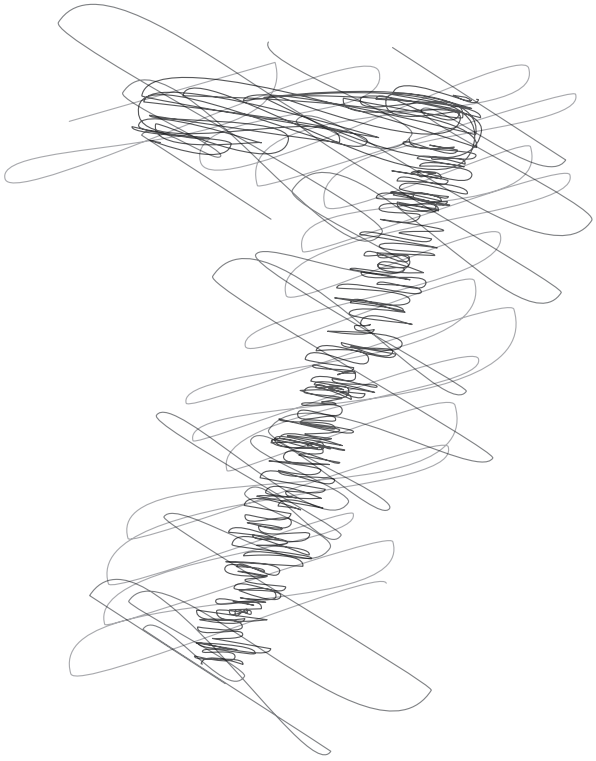

CHAPTER 7: Summary, concluding remarks and future perspectives

SUMMARY

Motor disturbances are frequently reported in Complex Regional Pain Syndrome (CRPS) and may involve muscle weakness and problems with initiation and execution of movements.[1-6] Fixed dystonia is the most frequently reported movement disorder in CRPS and is characterized by loss of voluntary muscle control and sustained abnormal postures from which a return to a neutral position is not possible, or only with great difficulty.[5, 7] The pathophysiological relation between CRPS and motor disturbances remains poorly understood, although sensory dysfunction and its role in deranging sensory-motor integration are assumed to play a role. The main aim of this thesis is to examine sensory disturbances in CRPS and assess their role in movement dysfunction. Secondary aims were to study the role of trauma in the onset of movement disorders and describe the phenomenology of peripherally-induced movement disorders, and to develop a method to quantify and monitor the severity of sustained abnormal postures.

Since CRPS usually has a traumatic onset, the dystonia that develops in the context of this condition (i.e. CRPS-related dystonia) is often preceded by a trauma, although with a variable delay. Van Rijn et al found that the median latency between the onset of CRPS and the onset of dystonia was 61 days. However, peripheral trauma may also lead to dystonia or other movement disorders without the development of CRPS, the so-called peripherally-induced movement disorders (PIMDs). As many people experience a peripheral trauma in their lifetime while only few develop a movement disorder, the causal relationship between the two and the potential underlying pathophysiology have been debated. To gain more insight in the phenomenology of movement disorders that developed after a peripheral trauma, we systematically reviewed all reported cases in the literature in **Chapter 2**. Results of 713 patients from 133 publications were included in the review. Data regarding patient characteristics, type of movement disorder and type of injury were collected, together with information on the spread of the movement disorder, predisposing factors, psychological characteristics, presence of nerve lesions and treatment. Fixed dystonia was the most frequently reported movement disorder, and was commonly associated with pain. Moreover, about one third of PIMDs were preceded by nerve injury, while sensory abnormalities were present in

up to half of all affected body parts. One third of patients was diagnosed with CRPS, of which only eight percent had an identified nerve injury and, by definition, thus actually suffered CRPS type II. CRPS patients were younger, had a shorter interval before developing a movement disorder and more often showed spread of movement disorders to other body parts than non-CRPS patients. Based on these results it was postulated that the initial insult interferes with normal sensory processing, which subsequently impairs spinal or supraspinal sensory-motor integration. Given the lack of understanding how peripherally-induced movement disorders evolve and their incongruence with clinical characteristics of movement disorders of known pathophysiology, a psychogenic cause is frequently assumed. Patients from the case series who were diagnosed with psychogenic movement disorders were therefore compared to those without such a diagnosis. Clinical characteristics overlapped between both groups, in particular regarding the presence of fixed dystonia and pain. We concluded that while there is overlap in clinical characteristics between peripherally-induced movement disorders and psychogenic movement disorders, the current review indicates that there are many well-documented organic cases of peripherally-induced movement disorders. This suggests that movement disorders, such as dystonia, tremor, myoclonus and tics, may under certain circumstances (e.g. nerve lesions or genetic predisposition) be triggered by peripheral trauma. However, it should be kept in mind that the quality of reported data differed considerably between studies, with some articles providing insufficient information on the characteristics of interest (or were not evaluated for all features) and that the data are subject to recall bias.

In Chapter 3 the relation between sensory and motor functioning in CRPS patients with and without dystonia is investigated. To this end, patients with affected arms and healthy controls were subjected to a comprehensive quantitative sensory testing (QST) protocol which also included two-point discrimination and a hand laterality recognition test. Motor function was quantified by kinematic analysis of repetitive movements during a finger tapping task, while dystonia severity was assessed with the Burke Fahn Marsden scale. Both CRPS groups showed thermal hypoesthesia to cold and warm stimuli and hyperalgesia to cold stimuli. A decreased pressure pain threshold, reflecting muscle hyperalgesia, emerged as the most prominent sensory abnormality in both

patient groups and was most pronounced in CRPS patients with dystonia. Moreover, the decreased pressure pain threshold was the only nociceptive parameter that was related to parameters of the finger tapping task, in both patients and controls. Besides, in CRPS patients with dystonia, the pressure pain threshold value also correlated with the BFM score. Significant differences between all groups were found for velocity and frequency on the finger tapping task, with CRPS patients with dystonia performing worse than patients without dystonia. CRPS patients with dystonia had an increased 2-point discrimination as compared to controls and CRPS patients without dystonia. This finding was also reported in other types of dystonia and has been associated to cortical reorganization in response to impaired motor function. This is the first study linking a sensory dysfunction, ie, muscle hyperalgesia, to motor impairment in CRPS. We hypothesize that increased sensitivity of the circuitry mediating muscle nociception may play a crucial role in impaired motor control in CRPS.

Sensory abnormalities are not only present in the affected limbs of CRPS patients, altered sensory perception levels (e.g. thermal and mechanical hyperalgesia and hypoesthesia) have also been demonstrated in unaffected body parts of CRPS patients.[3, 8-12] The spread of hyperalgesia to unaffected body regions may relate to the mechanisms underpinning the chronification of pain and may predispose patients to the spread of CRPS symptoms, which sometimes can occur spontaneously or be triggered by a seemingly insignificant injury.[13] The aim of Chapter 4 was therefore to systematically examine whether sensory dysfunction is observed in unaffected body parts of CRPS patients, and to investigate if the extent of dysfunction is similar for the various sensory modalities. The QST data of unaffected extremities and cheeks of 48 patients diagnosed with CRPS of the arm (31 with dystonia) was obtained from the population described in Chapter 3. In line with the results in the affected hands, the most prominent abnormality was the pressure pain threshold. A consistent pattern of higher sensitivity to pressure pain was shown in unaffected contralateral arms and unaffected legs, as well as the cheek, and this modality demonstrated the largest effect sizes. Except for a lower vibration threshold in the contralateral leg of CRPS patients with dystonia, no differences in sensory modalities were found between CRPS patients with and without dystonia. Taken together, these results point to a general disturbance in central pain processing

in patients with CRPS, and hint in particular at the involvement of impaired endogenous pain control. The relation between motor function and pressure pain threshold in unaffected limbs could not be directly investigated in this study, since no objective measure to quantify movements of the legs was incorporated. Since pressure pain is the most deviant sensory abnormality in both unaffected and affected body regions of CRPS patients, this test may serve as an important outcome parameter in future (therapeutic) studies and may be used as a tool to monitor the course of the disease.

Chapter 5 evaluates the characteristics of voluntary force modulation during an isometric force matching task in CRPS patients with and without dystonia. Because force modulation at least partly relies on proprioception, the task was performed with and without on-line 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. The task was performed with the affected upper extremity by 28 CRPS patients with abnormal postures and 12 CRPS patients without abnormal postures, and compared to performance of the non-dominant hand of 32 healthy controls. The results demonstrated an impairment of the voluntary force modulation in CRPS patients, which was more pronounced 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. Interestingly, the effects of visual feedback removal appeared largely similar for the two patient groups and controls. However, when potential confounding effects of motor impairment on group comparisons were minimized by restricting the analysis to the lowest force level, the findings with respect to force reproduction errors suggested that an impaired sense of force production may contribute to the motor dysfunction in CRPS. This experiment was also performed in a smaller number of CRPS patients with affected lower extremities (15 with abnormal postures, 11 without abnormal postures, 32 healthy controls). Analysis of data obtained from the lower extremity largely supported our findings obtained from the upper extremity, and strengthen our results. In these experiments the pressure pain threshold was

also measured and found to be correlated with the maximum voluntary force in CRPS patients with and without dystonia. Specifically, lower detection thresholds (i.e., higher levels of muscle hyperalgesia) were associated with lower values of maximum voluntary contraction. The impaired voluntary modulation force output and the reduced sense of force production at the lowest force level indicate that therapeutic strategies aimed at the restoration of proprioceptive impairments, possibly using online visual feedback, may be worthwhile to explore to promote the recovery of motor function in CRPS.

In Chapter 6 we described the development of the Range of Motion Scale (ROMS), a new clinical rating scale to assess the severity of fixed abnormal postures based on the possible active range of motion of all joints (arms, legs, trunk and neck). The scale contains 18 items with response options ranging from 0 to 3, which sums up to a maximum score of 54. In this study the reliability and validity of the ROMS is examined. Inter- and intra-rater reliability of the ROMS was determined in 16 patients with sustained abnormal postures in the context of fixed dystonia, who were video-taped following a standard video protocol. The recordings were rated by a panel of international experts. Inter-rater reliability for total ROMS scores showed an intra-class correlation (ICC) of 0.85. The majority of the scores for the separate joints (13 out of 18) demonstrated an almost perfect agreement with ICCs ranging from 0.81-0.94; of the other items one showed fair, one moderate and three substantial agreement. The ICC's for the intra-rater reliability ranged from moderate to almost perfect (0.68-0.98). The construct validity was determined by clinically testing 30 patients with both the Burke Fahn Marsden (BFM) scale as well as the ROMS. Spearman's correlation coefficients between corresponding body areas as measured with the ROMS and BFM were all above 0.82.

This study demonstrates that the ROMS is a reliable and valid instrument to easily investigate the distribution and severity of sustained abnormal postures. Further clinimetric testing of the scale is required before it can be used in other disorders presenting with abnormal postures.

CONCLUDING REMARKS

Contribution of sensory dysfunction to the pathophysiology of CRPS related dystonia

In this thesis, quantitative techniques are used to examine the detection and pain thresholds for mechanical and thermal stimuli in CRPS patients. This approach allows the evaluation of standardized noxious responses to the smallest nerve fibers, namely C and A-delta fibers in skin and muscle. The results provide several indications that muscle hyperalgesia may play a role in CRPS related dystonia. First, a decreased pressure pain threshold emerged as the most prominent sensory abnormality, and this value was lower in patients with dystonia as compared to those without dystonia (Chapter 3). Second and most importantly, pressure pain threshold was the only measure of nociceptive function that related to measures of motor function. Lower pain thresholds correlated with impaired performance on a finger tapping task (Chapter 3), higher dystonia severity scores as measured by the BFM scale in patients with dystonia (Chapter 3) and with lower maximum voluntary contraction levels (Chapter 5).

What does this reduced pressure pain threshold actually represent? Pressure algometry executed on muscles predominantly activates muscle nociceptors (III and IV afferents), as cutaneous analgesia has a marginal influence on the test response,[14-16] The results presented in this thesis, together with the correlation between pressure pain threshold and hand dexterity as measured by the Sequential Occupational Dexterity Assessment in patients with CRPS without dystonia,[3] imply a role of this sensory modality across the spectrum of motor deficits in patients with CRPS. Circuitries mediating muscle nociception may therefore play an important role in impaired motor control in CRPS.

A possible contribution of another sensory modality – proprioception – was shown by a force matching task (Chapter 5). When the analysis was restricted to lowest force level, the only level that CRPS patients with dystonia could produce adequately, a disturbance of sense of force production was inferred. This is in line with other findings that showed impaired joint perception sense[17] and aberrant feedback from the Golgi tendon as determined by computational modeling.[18, 19]

A general limitation is that sensory abnormalities in CRPS patients with dystonia were obtained in cross-sectional studies, and the relations between muscle hyperalgesia and motor function were based on correlations. Therefore, no inferences on causal relations can be made. Hence, we do not know if dystonia results in sensory disturbances, or, conversely, if sensory dysfunction can lead to dystonia. In addition, a third variable (e.g. disease severity) could theoretically cause dystonia as well as more severe muscle hyperalgesia, which would also result in a significant correlation. However, given that the disease duration and pain scores were similar across both CRPS groups we consider this less likely. Another point to consider is that we did not quantify disuse and therefore cannot rule out the differences between the CRPS patients with dystonia and those without dystonia reflect an epiphenomenon of disuse. It is possible that the extremities of patients with CRPS-related dystonia are less active than the extremities of patients who have CRPS without dystonia. However, the observation that muscle hyperalgesia was also the most prominent abnormality in unaffected extremities of CRPS patients as shown in Chapter 4, renders a role of disuse unlikely.

How might sensory dysfunction play a role in the development of CRPS related dystonia? Following tissue injury, which commonly precedes the onset of CRPS, C and Aδ fibers of sensory nerves are excited and induce neurogenic inflammation.[20-22] Mediators of neurogenic inflammation released at the site of tissue injury may sensitize the peripheral nociceptors, which in turn enhances sensory neuron background activity, lowers mechanical thresholds, and increases activity in response to suprathreshold stimuli.[15] Besides a peripheral response, nociceptive neurons in the dorsal horns of the spinal cord may become sensitized, which in turn make these neurons more excitable to peripheral input,[23] a phenomenon called central sensitization.[24] Central sensitization is associated with the development of clinical signs of hyperalgesia and allodynia,[25, 26] Moreover, compelling evidence for central sensitization in CRPS originates from the fact that sensory changes are also found beyond the affected extremity in patients with CRPS, such as hyperalgesia in the ipsilateral forehead, hemisensory impairment, impaired joint proprioception[4, 10, 12, 17] and muscle hyperalgesia (this thesis). In line with the results on sensory dysfunction, motor impairments have also been

found in unaffected limbs of patients with CRPS. Patients with unilateral upper extremity CRPS may exhibit bradykinesia and impairment of fine motor skills (i.e. drawing) of the unaffected contralateral extremity.[27, 28] Once an extremity is affected with dystonia, there is an increased risk to develop abnormal postures in another limb and the hazard increases with the number of affected extremities, which may also point to maladaptive plasticity.[29] Given the close link between sensory feedback from different modalities and the coordination of movements,[30] it seems likely that impaired central processing of sensory information affects sensory-motor integration. Indeed, in animal studies, there is evidence that central sensitization enhances nociceptive withdrawal reflexes and impairs spinally-mediated simple motor learning tasks.[31, 32] The associations between motor function and muscle hyperalgesia support this hypothesis of disturbed sensory-motor integration in CRPS (Chapter 4). However, a reduced pressure pain threshold was also the most prominent abnormality found in unaffected extremities of CRPS patients (Chapter 4), indicating that muscle/pressure hyperalgesia is a widespread characteristic of CRPS. Besides, pressure hyperalgesia in areas remote from the primary locus of pain is a shared characteristic with other chronic pain syndromes, including fibromyalgia, low back pain, chronic temporomandibular disorder, knee osteoarthritis, chronic tension-type headache, and rheumatoid arthritis.[33-38]

The fact that these thresholds are lower in unaffected extremities of chronic pain patients, implies that this test provides information about the function of the endogenous pain system. QST measures the (conscious) response to a noxious stimulus and does not simply reflect pain. The potential role of pain in motor dysfunction in CRPS was shown by Schilder et al. (2013).[39] Intravenous administration of ketamine, a potent N-methyl-D-aspartate (NMDA) receptor antagonist, was beneficial in decreasing pain severity in patients with CRPS.[40] When the effect of ketamine on motor parameters was studied in more detail using kinematic parameters obtained during a finger tapping task, it was found that pain relief, regardless its cause (ketamine or placebo), was associated with improved motor function.[39] However, in our experience, intravenous ketamine has no clear effect on dystonia in CRPS.

Central sensitization is associated with loss of inhibition along the neuraxis in CRPS with and without dystonia,[41-44] which can be influenced by the administration of intrathecal medication. CRPS patients with dystonia respond to the γ-aminobutyric acid receptor B ($GABA_B$) agonist baclofen, which enhances spinal GABAergic inhibition,[45-47] but not to the intrathecal administration of glycine, a major neurotransmitter involved in central inhibition.[48] These results point to a specific role of GABA-ergic mechanisms in CRPS patients with dystonia.

Cortical reorganization may also contribute to sensory and motor dysfunction. Shrinkage of the somatotopic map in the primary somatosensory cortex (S1) contralateral to the affected limb was shown in CRPS,[49] the extent of which was associated with spontaneous pain and mechanical hyperalgesia. Reversal of the S1 cortical reorganisation was found when CRPS symptoms decreased after treatment.[50] A systematic review showed that with respect to primary motor cortex dysfunction, there is only limited evidence for bilateral M1 disinhibition in CRPS of the upper limb.[51] Altered sensory-motor processing at a cortical level was shown in a study using magnetoencephalography, which suggested a modified inhibition between S1 and the motor cortex.[52]

Taken together, there is evidence showing that CRPS related dystonia is associated with abnormal sensory processing and disturbed sensory-motor integration. (Chronic) pain may contribute to its development, but the pathophysiological mechanism underlying dystonia in CRPS patients is still not fully elucidated and requires further investigation.

The role of psychological factors

The discussion on the possible role of psychological factors in the development of fixed dystonia after a peripheral trauma is complicated by the considerable overlap in clinical characteristics between patients that were diagnosed with psychogenic dystonia and patients with CRPS related dystonia (Chapter 2).[7] The role of psychogenic factors were emphasized by a few examples of patients with fixed dystonia (some with CRPS) that showed a dramatic immediate response to a very small quantity of botulinum toxin.[53] Designating symptoms as psychogenic assumes that psychogenic disorders can be distinguished from neurological disorders through clinical assessment[54] Additional neu-

rophysiological or imaging data can support the diagnosis of psychogenic symptoms.[55] For example, in tremor and myoclonus several neurophysiological tests can help in distinguishing psychogenic movement disorders from their 'organic' counterparts, but this is much more difficult in dystonia. So far, studies on objective physiological markers have not revealed any differences between psychogenic or organic dystonia.[43, 56, 57]

So far, there is no substantial evidence to assume that there is a psychological background for the development of CRPS,[58, 59] nor for the dystonia that developed in the context of CRPS.[60, 61] One study found no differences in psychological profile between CRPS patients who did and did not develop dystonia,[60] while another study demonstrated that CRPS patients with dystonia do not exhibit particular psychological traits or a unique psychological profile,[61] although in the latter an association with early traumatic experiences was found. Interestingly, it has been questioned whether it is appropriate to ascribe psychogenic movement disorders to psychological factors, just because the abnormal movements are distractible, inconsistent, incongruent with known movement disorders, or because they respond to cognitive behavioural therapy or placebo.[62] The term psychogenic (or somatisation, or conversion) refers to a presumed underlying psychiatric cause, which frequently cannot be demonstrated.[6, 62, 63] It was therefore proposed to use the term 'functional' instead of 'psychogenic', since the former presumes no causal mechanism and is acceptable to patients.[64] A recent position paper on functional movement disorders suggests that instead of focusing on the dualism between mind and brain, a more integrated view of brain dysfunction, incorporating biological, psychological and social perspectives, provides a better basis for future research in this field.[65]

Recently a neurobiological framework - based on Bayesian models -, that accounted for all functional sensory and motor symptoms was proposed.[66] In this theory, the explanation of symptoms is based on the key (im)balance between prior beliefs and sensory evidence that is mediated by (body focused) attention, symptom expectations, physical and emotional experiences, as well as beliefs about illness. For example, during a physical trauma, excessive weight is given to sensations perceived during this event, which may lead to the negative affect associated with somatic symptoms. Using a paradigm in which the probabilities of events on the basis of empirical evidence were test-

ed, it was shown that patients with functional motor symptoms 'jump to conclusions', suggesting that these patients have the tendency to overweigh the available evidence.[67]

These studies show that borders between neurology and psychiatry are starting to fade over the last few years and the field of movement disorders is set as an example where collaborative effort may advance our understanding of this complex field.[68] While some may focus on the functional explanations of fixed dystonia, others may concentrate on biological aspects, such as the cascade of (inflammatory) events that may follow a physical injury, genetic predisposition, or a role for auto-immunity as proposed by Cooper & Clark (2013). These authors suggest that fixed dystonic postures in CRPS may reflect a functional consequence of a 'seroconversion' event, with autoantibodies serving as the initiators of neurological and neuropsychiatric symptoms.[69] Hopefully, future studies will lead to a better understanding of the different mechanisms contributing to this complex disorder.

FUTURE PERSPECTIVES

Reduced pressure pain thresholds emerged as the most deviant abnormality in CRPS patients, both with and without sustained abnormal postures. The assessment of pressure pain threshold is easy to perform and does not require complex equipment such as those applied to evaluate thermal perception and pain thresholds. Given the consistent pattern of pressure pain thresholds compared to other tests, this test may be a good candidate to be used in the clinic to monitor the course of the pain condition, even though it is not specific to CRPS.

However, all findings on pressure pain thresholds in CRPS are derived from cross-sectional studies. Therefore, future studies should first address the feasibility of pressure pain thresholds as an assessment method to be used in longitudinal studies and the possible use as a clinical surrogate of endogenous pain modulation. Moreover, pressure pain thresholds may assist in phenotyping patients, although stimulus sensitivity by itself is not enough and should ideally be combined with objective measures of central activity, such as fMRI.[70] A very important question in current pain research is whether we can identify patients that are likely to develop chronic pain. Promising developments were shown in the field of chronic back pain, where an fMRI study iden-

tified neural mechanisms predicting the transition from acute to chronic pain.[71] These studies could also serve as model for the identification of risk factors in the development of movement disorders.

Studies investigating CRPS related dystonia are hampered in several ways: studies usually have a cross-sectional design and were mostly performed in chronic pain populations, therefore cause and effects are impossible to disentangle. Another problem is that CRPS - and especially CRPS with fixed dystonia - has a low incidence. Identifying the role of factors such as peripheral trauma, pain, genetic susceptibility, life events, aberrant immune responses are difficult as sufficient sample sizes are hardly achieved. To increase the number of patients with fixed dystonia in studies, multicenter collaborations should be launched, which ideally extend across country borders. Within these (inter)national collaborations standardized registration and investigation of patients may yield valuable information on potential predisposing factors and the long term outcomes. The increasing use of electronic patient databases also enhances the feasibility to study larger patient groups, especially in retrospective studies. An excellent example is the use of a large database with electronic patient records of more than 150 general practioners in determining the incidence of CRPS in the Netherlands[72] and the collaboration within the TREND consortium.

To gain further understanding in the disturbed sensory-motor integration, intervention studies investigating new therapeutic strategies could be used to disentangle the multiple factors which may play a role in the motor disturbances of patients with CRPS. For example, transcranial magnetic stimulation (TMS) could be used to enhance insights in the role of cortical involvement and (inter)hemispherical inhibitions. TMS is produced by a magnetic pulse that can induce an electric current in the brain. Action potentials evoked on the cortex can have either a stimulatory or inhibitory effect on neural networks depending on the stimulation parameters. Other therapeutic strategies could focus on restoring sensory dysfunction.

Regarding the definition of fixed dystonia, emerging evidence questions whether the term dystonia is still an appropriate designation for the observed abnormal postures.

While isolated dystonia (previously named primary dystonia)[73] is characterized by sustained or intermittent muscle contractions that cause abnormal, often twisting,

repetitive movements and/or postures,[73, 74] the term fixed or tonic dystonia has been used to describe cases who exhibit abnormal sustained postures without any mobile component. [6, 75, 76] Given that the phenotype of fixed dystonia differs significantly from its mobile counterpart, the term 'dystonia' is in fact inappropriate. Moreover, a recent electromyography study revealed that abnormal hand postures in CRPS were not associated with sustained muscle contractions, and limitations of the active range of motion were not attributable to excessive co-contraction[1] – at least in those patients with some active range of motion. Though the terms abnormal postures, fixed and tonic dystonia were used interchangeably in this thesis, 'sustained abnormal postures' may be a more appropriate term for this motor feature in the future.

A promising approach for future research considering the etiology of sustained abnormal postures, are the recent initiatives not to focus on the dualism between mind and brain, and instead use a more integrated view of brain dysfunction, incorporating biological, psychological and social perspectives.[65] Within this view, attentional modulation may play an important role in (the pathophysiology of) functional movement disorders.[77, 78] Patients with functional movement disorders performed better on a motor task that involved less explicit (i.e., more automatic) voluntary control[77] and showed an impaired sense of volition.[78] Besides, attentional bias towards executing movement were also demonstrated in patients with functional paralysis.[79] Clinical observations during our experiments, confirm that a proportion of fixed dystonia patients may show a different motor behavior during the performance of voluntary movements as opposed to involuntary movements. Moreover, a contribution of attention deficits towards the affected limb in CRPS seems plausible in this regard, given that CRPS patients with abnormal postures showed more neglect-like symptoms with respect to their affected limb than CRPS without abnormal postures (Chapter 5). Investigations on the pathophysiological mechanisms that may explain the discrepancy between voluntary and involuntary movement may advance our knowledge on impaired voluntary control in CRPS patients with abnormal postures. Also studies in which fMRI and transcranial magnetic stimulation are combined may shed light on how chronic pain may differentially impair voluntary motor processing, and thereby provide valuable information for future studies aiming to improve motor function in patients with CRPS and other chronic pain disorders.

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