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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, 2007).
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 vicious 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.