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

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Chapter 1

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 [9]. 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)[76], 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[82], neuralgic amyotrophy[87] and lower limb amputations with or without phantom limb pain[82,88,89]. 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 [3,4], 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 in than 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[38–45,122,123]. These studies followed clinical observations of altered central processing of sensory stimuli[48–51] and motor control[52–54]. However, some of these studies had a high risk of bias[124,125], 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[161,163,228,229]. However, two of these studies[161,162] 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 supress emotional responses

to a negative emotional stimulus[191,192]. 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[128,230]. 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[231]. 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[38,232] and was hypothesized to result in erroneous motor output that would be interpreted by the brain as painful[39,232]. 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[122,233,234]. Furthermore, evidence for therapeutic effects of treatment strategies designed to restore maladaptive cortical reorganisation in CRPS is now considered insufficient[235].

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 *in*distinct 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[120] and data reporting a shift from pain-related brain circuitry to emotion-related circuitry in chronic pain conditions[196]. 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[85]. 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[155]. 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[122,233,234]. In addition, brain activity previously dubbed as pain biomarkers are increasingly disputed as similar patterns can be elicited by other non-painful stimuli[236]. Lastly, there is a lack of evidence for treatment strategies focussing on restoring maladaptive cortical reorganization[235] as well as for seemingly effective brain-modulation treatments such as repetitive transcranial magnetic stimulation or transcranial direct current stimulation[237].

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[199,200], 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[238]; 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[239,240]. 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 therefor provide new insights. The same applies for improvements in software engineering. Resent advances in artificial intelligence are huge and, when applied correctly[236], 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[237], 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[241,242]. However, despite its efficacy in the treatment of pain, SCS performed in chronic CRPS-1 showed no important improvement in functional outcome[243]. Recently promising results emerged in favor of dorsal root stimulation in CRPS[244]. 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[22,23,245–247] and increased systemic T-cell activity[20,23]. These results are now complemented by reports of sex-specific pro-inflammatory cytokine concentrations in rodent models of CRPS[248] 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[249,250]. Possibly, these sex-related differential immune responses account for the higher incidence of CRPS in women[4,72] 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.