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## **Sex, quality of life and brain function in complex regional pain syndrome**

Velzen, G.A.J. van

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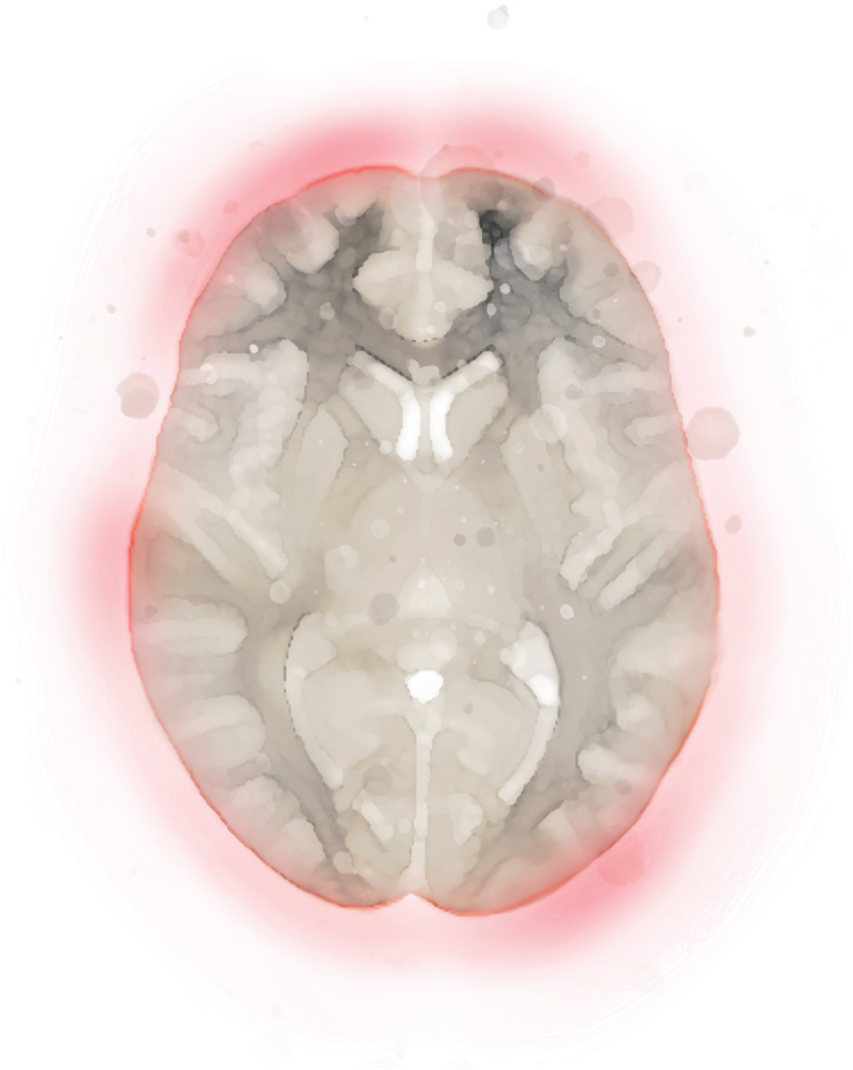
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# Sex, quality of life and brain function in Complex Regional Pain Syndrome

G.A.J. van Velzen



**SEX, QUALITY OF LIFE AND BRAIN  
FUNCTION IN COMPLEX REGIONAL PAIN  
SYNDROME**

**G.A.J. van Velzen**

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Sex, quality of life and brain function in Complex Regional Pain Syndrome

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# Chapter 1

## **General introduction and aims**



# CLINICAL CHARACTERISTICS

Complex regional pain syndrome (CRPS) is a severely disabling pain syndrome characterized by autonomic, sensory, trophic and motor disturbances of the affected limb. In the initial stage, the affected limb of a patient is very painful, swollen, red and warm and shows changes in hair and nail growth. In the course of the syndrome these inflammatory and trophic signs can subside, but pain including allodynia, decreased temperature and motor disturbances of the affected limb can persist and even progress to adjacent or distant limbs<sup>1</sup>.

Two CRPS subtypes are being recognised based on possible nerve damage; CRPS type 1 without obvious nerve damage (formerly known as reflex sympathetic dystrophy) and CRPS type 2 with definitive nerve damage (formerly known as causalgia). In this thesis we will focus on patients with CRPS type 1. To date, due to the lack of definitive biomarkers, the diagnosis is made on clinical signs and symptoms using the International Association for the Study of Pain (IASP) Budapest research or clinical criteria<sup>2</sup> (table 1).

**Table 1**

| IASP Budapest criteria for CRPS                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1                                                                       | Continuing pain, which is disproportionate to any inciting event                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 2                                                                       | Symptoms: <ul style="list-style-type: none"> <li>• Sensory: Reports of hyperesthesia and/or allodynia</li> <li>• Vasomotor: Reports of temperature asymmetry and/or skin colour changes/asymmetry</li> <li>• Sudomotor/edema: Reports of edema and/or sweating changes/asymmetry</li> <li>• Motor/Trophic: Reports of decreased range of motion and/or motor disfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)</li> </ul>                                                                                       |
| 3                                                                       | Signs: <ul style="list-style-type: none"> <li>• Sensory: Evidence of hyperalgesia and/or allodynia (to light touch/temperature sensation/deep somatic pressure/joint movement)</li> <li>• Vasomotor: Evidence of temperature asymmetry (&gt;1°C) and/or skin colour changes/asymmetry</li> <li>• Sudomotor/Edema: Evidence of edema and/or sweating changes/asymmetry</li> <li>• Motor/Trophic: Evidence of decreased range of motion and/or motor disfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)</li> </ul> |
| 4                                                                       | There is no other diagnosis that better explains the signs and symptoms.                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Clinical criteria: three symptoms and two signs in different categories |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Research criteria: four symptoms and two signs in different categories  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

## EPIDEMIOLOGY

The incidence ranges from 5.5 to 26.2 per 100,000 person years, with the highest incidence rates occurring between 61 and 70 years. Arms are more often affected than legs (3:2) and females are affected 3–4 times more often than men<sup>3,4</sup>. The prognosis is worrisome. In a recent prospective study, 25% percent of patients (n=59) still fulfilled the strict Budapest research criteria at one year follow up<sup>5</sup>. In line with these findings, Beerthuizen<sup>6</sup> reported that none of the 205 CRPS patients (fulfilling the previous IASP criteria known as the Orlando criteria<sup>7</sup>) were symptom-free after 1 year and De Mos<sup>8</sup> found that the majority of patients had persistent impairments after 2 years. In addition, 64% of the patients continued to meet the Orlando criteria after almost 6 years.

### *Quality of life*

Not depicted in the epidemiological data but equally worrisome is the impact of the syndrome on health-related quality of life (HRQoL, in short QoL). HRQoL encompasses those aspects of overall quality of life that can be clearly shown to affect health, either physical or mental<sup>9</sup>. It includes different domains such as physical and mental health perceptions, functional status, social support and socioeconomic status<sup>9</sup>. Previous studies in CRPS reported poor QoL due to high levels of disability, chronic pain and motor disturbances, making patients unable to (fully) take part in the most basic parts of today's life: family relations, work and education<sup>10</sup>. However, these data are derived from studies with small sample sizes or selection bias, which renders the generalizability of the findings difficult<sup>11–15</sup>.

### *Sex differences*

To date, little is known about possible sex-differences in CRPS other than the disparity in incidence. Studies in the general population reported that women have more severe levels of pain, longer disease duration, more affected regions of the body<sup>16</sup> and more often neuropathic pains<sup>17</sup>. Many hypotheses have been postulated for these apparent sex effects including; hormonal differences, less effective endogenous pain modulatory mechanisms such as decreased *diffuse noxious inhibitory controls* (pain induced in distant body parts elicit analgesia), increased susceptibility to allodynia and secondary hyperalgesia as well as psychological and social factors<sup>18</sup>. Across the studies, however, the results are inconclusive and often contradictory<sup>18,19</sup>.

## PATHOPHYSIOLOGY

### *Aberrant inflammation and endothelial dysfunction*

The pathophysiology of CRPS is multifactorial: In the acute phase after tissue damage due to a traumatic event, a combination of classic and neurogenic inflammation is initiated. The

classic inflammation is thought to be mediated by T-lymphocytes and mast cells, resulting in the release of proinflammatory cytokines such as interleukine-1 $\beta$ , -2, -6 and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ )<sup>20-23</sup>. The neurogenic inflammation is induced by affected nociceptive fibers, resulting in the release of neuropeptide mediators such as substance P, calcitonin gene-related peptide (CGRP) and bradykinin<sup>24,25</sup>. Together these mediators induce vasodilation, increased vascular permeability and increased protein extravasation which clinically reflects the classic signs of calor (elevated temperature), tumor (swelling) and rubor (red colour) of the affected limb. However, later in the course of the disease when the initial inflammation subsides, the vasomotor signs can alter significantly: The affected limb often becomes cold and bluish due erroneous vasoconstriction. The vasoconstriction is likely mediated by a combination of endothelial dysfunction<sup>26,27</sup> and peripheral adrenergic receptor upregulation<sup>28</sup>. This in turn leads to local tissue hypoxia which is thought to account for the trophic signs of CRPS<sup>29</sup>.

### *Involvement of the central nervous system*

The proinflammatory neuropeptides that are released during neurogenic inflammation reduce the thermal and mechanical thresholds of peripheral nociceptive fibers and increase their firing rate<sup>30,31</sup>. This is called peripheral sensitisation and accounts for another characteristic sign of CRPS, namely hyperalgesia. Hyperalgesia is the term for increased pain perception of a painful stimulus. Furthermore, the peripheral neurogenic inflammation also induces activation of spinal cord based glial cells<sup>32-34</sup>. The latter is associated with upregulation of N-methyl-D-aspartic-acid (NMDA) receptors of spinal nociceptive neurons and a loss of function of intraneuronal circuits mediating inhibition<sup>35,36</sup>. Lastly, some data suggest an additional reduced supraspinal modulation of nociceptive input based on differential activation of subcomponents of the endogenous pain modulatory system<sup>37</sup>. Collectively, this culminates in increased excitability of the spinal cord which is called central sensitization. Central sensitization is clinically identifiable as allodynia: a non-painful stimulus is perceived as painful<sup>24,25</sup>.

Next, central sensitization is seen as the driving force of aberrant neuroplasticity in the spinal cord and brain. In the brain this neuroplasticity is depicted by cortical sensorimotor reorganization of the affected limb<sup>38-40</sup>, changes in local grey matter volume<sup>41-44</sup>, altered cortical activity patterns in rest<sup>45</sup> and alterations in cortical excitability and inhibition<sup>46,47</sup>. Many of these changes are assumed to underlie the clinical observations of altered central processing of sensory stimuli<sup>48-51</sup> and motor control<sup>52-54</sup>. Unfortunately, many of the reported findings are inconsistent in terms of spatial or quantitative measures and correlations with clinical features. In addition, the nature of movement disorders in CRPS has been a source of debate. Although evidence has been published suggesting a mismatch between aberrant afferent signals and the internal sensory representation of a limb as the source of motor disturbances<sup>55-57</sup> many clinicians consider CRPS movement disorders as functional movement

disorders<sup>58</sup> due to their clinical similarities; functional movement disorders are movement disorders that lack an organic substrate and are associated with psychological stressors<sup>59,60</sup>, peripheral trauma, pain and fixed postures<sup>59-62</sup>.

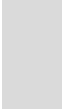
To further substantiate this rationale, studies should investigate neurophysiological characteristics between patients with CRPS and functional movement disorders. Conventional neurophysiological tests are unable to reliably differentiate between ‘organic’ and ‘functional’ movement disorders<sup>63</sup>. However, studies on specific cortical excitability measures during motor tasks show promising results in differentiating both groups. In functional paresis a dissociation in motor cortical excitability was seen between explicit, voluntary tasks and implicit automatic motor tasks<sup>64-66</sup>. This dissociation was regarded as the result of interference from other, possibly limbic, brain areas in line with the established rationale of psychological stressors as the source of functional movement disorders. The question therefore is, if this approach may shed new light on the nature of CRPS associated movement disorders.

### *Aims and outline of this thesis*

This thesis is divided in two parts. In the first part (chapter 2 and 3) we evaluate health-related quality of life (QoL) and possible sex differences in CRPS using data of The Netherlands’ database of CRPS patients. More specifically, in chapter 2 we investigate the influence of sex, pain, pain duration, and type of affected limb on quality of life. These data are important since many patients struggle with pain and disabilities years after the first diagnosis and a cure is not yet in sight. Insights into factors that may play a role in QoL of patients with CRPS may contribute to more tailored treatment approaches.

In chapter 3 we study possible differences in the way CRPS expresses between the sexes: Are there differences in terms of pain, disability and psychological factors between both sexes? Potential differences may be rooted in basic biological differences, as well as in cultural and socioeconomic factors. If so, these sex differences potentially may require differential treatment approaches.

In part two (chapter 4, 5 and 6) the aim is to evaluate if CRPS is associated with changes in the brain. More specifically, in chapter 4 we search for CRPS-specific and relevant changes in brain function in rest using multiple modalities of magnetic resonance imaging (MRI) of the brain. In addition, we compare our results with those published in literature and evaluate the current evidence for specific, clinically relevant changes in brain structure and function in rest in CRPS. This is relevant since some therapies are based on the presumptive changes in brain structure and function.



In chapter 5 we focus on brain activation in response to a painful stimulus administered to the affected arm of CRPS patients and the right hand of healthy controls to better understand the networks involved in somatosensory, motor and behavioural processing.

Lastly, in chapter 6, we focus on the (dis)similarities of CRPS movement disorders with functional movement disorders by using Transcranial Magnetic Stimulation (TMS) during motor imagery. Motor imagery is the neuronal correlate of motor activity without the actual execution of the movement itself. Using this method, we aim to evaluate if cortical brain activations in CRPS are similar to those previously reported in functional movement disorders.

Chapters 7 (With Dutch translation) provides a summary of the main conclusions, a general discussion of the results and suggestions for further research.

# Chapter 2

# Health-related quality of life in 975 patients with complex regional pain syndrome type 1

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## ABSTRACT

There are limited data available on health-related quality of life (QoL) in patients with complex regional pain syndrome (CRPS). In the present study we examined QoL in 975 CRPS patients attending 6 different clinics in the Netherlands. QoL was assessed using the MOS 36-Item Short-Form Health Survey (SF-36) with the Mental Health Summary Score (MHS) and the Physical Health Summary Score (PHS) as dependent variables. The influences of gender, type of affected limb, disease duration, pain scores, CRPS severity and set of diagnostic criteria used were investigated. We found the lowest scores of QoL in the physical domains of the SF-36, with lower-limb CRPS patients reporting poorer results than patients with an affected upper limb. Influence of gender on QoL was not observed, and correlations of QoL with disease duration and the CRPS severity score were weak. Pain correlated moderately with QoL. In addition, patients fulfilling stricter diagnostic criteria (ie, the Budapest criteria) had lower QoL scores than patients fulfilling less strict criteria (ie, the Orlando criteria). We conclude that loss of QoL in CRPS patients is due mainly to reduced physical health. A comparison with data available from the literature shows that CRPS patients generally report poorer QoL than patients with other chronic pain conditions, particularly in the physical domains. Pain correlated moderately with QoL and therefore deserves ongoing attention by physicians. Finally, patients meeting the diagnostic Budapest criteria have lower QoL scores than patients meeting the Orlando criteria, highlighting the impact of different sets of criteria on population characteristics.

# INTRODUCTION

Complex regional pain syndrome (CRPS) is a condition that may have a profound effect on daily life, often invalidating patients for many years<sup>67,68</sup>. Typically, CRPS develops after a trauma to 1 of the limbs, but occasionally progresses to other limbs<sup>69–71</sup>. In the acute phase, patients report intense pains accompanied by autonomic, trophic and motor disturbances of the affected limb<sup>1</sup>. A considerable number of patients develop a chronic course in which autonomic signs are usually less pronounced and pain, along with sensory and motor disturbances predominates<sup>13</sup>. The incidence ranges from 5.5 to 26.2 per 100,000 person-years<sup>4,72</sup>, with the highest incidence rates occurring between 61 and 70 years and with females being affected 3 to 4 times more often than men<sup>4</sup>.

Although, in recent years, considerable progress has been made in the understanding of the pathophysiology of CRPS<sup>1</sup>, this has not translated into an effective therapy from which all patients benefit; a large group of patients experience incomplete recovery and are confronted with long-term disability and partial or complete inability to resume their former jobs<sup>10,73</sup>.

It is self-evident that such disease consequences may have grave impact on the lives of CRPS patients. Indeed, previous studies on quality of life (QoL) of CRPS patients reported high levels of disability, continuing pain and motor disturbances. However, these studies were usually performed in small samples<sup>11–14</sup> or involved patients in trials who had to meet certain eligibility criteria, which affected the generalizability of the findings<sup>14,15</sup>. In the present study we therefore analysed the QoL data of almost a 1000 Dutch patients collected over the past 10 years in 5 major CRPS clinics. Specifically, we studied the influence of gender, type of involved extremity (upper or lower), disease duration and pain on perceived QoL.

In addition we studied the influence of diagnostic criteria on QoL, as the profile of signs and symptoms differs according to the diagnostic criteria the patient fulfils<sup>74</sup>, whereas QoL may vary with perceived complaints. Lastly, we included the CRPS severity score, a recently developed severity index that counts the number of the patient's signs and symptoms, to study the relationship between the number of occurring signs and symptoms and perceived QoL<sup>75</sup>.

## METHODS

### *Participants*

Patients were recruited from 5 pain clinics and one department of neurology of university hospitals participating in TREND (short for Trauma RElated Neuronal Dysfunction, a

Dutch knowledge consortium that integrates research on CRPS; [www.trendconsortium.nl](http://www.trendconsortium.nl)). All patients were 18 years or older; fulfilled either the diagnostic criteria for CRPS adopted at the 1993 consensus conference ('Orlando criteria')<sup>7</sup>, the Budapest clinical (Bdp-c) or the Budapest research (Bdp-r) criteria<sup>75</sup>; and did not have any other conditions that could account for the signs and symptoms encountered. Exclusion was made at the presence of dementia, cognitive impairment or any other kind of inability to understand and to complete self-assessment questionnaires.

### *Assessment methods and measurement instruments*

Methods of examining patients were standardised across centres by the use of a universally applied measurement protocol and 3-monthly plenary training sessions. Signs and symptoms were recorded on a standard score sheet. Patients also completed a set of questionnaires. All data were stored in a NEN-7511 certified, central web-based data management system (ProMISe©). Written informed consent was obtained from all participants, procedures were in accordance with the Declaration of Helsinki, and the protocol was approved by the medical ethical committees of all participating centres.

We classified patients in 3 groups to examine the influence of the involved limb on QoL; 1 upper limb affected, 1 lower limb affected and more than 1 limb affected. To evaluate the influence of diagnostic criteria on perceived QoL, we allocated patients to the most strict criterion they met (Orlando < Bdp-c < Bdp-r).

The Dutch version of the Medical Outcomes Study Short Form 36 (SF-36) was used as outcome measure of QoL in this study<sup>76</sup>. This generic questionnaire consists of 8 health domains: 1) limitations in *Physical Functioning*; 2) limitations in usual role activities due to physical problems (*Role Physical*); 3) *Bodily Pain*; 4) *General Health* perceptions; 5) *Vitality*; 6) limitations in *Social Functioning* due to physical problems; 7) limitations in usual role activities due to emotional problems (*Role Emotional*) and 8) general *Mental Health*. For the main analysis, the Physical Health sum Score (PHS) (mean of domains 1-4) and the Mental Health sum Score (MHS) (mean of domains 5-8) were used. Scores are presented as percentages (0-100), with higher scores indicating better QoL.

Pain was quantified using the pain rating index of the McGill Pain Questionnaire<sup>77</sup> and the Numeric Rating Scale. The McGill Pain Questionnaire consists of 20 categories of 3 or 4 rank ordered words that evaluate different aspects of pain (range 0-63; higher scores indicating more pain). For the Numeric Rating Scale score, we asked patients to rate the average pain intensity of the previous week on a scale from 0 to 10, with 10 reflecting the worst pain imaginable.

As an indicator of severity of CRPS, we used the CRPS Severity Score, a checklist consisting of 17 CRPS associated signs and symptoms<sup>75</sup>.

The following questionnaires were not used in the primary analyses of this study, but were included to provide a broader perspective on the mental and physical health of patients: The Hospital Anxiety and Depression Scale<sup>78</sup>; the Radboud Skills Questionnaire<sup>79</sup>; and the Questionnaires on Walking and Rising<sup>80,81</sup>. The Hospital Anxiety and Depression Scale measures the presence and severity of mood disorders (range 0–42, with higher scores indicating more severe anxiety or depression); in the present study, the mean Anxiety and Depression scores of this questionnaire were used. The Radboud Skills Questionnaire measures the difficulty that patients with an affected upper limb perceive when performing manual activities of daily life (range 1–5, with higher scores indicating worse functioning). The Questionnaires on Walking and Rising measures limitations in walking and rising in patients with an affected lower limb (range, 0–30; summary score of ‘walking inside’, ‘walking outside’ and ‘rising’, with higher scores indicating worse functioning; because of the different number of items in these three scales, all scores were first transformed to a 0–10 scale and next summed).

### *Statistics*

All statistical analyses were performed with IBM® SPSS® Statistics version 20 (IBM Corporation). Normality of the data was checked by inspecting histograms of frequency distributions, normal probability plots, residual scatter plots and the Kolmogorov-Smirnov test. Data were considered statistically significant when P values were less than .05 and corrected for multiple comparisons (Bonferroni) when multiple analyses were performed within the same research question.

For the difference in QoL scores between sexes the independent t-test was used, and an Analysis of Variance (ANOVA) was carried out to examine the influence of type of limb or CRPS criteria on QoL. The Pearson correlation coefficient was calculated to examine the correlation between QoL and age, disease duration, symptom severity or pain. Coefficients of 0.70 or higher were classified as strong, those 0.30–0.69 as moderate and those less than 0.30 as weak<sup>82</sup>. Data are presented as mean scores  $\pm$  standard deviations (SD).

## **RESULTS**

### *Study participants*

A total of 975 patients (age:  $46.8 \pm 14.3$  years; 817 female) were included in the analysis, of whom 374 (38.4%) had an affected upper limb and 408 (41.8%) had an affected lower limb (Table 1). In 193 (19.8%) patients more than one limb was affected: 28 (2.8%) patients had

2 affected upper limbs, 25 (2.6%) had 2 affected lower limbs, and the remaining 140 (14.4%) had a combination of an affected upper and lower limb (n=53; 5.4%) or more than 2 affected limbs (n=87; 8.9%). Mean disease duration was  $4.73 \pm 6.64$  years. All 975 patients fulfilled the Orlando criteria, while 697 (71.5%) met the Bdp-c and 447 (45.8%) the Bdp-r criteria.

**Table 1**

| Demographic and clinical characteristics of study patients. |                  |
|-------------------------------------------------------------|------------------|
| N (% females)                                               | 975 (83.9)       |
| Mean (SD) age, years                                        | 46.8 (14.3)      |
| Mean (SD) age at onset, years                               | 42.1 (15.6)      |
| Median (IQR) disease duration, years                        | 1.8 (0.4–6.7)    |
| Employed / unemployed / retired / missing %                 | 51 / 28 / 9 / 12 |
| N 1 arm / 1 leg / >1 limb                                   | 374 / 408 / 193  |
| Fulfilling only Orlando criteria (%)                        | 975 (100)        |
| Fulfilling Bdp-c criteria (%)                               | 697 (71.5)       |
| Fulfilling Bdp-r criteria (%)                               | 447 (45.8)       |
| CRPS Severity Score, median (IQR)                           | 11.0 (8–13)      |
| Hospital Anxiety and Depression Scale, mean (SD)            |                  |
| Anxiety                                                     | 6.17 (3.8)       |
| Depression                                                  | 4.93 (3.8)       |
| McGill Pain Questionnaire, mean (SD)                        | 25.50 (11.7)     |
| Walking and Rising Questionnaire, mean (SD)                 | 18.73 (7.7)      |
| Radboud Skills Questionnaire SQ, mean (SD)                  | 3.05 (0.9)       |
| SF-36                                                       |                  |
| Physical Health Summary score, mean (SD)                    | 34.9 (18.0)      |
| Physical Functioning, mean (SD)                             | 41.4 (26.1)      |
| Role Physical, mean (SD)                                    | 18.1 (30.7)      |
| Bodily Pain, mean (SD)                                      | 27.5 (20.5)      |
| General Health, mean (SD)                                   | 52.1 (21.7)      |
| Mental Health Summary score, mean (SD)                      | 58.4 (21.1)      |
| Vitality, mean (SD)                                         | 47.3 (19.9)      |
| Social Functioning, mean (SD)                               | 58.9 (26.8)      |
| Role Emotional, mean (SD)                                   | 60.2 (44.3)      |
| Mental Health, mean (SD)                                    | 67.1 (18.4)      |

Bdp-c = Budapest clinical criteria; Bdp-r = Budapest research criteria; IQR = interquartile range; SD = standard deviation; SF-36 = MOS 36-Item Short-Form Healthy Survey.

The results of the Numeric Rating Scale, McGill Pain Questionnaire, Hospital Anxiety and Depression Scale, CRPS severity score, Radboud Skills Questionnaire and questionnaires on Walking and Rising are listed in table 1.

### *General results of the SF-36*

The SF-36 scores were substantially lower in the physical domains, in particular, in *Role Physical* and *Bodily Pain* sections, in comparison to the mental domains (Table 1).

### *QoL and gender differences*

No difference in gender was found for the PHS ( $t(973)=0.728$ ,  $p=.47$ ), the MHS ( $t(973)=-.43$ ,  $p=.67$ ), or for any of the subdomains, although a trend was seen for *Vitality* ( $t(965)=2.81$ ,  $p=.005$ ) which just did not survive the correction for multiple comparisons (Table 2).

**Table 2** SF-36 scores according to gender

| SF-36 domains                    | Male                | Female              | p-value (sig.<0.005) |
|----------------------------------|---------------------|---------------------|----------------------|
| Physical functioning             | 45.88 (26.2)        | 40.49 (25.8)        | .018                 |
| Role physical                    | 16.34 (30.5)        | 18.48 (30.8)        | .429                 |
| Bodily pain                      | 28.27 (22.2)        | 27.36 (20.2)        | .608                 |
| General health                   | 52.45 (22.0)        | 52.00 (21.6)        | .815                 |
| <i>Physical health sum score</i> | <i>35.86 (17.1)</i> | <i>34.71 (18.2)</i> | <i>.467</i>          |
| Vitality                         | 51.38 (21.0)        | 46.50 (19.6)        | .005                 |
| Social functioning               | 59.89 (25.6)        | 58.79 (27.0)        | .639                 |
| Role emotional                   | 54.08 (45.0)        | 61.44 (44.1)        | .059                 |
| Mental health                    | 65.21 (19.3)        | 67.44 (18.2)        | .165                 |
| <i>Mental health sum score</i>   | <i>57.72 (20.9)</i> | <i>58.51 (21.1)</i> | <i>.669</i>          |

SF-36 = MOS 36-Item Short-Form Healthy Survey. Numbers represent means (standard deviations); Domains were considered statistically different when p-value < 0.005 (Bonferroni corrected 0.05).

### *QoL and affected limb*

Although no difference in MHS score was found between patients with 1 affected upper limb, 1 affected lower limb, or more than 1 affected limb ( $F(2,972)=1.84$ ,  $p=.042$ ) (Bonferroni-corrected p-value,  $p<.017$ ), analysis of the constituting domain scores indicated differences in *Vitality* (with patients with multiple affected limbs reporting lower scores than both other groups) and *Social Functioning* (with patients with an affected upper limb reporting higher scores than both other groups), but not in *Role Emotional* or *Mental Health* (table 3).

For the PHS a significant difference between the groups was found ( $F(2,972)=36.86$ ,  $p<.001$ ). Post-hoc analysis showed worse scores for patients with an affected lower limb in comparison to patients with an affected upper limb, with the lowest scores being found for

patients who had more than 1 affected limb. In addition, significant differences were found for all physical domain scores except *Role Physical*, with patients who had multiple affected limbs reporting lower scores than patients with 1 affected upper limb, but not than those with 1 affected lower limb.

**Table 3** SF-36 scores of patients classified according to type of affected limbs.

| SF-36 domains                    | 1<br>1 upper limb                  | 2<br>1 lower limb                  | 3<br>>1 limb                       | Omnibus p value |
|----------------------------------|------------------------------------|------------------------------------|------------------------------------|-----------------|
| Physical functioning             | 57.85 (21.5) <sup>2,3</sup>        | 32.55 (22.6) <sup>1</sup>          | 28.23 (24.5) <sup>1</sup>          | <.001           |
| Role physical                    | 16.62 (29.1)                       | 20.12 (32.0)                       | 16.88 (31.2)                       | .237            |
| Bodily pain                      | 29.62 (22.2) <sup>3</sup>          | 27.44 (19.4)                       | 23.55 (19.0) <sup>1</sup>          | .004            |
| General health                   | 56.35 (21.4) <sup>3</sup>          | 53.06 (20.9)                       | 41.70 (20.4) <sup>1</sup>          | <.001           |
| <i>Physical health sum score</i> | <i>40.33 (17.4) <sup>2,3</sup></i> | <i>33.36 (17.2) <sup>1,3</sup></i> | <i>27.62 (17.7) <sup>1,2</sup></i> | <i>&lt;.001</i> |
| Vitality                         | 50.26 (20.4) <sup>3</sup>          | 47.20 (19.3) <sup>3</sup>          | 41.75 (19.2) <sup>1,2</sup>        | <.001           |
| Social functioning               | 65.39 (25.2) <sup>2,3</sup>        | 54.98 (26.7) <sup>1</sup>          | 54.97 (27.8) <sup>1</sup>          | <.001           |
| Role emotional                   | 59.67 (44.0)                       | 59.11 (44.6)                       | 63.70 (44.2)                       | .477            |
| Mental health                    | 66.88 (18.5)                       | 66.41 (18.4)                       | 68.89 (18.2)                       | .293            |
| <i>Mental health sum score</i>   | <i>60.53 (21.5)</i>                | <i>56.93 (20.5)</i>                | <i>57.30 (21.4)</i>                | <i>.042</i>     |

SF-36 = MOS 36-Item Short-Form Healthy Survey. Numbers represent means (standard deviations); Domains were considered statistically different when p-value <.005 (Bonferroni corrected .05) Numbers in superscript indicating significant differences with other groups (p<0.017) for the same domain.

No significant differences in MHS or PHS were found between patients with 1 or 2 affected upper or lower limbs (all four P-values >.06).

### *QoL, disease duration and age*

Correlations between of disease duration and age and with the various summary and domain scores were all weak (table 4). When we divided the patients in 3 approximately equal age-groups, namely  $\leq 40.0$ ,  $40.1-55.0$ ,  $\geq 55.1$  years, it was apparent that the oldest CRPS patients had the highest PHS scores ( $32.73 \pm 16.53$ ,  $33.99 \pm 17.62$ ,  $38.33 \pm 19.47$ , respectively) ( $F(2,974)=8.24$ ,  $p<.001$ ) and the highest MHS scores ( $57.17 \pm 20.24$ ,  $56.68 \pm 21.77$ ,  $61.80 \pm 20.74$ , respectively) ( $F(2,974)=5.56$ ,  $p=.004$ ). Post-hoc analysis showed that only *Bodily Pain* (from the PHS) and *Vitality* (from the MHS) were significantly related to age.

### *QoL and pain*

Correlations with the Numeric Rating Scale or McGill Pain Questionnaire were generally higher for the physical domains scores than for the mental domain scores, with the physical domain scores mostly showing moderate correlations with pain ratings. The highest correlations were found with the *Bodily Pain* scale (table 4).

**Table 4** Matrix showing correlations between QoL and other variables

| SF-36 domains                    | Age            | Disease duration | NRS              | MPQ              | Severity score   |
|----------------------------------|----------------|------------------|------------------|------------------|------------------|
| Physical functioning.            | 0.085          | -0.185 **        | -0.374 **        | -0.365 **        | -0.109 *         |
| Role physical                    | 0.029          | 0.094 *          | -0.275 **        | -0.273 **        | -0.136 **        |
| Bodily pain                      | 0.118 **       | 0.025            | -0.600 **        | -0.472 **        | -0.161 **        |
| General health                   | 0.085          | -0.238 **        | -0.296 **        | -0.293 **        | -0.039           |
| <i>Physical health sum score</i> | <i>0.111 *</i> | <i>-0.095 *</i>  | <i>-0.514 **</i> | <i>-0.472 **</i> | <i>-0.158 **</i> |
| Vitality                         | 0.205 **       | -0.122 **        | -0.305 **        | -0.392 **        | -0.086           |
| Social functioning               | 0.090          | -0.036           | -0.320 **        | -0.419 **        | -0.060           |
| Role emotional                   | -0.014         | 0.116 **         | -0.157 **        | -0.188 **        | -0.021           |
| Mental health                    | 0.049          | 0.055            | -0.204 **        | -0.275 **        | -0.026           |
| <i>Mental health sum score</i>   | 0.080          | 0.032            | -0.302 **        | -0.382 **        | -0.056           |

MPQ = McGill pain questionnaire; NRS = numeric rating scale; QoL = quality of life; SF-36 = MOS 36-Item Short-Form Health Survey. Pearson's correlation was considered significant when \* $r = P < .005$ , \*\* $r = P < 0.001$

**Table 5** SF-36 scores of patients classified according to strictest criteria they fulfilled

| SF-36 domains                    | 1<br>Orlando                       | 2<br>Bdp-c                       | 3<br>Bdp-r                       | Omnibus<br>p value |
|----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------|
| Physical functioning             | 47.94 (26.2) <sup>3</sup>          | 42.36 (25.3) <sup>3</sup>        | 36.75 (25.5) <sup>12</sup>       | <.001              |
| Role physical                    | 26.01 (35.9) <sup>2,3</sup>        | 16.70 (29.7) <sup>1</sup>        | 14.09 (26.8) <sup>1</sup>        | <.001              |
| Bodily pain                      | 34.96 (22.9) <sup>2,3</sup>        | 25.97 (19.6) <sup>1</sup>        | 23.72 (18.1) <sup>1</sup>        | <.001              |
| General health                   | 56.28 (22.2) <sup>3</sup>          | 51.74 (21.4)                     | 49.66 (21.2) <sup>1</sup>        | <.001              |
| <i>Physical health sum score</i> | <i>41.37 (20.3) <sup>2,3</sup></i> | <i>34.48 (17.7) <sup>1</sup></i> | <i>31.11 (15.4) <sup>1</sup></i> | <i>&lt;.001</i>    |
| Vitality                         | 51.87 (20.1) <sup>2,3</sup>        | 46.25 (19.7) <sup>1</sup>        | 45.05 (19.5) <sup>1</sup>        | <.001              |
| Social functioning               | 65.53 (27.3) <sup>2,3</sup>        | 58.24 (26.5) <sup>1</sup>        | 55.30 (26.0) <sup>1</sup>        | <.001              |
| Role emotional                   | 67.04 (42.3) <sup>2</sup>          | 55.74 (44.8) <sup>1</sup>        | 58.54 (44.8)                     | .009               |
| Mental health                    | 68.47 (18.1)                       | 66.51 (19.1)                     | 66.55 (18.7)                     | .337               |
| <i>Mental health sum score</i>   | <i>63.21 (20.9) <sup>2,3</sup></i> | <i>56.61 (21.3) <sup>1</sup></i> | <i>56.38 (20.6) <sup>1</sup></i> | <i>&lt;.001</i>    |

SF-36 = MOS 36-Item Short-Form Healthy Survey. Numbers represent means (standard deviations); Domains were considered statistically different when p-value <.005 (Bonferroni corrected 0.05) Numbers in superscript indicating significant differences with other groups ( $p < 0.017$ ) for the same domain.

### QoL and symptom severity

The CRPS severity score for patients affected in one limb significantly correlated with the PHS ( $r = -0.16$ ,  $p < .001$ ) but not with the MHS ( $r = -0.06$ ,  $p = 0.13$ ) (table 4). Post-hoc analysis showed that the strongest correlations were found for *Physical Functioning*, *Role Physical* and *Bodily Pain*. However, when the patient group was divided in subgroups based on the set of CRPS criteria they fulfilled, correlations were no longer significant.

### *QoL and CRPS criteria*

Table 5 shows the data of the MHS and PHS for patients meeting the different sets of diagnostic criteria. A significant difference between the groups emerged for MHS ( $F(2,972)=10.4$ ,  $p<.001$ ) and PHS ( $F(2,972)=29.6$ ,  $p<.001$ ), with the post-hoc analysis showing a significantly higher MHS and PHS for the Orlando group than the Bdp-c or Bdp-r group, while no difference was found between both Budapest groups.

## DISCUSSION

This study examined QoL in a large group of almost a 1000 Dutch patients with CRPS. We observed the following: 1) QoL in CRPS patients was mostly determined by the loss of physical capabilities, and less so by mental complaints; 2) no gender differences in QoL of patients with CRPS; were found 3) CRPS patients with an affected lower limb have worse PHS scores than patients with an affected upper limb; 4) pain intensity is moderately associated with both the PHS and MHS of the SF-36 in CRPS; 5) correlations between QoL and symptom severity were weak for the PHS, and absent for the MHS; and 6) patients meeting the Budapest diagnostic criteria have worse QoL as compared to patients meeting the Orlando criteria, underscoring the impact of different sets of criteria on sample characteristics.

### *QoL, type of affected limb, and physical functioning*

Although, in CRPS patients, both PHS and MHS are lower than in the general population<sup>83</sup>, our findings indicate that patients are burdened mainly by the physical consequences of CRPS.

PHS was lower in patients with an affected lower limb as compared to patients with an affected upper limb, which was largely due to the lower scores in the *Physical Functioning* domain. This finding is likely explained by a bias of this domain towards lower limb functions: 9 out of 10 *Physical Functioning* items apply to lower limb function, whereas only 4 of 10 apply to upper limb function. Nevertheless, as illustrated by the scores of the Radboud Skills Questionnaire and questionnaires on Walking and Rising, CRPS is associated with severe disability, which corresponds with findings of others showing that a large proportion of CRPS patients experience partial or complete inability to resume their former job<sup>10,73</sup>.

Clear explanations for the poor physical functioning of CRPS patients cannot be inferred from this study and are still a major question mark in CRPS research. The small but significant negative correlation between disease duration and *Physical Functioning* shows at least that long-term CRPS may have a negative effect on physical function. A role for kinesiphobia, often hypothesised to have a strong negative influence on physical function in CRPS, could

not be confirmed in recent studies<sup>84,85</sup>; instead a negative association of functional limitations with perceived harmfulness of activities and “resting” as a pain coping strategy was found. This seems to point out that patient’s attitude and behaviour towards pain is a very important aspect in the physical impairments they experience. In line with these findings, new therapies for CRPS patients are being developed focussing on improvement of physical function rather than pain reduction<sup>84,86</sup>. The question, however, remains why precisely CRPS patients show these low *Physical Functioning* and *Role Physical* scores, which are lower than scores in other musculoskeletal or neuropathic pain conditions, such as rheumatoid arthritis<sup>82</sup>, neuralgic amyotrophy patients<sup>87</sup>, and lower limb amputees with or without phantom limb pain<sup>82,88,89</sup>. Only fibromyalgia patients exhibit worse scores in many domains<sup>90</sup>, however, in contrast to fibromyalgia, in which the condition also greatly affects mental health<sup>90</sup>, QoL of CRPS patients is best explained by the impact of the condition on physical health. This is further substantiated by the fact that the Hospital Anxiety and Depression Scale scores in this cohort were considerably better than in a large group of fibromyalgia patients<sup>91</sup>.

In previous studies, it has often been assumed that physical complaints experienced by CRPS patients start off initially with an aberrant host response to tissue damage that triggers a cascade of reactions leading to peripheral and central sensitization, which may have profound and prolonged influence on pain and function, although the precise mechanisms are not clear<sup>52</sup>. In addition, CRPS is associated with central changes in sensorimotor cortical networks<sup>40</sup>, which may further add to functional limitations.

### *QoL and gender*

We found no difference in QoL between males and female CRPS patients. This is in contrast with the somewhat worse scores found for women in the general Dutch population<sup>92</sup> and with the results of many studies on QoL in the chronically ill (see Sprangers et al<sup>93</sup> for a review on QoL in a range of different chronic patient groups). The pain scores of men and women were also similar, which again is quite remarkable if one considers that women generally have less efficient pain inhibitory controls than men<sup>73</sup>. Hypothetically this might indicate that once men are afflicted with CRPS, the characteristics of CRPS have the same impact on QoL as in females.

### *QoL and age*

In this study, younger CRPS patients exhibited lower QoL scores than older CRPS patients. Given that we found no difference in the CRPS severity score between age groups:  $\leq 40$  years ( $10.6 \pm 3.57$ ), 40.1–55.0 years ( $10.6 \pm 3.52$ ) and  $\geq 55.1$  years ( $10.1 \pm 3.45$ ),  $p = .24$ , one may speculate that this could be due to the more demanding societal activities with which younger people tend to be confronted (e.g. work, family duties), which can be severely hindered by CRPS. However, conclusions drawn from these results must be interpreted with

caution, given the cross-sectional nature of this study and the facts that absolute differences were small and correlations between the SF-36 domains and age were weak.

### *QoL and pain*

Pain scores correlated moderately with the PHS and MHS. Although one might have expected these correlations to be stronger, it is known that pain intensity is a moderate predictor of disability<sup>3</sup> and that pain reduction per se does not necessarily result in a significant increase in *Physical Functioning*<sup>94</sup>, the domain with 1 of the lowest scores in our patient group. In our data, the correlation between the Numeric Rating Scale or McGill Pain Questionnaire and *Physical Functioning* or *Role Physical* was not strong.

### *QoL and CRPS criteria and severity*

It is again noteworthy that of all patients who fulfil the Orlando criteria, only two thirds fulfilled the Bdp-c criteria whereas less than one-half met the Bdp-r criteria. It is obvious that criteria matter. The main difference between the Orlando criteria (the former IASP criteria) and the Bdp-c and Bdp-r criteria is, besides the inclusion of signs, the addition of motor symptoms and signs to the Budapest criteria<sup>2</sup>. Therefore it is not surprising that patients who fulfilled the Budapest criteria had lower QoL scores and, in particular, lower PHS scores, than patients who fulfilled the Orlando criteria.

CRPS severity measured with the number of signs and symptoms showed only weak correlation with the PHS. These correlations were lower than those in a study that found significant correlations between all SF-36 domains (except *General Health*) and the CRPS severity score<sup>75</sup>. We have no clear explanation for this difference, especially as scores on the PHS domains were remarkably similar to those in our study. Still, the reported correlations in that paper were generally weak as well. This once more underlines that relations between impairments and disabilities are not as direct and strong as one might expect. The physical consequences of having a complex pain *syndrome* are apparently much more complicated than can be inferred from a simple summation of the associated signs and symptoms.

### *Limitations*

Several aspects should be taken into account when interpreting the results of this study. First, the institutes that participated in this study are nearly all specialised academic centres, and generalization of the results is therefore limited. However, due to the complexity of the diagnosis and treatment of the condition, CRPS patients are generally referred to specialised clinics, which, in the case of The Netherlands, are often academic centres, which makes selection towards more severely affected cases in the present study less likely. Nevertheless, an earlier study in The Netherlands reported that about 25% of patients are not seen by a medical specialist but only by their general practitioner<sup>4</sup>, and therefore selection bias cannot



be ruled out completely. In addition, different specialists were involved in the collection of information on signs and symptoms, and although measures to reduce variability in assessment were imposed, this may have led to some residual inaccuracy.

To summarize, this is, to our knowledge, the largest report on QoL in patients with CRPS. The study shows that CRPS patients generally report a poorer QoL than patients with other chronic pain conditions, particularly in the physical domains. Gender and the type of affected limb do not influence QoL. In contrast, the diagnostic criteria used do matter: patients fulfilling stricter criteria (i.e., the Budapest criteria) had lower QoL scores than patient's fulfilling the Orlando criteria. Finally, pain scores correlated moderately with QoL, underscoring the need for further studies aimed at improving pain management in CRPS.

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# Chapter 3

# Sex matters in complex regional pain syndrome

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# ABSTRACT

## *Background*

Complex Regional Pain Syndrome (CRPS) is much more prevalent in women than men but potential differences in clinical phenotype have not been thoroughly explored to date. Differences in the clinical presentation between sexes may point at new avenues for a more tailored management approach of CRPS. We therefore explored if in CRPS the patient's sex is associated with differences in clinical and psychological characteristics.

## *Methods*

In this cross-sectional study of 698 CRPS patients (599 females) fulfilling the Budapest clinical or research criteria, CRPS signs and symptoms, CRPS severity, pain (average pain intensity in the previous week and McGill pain rating index), pain coping (Pain Coping Inventory), physical limitations (Radboud Skills Questionnaire (upper limb), Walking and Rising questionnaire (lower limb)), anxiety and depression (Hospital Anxiety and Depression scale) and kinesiophobia (Tampa scale for kinesiophobia) were evaluated.

## *Results*

Male CRPS patients used more often extreme words to describe the affective qualities of pain, used more passive pain coping strategies, and were more likely to suffer from depression and kinesiophobia.

## *Conclusion*

Sex-related differences are present in CRPS, but the effect is generally small and mainly concerns psychological functioning. A greater awareness of sex-specific factors in the management of CRPS may contribute to achieving better outcomes.

# INTRODUCTION

Complex Regional Pain Syndrome (CRPS) patients suffer from intense pain with sensory, autonomic, motor and trophic changes of the affected limb, resulting in profound loss of quality of life (this thesis, chapter 2). Typically the syndrome is preceded by tissue damage of the affected limb<sup>1</sup>. Previous research efforts suggest that CRPS is a multifactorial disorder that is associated with an aberrant host response to tissue injury<sup>1</sup>. The various involvement of perturbed biological pathways underlying aberrant inflammation, vasomotor dysfunction, and maladaptive neuroplasticity likely account for the clinical heterogeneity of CRPS<sup>1</sup>. Clinical heterogeneity is also encountered in studies directed at the development of therapeutic approaches for this condition, pointing to the existence of distinct subgroups that exhibit a varying response to treatment. Given the complex nature of CRPS, future treatment strategies likely will benefit from the identification of unique factors associated with treatment response in particular patients, enabling a more personalized approach. Although the syndrome is clearly much more common in females of all ages, affecting 2 to 4 times as many females as males, it is unclear if sex is associated with differences in the clinical presentation of CRPS<sup>4</sup>. Findings in the general population indicate that in experimentally-induced pain, women have lower pain thresholds and experience greater temporal summation of pain to brief, repeated, or dynamic stimuli than men; however, women also show greater adaptation to sustained stimuli than men<sup>95</sup>. In addition, women report higher prevalence and severity of pain in daily life, experience a higher severity of mood disturbance and seek more social support when suffering pain<sup>16,96-99</sup>. Knowledge of sex-related factors in the clinical presentation of CRPS patients could potentially reveal new avenues for a more tailored approach to management.

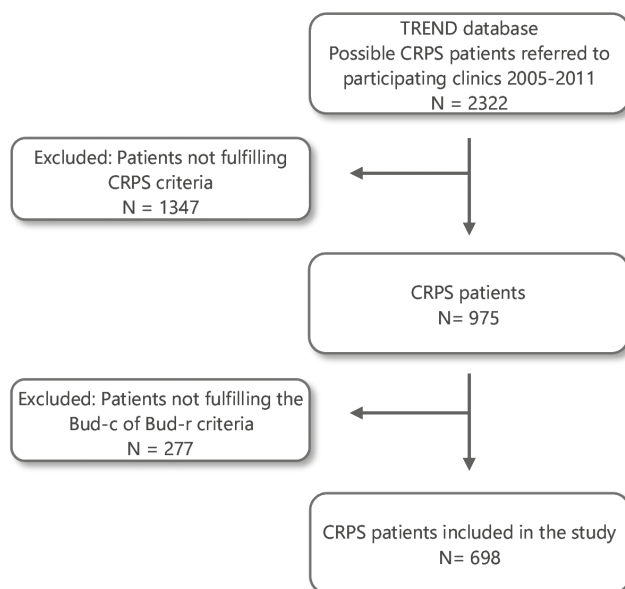
We therefore evaluated the clinical presentation of men and women with CRPS in a large cohort of almost 700 CRPS patients recruited in academic and regional hospitals in the Netherlands and used the term “sex” to denote the different groups. Specifically, we examined potential sex-related differences in signs and symptoms, pain coping, self-reported physical disability, anxiety, depression, and kinesiophobia.

## METHODS

### *Participants*

Patients were recruited between January 2005 and December 2011 from five pain clinics and one department of neurology of academic and regional hospitals in the Netherlands participating in TREND (short for Trauma RElated Neuronal Dysfunction, a Dutch knowledge consortium on CRPS). The included patients were all 18 years or older and fulfilled gener-

ally accepted CRPS criteria, specifically the ‘Budapest clinical’ (Bdp-c) or the ‘Budapest research’(Bdp-r) criteria (figure 1). We excluded patients if they had other conditions that could account for the signs and symptoms encountered, dementia, cognitive impairment or any other condition that could affect the ability to understand and complete self-assessment questionnaires. We use the term “*sex*” instead of “*gender*” to denote the different groups since we identify the patients based on their biological sexes, not “*gender*” which encompasses social and cultural values.



**Figure 1:** Flow-chart of inclusion. Bdp-c, Budapest clinical; Bdp-r, Budapest research; CRPS, complex regional pain syndrome; TREND, Trauma RElated neuronal dysfunction

### *Assessment methods and measurement instruments*

The protocol was approved by the medical ethical committees of all participating centres in accordance with the Declaration of Helsinki. All participants gave written informed consent. We standardised methods of examination across centres and recorded signs and symptoms on a standard score sheet. All data were stored in a NEN-7511 certified, central web-based data management system (ProMISe©).

### *CRPS signs and symptoms*

We examined 22 distinctive CRPS signs (observed during examination) and symptoms (reported by patients); specifically: allodynia (pain to normally innocuous stimuli) to light touch, to deep joint pressure and to movements; hyper- and hypoesthesia; hyper- and hypoalgesia; skin colour changes; temperature asymmetry; oedema; hyper- and hypohydrosis;

trophic changes of hairs, nails and skin; muscle atrophy; decreased range of motion; paresis; abnormal postures; tremors; myoclonic jerks and bradykinesia.

### *CRPS severity score*

We calculated the CRPS severity score (CCS)<sup>75</sup>, a measure designed to reflect the presence and severity of CRPS. The CCS is based on the presence or absence of 9 signs (hyperpathia/hyperalgesia to pinprick; hyperpathia/hyperalgesia to light touch [brush], cold, warm, vibration, or deep manual joint pressure; temperature asymmetry; skin colour changes; oedema; sweating asymmetry; trophic/dystrophic changes; motor changes; and decreased active range of motion) and eight symptoms (hyperpathia/allodynia (all types); bilateral temperature asymmetry; skin colour changes; oedema; sweating asymmetry; trophic/dystrophic changes (hair, nails, or skin); motor changes (e.g. weakness, tremor, dystonia); and decreased active range of motion. Range 0–17.

### *Pain*

We used 2 measurement instruments to evaluate pain. First, the numeric Rating Scale (NRS) which is the average pain intensity of the previous week on a scale from 0 to 10, with 10 reflecting the worst pain imaginable. Second, the McGill Pain Rating Index to quantify pain (range 0–63; higher scores reflect more pain)<sup>77,100</sup>. The Pain Rating Index is a sum score calculated over ranked words that express three qualities of pain, namely *sensory* qualities (such as temporal, spatial, pressure, thermal qualities), *affective* qualities (tension, fear, autonomic changes) and *evaluative* qualities (subjective intensity of pain).

### *Pain coping*

Patients completed the Pain Coping Inventory (PCI) questionnaire to assess pain coping strategies<sup>101,102</sup>. The questionnaire comprises 6 pain coping dimensions, grouped into “active” (Pain transformation, Distraction, Reducing demands; range 12–48) and “passive” domains (Retreating, Worrying, Resting; range 21–84); higher scores in these dimensions indicate more use of the corresponding strategy.

### *Self-reported physical disability*

To assess physical limitations in daily life, patients completed the Radboud Skills Questionnaire (RASQ)<sup>79,103</sup> if arms were affected and the Walking and Rising questionnaire (WRQ)<sup>81,104</sup> if legs were affected. The primary outcome of the RASQ is a summary score of 6 domains: personal care (e.g. personal hygiene), domestic activities (e.g. housekeeping), recreational activities (e.g. sports), social activities (e.g., going on outings), work (i.e., performing occupation) and other (e.g., using personal computer). Mean domain and total scores are calculated and range from 1 to 5, with higher scores reflecting worse functioning. For the WRQ we used the summary score of the following three domains: walking inside, walking

outside and rising; because of the different number of items for these 3 domains, subscale scores were first standardized to a 0–10 scale before adding up (total range 0–30; higher scores indicating worse walking ability). For regression analyses (see *statistics* section), we used the physical health sum score (PHS) of the MOS 36-Item Short-Form Health Survey (SF36)<sup>76,92</sup>, which measures limitations in physical function. We used this scale because it addresses physical disability of the whole body in contrast to the RASQ and WRQ, which only measure limitations in upper and lower extremity function.

### *Anxiety and depression*

To measure anxiety and depression, we used the Anxiety and Depression subscales of the Hospital Anxiety and Depression scale (HADS-A and HADS-D, respectively)<sup>105,106</sup>.

### *Kinesiophobia*

Kinesiophobia was measured using the Dutch version of the Tampa Scale for Kinesiophobia (TSK)<sup>107</sup>, a questionnaire consisting of 17 questions addressing patient's belief that activities that increase pain cause further harm (range 17–68, higher scores indicating more kinesiophobia).

### *Statistics*

We analysed all data using IBM® SPSS® statistics software version 23. First, we calculated group (sex) differences in all measures. In categorical data (dichotomous variables CRPS signs and symptoms; HADS-A and D) sex differences were calculated using Chi-square tests with exact significance values in conjunction with odds ratios as a measure of effect size. In continuous data, T-tests were used in conjunction with Hedges' *g* as a measure of effect size (Hedges' *g* due to unequal sample sizes of males and females; .20=small, .50=medium, .80=large effect)<sup>108</sup>. In addition, if the previous analyses resulted in differences in continuous measures, the analysis was followed up with a multiple regression analysis to control for the potential influence of confounders. Independent variables were added to the model using a simultaneous forced entry method ("ENTER" method), which is used when a hierarchical order of the independent variables is not a-priori known or considered relevant. We selected the following independent variables based on previous literature or on our assumption of possible interaction of the concerned variable with sex: "sex"; "age" at time of inclusion; "disease duration"; "McGill pain rating index"; "CRPS severity score"; "affected limbs" (upper limb(s), lower limb(s) or a combination of upper and lower limbs, imputed as 2 dummy variables in linear regression); and the "sum score physical health SF36 (PHS)". Missing values in the independent variables of the regression analysis were replaced by means if less than 5% of the independent variables were missing. Data were considered statistically significant if *p*-values were <.05. To control for false discovery rate, we used the Benjamini-Hochberg procedure<sup>109</sup> with an alpha of <.05 within the following different domains: CRPS

signs and symptoms, pain scores (NRS and McGill pain rating index), CCS, self-reported disability (WRQ, RASQ) and psychological variables (active and passive PCI, HADS&D and kinesiophobia). Data in the text are presented as mean scores  $\pm$  standard deviations.

## RESULTS

Six-hundred-ninety-eight patients (age:  $46.1 \pm 14.2$  years; 599 (86%) female) were included in the analysis, of which 267 (38.3%) with an affected upper limb, 278 (39.8%) with an affected lower limb and 153 (21.9%) with more than one limb affected. Mean disease duration at time of inclusion in male patients was  $4.7 \pm 6.9$  years and  $5.2 \pm 7.1$  years in female patients. All 698 patients fulfilled the Bdp-c criteria, of which 448 (64.2%) also the Bdp-r criteria. Six-hundred-eighty-six patients (589 female) completed the McGill pain questionnaire, 565 patients (481 female) the NRS, 385 patient (335 female) the RASQ, 401 patients (349 female) the WRQ, 609 (522 female) the PCI, 684 patients (587 female) the HADS and 679 patients (582 female) the TSK. In the regression analyses, missing independent variables were replaced by means, which occurred in no more than 2% (disease duration 99%, CRPS severity score 99%, McGill pain rating index 98% complete data). Baseline results are listed in table 1.

### *CRPS signs and symptoms*

No sex difference was found in CRPS signs and symptoms.(see supplementary data for the results of the uncorrected data).

### *CRPS severity score*

The CRPS severity score was not significantly different between sexes (females:  $11.8 \pm 2.7$ , males:  $11.5 \pm 3.0$ ):  $t(686) = -1.112$ ,  $p = .266$ .

### *Pain*

The average pain in the previous week as measured by the NRS was similar for female and male patients (females:  $6.5 \pm 1.8$ , males:  $6.3 \pm 2.0$ ),  $t(-.563) = -.816$ ,  $p = .390$ . In contrast, the McGill pain rating index was slightly higher for male CRPS patients than for female CRPS patients (females:  $27.0 \pm 11.5$ , males:  $29.4 \pm 12.0$ ),  $t(684) = 2.011$ ,  $p = .045$ ,  $g_{\text{Hedges}} = .22$  (uncorrected results). This result which was entirely driven by the difference in affective quality of pain: male patients more often used extreme words to describe the affective qualities of pain (females  $4.6 \pm 3.4$ , males  $5.9 \pm 3.6$ ,  $t(684) = 3.56$ ,  $p < .001$ ). *Sensory* qualities (females  $15.4 \pm 7.0$ , males  $16.2 \pm 7.3$ ,  $t(684) = .99$ ,  $p = .32$ ) and *evaluative* qualities (females  $7.3 \pm 2.9$ , males  $6.8 \pm 2.9$ ,  $t(684) = 1.45$ ,  $p = .15$ ) were not significantly different.

**Table 1** Demographic and clinical variables

|                                                                            |               | Male          | Female        |
|----------------------------------------------------------------------------|---------------|---------------|---------------|
| Number of included patients (%)                                            | 698           | 99 (14.2)     | 599 (85.8)    |
| Mean (SD) age, years                                                       | 46.1 (14.2)   | 49.0 (12.9)   | 45.7 (14.4)   |
| Mean (SD) age at onset, years                                              | 41.1 (15.4)   | 44.0 (13.5)   | 40.6 (15.7)   |
| Median (IQR) disease duration, years                                       | 2.0 (0.5–7.1) | 1.6 (0.4–6.1) | 2.1 (0.5–7.2) |
| N 1 arm / 1 leg / >1 limb                                                  | 267/278/153   | 40/42/17      | 227/236/136   |
| Fulfilling Bdp-r criteria (%)                                              | 448 (64.2)    | 60 (60.1)     | 388 (64.8)    |
| CRPS Severity Score, median (IQR)                                          | 12 (10–14)    | 11.5 (3.0)    | 11.8 (2.7)    |
| McGill Pain Rating Index, mean (SD)                                        | 27.2 (11.6)   | 29.4 (12.0)   | 26.9 (11.4)   |
| Sensory qualities                                                          | 15.6 (7.0)    | 16.2(7.3)     | 15.5(6.9)     |
| Affective qualities                                                        | 4.8 (3.4)     | 5.9 (3.6)     | 4.6 (3.4)     |
| Evaluative qualities                                                       | 6.9 (2.9)     | 7.3 (2.9)     | 6.8 (2.9)     |
| Numeric rating scale (NRS)                                                 | 6.5 (1.8)     | 6.3 (2.0)     | 6.5 (1.8)     |
| Pain Coping Inventory, active, mean (SD)                                   | 28.5 (5.2)    | 27.7 (5.6)    | 28.7 (5.1)    |
| Pain Coping Inventory, passive, mean (SD)                                  | 42.1 (9.1)    | 44.2 (10.4)   | 41.7 (8.9)    |
| RAdboud Skills Questionnaire, mean (SD)                                    | 3.2 (0.9)     | 3.1 (0.9)     | 3.3 (0.9)     |
| Walking and Rising Questionnaire, mean (SD)                                | 19.9 (7.4)    | 18.9 (7.5)    | 20.0 (7.4)    |
| Hospital Anxiety and Depression Scale- depression subscale, mean (SD)      | 5.1 (3.9)     | 6.1 (4.3)     | 4.9 (3.8)     |
| Dichotomous (cutoff $\geq 8$ ) (%)                                         | 164 (23.5)    | 32 (32.3)     | 132 (22.0)    |
| Hospital Anxiety and Depression Scale- anxiety subscale, mean (SD),        | 6.3 (3.8)     | 6.7 (4.0)     | 6.2 (3.7)     |
| Dichotomous (cutoff $\geq 8$ ) (%)                                         | 212 (30.4)    | 32 (32.3)     | 184 (30.7)    |
| Tampa Scale of Kinesiophobia, mean (SD)                                    | 38.1 (8.2)    | 40.6 (7.8)    | 37.7 (8.2)    |
| MOS 36-Item Short-Form Health Survey, Physical health Sum Score, mean (SD) | 32.3 (16.3)   | 33.9 (15.9)   | 32.1 (16.4)   |

Bdp-c = Budapest clinical criteria; Bdp-r = Budapest research criteria; CRPS = complex regional pain syndrome; IQR = interquartile range; SD = standard deviation.

### *Pain coping*

Male patients reported a higher use of *passive* pain coping mechanisms than female patients (females:  $41.7 \pm 8.9$ , males:  $44.2 \pm 10.4$ ),  $t(607) = 2.37$ ,  $p = .018$ ,  $g_{\text{Hedges}} = .15$ . Controlling for the potential effects of the confounders *age*, *disease duration*, *CRPS severity score*, *pain*, *physical health* and *affected limb*, the contribution of “sex” to the model remained significant, albeit small;  $\beta_{\text{st-sex}} = -.077$ ,  $p = .024$  [table 2].

No difference in *active* pain coping mechanisms were found (females:  $28.7 \pm 5.1$ , males:  $27.7 \pm 5.6$ )  $t(607) = -1.66$ ,  $p = .097$ ).

**Table 2** Linear regression model Pain Coping Inventory

| Variables                 | B(SE)          | $\beta_{st}$ | Sig. |
|---------------------------|----------------|--------------|------|
| Constant                  | 48.488 (2.298) |              |      |
| Sex                       | -1.882 (.832)  | -.077        | .024 |
| Age                       | -.002 (.021)   | -.004        | .907 |
| Disease duration          | .000 (.046)    | -.000        | .997 |
| CRPS severity score       | -.079 (.106)   | -.025        | .457 |
| McGill Pain rating index  | .141 (.029)    | .190         | .000 |
| Physical health sum score | -.195 (.020)   | -.371        | .000 |
| Affected limbs A          | -1.553 (.652)  | -.090        | .017 |
| Affect limbs B            | -3.804 (.945)  | -.167        | .000 |

$R^2$  (variance explained by the model) = .226; Sex: male>female; Sig. = significance ( $p < .05$ ); Affected limbs A = dummy variable affected lower limb(s) v.s. affected upper limb(s); Affected limbs B = dummy variable affected lower limb(s) and upper limb(s) v.s. affected upper limb(s).  $\beta_{st}$  = standardized  $\beta$ ; CRPS = complex regional pain syndrome; SE = standard error.

### *Self-reported physical disability*

We found no group differences in the RASQ (females:  $3.3 \pm .9$ , males:  $3.1 \pm .9$ )  $t(383) = -.999$ ,  $p = .318$  or WRQ (females:  $20.0 \pm 7.4$ , males:  $18.9 \pm 7.5$ )  $t(399) = -1.001$ ,  $p = .317$ .

### *Anxiety and depression*

No difference in anxiety scores (HADS-A) was found between the groups: (females  $6.1 \pm 3.1$ , males  $6.6 \pm 4.1$ )  $t(680) = -.294$ ,  $p = .769$ .

Male CRPS patients had higher depression scores (HADS-D) than female patients: (females  $4.9 \pm 3.8$ , males  $6.1 \pm 4.3$ )  $t(682) = 2.677$ ,  $p = .008$ . The adjusted effect of sex in the logistic regression model remained significant ( $\beta_{st} \text{ sex} = -.078$ ,  $p = .024$ ) [table 3].

### *Kinesiophobia*

Male patients had higher scores of kinesiophobia than female patients (female  $37.7 \pm 8.2$ , males  $40.6 \pm 7.8$ )  $t(677) = 2.94$ ,  $p = .001$ ,  $g_{\text{Hedges}} = .36$ ). The effect of sex in the regression model controlling for the potential influence of confounders remained significant ( $\beta_{st-\text{sex}} = -.113$ ,  $p = .002$ ) [table 4].

## DISCUSSION

We studied sex differences in 698 CRPS patients and found that male patients used more often extreme words to describe the affective qualities of pain, used slightly more often passive pain coping strategies, and were more likely to suffer from depression and kinesiophobia.

**Table 3** Regression model HADS-D

| Variables                 | B(SE)         | $\beta_{st}$ | Sig. |
|---------------------------|---------------|--------------|------|
| Constant                  | 9.139 (1.061) |              |      |
| Sex                       | -1.054 (.384) | -.096        | .006 |
| Age                       | .001 (.01)    | -.005        | .881 |
| Disease duration          | -.021 (.021)  | -.037        | .332 |
| CRPS severity score       | -.040 (.049)  | -.029        | .410 |
| McGill Pain rating index  | .033 (.013)   | .098         | .015 |
| Physical health sum score | -.091 (.009)  | -.384        | .000 |
| Affected limbs A          | -.800 (.301)  | -.103        | .008 |
| Affect limbs B            | -1.459 (.436) | -.142        | .001 |

$R^2$  (variance explained by the model) = .186; Sex: male>female; Sig. = significance ( $p<.05$ ); Affected limbs A = dummy variable affected lower limb(s) v.s. affected upper limb(s); Affected limbs B = dummy variable affected lower limb(s) and upper limb(s) v.s. affected upper limb(s).  $\beta_{st}$  = standardized  $\beta$ ; CRPS = complex regional pain syndrome; SE = standard error.

**Table 4** Linear regression model Tampa Scale of Kinesiophobia

| Variables                 | B(SE)          | $\beta_{st}$ | Sig. |
|---------------------------|----------------|--------------|------|
| Constant                  | 41.692 (2.324) |              |      |
| Sex                       | -2.621 (.842)  | -.113        | .002 |
| Age                       | .048 (.022)    | .084         | .026 |
| Disease duration          | -.004 (.046)   | -.003        | .933 |
| CRPS severity score       | .024 (.107)    | .008         | .825 |
| McGill Pain rating index  | .066 (.029)    | .094         | .024 |
| Physical health sum score | -.140 (.020)   | -.283        | .000 |
| Affected limbs A          | -1.441 (.659)  | -.088        | .029 |
| Affect limbs B            | -2.846 (.956)  | -.132        | .003 |

$R^2$  (variance explained by the model)=.120; Sex: male>female; Sig. = significance ( $p<.05$ ); Affected limbs A = dummy variable affected lower limb(s) v.s. affected upper limb(s); Affected limbs B = dummy variable affected lower limb(s) and upper limb(s) v.s. affected upper limb(s).  $\beta_{st}$  = standardized  $\beta$ ; CRPS = complex regional pain syndrome; SE = standard error.

The NRS, which depicts the average pain in the previous week, was similar for female and male patients. In contrast, pain evaluated with the McGill pain rating index was somewhat higher in male patients. Although surprising considering the overwhelming evidence for the opposite in the general- and pain population, the result appeared mainly driven by the questions concerning the affective qualities of pain; male patients more often used extreme words to describe the affective qualities of pain whereas sensory and evaluative qualities of pain were not significantly different between the groups. Therefore, although pain intensity was not significantly higher, male CRPS patients might have suffered more from the pain

than female patients, an effect that is potentially mediated by the higher levels of passive pain coping, depression and kinesiophobia found in male CRPS patients.

Male CRPS patients reported more passive pain coping strategies than female patients. Passive pain coping strategies are associated with decreased physical functioning and increased psychological distress<sup>110</sup>. Indeed, in our sample, passive pain coping was negatively correlated with physical health (depicted by the SF-36 Physical health Sum Score, table 1) and positively correlated with the RASQ and WRQ (Pearson's  $r = -.39$ ,  $r = .3.0$  and  $2.5$  respectively; all  $p < .001$ ). In CRPS patients with an affected lower limb, "resting" as a passive pain coping mechanism had the largest effect on difficulties in rising and walking<sup>85</sup>. This effect was even larger in comparison to pain or CRPS severity<sup>85</sup>. In addition, CRPS patients using active, instead of passive pain coping strategies do better in overall functioning, physical functioning, mood, and the ability to cope with pain and pain flare-ups<sup>111</sup>. Female pain patients generally use a wider range of coping mechanisms than male patients, seek more social support and are more prone to pain-related catastrophizing<sup>112</sup>. In contrast, male patients use less coping strategies, more avoidance, seek less social support, are more likely to use alcohol and more passive coping strategies when they perceive their pain as threatening<sup>113</sup>. In addition, male patients show lower levels of daily activities than female patients reporting the same pain severity<sup>99</sup>. Physicians may therefore consider assessing a patients' resilience by inquiring about social ties and community support, use of sedatives and avoidance behaviour, especially when managing male patients.

Of note is that we found no difference in anxiety scores between the sexes. In the general population females report higher anxiety scores and are at greater risk of anxiety disorders than men. Furthermore, in chronic (musculoskeletal) pain patients, anxiety has been found associated with pain in male, but not in female patients<sup>96</sup>. In contrast, in our sample, an equally weak, positive correlation between pain and anxiety was found in both groups (Pearson's  $r = .21$ ; with  $p = .04$  in males and  $p < .001$  in females). The presence of anxiety in CRPS patients is conceivable considering its influence on quality of life (this thesis, chapter 2), physical health, and clinical signs such as higher levels of pain, allodynia, motor disturbances, oedema, skin colour and temperature changes, independent of the sex. Possibly the comparatively high overall level of anxiety in this condition ( $>30\%$  were classified as 'anxious'), while mean group levels are close to the applied cut-off value) outweighs the potential contribution of sex on these features.

Surprisingly, male CRPS patients were more likely to suffer from depression. This contradicts the common notion that females, both in the general and chronic pain populations, are twice as likely to suffer from depression than males<sup>114</sup>. Moreover, in one much smaller study in CRPS patients ( $n=24$ ), female CRPS patients scored higher in depression<sup>115</sup>. For both sexes,

the association between CRPS and depression has been documented before [for review see<sup>116</sup>] and in one study previous-day-pain was a significant predictor of next day's negative and depressed mood<sup>117</sup>. However, there is evidence suggesting that in male patients with chronic pain, depression is associated with impairment of activity, and less so with pain<sup>118</sup>. Against this background it is relevant to take into account that CRPS is strongly associated with reduced physical health (this thesis, chapter 2), which may result in male patients being more depressed than female patients. Indeed, in our study we found a weaker negative correlation between physical health and depression in female as compared to male patients (Pearson's  $r = -.25$  and  $r = -.37$ , respectively; both  $p < .001$ ).

Male CRPS patients also had higher scores of kinesiophobia than female patients. This finding is in line with those of previous studies in chronic musculoskeletal pain patients<sup>107,119</sup>, although, to the best of our knowledge, a clear explanation for these findings is lacking. Kinesiophobia is common in CRPS and may contribute to functional limitations<sup>120,1</sup>, although this association was not found by others<sup>85</sup>. In addition, in patients with pain-related fear, therapies that focussed on physical exposure instead of pain reduction resulted in better physical performance<sup>84,121</sup>. This underlines the necessity of incorporating kinesiophobia assessment in the management of CRPS. Our data suggest that this might even be more important in male than female CRPS patients.

We found no significant differences in CRPS signs or symptoms. However, potential differences in signs and symptoms were much more difficult to detect, given that patients had to meet Budapest criteria to be included in the study. Concerning the results of the noncorrected data, subsequent research could focus on a potential difference in allodynia to deep joint pressure, since this sign was the most promising of all distinguishing female from male patients.

The strengths of this study are the large sample size and the use of – and regular training in – standardized assessments of CRPS signs and symptoms in the participating clinics. However, some main limitations need to be mentioned; one is the cross-sectional study design which makes it impossible to draw conclusions on causality. The second limitation is that this study was executed in patients who were treated in specialised academic centres and referral bias can therefore not be ruled out, although it should be noted that, in particular at the time the data for this study were collected, most CRPS patients in the Netherlands were referred to specialised clinics such as those in which the present data were collected. It is further of note that we have little reason to assume that any potential referral bias would have affected the relationship between sex and the variables that were identified. Third, all patients were recruited only in the Netherlands. It may be worthwhile to explore if they also hold for other regions.



To summarize, male CRPS patients seem to experience a slightly higher psychological burden than female CRPS patients in the absence of significant differences in clinical presentation. Of note is that, except for depression, the effect sizes were generally small and that variables other than sex often accounted for more of the variance in the investigated outcomes. Although results of cross-sectional studies cannot be causally interpreted, they may nevertheless provide clues that may be relevant to follow up. A greater awareness of sex-specific factors in the management of CRPS may contribute to achieving better outcomes.

### *Acknowledgement*

We commemorate prof. dr. Roberto Perez. A very enthusiastic, talented and kind colleague who passed away last year at the age of 49. Roberto was a true pioneer of CRPS research and a dedicated member of the TREND consortium. We here acknowledge Roberto's important contribution to the design and data collection of this study.

## SUPPLEMENTARY DATA

### CRPS signs

|                                  | Male<br>Nr (total) | Female<br>Nr (total) | Chi-square<br>(degrees of freedom) |
|----------------------------------|--------------------|----------------------|------------------------------------|
| Allodynia to light touch         | 47 (95)            | 271 (579)            | $X^2(1)=.23, p=.658$               |
| Allodynia to deep joint pressure | 47 (86)            | 360 (534)            | $X^2(1)=5.35, p=.027$              |
| Allodynia to movements           | 59 (88)            | 348 (534)            | $X^2(1)=.18, p=.809$               |
| Hyperesthesia                    | 43 (94)            | 257 (581)            | $X^2(1)=.08, p=.823$               |
| Hypoesthesia                     | 35 (85)            | 233 (540)            | $X^2(1)=.12, p=.814$               |
| Hyperalgesia                     | 58 (94)            | 372 (578)            | $X^2(1)=.25, p=.644$               |
| Hypoalgesia                      | 26 (86)            | 168 (538)            | $X^2(1)=.03, p=.901$               |
| Skin colour changes              | 62 (96)            | 366 (578)            | $X^2(1)=.06, p=.820$               |
| Temperature asymmetry            | 57 (96)            | 369 (579)            | $X^2(1)=.67, p=.426$               |
| Edema                            | 52 (96)            | 308 (580)            | $X^2(1)=.04, p=.912$               |
| Hyperhidrosis                    | 21 (94)            | 114 (576)            | $X^2(1)=.33, p=.580$               |
| Hypohidrosis                     | 5 (88)             | 26 (534)             | $X^2(1)=.11, p=.790$               |
| Trophic changes hair             | 27 (92)            | 136 (554)            | $X^2(1)=.96, p=.364$               |
| Trophic changes nails            | 22 (92)            | 158 (552)            | $X^2(1)=.87, p=.382$               |
| Trophic changes skin             | 30 (91)            | 155 (555)            | $X^2(1)=.97, p=.381$               |
| Muscle atrophy                   | 31 (91)            | 157 (564)            | $X^2(1)=1.49, p=.261$              |
| Decreased range of motion        | 71 (92)            | 454 (571)            | $X^2(1)=.62, p=.678$               |
| Paresis                          | 53 (87)            | 343 (548)            | $X^2(1)=.09, p=.812$               |
| Abnormal postures                | 18 (89)            | 119 (555)            | $X^2(1)=.07, p=.889$               |
| Tremors                          | 13 (88)            | 64 (555)             | $X^2(1)=.76, p=.480$               |
| Myoclonic jerks                  | 8 (86)             | 27 (542)             | $X^2(1)=2.63, p=.125$              |
| Bradykinesia                     | 50 (80)            | 317 (518)            | $X^2(1)=.05, p=.902$               |

Results are uncorrected for multiple comparison. Allodynia = pain to normally innocuous stimuli; Hyper- and hypoesthesia = increased/decreased sensitivity to touch; Hyper- and hypoalgesia = increased/decreased pain sensation; Bradykinesia = slowing of movements

## CRPS symptoms

|                                  | Male<br>Nr (total) | Female<br>Nr (total) | Chi-square<br>(degrees of freedom) |
|----------------------------------|--------------------|----------------------|------------------------------------|
| Allodynia to light touch         | 53 (95)            | 361 (579)            | $X^2(1)=1.48, p=.255$              |
| Allodynia to deep joint pressure | 43 (86)            | 297 (534)            | $X^2(1)=.94, p=.352$               |
| Allodynia to movements           | 55 (88)            | 352 (534)            | $X^2(1)=.39, p=.547$               |
| Hyperesthesia                    | 41 (94)            | 288 (581)            | $X^2(1)=1.15, p=.317$              |
| Hypoesthesia                     | 29 (85)            | 210 (540)            | $X^2(1)=.71, p=.405$               |
| Hyperalgesia                     | 55 (94)            | 361 (578)            | $X^2(1)=.53, p=.493$               |
| Hypoalgesia                      | 21 (86)            | 113 (538)            | $X^2(1)=.51, p=.481$               |
| Skin colour changes              | 85 (96)            | 514 (578)            | $X^2(1)=.01, p=1.00$               |
| Temperature asymmetry            | 87 (96)            | 553 (579)            | $X^2(1)=.23, p=.686$               |
| Edema                            | 83 (96)            | 488 (580)            | $X^2(1)=.34, p=.649$               |
| Hyperhydrosis                    | 62 (94)            | 323 (576)            | $X^2(1)=3.22, p=.091$              |
| Hypohydrosis                     | 9 (88)             | 56 (534)             | $X^2(1)=.01, p=1.000$              |
| Trophic changes hair             | 36 (92)            | 235 (554)            | $X^2(1)=.35, p=.571$               |
| Trophic changes nails            | 47 (92)            | 317 (552)            | $X^2(1)=1.29, p=.307$              |
| Trophic changes skin             | 33 (91)            | 211 (555)            | $X^2(1)=.10, p=.816$               |
| Muscle atrophy                   | 31 (91)            | 181 (564)            | $X^2(1)=.14, p=.718$               |
| Decreased range of motion        | 69 (92)            | 455 (571)            | $X^2(1)=1.05, p=.334$              |
| Paresis                          | 66 (87)            | 411 (548)            | $X^2(1)=.03, p=.895$               |
| Abnormal postures                | 43 (89)            | 295 (555)            | $X^2(1)=.72, p=.425$               |
| Tremors                          | 37 (88)            | 191 (555)            | $X^2(1)=1.93, p=.187$              |
| Myoclonic jerks                  | 8 (86)             | 27 (542)             | $X^2(1)=2.63, p=.125$              |
| Bradykinesia                     | 50 (80)            | 317 (518)            | $X^2(1)=.05, p=.902$               |

Allodynia = pain to normally innocuous stimuli; Hyper- and hypoesthesia = increased/decreased sensitivity to touch; Hyper- and hypoalgesia = increased/decreased pain sensation; Bradykinesia = slowing of movements

# Chapter 4

# Is the brain of complex regional pain syndrome patients truly different?

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# ABSTRACT

## *Background*

In recent years, changes in brain structure and function have been studied extensively in patients with Complex Regional Pain Syndrome (CRPS) following clinical observations of altered central processing of sensory stimuli and motor control. However, concerning MRI data, the evidence is complex to interpret due to heterogeneity in statistical methods and results.

## *Method*

The aim of this study is to determine if CRPS patients exhibit specific, clinically relevant changes in brain structure and function in rest. We do this by presenting MRI data on brain structure and function in 19 chronic, female CRPS patients and age and sex matched healthy controls (HCs). In addition, we analyse and report the data in multiple ways to make comparison with previous studies possible and to demonstrate the effect of different statistical methods, in particular concerning the correction for multiple testing.

## *Results*

Using family-wise error (FWE) correction for multiple testing, in our group of CRPS patients, we find no specific difference in brain structure or function in rest in comparison to healthy controls. In addition, we argue that previous found MRI results in literature are inconsistent in terms of localisation, quantity and directionality of the reported changes in brain structure and function.

## *Conclusion*

Previously published MRI-based evidence for altered brain structure and function in rest in CRPS patients is not consistent and our data suggests that no such phenomenon exists.

# INTRODUCTION

Complex regional pain syndrome (CRPS) is a severely disabling pain syndrome characterized by autonomic, sensory, trophic and motor disturbances of the affected limb. Current evidence suggests a multifactorial aetiology that includes aberrant inflammation, vasomotor dysfunction, and neuroplasticity in spinal cord and brain<sup>1</sup>. Aberrant neuroplasticity in the brain has been the focus of many studies in the last decade, following clinical observations of altered central processing of sensory stimuli<sup>48–51</sup> and abnormalities in motor control<sup>52–54</sup>. Specifically, studies reported cortical sensorimotor reorganization of the affected limb<sup>38–40</sup>, the unaffected limb<sup>122</sup>, changes in local grey matter volume throughout the brain<sup>41–44</sup>, and altered activity patterns in rest<sup>45,123</sup>. However, 2 recent systematic reviews concluded that evidence of aberrant neuroplasticity of the somatosensory and primary motor cortex in CRPS is limited and at high risk of bias<sup>124,125</sup>. In addition: the reported MRI results are inconsistent, correlations with clinical measures are lacking or inconclusive and the methods – especially concerning the correction for multiple testing – differ between the studies.

Considering these concerns, the aim of this study is twofold: First, to reproduce previous MRI findings in literature with current advocated statistical methods in a sample of 19 chronic female CRPS patients. Second, to assess the evidence for specific, clinically relevant changes in brain structure and function in CRPS by discussing our results and previous published MRI data in literature. In our patient sample, we first perform an analysis of local Grey Matter Volume (GMV) by Voxel Based Morphometry (VBM) and white matter connectivity by Diffusion Tensor Imaging (DTI) on all voxels of the brain. In a secondary VBM analysis, we focus specifically on the sensorimotor cortex in an attempt to replicate recent findings in this brain area that is thought to be of high importance in CRPS aetiology<sup>43</sup>. Second, we study resting state functional Magnetic Resonance Imaging measurements (rsfMRI) in the sensorimotor, parietal, right and left executive attentional, salient and default mode network based on their role in sensory, pain and motor processing and on previous reports of alterations in CRPS patients<sup>45</sup>.

Ultimately, transparently presented, statistical sound results of neuroplasticity in CRPS patients are imperative, since novel therapeutic strategies have been based on these results (e.g.<sup>126–130</sup>) and might well be in the future.

# METHOD

## *Participants*

In order to make the patient sample as homogeneous as possible, only female CRPS patients followed up at the neurology outpatient clinic of the Leiden University Medical Center (LUMC) in Leiden, the Netherlands, were asked to participate in this study between May 2011 and March 2013. We chose female CRPS patients because the incidence of CRPS among females is 3–4 times higher than among men<sup>4</sup>. All had to fulfil the Budapest clinical criteria for CRPS in an upper limb. If a patient was interested, a patient information sheet was sent to her home 2 weeks before the potential entry in the study. Before entering the study, a neurological examination was performed by the principal investigator (GAJV) and Budapest Criteria<sup>2</sup> were checked for inclusion to the study. Participants were excluded if they suffered from serious neurological illness, were younger than 18 years, male, had known psychiatric disorders or suffered from any condition other than CRPS that is associated with pain or functional impairment of an upper extremity. A group of healthy pain free controls, age and sex matched at group level to the CRPS patients were additionally investigated. All participants were screened for MRI contraindications before MRI acquisition. The study protocol was approved by the Medical Ethics Committee of the LUMC, and written informed consent was obtained from all patients and control subjects.

## *Demographic data and pain measurements*

At home on the day before research-day, patients completed questionnaires evaluating pain (McGill Pain Questionnaire, MPQ)<sup>77</sup> and manual activity of the affected hand (Radboud skills questionnaire, RSQ)<sup>131</sup>. On the day of examination we collected data on demographic variables, pain severity (numeric rating scale, NRS), CRPS (CRPS severity score)<sup>75</sup> and loss of voluntary motor control due to dystonic postures (Burke-Fahn-Marsden scale)<sup>132</sup>. Decreased active range of motion, weakness and slowness of movement of the affected hand were assessed during neurological examination.

## *MRI acquisition*

For standardization purposes, all scanning sessions were carried out in the early evening. To prevent hearing loss due to loud scanner noise, participants used earplugs and headphones. During the rsfMRI protocol, which always followed the T<sub>1</sub>-weighted and DTI imaging scanning protocols, participants were requested – and checked afterwards – to close their eyes, but not to fall asleep.

Imaging data was acquired on a Philips 3.0 T Achieva MRI scanner using a 32-channel SENSE head coil (Philips Medical Systems, Best, The Netherlands). Structural T<sub>1</sub>-weighted gradient-echo imaging (for VBM analysis) were acquired with the following parameters:

slices: 140, voxel size: 1.17 x 1.17 x 1.2mm; repetition time (TR): 9.8ms; echo time (TE): 4.6ms; flip angle: 8; in-plane matrix resolution: 256 x 256 slices; field of view: 224. DTI images were acquired using echo planar imaging in 60 slices with voxel size: 2 x 2 x 2mm; TR: 6580ms; TE: 71ms; flip angle: 90°; in-plane matrix resolution: 112 x 110; field of view: 224 x 224;  $b_0$ : 800s/mm<sup>2</sup>; in 32 diffuse directions and one non-diffusion weighted slice for head registration and head motion correction. RsfMRI imaging was done in 38 slices, voxel size: 2,75 x 2,75 x 2,75mm without a gap; TR: 2200ms; TE: 30ms; flip angle 80°; field of view: 220; acquisition matrix: 80x79, acquisition time: 7minutes and 30 second.

### *MRI analysis*

We analysed all MRI data twice using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) v5.0 (Oxford, UK)<sup>133–135</sup>; one analysis with mirroring of the hemispheres of patients affected in the left arm to stack all “affected” hemispheres onto the same, left hemisphere (toolbox: FSLswapdim). This data will be referred to as “flipped” data. Additionally, the analysis was performed with the original, non-flipped images to investigate possible asymmetrical differences, in particular in the right parietal lobe, since this region has been hypothesised to play a role in CRPS symptom aetiology<sup>136</sup>.

### *Brain volume*

Total grey matter volume was calculated using the FSL-tool: “Structural Image Evaluation using Normalisation of Atrophy”. The results were later used for correlation analysis with age, disease duration and fractional anisotropy (DTI analysis) and included in fMRI analysis as a nuisance variable.

Local GMV analysis was performed using the optimized VBM protocol in FSL-VBM<sup>137–139</sup>. First, structural images were brain extracted using Brain Extraction Tool (BET)<sup>140</sup> and grey matter segmented before being affine registered to the Montreal Neurological Institute (MNI) 152 standard space using non-linear registration with FMRIB’s nonlinear Image Registration Tool<sup>141</sup>. Next, the resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Subsequently all native grey matter images were non-linearly registered to this study-specific template and modulated to correct for local expansion due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 4mm. We used permutation based threshold-free cluster-enhancement (TFCE) for thresholding of significant clusters. This method has the advantage that it preserves the sensitivity of cluster-based-thresholding (in contrast to voxel-based thresholding which is more conservative), while there is no need for a predetermined cluster-forming threshold which is always arbitrary<sup>142</sup>. A voxel-wise general linear model (GLM) was applied with

permutation-based non-parametric testing<sup>143</sup>. Results were Family Wise Error controlled (FWE) for multiple testing across space:  $p < .05$ . Age was included as nuisance variable. Group differences were tested against 5000 random permutations. In a secondary analysis we focussed specifically on the primary sensorimotor cortex by using a mask of the primary sensorimotor cortex derived from the MNI152 standard space. Subsequent statistical analyses were performed only in this area thereby increasing the power of detecting group-differences.

Lastly, in the CRPS group, we studied the effect of pain intensity (NRS) and disease duration (in months) on GMV.

### *White matter structural connectivity (DTI)*

Voxel-wise statistical analyses of fractional anisotropy (FA) was carried out using tract-based spatial statistics (TBSS)<sup>144</sup>. FA is a measure of mean diffusivity along white matter tracts which represents the structural connectivity of those tracts<sup>145</sup>.

DTI images were first converted to “Neuroimaging Informatics Technology Initiative” files using a ExploreDTI v4.8.3 toolbox<sup>146</sup>. Next, subject movements and eddy current induced distortions were corrected with FSL-eddy. Subsequently we extracted the brain<sup>140</sup> and fitted a diffusion tensor at each voxel of the images. The resulting FA data were aligned into a common space<sup>141</sup>. The individual FA data were concatenated into a mean FA skeleton representing the centre of all common white matter tracts per group (CRPS and HC). Lastly, we used permutation-based non-parametric testing with TFCE (FWE  $p < .05$ ).

In a separate analysis we correlated the individual whole brain FA data to whole brain GMV to replicate previous results of a disrupted relationship between white matter connectivity and GMV in chronic CRPS patients<sup>41</sup>.

### *Resting state functional magnetic resonance imaging (rsfMRI)*

For rsfMRI analysis we used the graphical user interface of FSL- Multivariate Exploratory Linear Optimized Decomposition into Independent Components 3.12. Pre-processing of rs-fMRI images incorporated motion correction<sup>147</sup>, brain extraction<sup>140</sup>, spatial smoothing with a Gaussian kernel of 6-mm full width at half maximum and a high-pass temporal filtering of 0.01Hz. Images were registered to the high-resolution T<sub>1</sub>-weighted images (12 degrees of freedom) and subsequently to standard space MNI-152<sup>147,148</sup>.

Probabilistic independent component analysis<sup>149</sup> was performed using multi-session temporal concatenation with 25 components pre-set, and independent component map threshold of 0.5 (probability that a voxel belongs to a resting state network and not to background noise).



From these 25 networks we selected the sensorimotor, parietal, right and left executive attentional, salient and default mode network for further statistical analysis based on their role in sensory, pain and motor processing and on previous reports of alterations in CRPS patients<sup>45,123</sup>. We then made a mask of these networks (14,5% of total brain volume) and computed functional connectivity of each voxel within the mask with each of the 6 networks. Next, we performed dual regression<sup>150</sup>. Lastly, we used statistical between-group analysis with permutation-based non-parametric testing with TFCE (FWE  $p < .05$ ) to find significant group differences. A GLM was used with mean GMV and age as nuisance variables.

## RESULTS

### *Participants*

Data are presented as means  $\pm$  standard deviation when not stated differently. Nineteen female CRPS patients ( $48.1 \pm 11.6$  years) and 19 female healthy controls of similar age ( $49.4 \pm 14.3$  years; age:  $t(37)=0.31$ ,  $p=.76$ ) were included in the study. One patient (nr 19) could not complete the full scanning protocol due to nausea in the MRI scanner; therefore only structural images are available for this patient. RsfMRI and DTI data of one HC and rsfMRI data of patient 10 had to be excluded from the analysis due to significant motion artefacts. Therefore 19 patients and 19 HC's were included in the VBM analysis, 18 patients and 18 HC's in the DTI analysis, and 17 patients and 18 controls in the rsfMRI analysis.

Characteristics of the CRPS group can be found in Table 1. All patients had chronic CRPS, median 6.7 [2-11,75] years and were affected in at least one hand. The pain intensity in the examined hand was  $7.1 \pm 1.5$  on a scale of 0 to 10.

**Table 1** Patient characteristics

| CRPS patients | Age         | HD | Affected side | Disease duration (months) | CRPS severity score (0-17) | Budapest criteria | BFM | Loss VMC | NRS (0-10) | MPQ (0-63) | RSQ (0-5) | Pain- and centrally acting medication          |
|---------------|-------------|----|---------------|---------------------------|----------------------------|-------------------|-----|----------|------------|------------|-----------|------------------------------------------------|
| 1             | 54          | R  | R             | 120                       | 12                         | Research          | 16  | yes      | 5          | 26         | 3.68      | Zaldiar, arcoxia, lyrica,                      |
| 2             | 67          | L  | R             | 63                        | 14                         | Research          | 16  | yes      | 8          | 15         | 3.80      | Oxycontin, gabapentin, fexofenadin, betahistin |
| 3             | 48          | L  | R             | 141                       | 16                         | Research          | 29  | yes      | 7          | 42         | 2.82      | Temazepam, Rivotril                            |
| 4             | 27          | R  | L             | 25                        | 10                         | Clinical          | 0   | no       | 7          | 24         | 2.82      | Tramadol                                       |
| 5             | 34          | R  | R             | 69                        | 6                          | Research          | 16  | yes      | 6          | 18         | 3.26      | Diclofenac                                     |
| 6             | 35          | L  | L             | 80                        | 10                         | Clinical          | 32  | yes      | 9          | 39         | 4.67      | Oxycontin, baclofen, temazepam, oxynorm        |
| 7             | 56          | L  | R             | 35                        | 12                         | Clinical          | 17  | yes      | 6          | 29         | 3.36      | Lyrica, zolpidem                               |
| 8             | 50          | R  | R             | 150                       | 11                         | Clinical          | 18  | yes      | 10         | 51         | 4.56      | Morfine, diazepam, rivotril                    |
| 9             | 51          | R  | R             | 82                        | 10                         | Clinical          | 12  | yes      | 8          | 25         | 3.91      | -                                              |
| 10            | 64          | L  | L             | 121                       | 11                         | Clinical          | 11  | yes      | 8          | 18         | 3.20      | Amitriptyline, Panadol, diazepam               |
| 11            | 37          | R  | L             | 84                        | 14                         | Research          | 28  | yes      | 8          | 28         | 3.80      | Lyrica, baclofen, paracetamol                  |
| 12            | 50          | L  | L             | 324                       | 12                         | Research          | 17  | yes      | 8          | 26         | 2.93      | Gabapentin, baclofen, zolpidem                 |
| 13            | 33          | R  | R             | 204                       | 11                         | Research          | 33  | yes      | 5          | 38         | 4.19      | Lyrica, paracetamol, diazepam                  |
| 14            | 51          | R  | L             | 10                        | 9                          | Clinical          | 0   | no       | 8          | 29         | 2.59      | Lyrica, paracetamol, tramadol, tenazepam       |
| 15            | 55          | R  | L             | 360                       | 13                         | Research          | 14  | yes      | 5          | 27         | 2.76      | Lyrica                                         |
| 16            | 60          | R  | L             | 13                        | 14                         | Research          | 12  | Yes      | 7          | 25         | 3.77      | Tramadol, gabapentine                          |
| 17            | 37          | R  | R             | 24                        | 8                          | Clinical          | 0   | no       | 6          | 30         | 2.00      | Lyrica, amitriptyline                          |
| 18            | 42          | R  | L             | 18                        | 11                         | Research          | 0   | no       | 9          | -          | 2.63      | Amitriptyline                                  |
| 19            | 61          | R  | L             | 9                         | 12                         | Research          | 4   | yes      | 7          | -          | -         | Paracetamol                                    |
| Mean ± SD     | 48.1 ± 11.6 |    |               | 100.8 ± 100.5             | 11.5 ± 2.0                 |                   |     |          | 7.1 ± 1.5  | 28.8 ± 9.2 | 3.6 ± 1.1 |                                                |

CRPS = complex regional pain syndrome; HD = hand dominance; BFM = Burk-Fahn-Marsden scale; Loss VMC = loss of voluntary motor control; NRS = numeric rating scale; MPQ = McGill pain questionnaire; RSQ = Radboud skills questionnaire; L = left, R = right

## *MRI data*

### *Total and local grey matter volume*

Total brain grey matter did not differ between the two groups (CRPS:  $752.01 \pm 46.6 \text{ cm}^3$  vs HC:  $754.77 \pm 43.1 \text{ cm}^3$ ;  $t(38)=0.14$ ,  $p=.89$ ).

Local GMV analysis between CRPS patients and HC's using the flipped and non-flipped data did not result in significant FWE corrected differences between the two groups. Table 2 reports clusters with a minimum cluster volume of  $45 \text{ mm}^3$ <sup>42</sup> with uncorrected p-values ( $p<.001$ ) and the corresponding FWE corrected p-values ( $p<.05$ ). Subsequent analysis of only the sensorimotor cortex did not result in any significant cluster difference. Including total grey-matter in the analysis as an additional nuisance variable did not change the results.

In the patient group, local GMV did not correlate significantly with pain or disease duration in the flipped and non-flipped data set. Total brain grey matter correlated negatively with age (CRPS:  $r=-.556$ ,  $p=.013$ ; HC:  $r=-.684$ ,  $p=.001$ ), but the strength of the correlation did not differ significantly between the groups ( $z(38)=0.59$ ,  $p=.55$ ).

### *White matter connectivity*

No regional difference in FA was found between CRPS patients and HCs (table 3).

Mean whole brain FA of white matter correlated significantly with total GMV in both groups equally (CRPS:  $r=.722$ ,  $p=.001$  vs HC:  $r=.612$ ,  $p=.007$ ;  $z(36)=.55$ ,  $p=.58$ ) (Figure 1a&b).

### *Resting state networks*

Table 4 reports in total 10 clusters with one-tailed FWE corrected (per rs-network) differences between CRPS patients and HCs. Table 5 reports cluster differences with a minimum cluster size of  $150 \text{ mm}^2$ , uncorrected for multiple testing ( $p<.001$ )<sup>151</sup>.

The largest and most significant cluster was found in the non-flipped data in the left posterior cingulate cortex ( $1232 \text{ mm}^3$ ,  $p=.006$ ) (Figure 2). In CRPS patients, this cluster showed positive connectivity with the left executive attentional network (mean z-score:  $1.48 \pm 1.05$ ), while in HCs this connectivity was negative ( $z=-4.19 \pm 1.12$ ). No correlation between connectivity scores and pain scores, disease duration or CRPS severity was found.

Table 2 Local grey matter volume differences (VBM)

| Data and contrast | Cortical region          | Side | N voxels in cluster | Volume cluster mm <sup>3</sup> | MNI (mm) max |     |     | Local max t-value | Uncorrected p-value | FWE Corrected p-value |
|-------------------|--------------------------|------|---------------------|--------------------------------|--------------|-----|-----|-------------------|---------------------|-----------------------|
| Flipped data      |                          |      |                     |                                |              |     |     |                   |                     |                       |
| HC > CRPS         | Temporal lobe            | R    | 194                 | 1552                           | 28           | -26 | -32 | 2.280             | <.001               | .300                  |
|                   | Cerebellum               | R    | 55                  | 440                            | 18           | -32 | -48 | 2.124             | "                   | .378                  |
|                   | Temporal lobe            | L    | 39                  | 312                            | -30          | -22 | -22 | 2.021             | "                   | .451                  |
|                   | Cerebellum               | L    | 30                  | 240                            | -16          | -80 | -46 | 3.084             | "                   | .127                  |
|                   | Occipital fusiform gyrus | R    | 13                  | 104                            | 36           | -64 | -8  | 2.773             | "                   | .160                  |
| Non-flipped data  |                          |      |                     |                                |              |     |     |                   |                     |                       |
| CRPS > HC         | Frontal lobe             | R    | 184                 | 1472                           | 46           | 48  | -6  | 3.234             | <.001               | .417                  |
| HC > CRPS         | Temporal lobe            | L    | 102                 | 816                            | -30          | -24 | -24 | 2.537             | "                   | .347                  |

VBM = voxel based morphometry; HC = healthy control; CRPS = complex regional pain syndrome; MNI = Montreal neurological institute (brain model derived from mean

Table 3 White matter connectivity (FA)

| Data and contrast | Cortical region                | Side | N voxels in cluster | Volume cluster mm <sup>3</sup> | MNI (mm) max |     |     | Local max t-value | Uncorrected p-value | FWE Corrected p-value |
|-------------------|--------------------------------|------|---------------------|--------------------------------|--------------|-----|-----|-------------------|---------------------|-----------------------|
| Flipped data      |                                |      |                     |                                |              |     |     |                   |                     |                       |
| CRPS > HC         | Frontal                        | R    | 4                   | 4                              | 22           | 47  | 26  | 3.540             | <.01                | 1                     |
|                   | Inferior frontal gyrus         | L    | 24                  | 24                             | -42          | 14  | 22  | 1.163             | ''                  | .778                  |
|                   | Secondary somatosensory cortex | L    | 6                   | 6                              | -41          | -22 | 22  | 2.768             | ''                  | 1                     |
| Non-flipped data  |                                |      |                     |                                |              |     |     |                   |                     |                       |
| HC > CRPS         | Temporal lobe                  | R    | 15                  | 15                             | 25           | 0   | -30 | 2.028             | <.01                | 1                     |

FA = fractional anisotropy; HC = healthy control; CRPS = complex regional pain syndrome; MNI = Montreal neurological institute (brain model derived from mean 152 healthy persons); FWE = family wise error

**Table 4** Differences in resting state network activation, FWE corrected

| Data and contrasts | Cortical region        | Connectivity with resting state network | Side | N voxels in cluster | Volume cluster mm <sup>3</sup> | MNI (mm) Z | X   | Y  | Local max t-value | FWE Corrected p-value = one tailed |
|--------------------|------------------------|-----------------------------------------|------|---------------------|--------------------------------|------------|-----|----|-------------------|------------------------------------|
| Flipped data       |                        |                                         |      |                     |                                |            |     |    |                   |                                    |
| CRPS > HC          | Precentral gyrus       | r-EAN                                   | R    | 12                  | 96                             | 12         | -16 | 48 | 5.06              | .032                               |
| Non-flipped data   |                        |                                         |      |                     |                                |            |     |    |                   |                                    |
| CRPS > HC          | PCC                    | l-EAN                                   | L    | 154                 | 1232                           | -4         | -26 | 44 | 5.66              | .006                               |
|                    | Postcentral gyrus      | l-EAN                                   | R    | 25                  | 200                            | 4          | -38 | 72 | 4.17              | .038                               |
|                    |                        | l-EAN                                   | L    | 14                  | 112                            | -8         | -34 | 72 | 4.41              | .039                               |
|                    |                        | l-EAN                                   | L    | 11                  | 88                             | -14        | -42 | 70 | 4.04              | .044                               |
|                    | Precentral gyrus       | l-EAN                                   | L    | 3                   | 24                             | -16        | -26 | 74 | 4.46              | .044                               |
|                    | Superior frontal gyrus | l-EAN                                   | R    | 15                  | 120                            | 12         | 36  | 50 | 4.48              | .039                               |
|                    | Frontal pole           | l-EAN                                   | R    | 13                  | 104                            | 16         | 38  | 42 | 5.25              | .027                               |
|                    | Superior frontal gyrus | l-EAN                                   | R    | 12                  | 96                             | 4          | 26  | 48 | 4.47              | .043                               |
|                    | Lateral occipital lobe | l-EAN                                   | R    | 5                   | 40                             | 22         | -60 | 38 | 5.83              | .038                               |

HC = healthy control; CRPS = complex regional pain syndrome; MNI = Montreal neurological institute (brain model derived from mean 152 healthy persons); FWE = family wise error; PCC = posterior cingulate cortex; r-EAN = right executive attentional network; l-EAN = left executive attentional network

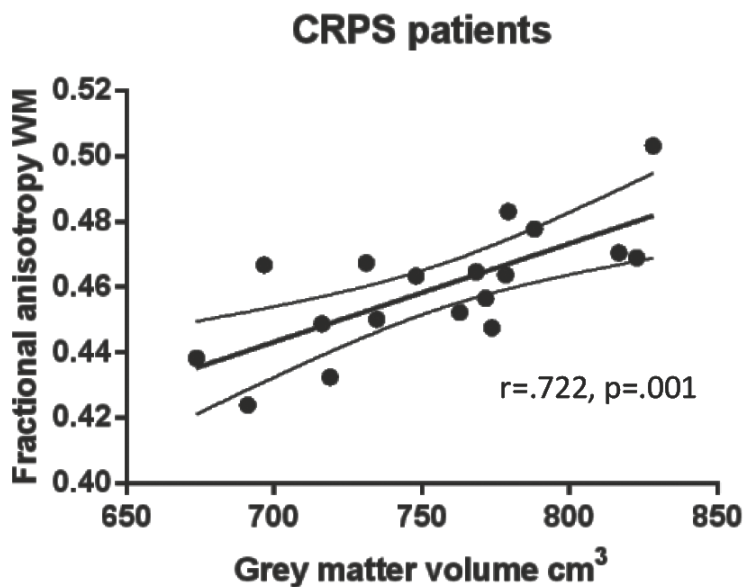


Figure 1a

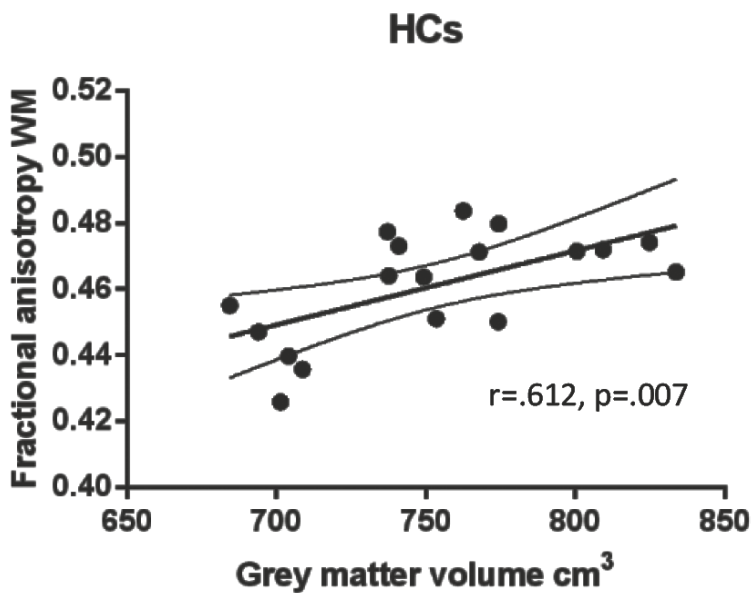


Figure 1b

(a) Correlation between white matter connectivity and grey matter volume. (b) Correlation between white matter connectivity and grey matter volume. Interpolate line with 95% confidence interval; CPRS = complex regional pain syndrome; HCs = healthy controls; WM = white matter

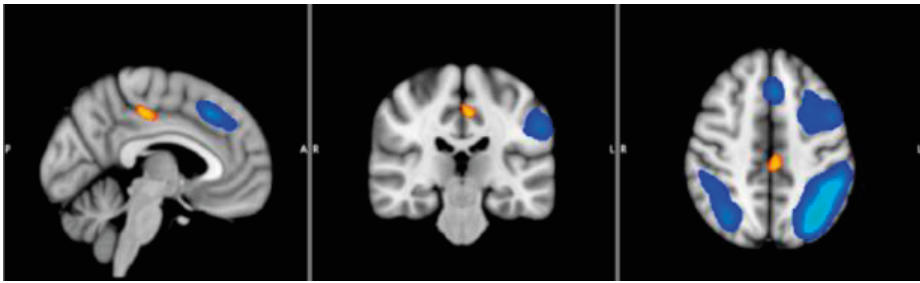
**Table 5** Differences in resting state networks activation, FWE uncorrected

| Data and contrasts | Connectivity with resting state network | Side | N voxels in cluster | Volume cluster mm <sup>3</sup> | MNI (mm) max |     |     | Local max t-value | Uncorrected p-value | FWE Corrected p-value |
|--------------------|-----------------------------------------|------|---------------------|--------------------------------|--------------|-----|-----|-------------------|---------------------|-----------------------|
|                    |                                         |      |                     |                                | Z            | X   | Y   |                   |                     |                       |
| Flipped data       |                                         |      |                     |                                |              |     |     |                   |                     |                       |
| CRPS > HC          | DMN                                     | R    | 37                  | 240                            | 30           | -40 | -12 | 5.17              | <0,001              | .477                  |
|                    |                                         | L    | 108                 | 864                            | -24          | 18  | 34  | 4.77              |                     | .116                  |
| I-EAN              |                                         | R    | 63                  | 504                            | 34           | 8   | 30  | 4.09              |                     | .220                  |
|                    |                                         | R    | 35                  | 280                            | 66           | -54 | -2  | 4.27              |                     | .547                  |
|                    |                                         | L    | 32                  | 256                            | -6           | -60 | 60  | 4.38              |                     | .145                  |
|                    |                                         | L    | 30                  | 240                            | -42          | -58 | 58  | 3.23              |                     | .428                  |
|                    |                                         | R    | 20                  | 160                            | 54           | 4   | 28  | 3.92              |                     | .457                  |
| Saliience          |                                         | L    | 80                  | 640                            | -40          | 40  | -16 | 4.28              |                     | .374                  |
|                    |                                         | L    | 33                  | 264                            | -44          | -56 | -16 | 4.43              |                     | .653                  |
| r-EAN              |                                         | R    | 180                 | 1440                           | 24           | -66 | 44  | 3.72              |                     | .152                  |
|                    |                                         | L    | 177                 | 1416                           | -18          | -76 | 38  | 3.83              |                     | .174                  |
|                    |                                         | R    | 142                 | 1136                           | 12           | -16 | 48  | 5.06              |                     | .032                  |
|                    |                                         | R    | 95                  | 760                            | 36           | -56 | 54  | 4.39              |                     | .101                  |
|                    |                                         | R    | 64                  | 512                            | 18           | 34  | 42  | 3.16              |                     | .425                  |
|                    |                                         | L    | 47                  | 376                            | -12          | -12 | 48  | 3.55              |                     | .155                  |
|                    |                                         | L    | 42                  | 336                            | -4           | 62  | 28  | 3.91              |                     | .220                  |
|                    |                                         | L    | 32                  | 256                            | -18          | 50  | 24  | 3.36              |                     | .241                  |
|                    |                                         | L    | 26                  | 208                            | -26          | 38  | 28  | 3.29              |                     | .276                  |
| SIM1               |                                         | -    | 25                  | 200                            | 0            | 20  | 52  | 3.35              |                     | .379                  |
|                    |                                         | L    | 25                  | 200                            | -4           | -38 | 28  | 4.32              |                     | .227                  |
|                    |                                         | R    | 20                  | 160                            | 14           | -50 | 18  | 3.56              |                     | .514                  |

**Table 5** Differences in resting state networks activation, FWE uncorrected (continued)

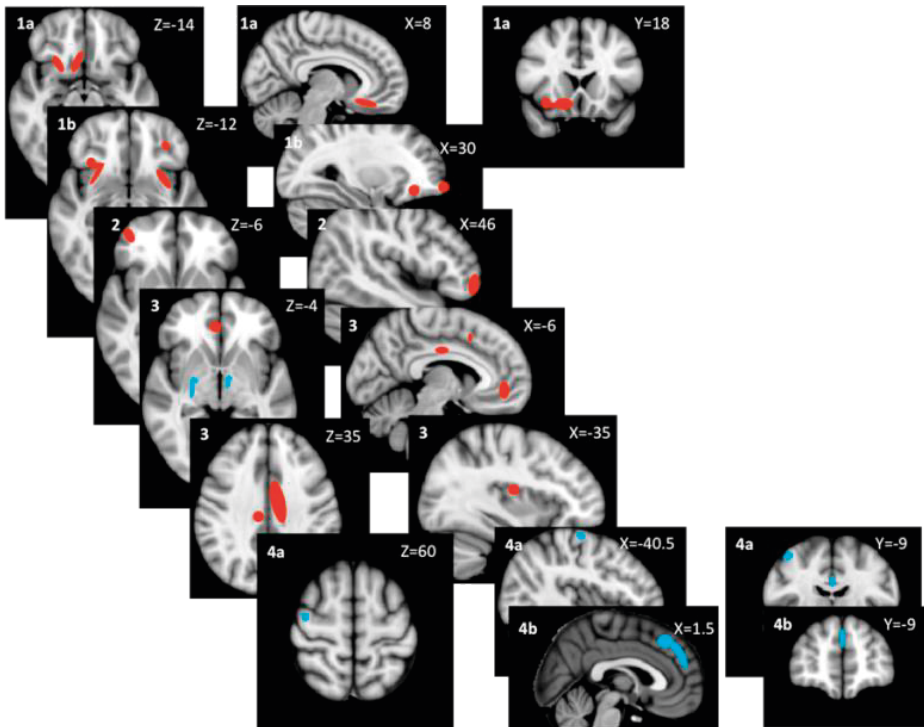
| Data and contrasts | Connectivity with resting state network | Side      | N voxels in cluster | Volume cluster mm <sup>3</sup> | MNI (mm) | max Z | max X | max Y | Local max t-value | Uncorrected p-value | FWE Corrected p-value |
|--------------------|-----------------------------------------|-----------|---------------------|--------------------------------|----------|-------|-------|-------|-------------------|---------------------|-----------------------|
| HC > CRPS          | DMN                                     | R         | 62                  | 496                            | 44       | 26    | 6     | 3.79  |                   | <0.001              | .301                  |
|                    |                                         | L         | 60                  | 480                            | -48      | -70   | -10   | 3.57  |                   |                     | .587                  |
|                    |                                         | R         | 36                  | 288                            | 4        | -6    | -2    | 4.11  |                   |                     | .650                  |
|                    |                                         | L         | 28                  | 224                            | -40      | -82   | 14    | 2.84  |                   |                     | .644                  |
|                    |                                         | R         | 21                  | 168                            | 40       | -4    | 62    | 3.23  |                   |                     | .623                  |
|                    |                                         | L         | 24                  | 192                            | -38      | -60   | 60    | 4.16  |                   |                     | .511                  |
| Non-flipped data   |                                         |           |                     |                                |          |       |       |       |                   |                     |                       |
| CRPS > HC          | l-EAN                                   | L         | 461                 | 3688                           | -4       | -26   | 44    | 5.66  |                   | <0.001              | .006                  |
|                    |                                         | L         | 427                 | 3416                           | -16      | -26   | 74    | 4.46  |                   |                     | .044                  |
|                    |                                         | L         | 135                 | 1080                           | -44      | -24   | 48    | 3.88  |                   |                     | .099                  |
|                    |                                         | L         | 34                  | 272                            | -4       | -26   | 64    | 3.39  |                   |                     | .065                  |
|                    |                                         | R         | 247                 | 1976                           | 16       | 38    | 43    | 5.15  |                   |                     | .027                  |
|                    |                                         | L         | 124                 | 992                            | -28      | 36    | 34    | 3.61  |                   |                     | .296                  |
| Salience           |                                         | R         | 92                  | 736                            | 22       | -60   | 38    | 5.83  |                   |                     | .038                  |
|                    |                                         | R         | 19                  | 152                            | 12       | -4    | 58    | 3.65  |                   |                     | .210                  |
|                    |                                         | R         | 97                  | 776                            | 20       | 48    | 14    | 5.29  |                   |                     | .079                  |
|                    |                                         | L         | 31                  | 248                            | -14      | -88   | 0     | 4.95  |                   |                     | .999                  |
|                    |                                         | R         | 133                 | 1064                           | 24       | 4     | 62    | 4.12  |                   |                     | .188                  |
|                    |                                         | HC > CRPS | Parietal cortex     |                                |          |       |       |       |                   |                     |                       |

HC = healthy control; CRPS = complex regional pain syndrome; MNI = Montreal neurological institute (brain model derived from mean 152 healthy persons); FWE = family wise error; SIM1 = primary sensorimotor cortex; r-EAN = right executive attentional network; l-EAN = left executive attentional network



**Figure 2**

Difference in functional connectivity between CRPS patients and HCs. Non-flipped data. P=posterior; A=anterior; S=superior; I=inferior. Centre of “gravity” for this cluster (mm):  $x=-4.16$ ,  $y=-23.3$ ,  $z=44.3$ : left hemisphere: posterior cingulate cortex. Activation shown (red-yellow): significant difference in connectivity between CRPS patients (positive) and HCs (negative) with left executive attentional network portrayed in blue.



**Figure 3**

Schematic representation of reported alterations in grey matter volume in CRPS patients and uncorrected data this paper. Red=decreased grey matter volume (GMV), Blue=increased GMV; coordinates (x/y/z) in mm; X=left-to-right axis; Y=posterior-to-anterior; Z=caudal-to-cranial; 1a=Geha et al.<sup>41</sup>; 1b=Baliki et al.<sup>44</sup>; 2=uncorrected data from this paper; 3=Barad et al.<sup>42</sup>; 4a=Pleger et al.<sup>43</sup> flipped data; 4b=Pleger et al, non-flipped data

## DISCUSSION

Contrary to previous studies, in our sample of chronic CRPS patients GMV and white matter connectivity did not differ with age and gender matched healthy controls. However, using less stringent correction methods in the VBM analysis, structural alterations were seen bilaterally in the cerebellum, temporal lobes, occipital fusiform gyrus and right lateral orbitofrontal cortex. We did find differences in functional connectivity networks, although the statistical and clinical significance of these results need further elaboration.

In the next section we discuss for each analysis the discrepancies between our results and previous published results in literature in adult CRPS patients with special attention to consistencies in terms of localisation, quantity and directionality of the previous reported changes in brain structure and function in rest. In the last section we discuss general observations that apply to all MRI analysis used.

### *Absence of local grey matter volume differences*

Our findings showing no FWE corrected differences in local GMV between CRPS patients and HCs contrasts with those of two earlier studies in CRPS showing decreased GMV in the right Anterior Insula (AI)<sup>41</sup> and bilateral AI<sup>44</sup> (see also figure 3). In Geha's paper, decreased GMV in the right AI significantly correlated with pain intensity only in young patients, while in Baliki's paper a reduction of GMV in the primary sensorimotor and insular cortex correlated with pain in patients with disease duration > 5 years. Of note, in our sample, GMV difference in the rAI for both the flipped and non-flipped data was close to zero ( $p \approx 1$ ).

A study of Pleger et al<sup>43</sup> in 20 acute and chronically ill CRPS patients with an affected upper limb, showed increased GMV in the dorsomedial prefrontal cortex (non-flipped data) and in M1 contralateral to the affected hand (flipped data). These changes did not correlate with any clinical feature.

Barad et al<sup>42</sup> studied a group of 15 right-handed CRPS patients with a wide range in disease duration, who all were affected in the right hand. They reported reduced GMV in the dorsal insula, left orbitofrontal cortex and "several aspects of the cingulate cortex" but increased GMV bilaterally in the dorsal putamen and right hypothalamus. Both negative and positive relations between clinical parameters and GMV changes in this study could not be explained by significant differences in GMV between the groups, and therefore authors concluded that the observed abnormalities "are not central to CRPS pathology"<sup>42</sup>. In our patient sample, no correlations were found for pain intensity and disease duration with local GMV.

Collectively, in total 5 studies – including the data presented in this study – on local GMV in CRPS yielded varying or absent GMV changes with no or inconsistent correlations with clinical features. This questions the clinical relevance of these findings.

### *Absence of white matter connectivity changes*

We found no difference in white matter connectivity between CRPS patients and HCs.

Only one other study evaluated DTI in CRPS<sup>41</sup> and found a disrupted correlation between total brain GMV and white matter anisotropy. This finding was suggested to indicate diffuse reorganisation of white matter tracts, however, the results did not correlate with clinical parameters. In our data sample, no such dissociation of GMV and white matter anisotropy was found in any of the groups. Collectively, there is so far no compelling evidence for changes in white matter connectivity in CRPS patients.

### *Alterations in resting state networks*

We found 10 “significant” clusters of altered resting state networks, all related to executive attentional networks (Table 4). However, there is a need for caution in interpreting these results. First, next to the absence of a prior hypothesis regarding the direction of activation differences (CRPS>HC or HC>CRPS), all FWE corrected results are 1-tailed tested. Second, the consecutive rs-networks should be considered as multiple tests. Therefore, when full correction for multiple testing is applied, the  $\alpha$  would change from  $<.05$  to  $\leq .0041$  (i.e.,  $.05 / (2 \text{ tailed} \times 6 \text{ tests})$ ) (FSL Dual regression user guide. Using this threshold, none of the results were significantly different between the groups. Third, no correlation with clinical parameters was found.

Two papers focussed on resting state networks in adult CRPS patients. First – Bolwerk et al – studied 12 heterogeneous CRPS patients (type 1 and 2) with affected upper and lower limbs<sup>45</sup>. They found significant reductions in default mode network (DMN)<sup>152</sup> activation in CRPS patients and a diffuse increase in connectivity of S1M1 with other brain regions (cingulate cortex, precuneus, thalamus and prefrontal cortex). None of these changes correlated significantly with pain scores. We could not replicate any of these results. In addition, when we used a similar cluster size threshold of  $150\text{mm}^3$  as Bolwerk et al., numerous clusters in many rs-networks that emerged in FWE uncorrected analysis (uncorrected p-value  $<.001$ ), appeared nonsignificant after correction of multiple comparisons.

Baliki et al<sup>123</sup> compared 5 resting state networks between healthy controls and 3 pain patients groups, including CRPS patients. Only the DMN showed significant differences in connectivity between pain patients and healthy controls, most notably decreased connectivity with

the medial prefrontal cortex and anterior cingulate cortex and increased connectivity with the precuneus. Unfortunately, no distinctive activation pattern for CRPS patients was found.

Collectively, absence of evidence in our sample, absence of distinctive CRPS associated changes in connectivity and absence of significant correlations with clinical features let us conclude that compelling evidence for specific resting state networks changes in CRPS patients is lacking.

### *General discussion*

We did not find compelling evidence for CRPS specific changes in brain structure and function in rest. Most striking was the absence of anticipated changes in somatosensory and limbic areas. Conflicting findings of all studies – including our own uncorrected VBM analysis data – and the absence of consistent clinical correlations questions the clinical relevance of previous MRI findings of reported altered brain structure and function in rest in CRPS patients. However, potential issues explaining the lack of results and discrepancies between the reported data should be considered. First, the lack of results might be the consequence of an underpowered study design, although the sample size did not differ significantly with the other papers. In addition, scanning parameters such as voxel sizes and repetition times differ between the studies and can have influence on the strength of results. Second, sample characteristics (gender, disease duration, CRPS type, applied diagnostic criteria, symptoms, and affected limbs) vary across studies. These differences may contribute to some variability in the magnitude of the results, laterality of findings if different limbs are examined, and spatial representation differences in primary and secondary sensorimotor cortices when affected upper limbs are compared with affected lower limbs. However, when CRPS would encompass uniform changes of the brain, at least the directionality of changes (increase or decrease) would be expected to be consistent between the different data sets as well as clinical parameters (e.g. pain) that correlate to these changes –which is not the case.

Third, changes in brain structure and function at rest may depend on disease stage, i.e. present in acute CRPS (<6months), when symptoms are more pronounced, or change during the course of the disease from nociceptive to emotional circuits<sup>153</sup>, decreasing overall group effects. Although our patients were all chronically ill, their disease durations varied which may have influenced the detection of a potential disease duration effect. However, the absence of a correlation between disease duration and MRI data, renders this explanation unlikely.

Fourth, centrally acting drugs could have obscured some changes in brain structure and function, especially in our patient sample with many very long chronically ill patients. However, in all cited papers, patients continued their medication and this therefore is an unlikely explanation for the different findings between studies.



Fifth, diversity in software packages and analysis options in (f)MRI research, in particular the methods used to correct for multiple testing, can have an enormous impact on the results, hampering a reliable comparison of findings between studies<sup>154,155</sup>. We used TFCE to find cluster differences between CRPS patients and healthy controls and based our conclusions on FWE controlled results. One could argue that this is too stringent considering our sample size. However, when we increased the power by limiting the amount of investigated voxels – by focussing solely on the sensorimotor cortex – during the VBM analysis we could still not find significant FWE corrected differences between the groups. For all other analyses, we choose a priori not to focus on one particular brain area since many previous interpretations of event-related fMRI research was based on uncorrected, albeit conservative p-values, making the results liable to type 1 errors<sup>124</sup>. Second; the *uncorrected* clusters we found in the VBM whole brain analysis did not correspond with the previous results in literature (figure 3). Collectively, this indicates that data of altered GMV in CRPS patients are inconsistent and questions the evidence for specific and clinically relevant changes in brain structure in CRPS patients.

Lastly, instead of specific changes in brain structure and function associated with CRPS symptoms, some evidence suggests that these symptoms are generated by a mismatch between aberrant afferent signals from the affected limb and the internal state of limb in the brain<sup>55–57</sup>. The resulting aberrant processing likely involves brain circuits containing many parts of the brain and probably changes depending on the afferent feedback –or location in space<sup>156</sup>– of the affected limb. Under such circumstances local grey matter or white matter changes are not to be expected, and common resting state networks would not be involved.

Future MRI studies should focus on this aberrant processing of external stimuli, which may one day result in the elucidation of these *complex* –and fascinating– symptoms.

## CONCLUSION

Absence of evidence is not evidence of absence. We therefore cannot prove that changes in brain structure and function in rest are absent in CRPS patients. However, current evidence for altered brain structure and function in rest in CRPS patients is not consistent and in our data in female patients not present. Caution is required when therapeutic strategies are based on these presumed changes of the brain.

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# Chapter 5

# Noxious heat elicits opposite responses in brain regions that mediate salience and affection in complex regional pain syndrome

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# ABSTRACT

*Background:* The nature of altered processing of sensory stimuli and motor control in complex regional pain syndrome (CRPS) patients is poorly understood. In an earlier study in patients with CRPS we found no convincing alterations of brain structure or function in rest. In this study we therefore investigated how central brain networks for somatosensory, motor and behavioural phenomena in CRPS respond to external stimuli and applied a painful heat stimulus, which elicits hyperalgesia, a key characteristic of CRPS.

*Method:* During functional MRI scanning, we administered the heat stimulus to the affected hand of CRPS patients and the right hand of healthy controls. Brain activations were compared between the groups. Activation patterns that significantly differed between the groups were further analysed by measuring their functional connectivity with other brain areas using psychophysiological interaction analyses.

*Results:* Fifteen female CRPS patients and 16 female healthy controls were included in the final analysis. Patients rated the evoked pain significantly higher than healthy controls. In both groups, a significant bilateral activation of the insula, thalamus, anterior cingulate cortex and the secondary somatosensory cortex was seen. Additionally, in comparison to healthy controls, we found an activation of the left temporal parietal junction (TPJ) in CRPS patients, a brain area involved in salience detection. Furthermore, brain activations in the left TPJ were negatively correlated with activity in prefrontal cortices in CRPS patients, not in healthy controls.

*Conclusion:* While experiencing a painful heat stimulus, CRPS patients display increased salience detection in combination with opposite activation of brain regions involved in reducing the affective burden of pain.

# INTRODUCTION

Complex regional pain syndrome (CRPS) is a neuropathic pain syndrome characterized by autonomic, sensory, trophic and motor disturbances of the affected limb. The pathophysiology is thought to encompass a pathologic host response to tissue injury, involving both the immune and nervous system, that in time leads to aberrant neuroplasticity of the spinal cord and brain<sup>1,157</sup>.

In CRPS, findings on processing of sensory stimuli<sup>49,158–160</sup> and motor control<sup>52–54</sup> in the brain while patients are at rest, are inconsistent. Interestingly, several studies in CRPS reported widespread cerebral activation in somatosensory, attentional- and motor brain areas during mechanically induced allodynia<sup>161,162</sup> and altered emotional processing in response to electrically induced pain<sup>158,163</sup>. However, 2 of these studies<sup>161,162</sup> were uncontrolled and all studies presented results insufficiently corrected for multiple comparison. Therefore, we investigated brain responses to a moderately painful heat stimulus in CRPS patients and healthy controls.

The heat stimulus is designed to elicit slow temporal summation of C-fibre-evoked responses of dorsal horn neurons which induce hyperalgesia. This process, termed windup<sup>164,165</sup>, is mediated by an upregulation of the N-methyl-D-aspartate (NMDA) receptor<sup>166</sup> which is thought to play a key role in the chronification of pain and a target for pain relief in CRPS<sup>167</sup>. Using this stimulus, we expect to be able to study networks involved in somatosensory, motor and behavioural processing adequately.

## METHODS

Part of the method section has been published before<sup>160</sup>. In short:

### *Participants*

Between May 2011 and March 2013, female CRPS patients followed up at the neurology outpatient clinic of the Leiden University Medical Center (LUMC) in Leiden, the Netherlands, who met at least the Budapest clinical criteria for CRPS type 1<sup>168</sup> in an upper limb were asked to participate in this study. Participants were excluded if they suffered from (serious) neurological illness, were younger than 18 years, male, had known psychiatric disorders or suffered from any condition other than CRPS that is associated with pain of functional impairment of an upper extremity.

A group of healthy, pain-free controls, age and sex matched to the CRPS patients were additionally included. Many were hospital staff from other departments, or (PhD) students not linked to our research group.

All participants were screened for MRI contraindications before MRI acquisition.

The study protocol was approved by the Medical Ethics Committee of the LUMC (protocol nr NL34614.058.11), and written informed consent was obtained from all patients and control subjects.

### *Demographic data and pain measurements*

During the week prior to the investigation, patients completed questionnaires measuring pain (McGill Pain Questionnaire, MPQ)<sup>77</sup> and dexterity of the affected hand (Radboud skills questionnaire, RSQ)<sup>131</sup>. On the day of examination we collected data on demographic variables, pain severity experienced in the past week (numeric rating scale (NRS) 0–10, with 10 reflecting the worst pain imaginable), CRPS (CRPS severity score)<sup>75</sup> and loss of voluntary motor control such as dystonic postures (Burk-Fahn-Marsden scale)<sup>132</sup>, decreased active range of motion, weakness and slowness of movement of the affected hand.

### *Pain administration*

During fMRI scanning, repetitive heat pulses were applied to the affected hand in CRPS patients and the right hand of healthy controls. If CRPS signs were present in both hands, then the most affected hand was used. The heat pulses were applied by CHEPS (Contact heat evoked Potential stimulator, Medoc Advanced Medical Systems, Ramat Yishai, Israel). This device is capable of delivering extremely fast heating and cooling stimulation rates of the skin, 70 °C/sec and 40 °C/sec, respectively, due to a Heat foil Peltier thermode (HP). The HP thermode can stimulate a circular skin area of 27-mm diameter (5,73 cm<sup>2</sup>) and is composed of 2 layers: (1) an external layer that is composed of a very thin, fast heating foil with 2 electronic thermal sensors that can measure skin and thermode temperature and (2) a second layer consisting of a Peltier element. The rapid heating is induced in the first layer, the cooling in the second.

To elicit maximal windup, 8 trains of 9 repetitive heat pulses of 47 °C from a baseline of 30 °C were applied on glabrous skin on the dorsal side of the affected limb<sup>164,165,169</sup>. Before every run, 40 seconds of baseline activity was measured followed by 3 seconds of repetitive heat pulses (3Hz) and 47 seconds of rest. Thus, in total 90 seconds per run and 12 minutes of fMRI acquisition. We used the same temperature settings for all participants because we were interested in possible differences in responsiveness of brain activity to the same sensory stimulus. The maximum temperature of 47 °C was based on a previous study in fibromyalgia

patients<sup>165</sup> and was validated in a small trial (not published) in 6 healthy controls to validate pain scores and fMRI activity in response to the stimulus.

### *Pain ratings*

Before and outside the MRI scanner, participants were asked to rate the pain induced by the thermode with 10 seconds apart using the NRS. The average of 3 measurements was recorded as pain score elicited by the thermode before the scanning procedure.

At the end of fMRI acquisition, patients were asked to report the mean pain score of the last heat pulse train using the NRS scale.

### *MRI acquisition*

All scanning sessions were in the beginning of the evening. To prevent hearing loss due to loud scanner noise, participants received earplugs and wore headphones. Before commencing the experiment, first T<sub>1</sub>-weighted, DTI and resting state fMRI scans were made of which the results were published previously<sup>160</sup>.

Imaging data was acquired on a Philips 3.0 T Achieva MRI scanner using a 32-channel SENSE head coil (Philips Medical Systems, Best, The Netherlands). Structural T<sub>1</sub>-weighted gradient-echo imaging (for registration purposes) was acquired with the following parameters: slices: 140, voxel size: 1.17 x 1.17 x 1.2mm, repetition time (TR) 9.8ms, echo time (TE) 4.6ms, flip angle 8°, in-plane matrix resolution 256 x 256 slices, field of view 224. fMRI imaging was done with 38 slices, voxel size 2.75 x 2.75 x 2.75mm without a gap, TR 2400ms, TE 30ms, flip angle 80°, field of view 220.

### *MRI analysis*

For the fMRI statistical analysis we used FSL v5.0, Oxford, UK<sup>133–135</sup> with FMRIB Expert Analysis Tool (FEAT). For the primary analysis, pre-processing of fMRI images incorporated mirroring (“flipping”) the hemispheres of patients affected in (and stimulated on) the left arm to stack all “affected” hemispheres onto the same, left hemisphere (toolbox: FSLswapdim). A secondary analysis was done using the “non-flipped data” to rule out a “flipping bias” since the flipping of hemispheres is performed in 7 patients, and not in healthy controls. Motion correction was done using FLIRT<sup>147</sup>, removing of physiological or scanner-related artefacts using MELODIC and Fsl\_Regfilt<sup>149,170</sup>, brain extraction with BET<sup>140</sup>, spatial smoothing with a Gaussian kernel of 6-mm full width at half maximum and a high-pass temporal filtering of 0.01Hz. Images were registered to the high resolution T1-weighted images (12 df) and subsequently to standard space MNI-152<sup>148</sup>. Due to limited range of view, the cerebellum was not completely scanned in all participants, yielding incomplete data. Therefore, these data were excluded from further analysis.

We used FMRIB's Improved Linear Model (FILM)<sup>171</sup> for first level (individual) analysis of the pain stimulus with cluster z-statistic threshold 2.3,  $p < .05$ . For group level analysis we used FMRIB's Local Analysis of Mixed Effects (FLAME) stage 1<sup>172</sup> with covariate age. Single group averages (one sample T-test) and unpaired 2-group differences (two sample unpaired T-tests) were calculated. Correction for multiple testing was done at the cluster level using Family-Wise Error (FWE) with pre-threshold masking of the two group activation averages and z threshold  $>2.3$  and  $p < 0.05$ .

For the additional analysis of task-specific functional connectivity between different brain areas, we imputed the significant clusters found in the primary analysis as seeds in the psychophysiological interaction (PPI) analysis<sup>173174</sup>. PPI is a statistical MRI analysis that measures task-specific correlations of brain activity -positive or negative- between different brain areas and is therefore a measure of 'functional connectivity'.

In order to extract the BOLD fMRI signal time-course of the seed per participant, we first non-linearly transformed the region of interest (ROI) from standard space to native space. We then ran a new first level FEAT analysis with three regressors: the block design as the psychological regressor, the time course of the ROI as physiological regressor and lastly the product of the first two regressors ("interaction"). Using the acquired results, we performed a group level analysis as described above, cluster corrected for multiple correction using FWE at  $p < 0.05$ .

## RESULTS

### *Participants*

Data are presented as means  $\pm$  standard deviation when not stated differently.

Nineteen female CRPS patients (Table 1) and 19 age-matched healthy female controls were included in the study. One patient (nr 19) could not complete the full scanning protocol due to nausea in the MRI scanner; one patient (nr 10) and one healthy control had to be excluded from the analysis due to significant motion artefacts; one patient (nr 11) refused to participate during the MRI procedure due to fear of significant increase of pain; in one patient (nr 13) and two healthy controls the fMRI protocol could not be completed due to technical errors. Therefore 15 CRPS patients (age  $47.9 \pm 10.9$  years) and 16 healthy controls (age  $49.0 \pm 15.4$  years:  $t(30)=0.35$ ,  $p=.80$ ) remained for the fMRI analysis.

All patients that completed the fMRI protocol had chronic CRPS, with a median [and inter quartile range] disease duration of 6.6 [IQR 2-12,5] years, and were affected in at least one

**Table 1** Patient characteristics

| CRPS patients | Age         | hd | Affected side | Disease duration (months) | CRPS severity score (0-17) | Budapest criteria | BFM | Loss VMC | NRS (0-10) | MPQ (0-63) | RSQ (0-5) | Pain- and centrally acting medication            |
|---------------|-------------|----|---------------|---------------------------|----------------------------|-------------------|-----|----------|------------|------------|-----------|--------------------------------------------------|
| 1             | 54          | R  | R             | 120                       | 12                         | Research          | 16  | yes      | 5          | 26         | 3.68      | Paracetamol, tramadol, etoricoxib, pregabalin    |
| 2             | 67          | L  | R             | 63                        | 14                         | Research          | 16  | yes      | 8          | 15         | 3.80      | Oxycontin, gabapentin, fexofenadine, betahistine |
| 3             | 48          | L  | R             | 141                       | 16                         | Research          | 29  | yes      | 7          | 42         | 2.82      | Temazepam, clonazepam                            |
| 4             | 27          | R  | L             | 25                        | 10                         | Clinical          | 0   | no       | 7          | 24         | 2.82      | Tramadol                                         |
| 5             | 34          | R  | R             | 69                        | 6                          | Research          | 16  | yes      | 6          | 18         | 3.26      | Diclofenac                                       |
| 6             | 35          | L  | L             | 80                        | 10                         | Clinical          | 32  | yes      | 9          | 39         | 4.67      | Oxycontin, baclofen, temazepam, oxycodon         |
| 7             | 56          | L  | R             | 35                        | 12                         | Clinical          | 17  | yes      | 6          | 29         | 3.36      | Pregabalin, zolpidem                             |
| 8             | 50          | R  | R             | 150                       | 11                         | Clinical          | 18  | yes      | 10         | 51         | 4.56      | Morphine, diazepam, clonazepam                   |
| 9             | 51          | R  | R             | 82                        | 10                         | Clinical          | 12  | yes      | 8          | 25         | 3.91      | -                                                |
| 10*           | 64          | L  | L             | 121                       | 11                         | Clinical          | 11  | yes      | 8          | 18         | 3.20      | Amitriptyline, paracetamol, diazepam             |
| 11*           | 37          | R  | L             | 84                        | 14                         | Research          | 28  | yes      | 8          | 28         | 3.80      | Pregabalin, baclofen, paracetamol                |
| 12            | 50          | L  | L             | 324                       | 12                         | Research          | 17  | yes      | 8          | 26         | 2.93      | Gabapentin, baclofen, zolpidem                   |
| 13*           | 33          | R  | R             | 204                       | 11                         | Research          | 33  | yes      | 5          | 38         | 4.19      | Pregabalin, paracetamol, diazepam                |
| 14            | 51          | R  | L             | 10                        | 9                          | Clinical          | 0   | no       | 8          | 29         | 2.59      | Pregabalin, paracetamol, tramadol temazepam      |
| 15            | 55          | R  | L             | 360                       | 13                         | Research          | 14  | yes      | 5          | 27         | 2.76      | Pregabalin                                       |
| 16            | 60          | R  | L             | 13                        | 14                         | Research          | 12  | Yes      | 7          | 25         | 3.77      | Tramadol, gabapentin                             |
| 17            | 37          | R  | R             | 24                        | 8                          | Clinical          | 0   | no       | 6          | 30         | 2.00      | Pregabalin, amitriptyline                        |
| 18            | 42          | R  | L             | 18                        | 11                         | Research          | 0   | no       | 9          | -          | 2.63      | Amitriptyline                                    |
| 19*           | 61          | R  | L             | 9                         | 12                         | Research          | 4   | yes      | 7          | -          | -         | Paracetamol                                      |
| Mean ± SD     | 48.1 ± 11.6 |    |               | 100.8 ± 100.5             | 11.5 ± 2.0                 |                   |     |          | 7.1 ± 1.5  | 28.8 ± 9.2 | 3.6 ± 1.1 |                                                  |

CRPS=complex regional pain syndrome; HD=hand dominance; BFM=Burk-Fahn-Marsden scale; Loss VMC = loss of voluntary motor control; NRS=numeric rating scale; MPQ=McGill pain questionnaire; RSQ=Radboud skills questionnaire; L=left, R=right

hand. The mean (and SD) pain intensity of the examined hand in rest of the patients was  $7.1 \pm 1.4$  (NRS).

### *Pain scores CHEPS*

Before the scanning procedure, CRPS patients rated the evoked pain significantly higher than healthy controls (NRS; CRPS:  $5.3 \pm 2.1$ , HC's  $3.5 \pm 1.5$ ;  $t(30) = -2.78$ ,  $p = .009$ ).

Patients, and particularly healthy controls, rated the last stimulus train slightly higher, which resulted in a non-significant group difference in pain ratings (CRPS  $5.8 \pm 2.5$ , HC's  $4.4 \pm 1.6$ ;  $t(30) = -1.78$ ,  $p = .084$ ). These pain scores in patients did not correlate with the MPQ or the NRS pain severity in the last week.

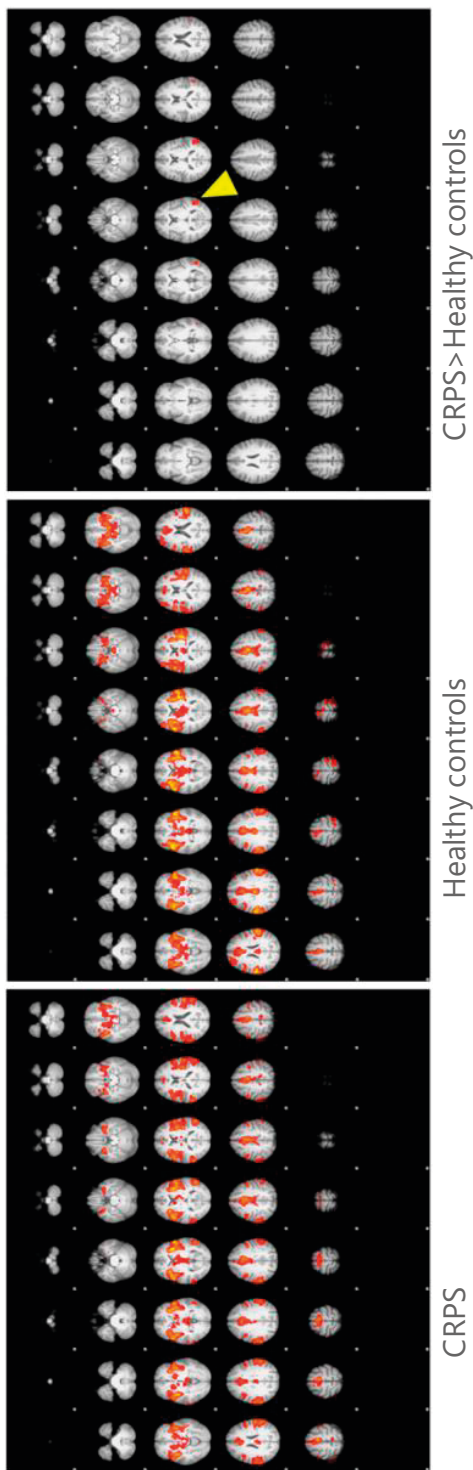
### *fMRI results*

During stimulation of the affected or right hand, CRPS patients and healthy controls had significant and robust activation of bilateral insula, thalamus, anterior cingulate cortex, and bilateral activation of the secondary somatosensory cortex (figure 1a, table 2). In CRPS patients an additional bilateral activation of the temporoparietal junction (TPJ) was seen, of which the cluster on the left side was significantly more activated in comparison to healthy controls (figure 1b). The mean activation in this cluster correlated with disease duration (Pearson's  $r = .55$ ,  $p = .03$ ) in CRPS patients. No significant correlation was found with any of the pain scores.

In both groups, using the cluster of the left TPJ as a seed, positive functional connectivity was found with bilateral secondary somatosensory cortex, anterior cingulate cortex (ACC) and insula. Negative functional connectivity was found bilaterally in the posterior cingulate cortex, precuneus, inferior parietal lobule and occipital cortex. In contrast to healthy controls, CRPS patients showed an additional negative functional connectivity with bilateral medial and lateral frontal cortices next to more extensive activation of bilateral operculum (figure 2, table 3).

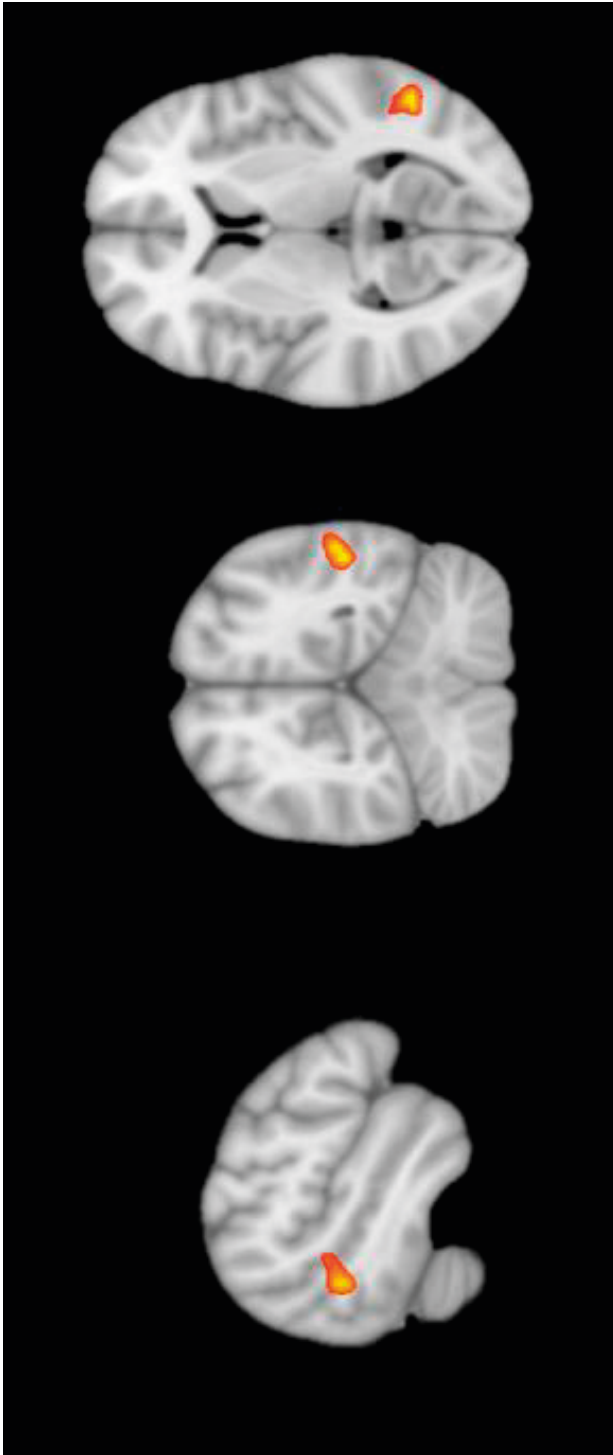
The secondary analysis of the “non-flipped” data showed a similar activation bilaterally in the TPJ, although no significant group difference was found. The correlation with disease duration was significant for the left TPJ (Pearson's  $r = .55$ ,  $p = .034$ ), but not for the right TPJ (Pearson's  $r = .48$ ,  $p = .068$ ). PPI analysis with the left TPJ as seed showed only in CRPS patients a negative connectivity with bilateral medial frontal cortex and left lateral frontal cortex, although this difference between the groups was non-significant. In this analysis, the difference in negative connectivity with the bilateral operculum decreased and was non-significant.

**Figure 1a**



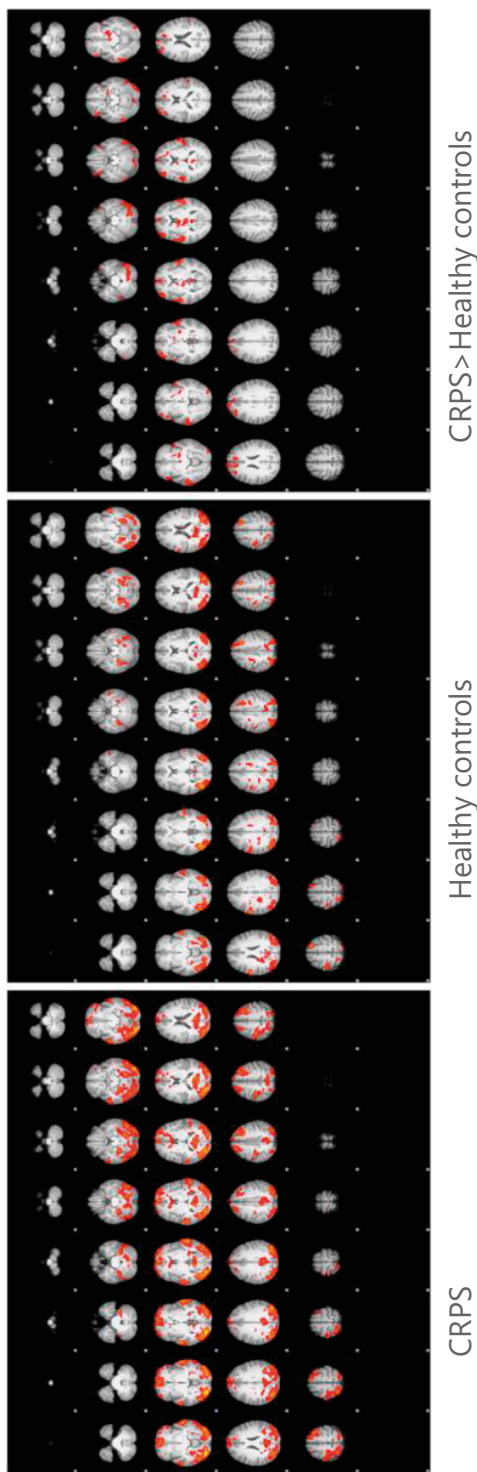
Brain activation during heat stimulus. Cluster threshold  $z > 2.3$ ,  $p < .05$ . In both groups robust activation of the bilateral insula, thalamus, anterior cingulate cortex, and secondary somatosensory cortices. Significant group difference was found in the left temporal parietal junction (yellow arrow), see also figure 1b.

Figure 1b



Brain activation during heat stimulus, CRPS > HC. Cluster threshold  $z > 2.3$ ,  $p < .05$ . Coordinates: MNI (mm) X=-54, Y=-58, Z=8

**Figure 2**



Negative functional connectivity with left temporal parietal junction (see figure 1a & b; CRPS > HC). Cluster threshold  $z \geq 2.3$ ,  $p < .05$ . In contrast to healthy controls, the left temporal parietal junction in CRPS patients shows a negative functional connectivity with many frontal brain areas during the application of the heat stimulus, most noticeably with medial and lateral frontal cortices and bilateral operculum.

**Table 2** Clusters of brain activation during heat stimulus, z-threshold > 4**CRPS**

| Cluster nr | Cluster size in voxels | Peak cortical region | Brodmann area | Maximum Z score | MNI (mm) |     |     | FWE Corrected p-value |
|------------|------------------------|----------------------|---------------|-----------------|----------|-----|-----|-----------------------|
|            |                        |                      |               |                 | X        | Y   | Z   |                       |
| 1          | 1720                   | l. insula            | 13            | 6.19            | -34      | 14  | 4   | <.000                 |
| 2          | 1436                   | r. COP               | 13            | 5.78            | 44       | 18  | 4   | <.000                 |
| 3          | 1058                   | l. SMC/<br>ACC       | 6             | 5.43            | -6       | 2   | 54  | <.000                 |
| 4          | 345                    | l. SMG               | 40            | 5.20            | -60      | -24 | 20  | <.000                 |
|            | 321                    | r. SMG               | 40            | 4.89            | 68       | -42 | 30  | <.000                 |
| 5          | 128                    | l. TPJ               | 39            | 5.05            | -54      | -58 | 8   | <.000                 |
| 6          | 82                     | r. TPJ               | 39            | 4.98            | 64       | -52 | 14  | <.000                 |
| 7          | 38                     | l. FT                | 38            | 4.43            | -32      | 8   | -22 | .004                  |
| 8          | 20                     | r. SMC/<br>ACC       | 6             | 4.27            | 56       | 2   | 50  | .015                  |
| 9          | 14                     | r. amygdala          | 53            | 4.49            | 28       | 6   | -22 | .025                  |
| 10         | 13                     | r. insula            | 13            | 4.34            | 40       | -14 | 16  | .028                  |
| 11         | 13                     | l. SMC/<br>ACC       | 6             | 4.43            | -48      | 0   | 38  | .028                  |
| 12         | 11                     | l. insula            | ND            | 4.34            | -36      | -14 | -10 | .03                   |
| 13         | 8                      | l. putamen           | ND            | 4.28            | -14      | 8   | -6  | .04                   |

Clusters of brain activation during painful stimulus. For mean activation scores per group a z-threshold >4 was used to illustrate the plurality of regions in the brain that are active during the heat stimulus. Group *differences* are depicted with z-threshold of >2.3. CRPS = complex regional pain syndrome; MNI = Montreal neurological institute (brain model derived from mean 152 healthy persons); SMC=supplementary motor cortex; ACC=anterior cingulate cortex; SMG = supramarginal gyrus; TPJ = temporal parietal junction, FT = frontal temporal; COP = central opercular cortex; IFG=inferior frontal gyrus; M = mesencephalon; ND = not defined; FWE = family wise error

**Healthy controls**

| Cluster nr | Cluster size in voxels | Peak cortical region | Brodmann area | Maximum Z score | MNI (mm) |     |     | FWE Corrected p-value |
|------------|------------------------|----------------------|---------------|-----------------|----------|-----|-----|-----------------------|
|            |                        |                      |               |                 | X        | Y   | Z   |                       |
| 1          | 2653                   | l. COP               | 6             | 6.35            | -54      | 0   | 4   | <.000                 |
| 2          | 2192                   | r. COP               | 44            | 6.15            | 58       | 8   | 6   | <.000                 |
| 3          | 1137                   | r. ACC               | 24            | 5.87            | 0        | -2  | 42  | <.000                 |
| 4          | 554                    | r. SMG               | 40            | 5.83            | 64       | -24 | 24  | <.000                 |
| 6          | 273                    | l. amygdala          | 53            | 5.14            | -20      | 0   | -16 | <.000                 |
| 7          | 138                    | r. amygdala          | 53            | 4.95            | 18       | 0   | -10 | <.000                 |
| 9          | 27                     | r. M.                | ND            | 5.09            | 12       | -26 | -12 | .009                  |
| 10         | 23                     | r. IFG               | 46            | 4.36            | 44       | 42  | 8   | .012                  |
| 11         | 9                      | r IFG                | 44            | 4.12            | 56       | 12  | 22  | .04                   |
| 12         | 8                      | pons                 | ND            | 4.3             | 0        | -20 | -22 | .04                   |

**CRPS > Healthy controls (z-threshold >2.3)**

| Cluster<br>nr | Cluster size in<br>voxels | Peak cortical<br>region | Brodmann<br>area | Maximum Z<br>score | MNI (mm) |     |   | FWE<br>Corrected<br>p-value |
|---------------|---------------------------|-------------------------|------------------|--------------------|----------|-----|---|-----------------------------|
|               |                           |                         |                  |                    | X        | Y   | Z |                             |
| 1             | 371                       | l.TPJ                   | 39               | 3.92               | -54      | -58 | 8 | .04                         |

**Table 3** PPI, negative functional connectivity with the left TPJ, z-threshold > 2.3**CRPS**

| Cluster nr | Cluster size in voxels | Peak cortical region | Brodmann area | Maximum Z score | MNI (mm) max |     |     | FWE Corrected p-value |
|------------|------------------------|----------------------|---------------|-----------------|--------------|-----|-----|-----------------------|
|            |                        |                      |               |                 | X            | Y   | Z   |                       |
| 1          | 33158                  | r.OC                 | 18            | 5.27            | 28           | -88 | -12 | <.000                 |
| 2          | 5366                   | l.FPC                | 10            | 4.46            | -26          | 68  | 4   | <.000                 |
| 3          | 2080                   | l.MFG                | 6             | 4.28            | -28          | 16  | 56  | <.000                 |
| 4          | 1172                   | l.PC                 | 7             | 3.7             | -2           | -38 | 68  | <.000                 |
| 5          | 1093                   | r.STG                | 41            | 4.35            | 60           | -8  | 0   | <.000                 |

**Healthy Controls**

| Cluster nr | Cluster size in voxels | Peak cortical region | Brodmann area | Maximum Z score | MNI (mm) max |     |     | FWE Corrected p-value |
|------------|------------------------|----------------------|---------------|-----------------|--------------|-----|-----|-----------------------|
|            |                        |                      |               |                 | X            | Y   | Z   |                       |
| 1          | 4737                   | r.OC                 | 19            | 4.94            | 40           | -72 | 2   | <.000                 |
| 2          | 4683                   | l.OC                 | 19            | 4.31            | -42          | -74 | 8   | <.000                 |
| 3          | 937                    | l.SFG                | 8             | 4.5             | -20          | 24  | 54  | .001                  |
| 4          | 868                    | r.PC                 | 23            | 3.38            | 12           | -54 | 10  | .002                  |
| 5          | 525                    | r.TFC                | 37            | 3.85            | 36           | -36 | -18 | .043                  |
| 6          | 521                    | l.STG                | ND            | 4.01            | -56          | -6  | -10 | .044                  |

**CRPS > Healthy controls**

| Cluster nr | Cluster size in voxels | Peak cortical region | Brodmann area | Maximum Z score | MNI (mm) max |     |     | FWE Corrected p-value |
|------------|------------------------|----------------------|---------------|-----------------|--------------|-----|-----|-----------------------|
|            |                        |                      |               |                 | X            | Y   | Z   |                       |
| 1          | 4484                   | l.ITG                | 37            | 3.98            | -52          | -60 | -24 | <.000                 |
| 2          | 2195                   | r.MFG                | 9             | 3.76            | 30           | 38  | 26  | <.000                 |
| 3          | 1279                   | l.COP                | 6             | 4.08            | -56          | 0   | 2   | <.000                 |
| 4          | 892                    | r.COP                | 41            | 3.76            | 54           | -8  | 6   | .002                  |
| 5          | 699                    | l.PCG                | 5             | 3.25            | -16          | -32 | 44  | .010                  |
| 6          | 660                    | l.PCC                | 10            | 3.21            | -34          | 54  | 10  | .013                  |

TPJ = temporal parietal junction; CRPS = complex regional pain syndrome; MNI = Montreal neurological institute (brain model derived from mean 152 healthy persons); PPI = psychophysiological interaction analysis; l. = left; r. = right; COP = central opercular cortex; MFG = middle frontal gyrus; PCC = posterior cingulate cortex; ND = not determined; ITG = inferior temporal gyrus; OC = occipital cortex; PC = precuneous cortex; STG = superior temporal gyrus; SFG = superior frontal gyrus; TFC = temporal fusiform cortex; PCG = precentral gyrus; FWE = family wise error

## DISCUSSION

In this study we evaluated central processing of a moderately painful heat stimulus in CRPS patients in comparison to healthy controls using functional MRI of the brain.

As expected, the initial heat stimulus was more painful in CRPS patients than healthy controls, who still rated the stimulus as moderately painful. This finding is in line with the results of other studies, suggesting that CRPS patients have lower pain thresholds and hyperalgesia<sup>175,176</sup>, although the results on *heat* hyperalgesia have been less consistent across studies<sup>177</sup>. During the scanning period which followed the administration of multiple stimuli, pain scores in both groups increased slightly, in healthy controls even more than CRPS patients.

During the administration of the heat stimulus both groups showed a robust activation of bilateral insula, thalamus, anterior cingulate cortex (ACC) and the secondary somatosensory cortex. This finding has been reported by others in response to a variety of heat stimuli in healthy controls<sup>178</sup> and subjects with other pain syndromes (meta-analyses<sup>179,180</sup>). This brain activation pattern reflects circuits involved in processing pain perception and attention to a salient external stimulus<sup>181</sup>.

We also found a significant bilateral activation of the temporal-parietal junction (TPJ) in CRPS patients. TPJ activation differed statistically from controls for the left side only. TPJ activation correlated positively with disease duration, but not with pain or any of the other clinical variables. This finding was unexpected since the TPJ is not involved in the *pain matrix* which includes the somatosensory cortices, ACC and insula<sup>182</sup>. There are several potential explanations for this finding. First, the TPJ is part of a multi-modal (nociceptive or non-nociceptive) sensory network that is involved in salience detection (right>left TPJ). The TPJ regulates sensory salience with top-down attentional control (left>right TPJ)<sup>183–185</sup> and negative emotions in relation to pain (left TPJ)<sup>186</sup>. (Of note, in the study of Orenius et al.<sup>186</sup> the TPJ was included in a cluster called the “secondary somatosensory cortex”). Further, the left TPJ has been shown to have a negative functional connectivity with brain areas involved in the default mode network (DMN)<sup>184</sup>. This brain network is associated with internally oriented attention when the brain is not engaged in any specific task and therefore considered the counterpart of externally directed cognition<sup>187</sup>. Indeed, next to a robust positive functional connectivity between the left TPJ and brain areas active during pain administration, we found a negative functional connectivity with brain areas associated with the DMN, that is, the bilateral precuneus and inferior parietal cortices. These brain areas are associated with recollecting prior experiences, consciousness and interpretation of sensory information<sup>187,188</sup>. However, only in CRPS patients we found an additional negative connectivity with the prefrontal cortex. The ventral medial component of the prefrontal cortex (VMPC) is part of the

DMN, next to (bi)lateral medial prefrontal cortices (LMPC), and thalamus. The VMPC plays a pivotal role in the processing and relaying of sensory information from the external world to structures such as the hypothalamus, the amygdala and the peri aqua ductal grey of the midbrain<sup>187</sup>. Its activity is influenced by peripheral nerve injury<sup>189</sup>, inversely correlated with central hyperalgesia<sup>190</sup>, and increased activation reduces nociceptive and affective symptoms of pain and successfully suppresses emotional responses to a negative emotional stimulus<sup>191,192</sup>. It therefore plays an important role in pain processing and inhibition<sup>188,189</sup>. Importantly, activity of the LMPC has been found to correlate negatively with hyperalgesia and pain catastrophising<sup>159</sup>, and its activity level was shown to normalise after successful pain treatment with cognitive behaviour therapy<sup>193</sup>. In CRPS pain catastrophising (and hyperalgesia) is common<sup>194</sup> and correlates with greater inter-network connectivity between the attention and salience networks<sup>195</sup>. Lastly, other studies have reported decreased thalamic connectivity in chronic pain patients<sup>179</sup> which is assumed to be related to altered thalamocortical connections, causing a disruption of thalamic feedback<sup>193</sup>. In essence, it reflects a shift in chronic pain states from sensory to emotional brain activity<sup>179,196</sup>.

We expected a negative influence of pain on motor cortex activity, since patients with CRPS commonly experience a loss of voluntary control of the affected limb<sup>197</sup>. However, we did not find any difference in brain activity of the motor cortices between CRPS and healthy controls during the pain stimulus. In addition, increased saliency did not influence primary motor cortical activity. While this could be due to the absence of a motor task, the fact that eleven of the fifteen patients had abnormal postures due to active muscle spasms rendering this explanation less likely. Alternatively, the lack of altered motor cortex activity may suggest that motor disturbances in CRPS are not directly linked to painful sensory afferent input. Motor disturbances might therefore originate from ‘upstream’ brain areas such as limbic or frontal cortices, as hypothesized in functional movement disorders<sup>198</sup>, or be the result of impaired central processing of proprioceptive Information<sup>55</sup>.

Lastly, although the analysis of the cerebellum was not included in this paper, our incomplete data of the cerebellum showed striking differences between the groups in functional connectivity between the left TPJ and cerebellum. Compelling evidence shows an important role for the cerebellum in circuitry involved in motor, emotional and pain processing (reviews<sup>199,200</sup>). Hence, future studies should include the whole cerebellum in field of view.

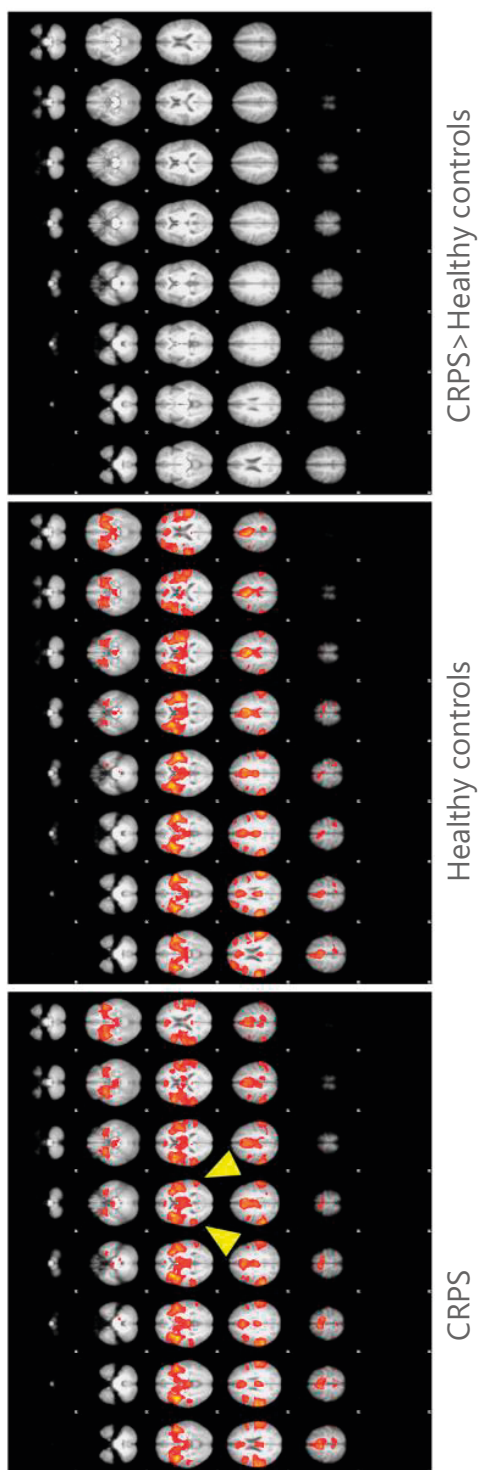
Collectively, in response to a painful stimulus, CRPS patients activate the TPJ involved in salience detection which, in turn, is negatively correlated with brain areas involved in reducing the affective burden of pain.



Interpreting the results of this study, several points should be considered. First, we flipped the data of CRPS patients affected on the left arm in order to stack all “affected” hemispheres onto the same, left hemisphere. This was necessary in order to interpret the contralateral brain activations in response to the 1x-sided pain stimulus. However, as previously noted, some data suggest that there is a slight difference in function of the right and left TPJ<sup>184</sup>. Because the left TPJ in the CRPS group in the “flipped” data is a compilation of the left and right TPJ, this could mean that the difference between the groups is in fact a difference between the left and right TPJ. However, it is unlikely that this issue has relevant effects on the conclusion of our findings since we did run an analysis of the “non-flipped” data (figure 3, supplementary data), and found similar results of significant bilateral activation of the TPJ in CRPS patients. However, we must emphasize that in that group analysis no significant differences were found. Therefore, preferably, our results should be substantiated using a new, larger cohort of CRPS patients. Second, the PPI results in the “non-flipped” data with the left TPJ as seed resulted in corresponding negative connectivity with prefrontal cortices in CRPS patients, not in healthy controls. In addition, PPI analyses do not allow inferences about the direction of informational flow. Therefore, whether increased activation of the left TPJ resulted in reduced activation of the functional correlated brain areas or vice versa is not known. Finally, as mentioned above, future studies should include the cerebellum in the analyses given its role in motor, emotional and pain processing.

In conclusion, while experiencing a painful stimulus, CRPS patients have increased salience detection in combination with opposite activation of brain regions involved in reducing the affective burden of pain.

**Figure 3**, supplementary data (unflipped data)





# Chapter 6

# **Motor cortical activity during motor tasks is normal in patients with Complex Regional Pain Syndrome**

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## ABSTRACT

Motor dysfunction in complex regional pain syndrome is often considered a functional movement disorder. Earlier studies in patients with functional movement disorders found evidence of cortical inhibition during explicit – but not during implicit – motor tasks, suggesting active inhibition from other brain areas. In this study we explored whether active inhibition occurs in complex regional pain syndrome patients. We compared patients with complex regional pain syndrome with 2 control groups: healthy controls matched for age and sex, and patients whose hand was immobilized to treat a scaphoid fracture. We used transcranial magnetic stimulation to measure corticospinal excitability at rest and during motor imagery (explicit motor task) and motor observation (implicit motor task). Motor corticospinal excitation measured at rest, and during implicit and explicit motor tasks was similar for CRPS patients and healthy controls. Patients with an immobilized hand showed an absence of motor cortical excitation of the corresponding hemisphere during motor imagery of tasks involving the immobilized hand, but not during motor observation.

The normal motor cortical processing during motor imagery and motor observation found in the corresponding hemisphere of complex regional pain patients suggests that the nature of motor dysfunction in this condition differs from that described in literature for patients with functional paresis or under circumstances of limb immobilization.

# INTRODUCTION

Complex regional pain syndrome (CRPS) is a debilitating pain syndrome that usually develops after a minor trauma to a limb. The condition is clinically characterized by neuropathic pain, autonomic disturbances and motor dysfunction<sup>1</sup>. Examples of the latter are a loss of voluntary motor control, slowness of movement, weakness and postural abnormalities ('fixed dystonia') of the affected limb<sup>201</sup>. The nature of motor dysfunction in CRPS, particularly 'fixed dystonia', has been a continuous source of debate<sup>59,61,62</sup>. On the one hand, fixed dystonia in CRPS has been viewed as a consequence of maladaptive neuronal plasticity or so-called central sensitization<sup>197</sup>, while some, on the other hand, emphasized a resemblance with functional movement disorders (i.e., movement disorders without a demonstrable organic substrate), such as a prior peripheral trauma, the prominent presence of pain, and the occurrence of fixed postures<sup>59,61,62,202</sup>.

Given the lack of a gold standard for the diagnosis of functional movement disorders<sup>59,203</sup>, Schwingenschuh et al.<sup>204</sup> attempted to develop laboratory tests to help establish the presence of a functional movement disorder. One such promising technique could be transcranial magnetic stimulation (TMS) during motor imaginary (MI) and motor observation (MO). During MI subjects rehearse a movement mentally without actually executing the movement, while in MO subjects observe someone else moving. In healthy controls both conditions activate similar brain areas involved in motor planning comparable to the actual execution of these movements, without being influenced by nerve or muscle disorders<sup>205–207</sup>. In patients with functional paresis, MI results in reduced primary motor cortex activation while normal activation is seen during motor observation<sup>65,66</sup>. This dissociation of motor cortex activation between the explicit, voluntary MI and the implicit, automatic MO is attributed to inhibitory activity of frontal or limbic brain areas during voluntary motor tasks<sup>66,208</sup>.

In view of the clinical resemblance between the movement disorders seen in patients with CRPS and patients with functional movement disorders, this study sought to investigate if CRPS patients also exhibit the different pattern of corticospinal excitability during explicit and implicit motor tasks found in patients with functional movement disorders. In order to accomplish this, we first measured baseline cortical excitability at rest using different intensities of TMS. Next, TMS measurements during MO and MI of weightlifting were performed using two distinct weights, to check the assumption that observed and imagined weightlifting results in a corresponding increase of cortical spinal excitability for heavier weights<sup>209</sup>. In addition, an extra control group was recruited consisting of patients who had one hand immobilized for a period of at least four weeks because of cast treatment for a scaphoid bone fracture (SBF) to control for the effects of underutilization of a limb, such as often seen in CRPS patients.

If the discrepancy in corticospinal excitability during explicit and implicit motor tasks is observed in patients with CRPS related motor dysfunction, this condition shares an important characteristic with functional movement disorders, which would require modification of therapeutic strategies.

## METHODS

### *Subjects*

Patients followed up at the neurology outpatient clinic of the Leiden University Medical Center (LUMC) in Leiden, the Netherlands, with documented CRPS of an upper limb were contacted by the principal investigator (GAJV) and informed on the purpose and procedures of the study, after which they were asked if they would consider participating in this study. If a patient was interested, a patient information sheet was sent to his or her home 2 weeks before the potential entry in the study. On the study day a neurological examination was performed by the principal investigator and Budapest Criteria <sup>2</sup> were checked to include or exclude a patient. Additional inclusion criteria were loss of voluntary motor control of the affected limb for over 6 months; weakness; slowness of movement, whether or not in combination with decreased active range of motion or fixed dystonia. These characteristics were all evaluated without the use of extra instrumentation. Exclusion criteria were any relevant neurological illness or any other condition with pain or functional impairment of an arm.

Between July 2012 and July 2013 we specifically included patients with a unilateral scaphoid bone fracture (SBF), because in this patient group, as opposed to patients with other forearm and wrist fractures, the pincher grip (first dorsal interosseus muscle, see below) was immobilised for at least 4 weeks. These patients were approached during their immobilisation period and included only if pain was minimal or absent (e.g.  $\leq 1$  on a numeric rating scale (NRS) ranging from 0 – 10). These patients were evaluated within an hour after cast removal. Lastly, healthy controls (HCs) were age and sex matched to the CRPS patients. These control subjects were volunteers from the hospital staff or relatives of the CRPS patients. Exclusion criteria were pain, neurological disease or any other condition that might affect proper hand function.

The study was approved by the Medical Ethics Committee of the LUMC, and written informed consent was obtained from all patients and control subjects.

### *Transcranial magnetic stimulation*

Subjects sat in an adjustable chair with supports for the head, arms and legs. Subjects rested their hands on a pillow, with the palms downwards. A computer screen was placed before the subjects at eye level (Appendix A).

We used a Magstim Rapid 2 (Whitland, Dyfed, UK) with a figure-of-8 shaped coil supported by a standard. We positioned the coil over the motor cortex and locked the coil on the position where the lowest stimulus intensity was needed to evoke a 100  $\mu$ V motor evoked potential (MEP). This position was considered as the “motor hotspot”. An optical measurement and positioning system (Polis Spectra, NDI, software: ANT ASA 4.7.3, Enschede, the Netherlands) ensured that the position of the coil was held constant.

We recorded and stored MEPs (Medelec Synergy 10, Oxford instruments) from the first dorsal interosseus (FDI) muscle of both hands using 23-mm-diameter Ag/AgCl surface electrodes. MEP amplitudes were measured peak-to-peak with a 30–3000 Hz bandpass filter. All consecutive TMS stimuli were given with an interstimulus interval of 4–6 seconds. The sequence of testing was always: motor threshold, input-output curve, motor observation, motor imagery with a 5 minutes break between the tests. The sequence in which hands were measured during the different tests was determined at random.

### *Motor threshold*

Patients were asked to relax and look in front of them. We defined the motor threshold (MT) as the lowest stimulus intensity needed to evoke MEPs with amplitudes of 50–100  $\mu$ V in at least 5 out of 10 trials during muscle relaxation<sup>210</sup>

### *Input-output curve (IO curve)*

We first established the stimulus intensity needed to evoke a 1 millivolt MEP at rest (=SI1mV) using the median of 10 consecutive repetitions. Next, we applied in total 60 TMS stimuli on the motor hotspot with 80, 90, 100, 110, 120, and 130% of SI1mV intensity (10 stimuli/intensity). Decreased cortical excitation as reflected by a flatter curve was considered as evidence of centrally active drugs used by the patients<sup>211</sup>. Conversely, a steeper curve has been associated with changes in cortical spatial motor representation<sup>212</sup>, extensive use<sup>213</sup> or prolonged disuse<sup>214</sup> of the hand.

### *Motor observation (MO)*

Subjects were ignorant of the purpose of the test. For both hands we screened 8 videos in which a left or right hand lifted either a heavy (1kg) or a light (50g) weight in the air for 15 seconds (pincer grip)<sup>209</sup>. The weight difference could be appraised by object size, inscriptions (1kg; 50g) and apparent strain on arm muscles. Signals added to the videos ensured perfect

timing of 3 TMS stimuli during weight lifting. The sequence of weights (heavy and light) and the order of hand used (right and left) was randomized. To ensure that subjects remained focused while keeping them ignorant about the real purpose of the test to prevent that this knowledge could bias the results, we instructed them to identify one of the used weights in the videos as a (in reality non-existing) phony weight.

### *Motor imagery (MI)*

First, subjects were given the weights to feel the weight in real life. Subsequently they closed their eyes and focused on the examined hand. We then instructed them to imagine lifting either the heavy or light weight, or to imagine the hand at rest (order again randomized). After 2 seconds, 3 consecutive TMS pulses were given. This procedure was repeated 4 times. After each session, subjects rated their subjective performance of imagined movements from 1-5 (1: very good image; 5: no image).

### *Secondary outcome measurements*

In the days before the research-day, patients completed questionnaires measuring pain (McGill Pain Questionnaire, MPQ)<sup>77</sup>, manual activity (Radboud skills questionnaire, RSQ)<sup>131</sup>, and the ability to perform imagined movements (Vividness of Movement Imagery Questionnaire-2, VMIQ-2)<sup>215</sup>. In addition, on the day of examination we collected data on demographic variables, pain severity (NRS), CRPS (CRPS severity score<sup>75</sup>), dystonia (Burk-Fahn-Marsden scale<sup>132</sup>), strength, active range of motion, slowness of movement and pressure pain thresholds. The latter was determined in 3 muscles (first dorsal interosseus, flexor and extensor digitorum), using an electronic algometer (FPX50; Wagner Instruments, Greenwich, CT, USA)<sup>216</sup>. The pressure pain threshold was used as a covariate in the main TMS analysis.

### *Sample size calculations*

Sample size calculation was based on data from Liepert et al<sup>66</sup>, patients and healthy controls. With a mean of  $74.8 \pm 16.4\%$  of MEP amplitude at rest during MI and  $128.9 \pm 15.4\%$  during MO, and considering an alpha of .05 and a power of 0.80, 6 patients would be sufficient. To be on the conservative side we aimed to include 12 patients in every group.

### *Data analysis*

We compared the affected hand of CRPS patients with the dominant hand of healthy controls because insufficient data was collected from the unaffected hand of CRPS patients: 1 patient had CRPS in both hands, 2 others had complaints of pain in the non-affected hand not fulfilling CRPS criteria, and in 3 patients MEPs could not be recorded from the unaffected hand (see limitations). The dominant hand of HCs was chosen because motor imagery of the dominant hand has been shown to yield better EMG results<sup>217</sup>. We analysed TMS results of the SBF group separately, due to the small number of subjects and the strong age

and sex difference with the other two groups. In this group the healthy hand was compared with the immobilized hand.

### *Statistics*

Data were analysed with IBM SPSS statistics version 20.

We checked normality of the data before using t-tests to assess differences in baseline characteristics and MT between CRPS patients and HCs. For the analyses involving SBF patients, nonparametric tests were used (Wilcoxon-signed-rank-test and Friedman-test) due to the small sample size.

In all TMS analyses we used the median of 10 (MT and IO curve) or 12 (MO en MI) consecutive TMS recordings. Linear mixed models were used for the analysis of the IO curve (fixed factors: “group” (CRPS or HC) and “TMS intensity” (80–130%)) and for the analysis of MO/MI (fixed factors: “group” (CRPS or HC), “task” (MO or MI) and “weight” (rest, light, heavy)). In both analyses “age” and “mean pressure-pain-threshold” were included as covariates<sup>216</sup>. Correlations between VMIQ-2 scores (low scores indicate good ability to perform IM) and MI EMG results were examined with Pearson’s correlation coefficient.

## **RESULTS**

Data of CRPS patients and HCs are presented as means  $\pm$  standard deviation and data of SBF patients as medians with interquartile range.

One-hundred-and-twenty-one patients were considered for inclusion in the study. Of these, 31 did not fulfil Budapest criteria for CRPS of a hand. In addition, 40 patients declined to participate, 28 were excluded because of comorbidities, while 10 patients could not be reached by telephone, mail or email.

Twelve CRPS patients (age:  $51 \pm 9.5$ ; 2 men) and 12 HCs (age:  $52 \pm 13.0$ ; 1 man) and 6 SBF-patients (age: 24 (20.5–33.5); 5 men) participated in the study. Age did not differ between CRPS patients and HCs ( $t(22)=0.034$ ,  $p=.97$ ), but did between CRPS and SBF patients ( $U=4.5$ ,  $z=-2.95$   $p<.01$ ), as well as between HCs and SBF patients ( $U=5.0$ ,  $z=-2.91$ ,  $p<.01$ ).

Characteristics of the CRPS and SBF group can be found in Table 1. All CRPS patients had a chronic disease course ( $88.0 \pm 26.9$  months) and experienced continuous pain. The immobilization period in the SBF group ranged from 4–10 weeks.

**Table 1** Patient characteristics

| CRPS patients | Age      | Sex | Hand dominance | Affected side | Disease duration (months) | CRPS severity score (0-17) | BEM        | MD                | NRS (0-10) | MPQ (0-63) | RSQ (0-5) | Centrally acting drugs                                                      |
|---------------|----------|-----|----------------|---------------|---------------------------|----------------------------|------------|-------------------|------------|------------|-----------|-----------------------------------------------------------------------------|
| 1             | 54       | F   | L              | R             | 120                       | 12                         | 16         | we, sl, drm, dyst | 5          | 26         | 3.68      | Tramadol-acetaminophen (Zaldiar), etoricoxib (Arcoxia), pregabalin (Lyrica) |
| 2             | 34       | F   | R              | L             | 75                        | 9                          | 28         | we, drm, dyst     | 8          | 41         | 3.39      | Oxycodon (OxyContin) baclofen, temazepam                                    |
| 3             | 58       | M   | R              | L             | 75                        | 14                         | 16         | we, sl, drm, dyst | 9          | 34         | 5.00      | Amitriptyline                                                               |
| 4             | 58       | M   | R              | L             | 60                        | 9                          | 9          | we, drm, dyst     | 7          | 27         | 2.71      | -                                                                           |
| 5             | 54       | F   | R              | L             | 360                       | 13                         | 14         | we, sl, drm, dyst | 5          | 27         | 2.76      | Pregabalin (Lyrica)                                                         |
| 6             | 50       | F   | R              | R             | 89                        | 9                          | 16         | we, sl, drm, dyst | 8          | 27         | 4.24      | -                                                                           |
| 7             | 58       | F   | R              | L             | 13                        | 14                         | 12         | we, sl, drm, dyst | 7          | 26         | 3.77      | Tramadol, gabapentin                                                        |
| 8             | 36       | F   | R              | R             | 24                        | 8                          | 0          | we, sl            | 6          | 30         | 2.00      | Pregabalin (Lyrica), amitriptyline                                          |
| 9             | 41       | F   | R              | L             | 72                        | 11                         | 0          | we, sl            | 9          | -          | 2.63      | Amitriptyline                                                               |
| 10            | 63       | F   | L              | L             | 120                       | 10                         | 9          | we, sl, drm, dyst | 7          | 0          | 1.76      | Amitriptyline, diazepam                                                     |
| 11            | 55       | F   | L              | R             | 39                        | 11                         | 28         | we, sl, drm, dyst | 3          | 26         | 4.04      | (1 / 4 months ketamine)                                                     |
| 12            | 43       | F   | R              | 1             | 9                         | 10                         | 0          | we, sl, drm       | 6          | 21         | 2.48      | -                                                                           |
| Mean (±SD)    | 51 (9.5) |     |                |               | 88 (93.3)                 | 10.8 (2)                   | 12.3 (9.6) |                   | 6.7(1.8)   | 25.9(10.0) | 3.2(1.0)  |                                                                             |

**Table 1** Patient characteristics (continued)

| CRPS patients | Age         | Sex | Hand dominance | Affected side    | Disease duration (months)     | CRPS severity score (0-17) | BFM | MD         | NRS (0-10) | MPQ (0-93) | RSQ (0-5)    | Centrally acting drugs |
|---------------|-------------|-----|----------------|------------------|-------------------------------|----------------------------|-----|------------|------------|------------|--------------|------------------------|
| SBF patients  | Age         | Sex | Hand dominance | Immobilized hand | Immobilization duration weeks |                            |     | NRS (0-10) | MPQ (0-93) | RSQ (0-5)  |              | Centrally acting drugs |
| 1             | 21          | F   | R              | R                | 9                             |                            |     | 0          | 9          | 1.67       |              | -                      |
| 2             | 26          | M   | R              | L                | 7                             |                            |     | 0          | 14         | 2.78       |              | -                      |
| 3             | 50          | F   | R              | L                | 8                             |                            |     | 0          | 1          | 2.20       |              | -                      |
| 4             | 28          | M   | L              | R                | 4                             |                            |     | 0          | 0          | 1.75       |              | -                      |
| 5             | 19          | M   | R              | R                | 6                             |                            |     | 1          | 1          | 2.33       |              | -                      |
| 6             | 22          | F   | R              | L                | 10                            |                            |     | 0          | 0          | missing    |              | -                      |
| Median        | 24          |     |                |                  |                               |                            |     |            | 5.0        |            |              |                        |
| (IQR)         | (20.5-33.5) |     |                |                  | 7.5 (5.5-9.3)                 |                            |     | 0 (0-1.0)  | (1.0-12.8) |            | 2.3(1.8-2.7) |                        |

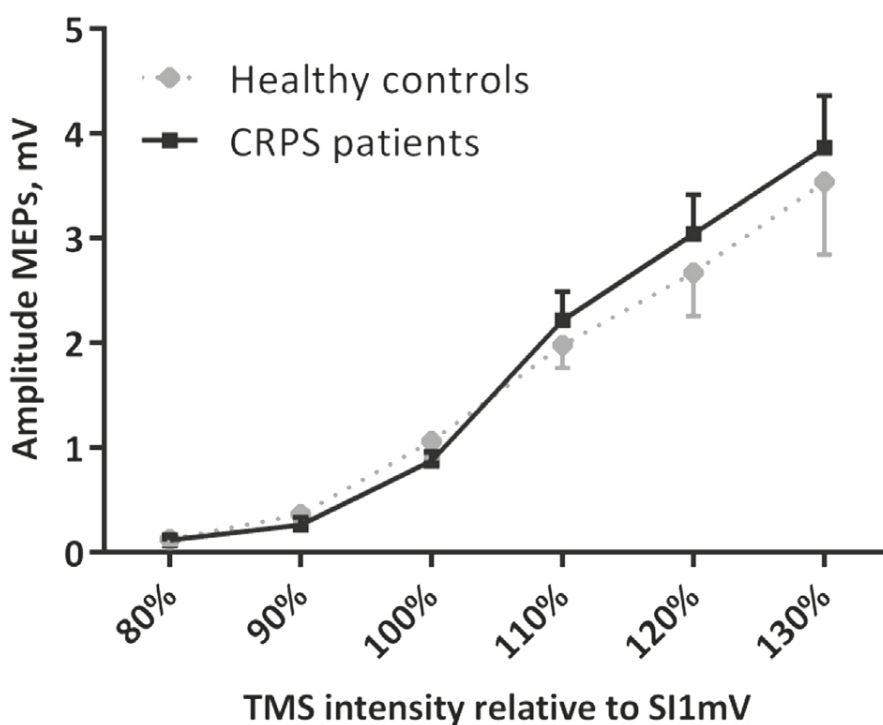
Abbreviations: BFM, Burk-Fahn-Marsden scale; MD, motor dysfunction; NRS, numeric rating scale; MPQ, McGill Pain Questionnaire; RSQ, Radboud Skills Questionnaire; F, female; L, left; R, right; we, weakness; sl, slowness; drml, decreased active range of motion; dyst, fixed dystonia; M, male; SD, standard deviation; IQR, interquartile range. NOTE. All patients exhibited loss of voluntary motor control.

No healthy control reported any pain. Eight of 12 CRPS patients used centrally acting drugs on the day of examination, and one had a ketamine infusion in the previous month.

Mean pressure pain threshold was significantly lower for CRPS patients ( $1.8 \pm 1.2$  kilogram force (kgf)) than for HCs ( $3.1 \pm 0.7$  kgf ;  $t(142)=-8.064$ ,  $p<.001$ ). In the SBF group no difference was seen between the healthy ( $3.0$  [2.2-3.6] kgf ) and immobilized hands ( $2.7$  [1.9-3.3] kgf;  $t=5$ ,  $z=-1.153$ ,  $p=.25$ ).

### *TMS results CRPS patients and healthy controls (Appendix B)*

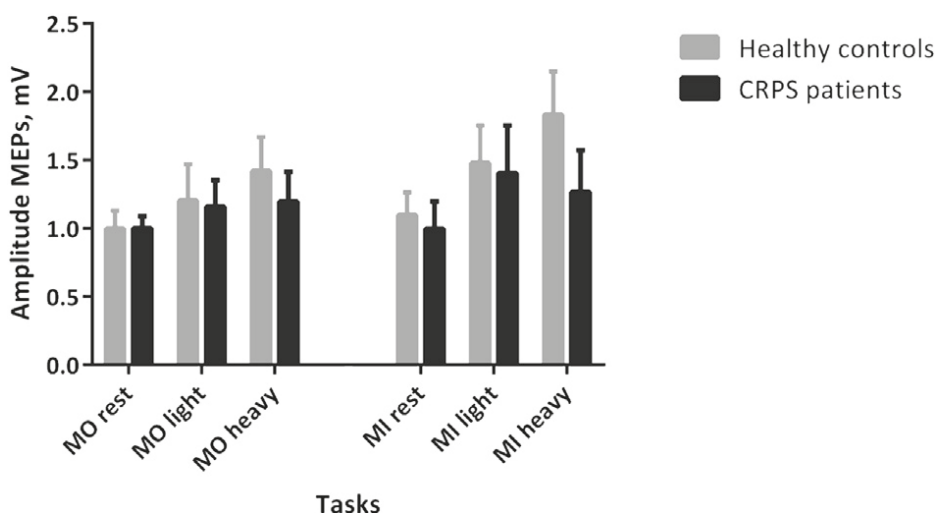
MT did not differ between the 'affected' hemisphere of CRPS patients and the dominant hemisphere of HCs ( $t(22)=-0.416$ ,  $p=.68$ ). Analysis of the IO curves revealed an expected increase in MEP amplitude with increasing stimulus intensity ( $F(5,22.2) = 70.1$ ,  $p <.01$ ), which was similar in both groups ( $F(1, 38.9) = 0.160$ ,  $p=.69$ ). There was no interaction between group and intensity ( $F(5,22.2) = 0.572$ ,  $p=.72$ ) (figure 1). Neither age ( $F(1, 18.9) = 3.26$ ,  $p=.09$ ) nor pain-threshold ( $F(1, 18.9) = 0.43$ ,  $p=.52$ ) affected the IO-curves.



**Figure 1**

IO curves for CRPS patients and HCs. Bars: means  $\pm$  standard errors. Note that no significant differences were found between the groups.

MI resulted in significantly higher MEP amplitudes than MO ( $F(1, 91.7) = 4.42, p=.04$ ) (figure 2). In addition, increasing weight resulted in higher MEPs ( $F(2, 59.6) = 7.65, p<.01$ ) in all occasions, except for ‘MI-heavy’ in CRPS patients. No difference was found between groups ( $F(1, 18.3) = 0.174, p=.68$ ). No significant interaction was found between group and task (i.e. CRPS/HC and MI/MO) ( $F(1, 90.5) = 0.843, p=.36$ ) or between group and weight ( $F(2, 56.6) = 1.469, p=.24$ ). Notably, only one CRPS patient showed decreased cortical excitability during MI (light or heavy) relative to MO-rest while this occurred in none of the HCs.



**Figure 2**

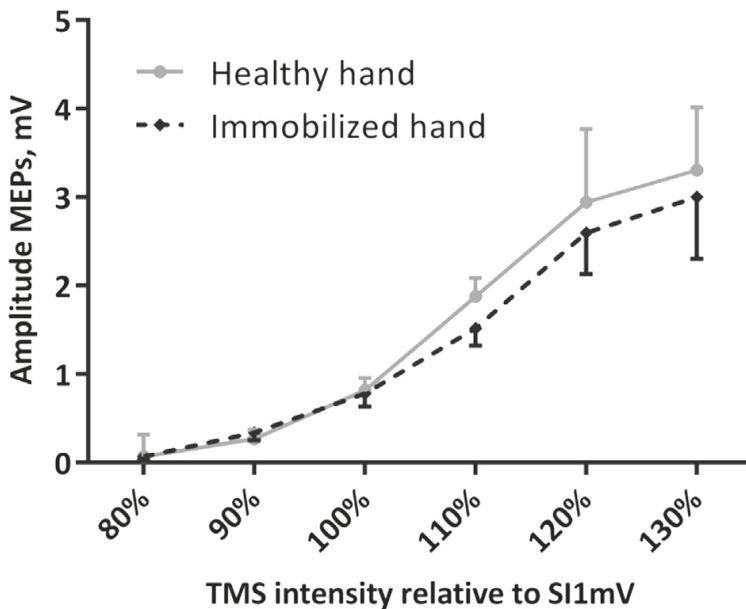
MO and MI results for CRPS patients and HCs. Bars: means  $\pm$  standard errors. For comparison purposes, data have been transformed to make MO rest precisely 1mV, statistics were performed on original data. Excitation of the primary motor cortex during MO and MI is similar in CRPS patients and HCs.

Influence of age ( $F(1, 18.0) = 0.79, p=.39$ ) and pain-threshold ( $F(1, 18.0) = 0.78, p=.39$ ) were both non-significant. Post-hoc analyses of MI-heavy resulted in a non-significant difference between CRPS patients and HC's ( $T(22) = -1.863, p=.09$ ).

Eight CRPS patients and 8 HCs designated the light weight as the phony weight during MO, whereas a heavy weight was indicated as phony by 3 HCs; 5 subjects (4 CRPS patients, 1 HC) were incapable of identifying the phony weight. The vividness of MI in CRPS patients was significantly worse than in HCs ( $T(22) = 3.34, p<.01$ ) and correlated with the EMG-MI results ( $r=-0.26, p=.03$ ). Similarly, results of the VMIQ-2 showed that CRPS patients ( $2.7\pm1.1$ ) exhibited significantly worse scores for MI of self-performed actions than HCs ( $1.8\pm0.6$ ), ( $T(21) = 2.5, p=.02$ ).

### *TMS results scaphoid bone fracture patients*

No significant difference in MT was found between the healthy and immobilized hand ( $T=5$ ,  $z=-1.153$ ,  $p=.31$ ). Increasing TMS intensities resulted in significantly higher MEPs in the healthy hand ( $X^2(5) = 28.4$ ,  $p<.01$ ) and the immobilized hand ( $X^2(5) = 24.5$ ,  $p<.01$ ) (figure 3). No differences between hands were found.

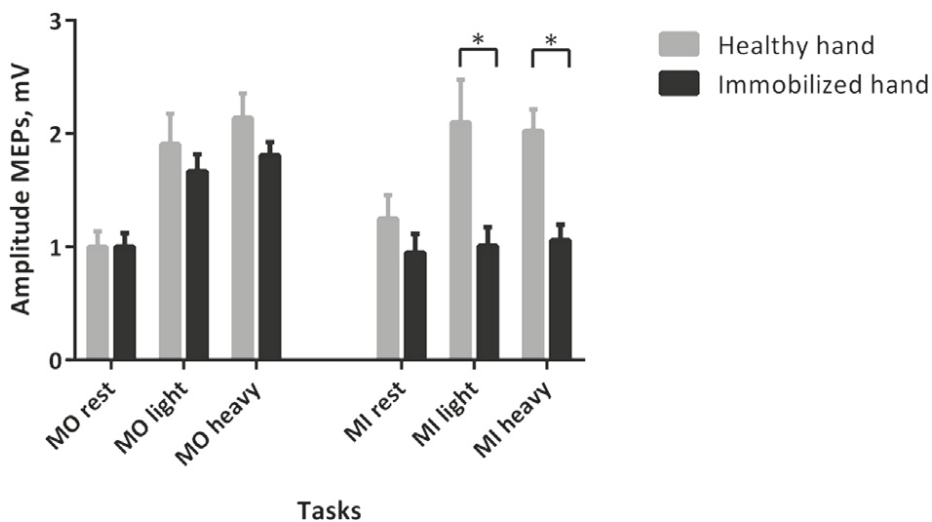


**Figure 3**

IO curves for SBF patients. Bars: means  $\pm$  standard errors. Note that no significant differences were found between hands.

MI of the immobilized hand did not result in an increase of MEPs such as seen in MI of the healthy hand ( $T = 0$ ,  $z=-2.201$ ,  $p=.03$ ), or as seen during MO ( $T=0$ ,  $z=-2.201$ ,  $p=.03$ ) (figure 4).

For the healthy hand no difference was observed between MO and MI ( $T = 7$ ,  $z=-0.734$ ,  $p=.56$ ) and MO did not differ between hands ( $T=2$ ,  $z=-1.782$ ,  $p=.09$ ). Vividness of MI was equal for both hands; healthy hand 1.9 [1.3-2.3], immobilized hand 1.6 [1.3-2.5], ( $T=5$ ,  $z=-0.680$ ,  $p=.50$ ).



**Figure 4**

MO and imagery in SBF patients. \* $P < .05$ , corrected for multiple comparison. Bars: means  $\pm$  standard errors. For comparison purposes, data have been transformed to make MO rest precisely 1mV, statistics were performed on original data.

## DISCUSSION

Using TMS, we studied corticospinal excitability of the affected hemisphere of CRPS patients with motor dysfunction at rest and during implicit and explicit motor tasks. Our findings show normal motor cortex activation at rest (MT/IO curve) and similar motor cortex excitation in MI and MO in comparison to results obtained from healthy controls, indicating normal motor processing without inhibitory interference from other brain areas such as seen in patients with functional paresis<sup>65,66</sup>. A second important finding is the absence of corticospinal excitation only in the hemisphere corresponding with the affected side during MI, but not during MO, in patients with unilateral hand immobilization due to a fracture.

### *CRPS patients and healthy controls*

The results of MTs and IO curves in CRPS patients are consistent with pooled results in a recent systematic review by Di Pietro et al<sup>124</sup>, and likely suggests that centrally active drugs did not influence our results. Additionally, motor cortical reorganization or an effect of prolonged disuse could not be demonstrated, although, hypothetically, the opposing effects of drugs (reduced excitability<sup>211</sup>), and immobilization (increased excitability in some studies<sup>214</sup>) could have neutralized each other.

The excitation of the primary motor cortex in the “affected” hemisphere during MO and MI in CRPS patients indicates that implicit and explicit motor planning in CRPS patients is similar to HCs. This finding contrasts with the results reported by Liepert et al. who found inhibition of MEP amplitudes during MI in 8 upper limb and 10 lower limb patients with a functional paresis compared to healthy controls, as well as in 2 patients with fixed dystonia<sup>65,66</sup>.

Given the partial overlap between clinical features of CRPS and functional paresis patients, similar activation patterns of the motor cortex might have been expected in the 2 conditions. However, previous results from imaging studies already showed that in CRPS patients and functional paresis patients, motor planning involves distinct cortical activation patterns: In CRPS patients *increased* activation of the primary motor cortex with decreased activation of parietal cortex was seen<sup>40,218</sup>, whereas in functional paresis patients *decreased* activation of the primary motor cortex<sup>219,220</sup> basal ganglia and thalamus<sup>221</sup> and increased activation of prefrontal and brain areas associated with emotional regulation<sup>222</sup> was observed.

While these imaging data display spatial differences in cortical activation patterns during motor planning, our data in CRPS, finding no difference in cortical excitability from HCs, and the results from Liepert et al in functional paresis<sup>65,66</sup>, finding distinct cortical excitability differences from HCs, show that quantitative changes in cortical excitability differ between the syndromes. Collectively, this suggests that motor processing in CRPS patients with motor dysfunction substantially differs from motor processing in patients with functional paresis.

The question remains why many CRPS patients develop motor dysfunctions. One possible explanation is that the initial adaptation of motor behaviour is aimed at a short-term protection from further pain, injury, or both. In susceptible subjects, the plastic changes associated with central sensitisation may have consequences for motor programming in the long term, rendering it difficult to return to the initial pattern of normal motor behaviour and contributing to the maintenance of motor dysfunctions in CRPS<sup>85,223</sup>. Another possible explanation for motor dysfunctions in CRPS could be the disturbed processing of afferent information. Recent data show that impaired central processing of proprioceptive information is related to motor dysfunction in CRPS<sup>55</sup>. Taken together this may suggest that although intrinsic properties of motor processing are intact, altered processing of afferent input is key in the development and maintenance of motor dysfunctions in CRPS patients. Consequently, therapeutic strategies should be focussed on restoring afferent processing, for example by stimulating afferent input in duration, intensity and modality as much possible (e.g. by using the affected limb, touching the skin, using different textures).

It has to be noted that post hoc analysis of the results of “MI of the heavy weight” show a lower excitation than might be expected (figure 2). This could suggest that MI of “heavy” labour is more difficult to perform than MI of light labour. Patient’s vividness of MI and the results of VMIQ-2 concur with this trend, which is consistent with earlier reports stating a negative relation between the ability to perform MI and loss of afferent input, a characteristic feature of CRPS<sup>50,55,224</sup>.

### *Scaphoid bone fracture patients*

No significant difference in motor excitability at rest was found between the immobilized and healthy hand of SBF-patients. This finding contrasts with that of a previous study showing increased IO curves and reduced MTs after 5 weeks of immobilization<sup>214</sup>. Whether methodological differences between both studies (powering, different TMS coil and different muscles examined) explain the different results remains unclear.

Results of the immobilized hand in the SBF-group showed an absence of increased motor cortical excitability during MI, while patients’ subjective vividness of MI was not different from HCs. Of note, these results are different from the motor cortex inhibition seen in patients with functional movement disorder since those patients showed a reduction in excitability relative to rest.

However, these results suggest that underutilization of the affected limb in CRPS patients does not affect motor cortical excitation during explicit motor tasks as present during cast immobilization, as we had anticipated. In addition, we found that immobilization causes a (temporary) inability to activate the primary motor cortex (published before<sup>225,226</sup>), whereas implicit motor observation activates the motor cortex in a classical way. These results are in line with those of a recent study,<sup>227</sup> in which the authors argue that MI is dependent on afferent feedback that continuously updates the state of a limb, while MO can directly activate the motor cortex without knowledge of the state of a limb. This implies that under circumstances of limb immobilization, explicit motor tasks are ineffective in activating the motor cortex.

### *Limitations*

No EMG recordings could be obtained from the unaffected side of three CRPS patients (3, 5 and 9). We have no explanation for this finding and could not find a similar report in the literature. However, discussion with other TMS researchers revealed that it is not unusual to find people unresponsive to TMS stimuli, although a unilateral absent response might be a novel finding. Second, we did not succeed in recruiting the planned 12 scaphoid bone fracture patients with a comparable age and sex as the CRPS patients. In fact, we only found 6 patients, who turned out to be significantly younger. For these reasons a direct comparison of the groups was not possible. Still, the validity of our findings is underscored by the findings

of Bassolino et al.<sup>227</sup>, who recently published on 24 HCs who had been immobilized for 10 hours.

In the present article we compared the results of the dominant hand of HCs with the affected hand of CRPS patients because motor imagery of the dominant hand has been shown to yield better EMG results<sup>217</sup>. However, although not reported here, comparisons of the data of the patients' affected hand with those of the non-dominant hand of HCs showed similar results as those of the dominant hand, indicating that the (arbitrary) choice of the hand of HCs did not alter the conclusions of this paper.

To summarize, we found no evidence for inhibited motor cortical excitation of the hemisphere corresponding with the affected side during motor tasks in CRPS patients, which suggests that the nature of motor dysfunction in CRPS patients differs from that encountered in patients with functional paresis or under circumstances of limb immobilization. This information is important for patients and pain clinicians, to prevent implementation of therapeutic strategies based on the wrong assumptions.

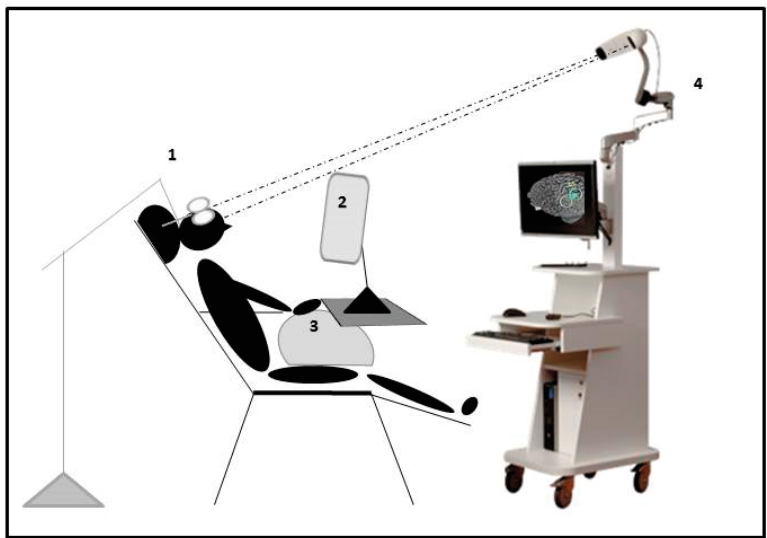
Future studies on motor dysfunction in CRPS patient should focus on structures peripheral to the primary motor cortex.

### *Acknowledgement*

This study was performed within TREND (Trauma RElated Neuronal Dysfunction), a knowledge consortium that integrates research on Complex Regional Pain Syndrome type 1. The project is supported by a Dutch Government grant (BSIK03016).

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# APPENDIX



**Appendix A:** Setup transcranial magnetic stimulation measurement.

1 = TMS figure-of-8 coil with standard, 2 = Screen for observation tasks, 3 = Pillow, 4 = Brain navigation for accurate TMS stimulation

**Appendix B** Appendix B: TMS results (MEPs) first dorsal interosseus muscle and vividness of motor imagery

|          | CRPS affected<br>n=12<br>mean (SD) | HC dominant<br>hand n=12<br>mean (SD) | SBF non-<br>immobilized<br>n=6 median,<br>(IQR) | SBF<br>immobilized<br>n=6<br>median (IQR) |
|----------|------------------------------------|---------------------------------------|-------------------------------------------------|-------------------------------------------|
| MT       | 52.2 (8.3)                         | 53.5 (7.4)                            | 50.5 (41.8–53.3)                                | 50.0 (45.5–56.5)                          |
| 80%      | 0.1 (0.1)                          | 0.1 (0.1)                             | 0.1 (0.0–0.1)                                   | 0.1 (0.0–0.1)                             |
| 90%      | 0.3 (0.3)                          | 0.4 (0.3)                             | 0.2 (0.1–0.4)                                   | 0.4 (0.2–0.5)                             |
| 100%     | 0.9 (0.3)                          | 1.1 (0.6)                             | 0.9 (0.4–1.0)                                   | 0.6 (0.6–1.1)                             |
| 110%     | 2.2 (0.9)                          | 2.0 (0.8)                             | 1.8 (1.5–2.3)                                   | 1.6 (1.3–1.8)                             |
| 120%     | 3.0 (1.3)                          | 2.7 (1.5)                             | 2.4 (1.4–4.2)                                   | 2.8 (1.6–3.5)                             |
| 130%     | 3.8 (1.4)                          | 3.5 (2.1)                             | 3.1 (1.7–4.8)                                   | 3.0 (1.6–4.4)                             |
| MO rest  | 0.9 (0.3)                          | 1.1 (0.5)                             | 0.9 (0.5–1.1)                                   | 0.7 (0.6–1.1)                             |
| MO light | 1.0 (0.7)                          | 1.3 (0.9)                             | 1.6 (1.2–2.4)                                   | 1.3 (1.2–1.8)                             |
| MO heavy | 1.1 (0.8)                          | 1.6 (0.8)                             | 2.2 (1.5–2.4)                                   | 1.5 (1.4–1.8)                             |
| MI rest  | 0.9 (0.7)                          | 1.2 (0.6)                             | 1.1 (0.8–1.5)                                   | 0.7 (0.5–0.9)                             |
| MI light | 1.3 (1.2)                          | 1.6 (0.9)                             | 1.9 (1.0–2.9)                                   | 0.8 (0.5–1.0)                             |
| MI heavy | 1.2 (1.1)                          | 1.9 (1.1)                             | 1.9 (1.4–2.3)                                   | 1.0 (0.6–1.0)                             |
| VMIQ-2   | 3.0 (1.1)                          | 1.8 (0.6)                             | 1.9 (1.3–2.3)                                   | 1.6 (1.3–2.5)                             |

TMS=transcranial magnetic stimulation; MEPs=motor evoked potentials; SD=standard deviation; IQR=interquartile range; CRPS=complex regional pain syndrome; HC=healthy controls; SBF=scaphoid bone fracture (patients); MT=motor threshold; %=percentage stimulus intensity to produce 1mV; MO=motor observation; MI=motor imagery; VMIQ-2=Vividness of Movement Imagery Questionnaire-2

# Chapter 7

## **Summary, general discussion and future perspectives**



## SUMMARY

In **chapter 1** we provide an overview of the clinical features of CRPS and its pathophysiological characteristics with special attention to plastic changes of the brain. Further, the aims of this thesis are outlined.

In **chapter 2** we report our results on health-related quality of life (QoL) in 975 CRPS patients who visited five pain clinics and one department of neurology (Leids Universitair Medisch Centrum) in the Netherlands between 2005 and 2011. For many patients, CRPS is a chronic and debilitating syndrome. It has a profound effect on many aspects of their lives, often extending far beyond their primary health problems. In medical terms, these effects on well-being are defined as health-related quality of life (HRQoL, in short QoL). QoL encompasses multiple health domains including physical and mental health perceptions and conditions, functional status, social support and socioeconomic status<sup>9</sup>. Knowledge of the QoL of CRPS patients may contribute in guiding the development of successful treatment strategies that aim to reduce the disease burden since to date no cure for CRPS is available.

In this study, we measured QoL using the Dutch version of the Medical Outcomes Study Short Form 36 (SF-36)<sup>76</sup>, a generic questionnaire consisting of 8 health domains, analogous to the ones described above. Data of the SF-36 were analysed and correlated with age, sex, disease duration and measures related to physical and psychosocial health. The findings were compared with those reported of other chronic pain syndromes. Our findings showed that loss of QoL in CRPS patients is severe, even in comparison to other painful diseases such as rheumatoid arthritis<sup>82</sup>, neuralgic amyotrophy<sup>87</sup> and lower limb amputations with or without phantom limb pain<sup>82,88,89</sup>. Further, loss of QoL was mostly determined by the loss of physical capabilities, and less so by mental complaints. Pain was moderately associated with physical- and mental health and patients meeting stricter diagnostic criteria of CRPS had lower QoL scores than patients fulfilling less strict criteria. Collectively, these results imply that above all, therapeutic strategies should focus on improving physical capabilities and reducing pain.

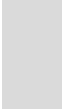
Apart from the obvious incidence disparity between women and men<sup>3,4</sup>, little was previously known about sex differences in CRPS. In **chapter 3** we searched for possible sex differences in 698 CRPS type I patients who fulfilled the Budapest clinical or research criteria. Sex differences were analysed for clinical characteristics, pain scores, pain coping, physical disability, anxiety, depression and kinesiophobia. In contrast to findings of the general population, our results show that while pain severity was comparable, emotional suffering in male CRPS patients was higher than in female CRPS patients. This effect is potentially mediated by the higher levels of passive pain coping, depression and kinesiophobia found in male CRPS

patients. A greater awareness of these sex-specific factors in the management of CRPS may contribute to achieving better therapeutic outcomes.

In **chapter 4** we searched for alleged CRPS specific structural and functional changes of the brain. Previously, a myriad of studies reported diverse changes in brain structure and function<sup>38–45,122,123</sup>. These studies followed clinical observations of altered central processing of sensory stimuli<sup>48–51</sup> and motor control<sup>52–54</sup>. However, some of these studies had a high risk of bias<sup>124,125</sup>, many used data that was uncorrected or insufficiently corrected for multiple comparisons and results were often inconsistent across studies. Due to these concerns, the aim of this study was twofold: First, to evaluate if previous MRI findings could be reproduced using currently advocated statistical methods. Second, to assess the evidence for specific clinical correlates of structural and functional changes in brain and compare findings with those from previously published MRI studies .

For this purpose, we used multiple Magnetic Resonance Imaging (MRI) techniques including Voxel Based Morphometry (VBM) for gray matter volumetrics, Diffusion Tensor Imaging (DTI) for analysis of white matter connectivity and resting state functional MRI for the analysis of functional changes of the brain in 19 female CRPS patient and 19 female healthy controls. We could not find compelling evidence for specific changes in brain structure or function in rest in our patient sample. In addition, when we reviewed previous published results, we found 1) an absence of consistent correlations with clinical measures and 2) conflicting results in terms of directionality of changes (more versus less gray matter volume, more or less brain activation in particular areas) and spatial representation.

Although we could not find significant changes in brain structure and function in rest (this thesis, **chapter 4**), previous studies showed evidence for altered processing of external (painful) stimuli, most noticeably in somatosensory and limbic brain areas<sup>161,163,228,229</sup>. However, two of these studies<sup>161,162</sup> were uncontrolled and all studies presented results uncorrected for multiple comparisons. In **Chapter 5** we therefore studied brain activity during the application of a painful stimulus to the affected hand of CRPS patients and the right hand of healthy controls. In a secondary analysis we measured the effect of these activations on brain networks involved in somatosensory, motor and behavioral processing. During the application of the heat stimulus, in CRPS patients specific activation of the left temporal parietal junction (TPJ) was seen, a brain area involved in salience detection. The magnitude of brain activity correlated positively with disease duration. In addition, only in the CRPS group we found a negative correlation between the left TPJ and the ventral medial prefrontal cortex (VMPC), a brain area that is known to relay sensory information from the external world to brain areas involved in emotional processing. Furthermore, increased activation of the VMPC is known to decrease the affective burden of pain and successfully suppress emotional responses



to a negative emotional stimulus<sup>191,192</sup>. No differences in brain activity of the motor cortices were seen between CRPS and healthy controls, suggesting that motor disturbances in CRPS are not directly linked to painful sensory afferent input. In conclusion, while experiencing a painful heat stimulus, CRPS patients display increased salience detection in combination with opposite activation of brain regions involved in reducing the affective burden of pain

The work presented in **Chapter 6** is focussed on movement disorders in CRPS patients. The nature of these movement disorders has been a continuous source of debate. On the one hand they are viewed as a consequence of maladaptive neuronal plasticity, whereas some, on the other hand, emphasized a resemblance with functional movement disorders (ie, movement disorders without a demonstrable organic substrate). Previous studies in functional movement disorders found a dissociation of motor cortex activation between explicit, voluntary motor tasks and implicit, involuntary motor tasks attributed to inhibitory interference of frontal or limbic brain areas during voluntary motor tasks. Using transcranial magnetic stimulation, we stimulated the primary motor cortex in rest and during explicit motor imagery and implicit movement observation in 12 CRPS patients with motor disturbances, 12 healthy controls and 6 patients treated with cast immobilisation to control for the effects of underutilizations of a limb. In comparison to healthy controls, CRPS patients had similar motor cortex excitability in rest and analogous increased cortical excitability during the implicit and explicit motor imagery tasks. Therefore, a dissociation in motor excitability during implicit and explicit motor tasks such as seen in functional movement disorders could not be corroborated and possible interference from other brain areas was, at least during these tasks, not considered likely. Second, we found that immobilisation of a limb causes a (temporary) inability to activate the primary motor cortex during explicit motor tasks.

## **General discussion and future perspectives**

Twelve years ago, as an intern neurology, I was involved in the case of a fifty-year old female patient who suffered from an incredible amount of pain. After listening to her story of a “tight cast after wrist fracture” she anxiously showed me a floppy, red, warm and swollen arm but declined a physical examination due to severe allodynia.

A neurologist diagnosed her condition as “complex regional pain syndrome” and thereafter I remained intrigued by the clinical presentation and followed a scientific internship in Bath, UK under the supervision of professor McCabe and a PhD course at the Leiden University Medical Center.

What intrigued me most were the, at that time, postulated similarities with phantom limb pain including sensory characteristics such as burning pain, cramping sensations, body perception disturbances and neglect-like symptoms of the affected limb. And above all, the possibility to

relieve the pain temporarily with interventions using a mirror box<sup>128,230</sup>. The latter was based on the assumption that a mismatch between the efferent motor commands and the expected, but absent (in case of phantom limb pain) or erroneous (in case of CRPS) afferent sensory feedback would be perceived as pain<sup>231</sup>. In addition, clinical signs of referred sensations were found to correlate with reorganisation of the somatotopic map in the primary somatosensory cortex. This, in turn, correlated very strongly with pain intensity<sup>38,232</sup> and was hypothesized to result in erroneous motor output that would be interpreted by the brain as painful<sup>139,232</sup>. At that time it was hypothesized that restoring visual afferent signalling using the mirror box would resolve the mismatch which in turn would reduce the pain severity.

However, more recent studies have forwarded strong arguments against the previously reported reorganisation of the sensorimotor cortex in CRPS<sup>122,233,234</sup>. Furthermore, evidence for therapeutic effects of treatment strategies designed to restore maladaptive cortical reorganisation in CRPS is now considered insufficient<sup>235</sup>.

The possibility of brain-derived-pain, and thus an important role for the brain in CRPS pathophysiology, fuelled a considerable number of studies on the potential functional and structural change of the brain, beyond those reported on the sensorimotor cortex (see introduction and discussion **chapter 4**). However, as discussed, the results across studies were very heterogeneous and generally lacked evidence of clinical correlations. Several issues contributed to the lack of uniform findings: First, over the last two decades, study designs, imaging techniques (increased spatial resolution due to more powerful MRI scanners) and statistical analysis showed important improvements. Second, clinical characteristics of patients in and between studies were very heterogeneous. This negatively influences the power since it increases the variability in the results. Furthermore, psychological characteristics are often not taken into account while these can differ enormously between patients. For example: presence of previous traumatic events, use of different pain coping strategies, or difference in views on the effect of physical exercise on pain. All factors may influence brain activity, both at rest (**chapter 4**), while perceiving sensory stimuli (e.g. **chapter 5**) or during motor tasks (e.g. **chapter 6**). Lastly, the mean disease duration of patients varies across many studies. This is important since disease duration may have a large influence on phenotype expression: after several months the initial neurogenic inflammation subsides and autonomic function alters significantly. Over time, many patients who were previously diagnosed with CRPS will no longer fulfil the criteria of CRPS, but still suffer from neuropathic pain. This implies that CRPS may progress from a distinct neuropathic pain syndrome with an initial specific (inflammatory) pathophysiology to a chronic disorder *indistinct* of other neuropathic pain syndromes characterised by a disinhibited pain system, as underscored by the results described in **chapter 5**.

So, how have the studies described in this thesis contributed to the current insights on CRPS? In **chapter 5** we report findings of increased saliency with corresponding decreased activation of brain regions involved in reducing the affective burden of pain in response to a painful stimulus in chronic CRPS patients. These findings correspond to previous reports of pain-related fear in chronic CRPS<sup>120</sup> and data reporting a shift from pain-related brain circuitry to emotion-related circuitry in chronic pain conditions<sup>196</sup>. In addition, findings in **chapter 2** and **3** show strikingly poor physical functioning in CRPS which have been linked to perceived harmfulness of activities and “resting” as a pain coping strategy<sup>85</sup>. Collectively, this suggests that patients’ attitudes and behaviour towards pain and physical exercise may play an important role in the physical impairments experienced by patients. Consequently, a multidisciplinary approach involving rehabilitation physicians, physiotherapists, psychologists, and pain specialists is strongly recommended when treating chronic CRPS patients.

The results of **chapter 4**, in particular the discussed heterogeneity of the previously published results in the literature have two implications: first, a critical attitude towards the applied methodology of neuroimaging is needed, otherwise we will be left chasing in the shadows<sup>155</sup>. This starts with researchers doing their best to avoid false positive results and willingness of journals to publish studies with negative results. Second, a number of developments question the wisdom of further imaging research into changes of the brain that play a role in the maintenance of CRPS: Growing evidence contradicts the reorganization of the sensorimotor cortex in CRPS<sup>122,233,234</sup>. In addition, brain activity previously dubbed as pain biomarkers are increasingly disputed as similar patterns can be elicited by other non-painful stimuli<sup>236</sup>. Lastly, there is a lack of evidence for treatment strategies focussing on restoring maladaptive cortical reorganization<sup>235</sup> as well as for seemingly effective brain-modulation treatments such as repetitive transcranial magnetic stimulation or transcranial direct current stimulation<sup>237</sup>.

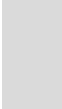
However, some specific issues in CRPS still require further research, in particular the motor disturbances seen in this disorder (see also next paragraph). In view of the motor disturbances, it is important to note that the above criticisms apply to research of the cerebrum, not the cerebellum. Given its important role in motor, emotional and pain processing<sup>199,200</sup>, future studies should try to elucidate its role in CRPS as this is currently insufficiently done. In addition, brain imaging could potentially contribute to patient selection procedures for studies and be used as an outcome measure for clinical trials (e.g. measure the effect of an intervention on brain activity of frontal and limbic brain areas). In addition, further research is needed to investigate whether neuroimaging techniques can be used for risk analyses<sup>238</sup>; for example: is it possible to develop predictors of chronicity in CRPS? If so, should certain interventions be recommended based on these results? A preferably longitudinal study design with repeated brain imaging during the course of the disease could provide insights on the feasibility of predictors of chronicity of the disease. Interestingly, similar methods have

been used in paediatric CRPS patients, although the influence of brain development in childhood have hampered the interpretation of findings of these studies<sup>239,240</sup>. Finally, we base our conclusions on the results we find, but lack the knowledge of what we cannot measure. For example, current fMRI techniques depend on the BOLD-signal (Blood-Oxygenation Level Dependent) which is a measure of oxygen consumption. This signal might not be refined enough to find relevant alterations in brain function in CRPS. Future techniques with increased spatial resolution may therefore provide new insights. The same applies for improvements in software engineering. Recent advances in artificial intelligence are huge and, when applied correctly<sup>236</sup>, could be used to improve the interpretation of imaging data in terms of patient's clinical characteristics.

From **chapter 6** we learned that motor control in CRPS patients does not correspond to previously published results in patients with functional movement disorders. Future studies in which both groups are included should confirm this finding. However, the question remains is if the method we used in **chapter 6** will yield sufficient differences between groups. TMS has the limitation that it only influences the activity of the primary motor cortex, which is the end stage of motor planning. Brain activity of the premotor cortex, supplementary motor area, basal ganglia and cerebellum is not uninfluenced by TMS. Therefore, It would be more interesting to combine TMS with fMRI, allowing new information to be obtained concerning the motor planning that preceded primary motor cortex activity. However, methodologically this is quite a challenge since the coil of a TMS apparatus interferes with the magnetic field of the scanner.

One main question that remains, concerns on which component of the CRPS pathophysiology new therapeutic strategies should focus in the future. Data shown in this thesis imply that alterations in brain structure or function are in fact ancillary effects of peripheral pathological processes (**chapter 5**). Therefore, the focus likely should return to the peripheral processes involved in CRPS.

CRPS patients may benefit most from therapies that prevent or moderate central sensitisation due to its profound negative effect on pain inhibition and ultimately quality of life. Spinal cord stimulation (SCS), which involves placement of electrodes in the epidural space posterior to the spinal cord<sup>237</sup>, is considered an effective therapy in the management of CRPS patients. Forty-one percent of the patients had at least 30% pain reduction at 11 years follow up<sup>241,242</sup>. However, despite its efficacy in the treatment of pain, SCS performed in chronic CRPS-1 showed no important improvement in functional outcome<sup>243</sup>. Recently promising results emerged in favor of dorsal root stimulation in CRPS<sup>244</sup>. Of 44 included CRPS type 1 patients with affected lower limb(s) treated with dorsal root stimulation, 82,5% obtained a pain reduction that succeeded 50% after 3 months with similar results after 12 months.



In addition, quality of life, including physical functioning, and psychological disturbances improved substantially. These results were superior to the spinal cord stimulation group also included in the study. However, the promising results should be viewed cautiously since the study was industry sponsored, lacked blinding or sham stimulation.

Interestingly, some reports based on animal models show that the initial aberrant peripheral inflammatory response may lead to increased levels of the pro-inflammatory cytokines in blister fluid and venous blood<sup>22,23,245–247</sup> and increased systemic T-cell activity<sup>20,23</sup>. These results are now complemented by reports of sex-specific pro-inflammatory cytokine concentrations in rodent models of CRPS<sup>248</sup> and sex hormone mediated immune reactions. In response to peripheral trauma, male rodents activate an innate immune response in the spinal cord, whereas female rodents activate an adaptive immune response<sup>249,250</sup>. Possibly, these sex-related differential immune responses account for the higher incidence of CRPS in women<sup>4,72</sup> and may have a role in the recurrences of CRPS signs and symptoms after new traumatic events. New therapies targeting these aberrant immune responses may prevent chronicity of CRPS and thus provide a potential means to alter the disease course and improve quality of life of patients.



## **Samenvatting, discussie en toekomstperspectieven**



## SAMENVATTING

In hoofdstuk 1 bespreek ik de klinische en pathofysiologische kenmerken van Complex Regionaal Pijn Syndroom (CRPS) met speciale aandacht voor neuronale plasticiteit in de hersenen. Hiernaast worden de doelstellingen van dit proefschrift besproken.

In **hoofdstuk 2** rapporteren we de gezondheidsgerelateerde kwaliteit van leven (in het Engels: “*health-related quality of life*” afgekort als QoL) van 975 CRPS-patiënten die tussen 2005 en 2011 vijf pijnklinieken en één afdeling neurologie (LUMC) in Nederland bezochten. Voor veel patiënten is CRPS een chronisch en invaliderend syndroom. CRPS heeft, naast het negatieve effect op de gezondheid, een diepgaand effect op veel andere aspecten van het leven en daarmee op het welzijn van de patiënt. In medische termen wordt dit welzijn gedefinieerd als gezondheidsgerelateerde kwaliteit van leven en wordt beoordeeld aan de hand van meerdere domeinen, waaronder fysieke en mentale gezondheidspercepties, fysiek en sociaal functioneren en sociaaleconomische status<sup>9</sup>. Kennis van de kwaliteit van leven van CRPS-patiënten kan bijdragen aan de ontwikkeling van succesvolle behandelstrategieën die gericht zijn op het verminderen van de ziektelast aangezien er tot op heden geen curatieve behandeling voor CRPS bestaat.

We maten de kwaliteit van leven met behulp van de Nederlandse versie van de Medical Outcomes Study Short Form 36 (SF-36)<sup>76</sup>. Dit is een generieke vragenlijst bestaande uit 8 gezondheidsdomeinen, analoog aan die hierboven beschreven. Gegevens van de SF-36 werden geanalyseerd en gecorreleerd aan leeftijd, geslacht, ziekteduur en metingen van fysieke en psychosociale gezondheid. De resultaten hebben we vergeleken met eerder gepubliceerde data van andere chronische pijnsyndromen.

We toonden aan dat het verlies van kwaliteit van leven bij CRPS-patiënten ernstig is, zelfs in vergelijking met andere pijn gerelateerde ziekten zoals reumatoïde artritis<sup>82</sup>, amyotrofische schouder neuralgie<sup>87</sup> en patiënten met onderbeen amputaties met en zonder fantoompijn<sup>82,88,89</sup>. Daarbij wordt het verlies van kwaliteit van leven vooral bepaald door fysieke beperkingen en in mindere mate door mentale klachten. Pijn was matig geassocieerd met fysieke en mentale gezondheid en patiënten die aan de strengere diagnostische criteria van CRPS voldeden, hadden lagere kwaliteit van leven dan patiënten die aan de minder strenge criteria voldeden. Samenvattend impliceren deze resultaten dat therapeutische strategieën zich vooral moeten richten op het verbeteren van fysieke mogelijkheden en het verminderen van pijn.

Afgezien van het duidelijke verschil in incidentie tussen vrouwen en mannen<sup>3,4</sup>, was er eerder weinig bekend over eventuele verschillen in ziektekenmerken tussen mannen en vrouwen

met CRPS. In **hoofdstuk 3** hebben we gezocht naar sekseverschillen bij 698 CRPS type I patiënten die voldeden aan de Boedapest criteria (“clinical” of “research”) van CRPS<sup>2</sup>. Tussen mannelijke en vrouwelijke CRPS-patiënten vergeleken we de klinische gegevens, pijnscores, pijn coping, lichamelijke beperkingen, angst, depressie en kinesiofobie. Het bleek dat het emotionele leed bij mannelijke CRPS-patiënten hoger was dan bij vrouwelijke CRPS-patiënten bij een vergelijkbare ernst van pijn. Dit effect werd mogelijk gemedieerd doordat mannen vaker gebruik maakten van passieve pijnverwerking strategieën en vaker leden aan depressie en kinesiofobie. Een groter bewustzijn van deze sekse-specifieke factoren kan bijdragen aan het bereiken van betere therapeutische behandelingsresultaten voor CRPS patiënten.

In **hoofdstuk 4** hebben we gezocht naar CRPS-specifieke veranderingen in structuur en functie van de hersenen. Eerder was er een verscheidenheid aan veranderingen gerapporteerd<sup>38–45,122,123</sup> die volgden op klinische bevindingen van veranderde waarneming van gevoelsprikkels<sup>48–51</sup> en motorische aansturing van ledematen<sup>52–54</sup>. Sommige van deze onderzoeken hadden echter een hoog risico op bias (“systematische vertekening”)<sup>124,125</sup>, veel studies gebruikten data die niet of onvoldoende waren gecorrigeerd voor herhaaldelijk statistisch testen en de resultaten waren vaak inconsistent tussen de studies. Vanwege deze gebreken was het doel van deze studie tweeledig: ten eerste om de eerdere Magnetic Resonance Imaging (MRI) resultaten te reproduceren met behulp van de huidige, correcte, statistische methoden. Ten tweede, om het bewijs voor specifieke structurele en functionele veranderingen van de hersenen die geassocieerd zijn met klinische kenmerken te beoordelen en de resultaten te vergelijken met die van eerder gepubliceerde MRI-onderzoeken.

Hiervoor hebben we bij 19 vrouwelijke CRPS-patiënten en 19 vrouwelijke gezonde controles meerdere MRI-technieken gebruikt, namelijk Voxel Based Morphometry (VBM) voor volumetrie van de grijze stof, Diffusion Tensor Imaging (DTI) voor analyse van de connectiviteit van de witte stof en functionele MRI voor de analyse van functionele veranderingen van de hersenen in rust. Met deze technieken konden we in onze studiepopulatie geen overtuigend bewijs vinden voor specifieke veranderingen van de hersenstructuur of hersenfunctie in rust. Bovendien, toen we eerder gepubliceerde resultaten kritisch beoordeelden, vonden we 1) een afwezigheid van consistente correlaties tussen de gemeten MRI-data en klinische kenmerken en 2) tegenstrijdige resultaten in termen van directionaliteit van de gemeten veranderingen (meer versus minder grijze stof, meer of minder hersenactivatie) en lokalisatie in de hersenen waar de veranderingen waren opgetreden.

Hoewel wij in CRPS patiënten geen significante veranderingen vonden in de structuur en functie van de hersenen in rusttoestand (**hoofdstuk 4** van dit proefschrift), is er in eerdere studies bewijs geleverd voor veranderde verwerking van (pijnlijke) stimuli, vooral in soma-

tosensorische- en limbische hersengebieden<sup>161,163,228,229</sup>. Echter twee van deze studies zijn uitgevoerd zonder een controlegroep<sup>161,162</sup> en alle studies presenteerden resultaten gebaseerd op statistische testen die niet (voldoende) waren gecorrigeerd voor herhaaldelijk testen.

In **hoofdstuk 5** bestudeerden we daarom de hersenactiviteit ten tijde van het toedienen van pijnlijke warmteprikkels op de aangedane hand van CRPS-patiënten en de rechterhand van gezonde controles. In de primaire analyse onderzochten we of er significante verschillen waren in hersenactiviteit tussen de groepen. In een secundaire analyse werden significante verschillen gebruikt om gecorreleerde hersenactiviteit van andere hersengebieden te meten, met name die hersengebieden die geassocieerd zijn met zintuigelijke waarneming, motoriek en gedrag. De resultaten waren als volgt: naast de verwachte hersenactiviteit in de pijn gerelateerde hersengebieden vonden we alleen in de CRPS patiënten een significante activering van de linker temporale pariëtale overgang (in het Engels ‘temporal parietal junction’, TPJ). Dit hersengebied is betrokken is bij de interpretatie van “opvallendheid” (in het Engels ‘saliency’) van zintuigelijke prikkels. De mate van hersenactiviteit correleerde positief met de ziekteduur, niet met de pijnintensiteit. Bovendien vonden we alleen in de CRPS-groep een negatieve correlatie tussen de linker TPJ en de ventromediale prefrontale cortex (VMPC), een hersengebied waarvan bekend is dat het sensorische informatie van de buitenwereld doorgeeft aan hersengebieden die betrokken zijn bij emoties. Bovendien is bekend dat verhoogde activering van de VMPC de affectieve last van pijn vermindert en met succes emotionele reacties op een negatieve emotionele stimulus onderdrukt<sup>191,192</sup>. Er werden geen verschillen in hersenactiviteit van de motorcortex gevonden tussen patiënten met CRPS en gezonde controles, wat suggereert dat de motorische stoornissen bij CRPS niet direct verband houden met pijnlijke sensibele input. Concluderend, in CRPS-patiënten tonen de hersenen een verhoogde mate van gewaarwording van pijnlijke warmtestimuli die negatief geassocieerd is met hersengebieden die betrokken zijn bij het verminderen van de affectieve last van pijn.

De studie die in **hoofdstuk 6** wordt besproken is gericht op bewegingsstoornissen die gezien worden bij CRPS-patiënten. De aard van deze bewegingsstoornissen staat al geruime tijd ter discussie. Enerzijds worden ze gezien als het gevolg van verkeerde neuronale plasticiteit, anderzijds wordt vaak een gelijkis gezien met functionele bewegingsstoornissen (d.w.z. bewegingsstoornissen zonder aantoonbaar organisch substraat). Bij functionele bewegingsstoornissen is in eerdere publicaties aangetoond dat corticale hersenactiviteit over de primaire motor cortex verdwijnt tijdens expliciete (bewuste) bewegingstaken, maar aanwezig is tijdens impliciete (onbewuste) bewegingstaken. Deze dissociatie is toegeschreven aan interfererende activiteit van frontale of limbische hersengebieden tijdens expliciete bewegingstaken.

Met transcraniële magnetische stimulatie (TMS) stimuleerden we de primaire motor cortex van 12 CRPS-patiënten met bewegingsstoornissen, 12 gezonde controles en 6 patiënten waarvan een hand langdurig was geïmmobiliseerd in verband met een scafoïdfractuur. Deze laatste groep was geïnccludeerd om te corrigeren voor het feit dat veel CRPS-patiënten hun aangedane hand in veel mindere mate, of helemaal niet, gebruiken. TMS werd uitgevoerd in de volgende situaties: in rust, tijdens een (expliciete) ingebeelde bewegingstaak en tijdens een (impliciete) bewegingsobservatietaak.

We vonden dat, in vergelijking met gezonde controles, de motor cortex van CRPS-patiënten een vergelijkbare corticale prikkelbaarheid in rust toonde en een analoge verhoogde corticale prikkelbaarheid tijdens de impliciete en expliciete motorische taken. Daarom kon een dissociatie in motore corticale prikkelbaarheid tijdens impliciete en expliciete bewegingstaken, zoals gezien bij functionele bewegingsstoornissen, niet worden bevestigd in CRPS-patiënten. Daarbij werd dus ook een mogelijke interferentie van andere hersengebieden, althans tijdens deze taken, niet waarschijnlijk geacht. Ten tweede vonden we dat immobilisatie van een ledemaat een (tijdelijk) onvermogen veroorzaakt om de primaire motor cortex te activeren tijdens expliciete bewegingstaken.

## ALGEMENE DISCUSSIE EN AANBEVELINGEN

Twaalf jaar geleden zag ik als coassistent neurologie een vrouwelijke patiënt van rond de vijftig die ongelooflijk veel pijn leed. Na het beluisteren van haar verhaal over “te strak zittend gips na een gebroken pols” toonde ze me met zeer veel tegenzin een slappe, rode, warme en gezwollen arm. Wegens allodynie weigerde ze verder lichamelijk onderzoek. Dit ziektebeeld fascineerde me zo dat het leidde tot een wetenschappelijke stage in Bath, VK onder supervisie van professor McCabe en een promotietraject in het Leids Universitair Medisch Centrum.

Wat me op dat moment het meest fascineerde waren de veronderstelde overeenkomsten met fantoompijn. Zo hebben CRPS-patiënten en fantoompijn-patiënten overeenkomstige gevoelsstoornissen waaronder brandende pijn, krampsensaties, stoornissen van de lichaamsperceptie en “neglect”-achtige symptomen van de aangedane ledemaat. Daarbij kon de pijn in beide syndromen worden verlicht met behulp van een spiegel<sup>128,230</sup>!

Dit laatste was gebaseerd op de veronderstelling dat een discrepantie tussen de efferente motore commando's vanuit de hersenen en de verwachte, maar afwezige (in geval van fantoompijn) of foutieve (in het geval van CRPS) afferente sensibele terugkoppeling als pijnlijk zou worden ervaren<sup>231</sup>. Bovendien bleken de eigenschappen van de aanwezige “referred sensations” (het voelen van een stimulus op een ander lichaamsdeel dan waar wordt gestimuleerd) te correleren met functionele reorganisatie van de primaire somatosensore cortex. Dit correleerde zeer sterk met de pijnintensiteit<sup>38,232</sup> en, zo werd gedacht, zou leiden tot een onjuiste motorische output die door de hersenen als (additioneel) pijnlijk zou worden ervaren<sup>39,232</sup>. In die tijd werd verondersteld dat met behulp van de spiegel de kwaliteit van afferente informatie zou verbeteren en daarmee de discrepantie tussen de verwachte en de ontvangen sensibele terugkoppeling zou normaliseren, wat op zijn beurt de ernst van de pijn zou doen verminderen.

Echter, recente studies hebben sterke argumenten aangevoerd tegen de eerder gemelde reorganisatie van de sensomotore cortex in CRPS<sup>122,233,234</sup>. Bovendien wordt het bewijs voor therapeutische effecten van behandelingsstrategieën die zijn ontworpen om de verkeerde corticale reorganisatie in CRPS te herstellen, nu als kwalitatief onvoldoende beschouwd<sup>235</sup>.

De mogelijkheid van pijn die z'n oorsprong kent in de hersenen, en dus een belangrijke rol voor de hersenen in de pathofysiologie van CRPS, resulteerde in een aanzienlijk aantal studies die ook andere functionele en structurele verandering van de hersenen onderzochten. Zoals eerder besproken waren de resultaten in alle studies echter zeer heterogeen en

ontbraken er correlaties met klinische kenmerken. Verschillende problemen droegen bij aan het gebrek aan uniforme bevindingen: ten eerste zijn er in de afgelopen twee decennia belangrijke verbeteringen doorgevoerd in studieontwerp, beeldvormingstechnieken (verhoogde ruimtelijke resolutie als gevolg van krachtigere MRI-scanners) en statistische analyses. Ten tweede zijn de klinische eigenschappen van patiënten in en tussen studies zeer heterogeen. Dit laatste heeft een negatieve invloed op de power ('onderscheidende kracht') van de statische testen, omdat het de variabiliteit in de resultaten verhoogt. Verder wordt er vaak geen rekening gehouden met psychologische kenmerken terwijl deze enorm kunnen verschillen tussen patiënten. Bijvoorbeeld: aanwezigheid van eerdere traumatische gebeurtenissen, gebruik van verschillende pijn coping-strategieën, of verschil in opvattingen over het effect van lichaamsbeweging op pijn. Alle factoren kunnen de hersenactiviteit beïnvloeden, zowel in rust (**hoofdstuk 4**), tijdens het waarnemen van zintuiglijke stimuli (bijv. **hoofdstuk 5**) of tijdens motorische taken (bijv. **hoofdstuk 6**).

Ten slotte varieert de gemiddelde ziekteduur van patiënten in veel onderzoeken. Dit is belangrijk omdat de duur van de ziekte een grote invloed kan hebben op de expressie van het fenotype: na enkele maanden neemt de initiële neurogene ontsteking in CRPS af en verandert de autonome functie aanzienlijk. Na verloop van tijd zullen veel patiënten die eerder de diagnose CRPS gekregen hebben niet langer voldoen aan de criteria van CRPS, maar nog steeds last hebben van neuropathische pijn. Dit impliceert dat CRPS kan evolueren van een neuropathisch pijnsyndroom met een initiële specifieke (inflammatoire) pathofysiologie naar een chronische aandoening die overeenkomsten vertoont met andere neuropathische pijnsyndromen die worden gekenmerkt door een ontregeld pijnsysteem, zoals de resultaten van **hoofdstuk 5** lijken aan te tonen.

Dus, hoe hebben de studies die in dit proefschrift worden beschreven bijgedragen aan de huidige inzichten over CRPS? In **hoofdstuk 5** rapporteren we bevindingen van verhoogde gewaarwording van pijnlijke warmtestimuli die negatief geassocieerd is met hersengebieden die betrokken zijn bij het verminderen van de affectieve last van pijn. Deze bevindingen komen overeen met eerdere meldingen van pijn gerelateerde angst bij chronische CRPS<sup>120</sup>. Daarbij heeft een eerdere studie aangetoond dat bij chronische pijn aandoeningen er een verschuiving optreedt van activatie van pijn-gerelateerde hersencircuits naar activatie van emotie-gerelateerde hersencircuits<sup>196</sup>. Bovendien blijken CRPS-patiënten, zoals beschreven in **hoofdstuk 2** en **3**, opvallend slecht fysiek te functioneren. Dit is eerder verklaard door de vaak aanwezige notie dat beweging schadelijk kan zijn voor de aangedane ledenmaat en het gebruik van "rust" als pijn coping-strategie<sup>85</sup>.

Concluderend suggereert dit dat de houding en het gedrag van patiënten ten opzichte van pijn en lichaamsbeweging een belangrijke rol spelen in de fysieke beperkingen die patiënten

ervaren. Daarom wordt een multidisciplinaire aanpak met revalidatieartsen, fysiotherapeuten, psychologen en pijnspecialisten sterk aanbevolen in de behandeling van chronische CRPS-patiënten.

De resultaten van **hoofdstuk 4**, in het bijzonder de besproken heterogeniteit van de eerder gepubliceerde resultaten in de literatuur, impliceren twee dingen: ten eerste, er is een kritische houding ten opzichte van de toegepaste methodologie van MRI hersenonderzoek nodig<sup>155</sup>. Dit begint met onderzoekers die er naar streven om vals-positieve resultaten te vermijden en tijdschriften die studies met negatieve resultaten verwelkomen. Ten tweede is het de vraag of verder onderzoek naar veranderingen van de hersenen die CRPS symptomen zouden onderhouden of veroorzaken zinvol is. Zo worden er steeds meer onderzoeken gepubliceerd die geen bewijs vinden voor de oude hypothese van functionele reorganisatie van de primaire sensomotore cortex in CRPS<sup>122,233,234</sup>. Ook worden patronen van hersenactiviteiten die voorheen werden geduid als biomarkers voor pijn in toenemende mate betwist omdat vergelijkbare patronen kunnen worden uitgelokt door de toediening van niet-pijnlijke stimuli<sup>236</sup>. Ten derde is er een gebrek aan bewijs voor behandelingsstrategieën die zich richten op het herstellen van de gehypothetiseerde corticale reorganisatie<sup>235</sup> en voor behandelingen die zich richten op het beïnvloeden van de corticale hersenactiviteit zoals repetitieve transcraniële magnetische stimulatie of transcraniële gelijkstroomstimulatie<sup>237</sup>.

Sommige specifieke symptomen van CRPS vereisen echter nog nader onderzoek, met name de motorische stoornissen die bij deze aandoening worden gezien (zie ook de volgende paragraaf). Gezien de motorische stoornissen is het belangrijk op te merken dat bovenstaande kritiek van toepassing is op onderzoek van het cerebrum, niet het cerebellum. Gezien de belangrijke rol van het cerebellum in motorische aansturing, emotie- en pijnverwerking<sup>199,200</sup>, zouden toekomstige beeldvormende studies zich kunnen richten op de rol van het cerebellum in CRPS, aangezien dit momenteel onvoldoende gedaan is. Bovendien zou beeldvormend onderzoek wel gebruikt kunnen worden voor patiëntselectieprocedures voor wetenschappelijke onderzoeken en als uitkomstmaat voor klinische onderzoeken (bijvoorbeeld om het effect van een interventie op hersenactiviteit van frontale of limbische hersengebieden te meten). Daarnaast is verder onderzoek nodig om te onderzoeken of beeldvormende technieken gebruikt kunnen worden voor risicoanalyseonderzoeken<sup>238</sup>. Bijvoorbeeld: is het mogelijk om voorspellers van chroniciteit bij CRPS te vinden? Zo ja, moeten op basis van deze resultaten bepaalde interventies worden aanbevolen? Bij voorkeur zou een longitudinaal onderzoeksdesign met herhaalde beeldvorming van de hersenen tijdens het ziekteverloop hierin inzicht kunnen verschaffen. Interessant is dat vergelijkbare methoden al gebruikt zijn bij kinderen met CRPS, echter de invloed van hersenontwikkeling in de kindertijd bemoeilijkt de interpretatie van die bevindingen<sup>239,240</sup>.

Ten slotte, we baseren onze conclusies op de resultaten die we vinden, maar we missen de kennis van wat we niet kunnen meten. De huidige fMRI-technieken zijn bijvoorbeeld afhankelijk van het BOLD-signaal (Blood-Oxygenation Level Dependent) dat een maat is voor het zuurstofverbruik. Dit signaal is mogelijk te grof om relevante veranderingen in de hersenfunctie bij CRPS te vinden. Toekomstige technieken met verhoogde ruimtelijke resolutie kunnen daarom nieuwe inzichten opleveren. Hetzelfde geldt voor verbeteringen in softwareontwikkeling. De recente ontwikkelingen op het gebied van kunstmatige intelligentie zijn enorm en zouden, indien correct toegepast<sup>236</sup>, kunnen worden gebruikt voor een verbeterde interpretatie van de MRI data in het licht van de klinische kenmerken van de patiënt.

Van **hoofdstuk 6** hebben we geleerd dat de aansturing van de motoriek bij CRPS-patiënten niet overeenkomt met eerder gepubliceerde resultaten bij patiënten met functionele bewegingsstoornissen. Toekomstige studies waarin beide groepen zijn opgenomen zouden deze bevinding moeten bevestigen. De vraag is echter of de methode die we in **hoofdstuk 6** hebben gebruikt voldoende onderscheidend vermogen heeft. TMS heeft de beperking dat het alleen de activiteit van de primaire motorische cortex beïnvloedt, wat het eindstadium is van motorische planning. De hersenactiviteit van de premotorische cortex, de supplementaire motorische schors, de basale ganglia en het cerebellum wordt niet direct beïnvloed door TMS. Daarom zou het interessanter zijn om TMS te combineren met fMRI, zodat nieuwe informatie kan worden verkregen over de motorische planning die voorafging aan de activiteit van de primaire motorcortex. Dit is echter methodologisch een hele uitdaging, aangezien de spoel van een TMS-apparaat interfereert met het magnetische veld van de scanner.

Een belangrijke vraag die resteert is op welk onderdeel van de CRPS-pathofysiologie nieuwe therapeutische strategieën zich in de toekomst moeten richten. De resultaten van dit proefschrift impliceren dat veranderingen in de hersenstructuur of -functie in feite neveneffecten zijn van perifere pathologische processen. Daarom moet de aandacht verlegd worden naar de perifere processen die betrokken zijn in CRPS. Met name therapieën die centrale sensitisatie voorkomen of verminderen zouden effectief kunnen zijn vanwege het diepgaande negatieve effect op pijnremming en uiteindelijk op kwaliteit van leven. Ruggenmergstimulatie (SCS), waarbij elektroden worden geplaatst in de epidurale ruimte achter het ruggenmerg<sup>237</sup>, is zo'n behandeling en wordt beschouwd als een effectieve therapie bij de behandeling van CRPS-patiënten. Eenenvierde van de patiënten heeft ten minste 30% pijnvermindering na 11 jaar follow-up<sup>241,242</sup>. Echter, ondanks de pijnvermindering, vertoonde SCS uitgevoerd bij chronisch CRPS-1 geen belangrijke verbetering in fysieke uitkomstmaten<sup>243</sup>. Veelbelovend zijn daarom recente resultaten die een beter effect laten zien van dorsale wortelstimulatie<sup>244</sup>. Van de 44 geïncludeerde patiënten met CRPS type 1 met aangedane onderste ledematen

die werden behandeld met dorsale wortelstimulatie, kreeg 82,5% een pijnvermindering van 50%, wat aanhield na 3 maanden en 12 maanden. Bovendien verbeterde de kwaliteit van leven aanzienlijk, inclusief fysiek functioneren en psychische belasting. Deze resultaten waren superieur aan de resultaten van de ruggenmergstimulatiegroep die ook in het onderzoek was opgenomen. Veelbelovend, echter de resultaten zullen moeten worden gereproduceerd door een onafhankelijke groep aangezien de studie was gesponsord door de industrie, de resultaten niet geblindeerd waren en een schijnstimulatie ontbrak.

Interessant is dat sommige studies op basis van diermodellen aantonen dat de aanvankelijk afwijkende perifere ontstekingsreactie kan leiden tot verhoogde niveaus van de pro-inflammatoire cytokines in blaarvloeistof en veneus bloed<sup>22,23,245-247</sup> en verhoogde systemische T-celactiviteit<sup>20,23</sup>. Deze resultaten worden nu opgevolgd door resultaten van geslacht specifieke pro-inflammatoire cytokineconcentraties in knaagdiermodellen van CRPS<sup>248</sup> en geslachtshormoon-gemedieerde immuunreacties. Namelijk, als reactie op perifeer trauma activeren mannelijke knaagdieren een aangeboren immuunrespons in het ruggenmerg, terwijl vrouwelijke knaagdieren een adaptieve immuunrespons activeren<sup>249,250</sup>. Mogelijk verklaren deze geslachtsgebonden differentiële immuunresponsen de hogere incidentie van CRPS bij vrouwen<sup>4,72</sup> en kunnen ze een rol spelen bij het terugkeren van CRPS-symptomen na nieuw fysiek letsel. Nieuwe therapieën die zich richten op deze afwijkende immuunresponsen zouden de chroniciteit van CRPS kunnen voorkomen en daarmee een potentieel middel bieden om het ziekteverloop te veranderen en de kwaliteit van leven van patiënten te verbeteren.



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van Velzen GAJ, Perez RSGM, van Gestel MA, et al. Health-related quality of life in 975 patients with complex regional pain syndrome type 1. *Pain*. 2014;155(3):629-634. doi:10.1016/j.pain.2013.12.017

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## REWARDS

European Pain Federation – Fondazione IBSA publication award 2016 voor “Is the brain of complex regional pain syndrome patients truly different?”

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## CURRICULUM VITAE

Gijsbrecht Abraham Johan van Velzen was born on the 24th of May, 1984. After graduating high school (Stedelijk Gymnasium Leiden) in 2002, he studied Political Science at the University of Leiden for one year. In 2003 he was accepted at the medical school (University Leiden) which he completed in 2010. In his last year of medical school he attended a scientific internship in Bath, United Kingdom, under the supervision of Candy McCabe. In May 2010 he started his PhD research at the department of neurology in the Leiden University Medical Center, under the supervision of prof. J.J. van Hilten and dr. J. Marinus. This was followed up by one year of residency neurology-not-in-training (ANIOS) in the Reinier de Graaf Gasthuis. In July 2015 he started his residency neurology at the Leiden University Medical Center which he completed in October 2021. After two months as chef de clinique in Franciscus Gasthuis en Vlietland, he started as a neurologist in the Noord West Ziekenhuisgroep from the first of January 2022.

Gijsbrecht has a beautiful fiancé Janneke Schilder and three children (Klaas, Emma and Tijn).



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