor control, our findings emphasize the importance of thorough evaluation of EMG characteristics prior to deciding on the treatment strategy: pharmacological intervention aimed at muscle relaxation versus treatment aimed at prevention of muscle atrophy (e.g., by means of physical therapy and stimulation of using the affected limb).

Activity-related pain may form a barrier to patient compliance in the currently advocated multi-disciplinary rehabilitation-focused approach for management of CRPS, which emphasizes reactivation of the affected extremity (Harden et al., 2013; Schrag et al., 2004; Stanton-Hicks et al., 2002; Turner-Stokes and Goebel, 2011). This suggests that recovery of motor function may benefit from therapeutic procedures that slightly distract a patient from pain-related processes in the affected limb. Against this background, bilateral rhythmic arm training, whose positive effects have been reported in stroke patients (van Delden et al., 2013; Whitall et al., 2000), might provide a useful complement to conventional therapeutic strategies aimed at improving motor function of the affected limb in patients with unilateral CRPS. During bimanual coordination, patients are forced to distribute their attention among the affected and unaffected limb, whereas at the same time sources of interlimb coupling are exploited to help improve motor function of the affected side. In Chapter 7, it was demonstrated that motor function of the affected side benefits from intended synchronization with active or passive movements of the unaffected side. However, one should be aware that the unaffected side may also be inclined to adapt to the deteriorated functioning of the affected side (Chapter 7; in line with Steenbergen et al., 1996, 2008).

Since the results presented in Chapter 4 and 5 point at a significant role for impaired central processing of proprioceptive information, it would also be worthwhile to explore whether therapeutic strategies aimed at identification of proprioceptive impairments and their restoration (e.g., using some form of mirror therapy or online visual feedback) may promote the recovery of motor function in CRPS patients.

Future perspectives

CRPS is characterized by (severe) pain with various combinations of sensory, autonomic, trophic and motor abnormalities. Interindividual differences in the extent to which various pathophysiological mechanisms are affected (i.e., related to inflammation, vasomotor dysfunction, or maladaptive plasticity of the central nervous system; see Chapter 1) may account for the clinical heterogeneity of the syndrome (Marinus et al., 2011). The chronic stage of CRPS is typically dominated by pain and motor disturbances. However, this does not imply that patients with longstanding CRPS form a uniform group. The range of motor symptoms is broad and may vary from muscle weakness and tremor to prominent abnormal posturing. Some patients present with sensory gain (e.g., hyperalgesia, allodynia) and others present with sensory loss (e.g., hypoalgesia, hypoesthesia), whereas the majority of patients exhibit a combination of these positive and negative sensory symptoms (Gierthmühlen et al., 2012; Maier et al., 2010). In addition, there are large inter-individual variations with regard to the presence and severity of vasomotor symptoms, the cognitive and emotional responses to (chronic) pain, and the history of pharmacological and non-pharmacological therapeutic interventions.

Comparisons at the group level, as presented in this thesis, are essential to further our understanding of mechanisms underpinning the motor dysfunction of CRPS, and thus to help create a better foundation for therapeutic interventions. However, given the striking inter-individual differences, selection of the optimal strategy for the treatment of a specific patient requires that the mechanisms involved in motor control can be evaluated on an individual level. Future research should therefore be aimed at developing diagnostic tools that allow identification of the weakest link(s) in the motor system at the level of an individual patient. Ultimately, this should result in a compact set of easily applicable tests that allows the physician or physiotherapist to determine whether motor impairments of an individual patient are mainly attributable to structural or functional alterations of the skeletal muscle tissue, altered sensitivity of proprioceptive receptors, disturbances in the central processing of proprioceptive information, disturbances of the body image, impairment of attentional processes, or psychological factors such as pain-related fear of movement.

For many years, the psychogenic or organic etiology of CRPS-related motor dysfunction, in particular of abnormal posturing ('fixed' dystonia – i.e., without any evidence of joint mobility – in particular), has been the subject of ongoing debate (Munts et al., 2010; Ochoa and Verdugo, 2005; Schrag et al., 2004; Verdugo and Ochoa, 2000). In view of selecting the optimal strategy for treatment, it is of great importance to develop a diagnostic tool for the assessment of a possible functional (i.e., psychogenic) component that may be superimposed on an organic fundament. Given that the border between psychogenic and organic has become increasingly blurred in recent years (Munts et al., 2010), this will likely constitute a major methodological challenge. Despite new insights from functional imaging and neurophysiological studies, hitherto no uncontested and reliable diagnostic tool has been available. Although it was long thought that the Bereitschaftspotential could be used to discriminate between voluntary and involuntary movements, the significance of its presence or absence has been questioned (Hallett, 2010). Whereas foundations have been laid for a laboratory-supported diagnosis of psychogenic tremor (Schwingenschuh et al., 2011), the associated tests for this hyperkinetic movement disorder (e.g., changes in tremor frequency or amplitude induced by contralateral tapping or loading of the affected limb) are not applicable to the hypokinetic movement disorders that are observed in the context of CRPS. The paradigm as applied in Chapters 6 and 7 may shed light on an apparent dissociation between involuntary and voluntary aspects of movement. The presence of strong involuntary interlimb interactions would advocate an organic origin. However, it may be clear from the preceding discussion on sensory-motor integration (p. 210-212) that impairment of intended interlimb interactions does not necessarily imply a psychogenic origin. Against this background, future research on potentially shared pathophysiological aspects between the loss of voluntary control in CRPS and functional movement disorders may prove valuable.

The tricky part of research on movement disorders is that it generally cannot do without any (preferably objective) measurement of movement. The complete loss of voluntary control that is observed in some patients limits the possibilities in this regard. Some patients may be unable to perform even the simplest tasks (such as flexion and extension of the fingers or wrist, or flexion of the toe), not to mention their inability to

perform functional tasks that more closely resemble those encountered in daily life. Most of the studies presented in this thesis probably provide an underestimation of the sensory and motor impairments in CRPS, because some severely affected patients were unable to perform the experimental tasks, and sometimes (those parts of) a trial that reflected the worst performance could not be included in the analysis. For example, patients were only enrolled in the studies presented in Chapters 3, 4, 6 and 7 if their wrist AROM was at least 30°. The presented findings thus relate to CRPS patients with at least some degree of voluntary motor control. It remains to be investigated whether patients who present with fixed postures and a complete loss of motor control represent a more severe manifestation of symptoms identified in the current study, or form a subgroup with a distinct phenomenology and underlying pathophysiology.

Finally, it should be noted that the findings presented in this thesis relate to the *chronic* stage of CRPS; hence our findings do not allow conclusions on the potential role of these factors in an earlier stage of the disease. Prospective longitudinal studies are needed to identify risk factors that can predict which patients will develop movement disorders and who will not. Such longitudinal studies may help to identify the primary site where pathological alterations originate and shed light on the cascade of (possibly compensatory) processes leading to the sensory and motor disturbances that characterize the chronic stage of the disorder. In so doing, it may provide a foundation for targeted interventions to break the vicious cycle that seems to be responsible for maintenance of symptoms in the chronic stage of CRPS (Bruehl, 2001; Bruehl and Chung, 2006), or even better, to interrupt this cascade of processes in an earlier stage of CRPS. After all, prevention is better than cure.

Chapter 9

Samenvatting, conclusies en perspectieven

Samenvatting

Complex Regionaal Pijn Syndroom (CRPS) wordt gekarakteriseerd door (hevige) pijn in combinatie met diverse sensibele, autonome, trofische en motorische afwijkingen. Het uitgebreide scala aan klinische verschijnselen dat wordt waargenomen bij CRPS is een resultaat van complexe interacties tussen de veronderstelde pathofysiologische mechanismen van CRPS, zoals buitenproportionele ontsteking, vasomotore disfunctie en maladaptieve plasticiteit van het centrale zenuwstelsel. De chronische fase van CRPS wordt veelal gedomineerd door pijn en bewegingsstoornissen. Hierdoor zijn patiënten vaak ernstig beperkt in hun dagelijks functioneren. De motorische problemen in CRPS worden voornamelijk gekarakteriseerd door een vermindering of verlies van vrijwillige sturing, waarbij de aangedane ledemaat bij sommige patiënten een abnormale stand aanneemt. Aangenomen wordt dat veranderingen in de structuur en functie van spierweefsel kunnen bijdragen aan de bewegingsstoornissen van CRPS. Steeds meer studies wijzen echter op veranderingen in het centrale zenuwstelsel. Zo wordt verondersteld dat verminderde remming (inhibitie) van het motorisch systeem, veranderingen in de verwerking van sensibele informatie en problemen met de integratie van sensorische en motorische signalen (sensomotorische integratie) een rol spelen bij CRPS. Het overkoepelende doel van dit proefschrift is om de relaties tussen deze aspecten te bestuderen teneinde meer inzicht te krijgen in de pathofysiologische mechanismen die ten grondslag liggen aan CRPS-gerelateerde bewegingsstoornissen en daarmee een bijdrage te leveren aan de wetenschappelijke onderbouwing van therapeutische interventies.

Pijn, een van de belangrijkste kenmerken van CRPS, kan verregaande gevolgen hebben voor het motorisch functioneren. Om een beeld te krijgen van de relatie tussen pijn en bewegen, bevat Hoofdstuk 2 een uitgebreid systematisch overzicht van de literatuur over de effecten van experimenteel geïnduceerde pijn op het motorisch systeem van gezonde proefpersonen. De daaropvolgende hoofdstukken beschrijven een aantal studies naar de veronderstelde pathofysiologische mechanismen van CRPS-gerelateerde bewegingsstoornissen. In Hoofdstuk 3 en 6 werd de vermeende rol van verminderde remming (inhibitie) van het motorisch systeem onderzocht. Aan de hand van uitgebreide

analyses van spieractiviteit werd getracht vast te stellen of de verminderde sturing van vrijwillige bewegingen en de standsafwijkingen bij CRPS kenmerken vertonen die typisch zijn voor dystonie, namelijk overmatige spieractiviteit (Hoofdstuk 3) en 'gespiegelde spieractiviteit' (Hoofdstuk 6). De studies beschreven in Hoofdstuk 4 en 5 richtten zich op de bestudering van proprioceptieve stoornissen (te weten het gevoel van gewrichtspositie en krachtproductie) en hun vermeende bijdrage aan de verminderde motorische functie in CRPS. Ten slotte werden in Hoofdstuk 6 en 7 de intentionele en niet-intentionele (senso)motorische interacties tussen de aangedane en niet-aangedane ledemaat onderzocht. In Hoofdstuk 8 (waarvan dit de Nederlandse vertaling is) worden de eerdere hoofdstukken samengevat en worden de hoofdbevindingen van het proefschrift besproken, alsmede de bijdrage ervan aan ons begrip van de bewegingsstoornissen bij CRPS.

Wanneer er sprake is van chronische pijn, zoals bij CRPS, wordt het bewegingsgedrag gevormd door een complexe wisselwerking tussen verschillende factoren: naast de directe gevolgen van pijnprikkels kunnen ook weefselbeschadigingen, psychologische aspecten van chronische pijn en langetermijngevolgen van aanpassingen aan pijn een rol spelen. In dergelijke omstandigheden is het daarom moeilijk om de complexe oorzaak-gevolg relatie tussen pijn en motoriek te doorgronden. Om inzicht te krijgen in de directe gevolgen van pijnprikkels, wordt in **Hoofdstuk 2** verslag gedaan van een uitgebreid systematisch onderzoek van de literatuur waarin de motorische consequenties van experimenteel geïnduceerde (sub)cutane pijn, gewrichtspijn, spierpijn en peespijn werden onderzocht bij gezonde proefpersonen. De resultaten van dit literatuuronderzoek toonden aan dat pijn diverse aspecten van bewegingssturing beïnvloedt op meerdere niveaus van het zenuwstelsel (van spinaal tot corticaal). Daarbij lijken de effecten van pijn grotendeels onafhankelijk te zijn van de herkomst ervan (huid, gewricht, spier of pees). In het algemeen zorgt pijn voor een remming (inhibitie) van activiteit van de (pijnlijke) agonist en de (niet-pijnlijke) antagonisten en synergisten, vooral bij hogere intensiteit van spiercontractie. Desondanks werden er slechts subtiele veranderingen waargenomen in de kinetica (krachten en momenten) en de daaruit voortvloeiende kinematica (gewrichtshoeken, snelheden en versnellingen) van bewegingen. De uitvoering van verschillende motorische taken was zelfs grotendeels onaangetast, waarschijnlijk dankzij

een herverdeling van spieractiviteit – zowel binnen de (pijnlijke) agonist als tussen de verschillende niet-pijnlijke spieren die betrokken zijn bij de taak. Samengevat laten de bevindingen van dit literatuuronderzoek zien dat kortdurende, experimenteel geïnduceerde pijn in een ledemaat direct veranderingen teweegbrengt op verschillende niveaus van bewegingssturing. Mogelijk zijn deze veranderingen, die grotendeels onafhankelijk lijken van de exacte herkomst van de pijn, gericht op het bevorderen van beschermend en compensatoir gedrag. Wanneer er sprake is van chronische pijn, zoals bij CRPS, wordt het bewegingsgedrag gevormd door een complexe wisselwerking tussen de in dit hoofdstuk beschreven veranderingen en andere factoren, zoals structurele weefselschade, langetermijngevolgen van aanpassingen aan pijn en emotionele en cognitieve reacties op (chronische) pijn.

De met CRPS samenhangende bewegingsstoornissen worden over het algemeen gekenmerkt door een beperkte actieve bewegingsuitslag (AROM), een verhoogde weerstand tegen passieve bewegingen en een abnormale voorkeurshouding van de aangedane ledemaat. Het experiment beschreven in **Hoofdstuk 3** had tot doel om meer inzicht te verkrijgen in de mechanismen die ten grondslag liggen aan deze specifieke motorische stoornissen, en in het bijzonder om te onderzoeken of zij een uiting zijn van dystonie. Daartoe werden de karakteristieken van oppervlakte-ElektroMyoGrafie (EMG) van de flexor carpi radialis en de extensor carpi radialis onderzocht tijdens het actief handhaven van verschillende flexie-extensie houdingen van de pols. EMG karakteristieken van zowel de aangedane als de niet-aangedane zijde van 15 chronische CRPS-patiënten werden vergeleken met EMG-karakteristieken van de niet-dominante zijde van 15 gezonde controlepersonen. De resultaten toonden aan dat de standsafwijkingen bij de onderzochte chronische CRPS-patiënten, die allen nog in enige mate hun pols actief konden bewegen, niet werden gekenmerkt door aanhoudende spiercontracties, en dat de AROM niet was gelimiteerd door overmatige co-contractie van de agonist en antagonist. Er bleek zelfs sprake van een tekort aan spieractiviteit: zowel de agonist als de antagonist werd slechts in beperkte mate geactiveerd, in overeenstemming met het beperkte bewegingsbereik. Aangezien dystonie is gedefinieerd als “een syndroom van aanhoudende spieractiviteit en abnormale co-contractie van agonist en antagonist spieren” (Fahn, 1988) kan worden geconcludeerd dat de beperkte AROM en de

standsafwijkingen bij patiënten met langdurige CRPS niet de typische kenmerken van dystonie vertonen. Deze bevinding kan belangrijke implicaties hebben voor de klinische praktijk, waarin de behandeling van CRPS-patiënten met dergelijke standsafwijkingen vaak is gericht op het verminderen van de activiteit van de spieren die verantwoordelijk worden gehouden voor de ontwikkeling en instandhouding van de abnormale gewrichtsstand, bijvoorbeeld door intramusculaire injecties met BotulineToxine of door orale toediening van spierverslappende medicatie. De huidige bevindingen benadrukken dus het belang van een grondige evaluatie van EMG-karakteristieken voordat een behandelstrategie wordt geselecteerd. Van een behandeling die is gericht op het verminderen van spieractiviteit kan vanzelfsprekend geen verbetering van het motorisch functioneren worden verwacht indien er helemaal geen sprake is van overmatige spieractiviteit. In dergelijke gevallen zou een behandelingstraject gericht op het voorkómen van verminderde spieractiviteit tot betere resultaten kunnen leiden (bijvoorbeeld door middel van fysiotherapie en oefentherapie waarbij gebruik van de aangedane ledemaat wordt gestimuleerd).

Voor adequate bewegingssturing is het essentieel om te beschikken over proprioceptieve informatie, dat wil zeggen, informatie omtrent de huidige positie en beweging van de ledematen en de hoeveelheid kracht die wordt geproduceerd. In verschillende studies zijn aanwijzingen gevonden dat verstoorde verwerking van proprioceptieve informatie een belangrijke rol kan spelen in de bewegingsstoornissen bij CRPS. Helaas is er nog weinig bekend over proprioceptie in relatie tot CRPS. De studies beschreven in Hoofdstukken 4 en 5 richtten zich daarom op de bestudering van proprioceptieve stoornissen en hun vermeende bijdrage aan de motorische disfunctie bij CRPS.

Hoofdstuk 4 beschrijft de nauwkeurigheid en de precisie van positiezin rond het polsgewricht van de aangedane en niet-aangedane zijde in 25 patiënten met chronische CRPS en in 50 gezonde controlepersonen. De geteste hand (die niet zichtbaar was voor de proefpersoon) werd bewogen naar vijf verschillende flexie- en extensieposities, ofwel door actieve bewegingen van de proefpersoon zelf, ofwel door passieve bewegingen die werden opgelegd door een motor. Zodra de doelpositie was bereikt, diende de geschatte handpositie aangegeven te worden door middel van een pijl. De fout tussen deze geschatte

handpositie en de werkelijke handpositie werd vervolgens onderworpen aan een uitgebreide analyse. De resultaten toonden aan dat CRPS-patiënten minder goed in staat waren om de handpositie juist in te schatten, zowel aan de aangedane zijde als de niet-aangedane zijde. De systematische 'misperceptie' werd voornamelijk gekenmerkt door een overschatting van gewrichtshoeken in de richting van extensie. De precisie van de geschatte handposities was sterker verminderd aan de aangedane zijde. Het is daarbij belangrijk om op te merken dat verschillen tussen CRPS-patiënten en controlepersonen niet alleen werden waargenomen wanneer de tests werden uitgevoerd voor identieke percentages van de maximale bewegingsuitslag van elk individu, maar ook wanneer controlepersonen werden getest op exact dezelfde polshoeken als de aangedane zijde van de patiënten. Bovendien werden ernstigere bewegingsbeperkingen van de aangedane zijde geassocieerd met een slechtere proprioceptie. Om te bepalen in welk stadium van informatieverwerking de waargenomen proprioceptieve stoornissen ontstaan, werden resultaten van aanvullende sensorische tests bestudeerd, werden vergelijkingen tussen condities met actieve en passieve polsbewegingen uitgevoerd en werd onderzocht hoe de nauwkeurigheid en precisie varieerden over de verschillende testposities. De resultaten van deze analyses suggereerden dat de verstoorde proprioceptie waarschijnlijk het gevolg was van veranderde verwerking van afferente (in plaats van efferente) informatie en de daaropvolgende interpretatie in het kader van een vervormd 'lichaamsschema'.

De onderzoeksvraag die in **Hoofdstuk 5** centraal stond, was of verstoringen in het gevoel van krachtproductie bijdragen aan de verminderde krachtsturing in patiënten met CRPS. De kenmerken van vrijwillige modulatie van kracht werden onderzocht in de aangedane ledemaat (bovenste extremiteit) in 28 CRPS-patiënten met abnormale gewrichtsstanden, in 12 CRPS-patiënten zonder abnormale gewrichtsstanden en in 32 gezonde controlepersonen. Isometrische grijpkracht werd vergeleken tussen condities mét en zónder visuele terugkoppeling van de geleverde kracht om te evalueren of proprioceptieve en tactiele informatie in voldoende mate bijdroegen aan de regeling van de krachtproductie. Zo konden mogelijke stoornissen in het gevoel van krachtproductie worden geïdentificeerd. De resultaten van dit experiment lieten zien dat de vrijwillige modulatie van grijpkracht was verminderd bij CRPS-patiënten. In het bijzonder CRPS-patiënten met een abnormale stand van de aangedane ledemaat vertoonden een

verminderde maximale kracht, een verminderd vermogen om de grijpkracht te verhogen volgens de taakinstructie, een hogere variabiliteit van de geleverde kracht en een minder adequate correctie van afwijkingen ten opzichte van het gewenste krachtsniveau. Op het eerste gezicht leken de effecten van het verwijderen van de visuele terugkoppeling grotendeels vergelijkbaar voor de twee patiëntengroepen en de groep controlepersonen. Echter, wanneer de analyse van 'fouten in krachtreproductie' werd beperkt tot het laagste krachtsniveau (1 N) om mogelijke verstorende effecten van motorische beperkingen te minimaliseren, bleek dat de CRPS-patiënten met een standsafwijking minder goed in staat waren om in te schatten hoeveel kracht zij uitoefenden op de sensor. Dit experiment werd tevens uitgevoerd voor de onderste extremiteit. Bij 15 CRPS-patiënten met abnormale gewrichtsstanden, bij 11 CRPS-patiënten zonder abnormale gewrichtsstanden en bij 32 gezonde controlepersonen werd de buigkracht van de grote teen geëvalueerd. De conclusies op basis van de bovenste extremiteit werden grotendeels bevestigd door de resultaten met betrekking tot de onderste extremiteit. Hierbij dient wel te worden opgemerkt dat bij de CRPS-patiënten de vrijwillige sturing van de onderste extremiteit ernstiger leek aangedaan dan de sturing van de bovenste extremiteit. Deze ernstige motorische beperkingen van de onderste extremiteit belemmerden de detectie van proprioceptieve stoornissen.

Verstoringen in de verwerking van proprioceptieve informatie, zoals beschreven in Hoofdstuk 4 en 5, en problemen met sensomotorische integratie hebben niet alleen invloed op het motorisch functioneren van de aangedane ledemaat, maar kunnen ook gevolgen hebben voor de coördinatie tussen de bewegingen van twee ledematen. Hoewel er aanwijzingen zijn voor abnormale koppeling tussen de aangedane en niet-aangedane ledemaat in CRPS, zijn de mogelijke consequenties hiervan nog onvoldoende duidelijk. Hoofdstuk 6 en 7 beschrijven daarom een onderzoek naar de (senso)motorische interacties tussen de aangedane en niet-aangedane arm. In deze hoofdstukken is getracht een onderscheid te maken tussen niet-intentionele en intentionele aspecten van koppeling tussen de ledematen om meer inzicht te krijgen in de schijnbare discrepantie tussen de uitvoering van automatische en vrijwillige bewegingen die in sommige gevallen van CRPS wordt waargenomen – een verschijnsel dat door sommige auteurs wordt beschouwd als bewijs dat de bewegingsstoornis psychogeen is.

Hoofdstuk 6 had als doel om vast te stellen of de abnormale standen en het verlies van vrijwillige sturing van de aangedane ledemaat samenhangen met niet-intentionele ontremming (disinhibitie) van contralaterale motorische activiteit. Een niet-intentionele 'overflow' of 'neuronale overspraak' van motorische stuursignalen van de vrijwillig aangestuurde arm naar overeenkomstige spieren in de contralaterale passieve arm is namelijk een bekend verschijnsel van dystonie (de zogenoemde 'spiegeldystonie'). Om te bepalen of een dergelijke niet-intentionele koppeling tussen de aangedane en niet-aangedane zijde een rol speelt bij CRPS, werd 'gespiegelde spieractiviteit' geëvalueerd tijdens ritmische flexie-extensie bewegingen van één hand. Deze unimanuele taak werd uitgevoerd door 20 chronische CRPS-patiënten (zowel met de aangedane als de niet-aangedane zijde) en 40 gezonde controlepersonen (zowel met de niet-dominante als de dominante zijde). Een geavanceerde, sensitieve analysemethode werd toegepast op de EMG-metingen van de passieve arm om korte episodes van spiegelactiviteit te identificeren. Vervolgens werd bepaald in hoeverre het dominante ritme en de relatieve timing van deze niet-vrijwillige spieractiviteit in de passieve arm overeenkwamen met die van de overeenkomstige spier in de bewegende arm. Het aantal gedetecteerde episodes van spiegelactiviteit was vergelijkbaar voor beide zijden van de CRPS-patiënten en de controlepersonen. Bovendien was de spiegelactiviteit in de aangedane arm van de CRPS-patiënten (tijdens beweging van de niet-aangedane arm) vergelijkbaar met de spiegelactiviteit die werd waargenomen in de controlepersonen. De episodes met spiegelactiviteit in de niet-aangedane arm van de CRPS-patiënten (tijdens beweging van de aangedane arm) waren echter van kortere duur en vertoonden minder gelijkenis met activiteit van de overeenkomstige spier in de bewegende arm (in termen van het dominante ritme en de relatieve timing) dan de episodes van spiegelactiviteit in de controlegroep. Mogelijk was dit een secundair effect van de verminderde vrijwillige sturing van de aangedane arm. De kleinere bewegingsuitslagen van de aangedane arm hingen namelijk samen met lagere niveaus van spieractivatie, en een lagere intensiteit van motorische stuursignalen gaat waarschijnlijk gepaard met minder neuronale overspraak naar de contralaterale (niet-aangedane) zijde. De uitgebreide evaluatie van gespiegelde spieractiviteit leverde dus geen bewijs op voor ontremming van netwerken in het centrale zenuwstelsel die betrokken zijn bij het inhiberen of faciliteren van contralaterale

activiteit. Samengevat kan uit de resultaten van Hoofdstukken 3 en 6 worden geconcludeerd dat de onderliggende mechanismen van CRPS-gerelateerde bewegingsstoornissen niet overeenkomen met de mechanismen die ten grondslag liggen aan dystonie.

In **Hoofdstuk 7** is getracht onderscheid te maken tussen de vrijwillige (intentionele) en automatische (niet-intentionele) aspecten van de koppeling tussen de handen. In de literatuur wordt verondersteld dat de bimanuele taakuitvoering (bewegingen met twee handen) kan worden beïnvloed door verschillende bronnen van koppeling tussen de handen. De eerste bron weerspiegelt de processen die gerelateerd zijn aan de intentionele planning van het bimanuele coördinatiepatroon. De tweede bron weerspiegelt de intentionele correctie van fouten in het coördinatiepatroon zoals die worden waargenomen op basis van afferente informatie. De derde bron, tenslotte, weerspiegelt niet-intentionele reflex-achtige invloeden van afferente signalen van de andere hand, die zich uiten in aantrekking tot bepaalde coördinatiepatronen tussen de handen (fase-aantrekking). Twintig chronische CRPS-patiënten en 40 gezonde controlepersonen voerden een reeks unimanuele en bimanuele taken uit. Deze taken bestonden uit ritmische flexie-extensie bewegingen van de pols en verschilden in de mate waarin de genoemde bronnen van intentionele en niet-intentionele koppeling tussen de handen betrokken waren bij de taakuitvoering. Zo werd de intentionele koppeling tussen de handen niet alleen onderzocht tijdens actieve aansturing van de twee handen – om de invloed van bilaterale planning te onderzoeken, maar ook tijdens een taak waarbij actieve bewegingen van een hand moesten worden afgestemd op passieve bewegingen van de andere hand – om de invloed van foutencorrectie op basis van afferentie te onderzoeken. Niet-intentionele koppeling tussen de handen werd onderzocht in termen van fase-aantrekking tussen de handen, dat wil zeggen, de mate waarin actieve handbewegingen onbedoeld werden aangetrokken tot synchronisatie met het ritme van passieve bewegingen van de andere hand. Analyse van temporele aspecten van de koppeling tussen de handen toonde aan dat de coördinatie tussen de handen minder stabiel was bij CRPS-patiënten dan bij controlepersonen, vooral wanneer de aangedane zijde actief moest worden bewogen. Niet alleen waren de stabiliserende invloeden van bimanuele planning minder uitgesproken bij patiënten dan bij controlepersonen, ook vertoonden CRPS-

patiënten minder 'foutcorrectie' met de aangedane hand. Er werden geen aanwijzingen gevonden voor abnormale fase-aantrekking. Analyse van de spatiële koppeling tussen de twee handen toonde aan dat bij CRPS-patiënten de relatief kleine bewegingsamplitude van de aangedane hand enigszins werd vergroot tijdens actieve of passieve bewegingen van de niet-aangedane hand. Daarentegen bewoog de niet-aangedane hand met een iets kleinere amplitude tijdens intentionele coördinatie met de (over het algemeen kleinere) bewegingen van de aangedane hand. Alle resultaten bij elkaar genomen, blijkt uit Hoofdstuk 6 en 7 dat de motorische problemen in chronische CRPS grotendeels te wijten zijn aan verstoord functioneren van hogere-orde neurale centra die betrokken zijn bij de sturing van vrijwillige bewegingen van de aangedane ledemaat. Dit heeft echter ook gevolgen voor de temporele en spatiële koppeling tussen aangedane en niet-aangedane ledematen, vooral voor vrijwillige (intentionele) koppeling, in tegenstelling tot automatische (niet-intentionele) koppeling.

Concluderende opmerkingen

De chronische fase van CRPS wordt veelal gedomineerd door pijn en motorische problemen. De bewegingsstoornissen worden voornamelijk gekenmerkt door een vermindering of verlies van vrijwillige bewegingssturing en door abnormale standen van de aangedane ledemaat. Dit proefschrift beschrijft de resultaten van een aantal studies waarin de vermeende rol van verminderde remming (inhibitie) van het motorische systeem, veranderingen in de verwerking van sensibele informatie en problemen met de integratie van sensorische en motorische signalen (sensomotorische integratie) werd onderzocht. De volgende paragrafen bevatten een korte beschouwing van de verkregen inzichten met betrekking tot deze veronderstelde pathofysiologische aspecten en de mogelijke rol van pijn-gerelateerde processen. Tevens worden de mogelijke implicaties voor therapie kort besproken.

Verminderde inhibitie van het motorisch systeem?

In dit proefschrift werd geen bewijs gevonden voor verminderde inhibitie van het motorisch systeem. Ten eerste leverde de uitgebreide evaluatie van gespiegelde spieractiviteit in Hoofstuk 6 geen aanwijzingen voor ontremming van neurale circuits die betrokken zijn bij contralaterale motorische activiteit. Dit werd nog eens bevestigd door de observatie in Hoofdstuk 7 dat de stabiliteit van bimanuele coördinatie duidelijker was verminderd voor in-fase-coördinatie (spiegelsymmetrische bewegingen van de handen) dan voor tegenfase-coördinatie (bewegingen van beide handen in dezelfde richting). Wanneer er bij CRPS sprake zou zijn van ontremming van contralaterale motorische activiteit, zou men juist het tegenovergestelde resultaat mogen verwachten. Ten tweede werd er geen bewijs gevonden voor abnormale reflex-achtige fase-aantrekking (Hoofdstuk 7).

De huidige bevindingen lijken onverenigbaar met de resultaten van eerdere studies die suggereren dat er bij CRPS-gerelateerde bewegingsstoornissen sprake is van een verminderde remming van het motorisch systeem. In eerdere studies werd bijvoorbeeld gebruik gemaakt van een vibrerende stimulus om inhibitie van de H-reflex te onderzoeken (van de Beek et al., 2002), werd (modulatie van) de exciteerbaarheid van corticospinale banen onderzocht door middel van transcraniële magnetische stimulatie (Eisenberg et al. 2005; Krause et al., 2004; Schwenkreis et al., 2003) en werden veranderingen in ritmische hersenactiviteit als reactie op een pijnprikkel in kaart gebracht met behulp van MagnetoEncefaloGrafie (Juottonen et al., 2002; Kirveskari et al., 2010). Tot nu toe is de vermeende rol van (dis)inhibitie echter voornamelijk onderzocht in rust, terwijl de huidige bevindingen betrekking hebben op het motorisch systeem 'in actie', tijdens de uitvoering van motorische taken.

Een andere aanwijzing voor disinhibitie van het motorisch systeem komt voort uit de significante vermindering van CRPS-gerelateerde bewegingsstoornissen door intrathecale toediening van de gamma-aminoboterzuur-B ($GABA_B$) receptor agonist baclofen (van Hilten et al., 2000; van Rijn et al., 2009). Hoewel deze bevindingen suggereren dat een verlies van spinale GABA-erge inhibitie kan bijdragen aan een verminderde motorische functie, dient te worden opgemerkt dat de werkingsmechanismen van baclofen nog grotendeels onbekend zijn. Er kan bijvoorbeeld

niet worden uitgesloten dat een deel van het effect van baclofen, als gevolg van een meer rostrale diffusie, wordt gemedieerd op een supraspinaal niveau.

Zoals vermeld in Hoofdstuk 1, was het tot op heden onduidelijk of de veelvuldig waargenomen bewegingsstoornissen bij CRPS die zijn onderzocht in dit proefschrift (verlies van vrijwillige bewegingssturing, een beperkte AROM, verhoogde weerstand tegen passieve bewegingen, en abnormale gewrichtsstanden) een uiting zijn van dystonie. Uit onze bevindingen (Hoofdstuk 3 en 6) blijkt echter dat deze specifieke bewegingsstoornissen bij chronische CRPS niet de typische kenmerken vertonen van dystonie. Ten eerste werden de standsafwijkingen bij chronische CRPS-patiënten, in ieder geval bij patiënten die hun pols in enige mate actief konden bewegen, niet gekenmerkt door aanhoudende spiercontracties en was de AROM niet gelimiteerd door overmatige co-contractie van de agonist en antagonist (Hoofdstuk 3, in overeenstemming met de resultaten van Van de Beek et al., 2002). Ten tweede vertoonde de aangedane arm geen verhoogde niveaus van spiegelactiviteit tijdens ritmische bewegingen van de niet-aangedane zijde (Hoofdstuk 6). Dit in tegenstelling tot de 'spiegeldystonie' die optreedt in de aangedane hand van patiënten met focale dystonie tijdens het uitvoeren van een taak met hun niet-aangedane hand, een verschijnsel dat wordt toegeschreven aan disfunctionele inhibitoire verbindingen tussen de hemisferen (Beck et al., 2009; Nelson et al., 2010). Ondanks de aanzienlijke gelijkenis in de klinische presentatie van CRPS-gerelateerde motorische disfunctie en dystonie, lijken er dus verschillende mechanismen ten grondslag te liggen aan deze bewegingsstoornissen.

De huidige bevindingen hebben betrekking op CRPS-patiënten met ten minste enige mate van vrijwillige motoriek (d.w.z., AROM > 30°). Het kan derhalve niet worden uitgesloten dat patiënten met een gefixeerde standsafwijking en een volledig verlies van bewegingssturing – die kunnen profiteren van intrathecale toediening van baclofen (van Hilten et al., 2000; van Rijn et al., 2009) – wél kenmerken van dystonie vertonen.

Veranderingen in sensorische verwerking?

Sensibele stoornissen bij CRPS, waaronder een veranderde gevoeligheid van afferenten in de huid en spieren (Hoofdstuk 3, 4 en 5; Eberle et al., 2009; Huge et al., 2008; Kemler et al., 2000; Maier et al., 2010; van Rooijen et al., 2013a), kunnen

interfereren met de motoriek. De in dit proefschrift beschreven studies leverden direct bewijs voor verstoorde verwerking van informatie gerelateerd aan gewrichtspositie (Hoofdstuk 4; in overeenstemming met Lewis et al., 2010) en krachtproductie (Hoofdstuk 5), en daarmee voor de nauwe relatie tussen proprioceptieve stoornissen en CRPS-gerelateerde bewegingsstoornissen. In Hoofdstuk 4 werd aangetoond dat CRPS-patiënten minder goed in staat waren om de polshoek juist in te schatten, waarbij de systematische 'misperceptie' voornamelijk werd gekenmerkt door een overschatting van gewrichtshoeken in de richting van extensie. Opvallend hierbij was dat de grootste verstoringen in proprioceptie werden waargenomen op extensieposities, precies daar waar de bewegingsbeperking het grootst was. Bovendien waren ernstigere bewegings-beperkingen van de aangedane hand geassocieerd met een lagere precisie (d.w.z., hogere variabiliteit) van de geschatte handposities. De resultaten van Hoofdstuk 5 wezen op een verminderde precisie in het gevoel van krachtproductie (gereflecteerd in een verhoogde variabele fout). Juist de precisie van sensibele informatie is van cruciaal belang voor adequate bewegingssturing. Om te kunnen beschikken over nauwkeurige kennis met betrekking tot de toestand van het lichaam wordt proprioceptieve, tactiele en visuele informatie geïntegreerd in het centraal zenuwstelsel, waarbij het grootste gewicht wordt gegeven aan de meest precieze bron van zintuiglijke informatie (dit wordt ook wel 'zintuiglijke weging' genoemd; Bays en Wolpert, 2007; Ernst en Bülthoff, 2004).

Adequate proprioceptie omvat drie opeenvolgende fasen van informatieverwerking: *(1)* de detectie en transmissie van afferente informatie; *(2)* de integratie van informatie uit verschillende perifere en centrale bronnen; en *(3)* de interpretatie van deze informatie in het kader van een lichaamsschema (Proske en Gandevia, 2012). Aan de hand van een uitgebreide evaluatie van de op proprioceptie gebaseerde inschattingen (zoals gepresenteerd in Hoofdstuk 4) is getracht vast te stellen in welke van deze fasen de proprioceptieve stoornissen bij CRPS hun oorsprong hebben. Mogelijk is de gevoeligheid van de bij proprioceptie betrokken receptoren (in spier, gewricht en/of huid) veranderd, bijvoorbeeld als gevolg van CRPS-gerelateerde trofische veranderingen of suboptimale aanpassing aan het kleinere bewegingsbereik van de aangedane ledemaat. Een verstoring in de centrale verwerking lijkt echter meer plausibel, aangezien pijn kan interfereren met de verwerking van afferente signalen die bijdragen aan de positiezin (zie Hoofdstuk 2) en

CRPS-patiënten dikwijls beschikken over een vertekend mentaal beeld van hun aangedane ledemaat (Förderreuther et al., 2004; Frettlöh et al., 2006; Lewis et al., 2007, 2010; Moseley, 2005; Peltz et al., 2011). De bevindingen van Hoofdstuk 4 wijzen inderdaad op veranderingen in de centrale verwerking van afferente informatie en suggereren dat de verkregen informatie wordt geïnterpreteerd in het kader van een 'lichaamsschema' dat niet geheel overeenkomt met de werkelijke toestand van de ledemaat.

Problemen met sensomotorische integratie?

Het al dan niet correct uitvoeren van een vrijwillige beweging is sterk afhankelijk van het vermogen om gebruik te maken van perifere sensibele feedback ter ondersteuning van de uitvoering van een motorische taak. Tijdens een beweging wordt de werkelijk verkregen sensorische informatie (zoals proprioceptieve, tactiele en visuele informatie) voortdurend vergeleken met de voorspelde sensorische uitkomsten (op basis van kopieën van de motorische stuursignalen en informatie over de starthouding van de ledemaat; Festinger en Canon, 1965). Het verschil tussen de werkelijke en voorspelde sensorische uitkomsten wordt vervolgens gebruikt door terugkoppelmodules die signalen genereren om de beweging bij te sturen (Bays en Wolpert, 2007; Wolpert en Ghahramani, 2000). Bij CRPS-patiënten kan de werkelijke sensorische uitkomst van een beweging afwijken van de voorspelde uitkomsten door functionele en structurele veranderingen in het spierweefsel (Hulsman et al, 2009; Tan et al., 2011; van der Laan et al., 1998; Vas et al., 2013) of door stoornissen in de verwerking van informatie van afferenten uit huid of spier (e.g., Eberle et al., 2009; Huge et al., 2011; Kemler et al., 2000; Maier et al., 2010; van Rooijen et al., 2013a). Tegelijkertijd kunnen verstoringen in het mentale beeld van de aangedane ledemaat (Förderreuther et al., 2004; Frettlöh et al., 2006; Lewis et al., 2007; Peltz et al., 2011) bijdragen aan foutieve voorspellingen van de sensorische uitkomsten van een bepaald motorisch stuursignaal. Dit impliceert dat de proprioceptiestoornissen in CRPS (zoals beschreven in Hoofdstuk 4 en 5) een negatief effect kunnen hebben op de motoriek; de uitvoering van een specifieke beweging kan worden aangepast op basis van zowel onjuist waargenomen als onjuist voorspelde sensorische uitkomsten van die beweging. De proprioceptiestoornissen in CRPS kunnen echter ook op de lange termijn gevolgen hebben voor de motoriek, aangezien het voorwaartse model dat de gevolgen van

geplande acties voorspelt onderhevig is aan processen die samenhangen met leren, adaptatie en onderhoud. Aangenomen wordt dat het cerebellum een belangrijke rol speelt bij deze processen (Ito, 1970; Miall et al., 1993; Wolpert and Kawato, 1998).

Het nauwe verband tussen proprioceptie en bewegingssturing werd treffend geïllustreerd in de 'kinesthetische tracking'-taak in Hoofdstuk 7. Wanneer bewegingen van de aangedane hand moesten worden afgestemd op passieve bewegingen van de andere hand, waren CRPS-patiënten minder goed in staat om fouten in het bewegingspatroon te corrigeren. De sturing van vrijwillige bewegingen van de aangedane ledemaat was dus aangetast door inadequate integratie van efferente en afferente informatie uit de vrijwillig bewogen aangedane hand met proprioceptieve informatie uit de passief bewogen niet-aangedane hand. De CRPS-patiënten bleken echter vrij goed in staat om bewegingen van de niet-aangedane hand af te stemmen op passieve bewegingen van de aangedane hand. Dit suggereert dat het eigenlijke probleem niet zit in de proprioceptieve informatie uit de aangedane ledemaat per se. Op basis van deze bevindingen kan worden verondersteld dat de verslechtering van bimanuele coördinatie voornamelijk is toe te schrijven aan foutieve integratie van afferente en efferente signalen in de hogere-orde centra die betrokken zijn bij de aansturing van de aangedane ledemaat.

In overeenstemming met deze hypothese was bij CRPS-patiënten de stabiliteit van bimanuele coördinatie vooral verminderd voor de taken waarbij de aangedane hand vrijwillig moest worden aangestuurd. Misschien hebben veranderingen in spierweefsel bijgedragen aan de beperkingen in vrijwillige modulatie van kracht en bewegingsamplitude bij patiënten met langdurige CRPS (Hulsman et al., 2009; Tan et al., 2011; van der Laan et al., 1998; Vas et al., 2013). Het in Hoofdstuk 6 en 7 gepresenteerde onderzoek suggereert echter dat de bewegingsstoornissen van CRPS grotendeels te wijten zijn aan disfunctie van neurale netwerken in de hersenhelft die verantwoordelijk is voor het aansturen van de aangedane ledemaat. Dit lijkt op zijn beurt weer gerelateerd te zijn aan verstoorde verwerking van proprioceptieve informatie (Hoofdstuk 4 en 5). In overeenstemming met eerdere suggesties dat de bewegingsstoornissen bij CRPS gerelateerd zijn aan verstoord functioneren van *hogere-orde centra* betrokken bij de *bewegingssturing van de aangedane ledemaat* (Maihöfner et al., 2007; Swart et al., 2009) werd er in dit proefschrift geen bewijs gevonden voor abnormale reflex-achtige fase-

aantrekking (Hoofdstuk 7) of ontremming van circuits die betrokken zijn bij contralaterale motorische activiteit (Hoofdstuk 6).

Potentiële rol van pijn-gerelateerde processen

Aangezien alle CRPS-patiënten matige tot zeer hevige pijn ervaren, is het verleidelijk om de waargenomen sensibele en motorische stoornissen simpelweg toe te schrijven aan pijn-gerelateerde processen. Zo kan pijn concurreren met andere aandacht-vereisende prikkels om een beperkte cognitieve capaciteit (Eccleston and Crombez, 1999; Grisart and van der Linden, 2001), of kunnen patiënten terughoudend zijn om een uiterste inspanning te leveren als gevolg van toenemende pijn. Toch zou een dergelijke verklaring geen recht doen aan de talrijke aanwijzingen voor betrokkenheid van andere factoren. Zo zijn de prominente beperkingen in krachtmodulatie bij CRPS-patiënten met abnormale gewrichtsstanden (Hoofdstuk 5) en variaties in bewegingsamplitude en stabiliteit van bimanuele coördinatie (tussen de verschillende taken beschreven in Hoofdstuk 7) waarschijnlijk toe te schrijven aan andere factoren dan pijn. Pijnscores waren immers vergelijkbaar voor de twee patiëntengroepen in Hoofdstuk 5 (CRPS mét en zónder abnormale standen) en voor alle taken en condities van het in Hoofdstuk 7 beschreven experiment.

Het valt echter niet te ontkennen dat pijn een belangrijke rol speelt in de bewegingsstoornissen bij CRPS. In een recente studie werd aangetoond dat pijnvermindering – ongeacht of deze werd bereikt door toediening van intraveneus ketamine of placebo – was geassocieerd met verbetering van het motorisch functioneren van CRPS-patiënten (Schilder et al., 2013). De relatie tussen pijn en verstoorde motorische functie in CRPS wordt verder onderstreept door verschillende cross-sectionele studies (waaronder Huge et al. 2011; van Rooijen et al., 2013a). In dit proefschrift werd een significante relatie gevonden tussen spierhyperalgesie en verminderde grijpkracht (Hoofdstuk 5). Daarnaast was hogere pijnintensiteit geassocieerd met lagere stabiliteit van de coördinatie tijdens taken waarbij de aangedane hand vrijwillig moest worden aangestuurd (Hoofdstuk 7). In het bijzonder voor patiënten met hogere pijnscores was het stabiliserende effect van bimanuele planning minder uitgesproken en werd de coördinatieve stabiliteit van de niet-aangedane hand sterker verminderd door passieve

bewegingen van de aangedane zijde. Potentiële relaties tussen pijn en de andere aspecten van sensorisch en motorisch functioneren werden onderzocht in Hoofdstuk 3, 4, 5 en 6, maar werden mogelijk gemaskeerd door beperkte variabiliteit in de gerapporteerde pijnmaten.

In Hoofdstuk 2 werd aangetoond dat kortdurende experimenteel geïnduceerde pijn in een ledemaat, ongeacht de exacte locatie, onmiddellijke veranderingen teweegbrengt op alle niveaus van het motorisch systeem ter ondersteuning van beschermend gedrag en compensatoire bewegingsstrategieën. In het geval van chronische pijn, zoals bij CRPS, wordt de motoriek echter niet alleen beïnvloed door de in Hoofdstuk 2 beschreven veranderingen, maar ook door andere factoren zoals weefselschade, langetermijngevolgen van aanpassingen aan pijn, en psychologische aspecten van chronische pijn (Hodges en Tucker, 2011).

Emotionele en cognitieve reacties op (chronische) pijn kunnen grote invloed hebben op het motorisch gedrag. Zo manifesteert angst voor pijn zich meestal in gewijzigde bewegingsstrategieën (Vlaeyen en Linton, 2000). De overtuiging dat een bepaalde activiteit schade zal toebrengen aan de aangedane ledemaat leidt dikwijls tot het vermijden van fysieke activiteit en 'onbruik' van de ledemaat in kwestie (zie bijvoorbeeld Rainville et al., 2011; Zale et al., 2013). Het is dan ook niet verwonderlijk dat wetenschappers in hun zoektocht naar determinanten van lichamelijke invaliditeit (zie Zale et al. 2013 voor een overzicht) en voorspellers voor de overgang van acute naar chronische pijn (bijvoorbeeld Gatchel et al., 1995; Hinrichs-Rocker et al., 2009; Pincus et al., 2002; Theunissen et al., 2012) vooral zijn geïntrigeerd door psychologische factoren. Gebaseerd op de veronderstelling dat pijn-gerelateerde onbruik de pathofysiologische mechanismen van CRPS kan beïnvloeden, waardoor een vicieuze cirkel in stand gehouden wordt (Bruehl, 2001), is er in de literatuur voor gepleit dat de behandeling van CRPS altijd een psychologische component zou moeten bevatten (Bruehl en Chung, 2006). Hoewel voor verscheidene chronische pijn-aandoeningen is aangetoond dat psychologische interventies een gunstig effect kunnen hebben op pijn en invaliditeit (Williams et al., 2012), zijn er tot op heden geen gerandomiseerde gecontroleerde studies naar de effectiviteit van psychologische interventies, alleen of in een multidisciplinaire context, bij CRPS gedaan. Wél zijn significante verbeteringen van pijnscores, het actieve

bewegingsbereik en het functioneren gerapporteerd voor een groep CRPS-patiënten die een multidisciplinaire interventie onderging – waarin fysiotherapie werd gecombineerd met trainingstechnieken gericht op het beheersen van pijn en het optimaliseren van pijn-coping (omgaan met pijn) – in vergelijking met een controlegroep die begeleid werd door een sociaal werker (Oerlemans et al., 1999, 2000b). Verder zijn onlangs veelbelovende resultaten van 'pain exposure'-therapie gepresenteerd met betrekking tot vermindering van pijn en verbetering van de motoriek (de Jong et al., 2005; Ek et al., 2009; van de Meent et al., 2011). Vanwege het ontbreken van een geschikte controlegroep kan echter nog geen uitspraak worden gedaan over de effectiviteit van deze vorm van therapie, die bestaat uit behandeling van pijn-vermijdingsgedrag en oefeningen gericht op progressieve belasting van de aangedane ledemaat waarbij de pijngrens van de patiënt wordt overschreden.

Concluderend kan worden gesteld dat pijn zeer waarschijnlijk een rol speelt in de bewegingsstoornissen van CRPS, maar dat de precieze manifestatie van pijn-gerelateerde processen nog moet worden onderzocht. Het zou interessant zijn om CRPS-patiënten te vergelijken met patiënten met chronische (neuropathische) pijn van andere origine om te bepalen in hoeverre de in dit proefschrift beschreven stoornissen van (centrale) sensorische en motorische functies specifiek zijn voor CRPS of zijn geassocieerd met chronische pijn in het algemeen.

Therapeutische implicaties

De behandeling van CRPS-patiënten die zich presenteren met een standsafwijking van de aangedane ledemaat is vaak gericht op het verminderen van activiteit van de skeletspieren die verantwoordelijk worden gehouden voor de standsafwijking, bijvoorbeeld door intramusculaire injectie van BotulineToxine of door orale toediening van spierverslappende medicatie. Grondige evaluatie van EMG-kenmerken (Hoofdstuk 3 en 6 van dit proefschrift) leverde echter geen bewijs voor overmatige spieractivatie in de aangedane ledemaat van patiënten met chronische CRPS en ten minste enige mate van vrijwillige beweging (AROM > 30°). Sterker nog, de motorische disfunctie van CRPS leek eerder samen te hangen met een tekort aan spieractivatie (Hoofdstuk 3). Het is dan ook niet verrassend dat behandelingen gericht op het verminderen van overmatige

spieractiviteit over het algemeen een teleurstellend resultaat hebben (van Rooijen et al., 2011). Het is zelfs aannemelijk dat verdere verzwakking van reeds zwakke spieren bij deze patiënten kan leiden tot een verdere verslechtering van de motorische functie. Op basis van het huidige onderzoek is het helaas niet mogelijk om conclusies te trekken met betrekking tot de potentiële rol van overmatige spieractiviteit bij patiënten zie zich presenteren met een gefixeerde standsafwijking en een volledig gebrek aan vrijwillige sturing van de aangedane ledemaat. Onze bevindingen benadrukken echter wél het belang van een grondige evaluatie van EMG-kenmerken voorafgaand aan een besluit over de behandelstrategie: Medicamenteuze interventie gericht op het verminderen van spierspanning? Of juist behandeling gericht op het voorkomen van spieratrofie (bijvoorbeeld door middel van fysiotherapie en stimulering van het gebruik van de aangedane ledemaat)?

In een multidisciplinaire, revalidatie-gerichte behandeling van CRPS, waarin reactivering van de aangedane ledemaat centraal staat (Harden et al. 2013; Schrag et al., 2004; Stanton-Hicks et al., 2002; Turner-Stokes en Goebel, 2011), kan activiteit-gerelateerde pijn de therapietrouw belemmeren. Dit probleem kan mogelijkerwijs worden ondervangen door procedures toe te passen die de patiënt tijdens de therapie enigszins afleiden van pijn-gerelateerde processen. Bij patiënten met eenzijdige CRPS zou ritmische-bilaterale-arm-training, waarvan positieve effecten zijn gerapporteerd bij patiënten met een eenzijdige armparese na een beroerte (van Delden et al., 2013; Whitall et al., 2000), een nuttige aanvulling kunnen vormen op conventionele therapeutische strategieën die zijn gericht op het verbeteren van motorische functies van de aangedane ledemaat. Wanneer bewegingen van beide handen op elkaar afgestemd dienen te worden, wordt een patiënt immers gedwongen om de aandacht te verdelen over de aangedane en niet-aangedane ledemaat, terwijl tegelijkertijd de tussenledemaatkoppeling wordt uitgebuit om de motoriek van de aangedane zijde te verbeteren. In Hoofdstuk 7 werd aangetoond dat het motorisch functioneren van de aangedane hand enigszins verbeterde wanneer synchronisatie met actieve of passieve bewegingen van de niet-aangedane hand werd nagestreefd. Men dient zich echter te realiseren dat de niet-aangedane zijde ook geneigd kan zijn om zich aan te passen aan het verminderde functioneren van de aangedane zijde (Hoofdstuk 7; in overeenstemming met Steenbergen et al., 1996, 2008).

Aangezien de resultaten van Hoofdstuk 4 en 5 duiden op een verstoorde centrale verwerking van proprioceptieve informatie, zou het ook de moeite waard zijn om te onderzoeken of het herstel van motorische functies bij CRPS-patiënten bevorderd kan worden door therapeutische strategieën gericht op identificatie en herstel van proprioceptieve stoornissen (bijvoorbeeld met behulp van spiegeltherapie of door 'on-line' visuele terugkoppeling van kracht of beweging).

Perspectieven

CRPS wordt gekarakteriseerd door (hevige) pijn en verschillende combinaties van sensibele, autonome, trofische en motorische afwijkingen. Interindividuele verschillen in de mate waarin verschillende pathofysiologische mechanismen een rol spelen (bijvoorbeeld met betrekking tot ontsteking, vasomotore disfunctie of maladaptieve plasticiteit van het centrale zenuwstelsel, zie Hoofdstuk 1) kunnen ten grondslag liggen aan de klinische heterogeniteit van het syndroom (Marinus et al., 2011). De chronische fase van CRPS wordt meestal gedomineerd door pijn en motorische stoornissen. Dit betekent echter niet dat patiënten met reeds lang bestaande CRPS een uniforme groep vormen. Het scala aan motorische symptomen is breed en kan variëren van spierzwakte en tremor tot opvallende standsafwijkingen. Daarnaast is er bij sommige patiënten sprake van toename van de sensibiliteit (bijvoorbeeld hyperalgesie en/of allodynie), terwijl er bij andere patiënten sprake is van een afname daarvan (bijvoorbeeld hypoalgesie en/of hypesthesie). De meerderheid van de patiënten vertoont echter een combinatie van deze positieve en negatieve sensibele symptomen (Gierthmühlen et al., 2012; Maier et al., 2010). Tevens bestaan er grote interindividuele verschillen wat betreft de aanwezigheid en ernst van vasomotore symptomen, de cognitieve en emotionele reacties op (chronische) pijn, en de voorgeschiedenis van medicamenteuze en niet-medicamenteuze therapeutische interventies.

Vergelijkingen op groepsniveau, zoals gepresenteerd in dit proefschrift, zijn essentieel om meer inzicht te verkrijgen in de onderliggende pathofysiologische mechanismen van CRPS en kunnen bijdragen aan de wetenschappelijke onderbouwing van therapeutische interventies. Gezien de enorme interindividuele verschillen is het voor

selectie van de optimale behandelstrategie van een specifieke patiënt echter noodzakelijk dat de mechanismen die betrokken zijn bij het motorisch functioneren op individuele basis worden geëvalueerd. Het verdient daarom aanbeveling om bij toekomstig onderzoek in te zetten op de ontwikkeling van diagnostische instrumenten waarmee het mogelijk is om voor elke individuele patiënt de zwakste schakel(s) in het motorisch systeem te identificeren. Hierbij zou gestreefd moeten worden naar een compacte set van gemakkelijk toepasbare testen waarmee de arts of fysiotherapeut kan bepalen of de motorische beperkingen van een patiënt het gevolg zijn van structurele of functionele veranderingen van het spierweefsel, veranderde gevoeligheid van proprioceptieve receptoren, stoornissen in de verwerking van proprioceptieve informatie, stoornissen in de regulering van aandachtsprocessen, vervormingen van het lichaamsbeeld, of psychologische factoren (bijvoorbeeld pijn-gerelateerde angst voor bewegen).

De psychogene dan wel organische etiologie van CRPS-gerelateerde bewegingsstoornissen, en de standsafwijkingen in het bijzonder, is al vele jaren onderwerp van discussie (Munts et al., 2010; Ochoa en Verdugo, 2005; Schrag et al., 2004; Verdugo en Ochoa, 2000). Om de optimale behandelstrategie voor een specifeke CRPS-patiënt te kunnen selecteren, is het van groot belang om een diagnostisch instrument te ontwikkelen ter beoordeling van een mogelijke functionele (ofwel psychogene) component, die gesuperponeerd kan zijn op een organisch fundament. Aangezien de grens tussen psychogeen en organisch de afgelopen jaren steeds verder is vervaagd (Munts et al., 2010), zal het ontwikkelen van een dergelijk diagnostisch instrument waarschijnlijk een aanzienlijke methodologische uitdaging vormen. Hoewel functionele beeldvorming en neurofysiologische technieken hebben geleid tot vele nieuwe inzichten, heeft dit tot op heden nog niet geresulteerd in een onomstreden en betrouwbaar diagnostisch instrument. Lange tijd werd gedacht dat men op basis van de aan- of afwezigheid van de Bereitschaftspotentiaal onderscheid zou kunnen maken tussen vrijwillige en onvrijwillige bewegingen, maar deze aanname is recentelijk in twijfel getrokken (Hallett et al., 2010). Onlangs is er een testbatterij ontwikkeld voor de diagnose van psychogene tremor, waarbij onder andere wordt gemeten in hoeverre de tremorfrequentie verandert onder invloed van ritmisch tikken met de contralaterale hand en in hoeverre de tremoramplitude verandert wanneer een extra gewicht wordt aangebracht op de

aangedane ledemaat (Schwingenshuh et al., 2011). Helaas kunnen de betreffende testen (die zijn ontwikkeld voor een hyperkinetische bewegingsstoornis als tremor) niet worden toegepast op de voornamelijk hypokinetische bewegingsstoornissen die worden gezien in het kader van CRPS. Het paradigma dat is toegepast in Hoofdstuk 6 en 7 zou daarentegen wel een licht kunnen werpen op de schijnbare dissociatie tussen onvrijwillige en vrijwillige aspecten van motoriek bij CRPS, waarbij een duidelijke afwijking in de niet-intentionele koppeling tussen de ledematen zou kunnen pleiten tégen een psychogene en vóór een organische oorsprong van de bewegingsstoornis. De huidige observatie dat CRPS-patiënten meer uitgesproken problemen hebben met de intentionele koppeling tussen de ledematen impliceert echter niet noodzakelijkerwijs dat de CRPS-gerelateerde bewegingsstoornissen psychogeen zijn, zoals duidelijk mag zijn uit de voorgaande discussie over sensomotorische integratie (p. 232-234). Tegen deze achtergond zou toekomstig onderzoek naar potentiële overeenkomsten en verschillen in de pathofysiologische aspecten van verminderde vrijwillige bewegingssturing bij CRPS en bij functionele (d.w.z., psychogene) bewegingsstoornissen kunnen leiden tot waardevolle inzichten en verbeterde behandelstrategieën.

Het lastige aan onderzoek naar bewegingsstoornissen is dat het in het algemeen niet kan plaatsvinden zonder enige (bij voorkeur objectieve) meting van het bewegen. Het volledige verlies van vrijwillige bewegingssturing waarmee sommige CRPS-patiënten kampen, zorgt in dit opzicht voor een enorme beperking van de mogelijkheden. Sommige patiënten zijn niet in staat om zelfs de eenvoudigste taken uit te voeren (zoals het buigen en strekken van de vingers of pols, of het buigen van de grote teen), laat staan dat zij in staat zijn om taken uit te voeren die meer gelijkenis vertonen met functionele taken in het dagelijks leven. Gezien de keuze voor relatief eenvoudige motorische taken, lijkt het dan ook aannemelijk dat er in het merendeel van de in dit proefschrift beschreven studies sprake is van een onderschatting van de sensibele en motorische beperkingen in CRPS. In sommige gevallen konden juist díe (gedeelten van) metingen waarin de beperkingen het sterkst tot uiting kwamen niet worden meegenomen in de analyse. Daarnaast waren juist de meest ernstig aangedane patiënten soms niet in staat de experimentele taken uit te voeren. Zo konden patiënten alleen deelnemen aan de in Hoofdstuk 3, 4, 6 en 7 gepresenteerde experimenten indien het actieve bewegingsbereik van de pols ten minste

30° bedroeg. De huidige bevindingen hebben dus alleen betrekking op CRPS-patiënten die beschikken over enige mate van vrijwillige sturing van hun aangedane ledemaat. Het moet nog worden onderzocht of er bij patiënten met een gefixeerde standsafwijking en een volledig verlies van motoriek simpelweg sprake is van een ernstigere manifestatie van de symptomen die in dit proefschrift zijn beschreven, of dat deze patiënten een subgroep vormen met een andere fenomenologie en onderliggende pathofysiologie.

Ten slotte dient te worden opgemerkt dat de in dit proefschrift gepresenteerde bevindingen betrekking hebben op de chronische fase van CRPS. Op basis van de huidige bevindingen is het derhalve niet mogelijk om conclusies te trekken over de mogelijke rol van de onderzochte factoren in een eerder stadium van de ziekte. Prospectieve longitudinale studies zijn nodig om factoren te identificeren die kunnen voorspellen hoe symptomen zich ontwikkelen in de tijd: Welke patiënten zullen een bewegingsstoornis ontwikkelen, en welke patiënten niet? Deze risicofactoren kunnen een aanknopingspunt bieden voor identificatie van de primaire locatie van pathologische veranderingen in CRPS. Prospectieve longitudinale studies kunnen tevens een licht werpen op de cascade van (mogelijk compensatoire) processen die uiteindelijk leiden tot de sensibele en motorische stoornissen die kenmerkend zijn voor de chronische fase van CRPS. Inzicht in de volgorde en dynamiek van veranderingen op perifeer, spinaal en supraspinaal niveau kan bijdragen aan de ontwikkeling van gerichte interventies om de vicieuze cirkel te doorbreken die verantwoordelijk lijkt te zijn voor de instandhouding van symptomen in de chronische fase van CRPS (Bruehl, 2001; Bruehl en Chung, 2006), of nog beter, om reeds in een eerder stadium van CRPS in te grijpen in deze cascade van processen. Voorkomen is immers beter dan genezen.

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List of Abbreviations

Abbreviations and symbols (used in the text)		Chapter
$AE_{total/target}$	Absolute error, calculated over all trials per condition or per target position, in °	4
ANOVA	Analysis of variance	3-7
AROM	Active range of motion, in °	1-9
BoNT	Botulinum neurotoxin	3,8
CCI	Co-contraction index, in RR	3
$CE_{total/target}$	Constant error: measure of accuracy or directional bias, calculated over all trials per condition or per target position, in °	4
$CE_{0,F/E}$	Constant error after flexion or extension movements towards the neutral position, in °	4
CMEP	Cervicomedullary motor evoked potentials	2
CRPS	Complex Regional Pain Syndrome	1-9
$CRPS_{AP/NoAP}$	CRPS patients with or without abnormal postures	5
$CSD_{\Phi/\Psi}$	Circular standard deviation: variability of relative phasing between hand and metronome, or between the hands	7
CV	Coefficient of variance: standard deviation divided by the mean	3,5
Δ_{pref}	Deviation between the preferred wrist orientation and the wrist's neutral position (i.e., the center of the active range of motion), in °	3

ECR	Extensor carpi radialis muscle	3,4,6,7
EEG	Electro-encephalography	2
E_{max}	Maximum wrist extension angle, in °	3
EMG	Electromyography (Chapter 2: sEMG, surface EMG; imEMG, intramuscular EMG; Chapter 6: rEMG, rectified EMG)	1-4,6-9
η_p^2	Partial eta squared: measure of the size of an effect in ANOVAs	4-7
FCR	Flexor carpi radialis muscle	3,4,6,7
F_{CV}	Variability of force output, expressed as coefficient of variation	5
F_{error}	Average absolute discrepancy between actual force and target force, in N	5
F_{mean}	Mean force output, in N	5
f_m	Movement frequency, in Hz	6,7
F_{max}	Maximum wrist flexion angle, in °	3
$GABA_B$	Gamma-Amino-Butyric-Acid-B	1,3,8,9
HC	Healthy controls	4,5
IASP	International Association for the Study of Pain	4,6
ITB	Intrathecal baclofen	3
MEP	Motor evoked potential	2
MPQ-PRI	McGill Pain Questionnaire – Pain Rating Index	3-7
MVC	Maximum voluntary contraction	2,3,5
n	Number of studies on which the description of results is based	2
	Number of participants	3-7
NF	'No visual feedback' phase, during which no visual feedback on the participant's force output was provided	5
NMDA	N-Methyl-D-Aspartic-acid	1,3
NRS	Numeric rating scale	3-7
NWR	Nociceptive withdrawal reflex	2

$Pain_{task}$	Average pain experienced during the experimental task, scored on an 11-point numeric rating scale (0 = no pain, 10 = unbearable pain)	3-7
$Pain_{week}$	Average pain experienced during the week preceding the experiment, scored on an 11-point numeric rating scale (0 = no pain, 10 = unbearable pain)	3-7
Φ	(Point estimate of) relative phase between the hands, in °	7
$\Delta\Phi_{ActBi\text{-}Kin}$	Difference in relative phase between the hands for active bimanual coordination compared with kinesthetic tracking, in °	7
$\Delta CSD_{\Phi,ActBi\text{-}Kin}$	Difference in variability of the relative phase between the hands for active bimanual coordination compared with kinesthetic tracking: measure of the stabilizing influence of intended bimanual planning, in °	7
P_M	Probability of detecting a given number of mirror epochs in a given number of evaluations by chance alone	6
PPT	Pressure pain threshold, in kgf	3-5
PROM	Passive range of motion, in °	3,4
Ψ	(Point estimate of) relative phase between hand and metronome, in °	7
$\Delta\Psi_{0\text{-}30°}$	Change in relative phase between the hand and metronome induced by 30° phase-shifted passive movements of the contralateral side: measure of unintended entrainment, in °	7
PT	Patients	4
R_{EC}	'Error correction correlation': correlation between signed error in relative phasing at peak flexion or extension and duration of the subsequent half cycle	7
ROM	Range of motion, in °	1,3,4
RR	Ratio to rest (normalization of EMG values to the resting EMG value)	3,4,7
RSQ	Radboud Skills Questionnaire	3-7

τ	(Midpoint of) a sliding time-window that is used for Gabor transform of EMG recordings, which allows identification of periods of mirror activity within EMG signals of the passive arm during unimanual rhythmic movement	6
TECS	Transcranial electric current stimulation	2
T_{mean1}	Time from the first contact between finger and sensor to the first moment that force output exceeded F_{mean}, in s	5
TMS	Transcranial magnetic stimulation	2
TPD	Two-point discrimination, in mm	4
VAS	Visual analog score	2
VDT	Vibration detection threshold, in µm	4
$VE_{total/target}$	Variable error: measure of precision or reproducibility of estimates, calculated over all trials per condition or per target position, in °	4
VF	'Visual feedback' phase, during which real-time visual feedback of the participant's force output was provided on a computer screen	5

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Curriculum Vitae

Paulina Johanna Maria Bank (given name: Linda) was born in Haarlem, The Netherlands, in 1986. After she graduated cum laude for pre-university education in 2004, she started studying Human Movement Sciences at VU University Amsterdam. In the meantime, she practiced her sport (swimming) on an international level, culminating with participation in the Olympic Games of Beijing in 2008. After this memorable experience, she decided to end her career as a professional athlete and focus entirely on the completion of her studies. In 2009, she graduated cum laude with both her Bachelor's and Master's degree (specialization: 'coordination, learning and the development of action'). In October 2009, she started her PhD research at the department of Neurology in the Leiden University Medical Center (LUMC) under the supervision of Prof. dr. J.J. van Hilten and dr. J. Marinus (Department of Neurology, LUMC), and Prof dr. P.J. Beek and dr. C.E. Peper (Faculty of Human Movement Sciences and Research Institute MOVE, VU University Amsterdam). The aim of the project, which resulted in this PhD thesis, was to obtain a better understanding of the motor dysfunction in patients with Complex Regional Pain Syndrome by means of evaluating changes in the motor system, changes in sensory processing and problems in sensory-motor integration. Linda's expertise and main research interests lie in the interplay between the systems involved with movement coordination and interaction with the environment (i.e., the musculoskeletal system, the nervous system and the senses). At present, she works as a post-doctoral researcher at the departments of Neurology and Rehabilitation Medicine of the LUMC. She strives to build a bridge between clinicians and engineers in order to develop an encompassing set-up that allows to search for the weak(est) links in the patient's motor performance.

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Bank, P.J.M., Peper, C.E., Marinus, J., Beek, P.J., van Hilten, J.J. (in press). Evaluation of mirrored muscle activity in patients with Complex Regional Pain Syndrome. *Clin Neurophysiol*

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