Summary

The research presented in this thesis are aimed on the assessment, the involvement of NMDA receptors and the value of NMDA receptor antagonists (in particular magnesium) in CRPS 1. In *chapter 1*, complaints, possible pathophysiological mechanisms and problems with the diagnosis and treatment of CRPS 1 are introduced, followed by the aim and outline of our thesis.

Chapter 2, 3 and 4 focus on measurement techniques to optimize the assessment of CRPS 1. In *chapter 2*, we present the consequences of the mixed use of different criteria for the diagnosis of CRPS 1. The Veldman et al., IASP and Bruehl et al. criteria, based on reportage and assessments of signs and symptoms by patients and physicians respectively, were compared in 372 outpatients suspected of having CRPS 1. Agreement in diagnosing CRPS 1 among the three sets was poor. In addition, significant differences in patient profiles between the criteria sets were found with regard to the number of patients reporting continuing disproportionate pain, a larger area affected than the initial trauma, increase of symptoms due to exercise, edema, temperature asymmetry, hyperesthesia, allodynia and hyperalgesia, and concerning physicians' observation of allodynia and hyperalgesia. The highest combined diagnostic values for the strongest cases of presence or absence of CRPS 1 were found for reported hyperesthesia, allodynia, observed color asymmetry, hyperesthesia, temperature asymmetry and edema. We concluded that the use of different diagnostic sets could lead to different numbers and subgroups of CRPS 1 patients. Explicit reference to diagnostic criteria used in studies, and registration of a broad variety of CRPS 1 features are needed to make subgroup phenotyping and post hoc analyses based on different diagnostic criteria possible.

In *chapter* 3, the development and reliability of a broad range CRPS 1 symptoms questionnaire; the TREND Symptom Inventory (TSI) are presented. The test-retest reliability was assessed on two identical questionnaires filled out within one week by 26 CRPS 1 and 42 fibromyalgia patients. The practical use and the content validity of the TSI were assessed using a short questionnaire, inquiring after the clarity of questions, response options and of the used terminology of the TSI. The TSI was shown to be valid and reliable for both CRPS 1 and fibromyalgia patients. Comparison of reported complaints by CRPS 1 and fibromyalgia patients demonstrated that a change in cold perception, discoloration, change in skin temperature, change in sweating behavior, change in the severity of edema during exercise, and trophic changes of skin were reported significantly more often by CRPS 1 patients, whereas complaints of the (upper and lower) back, constipation, urine retention, and

experiencing a dry mouth were reported significantly more often by fibromyalgia patients. Sensory complaints (except for change in cold perception), motor complaints, and visceral complaints (diarrhea and incontinence) were reported by both CRPS 1 and fibromyalgia patients. It was concluded that the TSI can be used in the evaluation of similarities and differences between CRPS 1 and fibromyalgia.

Chapter 4 describes the use of the Semmes Weinstein Monofilaments (SWM) to measure coetaneous sensibility in the feet. The reliability, normal reference scores and the stability, by determining systemic changes in sensory thresholds, of the SWM was assessed in the feet of 60 healthy subjects. Median interrater-reliability was assessed on five locations of the plantar side of both feet using monofilaments 1.65, 2.36, 2.44, 2.83, 3.22, 3.61, 3.84, 4.08, 4.31, 5.56, 6.65 by two or three investigators. Median intrarater-reliability and systematic changes in sensory thresholds were assessed three weeks later by one investigator. Median interrater-reliability for both feet was found to be poor to moderate, while good and poor to moderate median intrarater-reliability were found for respectively the left and right foot. Given the observed reliability of the SWM, a normal sensory score for the feet was situated between monofilament 3.22 and 4.08. Based on these findings we conclude that the SWM are reliable when measured by one researcher. Systematic changes in sensory thresholds were observed; therefore, we could not verify the stability of the SWM for use in prospective studies.

Chapter 5, 6, 7 and 8 address the involvement of NMDA receptors in the pathophysiology of CRPS 1 and the treatment of CRPS 1 with NMDA receptor antagonists. In *chapter 5*, the results of a qualitative immunohistochemistry analysis are presented. The expression of NMDA1, phosphorylated NMDA1 (pNMDA1), NMDA2B and NMDA2D receptor subtypes in skin obtained from the dorsum of the hand and forearm of six CRPS 1 patients, one CRPS 2 patient and control tissue from four cadavers were assessed. NMDA1 and pNMDA1 positive structures were found in the epidermis and external root sheath of hair follicles in both CRPS 1 and non-CRPS 1 hand tissues. In CRPS 1 hand tissue however, NMDA1 and pNMDA1 positive structures were also found in the epithelium of secretory units of sweat glands. Furthermore, sweat gland density appeared to be higher in CRPS 1 patients compared to controls. NMDA2D and NMDA2B were not detected in the hand and no positive NMDA structures were found in the forearm. These findings suggest that the increased expression of NMDA1 and pNMDA1 receptors found in sweat glands

of CRPS 1 hand tissue may contribute to sensory abnormalities experienced by CRPS 1 patients.

In *chapter 6,* a systematic evaluation of the literature regarding the efficacy of different NMDA receptor antagonists for the treatment of pain in different neuropathic pain conditions (including CRPS 1) is presented. PubMed (including MEDLINE), EMBASE and CENTRAL were searched up to October 26th, 2009 for randomized placebo controlled trials (RCTs) on neuropathic pain. The methodological quality of the included trials was independently assessed by two authors using the Delphi list. Fixed or random effects model were used to calculate the summary effect size using Hedges' g. Twenty-eight studies were included meeting the inclusion criteria. Summary effect sizes were calculated for subgroups of studies evaluating ketamine IV in CRPS, oral memantine in postherptic neuralgia and respectively ketamine IV and oral memantine in post-amputation pain, where a significant pooled effect was only found for treatment of post-amputation pain with ketamine IV. Based on this systematic review, no conclusions can yet be made about the efficacy of NMDA receptor antagonists on neuropathic pain. Additional RCTs in homogenous groups of pain patients are needed to explore the therapeutic potential of NMDA receptor antagonists in neuropathic pain.

Chapter 7 describes a blinded randomized pilot study on intravenous magnesium, an uncompetitive NMDA receptor antagonist, for the treatment of CRPS 1. Eight patients received 70 mg/kg magnesium sulphate infusions in four hours for five days. For blinding purposes, two patients received equal amount NaCl 0.9% solutions. Interventions were accompanied by standardized physical therapy. Pain was assessed using an 11-point Box scale (three times daily for a week) and the McGill Pain Questionnaire. Skin sensitivity was measured with the SWM, (other) impairments with the Impairment level Sum Score. In addition, functional limitations (Radboud Skills Questionnaire, questionnaire rising and sitting down) and quality of life (Short Form-36, EuroQol) were evaluated. Assessments were performed at baseline, 1, 3, 6, and 12 weeks after intervention. Mild systemic side effects were experienced and the infusions were locally well tolerated. Pain was significantly reduced at all follow up compared with baseline. The McGill sensory subscale number of words chosen and pain rating index improved significantly at T1. Impairment level and quality of life were significantly improved at T12. No improvement was found for skin sensitivity and functional limitations. It was concluded that the findings of this

pilot study are encouraging and that magnesium IV as a treatment in CRPS 1 should be further explored in a large size formal trial design.

In *chapter 8* the results are presented of a study in which the relationship between differences in individual response to intravenous magnesium treatment and differences in magnesium status of CRPS 1 patients is investigated. In 25 CRPS 1 patients meeting the IASP diagnostic criteria, magnesium status was obtained with the magnesium retention test. Using this test it was calculated how much of the 0.56 mmol/kg intravenously administered magnesium was retained by the patient. Patients with magnesium retention of more than 29% were considered magnesium deficient. Pain reduction was measured on an 11-point Box scale (three times daily for a week) and the McGill pain questionnaire at baseline, and at 1 and 3 weeks after the intervention. Median percentage of retained magnesium was 26% IQR 14-35%, whereby twelve patients were considered magnesium deficient. Median box pain and McGill scores at baseline and follow-up did not differ significantly between deficient and non-deficient patients. However, for the magnesium deficient patients a significantly longer duration of pain reduction was observed and more subscales of the McGill questionnaire were improved compared to non-deficient patients. The high percentage of patients considered magnesium deficient in our sample of CRPS 1 patients provide an indication for deficiency in magnesium accessibility in a subgroup of patients, possibly leading to prolonged sensitization of nociceptors and/or increased inflammatory response observed in CRPS 1. Indications with regard to a relationship between magnesium status and the occurrence of sensory symptoms, and differing response to treatment with magnesium should be evaluated further.

In *Chapter 9*, the main findings of this thesis are discussed, and suggestions for further research are presented.