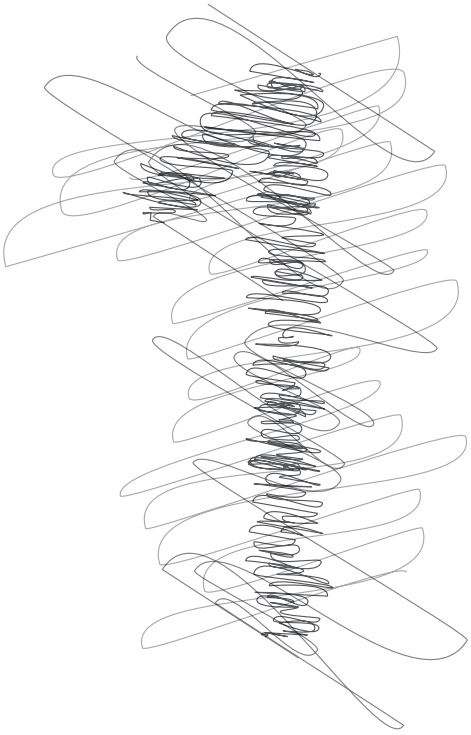


CHAPTER 1: General introduction

COMPLEX REGIONAL PAIN SYNDROME

In 1864 Silas Weir Mitchell described patients with gunshot wounds who experienced burning pain and developed a shiny red skin after nerve injury, and named the condition 'causalgia' (Mitchell, 1864). This cluster of symptoms was one of the first descriptions of a disorder which is now named complex regional pain syndrome (CRPS), and which previously carried the names algodystrophy, Sudeck's dystrophy and reflex sympathetic dystrophy (Sudeck, 1900; Evans, 1946). CRPS is chronic pain disorder which can be triggered by a (minor) trauma and is characterized by sensory (allodynia, hypo/hyperesthesia, hypo/hyperalgesia), autonomic (edema, skin colour and temperature changes), trophic (skin changes, changes in hair and nail growth) and motor abnormalities. Motor disturbances in CRPS may involve muscle weakness, bradykinesia and difficulties in initiating movements.[1-5] About 25% of patients develop tonic or fixed dystonia, which is characterized by loss of voluntary muscle control and sustained abnormal postures that do not return, or with great difficulty, to a neutral position *(Figure 1.1)*.[1,6] Other movement disorders like tremor and myoclonus have also been reported.[1,7] Clinical features may spread to other limbs over time.[8]

The diagnosis of CRPS relies on criteria that are based on the presence of signs and symptoms. In 1993 the first well-validated criteria set was described by Veldman et al.[9] The most frequently used criteria were, however, those developed under the auspices of the International Association for the Study of Pain *(Table 1.1)*,[10] until they were recently replaced by the Budapest criteria, which showed higher specificity and also included motor features *(Table 1.2)*.[11] A distinction is made between CRPS type 1 (without identified nerve lesion) and type 2 (with identified nerve lesion). This difference has been criticized, as studies in amputated limbs and skin biopsies of CRPS type 1 patients have shown degeneration of small C and Aδ nerve fibers.[12]

Epidemiology and risk factors

The reported incidence of CRPS ranges from 5.5 to 26.2 per 100,000 person years.[13,14] Thereby, woman are 3-4 times more frequently affected than men. Although in most cases CRPS is triggered by a (minor) trauma, like a fracture, sprain or surgery, [13] sponta-

neous onset of CRPS is also reported.[15] The phenotype of patients with a spontaneous onset does not differ from cases with a trauma-induced onset. However, spontaneous-onset cases had a lower age at onset, which may indicate that genetic factors play a role in the development of CRPS.[15] There are several other indications that genetic predisposition may play a role in CRPS. First, the fact that so many people are faced with a trauma, while only so few develop CRPS may hint at genetic susceptibility. Second, a few families with CRPS have been described,[16] and siblings of young-onset cases have an increased risk of developing CRPS.[17] Third, genetic associations have been shown with the HLA region, which plays an important role in regulating the immune response.[18, 19] Significant associations were shown with HLA-DQ1, HLA-DR-6 and HLA-DR-13.[20-23] However, these studies were hampered by phenotypic heterogeneity, statistical analysis of unplanned post-hoc analyses and underpowered studies. These limitations were overcome in a large case-control study that included 150 CRPS patients with dystonia, in which it was shown that HLA-B62 and HLA-DQ-8 were significantly associated with the presence of dystonia.[24]

Besides possible genetic susceptibility to CRPS, several other factors have been associated with higher risk of developing CRPS, such as the presence or history of asthma, osteoporosis, migraine and the use of ACE-inhibitors (which enhance an inflammatory response).[25, 26] Moreover, there are indications that immobilization of the affected limb after trauma is a possible risk factor.[27, 28] Psychological factors have also been suggested as a potential cause of CRPS symptoms in the absence of an accepted somatic cause.[29, 30] However, two large studies (one of which involved a large group of prospectively studied patients with single fractures) were not able to identify psychological risk factors for the development of CRPS.[25, 31]

Pathophysiology

Over the years, extensive research suggests that CRPS is a multifactorial disorder in which environmental and genetic factors may play role. The clinical heterogeneity seen in CRPS may be a reflection of different combinations of biological pathways presumed to be involved in CRPS that include aberrant inflammation, vasomotor dysfunction, and maladaptive neuroplasticity.[32]

Inflammation

Several signs of CRPS, such as increased temperature, redness and swelling are signs that resemble a classic inflammatory response to tissue injury, and has led to the hypothesis that aberrant inflammation is involved in the pathophysiology of CRPS. Several findings corroborate with this idea. The pro-inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor(TNF) alpha were elevated in fluid of experimentally induced blisters of the affected arm compared to the unaffected arm.[33] Moreover, the levels of IL-1 and TNF alpha remained elevated over a period of 3 years.[34]

Besides the classic immune response, evidence points to the involvement of neurogenic inflammation in CRPS. The immune response after peripheral trauma may trigger primary afferent neurons to release neuropeptides as substance P (SP) and calcitonin-gene-related peptide (CGRP), which in turn mediate an inflammatory reaction by evoking vasodilatation and protein extravasations.[35] Both SP and CGRP were shown to be increased in CRPS.[36, 37] A recent systematic review revealed that the pro-inflammatory state in blood, cerebral spinal fluid and blister fluid has different inflammatory profiles during the acute (<6 months) and chronic phase (≥ 6 months) of CRPS.[38] Additionally, auto-immunity may play a role in the inflammatory signs and symptoms of CRPS, which was demonstrated by the findings of auto-antibodies against the muscarinic-2 receptor and b2 adrenergic receptor in CRPS.[39]

Vasomotor dysfunction

Skin temperature and color asymmetries between the affected and unaffected extremity mark microvascular disturbances in CRPS. While in the acute stage the affected extremity is usually warmer, the temperature may turn colder in more advanced stages.[28] Next to the classic inflammatory vasodilatation, there are indications that sympathetic dysfunction contributes to the vascular dysfunction.[40] A study that used whole-body warming and cooling showed that vasodilatation in the acute phase is due to unilateral inhibition of the cutaneous sympathetic vasoconstrictor neurons. This is most likely centrally mediated as there is no evidence of degeneration of sympathetic efferents.[40] In later phases of CRPS, vasoconstriction plays a more prominent role,[41] presumably explained by non-neural mechanisms, such as hyperreactivity of the blood vessels to

catecholamines[42] and endothelial dysfunction.[43, 44] Notably, about 20% of patients reported that their affected limbs were cold from the onset of the CRPS symptoms,[45] pointing to differential involvement of mechanisms like vasomotor dysfunction in subgroups of patients.

Central nervous system changes

Continuous nociceptive input from the periphery, but also the presence of neuropeptides and pain may evoke functional and structural changes throughout the central nervous system. This can lead to central sensitization in the dorsal horns of the spinal cord, which is associated with the development of hyperalgesia, allodynia, and the spreading of pain to adjacent non-injured areas.[46-48] Moreover, several supraspinal changes have been shown in CRPS (see for review of cortical changes[49]) that may contribute to the different sensory and motor signs. For instance, a smaller representation of the affected hand compared to the unaffected side was shown on the primary somatosensory map, which was associated with pain intensity and pinprick hyperalgesia.[50] Besides, reorganization of central motor circuits in CRPS patients was also demonstrated, with an increased activation of primary motor and supplementary motor cortices during a finger tapping task.[51] In addition, a proportion of patients experience body perception disturbances[52-55] and neglect-like symptoms,[56] which also originate at a supraspinal level.

DYSTONIA IN CRPS, AN ORGANIC OR FUNCTIONAL SIGN?

Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions that cause abnormal, often twisting, repetitive movements and/or postures.[57, 58] While patients with isolated dystonia (previously named primary dystonia) often display mobile movements[57], the term fixed dystonia is used to indicate those cases who exhibit abnormal postures without any mobile component.[59, 60] As there currently is no consensus on the definition of these abnormalities in CRPS, the terms abnormal postures, fixed and tonic dystonia are used interchangeably throughout this thesis.

Dystonia in CRPS is dominated by flexion postures and are most prominently present in hands and feet.[1, 61] Once an extremity is affected, there is an increased risk to develop dystonia in another limb and the hazard increases with the number of affected extremities, which may point to maladaptive plasticity.[62]

Interestingly, fixed dystonia may also develop after a peripheral trauma without signs and symptoms of CRPS. In those cases the movement disorder is believed to result from a psychogenic or 'functional' origin, rather than a primary neurological cause.[6, 63] In 1988 the first patient series with psychogenic dystonia was described, together with clues for its identification and criteria for diagnosis. Main clues to identify patients with psychogenic dystonia were an acute onset, the presence of abnormal postures at rest, pain, incongruent behavior and a reduction of symptoms with distraction and/or psychotherapy.[63] As the clinical presentation of patients with fixed dystonia with and without CRPS show considerable overlap, the pathophysiology of this disorder has been subject of ongoing debate.[64-66] On the one hand, it was suggested that peripheral trauma could trigger a peripherally induced movement disorder in genetically or otherwise susceptible subjects with a pre-existent or subclinical movement disorder. [67-69] On the other hand, a functional cause is motivated by the view that current accepted theories on the pathogenesis of movement disorders have assumed a central origin of most of them, which could not be identified or supported in patients fixed dystonia. Second, characteristics related to the onset, progression, phenotype, and associated sensory problems differ from patients with typical primary dystonia. The third and last argument favoring the functional hypothesis is that some patients with fixed dystonia had co-existent psychological problems, a history of psychiatric disease, or other clinical features that supported the 'psychogenic' basis. Neuropsychiatric assessment in a large group of fixed dystonia patients (of whom 20% had CRPS and 37% fulfilled the criteria for psychogenic dystonia), demonstrated associative and somatoform disorders in a proportion of the group, but not in all patients.[59] On the contrary, in a study where psychological factors in CRPS patients with fixed dystonia were investigated, an elevated general level of psychopathology was shown, but these total scores were significantly lower than those of patients with conversion disorder or affective disorder.[70] Moreover, the elevated scores were no different from other chronic pain populations described in

the literature. One variable that was identified in this study involved traumatic early-life experiences, which were more frequently present in this group and thus may be a predisposing factor to develop the disorder.[70]

Where objective physiological markers as nuclear imaging and neurophysiological investigations have been used to identify functional signs in tremor and myoclonus,[71-73] these techniques have so far not been able to reliably discriminate between 'organic' and psychogenic dystonia.[74 75 76, 77] Taken together, the pathophysiology and the role of central and peripheral factors in fixed dystonia in CRPS are still poorly understood and remain an important subject of investigation.

QUANTIFICATION OF ABNORMAL POSTURES

Irrespective of the etiology of the abnormal postures in CRPS, it is important for clinical and research purposes to reliably quantify this motor abnormality. Currently, there is no adequate instrument to assess the severity of the abnormal postures, to monitor the progression of the disorder or to evaluate treatment effects. Abnormal postures are usually scored with the Burke Fahn Marsden (BFM) scale.[78] However, the BFM was primarily intended for rating abnormal movements in isolated dystonia. Given the differences between the mobile and twisting movements in primary dystonia, and the relatively fixed postures in CRPS, the BFM has several drawbacks.

Firstly, the score of the BFM contains a provoking factor, which depends on the presence over time. Although this factor does include the response option 'dystonia present at rest', this distinction is not useful as the abnormal postures are (nearly) always present. Secondly, the provoking factor is combined with a severity factor which is based on a rather complex movement, for example 'grasping an object' in the evaluation of the arms, instead of more simple movement like flexion-extension. Moreover, the BFM does not differentiate between involvement of several joints in the same limb, hence the maximum score for an arm can be achieved even when only the fingers are affected.

As dystonia in CRPS is particularly characterized by abnormal postures, which are usually accompanied by restrictions in ROM, a new measurement instrument should focus on

this aspect. In this respect it is important to note that although the term 'fixed dystonia' may imply complete absence of joint mobility, active movement may still be possible.[1, 79]

SENSORY–MOTOR DISTURBANCES

It is well recognized that the presence of pain may influence motor performance, although the mechanisms and physiological consequences of the adaptation of motor behavior to pain remain poorly understood.[80] Experimental pain studies in animal models show that noxious stimuli are associated with a protective motor response to nociceptive stimuli,[81] while acute pain in human controls has been shown to influence the recruitment of muscle fibers.[82] However, these results cannot be directly extrapolated to pain that occurs in the context of a chronic pain condition, which is a more complex phenomenon of which the effects are more difficult to assess.

Sensory feedback is essential in coordinating movements; information from the skin, muscle spindles, tendon organs and vision is integrated with motor commands for an optimal motor performance.[83] In CRPS, several sensory abnormalities have been reported that may interfere with motor control. These disturbances include thermal and mechanical hyperalgesia and hypoesthesia,[4, 45, 84-86] aberrant feedback from the Golgi tendon as determined by computational modeling,[61, 87] and the fact that some CRPS patients need to watch their limb to control movements.[88] Moreover, there are indications that central sensory-motor processing is disturbed.[51, 89] However, it is unknown to what extent sensory dysfunction contributes to motor disturbances in CRPS.

AIMS AND OUTLINE OF THIS THESIS

The general aim of this thesis is to investigate the contribution of sensory dysfunction to motor deficits in CRPS patients and to improve quantification of motor dysfunction.

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**. Additionally, potential mechanisms that may explain the underlying pathophysiology are discussed.

To examine the contribution of sensory dysfunction to motor dysfunction in CRPS, patients with and without abnormal postures underwent comprehensive Quantitative Sensory Testing (QST) in **Chapter 3.** The relation between sensory and motor function is investigated by correlating values of sensory parameters obtained by QST to outcomes of a kinematic analysis of repetitive finger movements and measures of dystonia severity. In **Chapter 4** we examine whether sensory dysfunction is observed in unaffected body parts of CRPS patients, and whether the extent of dysfunction is similar for the various sensory modalities. The potential role of proprioceptive deficits to motor dysfunction in CRPS is assessed in an isometric force matching task in **Chapter 5**, where CRPS patients with and without abnormal postures performed the task with and without visual feedback. Moreover, the characteristics of voluntary force modulation are evaluated. In **Chapter 6** the development of the Range of Motion Scale (ROMS), a new measurement instrument to assess the severity and distribution of the (fixed) abnormal postures in CRPS, is described. The rating scale is based on the possible active range of motion of all joints (arms, legs, trunk and neck). The intra- and inter-rater reliability and validity of the ROMS are examined. The main findings and conclusions of this thesis are discussed in **Chapter 7**, together with suggestions for future research.

Table 1.1: IASP diagnostic criteria

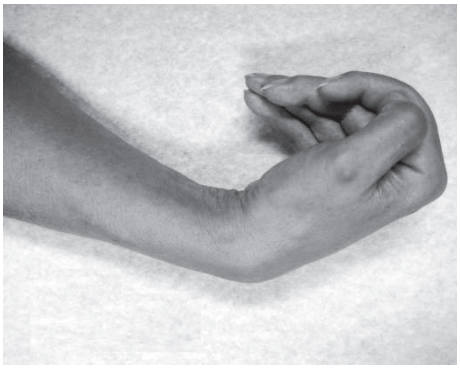
1. the presence of an initiating noxious event, or a cause of immobilization
2. continuing pain, allodynia, of hyperalgesia with which the pain is disproportionate to any inciting event
3. evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
4. the diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

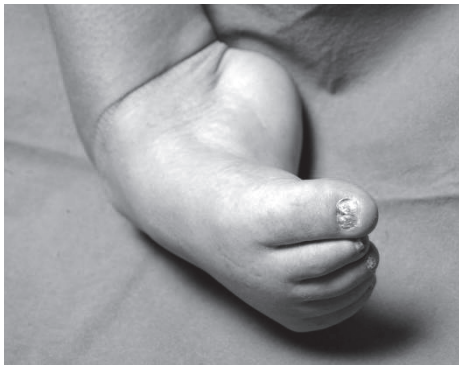
Note: criteria 2-4 must be satisfied

Table 1.2: Budapest diagnostic criteria for CRPS (ref harden validation)

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three (clinical diagnostic criteria) or four (research diagnostic criteria) of the following categories:
   - Sensory: hyperesthesia or allodynia
   - Vasomotor: temperature asymmetry, skin colour changes, or skin colour asymmetry
   - Sudomotor or oedema: oedema, sweating changes, or sweating asymmetry
   - Motor or trophic: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
3. Must display at least one sign at time of diagnosis in two or more of the following categories:
   - Sensory: hyperalgesia (to pinprick) or allodynia (to light touch, deep somatic pressure, or joint movement)
   - Vasomotor: temperature asymmetry, skin colour changes or asymmetry
   - Sudomotor or oedema: oedema, sweating changes, or sweating asymmetry
   - Motor or trophic: decreased range of motion, or motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
4. No other diagnosis better explains the signs and symptoms.

Figure 1.1: Hand and foot of chronic CRPS patients with abnormal postures.





REFERENCES

(1) Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. *Neurology* 1990 Jan;40:57-61.

(2) Gierthmuhlen J, Maier C, Baron R, Tolle T, Treede RD, Birbaumer N, Huge V, Koroschetz J, Krumova EK, Lauchart M, Maihofner C, Richter H, Westermann A. Sensory signs in complex regional pain syndrome and peripheral nerve injury. *Pain* 2012 Apr;153:765-774.

(3) Schilder JC, Schouten AC, Perez RS, Huygen FJ, Dahan A, Noldus LP, van Hilten JJ, Marinus J. Motor control in complex regional pain syndrome: A kinematic analysis. *Pain* 2012 Apr;153:805-812.

(4) Huge V, Lauchart M, Magerl W, Beyer A, Moehnle P, Kaufhold W, Schelling G, Azad SC. Complex interaction of sensory and motor signs and symptoms in chronic CRPS. *PLoS One* 2011;6:e18775.

(5) Birklein F, Riedl B, Sieweke N, Weber M, Neundorfer B. Neurological findings in complex regional pain syndromes--analysis of 145 cases. *Acta Neurol Scand* 2000 Apr;101:262-269.

(6) Schrag A, Trimble M, Quinn N, Bhatia K. The syndrome of fixed dystonia: an evaluation of 103 patients. *Brain* 2004 Oct;127:2360-2372.

(7) Munts AG, Van Rootselaar AF, Van Der Meer JN, Koelman JH, van Hilten JJ, Tijssen MA. Clinical and neurophysiological characterization of myoclonus in complex regional pain syndrome. *Mov Disord* 2008 Mar 15;23:581-587.

(8) van Rijn MA, Marinus J, Putter H, Bosselaar SR, Moseley GL, van Hilten JJ. Spreading of complex regional pain syndrome: not a random process. *J Neural Transm* 2011 Sep;118:1301-1309.

(9) Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet* 1993 Oct 23;342:1012-1016.

(10) Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms, 2nd ed. Seattle: IASP Press, 1994.

(11) Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine JJ. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. *Pain* 2010 Aug;150:268-274.

(12) Oaklander AL, Fields HL. Is reflex sympathetic dystrophy/complex regional pain syndrome type I a small-fiber neuropathy? *Ann Neurol* 2009 Jun;65:629-638.

(13) de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: a population-based study. *Pain* 2007 May;129:12-20.

(14) Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain* 2003 May;103:199-207.

(15) de Rooij AM, Perez RS, Huygen FJ, Eijs FV, Kleef MV, Bauer MC, van Hilten JJ, Marinus J. Spontaneous onset of Complex Regional Pain Syndrome 1. *Eur J Pain* 2009 Sep 28.

(16) de Rooij AM, de Mos M, Sturkenboom MC, Marinus J, van den Maagdenberg AM, van Hilten JJ. Familial occurrence of complex regional pain syndrome. *Eur J Pain* 2009 Feb;13:171-177.

(17) de Rooij AM, de Mos M, van Hilten JJ, Sturkenboom MC, Gosso MF, van den Maagdenberg AM, Marinus J. Increased risk of complex regional pain syndrome in siblings of patients? *J Pain* 2009 Dec;10:1250-1255.

(18) Klein J, Sato A. The HLA system. First of two parts. *N Engl J Med* 2000 Sep 7;343:702-709.

(19) Shiina T, Hosomichi K, Inoko H, Kulski JK. The HLA genomic loci map: expression, interaction, diversity and disease. *J Hum Genet* 2009 Jan;54:15-39.

(20) Kemler MA, van de Vusse AC, van den Berg-Loonen EM, Barendse GA, van KM, Weber WE. HLA-DQ1 associated with reflex sympathetic dystrophy. *Neurology* 1999 Oct 12;53:1350-1351.

(21) Vaneker M, van der Laan L, Allebes WA, Gorsi R.J. Genetic factors associated with complex regional pain syndrome 1: HLA DRB and TNF alpha promotor gene polymorphism. *Disabil Med* 2002;2:69-74.

(22) van de Beek WJ, van Hilten JJ, Roep BO. HLA-DQ1 associated with reflex sympathetic dystrophy. *Neurology* 2000 Aug 8;55:457-458.

(23) van Hilten JJ, van de Beek WJ, Roep BO. Multifocal or generalized tonic dystonia of complex regional pain syndrome: a distinct clinical entity associated with HLA-DR13. *Ann Neurol* 2000 Jul;48:113-116.

(24) de Rooij AM, Gosso MF, Marinus J, Verduijn W, Claas FH, van den Maagdenberg AM, van Hilten JJ. HLA-B62 and HLA-DQ8 are associated with Complex Regional Pain Syndrome with fixed dystonia. *Pain* 2009 Sep;145:82-85.

(25) de Mos M, Huygen FJ, Dieleman JP, Koopman JS, Stricker BH, Sturkenboom MC. Medical history and the onset of complex regional pain syndrome (CRPS). *Pain* 2008 Oct 15;139:458-466.
(26) de Mos M, Huygen FJ, Stricker BH, Dieleman JP, Sturkenboom MC. The association between ACE inhibitors and the complex regional pain syndrome: Suggestions for a neuro-inflammatory pathogenesis of CRPS. *Pain* 2009 Apr;142:218-224.
(27) Schwartzman RJ, McLellan TL. Reflex sympathetic dystrophy. A review. *Arch Neurol* 1987 May;44:555-561.
(28) Marinus J, Moseley GL, Birklein F, Baron R, Maihofner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol* 2011 Jul;10:637-648.
(29) Ochoa JL, Verdugo RJ. Reflex sympathetic dystrophy. A common clinical avenue for somatoform expression. *Neurol Clin* 1995 May;13:351-363.
(30) Beerthuizen A, van 't SA, Huygen FJ, Klein J, de WR. Is there an association between psychological factors and the Complex Regional Pain Syndrome type 1 (CRPS1) in adults? A systematic review. *Pain* 2009 Sep;145:52-59.
(31) Beerthuizen A, Stronks DL, Huygen FJ, Passchier J, Klein J, Spijker AV. The association between psychological factors and the development of complex regional pain syndrome type 1 (CRPS1)--a prospective multicenter study. *Eur J Pain* 2011 Oct;15:971-975.
(32) Marinus J, Moseley GL, Birklein F, Baron R, Maihofner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol* 2011 Jul;10:637-648.
(33) Huygen FJ, de Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ. Evidence for local inflammation in complex regional pain syndrome type 1. *Mediators Inflamm* 2002 Feb;11:47-51.
(34) Wesseldijk F, Huygen FJ, Heijmans-Antonissen C, Niehof SP, Zijlstra FJ. Six years follow-up of the levels of TNF-alpha and IL-6 in patients with complex regional pain syndrome type 1. *Mediators Inflamm* 2008;2008:469439.
(35) Holzer P. Neurogenic vasodilatation and plasma leakage in the skin. *Gen Pharmacol* 1998 Jan;30:5-11.
(36) Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). *Neurosci Lett* 2008 Jun 6;437:199-202.
(37) Schinkel C, Gaertner A, Zaspel J, Zedler S, Faist E, Schuermann M. Inflammatory mediators are altered in the acute phase of posttraumatic complex regional pain syndrome. *Clin J Pain* 2006 Mar;22:235-239.
(38) Parkitny L, McAuley JH, Di PF, Stanton TR, O'Connell NE, Marinus J, van Hilten JJ, Moseley GL. Inflammation in complex regional pain syndrome: a systematic review and meta-analysis. *Neurology* 2013 Jan 1;80:106-117.
(39) Kohr D, Singh P, Tschernatsch M, Kaps M, Pouokam E, Diener M, Kummer W, Birklein F, Vincent A, Goebel A, Wallukat G, Blaes F. Autoimmunity against the beta2 adrenergic receptor and muscarinic-2 receptor in complex regional pain syndrome. *Pain* 2011 Dec;152:2690-2700.
(40) Wasner G. Vasomotor disturbances in complex regional pain syndrome-a review. *Pain Med* 2010 Aug;11:1267-1273.
(41) Wasner G, Heckmann K, Maier C, Baron R. Vascular abnormalities in acute reflex sympathetic dystrophy (CRPS I): complete inhibition of sympathetic nerve activity with recovery. *Arch Neurol* 1999 May;56:613-620.
(42) Kurvers HA, Jacobs MJ, Beuk RJ, van den Wildenberg FA, Kitslaar PJ, Slaaf DW, Reneman RS. Reflex sympathetic dystrophy: result of autonomic denervation? *Clin Sci (Lond)* 1994 Dec;87:663-669.
(43) Groeneweg JG, Antonissen CH, Huygen FJ, Zijlstra FJ. Expression of endothelial nitric oxide synthase and endothelin-1 in skin tissue from amputated limbs of patients with complex regional pain syndrome. *Mediators Inflamm* 2008;2008:680981.
(44) Groeneweg JG, Huygen FJ, Heijmans-Antonissen C, Niehof S, Zijlstra FJ. Increased endothelin-1 and diminished nitric oxide levels in blister fluids of patients with intermediate cold type complex regional pain syndrome type 1. *BMC Musculoskelet Disord* 2006;7:91.
(45) Eberle T, Doganci B, Kramer HH, Geber C, Fechir M, Magerl W, Birklein F. Warm and cold complex regional pain syndromes: differences beyond skin temperature? *Neurology* 2009 Feb 10;72:505-512.
(46) Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011 Mar;152:S2-15.

(47) Navarro X, Vivo M, Valero-Cabre A. Neural plasticity after peripheral nerve injury and regeneration. *Prog Neurobiol* 2007 Jul;82:163-201.
(48) Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000 Jun 9;288:1765-1769.
(49) Swart CM, Stins JF, Beek PJ. Cortical changes in complex regional pain syndrome (CRPS). *Eur J Pain* 2009 Oct;13:902-907.
(50) Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. *Neurology* 2003 Dec 23;61:1707-1715.
(51) Maihofner C, Baron R, DeCol R, Binder A, Birklein F, Deuschl G, Handwerker HO, Schattschneider J. The motor system shows adaptive changes in complex regional pain syndrome. *Brain* 2007 Oct;130:2671-2687.
(52) Lewis JS, Kersten P, McCabe CS, McPherson KM, Blake DR. Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). *Pain* 2007 Dec 15;133:111-119.
(53) Moseley GL. I can't find it! Distorted body image and tactile dysfunction in patients with chronic back pain. *Pain* 2008 Nov 15;140:239-243.
(54) Moseley GL, Gallace A, Spence C. Bodily illusions in health and disease: Physiological and clinical perspectives and the concept of a cortical 'body matrix'. *Neurosci Biobehav Rev* 2012 Jan;36:34-46.
(55) Katschnig P, Edwards MJ, Schwingenschuh P, Aguirregomozcorta M, Kagi G, Rothwell JC, Bhatia KP. Mental rotation of body parts and sensory temporal discrimination in fixed dystonia. *Mov Disord* 2010 Jun 15;25:1061-1067.
(56) Galer BS, Jensen M, Butler S. Neglect-like signs and symptoms in CRPS. *Pain* 2013 Jun;154:961-962.
(57) Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK. Phenomenology and classification of dystonia: A consensus update. *Mov Disord* 2013 Jun 15;28:863-873.
(58) Fahn S, Marsden CD, Calne DB. Classification and investigation of dystonia. In: Marsden C.D., Fahn S., eds. Movement disorders 2. London: Butterworths, 1987:332-358.
(59) Schrag A, Trimble M, Quinn N, Bhatia K. The syndrome of fixed dystonia: an evaluation of 103 patients. *Brain* 2004 Oct;127:2360-2372.
(60) Denny-Brown D. Clinical symptomatology of diseases of the basal ganglia. In: Vinken PJ, Bruyn GW, eds. Diseases of the basal ganglia. Amsterdam: North Holland Publishing Company, 1968:133-172.
(61) Munts AG, Mugge W, Meurs TS, Schouten AC, Marinus J, Moseley GL, van der Helm FC, van Hilten JJ. Fixed dystonia in complex regional pain syndrome: a descriptive and computational modeling approach. *BMC Neuro*l 2011;11:53.
(62) van Rijn MA, Marinus J, Putter H, van Hilten JJ. Onset and progression of dystonia in complex regional pain syndrome. *Pain* 2007 Aug;130:287-293.
(63) Lang AE. Psychogenic dystonia: a review of 18 cases. *Can J Neurol Sc*i 1995 May;22:136-143.
(64) Jankovic J. Can peripheral trauma induce dystonia and other movement disorders? Yes! *Mov Disord* 2001 Jan;16:7-12.
(65) Weiner WJ. Can peripheral trauma induce dystonia? No! *Mov Disord* 2001 Jan;16:13-22.
(66) Hawley JS, Weiner WJ. Psychogenic dystonia and peripheral trauma. *Neurology* 2011 Aug 2;77:496-502.
(67) Jankovic J, Van der LC. Dystonia and tremor induced by peripheral trauma: predisposing factors. *J Neurol Neurosurg Psychiatry* 1988 Dec;51:1512-1519.
(68) Defazio G, Jankovic J. Does peripheral injury induce dystonia? *Moving Along* 2010;14:1-9.
(69) Fletcher NA, Harding AE, Marsden CD. The relationship between trauma and idiopathic torsion dystonia. *J Neurol Neurosurg Psychiatry* 1991 Aug;54:713-717.
(70) Reedijk WB, van Rijn MA, Roelofs K, Tuijl JP, Marinus J, van Hilten JJ. Psychological features of patients with complex regional pain syndrome type I related dystonia. Mov Disord 2008 Aug 15;23:1551-1559.
(71) Hallett M. Physiology of psychogenic movement disorders. J Clin Neurosci 2010 May 19;17:959-965.
(72) van der Salm SM, Koelman JH, Henneke S, Van Rootselaar AF, Tijssen MA. Axial jerks: a clinical spectrum ranging from propriospinal to psychogenic myoclonus. *J Neurol* 2010 Aug;257:1349-1355.
(73) Esposito M, Edwards MJ, Bhatia KP, Brown P, Cordivari C. Idiopathic spinal myoclonus: a clinical and

neurophysiological assessment of a movement disorder of uncertain origin. *Mov Disord* 2009 Dec 15;24:2344-2349.

(74) Avanzino L, Martino D, van de Warrenburg BP, Schneider SA, Abbruzzese G, Defazio G, Schrag A, Bhatia KP, Rothwell JC. Cortical excitability is abnormal in patients with the "fixed dystonia" syndrome. *Mov Disord* 2008 Apr 15;23:646-652.

(75) Espay AJ, Morgante F, Purzner J, Gunraj CA, Lang AE, Chen R. Cortical and spinal abnormalities in psychogenic dystonia. *Ann Neurol* 2006 May;59:825-834.

(76) Rosenkranz K. Plasticity and intracortical inhibition in dystonia--methodological reconsiderations. *Brain* 2010 Jun;133:e146.

(77) Quartarone A., Rothwell J. Reply: Plasticity and intracortical inhibition in dystonia--methodological reconsiderations. *Brain* 2010 Jun;133:e147.

(78) Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. *Neurology* 1985 Jan;35:73-77.

(79) Schrag AE, Mehta AR, Bhatia KP, Brown RJ, Frackowiak RS, Trimble MR, Ward NS, Rowe JB. The functional neuroimaging correlates of psychogenic versus organic dystonia. *Brain* 2013 Mar;136:770-781.

(80) Hodges PW, Tucker K. Moving differently in pain: a new theory to explain the adaptation to pain. *Pain* 2011 Mar;152:S90-S98.

(81) Saito K, Konishi S, Otsuka M. Antagonism between Lioresal and substance P in rat spinal cord. *Brain Res* 1975 Oct 24;97:177-180.

(82) Bank PJ, Peper CE, Marinus J, Beek PJ, van Hilten JJ. Motor consequences of experimentally induced limb pain: A systematic review. *Eur J Pain* 2012 Jun 20;14:1460-1474.

(83) Proske U, Gandevia SC. The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. *Physiol Re*v 2012 Oct;92:1651-1697.

(84) Huge V, Lauchart M, Forderreuther S, Kaufhold W, Valet M, Azad SC, Beyer A, Magerl W. Interaction of hyperalgesia and sensory loss in complex regional pain syndrome type I (CRPS I). *PLoS One* 2008;3:e2742.

(85) Maier C, Baron R, Tolle TR, Binder A, Birbaumer N, Birklein F, Gierthmuhlen J, Flor H, Geber C, Huge V, Krumova EK, Landwehrmeyer GB, Magerl W, Maihofner C, Richter H, Rolke R, Scherens A, Schwarz A, Sommer C, Tronnier V, Uceyler N, Valet M, Wasner G, Treede RD. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 2010 Sep;150:439-450.

(86) Munts AG, van Rijn MA, Geraedts EJ, van Hilten JJ, van Dijk JG, Marinus J. Thermal hypesthesia in patients with complex regional pain syndrome related dystonia. *J Neural Transm* 2010 Dec 29.

(87) Mugge W, van der Helm FC, Schouten AC. Integration of sensory force feedback is disturbed in CRPS-related dystonia. *PLoS One* 2013;8:e60293.

(88) Galer BS, Butler S, Jensen MP. Case reports and hypothesis: a neglect-like syndrome may be responsible for the motor disturbance in reflex sympathetic dystrophy (Complex Regional Pain Syndrome-1). J *Pain Symptom Manage* 1995 Jul;10:385-391.

(89) Juottonen K, Gockel M, Silen T, Hurri H, Hari R, Forss N. Altered central sensorimotor processing in patients with complex regional pain syndrome. *Pain* 2002 Aug;98:315-323.