http://researchspace.auckland.ac.nz

University of Auckland Research Repository, ResearchSpace

Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form and Deposit Licence.
The Impact of Psychological Factors on

Complex Regional Pain Syndrome Type-1

Deborah Joy Bean

Abstract

**Background:** To date, very little research has assessed the outcomes of CRPS, relationships between psychological factors, pain and disability in CRPS, and the influence of psychological factors on the recovery process. This thesis therefore had three aims: 1.) To investigate the long-term outcomes of CRPS, 2.) To measure associations between psychological factors, pain and disability in CRPS, and 3.) To determine whether psychological factors are associated with future outcomes in CRPS.

**Methods:** 1.) A systematic review was conducted to investigate the outcomes of CRPS. 2.) A cross-sectional study was undertaken comparing chronic CRPS and low back pain patients in terms of the strength of associations between psychological factors, pain and disability. 3.) Cross-sectional data was utilised to assess the influence of psychological factors on disability and work status amongst acute CRPS patients. 4.) The same sample were followed prospectively for 12 months to determine the extent of symptomatic recovery, and to assess associations between baseline psychological factors and the outcomes of CRPS.

**Results:** 1.) The systematic review revealed inconsistencies in the literature. Whilst previous prospective studies demonstrated good outcomes in CRPS patients, retrospective and cross-sectional studies revealed high rates of chronic pain and disability. 2.) The cross-sectional study found that amongst CRPS compared to low back pain patients, stronger associations existed between psychological factors, pain and disability. 3.) Amongst the acute CRPS sample, depression was associated with greater disability and sick leave. 4.) The prospective study showed lower rates of recovery amongst CRPS patients than previously documented. It also demonstrated that those with higher levels of anxiety, pain-related fear and disability at baseline exhibited a poorer recovery, with greater pain and disability over 12 months.

**Conclusions:** The body of research showed that, in contrast with previous prospective studies, CRPS patients seldom make a complete recovery. Moreover, psychological factors are associated with greater pain and disability concurrently and are also associated with poorer long-term recovery. In future, researchers may wish to develop screening tools to identify those at risk of poor outcomes and/or develop early intervention treatments to prevent poor outcomes.
Acknowledgements

It gives me great pleasure to acknowledge the generous support and contribution of the many people without whom this body of work would not have been possible. First and foremost, I would like to express my gratitude to Malcolm Johnson, whose patient and persistent prompting led me to embark on the largest project of my life, and whose unwavering support, friendship, and ability to reassure (invariably over a cup of tea) allowed me to complete this venture. I’m also indebted to Rob Kydd, whose wisdom and ability to see the bigger picture provided the momentum needed at many critical points, and whose kindness, humour and calm approach also provided support and encouragement when needed.

The work in this thesis would not have been possible without the generous support of the University of Auckland, who provided a PhD scholarship, and the Oakley Mental Health Research Foundation, who recognised the importance of the research and provided a crucial research grant. Many groups and individuals also supported the research studies. I wish to thank Wolfgang Heiss-Dunlop and the team at the Counties-Manukau Orthopaedic, Plastic and Reconstructive Hand Service for supporting the study and recruiting participants. I am grateful to Alike, Shirley, Heidi and all of the Counties-Manukau hand therapists for their enthusiastic support and assistance with recruitment. I must also acknowledge Lynley and the nurses at Module 5, Manukau Superclinic, for always finding me clinic space despite the tight demands. Many hand therapists in private practice also supported the project, and I must acknowledge Sarah and the team at HandWorks, Eileen and the hand therapists at Hands Out West, and Rachel at Moving Hands Rehabilitation, without whom the research would not have been possible. I’m thankful to Simon Chinchanwala and the Waitemata DHB Orthopaedics Department, and to Keith Laubscher for his support with recruitment, and to all the team members at Waitemata and Counties chronic pain services for their enthusiasm, friendship and support of my research.

I wish also to acknowledge the support of Arier Lee, whose extensive knowledge of statistical modelling was greatly needed, and always provided with a gentle manner. Thank-you also to John Sollers for teaching me everything I know about autonomic activity, and to Nathan Consedine, whose ability to casually drop a pearl of wisdom is second to none. And to my fellow PhD students, Natalie, Margot, Lisa, Rebecca, Kate, Jordan, Francesca, Fiona, Anna, Justin and Amy, I am grateful for the supportive environment you all helped to create, for the open sharing of highs and lows, and for all the practical support with putting together this PhD.
I would also like to express my appreciation to Ian Kirk, Veema Lodhia and Carl Helmick for technical assistance and helping me to learn about a whole new world of technology. I’m also grateful to the lovely Josh Coulter and equally lovely Michael MacLean who worked tirelessly over the summer to support my research.

It gives me no greater pleasure than to thank both Drs Mike Butler and Bob Large, who inspired my interest in pain science, introduced me to the pain literature, and who taught me how to think about pain. I also express heartfelt appreciation to the whole of my TARPS team, especially to Brigitte Gertoberens, Bex Cornwall, Melissa Snyman, Peter Waddell, Kate McCallum and Jane Thomas, for steadfast support and encouragement. I also can say no greater thanks to Tipu Aamir, for utilising his extensive knowledge of pain science and readily agreeing to read this thesis and provide comment, no small task. Thank-you to both Cat Pollard and Trevor Coe, for assistance with identifying participants and saving me hours of time which would have been spent looking up patient records. A big thank-you also to Kieran Davis, for always finding the funding to make sure I attend inspiring and challenging pain meetings.

Of course, writing a thesis is also not possible without the great support of family and friends. Thank-you to Mum and James, Dad, Stacy and Laureen, Cathy and Andrew, Emma and Thomas, and all of the family and good friends who saw me through this process of writing this PhD. And of course, I owe my deepest gratitude to Jim, my husband and best friend, who saw value in my venture, supported me whole-heartedly along every step of the way, and who gave me the confidence to start this project, keep going when problems arose, and to celebrate each milestone. I’m sure we’ll celebrate many more.
Publishers’ approvals and third party copyright agreements


   Published by Wolters Kluwer Health Lippincott Williams & Wilkins©. Permission to reuse obtained January 1, 2015. Appears on pages 80-95.

   Published by Wolters Kluwer Health Lippincott Williams & Wilkins©. Permission to reuse obtained May 1, 2015. Appears on pages 96-114.

   Published by Springer Science and Business Media. Permission to reuse Figure 2 obtained on April 19, 2015. Appears on page 73.

   Published by Wolters Kluwer Health Lippincott Williams & Wilkins©. Permission to reuse obtained September 18, 2015. Appears on pages 135-153.
Co-Authorship Form

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. Please include one copy of this form for each co-authored work. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

- Chapter 3: The outcome of complex regional pain syndrome type 1: A Systematic review

<table>
<thead>
<tr>
<th>Nature of contribution by PhD candidate</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of contribution by PhD candidate (%)</td>
<td>Study conception and design, literature search and selection of studies, data extraction and integration of findings, study write-up and submission.</td>
</tr>
</tbody>
</table>

**CO-AUTHORS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm H. Johnson</td>
<td>Discussion of study conception, design and methods. Second screening of possible papers for inclusion, discussion of results and interpretation. Proofing manuscript and approving submission.</td>
</tr>
<tr>
<td>Robert R. Kydd</td>
<td>Discussion of study conception, design and methods, discussion of results and interpretation. Proofing manuscript and approving submission.</td>
</tr>
</tbody>
</table>

**Certification by Co-Authors**

The undersigned hereby certify that:
- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm H. Johnson</td>
<td></td>
<td>24/04/2015</td>
</tr>
<tr>
<td>Robert R. Kydd</td>
<td></td>
<td>24/04/2015</td>
</tr>
</tbody>
</table>

Last updated: 25 March 2013
Co-Authorship Form

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

**Chapter 5: Relationships between Psychological factors, Pain and Disability in Complex Regional Pain Syndrome and Low Back Pain**

doi:10.1097/AJP.0000000000000007

<table>
<thead>
<tr>
<th>Nature of contribution by PhD candidate</th>
<th>Study conception and design, ethical application, data collection and analyses, interpretation and write-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of contribution by PhD candidate (%)</td>
<td>95%</td>
</tr>
</tbody>
</table>

**CO-AUTHORS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm H. Johnson</td>
<td>Discussion of study conception, design and methods, assistance with data analyses, discussion of results, proofing manuscript and approving submission.</td>
</tr>
<tr>
<td>Robert R. Kydd</td>
<td>Discussion of study conception, design and methods, discussion of results, proofing manuscript and approving submission.</td>
</tr>
</tbody>
</table>

**Certification by Co-Authors**

The undersigned hereby certify that:
- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm H. Johnson</td>
<td></td>
<td>24/04/2015</td>
</tr>
<tr>
<td>Robert R. Kydd</td>
<td></td>
<td>24/04/2015</td>
</tr>
</tbody>
</table>

*Click here*

_Last updated: 25 March 2013*
This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

**Chapter 6: Factors Associated with Disability and Sick Leave in Early Complex Regional Pain Syndrome Type-1**


<table>
<thead>
<tr>
<th>Nature of contribution by PhD candidate</th>
<th>Study conception and design, ethical &amp; grant applications, participant recruitment, data collection and analyses, interpretation and write-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of contribution by PhD candidate (%)</td>
<td>95%</td>
</tr>
</tbody>
</table>

**CO-AUTHORS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm H. Johnson</td>
<td>Discussion of study conception, design and methods, assistance with data analyses, discussion of results, proofing manuscript and approving submission.</td>
</tr>
<tr>
<td>Wolfgang Heiss-Dunlop</td>
<td>Discussion of study conception, design and methods, assistance with recruitment and access to participants, proofing manuscript and approving submission.</td>
</tr>
<tr>
<td>Robert R. Kydd</td>
<td>Discussion of study conception, design and methods, discussion of results, proofing manuscript and approving submission.</td>
</tr>
</tbody>
</table>

**Certification by Co-Authors**

The undersigned hereby certify that:
- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm H. Johnson</td>
<td></td>
<td>24/04/2015</td>
</tr>
<tr>
<td>Wolfgang Heiss-Dunlop</td>
<td></td>
<td>1/05/2015</td>
</tr>
<tr>
<td>Robert R. Kydd</td>
<td></td>
<td>24/04/2015</td>
</tr>
</tbody>
</table>

Last updated: 25 March 2013
Co-Authorship Form

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

Chapter 7: Extent of Recovery in the First 12 Months of Complex Regional Pain Syndrome: A Prospective Study

**Nature of contribution by PhD candidate:** Study conception and design, ethical & grant applications, participant recruitment, data collection and analyses, interpretation and write-up.

**Extent of contribution by PhD candidate (%):** 95%

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm H. Johnson</td>
<td>Discussion of study conception, design and methods, assistance with data analyses, discussion of results, proofing manuscript and approving submission.</td>
</tr>
<tr>
<td>Wolfgang Heiss-Dunlop</td>
<td>Discussion of study conception, design and methods, assistance with recruitment and access to participants, proofing manuscript and approving submission.</td>
</tr>
<tr>
<td>Robert R. Kydd</td>
<td>Discussion of study conception, design and methods, discussion of results, proofing manuscript and approving submission.</td>
</tr>
</tbody>
</table>

**Certification by Co-Authors**

The undersigned hereby certify that:

✈ the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and

✈ in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm H. Johnson</td>
<td></td>
<td>24/04/2015</td>
</tr>
<tr>
<td>Wolfgang Heiss-Dunlop</td>
<td></td>
<td>1/05/2015</td>
</tr>
<tr>
<td>Robert R. Kydd</td>
<td></td>
<td>24/04/2015</td>
</tr>
</tbody>
</table>

*Last updated: 25 March 2013*
This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

Chapter 8: Who recovers from Complex Regional Pain Syndrome? A prospective study

<table>
<thead>
<tr>
<th>Nature of contribution by PhD candidate</th>
<th>Study conception and design, ethical &amp; grant applications, participant recruitment, data collection and analyses, interpretation and write-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of contribution by PhD candidate (%)</td>
<td>95%</td>
</tr>
</tbody>
</table>

### CO-AUTHORS

<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm H. Johnson</td>
<td>Discussion of study conception, design and methods, assistance with data analyses, discussion of results, proofing manuscript and approving submission.</td>
</tr>
<tr>
<td>Wolfgang Heiss-Dunlop</td>
<td>Discussion of study conception, design and methods, assistance with recruitment and access to participants, proofing manuscript and approving submission.</td>
</tr>
<tr>
<td>Arler C. Lee</td>
<td>Assistance with design of statistical analyses, advice on conducting statistical analyses, approving analyses, assistance with presentation of results, tables and figures, proofing manuscript and approving submission.</td>
</tr>
<tr>
<td>Robert R. Kydd</td>
<td>Discussion of study conception, design and methods, discussion of results, proofing manuscript and approving submission.</td>
</tr>
</tbody>
</table>

### Certification by Co-Authors

The undersigned hereby certify that:
- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malcolm H. Johnson</td>
<td></td>
<td>24/04/2015</td>
</tr>
<tr>
<td>Wolfgang Heiss-Dunlop</td>
<td></td>
<td>1/05/2015</td>
</tr>
<tr>
<td>Arler C. Lee</td>
<td></td>
<td>1/05/2015</td>
</tr>
<tr>
<td>Robert R. Kydd</td>
<td></td>
<td>24/04/2015</td>
</tr>
</tbody>
</table>
# Table of Contents

**ABSTRACT** ..................................................................................................................................... III

**ACKNOWLEDGEMENTS** ................................................................................................................ IV

**PUBLISHERS’ APPROVALS AND THIRD PARTY COPYRIGHT AGREEMENTS** ......................... VI

**CO-AUTHORSHIP FORMS** ........................................................................................................ VII

**TABLE OF CONTENTS** .................................................................................................................. XII

**LIST OF TABLES** ........................................................................................................................ XV

**LIST OF FIGURES** ........................................................................................................................ XVI

**LIST OF ABBREVIATIONS** ........................................................................................................ XVII

**CHAPTER 1: OVERVIEW** .............................................................................................................. 1

**CHAPTER 2: COMPLEX REGIONAL PAIN SYNDROME** ................................................................. 6

- What is Complex Regional Pain Syndrome? ................................................................................. 6
- Diagnosis of CRPS .......................................................................................................................... 6
- Epidemiology of CRPS .................................................................................................................... 7
- Causes & Pathophysiology of CRPS ............................................................................................... 10
- Overview: CRPS as a Protective Response .................................................................................... 27
- Psychological Factors as a Cause of or Risk Factor for CRPS ....................................................... 29
- Conclusions ................................................................................................................................. 34

**CHAPTER 3: THE OUTCOME OF COMPLEX REGIONAL PAIN SYNDROME TYPE 1: A SYSTEMATIC REVIEW** .................................................................................................................. 36

- Prelude ........................................................................................................................................ 36
- Citation ......................................................................................................................................... 38
- Abstract ....................................................................................................................................... 39
- Introduction ................................................................................................................................. 40
- Methods ..................................................................................................................................... 41
- Results ........................................................................................................................................ 43
- Discussion ................................................................................................................................. 58
List of Tables

Table 1. IASP (Orlando) Criteria for Complex Regional Pain Syndrome ................................................................. 7
Table 2: IASP (Budapest) Criteria for Complex Regional Pain Syndrome ............................................................... 8
Table 3: Characteristics of the Included Studies ........................................................................................................ 44
Table 4: Results of the Quality and Relevance Assessment for the Included Studies .................................................. 48
Table 5: Results of Retrospective Studies Measuring General Outcomes of CRPS .................................................. 54
Table 6: Results of Retrospective Studies Measuring Pain Outcomes in CRPS ...................................................... 55
Table 7: Results of Cross-Sectional & Correlational Studies on the Course of CRPS ................................................... 59
Table 8: Results of Studies Assessing Prognostic Indicators in CRPS ........................................................................ 65
Table 9: Demographic Details and Psychological Test Scores for the CRPS and Low Back Pain Patient Samples ........................................................................................................................................... 88
Table 10: Correlations Among Measures of Pain Intensity, Disability, and Psychological Variables ......... 89
Table 11: Regression Tables to Predict Disability and Pain ......................................................................................... 90
Table 12. Demographic and Clinical Features of the Sample .................................................................................. 106
Table 13. Pearson's Correlations Between Disability, CRPS Severity, Pain and Psychological Variables ...................................................................................................................................................... 107
Table 14. Associations Between Disability Scores and Symptoms/Signs of CRPS .................................................. 108
Table 15. Multiple Linear Regression to Predict Disability (PDI) Scores .................................................................. 109
Table 16. Work Status Prior to and Following CRPS Onset ..................................................................................... 110
Table 17. Differences Between Those who Continued Work/Study and Those on Sick Leave with CRPS ...................................................................................................................................................... 111
Table 18. Logistic Regression to Predict Work Status ............................................................................................... 112
Table 19. Demographic and Clinical Details of the Sample ...................................................................................... 125
Table 20. Mean (SD) Scores at Baseline, 6 & 12 Months for: CRPS Severity, Percentage of Participants Fulfilling CRPS Diagnostic Criteria, and Scores for Measured Signs, Pain, Disability, Work and Psychological Scales ........................................................................................................................................... 126
Table 21. Mean (SD) Scores for all of the Measured Variables at Baseline, 6 and 12 Months ................................. 146
Table 22. Results of Mixed Models for Repeated Measures Analyses to Identify Independent Variables Associated with CRPS Severity, Pain Intensity and Disability Assessed at Baseline, 6 and 12 Months ........................................................................................................................................... 148
Appendix 1: Table 23: Quality and Relevance Assessment Criteria for Systematic Review ................................ 168
Appendix 3: Table 24. Rates of CRPS Symptoms (Self-Reported) at Baseline, 6 and 12 Months .......................... 171
Appendix 4: Table 25. Rates of CRPS Signs (during Physical Examination) at Baseline, 6 and 12 Months ........................................................................................................................................... 172
List of Figures

Figure 1: The fear-avoidance model of chronic pain ................................................................. 73
Figure 2: Scatterplots showing the relationship between disability and depression for CRPS (panel a) and low back pain patients (panel b) ........................................................................................................ 91
Figure 3: Scatterplots showing the relationship between pain and anxiety for CRPS (panel a) and low back pain patients (panel b) ........................................................................................................ 91
Figure 4: Flowchart depicting the recruitment and retention of participants in the study .......... 124
Figure 5: Bar chart depicting changes in self-reported CRPS symptoms from baseline (T1) to 6 months (T2) and 12 months (T3) ........................................................................................................ 128
Figure 6: The percentage of the sample with mild, moderate or severe signs of CRPS on physical examination at baseline (T1), 6 months (T2) and 12 months (T3) ....................................................... 129
Figure 7: Line graphs demonstrating significant associations between baseline and outcome variables .................................................................................................................................................... 149
List of Abbreviations

ACE  Angiotensin Converting Enzyme
BCBPDS  Bath CRPS Body Perception Disturbance Scale
CGRP  Calcitonin Gene-Related Peptide
CNS  Central Nervous System
CRPS  Complex Regional Pain Syndrome
CRPS-1  Complex Regional Pain Syndrome Type-1
CRPS-2  Complex Regional Pain Syndrome Type-2
DASS  Depression Anxiety Stress Scale
fMRI  Functional Magnetic Resonance Imaging
HADS  Hospital Anxiety and Depression Scale
HLA  Human Leukocyte Antigen
HRV  Heart-Rate Variability
HPA  Hypothalamic-Pituitary-Adrenal
IL  Interleukin
IASP  International Association for the Study of Pain
MMP-9  Matrix Metalloproteinase-9
M1  Primary Motor Cortex
NE  Norepinephrine
NRS  Numerical Rating Scale
PCS  Pain Catastrophizing Scale
PDI  Pain Disability Index
RSD  Reflex Sympathetic Dystrophy
SFMPQ2  Short-Form McGill Pain Questionnaire-2
SNS  Sympathetic Nervous System
S1  Primary Somatosensory Cortex
TNF-2  Tumor Necrosis Factor-2
TREND  Trauma Related Neuronal Dysfunction
TSK  Tampa Scale for Kinesiophobia
VAS  Visual Analogue Scale
Chapter 1: Overview

Complex regional pain syndrome (CRPS) is a painful and often disabling condition for which historically, the pathophysiology has been poorly understood. Whilst research has advanced knowledge of the condition in recent years, an understanding of the condition as a whole remains elusive. CRPS has been known by a variety of names, including reflex sympathetic dystrophy, algodystrophy, Sudeck’s dystrophy and shoulder-hand syndrome (Alvarez-Lario, Aretxabala-Alcibar, Alegre-Lopez, & Alonso-Valdivielso, 2001). Some of these have emphasized the importance of various pathophysiological mechanisms, but the condition was renamed complex regional pain syndrome in 1994 to intentionally move away from the notion of a single causal mechanism (Merskey & Bogduk, 1994). Historically, research has also focussed on two streams: one biomedical stream has sought to explore physiological changes that accompany CRPS, such as autonomic activity or inflammatory processes, however no one mechanism has been shown to underpin CRPS. Another body of research sought to explore CRPS from a psychological perspective, and much of this research aimed to determine whether there were psychological causes of CRPS, or a personality-type that was associated with the condition (Feliu & Edwards, 2010), but this was also not found (Lohnberg & Altmaier, 2013). In other words, CRPS was investigated either as a condition of the body or of the mind, in keeping with the dualistic view of health first proposed by Rene Descartes in the 17th Century: that mind and body were separate entities.

The biomedical body of research has advanced our understanding of CRPS, for example, it has documented abnormalities in the genetic profiles, inflammatory markers, autonomic responses, and in the structure and function of the central nervous systems of CRPS patients (Bruehl, 2010; Marinus et al., 2011). However it is not known to what extent each of these variables might play a causal role in the condition, and whilst treatment advances have been made, none of these mechanisms have led to a universally effective intervention to either prevent or cure the condition. More recently, theoretical viewpoints have started to integrate this research and present hypotheses regarding the multifactorial nature of the condition (Marinus et al., 2011), suggesting that all of these physiological mechanisms might interact in an over-developed protective response to perceived threat, orchestrated at the level of the brain (Moseley, 2007). However, as yet no research has sought to examine this hypothesis as a whole or to investigate the psychological aspects of this ‘perceived threat’.
Instead, a reasonably extensive body of research has sought to determine whether CRPS is caused by underlying psychological distress, psychiatric conditions, or whether there is a “CRPS-prone” personality. This research has generally shown that the risk of developing CRPS is not elevated amongst those with elevated levels of distress or with particular personality profiles (Beertuizen, Stronks, Huygen, Passchier, Klein, & Spijker, 2011; Harden et al., 2003; Puchalski & Zyluk, 2005). Although such psychological causes of CRPS have been evaluated, it is surprising that very little research has sought to examine bidirectional influences between psychological factors and pain or other symptoms in CRPS. Health psychology models have proved beneficial to our understanding of a plethora of medical conditions, demonstrating that psychological factors such as mood, illness perceptions, health beliefs and expectations influence symptom perception, coping strategies, health behaviours and outcomes for conditions as diverse as cancer, heart disease, diabetes, and medically unexplained symptoms (Chida & Hamer, 2008; Chida, Hamer, Wardle, & Steptoe, 2008; Knoop, Prins, Moss-Morris, & Bleijenberg, 2010; Lichtman et al., 2008; Surdea-Blaga, Baban, & Dumitrascu, 2012).

In the field of pain medicine, similar psychological factors (beliefs, expectations, fear, mood, learning history and social influences, amongst others) have been shown to have a significant effect on experimental, clinical, procedural and chronic pain in humans and animals (Martin, Tuttle, & Mogil, 2014; Tracey, 2010; Turk & Okifuji, 2002), and treatments aimed at modifying these psychological factors have clinical benefit (Williams, Eccleston, & Morley, 2012). One model in particular which has been influential in pain medicine is the fear-avoidance model first described by Johan Vlaeyen, which proposes that fear of movement and re-injury leads to disuse, depression and disability and to ongoing pain (Vlaeyen, Kole-Snijders, Boeren, & van Eek, 1995; Vlaeyen & Linton, 2000). Variables proposed in this model, along with other psychological variables, have been studied prospectively in pain conditions such as low back pain, neck pain or post-surgical pain. For these pain conditions, such factors have been shown to influence not necessarily the initial development of pain, but the transition from acute pain to chronic pain, i.e. the recovery process (Carroll et al., 2009; Hinrichs-Rocker, Schulz, Järvinen, Lefering, Simanski, & Neugebauer, 2009; Melloh et al., 2009). As yet, relatively little research has evaluated whether similar psychological processes are also important in recovery from CRPS, though several uncontrolled treatment trials have suggested that exposure to feared activities leads to symptomatic improvement in CRPS (de Jong, Vlaeyen, Onghena, Cuypers, den Hollander, & Ruijgrok, 2005; Ek, van Gijn, Samwel, van Egmond, Klomp, & van Dongen, 2009; van de Meent et al., 2011).

The main aim of this thesis is to investigate the influence of psychological factors on pain, disability and symptoms of CRPS. Whilst one goal is to evaluate whether relationships exist between these variables in cross-sectional data, the primary question of interest is whether psychological factors...
have a measurable influence on the recovery process, or trajectory of CRPS. A brief overview of the thesis, and how each chapter relates to this overall aim, is outlined below.

This thesis begins in Chapter 2 with an overview of the literature to date on CRPS. Here the review describes the complex pathophysiology of CRPS and current understandings of the condition, in particular commenting on research that has sought to establish the causes of the condition. Research studies on psychological factors that have sought to examine possible psychological causes of the condition are also described here. This chapter presents the hypothesis that CRPS may result not from a single simple physiological process nor from an abnormal psychological profile, but rather from an interacting set of mechanisms that play out as an exaggerated protective response to perceived threat to the body.

In Chapter 3, the focus moves from understanding the pathophysiology of CRPS to looking at variability in the recovery process, outcomes, or natural history of CRPS. Chapter 3 presents a systematic review of published studies which have sought to document recovery rates or outcomes of CRPS (Bean, Johnson, & Kydd, 2014a). This is the first systematic review of its kind in CRPS, and was considered an important undertaking in order to determine the extent of variability in the recovery process and outcomes of CRPS. Of particular interest was whether CRPS, like other chronic pain conditions, follows a pattern whereby some patients make a good recovery in the early stages, whilst others develop chronic symptoms. In other pain conditions, psychological variables have differentiated between these two groups, and in order to determine whether or not a similar pattern would be worthwhile investigating in CRPS, this review was considered integral.

Chapter 4 then presents a review of the few previously conducted studies that have identified prognostic indicators in CRPS, along with a discussion of the limited quality of that literature. The chapter continues with a presentation of the possible psychological constructs to be explored in relation to the outcomes of CRPS, and a presentation of one of the theoretical models relevant to the research (the fear-avoidance model). In order to determine the possible relevance of these psychological constructs to CRPS, this chapter describes previous research examining the psychological variables prospectively in other pain conditions, along with a discussion of any research relating these psychological factors to CRPS. Possible mechanisms by which psychological factors might be associated with CRPS are also discussed.
Chapter 5 presents the first of the original research studies in the thesis, an exploration of the relationships between psychological variables and two outcome variables: pain and disability, in a sample of chronic CRPS patients (Bean, Johnson, & Kydd, 2014b). These relationships are compared to those of a matched control group of low back pain patients to determine whether similar relationships exist between the conditions. Several psychological variables, all linked to threat perception and/or pain-related fear, are evaluated and multivariate statistics are used to determine which psychological variables influence pain and disability independently. The study showed that depression, anxiety and pain-related fear were all associated with poorer outcomes for CRPS patients, and that several associations between psychological variables and outcomes were stronger in the CRPS groups compared to the low back pain patients.

There were some limitations associated with the cross-sectional study, notably its reliance on a sample with longstanding CRPS, and self-report data. The study presented in Chapter 6 overcomes some of these limitations by exploring the associations between psychological variables and outcomes in a sample of patients with recently-onset CRPS, and also by looking at work status as an outcome variable. Work is noted to be an important outcome variable in its own right, but as working is also associated with better health outcomes (Waddell & Burton, 2006), may also be an important variable in the recovery process. The study revealed a significant link between depression and both disability and sick leave amongst CRPS patients.

Finally, in both Chapters 7 and 8, the results of a prospective study are presented. This study aimed not only to identify the extent to which CRPS patients recover over the course of 12 months, but also to determine whether psychological factors associated with threat perception or altered perceptions of the affected limb predicted the extent of recovery. This study revealed that lasting pain and symptoms are common even 12 months after developing CRPS, which conflicts to some degree with the prospective studies described in Chapter 3, and possible reasons for this are discussed. The study also found that poor recovery from CRPS was associated with initial CRPS severity, pain intensity, disability, anxiety and pain-related fear. All are considered aspects of threat perception and thus the study has implications for understanding the pathophysiology of CRPS according to the hypothesis that the condition represents an aberrant response to perceived threat; the findings also have clinical implications for treatment.

The body of work as a whole and the key findings from the thesis are summarised in the discussion in Chapter 9, and the work is integrated back into the broader literature on CRPS and on pain and health
psychology. The key issues are discussed and the implications of the research for understanding CRPS are explored. The research limitations are acknowledged and the thesis concludes with a discussion of future research possibilities and directions.
Chapter 2: Complex Regional Pain Syndrome

What is Complex Regional Pain Syndrome?

Complex regional pain syndrome (CRPS) is a painful and often disabling condition which usually affects a patient’s arm, wrist or hand, leg, ankle or foot, in which pain is substantially out of proportion to the nature and extent of the initiating event. It can occur after fracture, soft tissue injury, stroke or surgery, but in some cases it occurs spontaneously. CRPS is divided into two subtypes. CRPS Type-I was previously known as reflex sympathetic dystrophy and occurs in the absence of a specific nerve injury. CRPS Type-II, formerly called causalgia, is accompanied by a nerve injury (Harden et al., 2013).

The broad (and at times dramatic) range of symptoms that accompany pain in CRPS include sensory changes: allodynia (pain with usually non-painful stimulation) and hyperalgesia (disproportionately elevated pain on painful stimulation). The affected limb usually swells and sweating may be either increased or reduced. Temperature disturbance is common and the limb may be either warm or cool. Typically the limb changes colour, often appearing red, blotchy or cyanotic. In addition, trophic changes can occur and the limb may appear shiny, and nail and hair growth may either increase or reduce. Movement is usually restricted and slow, and in extreme cases, tremor and fixed dystonia may be present. This chapter will discuss the range of physiological processes shown to occur with CRPS and discuss the hypothesis proposed by Moseley (2007) and Marinus et al. (2011) that CRPS represents an aberrant protective response to perceived tissue threat.

Diagnosis of CRPS

Historically, the constellation of symptoms now known as CRPS has been known by a wide variety of names, with significant variability in the diagnostic criteria applied to the condition. Previous names for CRPS include algodystrophy, sudeck’s dystrophy, reflex sympathetic dystrophy, shoulder-hand syndrome, post-traumatic pain syndrome, painful post-traumatic osteoporosis, and transient migratory osteoporosis. The term complex regional pain syndrome is relatively new, having come into being in 1994 following a consensus meeting of experts in the field, led by the International Association for the Study of Pain (IASP) (Merskey & Bogduk, 1994).

Most diagnoses were based on matching symptoms to a list of criteria, and the list of criteria used has varied widely, with some diagnostic criteria focussing on so-called ‘sympathetic’ symptoms and not
requiring the presence of pain, whilst other criteria have focused on pain and sensory symptoms. There has been significant debate in the literature about appropriate diagnostic criteria for CRPS, and the three most common sets of criteria used today are Veldman’s criteria (Veldman, Reynen, Arntz, & Goris, 1993), the 1994 IASP (Orlando) criteria (Merskey & Bogduk, 1994), the new IASP (Budapest) criteria (Harden et al., 2010a).

Table 1. IASP (Orlando) Criteria for Complex Regional Pain Syndrome (Merskey & Bogduk, 1994)

1. The presence of an initiating noxious event, or a cause of immobilization.

2. Continuing pain, alldynia, or hyperalgesia in which the pain is disproportionate to any inciting event.

3. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.

4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Table 1 shows the 1994 IASP (Orlando) diagnostic criteria that formed the basis of much research, but which have been criticised for being too broad. Research showed that whilst these criteria are highly sensitive, they have low specificity (Harden, Bruehl, Stanton-Hicks, & Wilson, 2007). This led to the proposal of the “Budapest” criteria, following another meeting of experts in 2003. This set of criteria retained a fairly high level of sensitivity (0.99) but had improved specificity (0.68, or 0.79 if the research criteria are used), meaning that it produces fewer cases of “false-positive” results (Harden et al., 2010a). These newer criteria are displayed in Table 2 (page 8).

Epidemiology of CRPS

Two large population-based studies have sought to identify the incidence of CRPS. The first searched medical records for cases of CRPS in Olmsted County, USA, and reported an incidence rate of 5.46 cases per 100,000 person years (Sandroni, Benrud-Larson, McClelland, & Low, 2003). This study contrasted with the findings of de Mos and colleagues (2007), who searched the primary care database for a population of 600,000 people in the Netherlands, for any records of CRPS between 1996 and 2005. They reported that there was an incidence of 26.2 cases per 100,000 person years, which was more than four times the incidence reported by the earlier study. This might be due to the methodology used by Sandroni and colleagues (2003), which has been criticised because they
excluded cases of CRPS which had been diagnosed by doctors, but which failed to note the specific symptoms of CRPS in medical records. The case records of only 19% of the patients diagnosed by doctors mentioned sufficient symptoms to be included in the study. Hence the study likely underestimated the incidence rates. Both studies demonstrated that CRPS occurs more frequently in females than males, and upper compared to lower limbs. CRPS is reported to occur in all age ranges, though develops most commonly amongst those who are middle-aged; de Mos et al. (2007) reported a mean age of onset of 52.7 years, whilst Sandroni et al. (2003) found that the median age of onset was 46 years. Both studies found that the incidence of CRPS was elevated in the age groups 50-59 and 60-69 compared to the incidence in both older and younger groups. A recent systematic review found that the risk factors for developing CRPS included female sex, and postmenopausal females are particularly at risk (Pons, Shipton, Williman, & Mulder, 2015).

Table 2: IASP (Budapest) Criteria for Complex Regional Pain Syndrome
(Harden et al. 2010)

1. Continuing pain, which is disproportionate to any inciting event.

2. Must report at least one symptom in three of the four following categories: (for research criteria: at least one symptom in each of four categories)
   a. Sensory: reports of hyperaesthesia and or allodynia.
   b. Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry.
   c. Sudomotor/oedema: reports of oedema and/or sweating changes and/or sweating asymmetry.
   d. Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

3. Must display at least one sign at time of evaluation in two or more of the following categories:
   a. Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement).
   b. Vasomotor: evidence of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry.
   c. Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry.
   d. Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

4. There is no other diagnosis that better explains the signs and symptoms.

Incidence of CRPS After Fracture
Fracture is the most common triggering event for CRPS, and a number of studies have followed patients after fracture to measure the percentage who develop signs and symptoms of CRPS. Much
of this research was done before the development of both the Orlando and the Budapest criteria, making interpretation difficult. The prevalence rates differ greatly between studies, with the lowest reported incidence after distal radius fracture being 1% (Dijkstra, Groothoff, ten Duis, & Geertzen, 2003), and the highest being 36% (Atkins, Duckworth, & Kanis, 1990). A further seven studies rate the incidence at somewhere between 11% and 28% following Colles’/distal radius fracture (Atkins, Duckworth, & Kanis, 1989; Bickerstaff & Kanis, 1994; Field & Atkins, 1997; Gradl, Steinborn, Wizgall, Mittlmeier, & Schurmann, 2003; Jellad, Salah, & Ben Salah Frih, 2014; Roumen, Hesp, & Bruggink, 1991; Zollinger, Tuinebreijer, Kreis, & Breederveld, 1999). Much of the variation in incidence reports seem to be due to either the diagnostic criteria utilised by the study (more specific criteria lead to lower incidence rates), or the timing of the follow-up assessment. Studies which follow patients up soon after fracture report higher incidence rates (Atkins et al., 1990; Bickerstaff & Kanis, 1994), and studies which follow patients at multiple or later time-points suggest that the incidence reduces over time (Atkins et al., 1989; Roumen et al., 1991).

**Incidence of CRPS After Surgery**

Several studies have examined the incidence of CRPS after surgery, and these have also produced conflicting results. Once again, the incidence rates reported by each study appear to depend quite heavily on the methodology employed. Studies which employ a retrospective review of patient medical notes, or which rely on clinical records, rather than specifically measuring symptoms, provide very low incidence reports. For example, Katz, Hungerford, Krackow & Lennox et al (1986) reported that only 0.8% of 662 patients who had undergone total knee arthroplasty developed reflex sympathetic dystrophy (as diagnosed by a positive response to sympathetic blockade). Likewise, Small (1988) reported a rate of reflex sympathetic dystrophy of 0.04%, from a sample of 10,262 arthroscopic procedures carried out by surgeons across the USA. In contrast to these findings, a study of foot and ankle surgery reported that 4.36% met the criteria for CRPS (Rewhorn, Leung, Gillespie, Moir, & Miller, 2014), Sennwald (1990) reported that 18% of cases undergoing surgery for Dupuytren’s disease developed reflex sympathetic dystrophy. Harden et al (2003) reported that, following total knee arthroplasty, the percentage of patients who met the IASP-Orlando criteria for CRPS was 21% at 1-month follow-up.

Not surprisingly, a lot of research has focussed on attempting to identify those who will develop CRPS following an incident such as fracture or surgery. Such research has included studies looking at demographic factors, various aspects of medical history, the nature of injury or surgery, activity of the autonomic nervous system, psychological factors, as well as pain levels. This research will be discussed below together with broader research assessing the pathophysiology of CRPS.
Causes & Pathophysiology of CRPS

The pathophysiology of CRPS is the subject of a significant amount of research, and more research is required before the condition will be completely understood. Whilst early researchers looked for a single cause of CRPS, more recent models suggest that multiple pathophysiological mechanisms interact to create and maintain the condition (Bruehl, 2010; Marinus et al., 2011). Research currently implicates the roles of the SNS, inflammatory factors, peripheral and central sensitization, changes to endogenous pain modulation, maladaptive brain plasticity as well as the possible roles of genetic factors and psychological experiences. Each will be discussed below. It is argued that all of the symptoms and the physiological changes that accompany CRPS may form part of an aberrant protective response to perceived threat to the tissues (Marinus et al., 2011; Moseley, 2007).

Genetics

Seventeen published studies to date have assessed a possible genetic contribution to CRPS in humans. Several of these studies have assessed whether CRPS might be associated with an abnormality of the human leukocyte antigen (HLA), which resides on chromosome 6, and which is generally associated with immune function and some autoimmune conditions. Higher frequencies of the following alleles have been reported amongst CRPS patients compared to controls: HLA-DR2 (Mailis & Wade, 1994; van de Beek, van Hilten, & Roep, 2000), HLA-DQ1 (Kemler, van de Vusse, van den Berg-Loonen, Barendse, van Kleef, & Weber, 1999), HLA-DR13 (van Hilten, van de Beek, & Roep, 2000), HLA-D6S1014, HLA-C1_2_5, HLA-C1_3_2 (van de Beek, Roep, van der Slik, Giphart, & van Hilten, 2003), HLA-B62, and HLA-DQ8 (de Rooij et al., 2009c; van Rooijen et al., 2012) and HLA-A_29_1 (Jin et al., 2013). Vaneker, van der Laan, Allebes, and Goris (2002) found that those with a predominantly cold CRPS limb had increased levels of HLA-DR6 and HLA-DQ1, whereas patients with a predominantly warm CRPS limb had a high frequency of the TNF2 (tumour necrosis factor-2) allele, and those who were homozygous for the TNF2 allele were more likely to have CRPS in multiple extremities. Overall, this research suggests that the HLA complex may play a role in CRPS, but there are inconsistencies between studies in terms of which particular alleles may be elevated in frequency.

Five genetic studies have looked outside of the HLA for differences between CRPS patients and healthy controls, but some results are inconsistent. Kimura, Komatsu, Hosada, Nishiwaki, and Shimada (2000) found that CRPS was associated with an increased frequency of the deletion polymorphism of the angiotensin converting enzyme (ACE) gene amongst Japanese patients. In contrast, Huhne, Leis, Schmelz, Rautenstrauss, and Birklein (2004) found no difference between CRPS patients and controls in the frequencies of the insertion/deletion polymorphism of the ACE gene. De
Rooij et al. (2010) reported that CRPS was not associated with a mutation of the SCN9A gene, which is associated with other painful conditions. In addition, Herlyn et al. (2010) found that the rs1048101 polymorphism of the α1a-adrenoceptor was associated with an increased risk of developing CRPS after distal radius fracture. Jin and colleagues (2013) conducted genome-wide expression profiling in CRPS patients and reported significant differences between CRPS patients and controls for 80 genes, most of which were associated with signal transduction, developmental processes, cell structure and motility, and immunity. They also suggested that up-regulation of the matrix metalloproteinase-9 (MMP-9) gene may be related to pain progression in CRPS.

A further body of research has examined patterns of familial CRPS. Several studies have recruited CRPS patients who also have family members with CRPS, and compared these individuals with CRPS patients who do not have a family member with the same condition. They reported that those with familial CRPS tend to be younger, are more likely to have had a spontaneous onset of the disorder, multiple extremities affected, a longer disease duration, and are more likely to have dystonia (de Rooij, de Mos, Sturkenboom, Marinus, van den Maagdenberg, & van Hilten, 2009a; Shirani et al., 2010). The familial pattern occurred in distant relatives as well as close relatives, suggesting that the basis for heritability could be genetic rather than environmental. The authors propose that there is a genetic component to a more severe form of CRPS which affects younger people. This suggestion is also supported by a study on the sibling risk ratio for CRPS, which found that the risk of experiencing CRPS was not higher amongst CRPS patients’ siblings in general. However, the risk was 3-6 times higher for siblings aged under 50 (de Rooij et al., 2009b). In addition, a pedigree analysis study of children with CRPS found evidence for maternal inheritance and an association between CRPS, other functional health complaints, and mitochondrial disease (Higashimoto, Baldwin, Gold, & Boles, 2008).

The body of literature on the genetic basis of CRPS is far from comprehensive but does offer some insight. It appears that several genetic profiles associated with inflammatory responses may be implicated, including abnormalities in the HLA complex, TNF-2 allele, and/or polymorphisms of the ACE gene. The genetic research suggests that those with a genetic profile associated with aberrant inflammatory responses may be at risk of CRPS. This is consistent with the body of research that has identified abnormal inflammatory responses present in CRPS patients, which will be discussed below. In addition, studies of familial inheritance of CRPS suggest that a distinct and severe form of CRPS affecting younger people may have a stronger genetic component than other forms of CRPS.
Inflammatory Processes

The classic symptoms of early CRPS (a swollen, hot, red painful limb) suggest that inflammation is present, and this has been the topic of a good deal of research. Whilst early research clearly showed that there is no infection associated with the condition, a number of studies have identified abnormalities in inflammatory markers of CRPS patients, suggesting that CRPS is associated with a pro-inflammatory state. The term ‘neurogenic inflammation’ has been coined to describe inflammation that occurs when neuropeptides and pro-inflammatory cytokines are released directly from nociceptive fibres (Bruehl, 2010), and this process is associated with CRPS. Studies have shown differences between CRPS patients and controls in the levels of pro-inflammatory and anti-inflammatory cytokines, as well as several neuropeptides. These include tumour necrosis factor alpha (TNF-α), and interleukin (IL)-1β, IL-2, IL-6 and IL-8 in local blister fluid, circulating plasma or spinal fluid (Alexander, van Rijn, van Hilten, Perreault, & Schwartzman, 2005; Huygen, De Bruijn, De Bruin, Groeneweg, Klein, & Zijlstra, 2002; Kramer et al., 2011; Lenz et al., 2013; Schinkel, Gaertner, Zaspel, Zedler, Faist, & Schuermann, 2006). CRPS patients also have lower systemic levels of the anti-inflammatory cytokines IL-4 and IL-10 compared to healthy controls (Uceyler, Eberle, Rolke, Birklein, & Sommer, 2007). This excess of pro-inflammatory cytokines and relative lack of anti-inflammatory cytokines suggests that an inflammatory process is associated with CRPS. Additionally, recent studies suggest that the presence of autoantibodies is higher amongst CRPS patients than a healthy population (Dirckx, Schreurs, de Mos, Stronks, & Huygen, 2015). A recent review found that the pattern of inflammatory abnormalities differs in the acute stages of CRPS compared to the chronic stages, with a larger number of inflammatory markers showing elevated concentrations in chronic CRPS (Parkitny et al., 2013). For example, in acute CRPS, activation of keratinocytes and mast cells leads to up-regulated TNF-α and IL-6 expression, whereas in chronic CRPS, there is a decrease in keratinocyte proliferation (Birklein et al., 2014). The extent to which these inflammatory processes contribute to the development or maintenance of CRPS has not been examined in prospective studies to date. However, Maihofner, Handwerker, Neundorfer and Birklein (2005) found that CRPS patients with hyperalgesia had higher levels of TNF-α compared to CRPS patients without hyperalgesia and healthy controls, which suggests that TNF-α is associated with sensory abnormalities in CRPS. However, Lenz et al. (2013) found that an observed reduction in pro-inflammatory cytokines after 6 months analgesic treatment did not correspond with clinical improvement. Research from other fields has also shown that some cytokines and nerve growth factor excite nociceptors and can induce long-term peripheral sensitization (Sommer & Kress, 2004), which is one mechanism by which inflammatory processes could interact with pain, and this process is discussed further below.
Research has also looked at the role of neuropeptides in CRPS. The neuropeptides involved in neurogenic inflammation include substance P, bradykinin and calcitonin gene-related peptide (CGRP), and these could account for some of the symptoms of CRPS (heat, redness, swelling, sweating and hair growth abnormalities) (Cheng & Ji, 2008). The research on CRPS has shown that patients have elevated plasma levels of bradykinin and CGRP (Blair, Chinthagada, Hoppenstehdt, Kijowski, & Fareed, 1998) as well as Substance P (Schinkel et al., 2006) compared to healthy controls. Also, treatment of CRPS which led to a reduction of symptoms (excluding pain) was associated with a decrease of CGRP (Birklein, Schmelz, Schifter, & Weber, 2001). Interestingly, epidemiological studies found that a history of migraine or asthma, or the use of angiotensin converting enzyme (ACE) inhibitors at the time of onset were risk factors for CRPS (de Mos, Huygen, Dieleman, Koopman, Stricker, & Sturkenboom, 2008; de Mos, Huygen, Stricker, Dieleman, & Sturkenboom, 2009a). The authors of these studies suggest that all three of these risk factors are associated with neurogenic inflammation, which might be the underlying mechanism that leads to the increased risk. Additionally, CRPS patients had higher levels of allergies and hypersensitive skin reactions to allergy testing compared to healthy controls (Li, Kenter, Newman, & O’Brien, 2014). All of these risk factors implicate neurogenic inflammation, as ACE inhibitors increase the availability of Substance P and bradykinin, and neurogenic inflammation is suggested to be an underlying mechanism for migraine and asthma (Marinus et al., 2011). One possibility is that the inflammatory abnormalities associated with CRPS represent an effect of CRPS rather than a cause of pain, and one study supports this view. The study showed that whilst CRPS patients had exaggerated pain responses to the application of topical capsaicin compared to controls, there was no corresponding increase in flare response, indicating that inflammation was not the mediator of this increased pain response (Terkelsen, Gierthmuhlen, Finnerup, Hojlund, & Jensen, 2014). However, it is also possible that inflammatory processes contribute to causing pain in CRPS, and one possible mechanism by which this might occur is peripheral sensitization.

The neuropeptides mentioned above, such as Substance P and bradykinin, as well as cytokines and nerve growth factor can increase the sensitivity and excitability of nociceptors, such that their background firing rate increases, their responsiveness to stimuli increases, and their threshold for firing decreases. This process is called peripheral sensitization, and may contribute to a range of chronic pain conditions, including CRPS (Bruehl, 2010; Cheng & Ji, 2008; Marinus et al., 2011; Sommer & Kress, 2004). It is therefore possible that inflammatory factors are important in the development of CRPS in the early stages of the condition, and that they lead to sensitization or other processes which contribute to the maintenance of CRPS. It is also possible that inflammation interacts with
other processes that contribute to the development of CRPS, such as changes in autonomic activity, as will be discussed below.

**Autonomic Nervous System Activity**
The autonomic nervous system, comprising the sympathetic and parasympathetic nervous systems, is responsible for the body’s stress, ‘fight-or-flight’, or protective responses to threat, as well as for restoring homeostasis following a stressor. As outlined below, a large body of research has identified abnormalities in various measures of autonomic function amongst CRPS patients, including abnormal vasomotor responses to SNS activation, abnormalities in levels of catecholamines and alterations in heart-rate variability. Recent research has also proposed several mechanisms by which autonomic processes may interact with inflammatory processes in CRPS.

**Vasomotor Changes**
Vasomotor changes form an important part of the clinical picture of CRPS. Some research has suggested that the early stages of CRPS are often characterised by a warm, reddish limb (associated with vasodilation) and in the chronic stages the limb appears cool and cyanotic (associated with vasoconstriction). As vasomotor activity is controlled by the SNS, early researchers hypothesised that the SNS must play an important role in CRPS, and the condition was duly labelled Reflex Sympathetic Dystrophy. Uncontrolled trials demonstrated that sympathetic blocks relieved pain in CRPS patients, and patients who responded to these blocks were labelled as having ‘sympathetically maintained pain’ (Price, Long, Wilsey, & Rafii, 1998). In addition, researchers showed that amongst those with sympathetically maintained pain, the pain relieved by sympathetic block could be rekindled via an injection of norepinephrine (Ali, Raja, Wesselmann, Fuchs, Meyer, & Campbell, 2000). However, controlled trials of sympathetic blocks have found no higher rates of responding to these blocks than placebo, and they are no longer considered the treatment of choice (Jadad, Carroll, Glynn, & McQuay, 1995; Ramamurthy, Hoffman, & Guanethidine Study Group, 1995). Thus the hypothesis that CRPS is due to abnormal sympathetic activity has been called into question.

A large body of research has tested the hypothesis that CRPS patients have altered vasomotor responses to SNS activation. This has shown that vasoconstrictor responses to sympathetic activation (which is generally induced by whole body cooling or warming) is significantly diminished or absent in CRPS patients compared to healthy controls (Baron, Schattschneider, Binder, Siebrecht, & Wasner, 2002; Birklein, Kunzel, & Sieweke, 2001; Schurmann, Gradl, Andress, Furst, & Schildberg, 1999; Wasner, Heckmann, Maier, & Baron, 1999). Several reports suggest that this altered SNS response
might be associated with CRPS pain. For example, amongst those diagnosed by sympathetic block as having sympathetically maintained pain, whole body cooling (which activated the SNS) was associated with a 22% increase in pain ratings and a spreading of hyperalgesia (Baron et al., 2002). Drummond, Finch, Skipworth and Blockey (2001) reported that the decrease in pain ratings healthy volunteers experience in response to SNS activation was rarely present amongst CRPS patients, around 40% of whom experience an increase in pain in response to SNS activation. This research suggests that there are complex interactions between sympathetic activity and pain in CRPS, such that SNS activity can affect pain levels. However based on this research, it is not clear whether such abnormalities are a cause, consequence or correlate of the condition.

One study has tested whether or not altered SNS responses might predict the development of CRPS, by measuring vasoconstriction post-fracture to determine whether abnormalities differentiate between those who do and do not develop CRPS (Schurmann, Gradl, Zaspel, Kayser, Lohr, & Andress, 2000). They found that impaired SNS responses in the affected limb were present in all fracture patients on the first day post-fracture. In those whose SNS response continued to be diminished over the entire 12-week study period, and for whom SNS responses were diminished in both limbs, CRPS developed. Thus it was possible to predict the development of CRPS based on SNS dysfunction in the days following fracture. Whilst this study cannot determine causality, it provides some support for the hypothesis that sympathetic function plays a role in the development of CRPS. Unfortunately, it has not yet been replicated. Several papers have shown that normalisation of sympathetic activity accompanies recovery from CRPS (Gradl & Schurmann, 2005; Wasner et al., 1999). However this is not consistent across the literature. For example, Vogel, Gradl, Ockert, Pellengahr and Schurmann (2010) showed that SNS dysfunction changed across time, and that there was no correlation between SNS responses and levels of pain or limb dysfunction. Interestingly, Ackerman and Ahmad (2008) found that impaired SNS responses were a risk factor for developing CRPS after surgery, amongst a sample of previous CRPS sufferers. However recovery from CRPS post-surgery was not accompanied by a normalisation of these SNS responses.

**Catecholamines**

A further body of research has examined the role of circulating catecholamines in CRPS. Harden and colleagues (1994) hypothesised that CRPS might be caused by increased sympathetic outflow, and patients would hence have higher levels of norepinephrine (NE) in the affected limb. However their research, along with other studies, showed decreased NE levels in the affected limb compared to the unaffected limb (Harden et al., 1994; Wasner et al., 1999). Thus they concluded that increased sympathetic outflow is not a feature of CRPS, but hypothesised that enhanced reactivity to
catecholamines could play a role in the condition. Interestingly two more recent studies examined the levels of NE in venous blood samples of CRPS patients and compared these with healthy controls, and both reported significantly higher levels in the CRPS group (Harden et al., 2004; Kaufmann et al., 2007). Thus it seems that CRPS patients have higher levels of circulating catecholamines in general compared to non-CRPS patients, but paradoxically the levels are even higher in the unaffected limb compared to the affected limb. Interestingly, cutaneous (rather than venous blood) levels of NE measured at the CRPS limb were no different to those of healthy controls, and responded similarly to sympathetic activation (Terkelsen et al., 2013), which suggests that the higher levels of circulating catecholamines measured in plasma samples may be due to muscular sympathetic activity. It is unclear to what extent catecholamines play a causal or maintaining role in CRPS, however one mechanism by which this might influence pain in CRPS is sympathetic-afferent coupling.

Sympathetic-afferent coupling has been suggested to occur based on animal studies and several human studies utilising those with CRPS-2 or phantom limb pain (Baron, Levine, & Fields, 1999). These studies have shown that significant interactions exist between the SNS and nociceptive systems following nerve injuries. They have demonstrated that, after nerve injury, nociceptive afferent fibres express adrenoceptors, so that stimulation of sympathetic nerves or injections of catecholamines can trigger nociception and increase pain behaviour, a phenomenon that was hypothesised to be important in the pathogenesis of CRPS (for a review, see Baron et al., 1999). This was supported by a study showing that the hyperalgesic skin of CRPS patients has more adrenoceptors than control skin (Drummond, Skipworth, & Finch, 1996), further supporting the hypothesis that sympathetic-afferent coupling occurs in CRPS. However one study used microneurography to simultaneously record the activity of sympathetic efferent fibres and C nociceptors in CRPS patients, during tasks known to activate sympathetic activity. They found no association between the sympathetic and nociceptive activity, questioning the role of sympathetic-afferent coupling in CRPS (Campero, Bostock, Baumann, & Ochoa, 2010). Overall, more research is needed in order to determine whether sympathetic-afferent coupling occurs in CRPS, particularly CRPS-1, where there is no specific nerve injury.

Heart-Rate Variability

An alternative method for measuring the activity of the autonomic nervous system is analysis of heart rate variability (HRV). This involves the measurement of variability in the interval between successive heartbeats. This variability is reflective of interplay between the sympathetic and parasympathetic nervous systems as well as humoral factors, and thus is a method for measuring autonomic function that is independent of assessing vasomotor activity in the periphery (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). HRV is also thought of as an objective index of emotionality. One small study
assessed HRV in CRPS patients, and found that they had significant differences in sympatho-vagal balance compared to healthy controls, suggesting increased SNS activity (Schulze & Troeger, 2010). Terkelsen et al. (2012) found that HRV was reduced in CRPS patients compared to healthy controls during rest, mental and orthostatic stress, and also showed reduced cardiac output and increased peripheral resistance during an orthostatic challenge. These changes were associated with pain duration but not pain intensity, and suggest that CRPS patients have a general autonomic imbalance which is associated with CRPS duration. Finally, Taneyama, Yokota, & Goto (2013) also found differences in HRV between CRPS patients and healthy controls, and several measures of HRV correlated with pain intensity, and returned to normal levels following successful treatment. Overall this body of research suggests that CRPS patients do have abnormal autonomic activity. Once again, it is unknown whether these abnormalities are a cause or consequence of CRPS, or whether it might contribute to the maintenance of the condition, and further research is needed before any conclusions can be drawn.

**Interactions Between Inflammatory & Autonomic Processes**

There are several mechanisms by which activity in the autonomic nervous system might interact with immune processes. Tracey (2002) proposed that the nervous system constantly monitors immune responses and activates cholinergic pathways to inhibit acute inflammation when necessary. Following inflammation, the vagus nerve modulates circulating TNF-alpha levels and decreases the production of other pro-inflammatory cytokines. This process is known as the inflammatory reflex, and it is possible that if vagal or cholinergic activity failed to regulate immune processes in CRPS, that this could contribute to the condition.

Immune cells also communicate directly with the brain via blood-borne signalling and well as neural pathways via the vagal nerve and glossopharyngeal nerve (Watkins & Maier, 2005). According to Watkins and Maier (2005), such immune-to-brain communication leads to enhanced pain sensitivity via the release of neurotransmitters and neuromodulators that activate glia in the spinal cord to release glial pro-inflammatory cytokines. The authors argue that this process could contribute to the maintenance of pathological pain states, and it is possible that such a process could play a role in complex regional pain syndrome.

A further possibility is that CRPS could be associated with an abnormal interaction between the hypothalamic-pituitary-adrenal (HPA) axis and inflammatory processes. Park and Ahn (2012) tested HPA axis function in CRPS. They reported that usually, inflammation activates the HPA axis, which in
The ANS in CRPS

Central Nervous System (CNS) Changes

Central Sensitization & Abnormalities in Endogenous Pain Modulation

Central sensitization is defined as an “increase in the excitability of neurons within the central nervous system so that normal inputs begin to produce abnormal responses” (Woolf, 2011). It describes the process whereby plasticity in the central nervous system can lead to the amplification of pain signals, and is characterised by a reduction in pain threshold (leading to allodynia), increased responsiveness to painful stimuli and prolonged after-effects (leading to hyperalgesia), as well as an expansion of the receptive field such that non-injured tissue can produce pain (secondary hyperalgesia) (Woolf, 2011). This is due to an increased strength of synaptic connections between nociceptors and neurons of the spinal cord, changes in synaptic connections within the spinal cord, and increased excitability of spinal cord neurons, which are all activity dependent. In addition, changes in microglia, astrocytes, gap junctions, membrane excitability and gene transcription all contribute to the maintenance of central sensitization. Clinical characteristics of central sensitization include the presence of dynamic tactile alldynia, secondary hyperalgesia, temporal summation (wind-up pain), sensory after-effects, and spread of pain sensitivity (Woolf, 2011).
It has been hypothesized that central sensitization is involved in the pathophysiology of CRPS and there is some evidence to support this view (Bruehl, 2010; Marinus et al., 2011; Woolf, 2011). A number of studies have examined the presence of the clinical signs and symptoms suggestive of central sensitization and/or altered endogenous pain modulation in CRPS patients, and have shown that CRPS patients exhibit mechanical hyperalgesia and exaggerated wind-up pain in the affected limb during both acute and chronic stages of the condition (Sieweke, Birklein, Riedl, Neundorfer, & Handwerker, 1999; Vaneker, Wilder-Smith, Schrombges, de Man-Hermsen, & Oerlemans, 2005; Vartiainen, Kirveskari, & Forss, 2008). In addition, similar clinical signs occur in the unaffected limb of CRPS patients, particularly those with chronic CRPS (Huge et al., 2008), and pain and/or CRPS symptoms have been noted to “spread” to other body regions by a number of authors (Maleki, LeBel, Bennett, & Schwartzman, 2000; Mazloomdoost, Agarwal, Lesley, Raja, Broatch, & Sharma, 2009; van Rijn, Marinus, Putter, Bosselaar, Moseley, & van Hilten, 2011). Sensory testing of CRPS patients who reported experiencing total body pain revealed sensory abnormalities over an average of 62% of the body surface (Edinger, Schwartzman, Ahmad, Erwin, & Alexander, 2013). Furthermore, one study showed more than a third of CRPS patients reported “other than everyday pain” prior to the onset of their CRPS (Birley & Goebel, 2014). These studies strongly suggest that a central process is involved in the pathophysiology of CRPS.

One brain imaging study also lends support to the hypothesis that central sensitization might be involved in CRPS. Vartiainen et al. (2008) used a whole-scalp neuromagnometer to show that CRPS patients had increased cortical responses to stimulation of the affected hand compared to the unaffected hand. The body of literature on central sensitization in CRPS is small but promising. It is possible that central sensitization could occur as a cause or effect of CRPS, and could interact with a range of other mechanisms.

In addition to central sensitization, other abnormalities in the way pain is processed by the central nervous system in CRPS are demonstrated by research on endogenous pain modulation mechanisms. In healthy individuals, central pathways project from the periaqueductal gray to the rostroventral medulla and then to the brainstem to send descending messages which can either inhibit or facilitate incoming nociceptive messages (Ossipov, 2012; Seifert, Kiefer, deCol, Schmelz, & Maihofner, 2009). “Top-down” processes such as psychological factors may influence this process, as well as “bottom-up” processes, such as other nociceptive signals from the periphery (Yarnitsky, 2015). The ability of this system to modulate pain can be tested experimentally using tests of conditioned pain modulation (which measures the ability of one pain to be inhibited in the presence of a second painful conditioning stimulus), wind-up (which measures the increase in perceived pain over time when a
repetitive stimulus is applied), or adaptation to a repetitive noxious stimulus (Seifert et al., 2009). The efficiency of conditioned pain modulation is reduced in many chronic pain conditions, such as fibromyalgia, irritable bowel syndrome, and osteoarthritis (Lewis, Rice, & McNair, 2012; Yarnitsky, 2015).

Several studies have examined endogenous pain modulation in CRPS. Seifert et al. (2009) compared CRPS patients and controls during repetitive noxious stimulation of both hands and found that CRPS patients exhibited a decreased ability to inhibit pain, as demonstrated by reduced adaptation to the repetitive stimulus in both hands over the course of testing. They also demonstrated increased pain facilitation (measured by secondary hyperalgesia) in the affected limbs of CRPS patients compared to both the unaffected limb and both limbs of healthy controls. Another study found that CRPS patients and healthy controls were similarly effective at suppressing pain, however fMRI revealed that CRPS patients were less able to activate brain regions associated with endogenous pain modulation (including the periaqueductal gray and cingulate cortex) (Freund et al., 2011). One further study assessed endogenous pain modulation in CRPS and reported that CRPS patients exhibited increased pain in response to cooling of the ipsilateral forehead, a technique which usually leads to reduced pain in healthy people and is thought to operate through conditioned pain modulation mechanisms. The authors suggest that endogenous pain modulation is impaired on one side of the body in CRPS compared to healthy controls. Overall this very small group of studies suggests that descending pain modulatory systems are impaired for CRPS patients.

Several studies suggest that CRPS may be associated with abnormalities in the endogenous opioid system. A study by Klega et al. (2010) measured opioid receptor binding potential (a measure of receptor availability), in CRPS patients and healthy controls. They found that CRPS patients had decreased opioid receptor availability in several brain areas contralateral to the affected limb (amygdala, parahippocampal cortex), and increased availability in several contralateral brain areas, suggesting that opioidergic mechanisms may be affected in CRPS. Additionally, a recent meta-analysis assessed the placebo effect in CRPS by performing a meta-analysis of placebo-controlled treatment trials. This showed that CRPS patients do not exhibit placebo responses other than in very short duration treatments (15-30 minutes) (Mbizvo, Nolan, Nurmikko, & Goebel, 2015). As endogenous opioids form part of the basis of the placebo effect, this further supports the theory that endogenous opioid systems may be impaired in CRPS, though does not confirm which aspects of endogenous pain modulation are impaired.
Cortical Changes and Maladaptive Neuroplasticity: Brain Imaging Studies

Use-dependent plasticity has been shown to occur not only in the spinal cord but also in the higher brain centres in CRPS, and a growing body of research has demonstrated significant changes in the somatosensory and motor cortices of CRPS patients which may contribute to the development and maintenance of the condition. One set of studies has focused on cortical reorganization on the primary somatosensory cortex (S1), which contains a use-dependent ‘map’ of body areas. Several studies have used functional brain imaging to demonstrate that CRPS patients have a shortened distance between the areas of cortex representing the thumb and little finger on the somatosensory cortex contralateral to the affected limb. In other words, the area of cortex representing the hand had reduced in size, suggesting a ‘blurring’ of cortical maps associated with the fingers (Juottonen, Gockel, Silen, Hurri, Hari, & Forss, 2002; Maihofner, Handwerker, Neundorfer, & Birklein, 2003; Pleger et al., 2004; Vartiainen et al., 2008). The extent of cortical change correlated with pain levels and measures of hyperalgesia, and normalised with recovery following rehabilitative and analgesic treatment (Maihofner, Handwerker, Neundorfer, & Birklein, 2004). Interestingly, the size of the hand representation on S1 for both the affected and unaffected sides of CRPS patients were compared with healthy controls. This showed that for CRPS patients, the representation of the affected hand was similar to that of either hand of healthy controls, and it was the unaffected hand of CRPS patients which demonstrated an abnormality: having a large representation compared to both the affected limb and the limbs of healthy controls (Di Pietro, Stanton, Moseley, Lotze, & McAuley, 2014). Various abnormalities have also been shown in the strength of signals in S1 during stimulation of the affected compared to the unaffected limbs (Juottonen et al., 2002; Pleger et al., 2006; Steinstraesser, Sand, Steinau, Stude, & Tegenthoff, 2009; Vartiainen et al., 2008). Several studies have shown abnormal patterns of S1 activation associated with hyperalgesia and mechanical allodynia (Maihofner, Handwerker, & Birklein, 2006; Maihofner et al., 2005). A systematic review of studies investigating S1 function in CRPS found evidence that the representation of the affected limb is different to the unaffected limb in CRPS patients but noted that this evidence stems from a limited number of studies (Di Pietro et al., 2013b).

Krause, Foerderreuther & Straube (2006) used TMS to map the area associated with the upper limb on the primary motor cortex (M1). They reported that in CRPS patients, the size of the representation of the affected hand was smaller than the size of representation of the unaffected limb, which parallels the findings from imaging studies of S1. Interestingly, healthy controls had smaller areas of representation of both limbs compared to the CRPS patients. CRPS patients also show larger areas of M1 activation during a finger-tapping task, and motor impairments were correlated with M1 activation (as well as activation of supplementary motor areas and the posterior...
parietal cortex) (Maihofner et al., 2007). The authors suggest that these changes could account for the motor symptoms seen in CRPS, but causality has yet to be established. A number of studies have also demonstrated abnormalities in the excitability of the motor cortex (i.e. motor cortex disinhibition), which has been shown to correlate with pain levels (Eisenberg, Chistyakov, Yudashkin, Kaplan, Hafner, & Feinsod, 2005; Juottonen et al., 2002; Kirveskari, Vartiainen, Gockel, & Forss, 2010; Krause, Foerderreuther, & Straube, 2004; Krause et al., 2006; Schwenkreis et al., 2003). However, motor cortex activity during motor imagery tasks was the same in CRPS patients and healthy controls, suggesting that motor cortical activity is not inhibited by other brain regions in CRPS (van Velzen, Marinus, van Dijk, van Zwet, Schipper, & van Hilten, 2015). Additionally, a recent study showed that CRPS patients have decreased grey matter density in M1, and that this is associated with decreased white-matter density in the internal capsule, suggesting that these two areas interact possibly in response to pain (Pleger et al., 2014). A systematic review assessed the evidence for changes to the spatial representation of the limb on M1, cortical excitability, reactivity and glucose metabolism, and reported that there is evidence of changes to cortical excitability but insufficient evidence regarding other aspects of M1 function (Di Pietro et al., 2013a). Some further evidence for the importance of the motor cortex in CRPS comes from several treatment trials, which have used repetitive transcranial magnetic stimulation (TMS) over the motor cortex as a treatment for small numbers of CRPS patients, and shown beneficial effects (Fonoff, Hamani, Ciampi de Andrade, Yeng, Marcolin, & Jacobsen Teixeira, 2011; Velasco et al., 2009).

Several studies have looked at broader structural changes in the brain in CRPS patients. Three studies reported changes in grey matter volume in various brain regions associated with pain, and that some of these changes in volume correlated with measures of pain duration and intensity (Barad, Ueno, Younger, Chatterjee, & Mackey, 2014; Geha, Baliki, Harden, Bauer, Parrish, & Apkarian, 2008; Pleger et al., 2014). There were also changes reported in the connectivity between grey and white matter in CRPS patients (Geha et al., 2008). Two studies reported significant differences between CRPS patients and controls in the functional connectivity of the resting state network (Bolwerk, Seifert, & Maihofner, 2013; Simons et al., 2014). The first found greater connectivity of S1/M1 and the intraparietal sulcus with various brain regions usually associated with pain (Bolwerk et al., 2013). The second described increased connectivity of the amygdala with multiple brain regions. Following successful multidisciplinary treatment, connectivity was dampened between the amygdala and M1, parietal lobe and cingulate cortex (Simons et al., 2014). Connectivity was also associated with pain-related fear, indicating that the threat value of pain may influence neural networks.
CNS Changes and Maladaptive Neuroplasticity: Clinical Studies

A wide range of studies have investigated symptoms in CRPS patients which are thought to be associated with the changes to S1 and M1, and which suggest that CRPS is characterised by impaired sensory-motor integration. Several studies have demonstrated that the two-point discrimination threshold (tactile acuity) of CRPS-affected limbs is poorer than that of unaffected limbs of CRPS patients, and the limbs of healthy controls, and that two-point discrimination threshold correlates with sustained pain levels (Maihofner & DeCol, 2007; Pleger et al., 2006; Reiswich, Krumova, David, Stude, Tegenthoff, & Maier, 2012). In addition, impairment in two-point discrimination thresholds paralleled cortical reorganization changes shown on functional magnetic resonance imaging (fMRI) (Pleger et al., 2006), and CRPS patients also showed poorer ability than control subjects to improve their tactile discrimination skills with training (Maihofner & DeCol, 2007). Several studies have also shown that tactile discrimination training is effective for relieving CRPS pain and leads to restoration of normal cortical maps on S1 (Moseley, Zalucki, & Wiech, 2008c; Pleger et al., 2005). Interestingly, despite limited tactile acuity, CRPS patients demonstrated no impairments in two dimensional object recognition, indicating that higher cognitive processes of object recognition are intact (Reiswich et al., 2012).

Another phenomena seen in CRPS, which is likely associated with cortical reorganization, is the presence of referred sensations or mis-localisation of tactile stimuli. Two studies demonstrated that during stimulation of the affected limb, around one third of CRPS patients described referred sensations, which were always a location adjacent to the stimulated area on Penfield’s homunculus or elsewhere on the same limb (Maihofner, Neundorfer, Birklein, & Handwerker, 2006; McCabe, Haigh, Halligan, & Blake, 2003a).

Several researchers have also used laterality tasks to investigate CRPS patients’ mental representations of their affected limbs. Laterality tasks involve asking an individual to identify a picture of a limb as either left or right. These studies found that CRPS patients are slower and less accurate to identify pictures of the affected limb compared to the unaffected limb (Moseley, 2004c; Schwoebel, Coslett, Bradt, Friedman, & Dileo, 2002; Schwoebel, Friedman, Duda, & Coslett, 2001). This task involves mentally rotating the mental image of one’s own limb then identifying whether it matches the picture, and this delay could be due to cortical reorganization of patients’ somatosensory and motor cortices. Slowness was also associated with the distance of rotation required, duration of CRPS symptoms, and patients’ predicted pain levels if they were to put their limb into the pictured position (Moseley, 2004c). Performing imaginary movements has also been reported to be painful and induce swelling amongst CRPS patients, about one third of whom report
increases in pain of more than 20mm on a 100mm visual analogue scale (Hall, Blake, & McCabe, 2009; Moseley, Zalucki, Birklein, Marinus, van Hilten, & Luomajoki, 2008b). Imaginary movement activates the cortical motor networks, but does not usually activate muscles. Thus it is likely that the increases in pain due to motor imagery are mediated cortically rather than via spinal or peripheral mechanisms.

Another interesting body of research has investigated symptoms of ‘neglect’ or ‘body perception disturbance’ in CRPS. Two neglect-like features in CRPS were first noted in the literature in the 1990s: ‘cognitive neglect’, whereby patients report that the limb feels foreign or strange, and ‘motor neglect’, whereby patients have to focus their attention in order to move the limb, and these were noted to occur in up to 84% of 224 CRPS sufferers responding to a postal survey (Galer, Butler, & Jensen, 1995; Galer, Henderson, Perander, & Jensen, 2000). Forderreuther, Sailer and Straube (2004) tested CRPS patients for signs of classic hemispatial neglect. They reported that whilst CRPS patients do not perform poorly on tests such as the line bisection task, they displayed poorer ability to identify which finger was being stimulated on their affected limb, and 54% of patients reported that their limb felt foreign to them. The authors suggest that whilst hemispatial neglect does not appear to be the problem, CRPS patients do display disturbances of self-perception of the hand, and that this might be associated with abnormalities in the CNS, such as reorganization of S1. This finding was replicated by Kolb, Lang, Seifert and Maihofner (2012) who found virtually no significant differences between CRPS patients, non-CRPS pain patients and healthy controls on neuropsychological tests of neglect.

This phenomenon was further explored by Lewis, Kersten, McCabe, McPherson and Blake (2007) in a qualitative survey of CRPS patients. After analysing patients’ descriptions of their limbs, they reported that five themes emerged: patients described feelings of hostility towards the affected limb, and feeling dissociated from the affected limb, they observed that the limb appears different visually from how it feels, patients also had a distorted mental image of the limb when they closed their eyes and visualised the limb, they tended to lack awareness of the position of the limb, and often avoided paying conscious attention to the limb. These symptoms were labelled ‘body perception disturbance’ and authors suggested that they may relate to the cortical reorganization that occurs in CRPS; it is possible that as the brain ‘erases’ the CRPS limb from the central body map in the cortex, patients are unable to identify with and unable to freely use the affected limb.

This was followed up in another study which established that upper limb CRPS patients have poorer accuracy than healthy controls when asked to put either of their arms into specific positions (Lewis et al., 2010). In addition, the researchers compared blindfolded and non-blindfolded conditions and
found that whilst being able to view the arm did not aid healthy controls, it did improve accuracy for patients. Furthermore this study also asked patients to describe their perceptions of their affected limbs with their eyes closed, and found that 95% of CRPS patients had some kind of disturbance. For example, patients perceived misshapen digits, an enlarged section of the arm, or were unable to visualise their limb at all. Further studies demonstrated the CRPS patients have an impaired sense of force production (Bank, van Rooijen, Marinus, Reilmann, & van Hilten, 2014) and impaired joint position sense (Bank, Peper, Marinus, Beek, & van Hilten, 2013). A number of researchers have investigated perceived limb size in CRPS patients and found that CRPS patients tend to perceive their limb to be larger than it really is (Lewis & Schweinhardt, 2012; Moseley, 2005; Peltz, Seifert, Lanz, Muller, & Maihofner, 2011). Limb size overestimation was also associated with poorer tactile acuity, higher pain intensity, CRPS duration, and high scores on questionnaire measures of neglect-like symptoms (Lewis & Schweinhardt, 2012; Peltz et al., 2011).

Not only do CRPS patients exhibit abnormalities in their perceptions of limb size and position, it appears that these phenomena are associated with pain. Moseley, Parsons, & Spence (2008a) had CRPS patients perform hand movements whilst viewing their limb through either a magnifying or minifying lens, and found that when the limb appeared larger (and closer), pain increased, whilst when it appeared smaller (and also further away), the pain associated with movement was reduced. Another study showed that when CRPS patients’ arms are in a neutral position, they prioritise tactile information from the unaffected limb (i.e. perceive stimuli more quickly), and the extent to which they prioritised this information was highly correlated with temperature difference between the limbs. However when they were asked to cross their arms over the body’s midline, they prioritised information from the affected limb, and this was once again related to temperature difference between the limbs (Moseley, Gallace, & Spence, 2009). This finding was replicated in a series of experiments which also found that crossing the affected arm across the body’s midline led to a warming of the affected limb, a decrease in pain and an increase in the patient’s sense of ownership over the limb. Crossing the unaffected limb across the midline resulted in cooling of the unaffected limb (Moseley, Gallace, & Iannetti, 2012). This led authors to theorise that that the brain uses spatial encoding of body parts to regulate tactile processing, pain and thermoregulation, and that this process is affected in CRPS. Once again, this strongly implicated the role of central factors in the pathophysiology of CRPS.

Overall it appears that whilst CRPS patients do not suffer from a classical hemineglect, they exhibit alterations in limb perception associated with the space the limb occupies, and this points to an altered ability to integrate information from various sources. In keeping with this, there have been a
number of studies showing that for CRPS patients, pain can be modified by vision. In addition to the study mentioned above using minifying lenses, CRPS patients have been shown to have an altered perceived body midline (Sumitani et al., 2007b), and wearing prism glasses (which shift the body midline) leads to pain relief (Moseley, Gallace, Di Pietro, Spence, & Iannetti, 2013; Sumitani et al., 2007a), as does mirror imagery where patients view a mirror image of their unaffected limb performing various movements (discussed further below). Moreover, viewing ambiguous visual stimuli or undergoing optokinetic stimulation have been shown to exacerbate pain in CRPS (Cohen, Hall, Harris, McCabe, Blake, & Janig, 2012; Hall, Harrison, Cohen, McCabe, Harris, & Blake, 2011; Knudsen & Drummond, 2015). Overall this research points to abnormalities of sensory-motor integration and suggests that the post-parietal cortex may play a role in the condition, as this is an area of the brain known to be associated with proprioceptive processing.

In conclusion, there is substantial evidence that changes occur in the central nervous systems of CRPS patients. For example, the representations of the limbs on the somatosensory and motor cortices change in size. This appears to be accompanied by an array of unusual phenomena, such as impaired tactile acuity, mis-localization of tactile stimulation, impaired ability to identify pictures of the affected limb, experiences similar to ‘neglect’ of the affected limb, disturbances in perception of the limb, and impaired position sense. The extent to which all of these phenomena contribute to cause or maintain CRPS is unclear. As yet, no research has tested the ability of these phenomena to predict either the development or maintenance of the condition, but some sense of their importance can be ascertained by treatment trials that measure the effects of treating these phenomena. Treatments such as mirror therapy and graded motor imagery, which are designed to normalise the brain’s representation of the limb, have led to some good results (McCabe, Haigh, Ring, Halligan, Wall, & Blake, 2003b; Moseley, 2004a, 2006), though they have not been shown to be universally effective (Johnson et al., 2012; Lagueux et al., 2012; Selles, Schreuders, & Stam, 2008; Tichelaar, Geertzen, Keizer, & van Wilgen, 2007).

**Immobilization**

Another factor thought to play a role in CRPS, and which may influence many of the physiological processes shown to accompany CRPS, is limb immobilization. Cast immobilization has been shown to produce signs and symptoms of CRPS such as cold hyperalgesia, skin temperature differences, a reduction in pain threshold, vascular and trophic changes, sensitivity to punctate, pressure and cold stimuli, and increased levels of inflammatory markers, a reduction in the size of the limb representation on S1, decreased use of the limb, and decreased tactile acuity (Lissek et al., 2009; Pepper, Li, Kingery, Angst, Curtin, & Clark, 2013; Terkelsen, Bach, & Jensen, 2008). Even brief
immobilization for 30 minutes has been shown to influence limb colour and temperature (Singh & Davis, 2006). Retrospective studies have also reported high rates of cast immobilization amongst CRPS patients, for example Allen, Galer and Schwartz (1999) found that 47% of CRPS patients had a history of physician-imposed immobilization. Galer (2000) found that 68% of CRPS patients recalled having their limb immobilized prior to developing CRPS, and 81% described having “not moved or slightly moved” their limb for a period of time.

**Overview: CRPS as a Protective Response**

The range of symptoms associated with CRPS, and the physiological changes that accompany the condition, have been theorized to represent an aberrant protective response to actual or perceived tissue injury (Marinus et al., 2011; Moseley, 2007). The body’s normal response to threat or injury involves the release of inflammatory mediators, changes in blood flow, and alterations to the excitability of peripheral nociceptors. Alongside the inflammatory response, the SNS is activated, norepinephrine is released and the body prepares to reinstate homeostasis by a cascade of events that comprise the fight-or-flight response. All of these physiological processes also occur in CRPS. It is proposed that a number of the symptoms and physiological processes that accompany CRPS could have been orchestrated to produce a protective response. Pain and motor dysfunction lead an individual to protect and immobilize their limb, and sensory symptoms such as mechanical allodynia extend this to the point that the individual may avoid any contact with the skin. The inflammatory changes that accompany CRPS are strongly suggestive of a protective state. Likewise, the activity of the SNS and release of catecholamines suggests that body is preparing for threat. Both peripheral and central sensitization could conceptually form part of a response to threat by encouraging the individual to avoid potentially painful stimuli. Changes to endogenous pain modulation mechanisms demonstrate that the brain avoids inhibiting pain, further alerting the individual to the perceived threat. Changes at the level of the brain may also be considered a response to threat. For example, a reduction in the size or a change in the excitability of the somatosensory or motor cortices will likely lead to reduced movement of the limb, particularly spontaneous movement. The neglect or dislike of the limb that appear to accompany this state would further enhance this process. It is also possible that changes to mood state, such as feelings of depression or fear, accompany this process, leading to a general withdrawal of the individual in an attempt to protect the body. It might be that this protective response is more likely to occur in those individuals whose genetic profile puts them at risk of a greater inflammatory response.
The notion that pain is a result of perceived threat is not a new idea, and pain is universally associated with protection against tissue damage. The definition of pain from the IASP describes pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”, implicitly drawing the connection between threat detection and the brain’s production of pain. Moseley (2007) described pain as a “conscious correlate of the implicit perception of threat to body tissues”, and the pain neuromatrix first proposed by Ronald Melzack (2005) has now been labelled the “salience detection matrix”, designed to detect potential threats, orient attention and react to salient sensory events (Legrain, Iannetti, Plaghki, & Mouraux, 2011). Furthermore, the pain neuromatrix hypothesis was expanded and labelled the “Threat Matrix” by Visser and Davies (2010). They proposed that the threat matrix is a “super system” encompassing neural, immune, endocrine, paracrine and cellular components which manages actual or potential threats to the body and is responsible for defensive responses such as pain, fear, itch, and sensations of heat or cold, for protective motor responses such as weakness or dystonia, and for sensory responses.

If CRPS does represent an unconscious aberrant protective response to perceived threat of tissue damage, then it makes sense that conscious awareness or perception of threat, or psychological processes associated with increased perception of threat, could also influence the process. Moseley (2007) hypothesised that in the presence of pain an individual makes a judgement about the level of danger that the pain represents, and this is influenced by expectations and beliefs, amongst other factors. The individual uses this information to construct a meaning from their pain, which further influences their expectations and level of anxiety. This threat perception leads the brain to set up a cascade of events influencing the motor, immune, sympathetic and endocrine systems, as well as influencing the individual’s experience of pain. Thus psychological factors that might influence threat perception include beliefs about tissue damage, feelings of fear or anxiety, catastrophic thoughts about pain, helplessness and depression. Furthermore, psychological stress, which reinforces sympathetic activity and catecholamine release, could also reinforce an aberrant protective response. If indeed threat perception drives the symptoms of CRPS, then it also likely influences the recovery process. Thus, threat-related psychological factors would be worth exploring in CPS. However, as described below, much of the psychological research has largely not focussed on psychological factors associated with threat perception, instead focussing on abnormal psychological states.
Psychological Factors as a Cause of or Risk Factor for CRPS

A good deal of previous research sought to establish whether or not psychological factors or psychiatric conditions play a causal role in CRPS. Historically, as the pathophysiology of CRPS was poorly understood, the condition was stigmatized as psychogenic (Feliu & Edwards, 2010) and psychological factors have been (and continue to be) the focus of significant research interest. Much of this literature may have resulted from clinical observations that CRPS patients exhibit high levels of distress. Some research supports this view, particularly amongst those with long-term cases of CRPS. For example, a survey of CRPS patients using a CRPS internet site found that three-quarters of patients described experiencing depression, three-quarters described anxiety and 49% had experienced suicidal ideation (Sharma, Agarwal, Broatch, & Raja, 2009). CRPS is also associated with poor quality of life, and it is not surprising that psychological distress results from such a condition (van Velzen et al., 2014). Overall, the quality of psychological research into CRPS has been variable, with studies generally following one of three designs: a) Prospective studies measuring psychological distress at the time of an injury, surgery or stroke, then following patients up to determine whether psychological factors predict the development of CRPS; b) Comparative studies measuring psychological distress or psychiatric disturbance in a group of CRPS patients and another group of pain patients or psychiatric patients. Such studies are designed to assess whether, for example, CRPS patients are more distressed than other pain patients, or whether they show similar attributes to a psychiatric group; c) Observational studies documenting the rates of psychological distress or psychiatric disturbance in a group of CRPS patients. Clearly the prospective studies are of greater value than the observational or comparative studies in trying to establish possible causal associations.

Prospective Studies

Ten prospective studies have been published that sought to determine whether psychological functioning predicts the development of CRPS after fracture, stroke or surgery. In these studies, psychological factors were measured prior to surgery or soon after fracture or stroke, then patients were followed up to assess possible symptoms of CRPS. The researchers of these studies then determined whether the psychological factors predisposed to CRPS development. Three of the ten studies reported significant predictors: one reported a weak but significant relationship between depression and CRPS development in 82 patients after stroke (Kocabas, Levendoglu, Ozerbil, & Yuruten, 2007). One found that in 120 patients after distal radius fracture, those classified as ‘type A’ personality were more likely to develop CRPS than those classified as ‘type B’ personality, but also reported that anxiety and depression did not predict CRPS development (Hootkani, Fayyazi, & Hasankhani, 2008). Another found that those with high levels of trait anxiety were more prone to
CRPS than others after distal radius fracture, but that state anxiety, anxiety sensitivity, depression and alexithymia did not predict the development of CRPS (Dilek et al., 2012). In addition to these prospective studies, one retrospective study indicated that 47% of those who developed CRPS following foot or ankle surgery had a pre-existing diagnosis of depression or anxiety, but they did not compare this with the incidence of anxiety and depression amongst those who did not develop CRPS, and did not provide statistical analysis of these results, which limits the interpretation of this study (Rewhorn et al., 2014).

The remaining seven studies found no significant associations between psychological factors and CRPS development: Field and Gardner (1997) reported that a measure of psychological distress did not differ between those who did and did not develop CRPS in the nine weeks after Colles’ fracture. Daviet et al. (2002) found no significant correlation between depression scores and CRPS-severity for patients 3 months post-stroke with hemiplegia. Dijkstra et al. (2003) measured risk factors for CRPS, including psychopathology and social life events in 88 distal radius fracture patients, then followed them for one year. However they found that only one patient developed CRPS, so their study was unable to identify predictors. A study of 77 total knee arthroplasty patients found that anxiety and depression did not predict CRPS at 3 or 6 months follow-up although pain intensity was a significant predictor (Harden et al., 2003). Interestingly, the authors re-analysed their results some years later, and found that early increases in levels of depression and anxiety post-operatively predicted greater CRPS severity at follow-up (Harden et al., 2010b), suggesting that although pre-surgical psychological factors did not cause CRPS, post-surgical psychological factors may have influenced the recovery process. Another study of 62 distal radius fracture patients showed that measures of neuroticism, extroversion, introversion, psychoticism, falsehood, personality, and depression did not predict the development of CRPS (Puchalski & Zyluk, 2005). A large study of 596 consecutive single fracture patients found that scores on the symptom checklist-90 (a measure of psychopathology) did not predict the development of CRPS (Beerthuizen et al., 2011). Finally, a recent study of 1549 patients post-fracture found that whilst levels of pain catastrophising differed significantly between those who did (N=55) and did not go on to develop CRPS, in multivariate analyses catastrophising was no longer a significant predictor (pain intensity was) (Moseley, Herbert, Parsons, Lucas, Van Hilten, & Marinus, 2014).

Overall, this body of literature shows that no robust relationship exists between pre-injury distress and the development of CRPS. The literature is limited by the types of psychological variables selected for inclusion in the studies, which have generally measured psychopathology. Thus it appears that studies have tended to follow a dualist model of health which would view the causes of
ill health as being either physical or psychological: the studies have generally sought to establish a psychological or psychiatric cause of CRPS, but a biopsychosocial model of pain would suggest that more complex interactions between psychological and physiological factors is more likely. A similar, dualist approach is demonstrated in many of the comparative studies.

**Comparative Studies**

Eighteen studies have compared CRPS patients with other patient groups to determine whether CRPS is associated with a similar level of distress compared to other patient groups. A number of these comparative studies have suggested that CRPS patients experience levels of distress similar that of other patient groups. Bruehl et al. (1996) found that CRPS patients, limb pain patients and low back pain patients all had high levels of distress on the Brief Symptom Inventory. Shiri et al. (2003) showed that CRPS patients scored similarly to conversion disorder patients on the MMPI. Other studies showed that CRPS patients have similar psychological profiles to rehabilitation outpatients (van der Laan, van Spaendonck, Horstink, & Goris, 1999), to those with local neuropathy (and largely similar to those with low back pain) (Ciccone, Bandilla, & Wu, 1997), limb pain patients (Bruehl, Chung, & Burns, 2003), and children with CRPS had similar levels of anxiety and depression to children with abdominal pain or headache (Logan, Williams, Carullo, Claar, Bruehl, & Berde, 2013). Three studies compared CRPS patients with other patient groups on psychiatric diagnoses as assessed in psychiatric interviews, and found similar rates of psychiatric diagnoses between groups (Monti, Herring, Schwartzman, & Marchese, 1998; Shiri et al., 2003; Vouilloz, Deriaz, Rivier, Gobelet, & Luthi, 2011). Given that many of these chronic pain conditions are known to be associated with elevated levels of distress compared to a healthy population, this suggests that CRPS patients, like others in pain, experience heightened psychological distress, which is probably a normal response to the experience of pain. Indeed, one study reported that CRPS patients have higher levels of depression and anxiety compared to healthy controls, which is not surprising given their symptoms (Shin et al., 2013).

Some studies have found higher levels of distress amongst CRPS patients compared to others in pain, but only for isolated measures, and none emerge as consistent differences. For example, one study found that CRPS patients scored higher than brachial plexus avulsion patients for 3 of the MMPI subscales (depression, hysteria and hypochondria) but not for the other 7 scales (Zucchini, Alberti, & Moretti, 1989). Another study found that men with CRPS had higher levels of anxiety than male surgical patients, and women with CRPS had higher levels of depression, inadequacy and emotional instability than female surgical patients, but there were no differences that were consistent for both men and women, and no differences on the other subscales of the SCL-90 (Geertzen, de Bruijn-Kofman, de Bruijn, van de Wiel, & Dijkstra, 1998a).
Some studies have also documented lower levels of distress amongst CRPS patients compared to others, but once again these are not consistent across studies. de Good et al. (1993) showed that CRPS patients were significantly less distressed than headache patients on 5 of the 11 subscales of the SCL-90, but compared to low back pain patients, there was only 1 subscale were CRPS patients were significantly less distressed. Nelson & Novy (1996) noted that compared to myofascial pain syndrome patients, those with CRPS scored lower for hypochondriasis, depression, hysteria and psychasthenia but higher on the hypomania subscale, and were similar on other MMPI subscales. Another study found that fibromyalgia patients had higher scores for psychological distress, phobic anxiety, depression, somatization and obsessive-compulsiveness compared to both CRPS patients and low back pain patients, whose scores on the SCL-90 were remarkably similar (Verbunt, Pernot, & Smeets, 2008). Finally, one study found that CRPS patients scored lower on the SCL-90 measures of psychopathology than patients with conversion disorder or affective disorders (Reedijk, van Rijn, Roelofs, Tuijl, Marinus, & van Hilten, 2008). In sum, this body of comparative studies using general psychopathology scales demonstrates no consistent pattern of distress unique to CRPS. Instead it seems that differences shown differ between studies and could perhaps be due to differences in recruitment sites and sample selection for different studies.

Five comparative studies assessed differences between CRPS patients and other groups in terms of the number of stressful life events patients had experienced. Two studies found that CRPS patients had significantly more stressful life events compared to hand surgery patients (Geertzen, de Bruijn, de Bruijn-Kofman, & Arendzen, 1994; Geertzen et al., 1998a). However, one study found no association between stressful life events and CRPS onset (Monti et al., 1998), one found that CRPS patients experienced fewer stressful events than those who recovered normally after fracture (Zyluk, 1998b), and another found that CRPS patients had fewer life events than conversion disorder or affective disorder patients (Reedijk et al., 2008). Two studies assessed previous trauma. One found that CRPS patients scored higher than conversion and affective disorder patients on measures of abuse and trauma (Reedijk et al., 2008), and the other found no difference on a measure of childhood trauma between CRPS patients and those with low back pain or painful local neuropathy (Ciccone et al., 1997). Overall, this literature suggests that there is no robust or consistent difference between CRPS patients and other patient groups in terms of stressful life events or trauma.

In sum, the body of comparative studies does not reveal any consistent differences in the psychological profiles of CRPS patients compared to other people in pain. Whilst some studies have shown significant differences between CRPS and other patient groups for certain scales, this is not consistent across different conditions, scales or studies. The research suggests that CRPS patients
experience a similar level of distress to other people experiencing significant pain, and not surprisingly, this is known to be higher than distress levels amongst a healthy population. Few studies have compared CRPS patients to healthy controls, and those studies have demonstrated increased distress levels (Shin et al., 2013).

Observational Studies

A body of literature has also assessed the possible role of psychological factors in CRPS in observational studies, by assessing the rates of various psychological problems in a group of CRPS patients but without comparing these rates to either a control group or population norm. Obviously, this is a fairly limited design due to the lack of comparison group or outcome variable. Six such studies assessed rates of depression amongst sample of CRPS patients, and reported rates ranging from 29% to 96% (Cruz, O’Reilly, Slomine, & Salorio, 2011; Rauis, 1999; Rommel, Willweber-Strumpf, Wagner, Surall, Malin, & Zenz, 2005; Sharma et al., 2009; Subbarao & Stillwell, 1981; Van Houdenhove, 1986). One noted that three-quarters of CRPS patients were at high risk for suicidal ideation (Lee et al., 2014). Four studies assessed rates of suspected factitious disorders or malingering in CRPS patients: one noted that in all of 104 CRPS cases, the work context revealed “an opportunity for inactivity” (Rauis, 1999), one described 7 cases of CRPS suspected of self-induced symptoms, however this paper is of particularly poor quality, and notes some of the normal signs and symptoms of CRPS as evidence of self-induced symptoms (Taskaynatan, Balaban, Karlidere, Ozgul, Tan, & Kalyon, 2005). Mailis-Gagnon and colleagues (2008) take a more careful approach and note that 4/26 cases of CRPS had some evidence of self-injurious behaviour. One final study found that 65% of CRPS patients performed poorly on at least one symptom validity test as part of neuropsychological testing, however this paper reveals a poor understanding of CRPS on the authors’ part, which they label a “behavioural pain disorder” and “chronic regional pain syndrome” (Dauty, Renaud, Deniaud, Tortellier, & Dubois, 2001). Two studies assessed whether there was a relationship between stressful events and the onset of CRPS: one of which noted a relationship in 29% of cases, the other noted a relationship in 97% of cases (Sharma et al., 2009; Van Houdenhove, 1986). Several studies noted rates of somatization or hypochondriasis in CRPS patients: one reported 42% experienced hypochondriasis (Subbarao & Stillwell, 1981), one found elevated hypochondriasis scores amongst CRPS patients (van Hilten, van de Beek, Vein, van Dijk, & Middelkoop, 2001), and the other reported that 64% experienced somatization (De Vilder, 1992). Finally, two studies assessed personality: one reported that 84% of CRPS patients showed pathological personality traits (Van Houdenhove, 1986), whilst the other simply noted that psychological inadequacies were found in all CRPS patients, with a preponderance of neurotic depressive traits, immature dependent behaviour and narcissism (Szeinberg-Arazi, Helm, Nadvorna, Ner, Szeinberg, & Azaria, 1993). From this body of
observational studies, it is not surprising that CRPS has been stigmatized as being psychogenic. However, the sources of bias in these studies include selective samples (e.g. only those seen by psychiatrists or only those undergoing amputation for CRPS), measurement bias (some include subjective physician report only), and some studies reveal a failure of the authors to understand the basic pathophysiology and symptoms of the condition. Overall, this body of research reveals that some CRPS populations experience very high rates of psychological distress or disturbance, though this may not represent the CRPS population as a whole.

**Psychological Factors as a Cause of CRPS: Conclusions**

Taken together, the body of research which has assessed the possible role of psychological factors as a cause of CRPS after injury or surgery has shown that the psychological factors that have been studied are not robust predictors of CRPS development, and that there is no known pattern of distress or personality trait unique to CRPS patients. Some of the studies found high rates of psychological distress amongst CRPS patients, perhaps similar to that of other groups of patients with painful or difficult symptoms. This would not be surprising, especially amongst populations with a long duration of CRPS, which is known to affect quality of life. However none of this research has evaluated whether psychological factors might contribute to the maintenance of pain or disability in CRPS patients, something which has been demonstrated in other conditions. This will be discussed in Chapter 4.

**Conclusions**

CRPS is a painful and often disabling limb condition which is accompanied by a range of vasomotor, sudomotor, trophic and motor symptoms. Whilst there are few epidemiological studies available, it appears that CRPS is not an uncommon occurrence after fracture or surgery. The pathophysiology of CRPS is not completely understood, but the following factors may contribute to causing CRPS: genetics, neurogenic inflammation, impaired vasoconstriction, SNS activity, and changes to the functioning of the CNS. Notably, psychological factors have been demonstrated not to predict the onset of CRPS, but their potential role in maintaining the condition will be discussed separately in Chapter 4. The research on pathophysiological factors in CRPS has generally documented abnormalities amongst CRPS patients compared to controls, but has not been able to demonstrate whether such abnormalities play a causal role in the condition. Current hypotheses both from the field of pain generally and from CRPS research suggest that the pain and symptoms of CRPS may represent an aberrant protective response to perceived threat to the tissues (Moseley, 2007). Very little research has identified what factors might influence the maintenance of CRPS once established.
As there is significant variability in the course of CRPS, such factors would be of great interest. This variability in the course of CRPS will be assessed in some detail in Chapter 3: The outcome of CRPS-1: A systematic review.
Chapter 3: The Outcome of Complex Regional Pain Syndrome Type 1: A Systematic Review

Prelude

Rationale for Study 1: Systematic Review

As described in Chapter 2, CRPS is a condition which can present a dramatic array of symptoms, but for which the pathophysiology is not entirely understood. Though research has observed a number of physiological abnormalities that accompany the condition, these may simply be effects of the condition rather than playing a causal role. No body of research has been able to consistently identify predictors of CRPS development, and thus it is not understood why one patient develops CRPS after a particular injury or procedure, whereas another has an uncomplicated recovery. In particular, a number of researchers have assessed psychological factors to determine whether these might differ between those who do and do not develop CRPS following an injury, surgery or stroke. This research has not produced any consistent or robust findings, suggesting that psychological factors do not play a major role in causing CRPS, and that those who develop CRPS were not psychologically different from those who do not. Despite this, a number of studies document high rates of distress amongst CRPS patients, similar to those seen in samples of patients with chronic pain (Bruehl et al., 2003; Bruehl et al., 1996; Ciccone et al., 1997; Logan et al., 2013; van der Laan et al., 1999). Therefore, a key research question for the field of CRPS research is: Do psychological factors influence the progression from acute to chronic symptoms following a new onset of CRPS? In other words, do psychological factors influence the recovery process? Interestingly, research from other fields of pain medicine has clearly demonstrated that psychological factors do play a role in the development of chronic pain following an acute pain episode (Carroll et al., 2009; Clay, Watson, Newstead, & McClure, 2012; Hinrichs-Rocker et al., 2009; Kent & Keating, 2008; Melloh et al., 2009); much of this research comes from populations with low back pain, neck pain or post-surgical pain, and is discussed in Chapter 4. Whilst one of the primary aims of the thesis is to consider the impact of psychological factors on CRPS, particularly on the recovery process, it appears that this recovery process, or usual trajectory of symptoms in CRPS, is also not well understood.

Background: The Course of CRPS

Traditionally, CRPS was considered to be a progressive condition, which progressed through three stages. The initial stage was said to involve a painful, warm, reddish limb, which then turned to a
dystrophic stage with osteoporosis, trophic changes and a cool, bluish limb. This was then said to lead to a third stage involving significant atrophy of bone and muscle (Bonica, 1990). Cross-sectional studies comparing patients with newly-onset CRPS and those with chronic symptoms may have in part led to the description of these stages, and such studies also suggested that the outcomes of CRPS were very poor, noting high rates of pain, sensory symptoms and the highest rates of atrophy and movement disorders in the patients with the longest duration of CRPS (Veldman et al., 1993). Other research studies have also found very low rates of recovery amongst CRPS patients, which suggests that the usual trajectory is for chronic pain and dysfunction, rather than recovery. For example, Beerthuizen et al. (Beerthuizen et al., 2012) reported that no CRPS-1 patient was symptom-free 12 months after fracture. Likewise, Field, Warwick and Bannister (1992) reported that 26% of patients who had experienced algodystrophy following Colles’ fracture continued to exhibit features of the condition 10 years later. A long-term follow-up study of young people with CRPS reported that 71% continued to experience pain 12 years after treatment (Greipp, 2000). Additionally, there is a growing body of research documenting highly disabling features of long-term CRPS, including dystonia, movement disorders and infection (van der Laan, Veldman, & Goris, 1998; Zyluk & Puchalski, 2013), which suggests that CRPS can lead to complete dysfunction of the limb. Another body of research has developed documenting the so-called ‘spread’ of symptoms from one body area to another in CRPS patients, which suggests that CRPS can lead to more widespread symptoms (Maleki et al., 2000; Mazloomdoost et al., 2009; van Rijn et al., 2011). Moreover, invasive or disabling treatments such as spinal cord stimulation (Sears et al., 2011) or amputation (Bodde, Dijkstra, den Dunnen, & Geertzen, 2011) are used to treat CRPS, suggesting that severe cases of CRPS may be highly problematic for both patients and the health systems treating them.

On the other hand, some studies have reported conflicting results, suggesting that CRPS resolves regardless of treatment and that the development of chronic symptoms is rare. For example, one large population based study reported that 74% of patients recovered from their CRPS, usually spontaneously, after a mean period of 11.6 months (Sandroni et al., 2003). Another found that two-thirds of patients were symptom-free by 8 months (Okudan & Celik, 2006). Likewise, Zyluk (1998a) reported that only 10% of patients in a study of the natural history of CRPS had to withdraw to seek treatment, all others completed the study without treatment and only one patient continued to meet the criteria for CRPS.

Thus there is great discrepancy in the literature between studies describing a poor trajectory with chronic pain and disability and those reporting much more optimistic results. Given that the major purpose of this thesis is to examine the role of psychological factors on the course of CRPS, or on this
recovery process, it is important to understand what that process more thoroughly. Therefore, a systematic review was undertaken to examine all of the published original studies which aimed to better understand this process.

Aims
The aims of the systematic review described here in Chapter 3 were:

1. To determine the percentage of patients who recover from CRPS-1 for each of the following:
   a. General measures of CRPS status
   b. Pain
   c. Function
   d. Sensory, sudomotor, vasomotor and trophic symptoms

2. To determine the extent to which patients recover from CRPS-1 for each of the following:
   a. General measures of CRPS status
   b. Pain
   c. Function
   d. Sensory, sudomotor, vasomotor and trophic symptoms

Citation
Abstract

Objectives: The purpose of this systematic review was to examine the outcome of complex regional pain syndrome (CRPS) type-1.

Methods: We searched Medline, Embase and Psychinfo for relevant studies, and included 18 studies, with 3991 participants, in this review. The following data were extracted: study details, measurement tools used, and rates or severity scores for the symptoms/signs of CRPS at baseline and follow-up, or in groups of patients with different disease durations. A quality assessment revealed significant limitations in the literature, with many studies utilising different diagnostic criteria.

Results: The 3 prospective studies demonstrated that for many patients, symptoms improve markedly within 6-13 months of onset. The 12 retrospective studies had highly heterogeneous findings, documenting lasting impairments in many patients. The 3 cross-sectional studies showed that rates of pain and sensory symptoms were highest amongst those with the longest duration of CRPS. Additionally, most studies showed that motor symptoms (stiffness and weakness) were the most likely to persist whilst sudomotor and vasomotor symptoms were the most likely to improve.

Discussion: Overall, this suggests that some CRPS patients make a good early recovery whilst others develop lasting pain and disability. As yet little is known about the prognostic factors that might differentiate between these groups.

Perspective

We found evidence that many CRPS patients recover within 6-13 months, but a significant number experience some lasting symptoms, and some experience chronic pain and disability. The quality of the evidence was poor. Future research should examine the factors associated with recovery and identify those at risk of poor outcomes.
Introduction

Complex regional pain syndrome (CRPS) is a painful condition which can occur after fracture, stroke, surgery or trauma, and most commonly affects a hand, wrist, foot or ankle. In CRPS, pain is accompanied by a range of symptoms, including allodynia, hyperalgesia, swelling, and abnormalities in colour, temperature, sweating, nail and hair growth, and movement. Traditionally, CRPS was considered a progressive condition with distinct ‘stages’. For example, Bonica (1990) described three stages: Stage one, the “acute stage” was characterised by a painful, swollen, warm, red limb. In stage two, the “dystrophic stage”, the limb was said to cool and appear cyanotic, with changes to hair and nail growth, osteoporosis, stiffness and muscle wasting. In stage three, the “atrophic stage”, irreversible atrophy of bones, muscles and nails was described. However, relatively little research data have been offered to support the three specific stages, and at least one study has refuted the idea that three stages exist (Bruehl, Harden, Galer, Saltz, Backonja, & Stanton-Hicks, 2002). Long-term follow-ups of CRPS patients report contradictory findings regarding the outcome of the condition. A number of studies have found that whilst the nature of symptoms might fluctuate over time, CRPS tends to persist, and only a minority of patients recover from the condition (De Boer et al., 2011; de Mos, Huygen, van der Hoeven-Borgman, Dieleman, Stricker, & Sturkenboom, 2009b; Galer et al., 2000; Schwartzman, Erwin, & Alexander, 2009; Sharma et al., 2009; Veldman et al., 1993). For example, a prospective study of 42 patients with CRPS after fracture found that no patient was symptom-free 12 months later (Beerthuizen et al., 2012). A follow-up of 134 CRPS patients at a mean of 5.8 years after diagnosis found that 64% still met the 1994 International Association for the Study of Pain (IASP) “Orlando” diagnostic criteria for CRPS (de Mos et al., 2009b), and one study of more than 600 CRPS patients showed that symptoms tended to be worse in those with a longer duration of CRPS compared to those with a shorter duration (Schwartzman et al., 2009). In addition, research has suggested that over time, CRPS patients can develop more widespread pain, and some researchers have described symptoms of CRPS “spreading” to affect multiple limbs (Schwartzman et al., 2009; van Rijn et al., 2011).

In contrast, there are also studies that present more optimistic data, and suggest that the majority of patients will recover from the condition within 12 months (Bickerstaff & Kanis, 1994; Duman, Dincer, Taskaynatan, Cakar, Tugcu, & Dincer, 2007; Goris, Leixnering, Huber, Figl, Jaindl, & Redl, 2007; Sandroni et al., 2003; Zyluk, 1998a). A population based study of medical records found that 74% of CRPS cases resolved, usually spontaneously, at a mean of 11.6 months post-onset (Sandroni et al., 2003). A prospective study requiring patients to have no treatment found that of the 30 participants, only 3 had severe symptoms and had to withdraw from the study for treatment, and of the 27
remaining participants, only 1 continued to have CRPS at the one-year follow-up (Zyluk, 1998a). Several studies have also shown that the majority of CRPS patients will return to employment following the condition (Duman et al., 2007; Dumas et al., 2011).

This review aims to examine these discrepancies in the literature, and to synthesize the published data concerning the course of CRPS symptoms over time, and to answer the following questions: In what proportion of CRPS patients do symptoms persist? To what extent do CRPS symptoms persist? We chose to limit the review to CRPS type-1 (CRPS-1, without a major nerve injury) because CRPS type-2 (CRPS-2) is associated with a specific nerve injury which likely affects outcome. We hypothesized that the majority of patients would show improvements in CRPS symptoms with time, but some would display chronic severe symptoms.

Methods
Selection of Studies
We systematically reviewed prospective, retrospective, and cross-sectional studies which provided data on the outcome of CRPS type-1. A literature search was conducted utilising the databases Medline, Embase and Psychinfo, from inception until 4 April 2012 (search date). We utilised the search terms recommended for systematic reviews on prognosis (Altman, 2001): “exp epidemiologic studies”, “incidence.sh”, “follow-up studies.sh”, “prognos:.sh”, “predict:.tw”, OR “course:.tw” AND “complex regional pain syndrome.mp”, “Reflex sympathetic dystrophy.mp”, OR “algodystrophy.mp”. The search was limited to peer reviewed journals and to studies including human subjects. The personal electronic libraries of the researchers were also searched for possible references. The reference lists of all relevant papers were searched by hand and an electronic search for citing articles of each paper was also conducted to ensure that all possible references were obtained.

Studies were considered for inclusion in the systematic review if they:

1.) Reported on ‘complex regional pain syndrome type-1’, or ‘reflex sympathetic dystrophy’ (RSD) or ‘algodystrophy’ or ‘sudeck’s dystrophy’. Studies with patients combined from several diagnostic groups (e.g. CRPS-1 & CRPS-2) were included if >80% of the sample had CRPS-1;
2.) Had the stated aim of investigating the course, natural history or outcomes of CRPS
3.) Had one of the following characteristics:
a. Reported on rates or severity of CRPS symptoms/signs or presence of CRPS diagnosis at more than one time-point, where the time-points are at least 6 months apart. Or,
b. Provide cross-sectional or correlational data comparing the symptoms/signs of CRPS between patients with differing CRPS duration or correlating symptom severity with duration. Or,
c. Retrospective studies documenting self-report of how symptoms changed over time. Or,
d. Retrospective studies or audits documenting residual symptoms/signs in a follow-up of a cohort more than 6-months after the CRPS patients were identified. Cohorts had to have been previously assembled or patients previously identified, so that the review only included retrospective studies that had a chance of capturing CRPS cases that had resolved.

Studies were excluded if they: 1.) Had a sample size of less than 10; 2.) Were not published in full article format or data could not be extracted from the article; 3.) Conducted in paediatric samples or in adult samples where the CRPS onset was during childhood (as there is suggestion that CRPS can manifest differently in children and adolescents), 4.) Published in languages other than English, French or German, 5.) Had follow-up or response rates <50%.

Quality & Relevance Assessment & Data Extraction
To assess study quality and relevance of studies for this review, we used a modified version of the quality evaluation method recommended for systematic reviews of prognostic variables (Centre for Reviews and Dissemination, 2009; Hayden, Cote, & Bombardier, 2006). Few studies assessed prognostic variables. Therefore our review focussed on clarifying the course of CRPS, so we excluded quality items on prognostic factor measurement and confounder measurement.

We assessed quality and relevance on the following four sources of bias: study participation (sampling method described, sample described, inclusion/exclusion criteria described, diagnostic criteria described, response rate, representative sample, assembled at common time-point >3months, follow-up >6months), study attrition (attrition described, attrition adequate, information on drop-outs), outcome measurement (outcomes defined, objective, measured appropriately), and analysis (relevant statistical analysis conducted, and appropriate). For each question, each study was scored positive (Y), negative (N), or unclear (?). For retrospective and cross-sectional studies, attrition items were scored not applicable (N/A). A detailed description of the quality assessment criteria is available in Appendix 1: Table 23, p.168).

We extracted data on the study population, diagnostic criteria, symptom duration at baseline & follow-ups (where applicable), the measurement tools utilised to assess each of the symptoms/signs of CRPS, and the mean and standard deviation scores on those measures at each time point. The symptoms/signs investigated were: pain, sensory symptoms, function (range of motion/stiffness and
limb strength), temperature asymmetry, colour asymmetry, swelling, abnormal sweating, and hair and nail growth abnormalities. We also extracted data on scores or measures of general recovery from CRPS. As a number of studies did not report mean scores, but rather the proportion of the sample with each symptom/sign either present or absent, for these studies, the percentage of the sample with the symptom/sign at each time point was recorded.

Data Synthesis
As there was significant heterogeneity in research methods, it was not possible to pool data quantitatively in any meaningful way. Instead, a qualitative analysis and synthesis of the data is presented here. We present the results of the prospective, retrospective and cross-sectional studies separately.

Results
Studies Selected
The literature search yielded 1741 papers. The titles, abstracts, and where necessary the full text of these were screened by the primary author. Ninety of these were selected for a closer review and were examined in detail. Of these, 18 studies (with 19 publications) met the inclusion and exclusion criteria, and were selected for this review (see Table 3). The second author screened any of the studies where it was unclear whether they met the inclusion/exclusion criteria and a decision was made by consensus.

Of the 18 studies included in the review, there were 3 prospective studies, 12 retrospective studies, and 3 cross-sectional or correlational studies. The median sample size of the studies was 71, but samples ranged from 17-888. The total number of participants included in this review is 3991. The study characteristics are described in Table 3. Few studies used the same diagnostic criteria. Three used the 1994 IASP-Orlando criteria (Merskey & Bogduk, 1994), 2 used the newer IASP-Budapest criteria (Harden et al., 2010a), 3 used the criteria described by Zyluk (1998a), and the rest used their own criteria or did not describe the criteria used. This reflects the changing taxonomy of CRPS over the years. Earlier studies utilised criteria for algodystrophy or RSD, whereas later studies tended to use the newer criteria for CRPS. There are large variations between the criteria, so for example studies that used the 1994 IASP-Orlando criteria would have captured many more patients than studies that utilised the new IASP-Budapest criteria (De Boer et al., 2011).
# Table 3: Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting, Location &amp; publication year</th>
<th>Sample &amp; Method</th>
<th>Diagnostic criteria used</th>
<th>CRPS duration at baseline/cohort assembly</th>
<th>CRPS duration at f-up/survey</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective Studies:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atkins et al. (1989)</td>
<td>Hospital Casualty Dept., Sheffield, UK, 1989</td>
<td>Assessed 109 unselected Colles’ fracture patients at 9 weeks and 6 months. Reports on persisting symptoms in 19 of the 27 patients with features of Algodystrophy at baseline.</td>
<td>Own criteria</td>
<td>9 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td>Bickerstaff &amp; Kanis (1994)</td>
<td>Hospital Casualty Dept., Sheffield, UK, 1994</td>
<td>Assessed 274 Colles’ fracture patients at 7 weeks, then monthly until symptoms abated (6 months for asymptomatic patients). Included 77 who developed Algodystrophy. No mention of response/dropout rates. Reports the percentage of algodystrophy patients with persisting symptoms at 6 and 12 months.</td>
<td>Atkins et al.’s criteria (1990)</td>
<td>7 weeks</td>
<td>6 &amp; 12 months</td>
</tr>
<tr>
<td>Zyluk (1998a)</td>
<td>Surgical Dept, Pomeranian Medical University, Poland, 1998</td>
<td>Assessed 30 RSD patients at 1, 2, 6, and approx. 13 months. Patients were required to receive no treatment. Three patients with severe symptoms withdrew for treatment, so the study reports on the rates of symptoms in the remaining 27.</td>
<td>Zyluk’s criteria (1998a)</td>
<td>At time of diagnosis: mean of 12 weeks post-diagnosis</td>
<td>6 &amp; 13 months post-diagnosis</td>
</tr>
<tr>
<td><strong>Retrospective Studies:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subbarao &amp; Stillwell (1981)</td>
<td>Clinic/setting not described, USA, 1981</td>
<td>Chart review of 125 upper limb RSD patients who had been discharged a mean of 14 months prior. Follow-up questionnaires sent to 123. 77 (63%) responded. Paper reports on rates of symptoms noted in questionnaire.</td>
<td>Pak et al.’s criteria (1970)</td>
<td>22 weeks</td>
<td>22 months</td>
</tr>
<tr>
<td>Reference</td>
<td>Setting, Location &amp; publication year</td>
<td>Sample &amp; Method</td>
<td>Diagnostic criteria used</td>
<td>CRPS duration at baseline/cohort assembly</td>
<td>CRPS duration at f-up/survey</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Gougeon et al. (1982)</td>
<td>French Society of Rheumatology, France, 1982</td>
<td>File review of 573 RSD cases from a survey of society members, 370 files selected for review. Of these, 227 files mentioned the duration of disease until resolution. Reports on percentage whose symptoms had resolved by 6, 12 and 36 months.</td>
<td>Not described</td>
<td>n/a</td>
<td>Followed-up until cured or 3 years max</td>
</tr>
<tr>
<td>Fialka et al. (1991)</td>
<td>Physical Medicine &amp; Rehabilitation Dept., Vienna, Austria, 1991</td>
<td>Followed 17 patients with lower limb RSD post-fracture, for a mean of 39 months. Performed physical assessment at follow-up. Reports on remaining symptoms, as well as scintigraphy.</td>
<td>Own criteria</td>
<td>14 weeks</td>
<td>3.5 years</td>
</tr>
<tr>
<td>Ehrler et al. (1995)</td>
<td>Functional Rehabilitation Centre, Strasbourg, France, 1995</td>
<td>Follow-up questionnaire sent to 47 algodystrophy patients who had taken part in a study 9 years earlier. 25 (53%) responded. Reports on percentage that continue to experience pain, stiffness, and reduced strength.</td>
<td>Not described</td>
<td>2 groups: 1= 1 week, 2 =28 weeks</td>
<td>Both groups 9 years later</td>
</tr>
<tr>
<td>Laulan et al. (1997)</td>
<td>Orthopaedic Services, University Hospital Trousseau, Tours, France, 1997</td>
<td>Recruited all 125 distal radius fracture patients seen over a 7-month period for surgical treatment and followed-up at 12 months. Of the 26 who had “definite algodystrophy” at 12 weeks, all were followed-up. Reports on those with stiffness and pain at 12 months.</td>
<td>Own criteria</td>
<td>n/a</td>
<td>12 months post-fracture</td>
</tr>
<tr>
<td>Geertzen et al. (1998b; 1998c)</td>
<td>Dept. Rehab., University Hospital Groningen, Netherlands, 1998</td>
<td>Invited all 93 patients treated for RSD from 1988-1994 for follow-up. 65 (70%) responded. Reports on measures of pain, quality of life and physical function.</td>
<td>Own criteria</td>
<td>n/a</td>
<td>5.5 years</td>
</tr>
<tr>
<td>Reference</td>
<td>Setting, Location &amp; publication year</td>
<td>Sample &amp; Method</td>
<td>Diagnostic criteria used</td>
<td>CRPS duration at baseline/cohort assembly</td>
<td>CRPS duration at f-up/ survey</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------------------------</td>
<td>-----------------</td>
<td>--------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Galer et al. (2000)</td>
<td>University of Washington Multidisciplinary Pain Center, USA, 2000</td>
<td>Questionnaire sent to 55 CRPS patients treated from 1997-1998. 31 (56%) responded. Asked patients to describe which symptoms had improved, worsened or remained unchanged.</td>
<td>1994 IASP-Orlando criteria (Merskey &amp; Bogduk, 1994)</td>
<td>n/a</td>
<td>3.3 years</td>
</tr>
<tr>
<td>Zyluk (2001)</td>
<td>Surgical Dept, Pomeranian Medical University, Poland, 2001</td>
<td>Chart review of all 146 patients treated for RSD from 1986-1997. Assessed the 94 (64%) with a previous good response to treatment, at mean 11 months post-treatment. Paper describes remaining symptoms.</td>
<td>Zyluk’s (2001) criteria</td>
<td>not stated, majority duration &lt;4mo (17 weeks)</td>
<td>11 months post treatment completed</td>
</tr>
<tr>
<td>Bejia et al. (2005)</td>
<td>Rheumatology Dept., University Hospital Monastir, Tunisia, 2005</td>
<td>Reviewed 60 algodystrophy cases seen from 1989 - 2003. Classified the outcome for each patient (poor/moderate/good/very good), and reports the percentage left with atrophy and pain.</td>
<td>Not described</td>
<td>13 weeks</td>
<td>15 months</td>
</tr>
<tr>
<td>de Mos et al. (2009b)</td>
<td>Integrated Primary Care Info. Project (GP Database), Erasmus Medical Centre, Rotterdam, Netherlands, 2009</td>
<td>Identified all 259 patients diagnosed with CRPS a minimum of 2 years earlier, from 48 clinics in GP database. Assessed 62% of patients. 40 later identified as not appropriate (never had CRPS/developed CRPS before the study period). Final sample: 102 CRPS patients (100 CRPS-1, 2 CRPS-2). Reports on % w/ symptoms/signs of CRPS at assessment.</td>
<td>1994 IASP-Orlando criteria (Merskey &amp; Bogduk, 1994)</td>
<td>1st mention in GP database; confirmed by patients</td>
<td>5.8 years</td>
</tr>
<tr>
<td>Savas et al. (2009)</td>
<td>Dept. Physical Medicine &amp; Rehab, Suleyman Demireal University Medical School, Turkey, 2009</td>
<td>Physical examination of all 30 CRPS-1 patients previously discharged with a good outcome 18 months later. Reports on remaining symptoms at this assessment.</td>
<td>Zyluk’s (2001) criteria</td>
<td>unclear</td>
<td>18 months post treatment</td>
</tr>
<tr>
<td>Reference</td>
<td>Setting, Location &amp; publication year</td>
<td>Sample &amp; Method</td>
<td>Diagnostic criteria used</td>
<td>CRPS duration at baseline/cohort assembly</td>
<td>CRPS duration at f-up/survey</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Sharma et al. (2009)</td>
<td>RSD Assn of America Website, USA, 2009</td>
<td>Asked RSD website users to complete online survey. Received 1359 responses. 35% excluded (likely never met diagnostic criteria). 888 responses included. Reports percentage describing remission at some point, percentage pain-free, and symptom change over time.</td>
<td>Modified IASP-Budapest criteria (Harden et al., 2010a) (used symptom report only as no physical examination)</td>
<td>n/a</td>
<td>5.5 years</td>
</tr>
</tbody>
</table>
| Veldman et al. (1993)    | Department of Surgery, Nijmegen University Hospital, Netherlands, 1993 | Recorded symptoms reported by 829 consecutive RSD patients. Assessed symptom prevalence in groups according to CRPS duration. | Veldman et al.’s (1993) criteria | Group 1: 0-2 months (n=156)  
Group 2: 2-6 months (n=242)  
Group 3: 6-12 months (n=200)  
Group 4: >12 months (n=231) | 1-46 year range. No mean duration reported. |
| Schwartzman et al. (2009) | Pain Clinic, Drexel University College of Medicine, USA, 2009 | Retrospectively analysed questionnaires completed by 656 CRPS-1 & 2 patients seen over a 10.5-year period. Correlated symptom severity scores with CRPS duration, reported on percentage with particular symptoms at different stages of CRPS duration. | IASP-Budapest criteria (Harden et al., 2010a) | 1-46 year range. No mean duration reported. |
| de Boer et al. (2011)    | Outpatient clinics of 5 hospitals in the TREND knowledge consortium, Netherlands, 2011 | Replicated Veldman et al.’s study with a group of 692 ambulatory CRPS-1 patients. | 1994 IASP-Orlando criteria (Merskey & Bogduk, 1994) | Group 1: 0-2 months (n=48)  
Group 2: 2-6 months (n=211)  
Group 3: 6-12 months (n=70)  
Group 4: >12 months (n=352) | 1-46 year range. No mean duration reported. |

IASP = International Association for the Study of Pain; TREND = Trauma Related Neuronal Dysfunction
Table 4: Results of the Quality and Relevance Assessment for the Included Studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins et al. (1989)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>N - fracture</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>n/a</td>
</tr>
<tr>
<td>Bickerstaff &amp; Kanis (1994)</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>?</td>
<td>N - fracture</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Zyluk (1998a)</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>?</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>n/a</td>
</tr>
<tr>
<td>Retrospective Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subbarao &amp; Stillwell (1981)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>n/a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gougeon et al. (1982)</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>?</td>
<td>?</td>
<td>N</td>
<td>Y</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>N</td>
<td>?</td>
<td>?</td>
<td>N</td>
<td>n/a</td>
</tr>
<tr>
<td>Fialka et al. (1991)</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>?</td>
<td>N</td>
<td>Y</td>
<td>n/a</td>
<td>n/a</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>n/a</td>
</tr>
<tr>
<td>Ehrler et al. (1995)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>?</td>
<td>?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>n/a</td>
</tr>
<tr>
<td>Laulan et al. (1997)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>n/a</td>
</tr>
<tr>
<td>Geertzen et al. (1998b; 1998c)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>n/a</td>
</tr>
<tr>
<td>Galer et al. (2000)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N – pain centre</td>
<td>N</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>n/a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zyluk (2001)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N - good outcome</td>
<td>N</td>
<td>Y</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>n/a</td>
</tr>
<tr>
<td>Bejia et al. (2005)</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>?</td>
<td>?</td>
<td>N</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Y</td>
<td>N</td>
<td>?</td>
<td>N</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>de Mos et al. (2009b)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>n/a</td>
<td>Y</td>
<td>n/a</td>
<td>n/a</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Savas et al. (2009)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>N - good outcome</td>
<td>N</td>
<td>Y</td>
<td>n/a</td>
<td>n/a</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Sharma et al. (2009)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>N - online support group</td>
<td>N</td>
<td>N</td>
<td>n/a</td>
<td>n/a</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>n/a</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------</td>
<td>-------------------</td>
<td>------------------------------------------</td>
<td>--------------------------------</td>
<td>---------------------</td>
<td>-----------------------</td>
<td>-------------------------</td>
<td>-------------------------------</td>
<td>------------------</td>
<td>---------------------</td>
<td>------------------------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-------------------------------</td>
<td>--------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Veldman et al. (1993)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>N</td>
<td>n/a</td>
</tr>
<tr>
<td>Schwartzman et al. (2009)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>y</td>
<td>N - chronic</td>
<td>N</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>de Boer et al. (2011)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>N – regional referral centre</td>
<td>N</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

Y = yes; N = no; ? = unclear; n/a = not applicable
Quality Assessment

The results from the quality and relevance assessment are presented in Table 4. In keeping with guidelines on quality assessment for systematic reviews of this nature, we chose not to create a ‘quality score’ for each study, but instead discuss the quality of the studies qualitatively (Centre for Reviews and Dissemination, 2009; Hayden et al., 2006). We note four major sources of bias in the included studies:

Unrepresentative Samples

As shown in Table 3 and Table 4, the majority of studies utilised samples that are unlikely to represent the CRPS population as a whole: some recruited only patients with a particular ‘trigger’ for their CRPS, such as a fracture, which has been suggested to influence outcome (Sandroni et al., 2003). Some recruited from specialist centres where patients with more severe cases of CRPS are likely to be referred, others included only patients with a previous ‘good outcome’, which is also like to influence later prognosis, and one study only included those with CRPS for more than 1 year. We determined that only 6 out of the 18 included samples met our criteria for utilising a ‘representative sample’. In addition, only 3 studies met our criteria for being considered an ‘inception’ cohort (i.e. samples selected at a common time-point less than 3 months after developing their CRPS). Thus most of the studies likely failed to include any CRPS patients who could have recovered in the first few months of their condition.

Attrition

Loss to follow-up is major source of bias for the studies included in this review, particularly if those lost to follow-up are those with a likely better or poorer outcome. Only 6 out of our 18 included studies could be scored for attrition, and of these, only 2 met our minimum criteria (<20% attrition). Three of the studies were cross-sectional (which meant that any patients who had recovered were not included), and 9 were retrospective follow-ups of a previously identified cohort. For these retrospective studies, we did not score them for ‘attrition’ but rather for ‘response rate’ (i.e. the percentage of the previously identified cohort who were included in the study). Of these 9 studies, 4 had response rates below our required cut-off of 75%, and the other 5 did not report response rate clearly in the published article. Thus attrition is a major and obvious source of bias in the included studies.

Measurement

Inadequate measurement of outcomes is a source of bias for this review. We assessed whether outcome measures were defined, whether any measures were objective, and whether they were
measured appropriately. We found that 15 out of the 18 papers defined their outcomes, that 11 studies included at least one objective measure (i.e. not self- or physician-report), and that 9 studies used some kind of standardized measure or scale. Overall, the studies performed better for this source of bias than for other major sources of bias, but the huge variation in measurement practices and lack of objective measures still likely affected results.

Statistics

Only 7 of the 18 studies performed relevant statistical testing, for example looking for statistically significant reductions in symptom severity over time, or comparing differences in measures of the affected an unaffected limbs at a follow-up. All 7 studies that performed statistical testing were deemed to use statistics appropriately. However a possible source of bias is the lack of statistical testing in the 11 other studies. This means that we do not know if differences between groups in the cross-sectional studies, or changes in symptom severity over time in prospective studies could be chance findings, and have to take the raw data on its merit.

Results from Prospective Studies

The three prospective studies presented the most optimistic outcome data, and demonstrated consistent symptom improvements over time (Atkins et al., 1989; Bickerstaff & Kanis, 1994; Zyluk, 1998a). Two of these studies systematically measured the symptoms/signs of CRPS early after diagnosis and then again at 12-13 month follow-up (Bickerstaff & Kanis, 1994; Zyluk, 1998a), whereas the other study briefly notes data from a 6-month follow-up (Atkins et al., 1989). The two prospective studies that measured pain or tenderness found that the proportion of CRPS patients with pain reduced from 100% at first assessment to 18% and 7% respectively at 12-13 month follow-up (Bickerstaff & Kanis, 1994; Zyluk, 1998a). The two studies that assessed the presence of swelling and reported rates of 87-100% at first assessment, which reduced to 12-15% at final follow-up (Atkins et al., 1989; de Mos et al., 2009b). Only one of the prospective studies measured changes in temperature disturbance, limb discolouration, sweating abnormalities, trophic changes to hair and nails, and sensory disturbances, and this study noted significant reductions in rates of signs over the course of 13 months (Zyluk, 1998a). One study found significant reductions in rates of “vasomotor instability” (a combination of abnormalities in limb colour, temperature and sweating) over the course of 12 months, from 91% at baseline to 29% at follow-up (Bickerstaff & Kanis, 1994). Another study grouped symptoms into a category labelled “vasomotor instability or swelling” and found that 42% of patients experienced these symptoms at 6 month follow-up (Atkins et al., 1989).
The symptoms/signs that were least likely to resolve in the prospective studies were stiffness and limb strength. Bickerstaff and Kanis (1994) found that 65% of patients continued to have stiffness at 12 months, and the grip strength of the affected limb was equivalent to 45% of the strength of the unaffected limb. This contrasted with a grip strength ratio of 80% in Colles’ fracture patients who did not develop algodystrophy. Zyluk (1998a) reported that 89% of RSD patients had reduced grip strength at 13 month follow-up, and reported that the grip strength was 45% that of the unaffected limb. Zyluk (1998a) also found that stiffness was highly prevalent, with 78% of RSD patients experiencing “stiffness in the morning” at 13-month follow-up. Atkins et al. (1989) reported lower rates of joint stiffness at 6 month follow-up (21%), but it is unclear from the results they present whether joint stiffness may also have affected the 42% of patients noted to have “vasomotor instability or swelling”.

Only one of the prospective studies had an overall measure of CRPS severity, the “Zyluk assessment of result”. This study reported that 73% of patients had a good result (no pain and full finger flexion), 13% had a moderate outcome (pain after load and loss of flexion of less than 3cm), whilst 13% had a poor result (persistent severe pain and loss of flexion greater than 3cm) (Zyluk, 1998a).

Of note, two of the prospective studies utilised the same criteria for “algodystrophy” and the other utilised criteria for “reflex sympathetic dystrophy”. All three prospective studies required 4 different symptoms/signs of CRPS to be present in order to meet diagnostic criteria, although the algodystrophy criteria were broader as a wider range of symptoms were accepted.

**Results from Retrospective Studies**

*Measures of Overall Rates of CRPS Symptoms or Severity*

There were 12 retrospective studies included in the review. Seven reported on results of an overall measure of CRPS presence or severity, with the majority of these studies quantifying the percentage of an original cohort who continued to have symptoms/signs of CRPS at a long-term follow-up assessment. The results are presented in Table 5. This shows that the outcomes were highly variable and are presented here in order from the most to the least positive. Gougeon, Eschard, & Moreau Hottin (1982) found that all but 22% of algodystrophy patients were “cured” at 3-year follow-up according to a chart review. A 9-year follow-up questionnaire sent to algodystrophy patients reported that 40% of patients had not “normalised” (Ehrler et al., 1995). Another study of algodystrophy patients indicated that 58% had “sequelae” with an elevated algodystrophy score calculated from a clinical and radiological examination at 12 months post-fracture (Laulan et al., 1997). A study of CRPS patients reported that 64% continued to meet the 1994 IASP criteria for CRPS at an
examination at a mean of 5.8 years post-diagnosis (de Mos et al., 2009b). Finally, a physical examination of CRPS patients who had previously had a good outcome found that 90% continued to experience symptoms 18 months after treatment (Savas et al., 2009). Overall, these findings are highly heterogeneous, with ratings as low as 22% and as high as 90% for those who continue to have symptoms at long-term follow-up.

One study rated patients’ outcome according to a clinical grading system, and found that 63% of algodystrophy patients had a very good or good outcome, 29% had a moderate outcome and 9% had a poor outcome according to a chart review (Bejia et al., 2005). Another interviewed patients about their clinical course and found that 30% considered themselves recovered, 54% rated their symptoms as stable, and 16% stated that their symptoms were progressive at a mean of 5.8 years after diagnosis (de Mos et al., 2009b).

One retrospective study reported on a measure of overall symptom severity in a cohort of patients examined at a mean of 5.5 years (Geertzen et al., 1998b; Geertzen et al., 1998c). They used the “RSD score”, a 60-point rating scale, and reported that whilst the score for RSD patients’ unaffected hands was 0.7/60 (on a scale where 0 = no RSD and 60 = worst RSD), on the affected side it was a mean of 6/60. They also reported that quality of life scores amongst patients were similar to population norms.

**Measures of Pain**

Ten retrospective papers reported on measures of pain amongst cohorts of patients followed up at least one year after diagnosis and these are presented in Table 6. Five of these studies reported on the percentage of patients who continued to experience pain and these results were highly variable. The most positive results showed that only 19% of algodystrophy patients continued to experience pain at 1 year, however 27% of the ‘algodystrophy’ sample in this study had never experienced pain at any time, which questions the similarity of this sample to others diagnosed with RSD or CRPS (Laulan et al., 1997). An assessment of CRPS patients at a mean of 5.8 years after diagnosis found that 32% still reported experiencing pain (de Mos et al., 2009b). Two postal questionnaire studies found that 36% of algodystrophy patients still report pain at 9 year follow-up (Ehrler et al., 1995) and 47% of RSD patients had hand pain at 22 months (Subbarao & Stillwell, 1981). Studies which examined patients at follow-up found that 71% of RSD patients with a previously good outcome still had pain 11 months post-treatment (Zyluk, 2001), and of CRPS patients, 86% had pain on movement and 76% had pain at rest, 18-months post-treatment (Savas et al., 2009).
Table 5: Results of Retrospective Studies Measuring General Outcomes of CRPS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>Mean follow-up time-point</th>
<th>Measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bejia et al. (2005)</td>
<td>60 algodystrophy patients</td>
<td>15 months</td>
<td>Criteria of French Society for Rheumatologists</td>
<td>Very good result: 16%; Good result: 46.5%; Moderate result: 28.7%; Poor result: 8.8%</td>
</tr>
<tr>
<td>Gougeon et al. (1982)</td>
<td>227 algodystrophy patients</td>
<td>Until cured, max 3 years</td>
<td>Chart review to determine % “cured”</td>
<td>21.6% not “cured” after 3 years</td>
</tr>
<tr>
<td>Ehrler et al. (1995)</td>
<td>25 algodystrophy patients</td>
<td>9 years</td>
<td>Questionnaire to determine % “normalised”</td>
<td>60% “normalised”; 40% symptomatic</td>
</tr>
<tr>
<td>Laulan et al. (1997)</td>
<td>26 algodystrophy patients post distal-radius fracture</td>
<td>12 months</td>
<td>% with “sequelae” on physical examination</td>
<td>57.7% had “sequelae”</td>
</tr>
<tr>
<td>De Mos et al. (2009b)</td>
<td>102 CRPS patients</td>
<td>5.8 years</td>
<td>% who still meet 1994 IASP-Orlando Criteria for CRPS</td>
<td>64% meet 1994 IASP-Orlando criteria</td>
</tr>
<tr>
<td>Savas et al. (2009)</td>
<td>30 CRPS patients with previous good outcome</td>
<td>18 months after treatment</td>
<td>% who met own criteria for CRPS</td>
<td>0 met criteria for CRPS; 10% were symptom-free, 90% symptomatic.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% who were symptom-free</td>
<td></td>
</tr>
<tr>
<td>Geertzen et al. (1998b; 1998c)</td>
<td>65 RSD patients</td>
<td>5.5 years</td>
<td>RSD Score (min=0, max=64, worse scores indicate more severe RSD); Short-form 36 (quality of life)</td>
<td>Unaffected side = 0.7 +/-1.5; Affected side = 5.6 +/-8.6; SF-36 scores similar to population norms</td>
</tr>
</tbody>
</table>

IASP = International Association for the Study of Pain
Table 6: Results of Retrospective Studies Measuring Pain Outcomes in CRPS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>Mean follow-up time-point</th>
<th>Measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laulan et al. (1997)</td>
<td>26 algodystrophy patients post-distal radius fracture</td>
<td>12 months</td>
<td>% with pain</td>
<td>19%</td>
</tr>
<tr>
<td>Ehrler et al. (1995)</td>
<td>25 algodystrophy patients</td>
<td>9 years</td>
<td>% with pain</td>
<td>36%</td>
</tr>
<tr>
<td>Subbarao &amp; Stillwell (1981)</td>
<td>77 RSD patients</td>
<td>22 months</td>
<td>% with pain in hand</td>
<td>41%</td>
</tr>
<tr>
<td>Zyluk (2001)</td>
<td>94 RSD patients with previous ‘good’ outcome</td>
<td>11 months post-treatment</td>
<td>% not completely pain-free</td>
<td>71%</td>
</tr>
<tr>
<td>De Mos et al. (2009b)</td>
<td>102 CRPS patients</td>
<td>5.8 years post-diagnosis</td>
<td>% reporting spontaneous pain</td>
<td>32%</td>
</tr>
<tr>
<td>Savas et al. (2009)</td>
<td>30 CRPS-1 patients with previous ‘good’ outcome</td>
<td>18 months post-treatment</td>
<td>% with hand pain after use; % with hand pain at rest; Mean VAS pain intensity</td>
<td>86%, 76%; 2.8cm+/−2.0</td>
</tr>
<tr>
<td>Geertzen et al. (1998b; 1998c)</td>
<td>65 RSD patients</td>
<td>5.5 years</td>
<td>Mean VAS pain intensity last 24 hours</td>
<td>1.2cm+/−1.8</td>
</tr>
<tr>
<td>Fialka et al. (1991)</td>
<td>17 lower-limb RSD patients</td>
<td>42 months</td>
<td>Mean 0-5 pain-rating (0=no pain, 5=intolerable pain)</td>
<td>2.1+/−1.1</td>
</tr>
<tr>
<td>Galer et al. (2000)</td>
<td>31 CRPS patients</td>
<td>3.3 years</td>
<td>Self-report –has pain changed over time?</td>
<td>Improved: 29%; No change: 42%; Worse: 29%</td>
</tr>
<tr>
<td>Sharma et al. (2009)</td>
<td>888 CRPS patients using RSD Assn America Website</td>
<td>5.5 years</td>
<td>Self-report (retrospective): pain NRS at onset and now</td>
<td>Onset estimate: 8.2/10; current intensity: 6.9/10</td>
</tr>
</tbody>
</table>

VAS = visual analogue scale; NRS = numerical rating scale.
Three retrospective studies reported results of measures of pain intensity. Savas et al. (2009) found that on a visual analogue scale (0-10cm), the mean pain score of CRPS patients was 2.8cm +/- 2.0 at a follow-up 18 months post-treatment. Geertzen et al. (Geertzen et al., 1998b; Geertzen et al., 1998c) reported even lower pain severity ratings at 5.5-year follow-up of RSD patients with a mean visual analogue score of 1.2cm +/- 1.8. Fialka, Zifko, Bochdansky, Schneider, & Schimmerl (1991) reported low-moderate pain intensity amongst a group of RSD patients at a 42 month follow-up: on a scale of 0 (no pain) to 5 (intolerable pain), the mean score was 2.1 +/- 1.1.

Two retrospective self-report studies asked groups of CRPS patients to recall how pain had changed over time. Galer et al. (2000) found that 29% of CRPS patients believed their pain had improved over time, 42% described no change, and 29% indicated that their pain had worsened. A survey of RSD patients found that on average, patients believed their pain had improved slightly since first developing their symptoms, but 79% stated that their symptoms had never gone into remission (Sharma et al., 2009). This last study was limited as it surveyed patients who were current users of an RSD website, so any who had recovered were unlikely to be included. The results of the retrospective studies that measured the prevalence or intensity of pain are presented in Table 6.

**Measures of Function**

Eight retrospective studies reported on follow-up measures of limb function amongst cohorts of CRPS patients. All of these studies showed the limb strength and/or stiffness continue to be affected in the long-term. For example, Geertzen et al. (Geertzen et al., 1998b; Geertzen et al., 1998c) found that there were small but statistically significant differences in the range of motion between the affected and unaffected limbs of RSD patients at a mean follow-up time of 5.5 years. They also reported that the grip strength of the RSD affected hand was 73% that of the unaffected hand, and that 62% of patients were limited in the activities of daily living. Similar significant range of motion and strength differences between the affected and unaffected limbs of CRPS patients were reported by Savas et al. (2009) at a mean of 18 months post-treatment. Fialka et al. (1991) found that 58.8% of patients had a slightly reduced range of motion, but none exhibited a markedly reduced range of motion at 39 month follow-up. Zyluk (2001) found that 28% of RSD patients had “morning stiffness” and 78% described decreased function of the hand 11 months after treatment. Grip strength of the affected hand was 37% of the strength of the unaffected side. Ehrler et al. (1995) reported that 36% of algodystrophy patients indicated that they had reduced strength in the limb, and 28% described stiffness 9 years after diagnosis. Subbarao and Stillwell (Subbarao & Stillwell, 1981) found that 51% of their sample experienced stiffness in the hand at 22 month follow-up. Of the 102 patients visited by de Mos et al. (2009b) at a mean of 5.8 years since CRPS-onset, 59-60% described a reduced range of motion or weakness of the limb, and these were observed by the researchers in 41-44%. Galer et al.
(2000) surveyed CRPS patients and asked them to recall the course of symptoms over time. They reported that weakness was noted to have improved by 48% of patients, but 25% noted that weakness tended to worsen and 23% noted no change. Overall, the retrospective studies that report on functional outcomes concur with the findings of the prospective studies, indicating that functional limitations such as weakness, stiffness and reduced range of motion may be quite prevalent in the long-term for CRPS patients.

Diagnostic Criteria Used in the Retrospective Studies
The diagnostic criteria used by the studies once again differed greatly. Three of the retrospective studies did not describe their criteria. Four required 4 symptoms/signs from a list of varying possible clinical features (Geertzen et al., 1998b; Geertzen et al., 1998c; Savas et al., 2009; Sharma et al., 2009; Zyluk, 2001). Two studies required 3 symptoms/signs from a list of possible clinical features along with particular radiological findings (Fialka et al., 1991; Laulan et al., 1997). Two studies used the broad 1994 IASP-Orlando criteria (de Mos et al., 2009b; Galer et al., 2000). One study described a range of symptoms/signs but did not state which were required for diagnosis (Subbarao & Stillwell, 1981). It appears that studies which used criteria for ‘algodystrophy’ tended to produce more optimistic results than studies which examined ‘RSD’ or ‘CRPS’. Also studies which conducted a chart review produced more optimistic results than studies that examined patients at follow-up.

Results from Cross-Sectional Studies
Three cross-sectional studies were included in the review. Two of the studies took samples of patients with diagnoses of RSD or CRPS and divided them into four groups based on their duration (less than 2 months, 2-6 months, 6-12 months and more than 12 months) (De Boer et al., 2011; Veldman et al., 1993). They measured the percentage of each group with each of the symptoms of CRPS and report these rates. One of the studies compared these four groups for statistically significant differences in the rates of symptoms (De Boer et al., 2011). The other study measured symptoms as well as CRPS duration, and performed correlations to see whether symptom prevalence or severity significantly correlated with CRPS duration (Schwartzman et al., 2009). These three studies had large sample sizes in comparison with the majority of the other papers (656-829 subjects).

The cross-sectional studies generally reported poorer outcomes than the prospective studies and the retrospective studies. For example, for pain, the 2 comparative studies reported that 85-92% of RSD/CRPS patients had pain during the first 2 months, and this increased steadily so that amongst those with CRPS for more than one year the rates were 95-97% (De Boer et al., 2011; Veldman et al., 1993). The correlational study reported a significant correlation of r=0.6 for numerical pain rating
The cross-sectional studies reported similar patterns of increasing rates for sensory symptoms such as allodynia and hyperaesthesia, although the actual rates of symptoms were lower than those for pain (De Boer et al., 2011; Veldman et al., 1993). The comparative studies showed that the proportion of patients experiencing temperature disturbance, limb discolouration and swelling tended to decrease with increasing CRPS duration (De Boer et al., 2011; Veldman et al., 1993), but this contrasted with the results of the correlational study, which reported significant positive correlations between rates of these symptoms and CRPS duration (Schwartzman et al., 2009). The results of the cross-sectional studies are presented in Table 7.

Each of the three cross-sectional studies used different diagnostic criteria for CRPS. One of the studies used Veldman’s criteria, which required the presence of at least 4 symptoms/signs of CRPS from a list of 5 possible clinical features, and also required that symptoms/signs worsened with use of the limb and that pain was present in a larger and more distal area of the limb than the original injury or surgery (Veldman et al., 1993). Schwartzman et al. (2009) reported using the “Budapest” criteria, which are much stricter. The third study used the 1994 IASP-Orlando criteria for CRPS, and also reported on the relatively low number of patients in their cohort who would have met Veldman’s criteria (42%) and the IASP-Budapest criteria (38%), and that the proportion of patients meeting these different criteria differed depending on the CRPS duration (De Boer et al., 2011). Thus it is likely that the patient group captured differs greatly between the three cross-sectional studies.

Discussion
The 18 studies reviewed here document highly variable outcomes of CRPS. The quality assessment revealed a number of significant limitations in the literature, which are discussed below. Bearing this in mind, we first comment on the general findings. The best rates of recovery were shown by the prospective studies, which found that the proportion of patients with pain, swelling, limb discolouration, and temperature disturbance reduced dramatically within 6-13 months. However functional outcomes such as weakness, stiffness and limited range of motion persisted in a majority of patients for more than one year. In contrast, the cross-sectional studies found that rates of pain, sensory symptoms, and motor dysfunction were highest amongst those with the longest duration of CRPS, which could be interpreted to mean that these symptoms progress and worsen over time. However because cross-sectional studies cannot capture cases that have resolved, this interpretation would be inappropriate. Instead, these results can only indicate that there is a cohort of CRPS patients with long-term symptoms including pain, sensory disturbance and impaired limb function.
Table 7: Results of Cross-Sectional & Correlational Studies on the Course of CRPS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Group</th>
<th>Pain</th>
<th>Allodynia</th>
<th>Hyperaesthesia</th>
<th>Temperature Disturbance</th>
<th>Discolouration</th>
<th>Oedema</th>
<th>Altered Sweating</th>
<th>Reduced Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Boer et al. (2011)</td>
<td>&lt;2 months</td>
<td>85%</td>
<td>31%</td>
<td>21%</td>
<td>68%</td>
<td>62%</td>
<td>60%</td>
<td>31%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>2-6 months</td>
<td>87%</td>
<td>28%</td>
<td>28%</td>
<td>58%</td>
<td>65%</td>
<td>45%</td>
<td>18%</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>6-12 months</td>
<td>93%</td>
<td>41%</td>
<td>39%</td>
<td>57%</td>
<td>62%</td>
<td>49%</td>
<td>20%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>12 months+</td>
<td>95%</td>
<td>45%</td>
<td>41%</td>
<td>51%</td>
<td>48%</td>
<td>38%</td>
<td>20%</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>(btw group differences)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>ns</td>
<td>ns</td>
<td>*</td>
<td>ns</td>
<td>*</td>
</tr>
<tr>
<td>Veldman et al. (1993)</td>
<td>&lt;2 months</td>
<td>92%</td>
<td></td>
<td>69%</td>
<td>98%</td>
<td>97%</td>
<td>86%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-6 months</td>
<td>88%</td>
<td></td>
<td>75%</td>
<td>91%</td>
<td>96%</td>
<td>80%</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-12 months</td>
<td>97%</td>
<td></td>
<td>72%</td>
<td>89%</td>
<td>90%</td>
<td>61%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 months+</td>
<td>97%</td>
<td></td>
<td>85%</td>
<td>91%</td>
<td>84%</td>
<td>55%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Schwartzman et al. (2009)</td>
<td>NRS correlated w/ duration (r=0.6*), SFMPQ didn’t correlate w/ duration (ns).</td>
<td>NRS correlated w/ duration (r=0.6*), SFMPQ didn’t correlate w/ duration (ns).</td>
<td>Intensity of touch allodynia correlated w/ duration (r=0.5*)</td>
<td>n/a</td>
<td>% w/ temp. disturbance in each category correlated w/ duration (r=0.4*)</td>
<td>% w/ colour disturbance in each category correlated w/ duration (r=0.5*)</td>
<td>% w/ oedema in each category correlated w/ duration (r=0.5*)</td>
<td>No correlation btw % w abn sweating in each category &amp; duration (r=0.2, ns)</td>
<td>No correlation btw % w loss of strength in each category &amp; duration (r=0.2, ns)</td>
</tr>
</tbody>
</table>

*p<.05; ns = non significant; SFMPQ = Short-Form McGill Pain Questionnaire; w/ = with; n/a = not applicable; abn = abnormal
The retrospective studies also showed that it is not uncommon for patients to have sequelae including pain and limb dysfunction many years after a diagnosis of CRPS. However, the studies’ findings were highly disparate, and there were several possible reasons for this. Studies that conducted careful interviews and examinations tended to identify more symptoms than those that conducted chart reviews or posted questionnaires. Studies that measured symptom severity showed that some persisting symptoms are fairly mild. For example, Geertzen et al. (Geertzen et al., 1998b; Geertzen et al., 1998c) found at follow-up that average pain scores were 1.2/10, and range of motion was 84-99% of the unaffected limb. It is unclear whether such mild symptoms would have been categorized as ‘present’ or absent’ in studies which dichotomized patients, and this likely contributed to the variability in results.

There were some common findings across all three types of studies included in the review. First, the vasomotor and sudomotor symptoms of CRPS (discolouration, temperature disturbance, altered sweating and oedema) tend to be most common in the early stages of the condition, and had the greatest likelihood of resolving. Second, pain and sensory symptoms persisted in some patients but not all, and long-term follow-ups show fairly low rates of mean pain intensity. Third, we found that motor symptoms such as weakness, stiffness, and limited range of motion are the symptoms most likely to persist in the long-term.

Overall, this review shows that CRPS has a highly variable course, with some patients experiencing a relatively brief syndrome (with some sequelae such as weakness and stiffness) whilst others experience lasting pain and symptoms. Interestingly, studies have documented high prevalence rates for CRPS after events such as fracture or surgery (up to 36%), (Atkins et al., 1990; Harden et al., 2003; Roumen et al., 1991; Sennwald, 1990) and it might that having features of CRPS briefly after such events is quite common, but that many symptoms resolve spontaneously, as was found by Zyluk (1998a). However, in severe cases of CRPS, disability may last years (Schwartzman et al., 2009), and invasive treatments such as spinal cord stimulation (Sears et al., 2011) or amputation (Bodde et al., 2011) are performed. This suggests that there is huge variability in the course of CRPS, and lends support to the idea that subtypes of CRPS patients might exist. Two studies (Bruehl et al., 2002; de Mos et al., 2009b) performed cluster analyses and showed that there were three subtypes of CRPS patients, including a group with florid symptoms across all categories. de Mos et al. (2009b) showed that this group experienced the poorest outcomes. Clinically, it would be useful to be able to identify those at risk of poor outcomes early in the trajectory of their CRPS, so that treatments can be targeted for these individuals.
Relatively few studies have assessed prognostic factors in CRPS, and a recent systematic review concluded that there were few quality studies and most of the evidence on prognostic factors is contradictory, although they did identify that sensory disturbance and cold skin temperature are associated with poor outcomes (Wertli, Bachmann, Weiner, & Brunner, 2013). The studies included in this review listed the following prognostic factors associated with poor outcome: longer pain duration (Katz & Hungerford, 1987; Ogilvie-Harris & Roscoe, 1987), more intense pain (Fialka et al., 1991), delay to receive treatment (Bejia et al., 2005; Ehrler et al., 1995), male sex (Bejia et al., 2005), female sex (Gougeon et al., 1982), younger age (Bejia et al., 2005), a more severe fracture, poorer grip strength, and low mobility (Laulan et al., 1997). The following have been reported to predict good outcome: having a fracture as the initiating event, the absence of sensory symptoms, the presence of swelling (Sandroni et al., 2003), having a warm limb in the early stages, no delay between the injury and CRPS onset (Bejia et al., 2005), and having a single joint involved (Gougeon et al., 1982). Research in other pain conditions has identified the importance of psychosocial factors for predicting the transition from acute to chronic pain. For example, factors such as depression, expectations, pain-related fear and avoidance of movement predict poor outcome in low back pain (Chou & Shekelle, 2010; Iles, Davidson, Taylor, & O’Halloran, 2009). As yet, it appears that little research has assessed whether psychological factors predict the transition from the acute to the chronic stages in CRPS. Whilst studies that have assessed whether psychosocial factors predict the onset of CRPS after fracture or surgery have produced mixed results (Beertuizen et al., 2011; Dilek et al., 2012; Harden et al., 2003; Hootkani et al., 2008; Puchalski & Zyluk, 2005), future researchers may wish to assess the role of such factors in CRPS recovery. Another factor that has been shown to predict CRPS following fracture and CRPS recurrence following surgery is activity of the SNS (Ackerman & Ahmad, 2008; Schurmann et al., 2000). It may also be valuable to assess whether SNS activity predicts the course or outcome of the condition.

Limitations
This review highlighted several limitations in the literature. At the most, 3 studies agreed on a diagnostic criteria (De Boer et al., 2011; de Mos et al., 2009b; Galer et al., 2000), and many studies either followed their own criteria or did not describe them. Although considerable efforts have been made by researchers to develop a common name (i.e. ‘complex regional pain syndrome’) and diagnostic criteria (e.g. the 1994 IASP-Orlando criteria and the IASP-Budapest criteria), even some studies published since this time have not utilised these terms or criteria. The differences in the criteria used, not to mention the way such criteria are interpreted, likely contributed to the variation in study results. For example, many studies assessing ‘algodystrophy’ reported more favourable outcomes than those assessing RSD or CRPS. As diagnostic criteria for algodystrophy often required fewer signs and symptoms or didn’t require the presence of pain (Atkins et al., 1989; Laulan et al.,
1997), this suggests that those with a more limited set of symptoms at the outset might make a fuller recovery. A recently published study which utilised the stricter “Budapest” diagnostic criteria found that of those with CRPS-1 after fracture, none were symptom-free at 12 months (Beerthuizen et al., 2012). This study did not meet the inclusion criteria for this systematic review and only briefly mentions its 12-month outcome data, but it does contrast strongly with the positive data reported by the 3 prospective studies included in this review, which all utilised “looser” diagnostic criteria. It is important that future research utilise a common diagnostic criteria for CRPS, and that researchers adopt a consistent set of measurement tools for assessing the signs and symptoms of CRPS.

Another major finding of this review was that the literature as a whole suffers from several sources of bias, and higher quality studies are needed to understand the outcomes of CRPS. First, few studies included samples that could be considered ‘representative’ of the CRPS population as a whole, and many did not adequately describe their recruitment processes. Future studies should seek to recruit from a wide variety of settings to include a broad range of CRPS patients and should state whether samples are consecutive patients or selected in another manner. Even when such processes were described, the samples recruited were often unrepresentative. For example, two studies recruited only patients who had previously responded well to treatment (Savas et al., 2009; Zyluk, 2001), which would be expected to bias results, and another study excluded severe cases who had to withdraw for treatment (Zyluk, 1998a). Second, several studies suffered from high attrition or low response rates. This is particularly problematic where there is a difference between those who do and do not participate. It is possible that those who have recovered would be less inclined to complete a follow-up than those who are still symptomatic and therefore motivated to support research into their condition. Future studies should try to reduce barriers to participation to ensure adequate participant recruitment and retention. The other limitations of the literature included differences in measurement tools used, and lack of relevant statistical testing. Also, the review process was limited in that we used just one reviewer to search the literature, with a second reviewer assessing suitability for inclusion when there was any doubt.

Conclusions
In conclusion, we found evidence from prospective studies that the rates of symptoms of CRPS reduce significantly over the first 6-13 months, but the results from retrospective studies indicate that the outcomes of CRPS are highly variable and the cross-sectional studies demonstrate that there are a group of patients for whom pain and sensory symptoms persist in the long term. Overall the quality of the evidence was poor, and the data should be interpreted with caution. At present there are few
studies which have assessed prognostic factors in CRPS, and such studies could help to identify those at risk of poor outcomes as well as help researchers identify possible target variables for treatment.
Chapter 4: Prognostic Factors in CRPS: Literature Review & Hypotheses

Prognostic Factors in CRPS

As shown in Chapter 3, the outcomes of CRPS in terms of pain, vasomotor and sudomotor symptoms have been shown to be generally favourable, especially amongst samples of patients identified early following an event such as fracture or surgery. However, retrospective and cross-sectional studies show that the outcomes can be poor for some patients, and CRPS can lead to long-term pain and disability. de Mos et al. (2009b) found that 14% of patients fell into a ‘poor outcome’ cluster, where none were able to resume former work, none described themselves as ‘recovered’ and rates of sensory, vascular, motor and trophic signs and symptoms were high. Moreover, several studies indicate that for CRPS patients who experience poor outcomes, further complications can result. Van der Laan, Veldman, & Goris (1998) found that a minority of patients experience movement disorders, infections and ulcers, which at times led to amputation. They also noted that for those who experienced a severe complication of CRPS, 91% experienced more than one severe complication, and that CRPS symptoms and/or complications could affect multiple limbs for the same patient. Thus the research suggests that a poor outcome from CRPS can be severe.

As yet, only a limited number of research studies have been designed to identify prognostic factors that could differentiate between those who will experience a relatively benign course of CRPS and those who might experience long-term symptoms and related disability. The majority of research that has been conducted has focussed on possible demographic or clinical indicators that could predict poor outcomes. The research is summarised in Table 8. Generally studies performed univariate statistics and only one reported multivariate results after controlling for co-morbid predictive factors (Dumas et al., 2011). Prognostic indicators in CRPS were the topic of a recently published systematic review, which included fewer studies than those noted here due to stricter inclusion criteria for the systematic review. The authors reported that the quality of the research was unsatisfactory but showed support for the prognostic role of cold skin temperature and the presence of sensory signs, both of which were associated with poorer outcomes (Wertli et al., 2013).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Outcome variable</th>
<th>Significant predictors of poor outcome</th>
<th>Factors shown not to predict outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gougeon et al. (1982)</td>
<td>% ‘cured’ at 12 months</td>
<td>• Female sex</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multiple joints affected</td>
<td></td>
</tr>
<tr>
<td>Ogilvie-Harris et al. (1987)</td>
<td>Hospital for Special Surgery Scale; Dynamometer recordings</td>
<td>• Diagnosis/treatment delayed &gt;6 months</td>
<td></td>
</tr>
<tr>
<td>Goris et al. (1990)</td>
<td>Risk of sequelae</td>
<td>• Cold extremity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Exacerbation of symptoms during exercise</td>
<td></td>
</tr>
<tr>
<td>Eulry et al. (1990)</td>
<td>‘Cure’</td>
<td>• ‘Psychological background’ delayed cure only for nontraumatic group.</td>
<td>• Work-related vs. non-work related accident</td>
</tr>
<tr>
<td>Fialka et al. (1991)</td>
<td>Pain (0-5 scale)</td>
<td>• Pain at previous examination</td>
<td></td>
</tr>
<tr>
<td>Ehrler et al. (1995)</td>
<td>Percentage ‘normalised’</td>
<td>• Delay to diagnosis &gt;28 weeks</td>
<td></td>
</tr>
<tr>
<td>Laulan et al. (1997)</td>
<td>Sequelae (limited active ROM)</td>
<td>• Initial algodystrophy score&gt;7</td>
<td>• Type of fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Manual work</td>
<td>• Treatment by K-wire</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe fracture</td>
<td>• Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Displaced fracture of ulnar styloid</td>
<td>• Sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pain at distal radioulnar joint</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Associated lesions</td>
<td></td>
</tr>
<tr>
<td>Zyluk et al. (1998b)</td>
<td>Good, fair or poor outcome</td>
<td>• Delay to receive treatment (&gt;12 months)</td>
<td>• Sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Later CRPS ‘stage’</td>
<td>• Loss finger flexion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Radiographic or Scintigraphic changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Psychological status (labile vs. stable)</td>
</tr>
<tr>
<td>Van der Laan et al. (1998)</td>
<td>Presence of severe complications</td>
<td>• Younger age</td>
<td>• Type of trauma</td>
</tr>
<tr>
<td>Reference</td>
<td>Outcome Variable</td>
<td>Significant Predictors of poor outcome</td>
<td>Factors shown not to predict outcome</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Dauty et al. (2001)</td>
<td>Delayed return to work</td>
<td>• Serious trauma&lt;br&gt;• Distal joint affected&lt;br&gt;• Non-sedentary profession&lt;br&gt;• Workplace injury</td>
<td>• Upper vs. lower limb&lt;br&gt;•</td>
</tr>
<tr>
<td>Sandroni et al. (2003)</td>
<td>Resolution</td>
<td>• Trigger other than fracture&lt;br&gt;• Sensory symptoms</td>
<td>• Age&lt;br&gt;• Sex&lt;br&gt;• Affected site</td>
</tr>
<tr>
<td>Bejia et al. (2005)</td>
<td>Good versus poor outcome; Duration of CRPS</td>
<td>• Early treatment&lt;br&gt;• Younger age&lt;br&gt;• Male sex&lt;br&gt;• Delay to onset of CRPS&lt;br&gt;• Cold skin temperature&lt;br&gt;• ‘secondary’ vs. ‘idiopathic’</td>
<td></td>
</tr>
<tr>
<td>Vaneker et al. (2005)</td>
<td>McGill Pain Questionnaire; Pain levels during quantitative sensory testing</td>
<td>• Initially cold skin temperature</td>
<td></td>
</tr>
<tr>
<td>Vaneker et al. (2005)</td>
<td>Impairment Sum Score at 8 years</td>
<td>• Pain at initial assessment&lt;br&gt;• Impairment score at initial assessment</td>
<td>• Cold skin temperature at initial assessment</td>
</tr>
<tr>
<td>Tan et al. (2009)</td>
<td>Short-Form 36 Health Survey</td>
<td>• Female sex&lt;br&gt;• Longer length of follow-up since initial diagnosis</td>
<td>• Age&lt;br&gt;• Trauma history&lt;br&gt;• Location of CRPS</td>
</tr>
<tr>
<td>De Mos et al. (2009b)</td>
<td>‘Poor’ outcome cluster on k-means cluster analysis</td>
<td>• Upper limb involvement&lt;br&gt;• Trigger other than fracture&lt;br&gt;• Initial cold skin temperature</td>
<td>• Age&lt;br&gt;• Medical history</td>
</tr>
<tr>
<td>Harden et al. (2010b)</td>
<td>CRPS Severity Score at 6 &amp; 12 months</td>
<td>• Increase in depression from pre-surgery to 4 weeks&lt;br&gt;• Increase in anxiety from pre-surgery to 4 weeks (6 months predictor only)</td>
<td>• Pre-surgical anxiety and depression</td>
</tr>
<tr>
<td>Dumas et al. (2011)</td>
<td>Return to work</td>
<td>• Lower limb involvement&lt;br&gt;• Presence of oedema&lt;br&gt;• Non-sedentary job&lt;br&gt;• Lower educational level&lt;br&gt;• Delay to receive treatment</td>
<td>• Sex&lt;br&gt;• Age&lt;br&gt;• Pain&lt;br&gt;• Symptoms other than swelling&lt;br&gt;• Treatment type&lt;br&gt;• Co-morbidities&lt;br&gt;• Company size</td>
</tr>
</tbody>
</table>
**Clinical Factors**

**Skin Temperature**

Table 8 shows that five studies found that having a colder affected limb in the initial stages of CRPS was associated with risk of complications, sequelae, higher pain scores later, and poor outcomes (Bejia et al., 2005; de Mos et al., 2009b; Goris et al., 1990; van der Laan et al., 1998; Vaneker et al., 2005). One study reported that cold temperature did not influence later impairment scores, but was from the same cohort which had shown that initial cold temperature led to poorer pain outcomes (Vaneker et al., 2006). Thus overall it appears the research is fairly consistent in showing that those with an initially cold limb are at risk of poorer outcomes. Few studies identified how a ‘cold’ limb was defined or measured, and research suggests that self-report of skin temperature may be poorly linked to measured limb temperature, and that limb temperature fluctuates frequently in CRPS (Bruggeman, Oerlemans, & Frolke, 2009; Schilder, Niehof, Marinus, & van Hilten, 2015).

**Pain/Sensory Symptoms**

Three studies found that amongst CRPS patients, those with more intense pain were at greater risk of poor outcomes, including experiencing more pain at follow-up, having greater impairment, and increased risk of sequelae (defined as decreased range of motion) (Fialka et al., 1991; Laulan et al., 1997; Vaneker et al., 2006). Sandroni et al. (2003) reported that those with sensory symptoms experienced lower rates of resolution of CRPS, although they did not mention which sensory symptoms were measured. In contrast, Dumas et al. (2011) found that the presence or absence of pain was not associated with return to work in CRPS, however they did not measure pain intensity or other sensory symptoms. Overall, it appears there is reasonable support for the predictive utility of pain and/or sensory symptoms in CRPS, with greater pain associated with poorer outcomes.

**Location of CRPS**

Two studies found that those with lower limb CRPS had poorer outcomes than those with upper limb CRPS, in terms of risk for complications and delayed return to work (Dumas et al., 2011; van der Laan et al., 1998). However one high quality study found that those with upper limb CRPS were more likely to fall into a poorer outcome cluster (de Mos et al., 2009b), and three studies found that the location of the CRPS did not affect outcomes (Dauty et al., 2001; Sandroni et al., 2003; Tan et al., 2009). One study reported that those with multiple joints affected by CRPS had lower chances of a cure by 12 months (Gougeon et al., 1982), and another study found that those with a distal joint affected (e.g. wrist or ankle) took longer to return to work than those with a proximal joint affected (e.g. shoulder, knee) (Dauty et al., 2001). Overall it appears that results are conflicting regarding the influence of CRPS location on outcomes.
Triggering Event

Two studies reported that having CRPS triggered by a fracture had a favourable prognosis compared to other triggering events (e.g. surgery) (de Mos et al., 2009b; Sandroni et al., 2003). In contrast, two further studies reported that trauma history and trauma type did not influence outcome (Tan et al., 2009; van der Laan et al., 1998). One study reported that having an idiopathic-onset was associated with a more favourable outcome compared to those where the CRPS was triggered by an injury (Bejia et al., 2005). However another study, which was not specifically designed to look at prognosis, found that having a spontaneous onset of CRPS was associated with both a familial history of CRPS and with more severe complications (de Rooij et al., 2009a). One study found that those whose CRPS onset was delayed following the injury were at risk of poorer outcomes (Bejia et al., 2005).

In terms of injury severity, one study reported that a more serious trauma led to poorer work outcomes (Dauty et al., 2001), and another found that those with a more severe fracture, or with a displaced fracture of the ulnar styloid, had poorer range of motion outcomes than those with less severe fractures (Laulan et al., 1997). However the same study also stated that fracture type did not influence outcome, so the findings are unclear. Overall, it appears that researchers have not systematically studied the influence of the nature of the triggering event on the prognosis of CRPS, and studies have each looked at differing aspects of the injury, and have found inconsistent results.

Delay

Four studies reported that a delay to receive a diagnosis or treatment was associated with poorer outcomes, including poorer outcome scores, a weaker limb, a reduced chance of cure, and slower return to work (Dumas et al., 2011; Ehrler et al., 1995; Ogilvie-Harris & Roscoe, 1987; Zyluk, 1998b). This appears to be a fairly consistent and undisputed finding, with no studies reporting otherwise. However it is unclear whether this is due to the delay per se, or due to the fact that any group of patients identified late may form a cohort which necessarily excludes patients who might have had a fast and spontaneous resolution of symptoms. Additionally, early identification allows early and more effective intervention which could explain this finding.

Other Factors

Two studies found that higher CRPS severity scores in the early stages predicted poorer outcome (Laulan et al., 1997; Vaneker et al., 2006). Other studies found no evidence that treatment history affects outcome (Dumas et al., 2011; Laulan et al., 1997), or that co-morbid conditions have any influence on prognosis (de Mos et al., 2009b; Dumas et al., 2011). No studies found an influence of radiographic or scinitgraphic findings on prognosis (Zyluk, 1998b).
Demographic Factors

Sex
Three studies found that women experienced greater complications, poorer quality of life and had a decreased chance of cure compared to men (Gougeon et al., 1982; Tan et al., 2009; van der Laan et al., 1998). However three studies reported that sex was not associated with outcomes (Dumas et al., 2011; Sandroni et al., 2003; Zyluk, 1998b), and one found that men took longer to recover from CRPS than women (Bejia et al., 2005). Thus overall the research is not conclusive regarding the influence of gender on prognosis in CRPS.

Age
Two studies found that younger age was a risk factor for poorer outcomes, including significant complications (Bejia et al., 2005; van der Laan et al., 1998), which is in keeping with genetic studies that suggest a more severe CRPS subtype can affect younger people (de Rooij et al., 2009a). However five studies found that age was not a significant predictor of outcomes in CRPS (de Mos et al., 2009b; Dumas et al., 2011; Laulan et al., 1997; Sandroni et al., 2003; Tan et al., 2009). Thus, overall it does not appear that age has a robust influence on CRPS prognosis. However, only four of the eight studies which looked at age as a predictor included children and/or adolescents.

Work-related factors
Three studies found that work-related factors affected CRPS outcomes. Those with manual or non-sedentary jobs were more likely to experience long-term deficits in range of motion (Laulan et al., 1997), and to have greater difficulty returning to work (Dauty et al., 2001; Dumas et al., 2011). Whilst one study reported that having a workplace injury as the trigger for CRPS had a negative influence on return to work (Dauty et al., 2001), another found that the injury location (work vs. not work) did not influence the chance of cure (Eulry et al., 1990). Overall the research suggests that workplace factors are likely to have an influence on work outcomes in CRPS but there is insufficient evidence regarding any influence on clinical outcomes.

Psychological Factors
Only four studies have assessed the role of psychological factors in predicting the prognosis of CRPS. One reported that amongst those whose CRPS had not been triggered by an injury, those with ‘psychological background’ took around 3 months longer to recover from CRPS (Eulry et al., 1990). In contrast, Zyluk (1998b) reported that those who were psychologically ‘labile’ were not at risk of poorer outcomes compared to those who were psychologically ‘stable’. Unfortunately these terms were not defined in the paper and no description is given of their measurement. Harden and
colleagues (2010b) found that after knee replacement, patients who experienced an increase in anxiety and depression in the first 4 weeks had higher CRPS severity scores at 6-month follow-up. Increases in depression also predicted severity scores at 12 months, though levels of anxiety and depression measured prior to surgery did not influence outcomes significantly. A further study mentions psychological factors as a limitation for several CRPS patients to return to work, noting that patients with chronic alcoholism or depression failed to return to work, but the study had no measure of depressive symptoms or alcohol consumption so could not test this statistically (Dauty et al., 2001). Overall, it appears that the literature assessing the influence of psychological factors on the prognosis of CRPS has been limited in the following ways: It has not followed any theoretical models, some of the studies have been conducted retrospectively, psychological factors and outcomes have often been poorly defined and measured, and generally multivariate statistics have not been used to control for covariates.

**Could Psychological Factors Influence the Course of CRPS?**

The biopsychosocial model of pain proposes that social, psychological and biological processes interact to influence pain, and extensive research has found that psychological factors influence pain and disability in pain conditions other than CRPS. Such psychological factors include perceptions or beliefs about one’s condition, expectations of pain or recovery, mood, learning history, fear of movement or re-injury, and one’s thoughts about pain (for example, catastrophic thoughts). These factors have been shown to influence pain in other conditions such as neck pain, low back pain or post-surgical pain (Carroll et al., 2009; Hinrichs-Rocker et al., 2009; Melloh et al., 2009). A smaller body of research has sought to explore these potential relationships in CRPS using cross-sectional studies or other designs, and will be discussed below.

**Mood**

*Mood Changes in CRPS Patients*

Several studies have explored the impact of CRPS on mood. It is highly likely that the pain and limited limb function experienced during CRPS would lead to some mood disturbance, such as feelings of frustration, sadness or anger, and research generally supports this idea. Galer, Henderson, Perander, & Jensen (2000) found that around three-quarters of a sample of chronic CRPS patients reported that CRPS interfered with their mood. Feldman, Downey, & Schaffer-Neitz (1999) had 109 CRPS patients complete daily diaries of pain, mood, conflict and perceived support. They found that having high levels of pain on the previous day led to increased levels of depression, anger, anxiety, negative mood and conflict on the present day. Also, social support buffered the effect of pain on mood, so that those with better support experienced less distress in response to their pain. A more recent diary
study found that pain was associated with poorer mood on the same day, but did not predict poorer mood the following day (Cho, McCracken, Heiby, Moon, & Lee, 2013). Huge et al. (2011) found significant correlations between pain, disability, depression and post-traumatic stress symptoms. Thus it is highly likely that CRPS leads to significant mood disturbance. There may be particular symptoms of CRPS that interfere with mood more than others. For example, Rommel et al. (2005) found that CRPS patients with allodynia were more distressed than those without allodynia, and Huge et al. (2011) found that hyperalgesia was associated with a measure of post-traumatic stress symptoms. In addition, Vouilloz et al. (2011) reported that amongst both patients with CRPS of the knee and those with other knee pain conditions, those with higher levels of pain were more likely to have psychiatric diagnoses. Overall, it seems fairly clear that CRPS can have a significant effect on mood.

*Does Mood Influence Pain or Symptoms in CRPS?*

A small number of studies have sought to determine whether or not mood influences pain or other symptoms in CRPS. The same diary study mentioned above found that in addition to the impact of pain on mood, there was an effect of mood on pain: those who were more depressed on the previous day had higher pain scores on the present day (Feldman et al., 1999). This study suggests that associations between pain and distress in CRPS are bidirectional, and could form a vicious cycle. Bruehl et al. (1996) assessed relationships between pain and depression/anxiety in CRPS, limb pain and low back pain patients. They found that relationships between distress and pain tended to be higher in those with CRPS or limb pain compared to low back pain patients. This study was unable to assess the direction of these relationships, but the authors suggested that such relationships could be mediated by emotional arousal and SNS activity for CRPS patients. The same group of authors also studied anger expression in CRPS and limb pain patients, and found that whilst ‘anger-out’ (expressing ones anger) was associated with lower pain ratings in limb pain patients, ‘anger-out’ was associated with higher pain for CRPS patients. Again the authors propose that the pain in CRPS might be more responsive to emotional states than other types of pain due to the influence of catecholamines or sympathetic arousal on pain. A recent study also showed that intrusive thoughts (particularly about one’s injury) were correlated with pain intensity, and independently predicted disability and quality of life (Lohnberg & Altmaier, 2014). Shin et al. (2013) investigated the ability of CRPS patients to recognise emotions from another’s eyes, and found that they performed more poorly on this task than healthy controls, and that scores correlated with affective pain scores, indicating that there is a relationship between emotional recognition and pain in CRPS patients. Thus there is a small body of evidence suggesting that mood or other aspects of one’s emotional state might influence pain experience in CRPS. This would not be surprising given the large body of
evidence from other conditions and even experimental settings, showing that depression and anxiety influence pain (Bair, Robinson, Katon, & Kroenke, 2003).

**Evidence From Other Pain Conditions**

Systematic reviews conducted in various pain conditions have shown that there is generally evidence that depression, anxiety and distress were associated with poorer prognosis. Ten systematic reviews found that these factors influence outcomes for back, neck, and musculoskeletal pain, as well as for chronic post-surgical pain and pain after significant orthopaedic trauma (Carroll et al., 2009; Clay et al., 2012; Crook, Milner, Schultz, & Stringer, 2002; Hinrichs-Rocker et al., 2009; Kent & Keating, 2008; Linton, 2000; Mallen, Peat, Thomas, Dunn, & Croft, 2007; Melloh et al., 2009; Pincus, Burton, Vogel, & Field, 2002; Pincus, Vogel, Burton, Santos, & Field, 2006). One study reported evidence that anxiety and depression do not influence work-related outcomes for low back pain (Iles et al., 2009), and two reviews found that there was insufficient evidence regarding anxiety and depression to conclude whether these factors influence prognosis (Ramond et al., 2011; Steenstra, Verbeek, Heymans, & Bongers, 2005). Overall the weight of the evidence suggests that poorer mood is associated with negative outcomes for pain patients.

As yet only the few studies mentioned above have assessed the role of mood or distress in influencing the course or outcomes of CRPS prospectively, and none have been specifically designed for this purpose. One goal of the present body of research is to evaluate the influence of mood on the outcomes of CRPS.

**Catastrophic Thinking, Fear and Avoidance**

The fear-avoidance model shown in Figure 1 proposes that in the presence of pain, a cycle can occur whereby negative affect and threatening illness information lead to catastrophic thinking (defined as a tendency to ruminate about pain, feel helpless in its presence, and to magnify pain sensations) (Sullivan, Bishop, & Pivak, 1995). This catastrophic thinking can lead to fear of pain or re-injury, and avoidance of activity. This is proposed to lead to disuse, depression and disability, which in turn exacerbate pain. The same model also proposes that if those in pain do not experience fear, they will confront potentially painful activities and recover (Vlaeyen et al., 1995). This model has been influential in the understanding and management of chronic pain conditions such as back or neck pain.
Evidence from other pain conditions

A number of systematic reviews have assessed the influence of aspects of the fear-avoidance model on pain outcomes, and these have demonstrated mixed evidence. All reviews that assessed pain-related fear were conducted in neck and/or back pain samples. Seven systematic reviews found evidence that greater levels of pain-related fear lead to poorer outcomes (Carroll et al., 2009; Crook et al., 2002; Iles, Davidson, & Taylor, 2008; Kent & Keating, 2008; Linton, 2000; Melloh et al., 2009; Shaw, Pransky, & Fitzgerald, 2001), and another reported that pain-related fear was associated with poor work outcomes for patients with subacute low back pain but not for those with very recent onset pain or those with chronic pain (Wertli et al., 2013). However, three systematic reviews evaluated the evidence and concluded that higher pain-related fear does not influence outcomes, including one systematic review that was designed only to assess pain-related fear and very carefully assessed the evidence (Pincus et al., 2002; Pincus et al., 2006; Verkerk, Luijsterburg, Miedema, Pool-Goudzwaard, & Koes, 2012). These inconsistencies in the literature might be due to differences in the outcome measures assessed, as many of the reviews note that pain-related fear was most strongly associated with work outcomes, and that relationships are stronger when questionnaires assess work-specific pain-related fear. In addition, research suggests that not all pain patients are fearful and avoidant, and it might be that pain-related fear is only disabling for those with the highest levels of pain-related fear (Wertli, Rasmussen-Barr, Weiser, Bachmann, & Brunner, 2014), which could limit the findings of studies which look for relationships whilst measuring fear-avoidance on a continuous scale.
Many studies have assessed the possible influence of coping strategies and/or catastrophic thinking (which is often measured as one of a list of coping strategies) on the prognosis of pain conditions, and nine systematic reviews reported that poor or passive coping strategies are associated with adverse outcomes such as pain, disability and poorer return to work (Carroll et al., 2009; Chou & Shekelle, 2010; Kent & Keating, 2008; Linton, 2000; Mallen et al., 2007; Melloh et al., 2009; Pincus et al., 2002; Ramond et al., 2011; Shaw et al., 2001). These systematic reviews have synthesized data from samples of back, neck, and musculoskeletal pain patients. Several systematic reviews have particularly mentioned that catastrophic thinking negatively influences outcomes (Linton, 2000; Pincus et al., 2002). No systematic reviews found that coping strategies were not linked to outcome, but Ramond et al. (2011) found that the evidence was mixed, with around half of the studies showing support for the influence of coping strategies, whilst around half did not.

**Catastrophising and Pain-Related Fear in CRPS**

A small number of studies have assessed concepts of pain-related fear in CRPS patients. Moseley et al. (2008b) had CRPS patients perform ‘imagined movements’ (where they had to imagine putting their painful limb into particular positions) and found that this increased the pain and swelling of the limb. This effect was greatest in those with high levels of catastrophic thinking and pain-related fear, supporting the idea that pain-related fear might influence CRPS symptoms. de Jong, Vlaeyen, de Gelder, & Patijn (2011) found that pain-related fear (measured using a limb specific photographic rating scale) was a significant predictor of disability and pain severity in chronic CRPS patients. For lower limb CRPS patients, this photographic assessment score explained 48% of the variance in pain severity, whilst for upper limb CRPS, it explained 54% of the variance in pain severity. However this study and one other found no association between pain-related fear (as measured by the Tampa Scale for Kinesiophobia (Miller, Kori, & Todd, 1991)) and disability (de Jong et al., 2011; Marinus et al., 2013). Marinus and colleagues (2010) also measured coping strategies in a group of 238 lower limb CRPS patients using the Pain Coping Inventory. They found those who used the strategies “resting” or “reducing demands” (i.e. those more likely to avoid activity) were more disabled than those who didn’t use those strategies, and these variables were significant predictors of disability even after including CRPS severity and pain intensity into the predictive model.

Several studies have assessed the efficacy of treatment aimed at reducing pain-related fear in CRPS. Such treatment aims to expose patients to their feared activities in a graded manner to extinguish the fear response. de Jong et al. (2005) used a multiple baseline design to investigate the effectiveness of exposure therapy in 8 chronic CRPS patients (all female) who all scored high on measures of pain-related fear. The intervention was highly effective, leading to large reductions in pain and disability,
and the virtual eradication of other limb symptoms in all participants by 6 months. Two further studies have tested the efficacy and safety of similar interventions labelled ‘pain exposure physical therapy’ and delivered by physiotherapists, and both have shown that at follow-up there were large clinically relevant improvements in pain and function (Ek et al., 2009; van de Meent et al., 2011). None of these studies have included control groups, though two included a multiple baseline design. It is not clear whether it is the reduction in fear per se that led to the changes or the increase in movement, or a combination of the two. Interestingly, treatments such as graded motor imagery and mirror therapy may also provide ‘exposure’ to feared activities, and it is possible that the effectiveness of these therapies is at least partly attributable to this.

As yet, no prospective studies have assessed the possible prognostic value of pain-related fear or catastrophising measures in CRPS. Given the research from other pain conditions, the cross-sectional data in CRPS and the effectiveness shown from uncontrolled treatment trials of exposure to feared activity, this is a promising area for research. One goal of the present body of research is to assess the influence of pain-related fear and catastrophic thinking on the outcomes of CRPS.

**Possible Mechanisms Linking Psychological and Physiological Processes in CRPS**

There are a number of possible mechanisms by which psychological factors could influence pain and symptoms in CRPS. There is a small amount of research that has measured psychological and physiological processes, and this is presented below, along with hypothesised pathways by which such influences could occur.

*Behavioural Mechanisms: Avoidance, Disuse & ‘Neglect’*

As mentioned above, the fear-avoidance model proposes that those who are fearful of, and avoid movement and activity will become increasingly disabled. In addition, the demotivation that accompanies depression could also lead to reduced activity levels. CRPS patients’ limbs may be immobilized with casts or splints for various reasons (for example post-fracture), but CRPS patients may also wear splints and aides voluntarily if they are fearful of reinjuring the limb. Furthermore, healthcare providers who are fear-avoidant themselves may prescribe such devices and reinforce patients’ fears. CRPS patients may also avoid movement without necessarily using splints, and this tendency has been observed to occur so strongly it has been labelled ‘neglect’ or ‘body perception disturbance’ (Lewis & McCabe, 2010) (see Chapter 2). Researchers have speculated that disuse and/or immobilisation could significantly contribute to many of the symptoms of CRPS and found some support for this hypothesis. For example, Singh & Davis (2006) found that even 30 minutes of immobilisation of one arm leads to colour and temperature differences between the arms. Studies of
cast immobilization of one arm for approximately one month show that this leads to cold hyperalgesia, reduced pain thresholds, and temperature differences between the limbs in healthy volunteers (Terkelsen et al., 2008), as well as cold and mechanical hyperalgesia, pain, oedema and temperature changes, and elevated levels of inflammatory cytokines in hand surgery patients (Pepper et al., 2013). The authors also reported that this increase in inflammatory markers was associated with pain levels a month later, suggesting that pain might result from disuse via inflammatory mechanisms. Thus it is possible that patients who feel distressed, helpless or fearful neglect using their limb to a greater degree and this neglect or disuse could exacerbate or prolong CRPS symptoms.

Autonomic Nervous System Activity & Impaired Immunity

Another possible mechanism that could link psychological factors to CRPS symptoms is activity of the autonomic nervous system. The influence of psychological factors such as stress or depression on autonomic activity is well established (Menezes Costa, Maher, Hancock, McAuley, Herbert, & Costa, 2012). As mentioned in Chapter 2, SNS activity is thought to play a significant role in the pathophysiology of CRPS. For example, altered vasoconstriction responses to sympathetic challenge have been demonstrated in CRPS patients (Wasner, 2010), and have been shown to differentiate between those who go on to develop CRPS and those who do not post-fracture (Schurmann et al., 2000). In addition, animal research has demonstrated that sympathetic-afferent coupling can occur, whereby nociceptors start to express adrenoceptors, so that circulating catecholamines can directly trigger nociception (Gibbs, Drummond, Finch, & Phillips, 2008).

Thus theoretically, any psychological state which influences SNS activity could influence CRPS. This has been the topic of only two studies, but both suggest this may be the case. Harden and colleagues (2004) measured plasma levels of norepinephrine and epinephrine in venous blood samples from 33 upper limb CRPS patients attending a chronic pain programme, and 33 healthy volunteers. They also measured depression, anxiety and personality in a subsample of 18 of the CRPS patients. They found higher circulating levels of norepinephrine and a non-significant trend for high levels of epinephrine amongst the CRPS patients compared to controls. They also found that those with higher levels of epinephrine had higher scores for depression, somatic focus, paranoia and avoidance/denial. The authors suggest that in CRPS, distressed patients with higher levels of circulating catecholamines could develop higher levels of pain, as the catecholamines can induce peripheral sensitization. Alternatively, if sympathetic-afferent coupling occurs, circulating catecholamines might directly trigger nociception. The authors propose that elevated levels of epinephrine and norepinephrine could be due to pain, distress or a combination of the two, though they note that patients with other chronic pain conditions do not have elevated levels of catecholamines. It is also possible that this
elevation of catecholamines reflects a premorbid state of adrenergic hyperactivity, which could predispose to CRPS. Notably, this study only included participants who had responded with pain reduction to a sympathetic ganglion block, and this could at least in part explain differences between patients and controls.

This study was extended by Kaufmann et al. (2007), who also found that CRPS patients have elevated levels of norepinephrine, a nonsignificant trend for higher levels of epinephrine (compared to healthy controls), impaired neutrophil function and high post-traumatic stress scores (compared to population norms). The study showed that CRPS patients had impaired plasma-enhanced phagocytosis, which is important for producing an effective antimicrobial response as well as for the removal of cellular debris after tissue trauma. The extent of this impaired phagocytosis was correlated with stress scores but could only partly be explained by the altered levels of catecholamines. Overall, the authors suggest that for CRPS patients, stress and the associated SNS activity and increase in catecholamines might at least in part lead to impaired innate immunity which could in turn influence pain and symptoms in CRPS.

Thus the research suggests that psychological factors influence autonomic activity and that autonomic activity plays a role in CRPS. It therefore follows that if psychological factors are related to the outcomes of CRPS, this effect could be mediated by autonomic activity.

**Endogenous Pain Modulation Systems**

Another possible mechanism by which psychological factors could influence CRPS is via the endogenous opioid system. Research on the placebo effect has shown that psychological factors have a powerful influence on the release of endogenous opioids (Wertli et al., 2014), and changes in central opioid neurotransmission are associated with other clinical pain states such as fibromyalgia (May & Rosedale, 2009). It is possible, therefore, that psychological factors influence pain via similar mechanisms in CRPS. As mentioned in Chapter 2, a study by Klega et al. (2010) found that compared to healthy controls, CRPS patients had decreased opioid receptor availability in several brain areas contralateral to the affected limb (amygdala, parahippocampal cortex), and increased availability in several contralateral brain areas. For several brain regions, those with greater pain, depression and anxiety had lower receptor availability, suggesting that those who were distressed had limited ability to utilise endogenous opioid analgesia. Research from non-pain patients has shown that sad emotions down-regulate opioid systems in depressed women (Carroll et al., 2009). Thus it is possible that negative emotional states lead to a state whereby endogenous opioids are less effective at reducing the pain of CRPS.
Endogenous pain modulation was also investigated in a study which induced pain in CRPS patients and controls during fMRI scanning, and asked subjects to suppress their pain as best they could (for example, with distraction). Both CRPS patients and healthy controls were able to suppress pain, but brain imaging from fMRI showed healthy controls were better able to activate several of brain regions associated with endogenous analgesia (periaqueductal grey and cingulate cortex) than CRPS patients (Freund et al., 2011). This suggests that CRPS patients may be less able to use psychological techniques to influence pain.

**Neuroplastic Changes in the CNS**

As discussed in Chapter 2, there are a number of changes that occur in the CNS of CRPS patients, including possible changes at the level of the spinal cord, alterations to the representation of the hand on the somatosensory and motor cortices, and structural changes to grey matter. Whilst no definitive studies have shown whether such changes are a cause or consequence of CRPS, treatments aimed at reversing such changes have demonstrated some clinical efficacy (Moseley, 2004a). A number of factors have been shown to be moderate neuroplasticity (mainly in animal research), including environmental enrichment, exercise, learning, brain stimulation and treatment with psychotropic medication (Granovsky, 2013). In addition, chronic stress, anxiety and depression have been shown to suppress neurogenesis, alter neuronal replacement, dendritic remodelling and synapse turnover (Campbell, Wynne-Jones, Muller, & Dunn, 2013; Granovsky, 2013). It is therefore possible that emotional states moderate the neuroplastic changes that accompany CRPS, and which could play either a causative or maintaining role in the condition.

Only one study has assessed the potential for psychological factors to influence CRPS via an effect on the neuroplasticity. Geha et al. (2008) found that CRPS patients have regional grey matter atrophy and disrupted grey-white matter relationships compared to healthy controls. Whilst these changes are considered to be a consequence of pain, they may also contribute to the long-term maintenance of the condition. Interestingly this study found that the strength of connectivity between several atrophied brain areas (ventromedial pre-frontal cortex and nucleus accumbens) was correlated with two anxiety measures (the Pain Anxiety Symptoms Survey, which is a measure of pain-related fear, and the Beck Anxiety Inventory, a measure of clinical anxiety). This study suggests that in the presence of anxiety, maladaptive plastic brain changes could be heightened in CRPS, and in turn it is possible that these plastic changes cause or maintain symptoms of CRPS. As yet no studies have assessed the influence of psychological factors on the neuroplastic changes that occur in the somatosensory and motor cortices of CRPS patients.
Conclusions

Very little research has assessed prognostic indicators in CRPS. Those studies that have demonstrated that initially cold skin temperature and pain or sensory symptoms are likely associated with poorer outcomes. Research from other pain conditions has provided fairly convincing evidence that psychological factors such as depressed or anxious mood, catastrophic thinking, and pain-related fear are associated with poorer long-term outcomes, but these variables have not been prospectively studied in CRPS. There are a number of possible mechanisms by which such variables might influence pain or symptoms in CRPS. It is possible that neglect, disuse or immobilization resulting from distress influences or drives CRPS symptoms. It might be that the increased SNS activity and inflammatory changes that result from psychological distress influence symptoms. Another possibility is that opioid systems are interrupted by psychological states, heightening pain. Finally, it is possible that psychological distress influences neuronal plasticity, leading to a heightened propensity for maladaptive plastic changes in the CNS.
Chapter 5: Relationships between Psychological factors, Pain and Disability in Complex Regional Pain Syndrome and Low Back Pain

Prelude

Rationale

As discussed in Chapters 2 and 4, whilst the evidence suggests that psychological factors are unlikely to cause CRPS, this body of research has tended to follow a dualistic, or Descartian model of health, seeing mind and body as separate, and seeking to find either biomedical or psychogenic causes of CRPS. In contrast, relatively little research has sought to explore the influence of psychological factors on symptom experience, function or recovery in CRPS, which might be considered a normal process. An extensive body of health psychology literature and theory supports the idea that psychological factors influence symptom perception, health behaviour and disability (Miller, Chen, & Cole, 2009), and there is no reason to suggest that this would not also be the case with a condition such as CRPS. Cognitive-behavioural models such as the fear-avoidance model propose that a relatively normal human response to pain (fear and avoidance) can lead to disuse, depression and disability and contribute to ongoing pain experience, and could therefore influence recovery (Vlaeyen, Linton, Boersma, & De Jong, 2012). However, in contrast with other pain conditions, relatively little research has evaluated this model in CRPS. The small number of studies that have explored relationships between psychological factors such as anger expression, daily mood states, catastrophic thinking or coping style and outcomes (such as pain levels, disability or even symptoms such as swelling), have shown that CRPS symptoms are influenced by psychological factors (Bruehl et al., 2003; Feldman et al., 1999; Marinus et al., 2013; Moseley, 2004b). However as yet, no published studies have been conducted with the primary aim to explore the influence of such factors on the recovery process, which is the overall goal of this thesis.

As also discussed in Chapter 4, one condition for which the role of psychological factors in the recovery process is established is low back pain. Systematic reviews of prospectively conducted studies have found evidence that depression, anxiety, pain-related fear and catastrophic thinking predict the development of chronic pain and/or disability following acute low back pain (Kent & Keating, 2008; Linton, 2000; Melloh et al., 2009). Thus it was hypothesized that if similar relationships exist in CRPS compared to low back pain, such relationships are likely to be meaningful.
The study presented here in Chapter 5 is a cross-sectional study, designed to assess whether pain and disability in CRPS are associated with three psychological variables: depression, anxiety and pain-related fear. These three variables were chosen based on the fear-avoidance model. Although the data is cross-sectional and therefore cannot provide evidence of the direction of relationships, it was hypothesized that if similar relationships existed between psychological factors and pain/disability in CRPS compared to low back pain, this would provide a justification for later exploring such relationships prospectively.

One previous study has followed a similar methodology: Bruehl et al. (1996) compared relationships between psychological distress (depression, anxiety and phobic anxiety) with both the sensory and affective domains of pain, and found that patients with CRPS had stronger relationships between distress and pain compared to low back pain patients. However this study was limited to CRPS patients whose pain responded to a sympathetic blockade and this likely constitutes a different sample to those who would meet today’s diagnostic criteria for CRPS. Additionally it may inflate relationships between distress and pain for this group (i.e. because those for whom a reduction in sympathetic activity leads to a reduction in pain may also be a group for whom an increase in sympathetic activity due to distress also influences pain levels). Also, Bruehl et al.’s (1996) study was not designed to look at components of a theoretical model such as the fear-avoidance model and therefore did not assess disability or pain-related fear. Thus the following study aimed to take a broader approach to exploring psychological factors in CRPS and low back pain.

Aims

1. To determine whether psychological variables based on the fear-avoidance model (pain-related fear, depression and anxiety) are associated with pain levels and disability amongst a sample of CRPS patients.
2. To compare the strength of these relationships to the relationships from an age-, sex-, and pain-duration-matched sample of low back pain patients.

Citation

Abstract

Objective: Cognitive and emotional factors are known to influence patients’ pain experiences in many conditions, including low back pain. However in complex regional pain syndrome (CRPS), their role is unclear. This study aimed to assess the relationships between psychological factors, pain and disability in CRPS, compared to low back pain. This could help to identify target variables for psychological treatment.

Methods: 88 CRPS patients and 88 low back pain patients completed measures of pain, disability, depression, anxiety, and pain-related fear. Mean scores between the two groups were compared, and correlations between psychological factors, pain and disability were compared between the two groups. Predictors of pain and disability were assessed using multiple regression analyses.

Results: The two groups had remarkably similar scores on measures of pain, disability, depression, anxiety, and pain-related fear. In both groups, those who were more depressed, anxious and fearful of pain were more disabled. For the CRPS group (but not the low back pain group), pain intensity significantly correlated with distress. Multivariate analyses showed that the unique predictors of disability for the two groups were pain and depression, and that depression had a stronger relationship with disability for the CRPS group. For both groups, pain intensity was predicted by pain-related fear, and anxiety was a unique predictor in the CRPS group only.

Discussion: In CRPS, disability and pain severity were more strongly associated with psychological factors than they were in low back pain. Cause and effect relationships could not be established by this cross-sectional study.
Introduction

A large body of literature has demonstrated that psychological and social factors influence people’s experience of pain in a variety of contexts, including experimental, acute, procedural, and chronic pain (Morley, 2008). The range of psychological factors that influence pain includes mood, cognitions and expectations, behavioural patterns, attentional states, and learning history. Whilst such psychological factors have been demonstrated to influence pain and disability in a range of chronic pain conditions, there have been relatively few studies demonstrating a significant influence of psychological factors in complex regional pain syndrome (CRPS). In fact, a recent systematic review identified no relationship between a number of psychological factors and CRPS type 1, except for a possible association of CRPS with more life events (Beerthuizen, van t Spijker, Huygen, Klein, & de Wit, 2009). Another recent literature review identified that there is no evidence that personality or psychopathology play a causal role in CRPS, however it did find that CRPS leads to a sequelae of negative psychological and social consequences (Lohnberg & Altmayer, 2013). Prospective studies which have measured psychological factors amongst a cohort of fracture, surgery or stroke patients then assessed patients at a later date for CRPS have reported few psychological risk factors for CRPS development (Beerthuizen et al., 2011; Dilek et al., 2012; Harden et al., 2003; Puchalski & Zyluk, 2005). There are no published randomised controlled trials of psychological treatments for CRPS, although smaller trials have provided some evidence of the efficacy of exposure based therapies aimed at reducing patients’ fear of movement or re-injury (de Jong et al., 2005; van de Meent et al., 2011).

Despite this lack of research, patients with longstanding CRPS are often treated in interdisciplinary pain clinics where psychological therapies are recommended and provided. The 2012 Royal College of Physicians’ guidelines recommends that psychological intervention is one of the four main arms of treatment for CRPS (Goebel, Barker, Turner-Stokes, & al., 2012). Psychologists providing this treatment likely generalise from the research on other chronic pain conditions in order to identify appropriate target variables for treatment and set treatment goals and activities. One such condition is low back pain, where a large body of literature has established the importance of psychological factors in predicting pain intensity and heightened disability (Nicholas, Linton, Watson, Main, & "Decade of the Flags" Working Group, 2011). Systematic reviews have shown that psychological factors such as depression, fear of movement and re-injury (pain-related fear), catastrophic thinking and poor expectations predict the progression of low back pain from an acute to a chronic timeframe (Chou & Shekelle, 2010; Heitz et al., 2009; Iles et al., 2008). Randomised controlled trials have demonstrated the efficacy of behavioural treatments for low back pain, at least in the short term (Henschke et al., 2010).
There are several possible reasons why previous research has not demonstrated a relationship between psychological factors and CRPS. On the one hand, it might be that no such relationship exists. On the other hand, it might be that previous research has suffered from methodological shortcomings, or has not assessed the right relationships. This may in fact be the case, as much of the previous research on psychological factors in CRPS has been based on a dualistic model of health and has sought to find psychological causes for CRPS (as mentioned above), or has focused on identifying psychopathology or personality disorders amongst these patients over and above what would be expected of a sample of people in pain (Monti et al., 1998; Nelson & Novy, 1996). This may be because was traditionally CRPS was stigmatized as ‘psychogenic’ (Feliu & Edwards, 2010; Katz et al., 1986; Zucchini et al., 1989). Research from other fields of pain has adopted a biopsychosocial model and suggests that psychological factors are not usually a singular cause of pain, but that unhelpful psychological and physical factors interact to produce heightened pain and disability. In line with this, the small number of studies that have aimed to identify more subtle influences of psychological factors on pain and disability in CRPS have shown some interactions between mood and pain levels (Feldman et al., 1999), anger-expressiveness and pain severity (Bruehl et al., 2003), and fear of movement and disability (de Jong et al., 2011; Moseley, 2004b). A prospective study reported that early increases in depression after knee replacement were associated with CRPS severity at 12 months, suggesting that psychological factors may interact with pain over time, leading to poorer outcome (Harden et al., 2010b). Bruehl and colleagues (1996) compared CRPS patients with non-CRPS limb pain and low back pain patients and found that whilst there were few differences between the groups on measures of distress, there were stronger relationships between distress and pain severity for the CRPS and limb pain groups than the low back pain group.

The aim for the present study was to further assess associations between distress and pain in CRPS, and to compare the strength of any associations with a sample of patients with low back pain. We aimed to further extend the findings of Bruehl et al. (1996) by also looking at the role of pain-related fear as a predictor variable and to look at disability as well as pain severity as outcome variables. Low back pain was chosen because in this group previous research demonstrates the importance of psychological factors, and therefore we hypothesized that if there were similarities between CRPS and low back pain groups these would be meaningful.

**Methods**

**Participants**

The participants were 88 consecutive CRPS patients and 88 low back pain patients seen at The Auckland Regional Pain Service (Interdisciplinary Pain Centre) between January 2009 and December
2011. The samples were matched for age, gender and pain duration and thus the low back pain patients were not a consecutive sample. Patients experiencing both CRPS and low back pain concurrently were excluded. The interdisciplinary pain centre typically sees patients with chronic pain who are referred after multiple treatments and who have seen specialists from other disciplines, and thus both samples are likely to be those severely affected by pain who have been difficult to treat. Both CRPS Type 1 and 2 were included in the CRPS sample. Patients in the low back pain sample were included if their primary complaint was pain in the low back and/or leg and this included patients with nonspecific back pain as well as other causes of low back pain.

**Procedure**

The study was a retrospective review and analysis of routinely administered psychological scales and medical records. The observational study was approved by the New Zealand Ministry of Health Northern X Ethics Committee. Patients were identified using previous clinic lists which code patients’ pain problems according to pain location. The first author searched the initial assessment reports from all patients coded with upper or lower limb pain to determine whether the patient was diagnosed with CRPS during their medical assessment at the interdisciplinary pain centre. CRPS is only diagnosed at the pain centre following a comprehensive assessment and examination by pain specialist doctors, and patient records were checked to ensure that patients met the 1994 IASP-Orlando criteria for CRPS (Merskey & Bogduk, 1994). The first author also searched the records of all patients coded with low back pain to determine whether this diagnosis was confirmed during the patient’s comprehensive assessment at the pain centre.

The following data were extracted from electronic patient records: age, gender, ethnicity, pain duration, condition (CRPS or low back pain), CRPS limb, and employment status (working or not working). The following scores were also extracted from questionnaires that patients are required to fill in prior to receiving an appointment, these questionnaires are scanned and stored electronically on the hospital computer system, and scores were extracted by the first author:

1. **Pain Numerical Rating Scale**: Patients were asked to rate their average pain intensity on a scale of 0 (no pain) to 10 (worst pain you can imagine).

2. **Pain Disability Index (PDI)** (Tait, Chibnall, & Krause, 1990): This seven item scale asks participants to rate their level of disability on a range of life domains. Scores range from 0 (no disability) to 70 (maximum disability).
3. Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983): This 14-item scale measures symptoms of depression and anxiety, producing two separate scores for the separate constructs. The scale is designed to limit the bias of physical health complaints on depression and anxiety scores. The scale ranges from 0 (very low levels of depression or anxiety) to 21 (very high levels of depression or anxiety). In the original paper, cut-off scores of 8 and above were suggested to identify borderline or possible cases of depression or anxiety, and scores of 11 and above were suggested to identify probable clinical cases of depression and anxiety.

4. Tampa Scale for Kinesiophobia (TSK) (Miller et al., 1991): This is a 17 item scale designed to measure pain-related fear (fear of movement and/or (re)injury). Scores range from 17 (low pain-related fear) to 68 (maximum pain-related fear).

Given that the data were collected as part of routine clinical care, there was some missing data which is reflected in the varying degrees of freedom reported for each of the statistical tests. There were more low back pain patients with full data sets (80/88) compared to CRPS patients (65/88) because when selecting matched controls for the CRPS patients, efforts were made to select those without missing data.

Data Analysis:
A power analysis was conducted using G-Power (Erdfelder, Faul, & Buchner, 1996). This was based on a 2-tailed, independent samples t-test, and demonstrated that the study had 90% power to detect a moderate effect size (d=0.5, α=.05), with 86 participants required in each group. Data were entered into SPSS for Windows. Not all variables displayed normal distributions. Thus nonparametric tests were used, but these produced the same results as parametric tests, so parametric test results are presented here for ease of comprehension.

Independent samples t-tests and chi-square tests were used to explore differences between the CRPS patients and low back pain patients on demographic details and psychometric test scores. Pearson’s correlations were used to assess relationships between pain intensity, disability scores, and scores on psychological variables for each patient group. The strength of the correlations between psychological variables and disability scores were compared between the two diagnostic groups by computing Fisher Z scores, with these compared statistically using z scores. This was done utilising the calculator from Preacher (2002).
Multiple regression analyses were used to determine unique predictors of the two dependent variables (pain and disability), and to assess whether the psychological predictors were equivalent for the two diagnostic groups. The psychological variables were entered into the regression analyses, along with diagnostic group (dummy coded), and interaction terms for each psychological variable ((psychological variable-mean of psychological variable) x diagnostic group (dummy coded)), thus the interaction terms were mean-centred. For the multiple regression with pain as the dependent variable, the residuals were not normally distributed (negatively skewed), so a square root transformation was applied to pain scores. This was successful, resulting in normally distributed residuals, so the results from the transformed data are presented.

Results

Demographics & Description of the Sample

The demographic characteristics of the two samples are described in Table 1. Because the samples were matched, there were no differences between the groups on age, gender, or pain duration. Both samples had a fairly long pain duration of approximately 3 ½ years. The CRPS patients were significantly less likely to be working, $\chi^2(1, N=172)=5.49, p=.019$ compared to the low back pain patients.

Of the CRPS sample, 66 (75%) had the upper limb affected and 22 (25%) had the lower limb affected. 40 (45%) of the CRPS patients had the left side affected, 42 (48%) had the right side affected, and 6 (7%) had CRPS affecting both sides of the body. Of the CRPS patients, 75 had CRPS Type 1 (85%), and 13 had CRPS Type 2 (15%).

We classified the low back pain patients into 3 diagnostic groups according to the guidelines of the American College of Physicians and American Pain Society (Chou et al., 2007). 72 (82%) had nonspecific low back pain, 13 (15%) had radiculopathy or spinal stenosis, and 3 (3%) had other causes of low back pain (e.g. cauda equina syndrome or vertebral compression fracture).

The percentage of patients in each group who scored above the “cut-offs” for the HADS are presented in Table 1. Over one third of each group scored over the cut-off for clinical cases of depression, and around half of each group scored above the threshold for clinical cases of anxiety disorders.
Differences Between Clinical Groups

There were no significant differences between the CRPS and low back pain samples on any of the psychometric test scores, as shown by t-tests for pain, $t(170)=-.40, p=.69$, disability, $t(159)=.46, p=.65$, depression, $t(155)=.52, p=.60$, anxiety, $t(155)=-1.08, p=.28$ and pain-related fear, $t(162)=-1.10, p=.27$. In fact, the groups scored very similarly. The results are presented in Table 9.

Table 9: Demographic Details and Psychological Test Scores for the CRPS and Low Back Pain Patient Samples

<table>
<thead>
<tr>
<th></th>
<th>CRPS  (N=88)</th>
<th>Low Back Pain (N=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>59%</td>
<td>59%</td>
</tr>
<tr>
<td>Age</td>
<td>45 (12.44)</td>
<td>45 (12.60)</td>
</tr>
<tr>
<td>Duration of pain (months)</td>
<td>43.15 (53.73)</td>
<td>43.42 (53.14)</td>
</tr>
<tr>
<td>Work status (% working)</td>
<td>20%</td>
<td>36%*</td>
</tr>
<tr>
<td>Pain (Numerical Rating Scale)</td>
<td>7.59 (1.77)</td>
<td>7.69 (1.58)</td>
</tr>
<tr>
<td>Disability (PDI)</td>
<td>44.92 (16.09)</td>
<td>43.89 (12.43)</td>
</tr>
<tr>
<td>Depression (HADS-D)</td>
<td>9.99 (4.04)</td>
<td>9.65 (4.00)</td>
</tr>
<tr>
<td>% scoring 8-10 (“borderline cases”)</td>
<td>23%</td>
<td>41%</td>
</tr>
<tr>
<td>% scoring ≥11 (“clinical cases”)</td>
<td>35%</td>
<td>38%</td>
</tr>
<tr>
<td>Anxiety (HADS-A)</td>
<td>10.34 (3.72)</td>
<td>11.06 (4.47)</td>
</tr>
<tr>
<td>% scoring 8-10 (“borderline cases”)</td>
<td>34%</td>
<td>28%</td>
</tr>
<tr>
<td>% scoring ≥11 (“clinical cases”)</td>
<td>49%</td>
<td>56%</td>
</tr>
<tr>
<td>Pain-related fear (TSK)</td>
<td>43.42 (10.17)</td>
<td>45.08 (9.11)</td>
</tr>
</tbody>
</table>

Mean (SD) displayed. *Indicates statistically significant difference at the $p<.05$ level

PDI = Pain Disability Index; HADS = Hospital Anxiety and Depression Scale; TSK = Tampa Scale for Kinesiophobia

Correlations Between Psychological Variables and Disability Scores

Correlations between pain, disability, depression, anxiety and pain-related fear for the two groups are presented in Table 10. Of particular interest, we wanted to see whether disability was associated with psychological distress. In both the CRPS and low back pain groups, all of the psychological variables significantly correlated with disability (at the $p<.05$ level), suggesting that those who were more depressed, anxious and fearful were more disabled. When we used a bonferroni correction for multiple comparisons (i.e. setting the critical p-value at 0.005 for 10 correlations), all correlations remained significant except for the correlation between pain-related fear and disability in the low back pain group. The correlation between depression and disability was significantly greater in the CRPS group than the low back pain group, $z=1.78, p=.038$. There was no significant difference between the CRPS and low back pain groups in terms of the relative strength of the correlation coefficients between disability and pain, disability and anxiety, and disability and pain-related fear.
Table 10: Correlations Among Measures of Pain Intensity, Disability, and Psychological Variables

<table>
<thead>
<tr>
<th></th>
<th>Disability</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Pain-related fear</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRPS Group:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>.552**</td>
<td>.375**</td>
<td>.384**</td>
<td>.357**</td>
</tr>
<tr>
<td>Disability</td>
<td>.561**</td>
<td>.384**</td>
<td>.426**</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>.611**</td>
<td>.507**</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td>.391**</td>
<td></td>
</tr>
<tr>
<td><strong>Low Back Pain Group:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>.403**</td>
<td>.172</td>
<td>.086</td>
<td>.231*</td>
</tr>
<tr>
<td>Disability</td>
<td>.306**</td>
<td>.334**</td>
<td>.289**</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>.595**</td>
<td>.377**</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td>.417**</td>
<td></td>
</tr>
</tbody>
</table>

* p<.05; **p<.01

Multiple Regression Analysis: Predictors of Disability

A multiple regression analysis demonstrated that the linear combination of pain, the psychological variables, diagnostic group, and interaction terms was a significant predictor of disability, accounting for about 38% of the variance in disability scores, $R^2 = .38$, $F(9, 135)=9.28$, $p<.001$. The results are presented in Table 11. Note that none of the demographic variables were significantly associated with disability, nor was pain duration, so these were not included in the analysis. The significant predictors that emerged were pain, depression, and the interaction between depression and diagnostic group. Those with greater pain intensity and who were more depressed were more disabled. Figure 2 demonstrates the interaction effect: the positive association between depression and disability was stronger in the CRPS group compared to the low back pain group.

Correlations Between Psychological Variables and Pain Scores

As shown in Table 10, in the CRPS group there were significant correlations indicating that pain intensity was associated with greater disability, greater depression, greater anxiety, and greater pain-related fear. In the low back pain group, the only psychometric variables that significantly correlated with pain intensity (at the $p<.05$ level) were disability and pain-related fear. After using a bonferroni correction for multiple comparisons (i.e. setting the critical $p$-value to 0.005 for 10 correlations), the correlations between psychological variables and pain remained significant in the CRPS group but in
the low back pain group the only correlation that remained significant was between disability and pain.

The correlation coefficient was significantly greater for the CRPS group than the low back pain group for the relationship between pain and anxiety, z=1.94, p=.03. There was no statistically significant difference in the strength of the correlations for: pain and disability, pain and depression, and pain and pain-related fear.

**Table 11: Regression Tables to Predict Disability and Pain**

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predictors of Disability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic Group</td>
<td>- .49</td>
<td>1.97</td>
<td>-.02</td>
<td>-.25</td>
<td>.805</td>
</tr>
<tr>
<td>Pain</td>
<td>3.33</td>
<td>.617</td>
<td>.40</td>
<td>5.41</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td>Depression</td>
<td>.91</td>
<td>.32</td>
<td>.26</td>
<td>2.81</td>
<td>.006**</td>
</tr>
<tr>
<td>Anxiety</td>
<td>.23</td>
<td>.32</td>
<td>.07</td>
<td>.70</td>
<td>.483</td>
</tr>
<tr>
<td>Pain-related fear</td>
<td>.06</td>
<td>.12</td>
<td>.04</td>
<td>.53</td>
<td>.598</td>
</tr>
<tr>
<td>Pain x diagnostic group</td>
<td>-.62</td>
<td>.62</td>
<td>-.07</td>
<td>-1.00</td>
<td>.318</td>
</tr>
<tr>
<td>Depression x diagnostic group</td>
<td>-.73</td>
<td>.32</td>
<td>-.21</td>
<td>-2.25</td>
<td>.026*</td>
</tr>
<tr>
<td>Anxiety x diagnostic group</td>
<td>.49</td>
<td>.32</td>
<td>.14</td>
<td>1.50</td>
<td>.135</td>
</tr>
<tr>
<td>Pain-related fear x diagnostic group</td>
<td>.05</td>
<td>.12</td>
<td>.03</td>
<td>.412</td>
<td>.681</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE B</th>
<th>β</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predictors of Pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic group</td>
<td>.03</td>
<td>.07</td>
<td>.03</td>
<td>.35</td>
<td>.730</td>
</tr>
<tr>
<td>Depression</td>
<td>-.02</td>
<td>.01</td>
<td>-.14</td>
<td>-1.36</td>
<td>.177</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-.02</td>
<td>.01</td>
<td>-.14</td>
<td>-1.29</td>
<td>.198</td>
</tr>
<tr>
<td>Pain-related fear</td>
<td>-.01</td>
<td>&lt;.00</td>
<td>-.19</td>
<td>-2.18</td>
<td>.031*</td>
</tr>
<tr>
<td>Depression x diagnostic group</td>
<td>-.01</td>
<td>.01</td>
<td>-.06</td>
<td>-.53</td>
<td>.596</td>
</tr>
<tr>
<td>Anxiety x diagnostic group</td>
<td>.03</td>
<td>.01</td>
<td>.24</td>
<td>2.27</td>
<td>.025*</td>
</tr>
<tr>
<td>Pain-related fear x diagnostic group</td>
<td>-.01</td>
<td>&lt;.00</td>
<td>-.01</td>
<td>-.15</td>
<td>.879</td>
</tr>
</tbody>
</table>

*Indicates statistically significant difference at the p<.05 level  
**Indicates statistically significant difference at the P<.01 level

**Multiple Regression Analysis: Predictors of Pain**

A multiple regression analysis demonstrated that the linear combination of psychological variables, diagnostic group, and the interaction term was a significant predictor of pain intensity, accounting for
about 16% of the variance in pain scores, $R^2 = .16$, $F(7, 142)=3.80$, $p=.001$. The results are presented in Table 11. The significant predictors that emerged were pain-related fear and the interaction between diagnostic group and anxiety. Those who had more pain-related fear had higher pain scores. Figure 3 illustrates the interaction effect and shows that a positive relationship between anxiety and pain existed for the CRPS group but not for the low back pain group.

Figure 2: Scatterplots showing the relationship between disability and depression for CRPS (panel a) and low back pain patients (panel b)
HADS = Hospital Anxiety and Depression Scale; PDI = Pain Disability Index

Figure 3: Scatterplots showing the relationship between pain and anxiety for CRPS (panel a) and low back pain patients (panel b)
HADS = Hospital Anxiety and Depression Scale; PDI = Pain Disability Index
Discussion

The present study showed that matched patients with CRPS and low back pain scored remarkably similarly on measures of pain, disability and psychological distress. Whilst some significant associations between psychological factors, pain and disability existed in the low back pain group, these tended to be stronger in the CRPS group. The only significant differences between the groups were that CRPS patients were less likely to be working. These results support several previous studies that found there were few differences between CRPS and low back pain patients on measures of distress, and the few differences that have been reported are not consistent between studies (Bruehl et al., 1996; Ciccone et al., 1997; DeGood et al., 1993; Monti et al., 1998). The present study provides further support that CRPS is not associated with a distinct psychological profile or greater level of distress compared to other people with chronic pain. Instead, it seems more likely that persistent pain leads to a pattern of psychological functioning that might be consistent between pain conditions, and this is likely a normal part of the human experience of chronic pain. We note that both groups’ psychological test scores were similar to those reported from patient groups in other interdisciplinary pain centres and published in normative data sets (Chibnall & Tait, 1994; Nicholas, Asghari, & Blyth, 2008).

The present study also found that greater disability was associated with higher levels of anxiety, depression and pain-related fear in both groups. This was further tested in a multiple regression analysis to predict disability scores, which showed that there were main effects for pain and depression, and an interaction effect of depression and diagnostic group. This means that disability was associated with depression after controlling for pain intensity, and that the relationship between depression and disability was stronger in the CRPS group than in the low back pain group. There has been very little previous research looking at factors that influence disability in CRPS. De Jong and colleagues (2011) found that perceived harmfulness of activities predicted functional limitations above and beyond pain severity in those with chronic CRPS (although not in acute CRPS). Our univariate results provide further support for the role of pain-related fear in CRPS. Overall it appears that the fear-avoidance model is promising in terms of understanding and treating disability in CRPS patients.

We also assessed the relationships between psychological factors and pain intensity. For the CRPS group, higher pain intensity was associated with greater depression, anxiety and pain-related fear. For the low back pain group, the only psychological variable that was associated with pain intensity was pain-related fear, although this relationship did not remain significant after controlling for multiple comparisons. The multivariate analyses showed that there was a main effect for pain-
related fear and an interaction between anxiety and diagnostic group. This indicates that pain-related fear is associated with pain for both groups, and that anxiety is associated with pain intensity for CRPS patients, but not for low back pain patients. We found that the psychological variables accounted for 16% of the variance in pain scores, which, if interpreted using Cohen’s effect sizes, would indicate a moderate effect size. The psychological variables, together with pain intensity, accounted for more than double the variance in disability scores (38%), which would equate to a strong effect size according to Cohen.

Our findings were also somewhat consistent with previous research which has sought to determine factors that influence pain severity in CRPS. Bruehl et al. (1996) reported that depression and anxiety were correlated with pain severity in CRPS patients, and that these correlations were stronger than those that existed in low back pain patients. The similarity of these results suggests this may be a fairly robust finding, and the present study goes further by also assessing the role of pain-related fear. Feldman et al. (1999) used a daily diary study to show that whilst pain leads to an increase in depression, anxiety and anger, depression and social support also influenced pain in CRPS. Moseley (2004b) found that catastrophic thinking about pain and pain-related fear led to greater pain intensity and swelling in response to imagined movements in CRPS.

There are several mechanisms by which psychological factors might be more strongly associated with disability and pain in CRPS than in low back pain. It is possible that psychological factors could influence CRPS symptoms via SNS activity. Research has shown that sympathetic activity influences CRPS symptoms in at least a subset of patients (Drummond, 2010), and therefore any psychological distress that causes a SNS response could influence CRPS symptoms. Another possibility is that psychological factors might have a closer relationship with CRPS compared to low back pain due to the range of symptoms experienced by CRPS patients, including swelling, colour and temperature changes, and sensory symptoms. These are more highly visible than symptoms in low back pain, so may be distressing for patients, and could reinforce fears of serious pathology, leading to poorer mood and a closer pairing of pain and distress. Rommel and colleagues (2005) reported that CRPS patients with alldynia were more distressed than those without alldynia, and it might be that the sensory abnormalities associated with CRPS also lead to a cycle of distress and avoidance, which could in turn reinforce pain and disability.

We note that our results are inconsistent with the previous prospective studies that have been conducted in CRPS, that have measured psychological factors either prior to surgery or at the time of a fracture, and found few psychological differences between those who subsequently develop CRPS.
and those who do not (Beerthuizen et al., 2011; Harden et al., 2003; Puchalski & Zyluk, 2005). This suggests that psychological factors might not be particularly important in the initial development of CRPS, and it might be that physiological factors such as neurogenic inflammation (Birklein & Schmelz, 2008) or SNS function (Schurmann et al., 2000) play a more important role at the early stage. Interestingly, a prospective study found that whilst pre-operative psychological factors did not predict the development of CRPS, early post-operative increases in distress levels predicted later CRPS severity (Harden et al., 2010b). More research is needed to assess the importance of psychological factors at different time points in the course of CRPS.

There are several clinical implications of the present study. At present, psychologists treating CRPS patients have a limited body of research available on which to base treatment decisions about which psychological variables to target. The present study suggests that psychological treatments aimed at reducing depression, anxiety and pain-related fear are worth trialling in CRPS. Our data suggest that it would be worth investigating whether psychological treatments that target depression lead to improvements in disability, and whether treatments that target anxiety lead to improvements in pain. There is already some evidence from multiple single-case design studies showing the efficacy of treatments aimed at pain-related fear (de Jong et al., 2005; van de Meent et al., 2011), and this data suggests that targeting depression and anxiety in addition may be worthwhile.

The main limitation of the study is that the data were collected at a single time and the direction of relationships is unclear. It is not only possible but quite likely that whilst psychological factors might influence pain and disability, that higher pain intensity and greater disability lead to poorer psychological wellbeing. It is also possible that a third (unknown) variable accounts for the relationship. Prospective studies are needed to better understand these relationships. The data are also limited by self-report bias. Another limitation is that there was some missing data, more so in the CRPS than in the low back pain group. Systematically missing data or selective attrition are a potential source of bias for this study, as it is possible that the difference between groups was due to the difference between those who complete questionnaires compared to those who do not. However, to investigate this, we re-ran the analyses utilising only the 60 CRPS and low back pain matched pairs with complete datasets, and our results were virtually identical to those presented here. One strength of the study was that the samples were matched for age, gender and pain duration, and this removes some possible sources of variation in measures of pain, disability and psychological wellbeing.
Conclusions
In conclusion, we found that there were remarkable similarities between CRPS patients and age, sex and pain-duration matched low back pain patients on measures of pain, disability, depression, anxiety and pain-related fear. In addition, we found that both pain and depression were associated with disability, and the association between depression and disability was stronger for the CRPS group than the low back pain group. We found that pain-related fear was associated with greater pain intensity, and that anxiety was associated with pain intensity in the CRPS group but not in the low back pain group. Although previous research has demonstrated a limited role for psychological factors in causing CRPS, our results support the hypothesis that in chronic CRPS, psychological factors might play a role in maintaining pain and disability in the same way they influence other types of acute, experimental and chronic pain.

Acknowledgements
The authors thank Catherine Pollard (BSc (Hons), Physiotherapy Diploma HE Orthopaedic Medicine), Dr Trevor Coe (MA, MB BChir, FRCA, FFPMANZCA) and the rest of The Auckland Regional Pain Service team for assistance with data collection, and the Oakley Mental Health Research Foundation for supporting our CRPS Research.
Chapter 6: Factors Associated with Disability and Sick Leave in Early Complex Regional Pain Syndrome Type-1

Prelude
Rationale
Chapter 5 presented data demonstrating that pain and disability were associated, at least cross-sectionally, with depression, anxiety and pain-related fear in a sample of patients with longstanding CRPS. Relationships were similar, albeit not identical, to those found in a matched sample of low back pain patients. However the research goes just part-way to addressing the main research question of this thesis: do psychological factors influence recovery from CRPS? The sample used comprised those with chronic symptoms recruited from an interdisciplinary pain clinic, and this likely represents those with the most significant symptoms. As much of the recovery from CRPS happens within the initial months after developing the condition, the sample for this study represents just those who have not made an early recovery. Furthermore, the chronic CRPS sample used may have exaggerated the problem of differentiating cause from effect in cross-sectional data: It is not only possible but also quite likely that CRPS patients who experienced the highest levels of pain or disability became more distressed and fearful as a result of their pain and limitations. This relationship could strengthen over time as a vicious cycle develops, leading to a stronger relationship between psychological factors and outcomes in chronic samples. It is possible that psychological factors influence outcomes differently in acute and chronic pain. For example, de Jong et al. (2011) reported that in early CRPS, pain-related fear was not associated with functional limitations, whereas in chronic CRPS, perceived harmfulness of activities was associated with limitations. Thus it is important to establish whether the associations between psychological factors and disability seen in Chapter 5 might also exist in early CRPS. Finally, the study was also limited by its reliance on self-report data, as both independent variables and dependent variables were measured using self-report questionnaires. It is possible that report-bias or negative affect influenced responding on both sets of questions, leading to an inflation of relationships.

The study presented here in Chapter 6 aimed to overcome some of these limitations. First, the study utilised a sample of those with newly onset CRPS-1, in order to see whether psychological factors influence disability in the early stages of the condition. Second, the study utilised not only a self-report measure of disability but also an objective measure, work status, to overcome self-report bias.
Relatively little research has looked at work status amongst CRPS patients. However, work is an important outcome variable in its own right, as work contributes significantly to the quality of life of an individual and their family, as well as producing benefits for society in terms of productivity and economic growth. Furthermore, loss of work might significantly affect an individual’s ability to cope with and recover from an injury or health condition. Worklessness has been shown to be associated with poorer physical and mental health as well as greater mortality, and even for sick or disabled people, returning to work is associated with better health outcomes (Waddell & Burton, 2006). It is possible that patients with CRPS who stop work are at risk for a poorer recovery. Thus assessing whether psychological factors influence work status in the early stages of CRPS is potentially important for examining the overall aim of the thesis: understanding the influence of psychological factors on recovery from CRPS.

**Aims**

1. To assess whether psychological factors, based on the fear-avoidance model, influence disability in early CRPS-1. Specific psychological factors are pain-related fear, catastrophic thinking, depression and anxiety
2. To assess whether psychological factors, based on the fear-avoidance model, influence work status in early CRPS-1.

**Power Analysis**

A power analysis was conducted prior to commencing the study. The power calculation was designed not only for the purposes of the baseline analyses (presented here in Chapter 6) but also for the subsequent prospective analyses (presented in Chapters 7 & 8). The power calculation was based on a multiple regression design, and demonstrated that a minimum of 65 participants will provide approximately 80% power with alpha set at 0.05 in a multiple regression with 7 predictors.

**Citation**

Abstract

Objective: Factors influencing disability and work absence in CRPS have not been thoroughly described in the literature. We sought to determine whether demographic variables, work-related factors, CRPS clinical severity ratings, pain scores or psychological variables were associated with disability and sick leave in early CRPS.

Methods: 66 CRPS-1 patients were recruited within 12 weeks of CRPS-onset. Patients completed measures of pain, depression, anxiety, stress, pain-catastrophising and pain-related fear. A physical examination was conducted to assess signs and symptoms of CRPS and to calculate a CRPS severity score. Demographic details, clinical details, treatments, work type and work status were recorded.

Results: In multivariate analyses, the following factors were associated with greater disability: higher pain scores, more restricted ankle or wrist extension, and higher levels of depression. Amongst the 49 who were either working or studying prior to developing CRPS, 28 had stopped work or study at the time of assessment. Multivariate analyses showed that sick leave was more likely amongst those who had a significant injury compared to those who had a minor injury as the trigger for their CRPS, amongst those with heavier versus lighter work, and amongst those with higher depression scores.

Discussion: Although the study was cross-sectional so cannot differentiate cause from effect, results suggest that even in the early stages of CRPS, a cycle of pain, disability, depression and work absence can emerge. Treatments aimed to prevent this cycle may help prevent adverse long-term outcomes.
Introduction

Complex regional pain syndrome (CRPS) is a condition which can occur after fracture, surgery, minor injury, stroke or spontaneously. It usually affects either the upper or lower limb, and symptoms include pain, allodynia, hyperalgesia, changes to skin colour and limb temperature, swelling, alterations to hair and nail growth, altered sweating, reduced range of movement, and motor changes such as weakness, tremor or dystonia. Previous studies have shown that the clinical outcomes of CRPS can vary considerably (Bean et al., 2014a), and whilst some studies show that the majority of patients make a good recovery (Zyluk, 1998a), some patients develop lasting symptoms (de Mos et al., 2009b). Very few studies have explored disability in CRPS patients but those that have suggest that CRPS patients can develop long-term disability. For example, Subbarao and Stillwell (1981) reported that only 30% of CRPS patients were able to resume 100% of their normal activities, even at 2-year follow-up. Similarly, Savas et al. (2009) found statistically significant limitations on 6 of the 8 dimensions of the SF-36 when comparing CRPS patients to healthy controls, 18 months after treatment. Only two studies appear to have assessed factors that might predict disability. de Jong et al. (2011) found that amongst those with chronic CRPS, patients who had higher pain-related fear (measured on a pictorial assessment tool) were more disabled, even after controlling for pain intensity. Interestingly, in both this chronic sample, and in an acute CRPS sample, pain-related fear, when measured by a questionnaire, did not predict disability above and beyond pain intensity (de Jong et al., 2011). This might be due to limitations in the measurement tool used, or might reflect that different processes influence disability at different time-points in the course of CRPS.

Psychological variables such as pain-related fear, pain catastrophising, depression and anxiety have been shown to predict disability in other pain conditions (for example low back pain) (Nicholas et al., 2011), and we previously found that depression had a stronger association with disability in a sample of chronic CRPS patients compared to low back pain patients (Bean et al., 2014b). Due to the relatively limited range of research that has been conducted early in the course of CRPS, and the potential for intervening at this time, we aimed to identify whether pain-related fear, as well as other psychological factors, influence disability in the first 3 months following the onset of CRPS. For the purposes of this study, the term ‘disability’ was operationalized to indicate not just physical impairments, but to encompass limitations in a broad range of life roles, including recreational, social, household, sexual, self-care and occupational activities. We also aimed to assess the influence of psychological factors on work status separately.

Previous studies have demonstrated that CRPS leads to sick leave and long-term work disability in a significant proportion of patients. For example, Subbarao and Stillwell (1981) reported that 3 years after developing CRPS around a third of patients were officially disabled, around a third either retired
or didn’t return to the same job, and around a third were back to their previous job. Similarly, de Mos et al. (2009b) reported that 41% of CRPS patients resumed their normal work, 28% adapted their work, and 31% stopped work altogether. Duman et al. (2007) reported on work outcomes for military personnel with CRPS who were all men, with a mean age of 23 years: 28% became officially disabled due to CRPS. Only two previous studies assessed predictors of work status amongst CRPS patients. The first found return to work was associated with younger age, a sedentary job, upper limb involvement, a higher level of education, and early analgesic treatment associated with physiotherapy (Dumas et al., 2011). The second reported that amongst 16 CRPS patients, return to work was quicker for those with a sedentary job, those whose CRPS started with a less serious injury, affected a proximal joint (e.g. shoulder, knee) rather than distal joint (e.g. wrist/ankle) and when the injury did not occur at work. The study was too small to conduct multivariate analyses or to determine which of these variables were independent predictors. It also reported that several patients did not get back to work due to psychological problems such as chronic alcoholism or depression (Dauty et al., 2001). Sandroni et al. (2003) found that 46% of CRPS patients did not claim any disability status, and 15% of these patients had not experienced ‘symptom resolution’, which suggests that some patients with CRPS are able to continue working despite ongoing symptoms, whilst others are not. As yet no studies have assessed the role of pain intensity or psychosocial variables in predicting the work status of CRPS patients. Psychosocial variables have been shown to predict work status in other pain conditions, so may be worthwhile exploring in CRPS (Heitz et al., 2009).

Previous research has shown that having pain patients either stay at work or return to work early is important. For example, one study of low back pain patients found the chances of return to work are relatively high within the first 6-12 weeks (approximately 70-75% had a successful or partially successful return to work), but these rates remain near constant at 1- and 2-year follow-ups (approximately 20% were off work at 2 years) (Dionne, Bourbonnais, Fremont, Rossignol, Stock, & Larocque, 2005). Identifying risk factors for those likely to go off work during these early stages could be valuable. Thus the present study, which recruited patients within 12 weeks of CRPS onset, aimed to assess the differences between those who stay at work, and those who stop work, and are therefore at risk of long term sickness absence (The Royal Australasian College of Physicians & The Australasian Faculty of Occupational & Environmental Medicine, 2010).
Methods

Participants
The participants were patients with newly-onset upper or lower limb CRPS type-1 referred to the study from orthopaedic, plastic surgery, hand therapy physiotherapy and pain clinics in Auckland, New Zealand between February 2012 and January 2014. Inclusion criteria were: 1. Patient meets the 1994 IASP-Orlando criteria for CRPS (Merskey & Bogduk, 1994); 2. Has had CRPS for less than 12 weeks; 3. Has CRPS type-1 (i.e. no evidence of specific nerve injury); 4. Aged over 18 years; 5. Able to communicate in English; 6. No prior history of CRPS.

In total, 93 patients were referred for the study. 5 could not be contacted via phone or letter and thus were excluded. 19 were excluded because they did not meet the inclusion criteria (13 had CRPS for longer than 12 weeks at the time the referral was received, 4 were deemed not to have CRPS-1 based on medical files and self-reported symptoms during a telephone call, 1 lived outside the study area and thus was not covered by ethics approval, and 1 had a previous history of CRPS). 2 declined to participate, leaving 67 who consented to the study. Following participation, a further participant was excluded as it was clear her CRPS symptoms had been present for longer than 12 weeks. This left a total of 66 participants.

Procedure
The study was approved by the New Zealand Ministry of Health Northern Y Ethics Committee.
Participants were recruited and seen for a 60-90 minute assessment, which consisted of the following measures:

1. CRPS Severity Score/ Signs and symptoms of CRPS: This was based on the tool described by Harden et al. (2010b). For each of the following, participants were asked whether they experienced the symptom (excluding hyperpathia), and the primary author examined the affected and unaffected limbs for signs as described below:
   a. Colour asymmetry: determined by visual inspection, scored none, mild moderate or severe.
   b. Trophic changes to hair and nails: determined by visual inspection, scored none, mild moderate or severe.
   c. Sweating asymmetry: determined by visual inspection, scored none, mild moderate or severe.
   d. Temperature asymmetry: bilateral temperature measured at 5 pre-defined points over the affected and unaffected limbs using a digital infrared thermometer.
e. Oedema: determined by a.) visual inspection and scored none, mild moderate or severe, and b.) bilateral measurement of circumference of wrist/ankle and digit 2/midfoot.

f. Motor changes: determined by visual inspection of rapid movement of bilateral fingers/toes, scored none, mild moderate or severe.

g. Range of motion: wrist or ankle flexion and extension measured bilaterally using goniometer.

h. Dynamic mechanical allodynia to brush: scored nil, mild, moderate or severe.

i. Hyperpathia to repetitive tap: present or absent.

Severity scores for each of the signs of CRPS were utilised, and in addition this information was used to calculate a CRPS Severity Score. This was calculated by summing the number of symptoms reported by the patient (out of a total of 8) and the number of signs observed (out of a total of 9), to give a total score out of 17. Higher scores represent more severe cases of CRPS. This scale has been shown to have good sensitivity to discriminate between CRPS and non-CRPS patients, and provides greater sensitivity to change compared to measuring CRPS as either present or absent (Harden et al., 2010b).

2. Short-form McGill Pain Questionnaire 2 (SFMPQ2) (Dworkin et al., 2009): This is a scale which asks participants to rate each of 22 pain descriptors on a scale from 0 (none) to 10 (worst possible). A total score is determined by calculating the average score over all 22 items. The SFMPQ2 has been demonstrated to have excellent reliability and validity (Lovejoy, Turk, & Morasco, 2012).

3. Pain Numerical Rating Scale: Participants were asked to rate their average pain level over the past 2 days on a scale from 0 (no pain) to 10 (worst pain you can imagine).

4. Disability: Pain Disability Index (Pollard, 1984): This 7-item scale asks participants to rate their level of disability for 7 domains of life on a scale from 0 (no disability) to 10 (total disability). A total disability score out of 70 is calculated by adding the items together. Higher scores represent greater disability. This scale has been shown to have good psychometric properties, although most of the research to date on this scale has been conducted in low back pain patients rather than limb pain patients (Tait & Chibnall, 2005).

5. Pain-related fear: Tampa scale for Kinesiophobia (Woby, Roach, Urmston, & Watson, 2005): This is an 11-item scale which asks participants to rate the extent to which they agree or
disagree with a range of statements endorsing pain-related fear. Scores are calculated between a minimum of 11 (no pain-related fear) and a maximum of 44 (high levels of pain-related fear). This scale has been demonstrated to have good reliability and validity (Woby et al., 2005).

6. Catastrophic thinking: Pain Catastrophizing Scale (Sullivan et al., 1995): This is a 13-item scale which asks participants to rate the extent to which they experience a range of catastrophic thoughts on a 5 point scale from 0 (not at all) to 4 (all the time). A total score out of 52 is calculated by summing all answers together. Higher scores indicate greater levels of pain catastrophising. The scale has been shown to have excellent reliability and validity (Sullivan et al., 1995).

7. Depression Anxiety Stress Scale 21 (Lovibond & Lovibond, 1995a): This 21-item scale consists of 7 items measuring depression, 7 measuring anxiety, and 7 measuring stress. Participants are asked to rate the extent to which they endorse each item on a scale from 0 (did not apply to me at all) to 3 (applied to me very much or most of the time). Items for each of the three subscales are added together to give three scores, each out of 21, with higher scores representing greater distress. The DASS has been shown to have very good reliability and validity (Lovibond & Lovibond, 1995a). Clinical cut-off scores for normal, mild, moderate, severe and extremely severe depression, anxiety and stress have also been published (Lovibond & Lovibond, 1995b).

8. Work Status: Participants were asked to indicate their work status prior to and following the onset of CRPS based on the following categories: Working, fulltime student, retired, sickness/invalids beneficiary, receiving accident (ACC) compensation, unemployment or domestic purposes beneficiary, reliant on family/fulltime home-maker, or no income. Where participants had more than one category (e.g. student also working part-time, or working part-time whilst receiving ACC compensation for remaining missing income), the predominant work status was recorded.

9. Work Type: The Occupational Classification According to Work Demands Coding System (de Zwart, Broersen, van der Beek, Frings-Dresen, & van Dijk, 1997) was used to classify each participant’s occupation on a four point scale where 0= minimal physical demands (mentally

---

1 The Accident Compensation Corporation (ACC) provides no-fault insurance cover for all accidental injuries in New Zealand, including funding of treatment, rehabilitation, and income replacement where an individual stops work due to an injury.
demanding work), 1=mixed physically and mentally demanding work, 2=light physically demanding work and 3=heavy physically demanding work.

10. Demographics: Age, gender and ethnicity were recorded

11. Clinical variables: Affected limb was recorded (upper or lower, dominant or non-dominant hand), and duration of CRPS was recorded in days. The accident compensation corporation (ACC) status of each participant was recorded (i.e. did they have a covered injury, regardless of whether or not they were claiming ACC earnings-related compensation). CRPS trigger was coded on the following 5-point scale:
   a. Fracture, crush or significant injury requiring surgical repair
   b. Fracture not requiring surgical repair
   c. Minor elective surgery (e.g. carpal tunnel release)
   d. Minor injury (e.g. sprain or soft tissue injury)
   e. No injury (knock or bump or spontaneous onset)

12. Treatments: Participants were asked to indicate whether they were receiving any of the following commonly prescribed medications for CRPS: Paracetamol, anti-inflammatories, tricyclic antidepressants, gabapentin, codeine, tramadol, other opiates, prednisone, clonidine patches, vitamin C or interventional medicine treatments (e.g. infusions, nerve blocks). They were also asked to indicate whether they were receiving hand therapy, physiotherapy, splinting, exercises, mirror therapy, graded motor imagery, psychological therapy or multidisciplinary pain management.

Statistical Analyses
Descriptive statistics were calculated for all variables. Variables were screened to ensure they met the assumptions of normality, and where necessary, transformations were utilised (square root transformations were used to reduce positive skew for scores on the depression anxiety stress scale and the pain catastrophising scale). When means and standard deviations are reported we have presented the untransformed data for ease of comprehension, but for the Pearson’s correlations and multivariate analyses the transformed scores were used.

Pearson’s correlations were used to determine which of the continuous variables were significantly associated with disability. T-tests and one-way analyses of variance were used to determine which of the categorical variables were significantly associated with disability. Multiple linear regression was
used to determine predictors of disability. Because there were many variables associated with
disability two regression analyses were performed: the first contained the clinical predictors (pain,
symptom severity scores). Significant predictors from this regression were entered onto the first step
of a second multiple regression, and psychological factors were entered on the second step.

To determine which factors predicted work status, participants who were not working or studying
prior to their CRPS onset were then excluded from the following analyses. T-tests and chi-square
tests were used to identify possible predictors of work status (continuing to work/study versus
stopping work/study). Significant variables were then entered into a binary logistic regression with
demographic or clinical variables on the first step and psychological variables on the second step.

Results

Participants
The sample consisted of 66 CRPS-1 patients, the majority were female, just over half identified their
ethnicity as New Zealand European, and the majority developed CRPS following either fracture or
surgery. The demographic and clinical variables are presented in Table 12. We assessed the
proportion of the sample that met cut-off scores on the DASS-21, and found the following percentage
in each category for depression: normal: 46%, mild: 10%, moderate: 19%, severe: 10%, extremely
severe: 12%. The percentage falling into each category for anxiety were: normal: 43%, mild: 4%,
moderate: 22%, severe: 10%, extremely severe: 20%.

Factors Associated with Disability: Univariate Analyses
Correlations showed that the following variables were associated with high levels of disability: higher
CRPS severity scores, higher pain scores, higher pain catastrophising, higher pain-related fear, and
higher levels of depression, anxiety and stress (Table 13). There were no significant relationships
between disability and the following variables: age, gender, ethnicity, accident compensation status,
CRPS trigger, affected limb (upper versus lower), and dominant versus non-dominant limb affected.
Associations between disability scores and the symptoms/signs of CRPS are displayed in Table 14.
This showed that those reporting alterations in sweating and mechanical allodynia, and those
observed to have reduced movement in the limb all had higher disability scores. Pearson’s
correlations showed that temperature differences between the affected and unaffected limbs did not
correlate with disability, \( R(66)=.02, p=.896 \). There were also no differences in disability scores
between those describing their limb as hot versus cold, or those whose limb temperature, when
measured, was hot compared to cold. There were however significant correlations between disability
scores and wrist/ankle flexion, $R(66) = -.344$, $p = .005$, and wrist/ankle extension, $R(66) = -.331$, $p = .007$.

We also assessed whether disability scores were associated with pre-CRPS occupational variables (work status and work type). T-tests and one-way analysis of variance showed no significant associations.

### Table 12. Demographic and Clinical Features of the Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) or proportion in each category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (N (%)) Female</td>
<td>48 (73%)</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>36 (55%)</td>
</tr>
<tr>
<td>Indian</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Maori</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (20%)</td>
</tr>
<tr>
<td>Nature of CRPS Onset:</td>
<td></td>
</tr>
<tr>
<td>Significant injury requiring surgical repair</td>
<td>16 (24%)</td>
</tr>
<tr>
<td>Fracture not requiring surgical repair</td>
<td>20 (30%)</td>
</tr>
<tr>
<td>Minor elective surgery</td>
<td>20 (30%)</td>
</tr>
<tr>
<td>Soft-tissue injuries</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>No injury/Spontaneous</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Affected limb (N (%)) Upper limb</td>
<td>60 (91%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.06 (14.03)</td>
</tr>
<tr>
<td>CRPS-1 Duration (days)</td>
<td>61.23 (22.58)</td>
</tr>
<tr>
<td>CRPS Severity Score</td>
<td>12.18 (2.41)</td>
</tr>
<tr>
<td>Pain NRS</td>
<td>5.52 (2.00)</td>
</tr>
<tr>
<td>Pain SFMPQ2</td>
<td>4.22 (2.22)</td>
</tr>
<tr>
<td>Disability (PDI)</td>
<td>37.15 (14.33)</td>
</tr>
<tr>
<td>Pain-related fear (TSK)</td>
<td>28.51 (7.21)</td>
</tr>
<tr>
<td>Catastrophising (PCS)</td>
<td>22.39 (15.44)</td>
</tr>
<tr>
<td>Depression (DASS)</td>
<td>6.33 (5.47)</td>
</tr>
<tr>
<td>Anxiety (DASS)</td>
<td>5.59 (5.41)</td>
</tr>
<tr>
<td>Stress (DASS)</td>
<td>9.45 (6.50)</td>
</tr>
</tbody>
</table>

NRS= Numeric Rating Scale; SFMPQ2= Short-Form McGill Pain Questionnaire 2; PDI = Pain Disability Index; TSK=Tampa Scale for Kinesiophobia; PCS=Pain Catastrophizing Scale; DASS=Depression Anxiety Stress Scale.
Table 13. Pearson’s Correlations Between Disability, CRPS Severity, Pain and Psychological Variables

<table>
<thead>
<tr>
<th></th>
<th>Disability</th>
<th>CRPS Severity Score</th>
<th>Pain (NRS)</th>
<th>Pain (SFMPQ2)</th>
<th>Pain-related fear</th>
<th>Catastrophising</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS Severity</td>
<td>.31*</td>
<td>.12</td>
<td>.27*</td>
<td>.63**</td>
<td>.48**</td>
<td>.51**</td>
<td>.53**</td>
<td>.40**</td>
<td>.33**</td>
</tr>
<tr>
<td>Pain (NRS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (SFMPQ2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-related fear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catastrophising</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<.05; ** p<.01; NRS= Numeric Rating Scale; SFMPQ2= Short-Form McGill Pain Questionnaire 2

There were some associations between treatment use and disability. Those who were using the following treatments had higher disability scores compared to those not using that treatment: gabapentin, tramadol, paracetamol and splinting. The most likely explanation for these findings is that those with a more disabling CRPS are more likely to be provided with these treatments. We checked this using ANCOVA to assess whether differences existed after entering pain intensity as a covariate, and there were no longer significant effects for gabapentin, tramadol or splinting. Paracetamol use still showed a significant relationship with disability, but this is likely to be an effect rather than cause, as paracetamol is not known to produce particularly sedative or disabling side effects. It is likely that those who were not particularly disabled chose not to use this common medication. Thus we did not enter treatment use into our regression analyses.

Factors Associated with Disability: Multivariate Analyses

Multiple regression was used to assess which variables were uniquely associated with disability and this is presented in Table 15. Because so many variables were significantly correlated with disability, this was performed in two separate analyses, as the sample size provided inadequate power for the number of predictors (NB. In reality, this made no difference and the results were the same as when the analysis was performed in a single regression analysis). In the first regression analysis (not shown in Table 15), all of the clinical variables that were significantly associated with disability were entered (CRPS severity score, pain (SFMPQ-2), ankle/wrist extension, ankle/wrist flexion, sweating symptom, allodynia symptom, and motor sign). The regression equation was significant ($R^2=.41$, $F(7, 58)=7.349$, $p<.001$***), with the only unique predictors being pain intensity (SFMPQ-2 scores), $B=.561$, $p<.001$. 

107
and ankle/wrist extension (which showed a non-significant trend), $B=-.250, p=.064$. In the second regression equation, these two predictors were entered on the first step, with all the psychological variables entered on the second step (depression, anxiety, stress, pain-related fear and pain catastrophising). Results are presented in Table 15. This showed that the independent predictors of

<table>
<thead>
<tr>
<th>Table 14. Associations Between Disability Scores and Symptoms/Signs of CRPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom (self-reported)</td>
</tr>
<tr>
<td>Colour difference</td>
</tr>
<tr>
<td>Swelling</td>
</tr>
<tr>
<td>Temperature difference</td>
</tr>
<tr>
<td>Sweating difference</td>
</tr>
<tr>
<td>Hair/nail changes</td>
</tr>
<tr>
<td>Reduced ROM</td>
</tr>
<tr>
<td>Motor symptom</td>
</tr>
<tr>
<td>Allodynia</td>
</tr>
</tbody>
</table>

| Sign (observed on examination) | Mean PDI Score for those without sign | Mean PDI Score for those with MILD sign | Mean PDI Score for those with MODERATE sign | Mean PDI Score for those with SEVERE sign | F (df=3,62) | p |
| --- |
| Colour difference | 35.12 (15.71) | 37.49 (14.20) | 34.61 (14.35) | 50.78 (6.37) | 1.897 | .139 |
| Swelling | 36.13 (14.22) | 34.64 (15.37) | 39.46 (13.19) | 51.71 (5.24) | 1.197 | .318 |
| Sweating difference | 36.75 (14.38) | 36.10 (14.20) | 54.00 (2.12) | (N=0) | 1.455 | .241 |
| Hair/nail changes | 38.10 (12.66) | 33.50 (14.72) | 39.13 (15.60) | 40.81 (17.10) | .653 | .584 |
| Motor changes‡ | 28.46 (12.56) | 34.79 (13.31) | 39.61 (15.72) | 46.50 (9.89) | 4.071 | .011* |
| Allodynia | 34.16 (13.57) | 43.09 (14.06) | 41.37 (13.19) | 41.08 (18.99) | 1.655 | .186 |
| Hyperpathia | 35.55 (14.25) | 40.85 (14.17) | (measured as present or absent only) | t=1.390 | .169 |

*p<.05, ‡nb: significant difference is between those with severe motor changes and no motor changes.
disability were pain intensity, ankle/wrist extension, and depression. Specifically, those who had
greater pain intensity, more restricted ankle or wrist extension and who were more depressed were
more disabled.

For completeness, 2 additional multiple linear regression analyses were conducted to explore
whether pre-CRPS work status or sociodemographic variables influenced disability scores or affected
the findings described above. The first showed that pre-CRPS work status was not a significant
predictor; it accounted for less than 1% of the variance in disability scores and did not affect the
findings described above. The second showed that the combination of age, sex and ethnicity also
accounted for just 4% of the variance in disability scores, and did not have a significant effect either
individually or combined.

Table 15. Multiple Linear Regression to Predict Disability (PDI) Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Step 1 B (p)</th>
<th>Step 2 B (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (SFMPQ2)</td>
<td>.605 (&lt;.001)**</td>
<td>.477 (.001)**</td>
</tr>
<tr>
<td>Ankle/wrist Extension</td>
<td>-.192 (.049)*</td>
<td>-.280 (.029)*</td>
</tr>
<tr>
<td><strong>Psychological Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-related fear</td>
<td>.219 (.071)</td>
<td></td>
</tr>
<tr>
<td>Pain Catastrophising</td>
<td>.016 (.921)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>.333 (.037)*</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>-.161 (.285)</td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td>-.142 (.308)</td>
<td></td>
</tr>
<tr>
<td><strong>Model Statistics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R^2=.41, F(2,63)=23.447, p&lt;.001$</td>
<td>$R^2=.48, F(7,58)=9.402, p&lt;.001$</td>
<td></td>
</tr>
<tr>
<td>$R^2$Change=.105, F Change (5, 53)=2.596, $p=.035$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<.05, **p<.01, ***p<.001

**Work Characteristics**
The dominant work status of the CRPS-1 patients prior to, and following their CRPS onset is presented
in Table 16. This shows that whilst 49 (74%) of the participants were either working or studying prior
to the onset of their CRPS, only 21 (32%) of the sample were working or studying after their CRPS
developed.
Table 16. Work Status Prior to and Following CRPS Onset

<table>
<thead>
<tr>
<th></th>
<th>N (%) prior to onset of CRPS</th>
<th>N (%) following onset of CRPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working</td>
<td>44 (67%)</td>
<td>19 (29%)</td>
</tr>
<tr>
<td>Student</td>
<td>5 (8%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Retired</td>
<td>6 (9%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Sickness/Invalids beneficiary</td>
<td>7 (11%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Accident (ACC) Compensation</td>
<td>1 (2%)</td>
<td>17 (26%)</td>
</tr>
<tr>
<td>Unemployment or domestic purposes benefit</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Reliant on family</td>
<td>1 (2%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>No income (applying for financial assistance)</td>
<td>0</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

Factors Associated with Sick Leave: Univariate Analyses

Differences between those who continued to work or study (‘work/study’ group) at the time of assessment, and those who were off work or study (‘sick leave’ group) following their CRPS are presented in Table 17. This shows that the only variables associated with sick leave were depression, disability, work physical demands and injury severity. Those who were more depressed, who rated themselves as more disabled, who had more severe injuries or whose job involved heavier work were more likely to stop work.

Chi-square tests found once again that those utilising paracetamol and gabapentin were more likely to take sick leave. We suspect that the most likely explanation for this is that those who have greater pain intensity or who are off work are more likely to be provided with treatments and thus did not include these factors in multivariate analyses.

Factors Associated with Sick Leave: Multivariate Analyses

Binary logistic regression was used to assess predictors of sick leave using all significant variables (seen in Table 17) as well as CRPS severity scores (included due to theoretical assumption that CRPS severity should predict work absence). On the first step, CRPS severity, CRPS trigger and work type were entered as predictors, and on the second step, depression was entered. Both the model computed on the first step and the model computed on the second step were significant. Variables with significant beta-weights were CRPS trigger, work type and depression (Table 18). Once again, this showed that those who had a significant injury compared to a minor injury, who worked in
manual jobs and those who were more depressed were more likely to go off work following CRPS. CRPS severity scores did not predict sick leave.

Table 17. Differences Between Those who Continued Work/Study and Those on Sick Leave with CRPS

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) in work/study group (N=21)</th>
<th>Mean (SD) in work absence group (N=28)</th>
<th>T</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45.29 (13.43)</td>
<td>45.00 (14.18)</td>
<td>.071</td>
<td>.943</td>
</tr>
<tr>
<td>CRPS duration (days)</td>
<td>61.43 (19.60)</td>
<td>60.04 (24.18)</td>
<td>.216</td>
<td>.830</td>
</tr>
<tr>
<td>CRPS Severity</td>
<td>11.81 (2.52)</td>
<td>12.36 (2.59)</td>
<td>-.741</td>
<td>.462</td>
</tr>
<tr>
<td>Pain NRS</td>
<td>5.50 (2.15)</td>
<td>5.77 (1.85)</td>
<td>-.467</td>
<td>.642</td>
</tr>
<tr>
<td>Pain SFMPQ2</td>
<td>3.86 (2.14)</td>
<td>4.67 (2.26)</td>
<td>-1.269</td>
<td>.211</td>
</tr>
<tr>
<td>Pain-related fear</td>
<td>26.85 (7.62)</td>
<td>30.29 (6.65)</td>
<td>-1.679</td>
<td>.100</td>
</tr>
<tr>
<td>Catastrophising</td>
<td>20.57 (14.52)</td>
<td>25.32 (15.70)</td>
<td>-1.082</td>
<td>.285</td>
</tr>
<tr>
<td>Depression</td>
<td>3.71 (3.48)</td>
<td>8.04 (6.16)</td>
<td>-2.883</td>
<td>.006*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.95 (3.67)</td>
<td>6.88 (6.28)</td>
<td>-1.901</td>
<td>.063</td>
</tr>
<tr>
<td>Stress</td>
<td>8.29 (5.85)</td>
<td>10.57 (6.55)</td>
<td>-1.264</td>
<td>.212</td>
</tr>
<tr>
<td>Injury severity</td>
<td>1.86 (1.31)</td>
<td>2.82 (1.12)</td>
<td>-2.76</td>
<td>.008*</td>
</tr>
<tr>
<td>Work physical demands</td>
<td>0.48 (.93)</td>
<td>1.67 (1.27)</td>
<td>-3.75</td>
<td>&lt;.001**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Proportion in work/study group (N=21)</th>
<th>Proportion in work absence group (N=28)</th>
<th>Chi-Square (df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>71% female</td>
<td>59% female</td>
<td>.608 (1)</td>
<td>.436</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>62% NZ European</td>
<td>50% NZ European</td>
<td>4.915 (5)</td>
<td>.426</td>
</tr>
<tr>
<td>ACC Cover</td>
<td>62% covered</td>
<td>82% covered</td>
<td>2.522 (1)</td>
<td>.112</td>
</tr>
<tr>
<td>Limb affected</td>
<td>81% upper</td>
<td>96% upper</td>
<td>3.137 (1)</td>
<td>.077</td>
</tr>
<tr>
<td>Dominant limb affected</td>
<td>38% dominant affected</td>
<td>57% dominant affected</td>
<td>1.742(1)</td>
<td>.187</td>
</tr>
</tbody>
</table>

*p<.05; **p<.001

For completeness, we also did a further analysis including sociodemographic factors (age, sex and ethnicity) on the first step. However the combined effect of these variables accounted for only 2% of the variance in sick leave outcomes, and greatly lowered the percentage of variance accounted for by the other variables, and hence sociodemographic factors were not included in the final analysis presented in Table 18.
Table 18. Logistic Regression to Predict Work Status

<table>
<thead>
<tr>
<th>Variables Entered</th>
<th>Step 1</th>
<th>Step 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRPS Severity Score</td>
<td>1.05 (.80-1.38)</td>
<td>0.95 (.71-1.29)</td>
</tr>
<tr>
<td>Trigger/injury severity</td>
<td>1.61 (.93-2.81)</td>
<td>2.17 (1.00-4.72)*</td>
</tr>
<tr>
<td><strong>Work Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work demands</td>
<td>2.27 (1.20-4.30)*</td>
<td>2.34 (1.19-4.60)*</td>
</tr>
<tr>
<td><strong>Psychological Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>2.76 (1.24-6.14)*</td>
<td></td>
</tr>
<tr>
<td>Model statistics</td>
<td>$X^2 (3) = 14.96^{**}$</td>
<td>$X^2 (4) = 23.57^{**}$</td>
</tr>
<tr>
<td></td>
<td>$R^2 = .268$</td>
<td>$R^2 = .388$</td>
</tr>
</tbody>
</table>

*p<.05; **p<.001

Discussion

The present study found that for patients with recently-onset CRPS, those who have higher pain scores, a more limited range of motion and higher levels of depression are more disabled. Those with heavier compared to lighter jobs, who had a more significant injury, or with higher levels of depression are more likely to stop work. Only two previous studies have identified predictors of disability in CRPS patients. We previously found that depression was associated with disability in a sample of chronic CRPS patients (Bean et al., 2014b), and this study extends this finding by demonstrating the same relationship in an acute sample. De Jong et al. (2011) reported that pain was the best predictor of disability in acute CRPS patients, which is also what we found here. They found that pain-related fear, as measured by the Tampa Scale for Kinesiophobia (TSK), was not a significant predictor of disability (after controlling for pain intensity) in recent-onset CRPS patients. This contrasts with several treatment studies which showed beneficial effects of treating pain-related fear in CRPS (de Jong et al., 2005; van de Meent et al., 2011), and questions the relevance of the fear-avoidance model in CRPS. Interestingly, we did find a non-significant trend for pain-related fear to predict disability ($p=.07$ in multivariate analyses), which provides some support for the model.

Anecdotally, we suspect that the Tampa Scale for Kinesiophobia may not be the most useful tool in limb pain patients, as some items refer to ‘exercise’, and several upper limb CRPS patients in our study were unclear whether this was referring to limb-specific movement (which they found difficult) or generally keeping fit (which they found ways to do without involving their affected limb). Of note, we found that our acute CRPS sample reported similar levels of disability to those found in previous
studies of low back pain patients recruited from spinal and rehabilitation clinics, suggesting that acute CRPS is associated with significant disability (Soer et al., 2013).

We also found high rates of work absence in our acute CRPS sample: of those who were working or studying prior to their CRPS, only 47% were working at the time of participating in the study. Only two previous studies have identified predictors of return to work in CRPS patients, and these studies looked predominantly at demographic and work related factors, rather than psychological variables (Dauty et al., 2001; Dumas et al., 2011). Our results had some similarity to previous studies, which reported that a sedentary job and higher education level predicted return to work. We coded participants’ work using the occupational classification according to work demands system (de Zwart et al., 1997), and found that those in physically demanding jobs were more likely to stop work compared to those with jobs that were not physically demanding. Thus it is worthwhile encouraging employers to find light duties for patients with CRPS, as lighter work options will likely facilitate a return to work. Although we did not measure educational level, our ‘lighter’ work categories often involved a greater degree of education than the physically demanding jobs. These findings are also in line with research from other health conditions, for example following limb injury, myocardial infarction or cancer, those with a higher educational level or less physically demanding job are more likely to return to work (Hou et al., 2012; Maeland & Havik, 1986; van Muijen et al., 2013; Waszkowska & Szymczak, 2009). One previous study also reported that those with more severe injuries took longer to return to work, which is in line with our findings (Dauty et al., 2001).

We found that depression scores were associated with both disability and sick leave, and just over half of our sample scored above ‘normal’ levels of depression on the DASS-21. Due to the cross-sectional nature of the study, we cannot state whether depression is a cause, consequence or correlate of disability and sick leave, but our data does show that depression is related to these poor outcomes in CRPS. Just one previous study had noted that depression prevented return to work for 2 CRPS patients, but had not collected data on depression systematically (Dauty et al., 2001). The association between depression, disability and work is not particularly surprising, as depression has been shown to be associated with poor work outcomes in conditions as diverse as cardiac disease, diabetes, and low back pain, and is a major cause of work disability in itself (Lerner & Henke, 2008; O’Neil, Sanderson, & Oldenburg, 2010; Schmitz et al., 2014). Depression can be treated with psychological therapy or pharmacotherapy, and the implications of the present study are that it may be worthwhile to prevent or treat depression in early CRPS patients to avoid a cycle of disability and work absence. Of the sample presented here, 55% were taking tricyclic antidepressants, but all at a low dose (10–75mg); none had been prescribed an ‘anti-depressant’ dose (100mg or more). 15%
were taking selective serotonin re-uptake inhibitors (SSRIs), and in all cases the SSRI was in place prior to the development of CRPS (i.e. for pre-existing depression). Given the fairly high rates of depression in the sample (as shown by the DASS scores), this suggests that more attention could be paid to screening and treating depression in early CRPS. At present, treatment guidelines recommend that in the early stages of CRPS, psychological interventions should comprise predominantly education (Harden et al., 2013), but the present study extends this and suggests that treatments aimed at preventing or treating depression should also be prioritised.

Limitations
Unfortunately the cross-sectional nature of our study precludes knowledge of causation. We do not know whether, for example, greater pain intensity, depression and limited range of motion lead to disability, or whether for those who are more disabled, disuse could cause depression and pain. Also, our sample consisted of just 66 CRPS patients, and only 49 who were working or studying prior to their CRPS, thus the small sample may not reflect the CRPS population as a whole. We had only a small proportion of lower limb CRPS patients, primarily because there are a number of specialist hand clinics in Auckland, who tended to refer more patients to the study. Because recruitment for our study involved clinicians identifying and referring patients, our sample might not be entirely representative of the CRPS population as a whole. Those with particularly mild cases of CRPS or who did not present to specialist services would not have been recruited to our study. Also, although having a sample of acute CRPS patients is valuable for determining early differences, it might be that for some participants, the effects of their injury or surgery were not quite spent at the time of their assessment, and this clearly influenced their work status (those with significant injuries were more likely to be off work than those with minor injuries).

Conclusions
A range of factors influence disability in CRPS, and the present study found that the most important associations were with pain, range of motion and depression. It is possible that patients with CRPS could find themselves in an unhelpful cycle of reduced movement, depression, pain and disability, even within three months of developing the condition. Also, sick leave was associated with work type, injury severity and depression but not with pain intensity or CRPS severity. The present study suggests that assisting patients who have CRPS and depression early may be beneficial for preventing long term poor outcomes.
Acknowledgements

We wish to thank the Oakley Mental Health Research Foundation for funding the study. We are grateful to the Auckland Regional Plastic and Reconstructive Hand Surgery Service, The Counties-Manukau Hand Therapy Service, The Auckland Regional Pain Service, Handworks, Moving Hands Rehabilitation, Hands Out West, Paincare, the Counties-Manukau Chronic Pain Service, the Waitemata Orthopaedics Department and Waitemata Pain Management Unit for supporting the study. We also thank all of the participants for their involvement in the research.
Chapter 7: Extent of Recovery in the First 12 Months of Complex Regional Pain Syndrome: A Prospective Study

Prelude

Rationale

The overall aim of this thesis is to investigate the role of psychological factors in the prognosis of CRPS. One important step in this process is to first understand what that prognosis is. As described in Chapter 4 (The Outcome of Complex Regional Pain Syndrome Type-1: A Systematic Review) there has been relatively little research conducted assessing the long-term outcomes or prognosis of CRPS. The three prospective studies that were identified in the systematic review were conducted some time ago and therefore used old nomenclature and diagnostic criteria (for algodystrophy or reflex sympathetic dystrophy), and these are substantially different to more recent criteria for CRPS. Interestingly, the three prospective studies identified that CRPS usually resolves and outcomes are optimistic (Atkins et al., 1989; Bickerstaff & Kanis, 1994; Zyluk, 1998a). However these findings contrasted with some carefully conducted retrospective and cross-sectional studies, which documented high rates of symptoms and disability amongst CRPS patients (de Mos et al., 2009b; Savas et al., 2009). There were also some limitations to the previously conducted prospective studies: they did not assess the outcomes for signs and symptoms of CRPS separately, they conducted no relevant statistical testing, and their samples were not necessarily representative (primarily they were patients with CRPS post-fracture, which might lead to better outcomes compared to those with CRPS from other initiating events (Sandroni et al., 2003)).

Aims

Thus the present study aimed to explore the extent of recovery from CRPS amongst a sample meeting diagnostic criteria for complex regional pain syndrome. We aimed to determine whether there is variability in recovery outcomes, and to assess outcomes for each symptom and sign of CRPS separately to ascertain whether some features of CRPS are more likely to resolve than others. We also aimed to determine whether improvements in CRPS symptoms and signs occur early in the trajectory of the condition (i.e. before 6 months), later in the trajectory (after 6 months) or across both time points. Finally, the study aimed to assess whether improvements in signs and symptoms are accompanied by improvements in disability and psychological wellbeing.
Citation
Abstract

Background: The literature concerning the outcomes of complex regional pain syndrome (CRPS) is contradictory, with some studies suggesting high rates of symptom resolution, whilst others demonstrate that CRPS symptoms can persist and lead to significant disability. The aim of the present study was to carefully document the extent of recovery from each of the signs and symptoms of CRPS.

Methods: A sample of 66 patients with recently-onset (<12 weeks) CRPS-1 were followed prospectively for 1 year, during which time they received treatment-as-usual. At baseline, 6 and 12 months, the following were measured: CRPS severity scores (symptoms and signs of CRPS), pain, disability, work status and psychological functioning.

Results: Analyses showed that rates of almost all signs and symptoms of CRPS reduced significantly over 1 year. Reductions in symptom severity were clinically relevant and were greatest in the first 6 months and plateaued thereafter. However, at 1 year, 2/3 of patients continued to meet the IASP-Orlando criteria for CRPS and 1/4 met the Budapest research criteria for CRPS. Less than 5% of patients were symptom-free at 12 months.

Conclusions: Overall the results were less optimistic than several previously conducted prospective studies and suggest that few cases of CRPS resolve completely within 12 months of onset. Improvements are generally greater in the first 6 months, and suggest that early intervention may be important to prevent long-term disability in CRPS.

What’s already known about this topic?
Previous studies on the outcomes of complex regional pain syndrome are contradictory, with some studies documenting high rates of spontaneous recovery and other studies documenting chronic disabling symptoms.

What does this study add?
This study followed CRPS-1 patients over 1 year and showed that whilst mean symptom severity decreased, few patients were symptom-free by 12 months. One quarter still met the Budapest research criteria for CRPS, and two-thirds still met the Orlando criteria for CRPS.
Introduction

Complex regional pain syndrome (CRPS) is a condition characterised by diffuse pain and a range of symptoms, including sensory, sudomotor, vasomotor and trophic changes. Traditionally, CRPS has been known by many different names and there have been many diagnostic criteria. In 1994 the International Association for the Study of Pain (IASP) endorsed the IASP (Orlando) criteria (Merskey & Bogduk, 1994), and more recently, the Budapest criteria have been published (Harden et al., 2010a), which are stricter, requiring both symptoms and observable signs to be present.

Information regarding the natural history of CRPS is limited and contradictory, with some studies reporting that CRPS usually resolves spontaneously (Sandroni et al., 2003; Zyluk, 1998a) whilst other studies document high rates of long-term pain and disability (Beerthuizen et al., 2012; de Mos et al., 2009b). Historically, CRPS was thought to progress through three ‘stages’; from an acute stage to a dystrophic stage to an atrophic stage (Bonica, 1990). However research has shown that although subgroups of CRPS patients might exist, they do not differ in terms of CRPS duration (Bruehl et al., 2002), suggesting that there is no clear ‘progression’ through these stages.

A systematic review found three prospective studies which aimed to assess outcomes of CRPS, however, all were based on old nomenclature and diagnostic criteria for CRPS, few described outcomes in detail, reported on both observed signs and self-reported symptoms of CRPS, and none utilised relevant statistical testing (Bean et al., 2014a). These studies showed that the majority of CRPS patients make a good recovery, with rates of pain and other symptoms reducing markedly in the 6-13 months post-diagnosis (Atkins et al., 1989; Bickerstaff & Kanis, 1994; Zyluk, 1998a). For example, only 7-18% of participants still experienced pain at 12-13 month follow-up (Bickerstaff & Kanis, 1994; Zyluk, 1998a). However, these optimistic findings contrasted with more recent studies, which demonstrated that a significant number of CRPS patients experience persistent pain and dysfunction (de Mos et al., 2009b; Savas et al., 2009). Consistent with this, a large multi-centre study found that no CRPS patient was symptom free 12-months later (Beerthuizen et al., 2012). Other evidence indicates that CRPS can lead to severe adverse outcomes, including dystonia or infection, and the use of invasive treatments such as amputation or spinal cord stimulation (Bodde et al., 2011; Kumar, Rizvi, & Bnurs, 2011; van der Laan et al., 1998). Some research has suggested that CRPS symptoms can “spread”, whereby pain or other CRPS symptoms are experienced in other parts of the body (van Rijn et al., 2011). This suggests that whilst previous prospective studies document positive outcomes, there are patients for whom CRPS is devastating. Overall the inconsistencies in this body of literature indicate that more prospective studies are needed to better understand the outcomes of CRPS.
The aim of the study was to document the rates of symptoms and signs of CRPS over the first 12 months of the condition. A second aim of the research was to identify variables that predict a favourable recovery, and results from this analysis have been reported separately (Bean, Johnson, Heiss-Dunlop, Lee, & Kydd, 2015b).

**Methods**

**Participants**

The participants were patients with recently-onset CRPS-1, recruited within 12 weeks of symptom onset or initiating event. Participants were recruited from both publicly and privately funded orthopaedic, plastic surgery, physiotherapy, hand therapy and pain clinics in the region of Auckland, New Zealand between February 2012 and March 2014. Participants were included if they met the following criteria:

1. Fulfils the IASP-Orlando (1994) criteria for CRPS (Merskey & Bogduk, 1994)
2. Has had CRPS signs/symptoms for less than 12 weeks
3. Has CRPS type-1 (i.e. no evidence of specific nerve injury)
4. Aged over 18 years
5. Able to communicate in English
6. No prior history of CRPS

**Procedure**

The study was approved by the New Zealand Ministry of Health Northern Y Ethics Committee, as well as the institutional review committees of each of the three district health boards in Auckland. Participants were contacted and screened to ensure they met the inclusion criteria. Each participant was scheduled for three 60-90-minute appointments:

1. As soon as possible after referral
2. 6 months after symptom-onset
3. 12 months after symptom-onset.

Each participant was given a $NZ50 gift or petrol voucher at each appointment.

Each assessment consisted of the following measures:

1. **CRPS Severity Score/ Signs and symptoms of CRPS**: This was based on the tool described by Harden et al. (2010b). For each of the following, participants were asked whether they experienced the symptom (excluding hyperpathia), and the primary author examined the affected and unaffected limbs for signs as described below:
a. Colour asymmetry: determined by visual inspection, scored on a 4-point scale (none, mild, moderate, or severe).
b. Trophic changes to hair and nails: determined by visual inspection, scored on a 4-point scale (none, mild, moderate, or severe).
c. Sweating asymmetry: determined by visual inspection, scored on a 4-point scale (none, mild, moderate, or severe).
d. Temperature asymmetry: bilateral temperature measured at 5 pre-defined points over the affected and unaffected limbs using a digital infrared thermometer.
e. Edema: determined by a) visual inspection and scored on a 4-point scale (none, mild, moderate, or severe), and b) circumference measurements of wrist and digit 2 for upper limbs, or ankle and mid-foot circumference of lower limbs. The ratio of the circumference of affected/unaffected limbs was calculated.
f. Motor changes: determined by visual inspection of rapid movement of bilateral fingers/toes, scored on a 4-point scale (none, mild, moderate, or severe).
g. Range of motion: wrist or ankle flexion and extension measured bilaterally using goniometer.
h. Dynamic mechanical allodynia to brush: scored on a 4-point scale (none, mild, moderate, or severe).
i. Hyperpathia to repetitive light tapping on the affected limb: noted as present or absent.

Severity scores for each of the signs of CRPS were utilised, and in addition the CRPS Severity Score was calculated by summing the number of symptoms (out of a total of 8) and the number of signs observed (out of a total of 9), to give a total score out of 17. Higher scores represent more severe cases of CRPS. This scale has been shown to have good sensitivity to discriminate between CRPS and non-CRPS patients, and provides greater sensitivity to change compared to measuring CRPS as either present or absent (Harden et al., 2010b).

2. Questionnaires (see Appendix 2 for a description of the scales and internal consistency scores):
   a. Short-form McGill Pain Questionnaire 2 (SFMPQ2) (Dworkin et al., 2009)
   b. Pain Numerical Rating Scale (0-10 point scale)
   c. Disability: Pain Disability Index (Pollard, 1984)
   d. Pain-related fear: Tampa scale for Kinesiophobia (Woby et al., 2005)
   e. Pain Catastrophizing Scale (Sullivan et al., 1995)
   f. Depression Anxiety Stress Scale-21 (Lovibond & Lovibond, 1995a)
   g. Bath CRPS Body Perception Disturbance Scale (Lewis & McCabe, 2010)
h. Perceived ownership of the affected limb, measured by a single 100mm visual analogue scale asking “How strong is your sense of ownership over the affected limb?”, as previously described by Moseley et al. (2009).

3. Work Status: Participants were asked to indicate their work status prior to CRPS and at the time of each assessment (working, fulltime student, retired, sickness/invalids beneficiary, receiving accident (ACC) compensation\(^2\), unemployment or domestic purposes beneficiary, reliant on family/fulltime home-maker, or no income). Work hours were also recorded.

4. Demographics: Age, gender and ethnicity were recorded.

5. Clinical variables: Affected limb was recorded (upper or lower, dominant or non-dominant hand), and duration of CRPS was recorded in days. The Accident Compensation Corporation (ACC) status of each participant was recorded (i.e. did they have a covered injury, regardless of whether or not they were claiming ACC earnings-related compensation). CRPS trigger was recorded as either:
   a. Major injury (fracture/crush/other) requiring surgical repair
   b. Fracture not requiring surgical repair
   c. Minor surgical procedure (e.g. carpal tunnel release)
   d. Soft tissue injury
   e. Minor incident/no known tissue injury

6. Treatments: Participants were asked to indicate whether they were receiving any of the following commonly prescribed medications for CRPS: Paracetamol, anti-inflammatories, tricyclic antidepressants, gabapentin, codeine, tramadol, other opiates, prednisone, clonidine patches, vitamin C, interventional techniques (e.g. nerve block, infusions), and any of the following interventions: hand therapy/physiotherapy/occupational therapy, splinting, exercises, mirror therapy, graded motor imagery, psychological therapy or multidisciplinary pain management.

7. Spread: At 6 and 12 months, participants were asked to indicate whether their pain and/or symptoms were restricted to the original area of pain or if pain had ‘spread’. Answers were coded as: a.) No spread; b.) Spread to proximal locations, e.g. from wrist to forearm or

---
\(^2\) The Accident Compensation Corporation (ACC) provides no-fault insurance cover for all accidental injuries in New Zealand, including funding of treatment, rehabilitation, and income replacement where an individual stops work due to an injury.
shoulder; c.) Spread to mirror locations, e.g. from left hand to right hand; d.) Spread to distant/multiple locations, e.g. from left wrist to left shoulder and right foot.

**Statistical Analyses**

Data were entered into IBM SPSS Statistics version 20. To investigate changes in the presence or absence of signs and symptoms over the course of the three assessments, a series of Cochran’s Q tests were conducted, with post-hoc MacNemar tests to investigate significant effects. A Bonferroni correction was applied to MacNemar tests to compensate for multiple testing. To investigate changes over 12 months for each variable measured on a continuous scale (CRPS severity, temperature, range of motion, edema, pain, disability and psychological factors), repeated measures ANOVA with Bonferroni post-hoc tests were conducted.

There was very little missing data; where data was missing for a participant that participant was excluded from any statistical analyses involving that variable. However when means, standard deviations, and rates of the presence or absence of symptoms are displayed, all available data were used.

**Results**

**Participants**

The participants were 66 CRPS-1 patients. The flow of referral, recruitment and retention of participants into the study is displayed in Figure 4. Reasons for excluding participants from the study were: 13 people had had CRPS for more than 12 weeks, 4 were deemed not to have CRPS-1 based on referral letters and/or self-reported symptoms during a telephone call, 1 lived outside the study area and thus was not covered by ethics approval, and 1 had a previous history of CRPS. One further participant was excluded following the initial assessment as her symptoms had been present for longer than 12 weeks. Retention was high, as is displayed in Figure 4; Of the 66 participants who were included, 65 completed at least one follow-up assessment and 63 completed both follow-ups. All instances of loss to follow-up occurred when the patient could not be contacted by telephone or mail. Although the IASP-Orlando criteria for CRPS had been utilised to recruit the sample, in reality, 89% of the sample also met the stricter Budapest research criteria for CRPS, indicating that clinicians tended only to refer participants to the study when they had a broad spectrum of signs and symptoms.
As is shown in Table 19, the majority of the participants were female, and most had their upper limb affected. Approximately half were of New Zealand European ethnicity and there was ethnic diversity amongst the sample in keeping with the demographics of Auckland city. Around two-thirds of the sample developed their CRPS following an injury which was covered by the New Zealand national no-fault accident compensation insurance system (the Accident Compensation Corporation (ACC)).
Table 19. Demographic and Clinical Details of the Sample

<table>
<thead>
<tr>
<th>Mean (SD) or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>N (%) Female</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>N (%) NZ European</td>
</tr>
<tr>
<td>N (%) Maori</td>
</tr>
<tr>
<td>N (%) Pacific Islander</td>
</tr>
<tr>
<td>N (%) Indian</td>
</tr>
<tr>
<td>N (%) Other</td>
</tr>
<tr>
<td>CRPS duration (days)</td>
</tr>
<tr>
<td>Circumstance of CRPS onset</td>
</tr>
<tr>
<td>N (%) major injury (fracture/crush/other) with surgery</td>
</tr>
<tr>
<td>N (%) fracture without surgery</td>
</tr>
<tr>
<td>N (%) minor surgical procedure</td>
</tr>
<tr>
<td>N (%) soft tissue injury</td>
</tr>
<tr>
<td>N (%) minor incident/no known tissue injury</td>
</tr>
<tr>
<td>N (%) with ACC cover</td>
</tr>
<tr>
<td>Affected Limb</td>
</tr>
<tr>
<td>N (%) upper limb</td>
</tr>
<tr>
<td>N (%) lower limb</td>
</tr>
</tbody>
</table>

ACC= Accident Compensation Corporation

Change in Overall CRPS Status over 12 Months

The primary outcome measure was the CRPS severity score, which sums the total number of signs and symptoms for each participant. A repeated measures ANOVA demonstrated that mean CRPS severity scores reduced significantly from baseline to 6 months and from 6 months to 12 months, as shown in Table 20. The CRPS severity score indicated that at baseline, participants had a mean of 12 signs and/or symptoms, and this dropped significantly to a mean of 8.5 at 6 months, and again dropped significantly to a mean of 6.7 signs/symptoms by 12 months. Only 3 participants (4.76%) had a CRPS severity score of 0 at 12 months, indicating that they were symptom-free.

The percentage of participants meeting both the IASP-Orlando criteria for CRPS as well as the Budapest research criteria reduced significantly over the 12 months, indicating that the general trajectory was for improvement. However at 12 months, two-thirds of the participants still met the IASP-Orlando criteria, and one-quarter met the more conservative Budapest research criteria. The percentage of participants who met each set of diagnostic criteria at each time-point is also displayed in Table 20.
Table 20. Mean (SD) Scores at Baseline, 6 & 12 Months for: CRPS Severity, Percentage of Participants Fulfilling CRPS Diagnostic Criteria, and Scores for Measured Signs, Pain, Disability, Work and Psychological Scales

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline 6 Months</th>
<th>12 Months</th>
<th>F / Q (df) p</th>
<th>Post-Hoc tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS severity score</td>
<td>12.18 (2.41)</td>
<td>8.52 (3.26)</td>
<td>6.75 (4.07)</td>
<td>53.87(^a) (2, 60) &lt;.001**</td>
</tr>
<tr>
<td>N (%) meeting IASP-Orlando criteria</td>
<td>66 (100%)</td>
<td>57 (89.06%)</td>
<td>42 (66.67%)</td>
<td>31.18(^a) (2) &lt;.001**</td>
</tr>
<tr>
<td>N (%) meeting Budapest research criteria</td>
<td>59 (89.39%)</td>
<td>25 (39.06%)</td>
<td>16 (25.40%)</td>
<td>54.39(^b) (2) &lt;.001**</td>
</tr>
<tr>
<td>Wrist/ankle ROM ratio (% of unaffected ROM)</td>
<td>60.45% (28.86)</td>
<td>82.82%</td>
<td>80.43% (21.75)</td>
<td>32.88(^a) (2, 59) &lt;.001**</td>
</tr>
<tr>
<td>Temperature difference between limbs (°C)</td>
<td>.50° (1.09)</td>
<td>-.15° (61)</td>
<td>-.19° (57)</td>
<td>11.04(^a) (2, 59) &lt;.001**</td>
</tr>
<tr>
<td>Wrist/ankle circumference ratio (% of unaffected limb)</td>
<td>103.15% (3.69)</td>
<td>101.20%</td>
<td>99.95% (2.43)</td>
<td>25.31(^a) (2, 58) &lt;.001**</td>
</tr>
<tr>
<td>Digit 2/midfoot circumference ratio (% of unaffected limb)</td>
<td>104.19% (6.24)</td>
<td>100.57%</td>
<td>99.80% (3.28)</td>
<td>16.60(^a) (2, 59) &lt;.001**</td>
</tr>
<tr>
<td>Pain intensity (0-10 scale)</td>
<td>5.46 (2.02)</td>
<td>3.51 (2.48)</td>
<td>2.77 (2.84)</td>
<td>45.35(^a) (2, 60) &lt;.001**</td>
</tr>
<tr>
<td>Pain (McGill) total</td>
<td>4.22 (2.22)</td>
<td>2.35 (2.10)</td>
<td>1.77 (2.09)</td>
<td>36.55(^a) (2, 60) &lt;.001**</td>
</tr>
<tr>
<td>Pain (McGill) continuous</td>
<td>4.67 (2.32)</td>
<td>2.88 (2.32)</td>
<td>2.11 (2.31)</td>
<td>32.02(^a) (2, 60) &lt;.001**</td>
</tr>
<tr>
<td>Pain (McGill) intermittent</td>
<td>4.25 (2.73)</td>
<td>2.14 (2.42)</td>
<td>1.55 (2.20)</td>
<td>26.04(^a) (2, 60) &lt;.001**</td>
</tr>
<tr>
<td>Pain (McGill) neuropathic</td>
<td>3.99 (2.20)</td>
<td>2.41 (2.28)</td>
<td>1.90 (2.19)</td>
<td>26.43(^a) (2, 60) &lt;.001**</td>
</tr>
<tr>
<td>Pain (McGill) affective</td>
<td>3.82 (3.04)</td>
<td>1.77 (2.33)</td>
<td>1.42 (2.39)</td>
<td>23.50(^a) (2, 60) &lt;.001**</td>
</tr>
<tr>
<td></td>
<td>Baseline (N=66)</td>
<td>6 Months (N=64)</td>
<td>12 Months (N=63)</td>
<td>F / Q (df) p</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td><strong>Disability Measures:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td>37.15 (14.33)</td>
<td>18.15 (15.13)</td>
<td>14.74 (16.08)</td>
<td>77.35a (2, 60)&lt;.001**</td>
</tr>
<tr>
<td>Work hours†</td>
<td>17.36 (20.88)</td>
<td>27.51 (21.23)</td>
<td>26.48 (22.62)</td>
<td>6.38a (2, 43).004**</td>
</tr>
<tr>
<td>N (%) working †</td>
<td>22 (44.90%)</td>
<td>33 (70.21)</td>
<td>31 (67.39%)</td>
<td>10.57b (2).005**</td>
</tr>
<tr>
<td><strong>Psychological Measures:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-related fear</td>
<td>28.51 (7.21)</td>
<td>22.81 (7.35)</td>
<td>21.66 (8.86)</td>
<td>21.01a (2, 60)&lt;.001**</td>
</tr>
<tr>
<td>Catastrophising</td>
<td>22.39 (15.43)</td>
<td>13.41 (14.05)</td>
<td>11.64 (13.93)</td>
<td>16.49a (2, 60).001**</td>
</tr>
<tr>
<td>Depression</td>
<td>6.33 (5.47)</td>
<td>4.34 (5.82)</td>
<td>4.05 (5.61)</td>
<td>4.43a (2, 60).016*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.59 (5.41)</td>
<td>3.62 (4.84)</td>
<td>3.67 (5.09)</td>
<td>4.16a (2, 60).020*</td>
</tr>
<tr>
<td>Stress</td>
<td>9.45 (6.50)</td>
<td>6.22 (5.82)</td>
<td>5.46 (6.10)</td>
<td>11.58a (2, 60)&lt;.001**</td>
</tr>
<tr>
<td>Body perception disturbance</td>
<td>18.19 (9.46)</td>
<td>15.48 (10.63)</td>
<td>12.30 (12.35)</td>
<td>7.70a (2, 60).001**</td>
</tr>
<tr>
<td>Perceived ownership</td>
<td>61.33 (31.41)</td>
<td>75.55 (27.34)</td>
<td>78.11 (29.44)</td>
<td>8.51a (2, 60).001**</td>
</tr>
</tbody>
</table>

*p<.05; **p<.001; T1= time 1 (baseline); T2= time 2 (6 months); T3= time 3 (12 months).
Change in Symptoms and Signs of CRPS over 12 Months

As shown in Figure 5, rates of all of the self-reported symptoms of CRPS reduced significantly over time, except for temperature disturbance. Cochran’s Q tests confirmed that changes were significant, and McNemar post-hoc tests determined at which time-points significant changes occurred. The only symptom which improved both between baseline and 6 months and between 6 and 12 months was discolouration. Rates of pain, swelling, reduced range of motion and alldynia all improved significantly in the first six months but not significantly thereafter. Rates of swelling, motor changes and hair and nail changes improved significantly between baseline and 12 months. Actual rates and the Cochran’s Q statistics are also reported in Appendix 3.

Figure 5. Bar chart depicting changes in self-reported CRPS symptoms from baseline (T1) to 6 months (T2) and 12 months (T3)

Note: *p<.05; Pain indicated by a score >0 on the numerical rating scale.

Figure 6 displays the rates of observed signs of CRPS at baseline, 6 and 12 months, excluding temperature disturbance and range of motion (which were measured on a continuous scale and are reported in Table 20). For the signs presented in Figure 6, statistical testing for change in severity
over time was conducted using dichotomous data (sign either present or absent), utilising Cochran’s Q tests. This showed that rates of swelling and hair and nail changes improved both between baseline and 6 months, and between 6 and 12 months. Rates of discolouration, motor changes, and dynamic mechanical allodynia improved between baseline and 6 months and not significantly thereafter. Rates of hyperpathia improved significantly between baseline and 12 months. Abnormal sweating was infrequently recorded, likely due to the lack of a specific measurement tool, and results did not show significant change. Data from which Figure 6 is taken is also presented in Appendix 4.

Figure 6. The percentage of the sample with mild, moderate or severe signs of CRPS on physical examination at baseline (T1), 6 months (T2) and 12 months (T3)

There were several CRPS signs that were measured on a continuous scale (temperature, swelling (circumference measures) and range of motion). For these variables, mean scores at each of the three time-points are presented in Table 20. Repeated measures ANOVA tests demonstrated that mean improvements over 12 months in range of motion, swelling and pain intensity were statistically significant. For wrist swelling, improvements occurred both between baseline and 6 months and

Note:

*<.05; hyperpathia was measured as either present or absent only, no severity ratings were given.
between 6 and 12 months. For range of motion and finger/mid-foot swelling, improvements were only statistically significant in the first 6 months.

Measures of pain intensity also improved significantly. The numerical rating scale, SFMPQ-2 total score and continuous pain score all improved significantly between baseline and 6 months and between 6 and 12 months. The SFMPQ-2 intermittent, neuropathic and affective subscales all improved significantly by 6 months but not significantly thereafter.

The percentage of patients who had noted their CRPS symptoms to ‘spread’ by 6 and 12 months were as follows: At 6 months, 29.7% reported proximal ‘spread’, 10.9% reported mirror ‘spread’ and 10.9% reported ‘spread’ to distant/multiple locations. At 12 months, 28.6% reported proximal ‘spread’, 3.2% reported mirror ‘spread’ and 7.9% reported ‘spread’ to distant/multiple locations. A chi-square test showed that more patients reported ‘spread’ at 6 months than at 12 months $\chi^2 (9) = 28.17, p=.001$, indicating that for some participants, this ‘spread’ was temporary.

Changes in Disability over 12 Months
Participants’ scores on the Pain Disability Index demonstrated that they were most disabled at baseline, and this improved significantly by 6 months and remained so at 12 months. A similar pattern of improvement occurred for work measures. For the subsample of participants who were working prior to developing CRPS, just less than half were working at baseline, and this increased significantly to around two thirds by 6 and 12 month follow-ups. The number of hours worked showed the same pattern. There were no significant improvements in disability or work status after 6 months. Scores for disability and work measures are presented in Table 20, along with the results of repeated measures ANOVA or Cochran’s Q tests of significance.

Changes on Psychometric Measures over 12 Months
Table 20 also displays the mean and standard deviation scores for the psychometric measures at baseline, 6 and 12 months. This shows that participants reported the highest mean levels of pain-related fear, catastrophic thinking, depression, anxiety, stress, and body perception disturbance, and the lowest level of perceived limb ownership at baseline. Repeated measures ANOVA with bonferroni post-hoc tests showed that mean scores on all variables except depression and body perception disturbance improved significantly by 6 months, and remained improved at 12 months. For depression, significant improvement was demonstrated between the baseline and 12-month scores, and for body perception disturbance, 12-month scores were significantly better than those at baseline or 6 months.
Treatments Received
The percentage of participants who received the following treatments over the course of 12 months are as follows: Tricyclic antidepressants: 71.4%; Gabapentin 47.6%; Paracetamol 85.7%; Anti-inflammatories 73%; Opioids 19%; Tramadol 41.3%; Clonidine 20.6%; Vitamin C 7.9%; Prednisone 17.5%; Intervventional treatments (infusions/nerve blocks) 3.2%; specialist hand therapy/physiotherapy/occupational therapy 98%; splinting/immobilization 93.5%; prescribed exercises 95.2%; desensitization 10.8%; mirror therapy 46%; graded motor imagery 33.3%; multidisciplinary pain management 20.6%; psychological therapy 15.9%.

Discussion
The present study demonstrated significantly less optimistic general outcomes of CRPS than have been previously documented by prospective studies (Atkins et al., 1989; Bickerstaff & Kanis, 1994; Zyluk, 2001). We found that at 12-month follow-up, two-thirds of CRPS patients continued to meet the IASP-Orlando criteria for CRPS and one-quarter met the stricter Budapest research criteria. Previously, Zyluk (1998a) reported that in a prospective study requiring patients to receive no treatment, only 10% of patients withdrew to receive treatment, and at the conclusion of the study only one patient warranted the diagnosis of “mild RSD”. Our results were more consistent with recently conducted studies which have also utilised the nomenclature and diagnostic criteria for complex regional pain syndrome. For example, de Mos and colleagues (2009b) found that 64% of patients continued to meet the IASP-Orlando criteria for CRPS at a mean of 5.8 years post-diagnosis. Savas et al. (2009) reported that only 10% of CRPS patients were symptom-free after 18 months. Beerthuizen et al. (2012) found that none of the patients who met the Budapest criteria for CRPS post-fracture were symptom-free 12 months later. Together with the findings presented here, it appears that CRPS has significantly greater long-term consequences than was previously noted in prospective studies.

However, we did note that rates and severity scores for all of the features of CRPS improved significantly over the 12 months, except for rates of temperature disturbance. Most of these reductions were clinically significant, for example, rates of swelling reduced from 77% at baseline to 23% at 12 months. Pain scores more than halved, restrictions in range of motion halved, and measures of the severity of swelling normalised compared to the unaffected limb. These findings are consistent with previous studies which have documented fairly low-severity symptoms in follow-ups of CRPS patients. For example, Geertzen et al. (1998c) found that the range of motion of CRPS patients’ affected limbs was a mean of 89% of the range of motion of their unaffected limb, 5 ½ years after diagnosis. The same study reported that visual analogue pain scores were just 1.23 on a 10
Similarly, Maihofner et al. (2004) found that the 45° difference in wrist range of motion present in the early stages of CRPS reduced to just 7°, and pain scores reduced from 7.2 to 1.4 (on a 10 point scale). Two other studies reported reductions in pain intensity from 4.5 and 5.3 at baseline to 1.7 at long-term follow-up (Herlyn et al., 2010; Zyluk, 2001). Similarly, our study found that pain scores reduced from 5.6 to 2.8 on a 10-point numerical rating scale, and from 4.1 to 1.8 for the McGill pain scale (also scored out of 10). Thus whilst a majority of patients continued to be affected by features of CRPS even 12 months after its development, the severity of symptoms appears to reduce meaningfully over this time.

Clinical guidelines state that early intervention is considered important in the treatment of CRPS, reporting that symptoms often improve or stabilize in the early stages, whilst later improvement is less common (Goebel, 2011; Turner-Stokes, Goebel, & Guideline Development Group, 2011). Our data support this conclusion in part. Interestingly, we found that statistically significant changes occurred both between baseline and 6 months and between 6 and 12 months for a number of measures. However the following were noted to improve only between baseline and 6 months, and not in a statistically significant manner thereafter: self-reported swelling, reduced range of motion and allodynia, intermittent, neuropathic and affective pain scores, observed discolouration, motor changes, temperature disturbance and mechanical allodynia, as well as the proportion of patients meeting the Budapest research criteria for CRPS. Inspection of the degree of change also indicated that greater change occurred in measures of symptom severity between baseline and 6 months than between 6 and 12 months. For example, pain scores reduce by a mean of 2 points on a 10-point scale in the first 6 months, then by approximately half a point in the later 6 months. The reduction observed in the CRPS severity score in the first 6 months (a reduction of a mean of 3.6 points) halved to a reduction of only 1.8 points in the second six months. Thus it appears from our data that although some CRPS signs and symptoms can continue to improve throughout the first 12 months, improvement is more rapid and pronounced in the early stages.

Interestingly, we observed that measures of disability, work hours, and the proportion of the sample working all improved significantly between baseline and 6 months but not thereafter. Thus any continued improvements in pain and symptoms did not translate into functional gains for patients after the 6-month window. This suggests that assisting patients to improve their function and return to work are likely to be most effective if provided in the acute stages. Similar findings have been reported in samples of low back pain patients, where rates of return to work dramatically plateau after just 12 weeks (Dionne et al., 2005). Similarly, mean scores on measures of pain-related fear, pain catastrophising, anxiety and stress all improved significantly in the first 6 months and not
thereafter, suggesting that early on in the course of CRPS is a critical time to intervene to prevent not only long-term disability, but also prolonged psychological distress.

**Limitations**

There were a number of limitations to the present study. First, our sample was made up those who were identified clinically and referred for the study. Thus, the sample is likely to be representative of those presenting in clinical settings but may have failed to capture any patients who did not present to healthcare providers or whose symptoms were not severe enough to raise clinicians’ concerns. Second, the sample is unlikely to be entirely representative; in particular we had only small numbers of patients with lower limb CRPS, so results need to be viewed with caution when applying them to this group. Some of our measures were not ideal; for example, we measured sweating by visual inspection but this proved to be insufficient with very few cases identified, and other measures, such as galvanic skin response would likely be more informative. Additionally, we used the IASP-Orlando diagnostic criteria for CRPS, which is less strict than the newer Budapest research criteria. In reality, 89% of the sample met the stricter criteria regardless, but this may limit the applicability of the results. In addition, our ‘baseline’ measure was up to 12-weeks after the development of CRPS symptoms; thus baseline measures may not capture the full severity of symptoms as some recovery could have already occurred. We made no attempts to control the treatments received by participants during the study, and allowed them to access usual care. It is likely that treatment influenced outcomes, however we were unable to demonstrate a beneficial effect of any of the treatments on outcomes (data not presented here but see Bean et al. (2015b)). This is likely due to the observational nature of the study: those with the most severe CRPS likely received more treatments. Ethical concerns would prevent a true ‘natural history’ study in CRPS, but future studies may wish to standardise treatment more strictly.

**Conclusions**

We found low rates of resolution amongst a sample of patients with recently-onset CRPS. Whilst rates of most signs and symptoms of CRPS and mean severity scores for the signs and symptoms of CRPS reduced significantly over 12 months, three quarters continued to experience pain, two thirds continued to meet the IASP-Orlando criteria for CRPS and one quarter continued to meet the Budapest criteria, indicating significant problems. Whilst a number of features of CRPS improved both in the first as well as in the later 6 months, measures of disability, work and distress plateaued at 6 months and did not improve thereafter, indicating that early intervention is likely required to prevent long-term disability in CRPS.
Acknowledgements

We thank all of the participants of the study for their time and cooperation. We would like to acknowledge the Oakley Mental Health Research Foundation for funding the study. We appreciated the support of the following teams for their involvement with the study: the Auckland Regional Plastic and Reconstructive Hand Surgery Service, The Counties-Manukau Hand Therapy Service, The Auckland Regional Pain Service, Handworks, Moving Hands Rehabilitation, Hands Out West, Paincare, the Counties-Manukau Chronic Pain Service, the Waitemata Orthopaedics Dept and Waitemata Pain Management Unit.
Chapter 8: Who recovers from Complex Regional Pain Syndrome? A prospective study

Prelude

Rationale

The final study presented here fulfills the main aim of this thesis: to determine whether psychological factors influence recovery from CRPS. As described earlier, much of the psychological research into CRPS (particularly the prospective studies) have focussed on determining whether or not psychological factors predict CRPS development, with the theory that some kind of psychological vulnerability may play a causal role in CRPS. Research has not supported this view, with the majority of studies showing that those who develop CRPS are not psychologically different from those who do not, following some kind of injury or surgery (Beerthuizen et al., 2011; Daviet et al., 2002; de Mos et al., 2008; Harden et al., 2003; Puchalski & Zyluk, 2005).

However, psychological factors are known to influence pain in a universal manner, whether it be chronic pain, acute clinical pain, or even the pain induced in experimental settings, and whether it occurs in humans or animals (Linton & Shaw, 2011; Martin et al., 2014; Wiech & Tracey, 2009). One particular branch of research has investigated the influence of psychological factors on the development of chronic pain and disability after an acute painful event, and many studies have shown that factors such as mood, pain-related thoughts and expectations, and fear or pain or re-injury influence this process. This has been demonstrated to occur in low back pain, neck pain, post-surgical pain and pain following major trauma (Carroll et al., 2009; Clay et al., 2012; Hinrichs-Rocker et al., 2009; Wertli et al., 2014). Therefore the central aim of the study described below was to determine whether the same occurs in CRPS.

Understanding prognostic factors in CRPS has been identified as an important area of research, and a recent systematic review found that previous research on prognostic factors was of poor quality and much of it was contradictory (Wertli et al., 2013). The only two studies identified as assessing the potential prognostic value of “contextual factors” were of low quality. One mentioned that two out of 16 workers who developed CRPS were unable to return to work due to chronic alcoholism (Dauty et al., 2001). The second reported that the presence of a ‘psychological background’ delayed treatment progress, but only for those whose CRPS started in a non-traumatic manner (Eulry et al., 1990). Another study, which was not included in Wertli et al.’s (2013) systematic review, reanalysed...
previously published data from a study which had followed patients post-knee arthroplasty to determine who developed CRPS (Harden et al., 2003). In this reanalysis the authors found no associations between pre-operative anxiety and depression and later CRPS severity, but reported that increases in anxiety and depression in the first 4 weeks post-surgery were associated with later CRPS severity (Harden et al., 2010b). Thus the body of research on the prognostic value of psychological factors in CRPS is very limited. There is a significant need for more research, and the study described below appears to be the first study with the explicit aim of determining these factors.

The following study selected a range of potential psychological factors to test as possible predictors of CRPS outcome, all of which might be considered to influence CRPS according to the theoretical viewpoint that CRPS represents an overprotective response to perceived threat (Marinus et al., 2011; Moseley, 2007). Moseley theorised that perception of the threat value of pain would likely be influenced by an individual’s beliefs about their pain, expectations, and level of fear or anxiety, amongst other factors. However, little research has examined the ways in which such factors influence pain in CRPS thus far. The present study included measures of anxiety and pain-related fear, as these have an obvious link to threat perception and were demonstrated to have associations with pain in one previously described study in this thesis (Bean et al., 2014b). We also measured pain catastrophising, noting that this assesses, to some extent, the extent to which patients’ beliefs about their pain are alarming, and the threat value associated with it. Previous research has shown that catastrophising and pain-related fear were associated with greater increases in pain and swelling when patients were performing ‘imagined movements’ (Moseley et al., 2008b). Additionally, we chose to include a measure of psychological stress, noting that previous systematic reviews on psychological factors in CRPS identified consistent positive findings of stressful life events in CRPS patients (Beertuizen et al., 2009; Lohnberg & Altmair, 2013), and that psychological stress theoretically increases the likelihood of the brain to perceive threat. We included a measure of depression, noting that this has been associated with greater CRPS-related disability and/pain intensity (Bean, Johnson, Heiss-Dunlop, & Kydd, 2015a; Bean et al., 2014b; Bruehl et al., 1996). Depression is also associated with feelings of helplessness likely to induce greater fear and perceived threat.

The study also aimed to look at some of the psychological constructs associated with how CRPS patients relate to, and engage with, their affected limb. One natural response to threat is avoidance, and it is possible that the brain disengages with the affected limb in order to immobilize and protect it in a situation where the limb is perceived to be under threat. As described in Chapter 2, CRPS is associated with features of ‘neglect’ or disuse of the affected limb, and describe features such as
dislike of the limb, mis-perceiving the limb’s location, struggling to move the limb, and having a distorted mental image of the limb. This constellation of features has been labelled ‘body perception disturbance’ (Lewis et al., 2007), and we also aimed to determine whether this might influence recovery. A related measure was ‘perceived ownership’ of the affected limb, which has been shown to be impaired in CRPS (Moseley et al., 2012). A final measure we chose to include was laterality task performance. Previous research has revealed that when asked to identify pictures of limbs as either left or right, CRPS patients take longer to identify a picture that corresponds to their affected hand, and are also slower when the pictured position of the hand would induce pain for them (Moseley, 2004c). The task involves mentally rotating an image of one’s own limb into the pictured position, something which is hypothesised to be difficult if one has a poor mental image of the limb or struggles to engage with the limb.

**Aims**

Thus the study tested a broad range of psychological variables as potential predictors of CRPS recovery. The main aims of the study were:

1. To determine whether psychological factors influence the course of three dependent variables in CRPS: CRPS severity (number of signs & symptoms), pain intensity, and disability.

2. To determine whether measures of engagement with the affected limb (body perception disturbance, perceived ownership of the affected limb, laterality task performance) influence the course of three dependent variables in CRPS: CRPS severity (number of signs & symptoms), pain intensity, and disability.

**Citation**

Abstract

Background: Previous studies have shown that the outcomes of complex regional pain syndrome (CRPS) vary significantly between patients, but few studies have identified prognostic indicators. The aim of the present study was to determine whether psychological factors are associated with recovery from recently-onset CRPS amongst patients followed prospectively for 1 year.

Methods: 66 CRPS (Type-1) patients were recruited within 12 weeks of symptom-onset and assessed immediately and at 6 and 12 months, during which time they received treatment-as-usual. At each assessment the following were measured: signs and symptoms of CRPS, pain, disability, depression, anxiety, stress, pain-related fear, pain catastrophising, laterality task performance, body perception disturbance and perceived ownership of the limb. Mixed-effects models for repeated measures were conducted to identify baseline variables associated with CRPS severity, pain and disability over the 12 months.

Results: Scores for all 3 outcome variables improved over the study period. Males, and those with lower levels of baseline pain and disability experienced the lowest CRPS severity scores over 12 months. Those with lower baseline anxiety and disability had the lowest pain intensity over the study period, and those with lower baseline pain and pain-related fear experienced the least disability over the 12 months.

Conclusions: Results suggest that anxiety, pain-related fear and disability are associated with poorer outcomes in CRPS and could be considered as target variables for early treatment. The findings support the theory that CRPS represents an aberrant protective response to perceived threat of tissue injury.

Summary: Amongst patients with recently-onset CRPS-1, those with higher levels of pain-related fear and anxiety at baseline experienced greater pain and disability over the following 12 months.
Introduction

Complex regional pain syndrome (CRPS) is characterised by pain, vasomotor, sudomotor, trophic and sensory symptoms. The course of CRPS varies, with some patients making a good recovery within 12-13 months, whilst others develop chronic symptoms (Bean et al., 2014a). Chronic CRPS can be severe and disabling; it can lead to complications such as dystonia (van Rijn, Marinus, Putter, & van Hilten, 2007), and invasive treatments such as amputation or spinal cord stimulation (Bodde et al., 2011; Sears et al., 2011). Thus one goal is to prevent long-term disability amongst those with recently-onset CRPS (McCabe, 2013). An understanding of prognostic indicators in CRPS would allow the identification of patients at risk of poor outcomes, shed light on the mechanisms that maintain CRPS and potentially allow early intervention to prevent long-term disability. A systematic review reported that the literature on the prognosis of CRPS was small and of poor quality, with inconsistent findings (Wertli et al., 2013). There were two indicators of poor prognosis identified: the presence of sensory symptoms and cold skin temperature.

Several factors are considered to contribute to the pathophysiology of CRPS, including neurogenic inflammation (Parkitny et al., 2013), sympathetic nervous system (SNS) activity (Drummond, 2010), and maladaptive neuronal plasticity (Di Pietro et al., 2013a; Woolf, 2011). One hypothesis is that CRPS represents an aberrant protective response to actual or perceived tissue injury (Marinus et al., 2011; Moseley, 2007), whereby the body’s defensive mechanisms are orchestrated to protect the limb. If this hypothesis is correct, then defensive physiological processes, such as inflammation and autonomic arousal, likely play a role in maintaining CRPS. It also makes sense that not only defensive physiological processes, but also psychological factors associated with perception of threat, could influence CRPS. Such psychological factors might include beliefs about tissue damage, pain-related fear, pain-catastrophising, anxiety, stress, or depression. These factors could influence autonomic arousal, inflammatory processes, or could operate through behavioural mechanisms. For example, the fear-avoidance model proposes that catastrophising and fear lead to avoidance of movement, significantly affecting recovery (Vlaeyen et al., 2012). Research demonstrates that psychological factors influence outcomes in a range of other pain conditions (Carroll et al., 2009; Clay et al., 2012; Hinrichs-Rocker et al., 2009; Melloh et al., 2009). Studies have shown that psychological factors do not cause CRPS (Lohnberg & Altmaier, 2013), but the influence of psychological factors on the later prognosis of CRPS have seldom been studied. Studies that exist used poorly-defined psychological constructs (Eulry et al., 1990; Zyluk, 1998b), though one higher-quality study showed that increases in distress after surgery influenced later CRPS severity (2010b).
Another feature of CRPS, likely associated with this aberrant protective response, is disuse of, and disengagement with, the affected limb. Patients with CRPS often avoid using the limb, and the term ‘body perception disturbance’ has been coined to describe neglect, dislike and misperception of the limb (Galer & Jensen, 1999; Lewis et al., 2007; Moseley, 2005). When asked to make left-right judgements, CRPS patients also take longer to recognise a picture of the affected limb compared to the unaffected limb (Moseley, 2004c), suggesting that the brain disengages with the affected limb. This disengagement likely leads patients to immobilize their limb, protecting it from further injury.

The aim of the present study was to determine whether psychological factors influenced the recovery process amongst a sample of patients with recent-onset CRPS.

**Methods**

**Participants**

CRPS-1 patients were recruited from both hospital-based and private clinics in the Auckland area between February 2012 and March 2014. Surgeons, physicians, hand therapists, physiotherapists, and staff at pain clinics were asked to refer any patient meeting the following criteria for the study:

1. Meets the 1994 IASP criteria for CRPS (Merskey & Bogduk, 1994)
2. Has had CRPS for less than 12 weeks
3. Has CRPS type-1 (i.e. no nerve injury as a cause for symptoms)
4. Aged over 18 years
5. Able to communicate in English
6. No prior history of CRPS

**Procedure**

The study was approved by the New Zealand Ministry of Health Northern Y Ethics Committee. Participants were contacted by phone and screened to ensure they met the inclusion criteria. Each participant was scheduled for 3 assessments:

1. As soon as possible after referral
2. 6 months after symptom-onset
3. 12 months after symptom-onset

Each assessment took 60-90 minutes, and occurred either at the clinics where the patients were receiving treatment, at the University of Auckland, or in participants’ own homes. Each participant was given a $NZ50 gift or petrol voucher at each appointment. During the first appointment, the physical examination and a discussion of the pain history and location was also used to confirm that participant met the 1994 IASP-Orlando criteria for CRPS (Merskey & Bogduk, 1994), and medical
records were scrutinised as necessary. Thus a triangulation method was used to ensure participants did have CRPS: comparing the referring clinician’s report, our own physical examination, and checking medical records.

**Measures**

At each of the three appointments, the following measures were taken:

1. **CRPS Severity Score/ Signs and symptoms of CRPS** (Harden et al., 2010b): For each of the following, participants were asked whether they experienced the symptom (excluding hyperpathia), and the primary author examined the affected and unaffected limbs for signs as described below:
   a. Colour asymmetry
   b. Trophic changes to hair and nails
   c. Sweating asymmetry
   d. Temperature asymmetry (bilateral temperature measured at 5 pre-defined points over the affected and unaffected limbs using a digital infrared thermometer).
   e. Edema
   f. Motor changes
   g. Range of motion
   h. Dynamic mechanical allodynia to brush (scored on a 4-point scale (none, mild, moderate, or severe).
   i. Hyperpathia to repetitive light tapping on the affected limb

The CRPS severity score was calculated by summing the number of symptoms reported by the patient (out of a total of 8) and the number of signs observed (out of a total of 9), to give a total score out of 17. Higher scores represent more severe cases of CRPS. This scale has been shown to have good sensitivity to discriminate between CRPS and non-CRPS patients, and provides greater sensitivity to change compared to measuring CRPS as either present or absent (Harden et al., 2010b).

2. **Pain Intensity: Short-form McGill Pain Questionnaire 2 (SFMPQ2)** (Dworkin et al., 2009): This scale asks participants to rate each of 22 pain descriptors on a scale from 0 (none) to 10 (worst possible). A total score is determined by calculating the average score over all 22 items, giving a total score ranging between 0 (minimum pain) and 10 (maximum pain). The SFMPQ2 has been demonstrated to have excellent reliability and validity (Lovejoy et al., 2012). Reliability was excellent for the present study’s baseline data (Cronbach’s α=.929), as well as at each of the 6 & 12 month follow-ups (Cronbach’s α=.959 & .969).
3. Disability: Pain Disability Index (PDI) (Pollard, 1984): This seven-item scale asks participants to rate their level of disability for seven domains of life on a scale from 0 (no disability) to 10 (total disability). A total disability score out of 70 is calculated by adding the items together. Higher scores represent greater disability. This scale has been shown to have good psychometric properties (Tait & Chibnall, 2005). Reliability was acceptable for the present study’s baseline data (Cronbach’s $\alpha=.796$), as well as at each of the 6 & 12 month follow-ups (Cronbach’s $\alpha=.907$ & .920).

4. Pain-related fear: Tampa scale for Kinesiophobia (TSK) (Woby et al., 2005): This is an 11-item scale which asks participants to rate the extent to which they agree or disagree with a range of statements endorsing pain-related fear. Scores are calculated between a minimum of 11 (no pain-related fear) and a maximum of 44 (high levels of pain-related fear). This scale has been demonstrated to have good reliability and validity (Woby et al., 2005). For the present study’s baseline data, reliability was good (Cronbach’s $\alpha=.834$).

5. Catastrophic thinking: Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995). This is a 13-item scale which asks participants to rate the extent to which they experience a range of catastrophic thoughts on a 5 point scale from 0 (not at all) to 4 (all the time). A total score out of 52 is calculated by adding all answers together. Higher scores indicate greater levels of pain catastrophising. The scale has been shown to have excellent reliability and validity (Sullivan et al., 1995). Reliability at baseline in the present study was excellent (Cronbach’s $\alpha=.955$).

6. Depression Anxiety Stress Scale 21 (DASS-21) (Lovibond & Lovibond, 1995a): This 21-item scale consists of 7 items measuring depression, 7 measuring anxiety and 7 measuring stress. Participants are asked to rate the extent to which they endorse each item on a scale from 0 (did not apply to me at all) to 3 (applied to me very much or most of the time). Items for each of the three subscales are added together to give three scores, each out of 21, with higher scores representing greater depression, anxiety or stress. The DASS has been shown to have very good reliability and validity (Lovibond & Lovibond, 1995a). Reliability (Cronbach’s $\alpha$) coefficients were good for the present study’s baseline data (Depression: $\alpha=.883$; Anxiety: $\alpha=.829$ Stress: $\alpha=.907$).

7. The Bath CRPS Body Perception Disturbance Scale (BCBPDS) (Lewis & McCabe, 2010): This 11-item measure consists of 4 items asking participants to rate the extent to which they feel connected to and aware of their affected limb, 4 items asking participants whether or not
they experience discrepancies between sensory and visual information associated with the affected limb, 2 items asking about participants’ desire to amputate their limb, and 1 item assessing the patient’s mental image of their affected and unaffected limbs. This scale is scored from 0-57, with higher scores representing greater body perception disturbance. The scale has been shown to have adequate internal consistency and inter-rater reliability (Lewis & Schweinhardt, 2012). However with the present study’s baseline data, the scale’s internal consistency was poor (Cronbach’s α=.533). This improved to acceptable levels after omission of item 3 (about attention paid to the limb) (Cronbach’s α=.611), but the study findings did not differ based on whether this item was included or excluded, so in the analyses presented, all items were included.

8. Perceived ownership of the affected limb (Moseley et al., 2009): Participants were asked “How strong is your sense of ownership over your affected limb?” and were asked to place a mark on a 100mm visual analogue scale with an anchor at one end “very weak – I feel like the limb doesn’t belong to me at all” and at the other end “normal – the same as all my other limbs”. Higher scores represent greater ownership over the limb.

9. Laterality Task Performance (Moseley, 2004c): Participants were asked to complete 5 trials of 30 images each (150 images total) of the NOI Group’s Recognise programme (“vanilla hands” or “vanilla feet” selection), available at http://www.noigroup.com/recognise (Neuro Orthopaedic Institute Ltd., 2001). This is a web-based application which presents pictures of hands (shown to upper limb CRPS patients) or feet (shown to lower limb CRPS patients). Participants have to respond by indicating whether the picture is a left or right limb by pressing one of two keys on the computer keyboard with their non-CRPS affected hand. The accuracy and mean speed of recognition were recorded for left limbs and right limbs, and this was averaged over the 5 trials. These scores were used to calculate a ratio of speed to identify a limb that correlates with the patient’s affected limb / speed to identify a limb that correlated with the patient’s unaffected limb. Previous studies have shown that CRPS patients take longer to recognise pictures of the affected limb, and that this deficit is related to duration of CRPS symptoms and predicted pain that would be evoked by adopting the pictured limb position (Moseley, 2004c). Laterality task training also forms part of established treatment programmes for CRPS (Moseley, 2004a).

10. Treatments: Participants were asked to indicate whether they were receiving any of the following commonly prescribed medications for CRPS: Paracetamol, anti-inflammatories, tricyclic antidepressants, gabapentin, codeine, tramadol, other opiates, prednisone, clonidine
patches, vitamin C, interventional procedures (e.g. nerve blocks, infusions) and any of the following interventions: hand therapy/physiotherapy/occupational therapy, splinting, exercises, mirror therapy, graded motor imagery, psychological therapy or multidisciplinary pain management.

11. Clinical variables: Affected limb was recorded (upper or lower, dominant or non-dominant hand), and duration of CRPS was recorded in days. The Accident Compensation Corporation (ACC) status\(^3\) of each participant was recorded (i.e. did they have a covered injury, regardless of whether or not they were claiming ACC earnings-related compensation). CRPS “trigger” was recorded as either:
   a. Major injury (fracture/crush/other) requiring surgical repair
   b. Fracture not requiring surgical repair
   c. Minor surgical procedure (e.g. carpal tunnel release)
   d. Soft tissue injury
   e. Minor incident/no known tissue injury

12. Demographics: Age, sex and ethnicity were recorded.

Data Analysis

Statistical analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA.). The method of mixed-effects models for repeated measures (MMRM) was used to identify independent variables associated with the three continuous outcome variables assessed at baseline, 6 and 12 months. The three outcome variables were: CRPS severity (measured by CRPS severity scores), pain (measured by the SFMPQ2), and disability (measured by the PDI). Analyses assumed a random intercept and random slope, to allow for individual differences at baseline and individual differences in recovery trajectories. The SAS PROC MIXED procedure was used to conduct MMRM analyses. The within-subject errors were modelled using an unstructured (co)variance structure. We used a restricted maximum likelihood estimation method. The first order Kenward-Roger method was used to estimate the denominator degrees of freedom for fixed effects. There was very little missing data. When a data point was missing that participant was still included in the mixed effects models, which used all available data from the participants.

---
\(^3\) The Accident Compensation Corporation (ACC) provides no-fault insurance cover for all accidental injuries in New Zealand, including funding of treatment, rehabilitation, and income replacement where an individual stops work due to an injury.
The following model building process was used for each of the three dependent variables:

A) Step 1: A MMRM was conducted to fit a random intercept and slope model with fixed effects of time and each possible confounding variable (confounding variables included were age, sex, CRPS duration at study entry, CRPS trigger/injury type, and affected limb (upper versus lower)).

B) Step 2: In order to identify which independent variables (measured at baseline) to include in our models, each independent variable was entered as a fixed effect individually into a random intercept and slope model along with fixed effects for time and confounding variables. The list of independent variables tested in this step included baseline scores for all of the psychological variables, perceived ownership of the limb, body perception disturbance, laterality task performance, each of the demographic and clinical variables not previously included as possible confounders, and measures of skin temperature disturbance and allodynia (included due to previous research demonstrating the importance of these factors). Baseline CRPS severity scores, pain scores and disability scores were also included as independent variables when they were not the outcome variable of interest.

C) Step 3: Combinations of the independent variables identified in step 2 as having significant effects were entered into the random intercept and slope model, starting with those with the strongest effects, adding others one-by-one, and retaining those variables whose effects remained significant when combined.

D) The final model presented is a random intercept and slope model with fixed effects of time, confounding variables and any independent variables shown to have significant effects on the outcome of interest in Step 3.

In addition, we tested whether or not we needed to control for any the treatments received by participants, by running MMRMs for each of the 18 treatment variables listed above (see ‘measures’). This demonstrated that none of the treatments were associated with better outcomes on any of the 3 dependent variables, so we did not enter treatments into our models as confounding variables.

**Results**

**Participants**

Figure 4 (page 124) displays the flow of recruitment and retention of participants. 93 potential participants were referred for the study and 88 were contactable. 19 patients were excluded for the following reasons: 13 people had had CRPS for more than 12 weeks, 4 were deemed not to have CRPS-1 based on referral letters and/or self-reported symptoms during a telephone call, 1 lived outside the study area and thus was not covered by ethics approval, and 1 had a previous history of
CRPS. The recruitment rate was high; only 2 out of the total 69 invited patients declined to participate. 1 further participant was later excluded following the initial assessment, as her symptoms had been present for longer than 12 weeks. The final study population for the data presented here comprises the 66 CRPS-1 patients who met the inclusion criteria and completed the baseline assessment. Retention was high; of the 66 participants who were included, 65 completed at least one follow-up assessment and 63 completed both follow-ups. The reason for loss to follow-up was the same in all 3 instances: the participants were unable to be contacted by telephone and mail.

The participants’ demographic and clinical characteristics are presented in Table 19 (page 125). This shows that the sample were made up of a majority of females (n=48, 72.72%), and participants with upper limb CRPS (n=60, 90.90%). The study population was ethnically diverse. Fifty-nine patients (89.39%) met the stricter Budapest research diagnostic criteria for CRPS (Harden et al., 2010a) in addition to the IASP-Orlando criteria (Merskey & Bogduk, 1994).

Improvements over 12 Months
Mean scores for each of the variables at each of the 3 time-points are reported in Table 21. This shows that mean scores for CRPS severity, pain intensity, disability, all of the psychological measures, body perception disturbance and perceived ownership of the limb improved over the study period. Laterality task performance did not change over time. In addition, a detailed description of improvements in each of the signs and symptoms of CRPS is reported separately (Bean, Johnson, Heiss-Dunlop, & Kydd, In press).

Table 21. Mean (SD) Scores for all of the Measured Variables at Baseline, 6 and 12 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline N=66</th>
<th>6 Months N=64</th>
<th>12 Months N=63</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS severity</td>
<td>12.18 (2.41)</td>
<td>8.52 (3.26)</td>
<td>6.75 (4.07)</td>
</tr>
<tr>
<td>Pain intensity</td>
<td>4.22 (2.22)</td>
<td>2.35 (2.10)</td>
<td>1.77 (2.09)</td>
</tr>
<tr>
<td>Disability</td>
<td>37.15 (14.33)</td>
<td>18.15 (15.13)</td>
<td>14.74 (16.07)</td>
</tr>
<tr>
<td>Pain-related fear</td>
<td>28.51 (7.21)</td>
<td>22.81 (7.35)</td>
<td>21.66 (8.86)</td>
</tr>
<tr>
<td>Catastrophising</td>
<td>22.39 (15.43)</td>
<td>13.41 (14.05)</td>
<td>11.64 (13.93)</td>
</tr>
<tr>
<td>Depression</td>
<td>6.33 (5.47)</td>
<td>4.34 (5.82)</td>
<td>4.05 (5.61)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.59 (5.41)</td>
<td>3.62 (4.84)</td>
<td>3.67 (5.09)</td>
</tr>
<tr>
<td>Stress</td>
<td>9.45 (6.50)</td>
<td>6.22 (5.82)</td>
<td>5.46 (6.10)</td>
</tr>
<tr>
<td>Body perception disturbance</td>
<td>18.19 (9.46)</td>
<td>15.48 (10.63)</td>
<td>12.30 (12.35)</td>
</tr>
<tr>
<td>Perceived ownership</td>
<td>61.33 (31.41)</td>
<td>75.55 (27.34)</td>
<td>78.11 (29.44)</td>
</tr>
<tr>
<td>Laterality task performance</td>
<td>1.01 (.18)</td>
<td>1.01 (.13)</td>
<td>1.03 (.29)</td>
</tr>
</tbody>
</table>

Laterality task performance measure = ratio of speed affected/unaffected limb pictures.
Variables Associated with CRPS Severity over 12 Months

Mixed-effects models were used to identify baseline variables associated with CRPS severity over the 12-month follow-up period. During the model-building process the following variables were shown to have significant effects when entered into a model without other independent variables: disability, depression, anxiety, stress, body perception disturbance, and perceived ownership of the limb. These variables were then tested in combination with each other and only those with significant effects were retained, resulting in the final model presented in Table 22. This demonstrates that time, pain intensity, sex and disability had statistically significant effects on CRPS severity. Specifically, CRPS severity reduced by an average of 2.74 points at each follow-up, and men, those with lower pain intensity at baseline, and those with lower disability scores at baseline had lower CRPS severity scores over the 12 months. The significant effects are also depicted in Figure 7. None of the other independent variables contributed significantly to explain further variance in CRPS severity.

Variables Associated with Pain over 12 Months

Mixed-effects models were also conducted to identify variables associated with pain scores over the 12 months. During the model-building process the following variables showed statistically significant effects on pain scores when entered into a model without other independent variables: the presence of allodynia, disability, depression, anxiety, stress, catastrophising, pain-related fear, body perception disturbance and perceived ownership of the affected limb. Combining these variables and retaining only those with significant effects resulted in the final model presented in Table 22. This showed that the effect of time on pain scores was statistically significant: at each follow-up visit, pain scores reduced by a mean of 1.22 points. The effects of disability and anxiety on pain scores were also statistically significant: those with lower disability and anxiety scores at baseline had lower pain intensity over the following 12 months. These effects are also displayed in Figure 7.

Variables Associated with Disability over 12 Months

Results of mixed-effects models to identify variables associated with disability over 12 months are also displayed in Table 22. The model building process identified that the following variables demonstrated statistically significant effects on disability scores when included in the model alone: depression, anxiety, stress, catastrophising, pain-related fear, body perception disturbance, and perceived ownership of the limb. When the variables were combined and only those that still showed significant effects on disability scores were retained, the final model had three significant effects: time, pain and pain-related fear. Specifically, disability scores reduced by a mean of 11.29 points at each follow-up visit, and those with lower pain and pain-related fear scores at baseline were less disabled over the following 12 months. Figure 7 also displays these significant effects.
Table 22. Results of Mixed Models for Repeated Measures Analyses to Identify Independent Variables Associated with CRPS Severity, Pain Intensity and Disability Assessed at Baseline, 6 and 12 Months

<table>
<thead>
<tr>
<th></th>
<th>DV: CRPS Severity</th>
<th>DV: Pain Intensity</th>
<th>DV: Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Est</td>
<td>SE</td>
<td>Pr&gt;F</td>
</tr>
<tr>
<td>Time (follow-up visit)</td>
<td>-2.74</td>
<td>.27</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td>Age (years)</td>
<td>.03</td>
<td>.02</td>
<td>.137</td>
</tr>
<tr>
<td>Sex (ref=male)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.18</td>
<td>.56</td>
<td>.039*</td>
</tr>
<tr>
<td>CRPS duration at T1 (days)</td>
<td>.01</td>
<td>.01</td>
<td>.342</td>
</tr>
<tr>
<td>CRPS trigger (ref = fracture w surgery)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture without surgery</td>
<td>-.42</td>
<td>.71</td>
<td>-.31</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>-.89</td>
<td>.73</td>
<td>.05</td>
</tr>
<tr>
<td>Soft tissue injury</td>
<td>-1.8</td>
<td>1.16</td>
<td>-.80</td>
</tr>
<tr>
<td>Minor incident (no tissue injury)</td>
<td>-.13</td>
<td>1.03</td>
<td>.54</td>
</tr>
<tr>
<td>Limb (ref=lower)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>-1.5</td>
<td>.87</td>
<td>-.36</td>
</tr>
<tr>
<td>CRPS severity at T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain intensity at T1</td>
<td>.31</td>
<td>.15</td>
<td>.041*</td>
</tr>
<tr>
<td>Disability at T1</td>
<td>.06</td>
<td>.02</td>
<td>.010*</td>
</tr>
<tr>
<td>Anxiety at T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-related fear at T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIC</td>
<td>947.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<.05; **p<.01; ref=reference group; T1=time 1 (baseline); AIC=Akaike information criterion
Figure 7. Line graphs demonstrating significant associations between baseline and outcome variables

Graph A. depicts the observed mean CRPS severity scores for males and females, and for those with high (top quartile) and low (bottom quartile) baseline pain and disability scores. Graph B. depicts the observed mean pain scores for those with high (top quartile) and low (bottom quartile) baseline anxiety and disability scores. Graph C. depicts the observed mean disability scores for those with high (top quartile) and low (bottom quartile) pain-related fear and pain scores. All error bars represent 95% confidence intervals. NB. Dichotomous data is displayed here for visual purposes, but note that MMRM analyses were conducted using continuous data. T1 = time 1 (baseline).
Discussion

The present study found that the prognosis of CRPS was associated with psychological factors related to threat perception, activity avoidance and protectiveness towards the affected limb. Specifically, those with lower levels of disability, anxiety or pain-related fear at baseline had better outcomes than those who were more disabled, anxious or fearful.

First, we found a significant link between baseline anxiety levels and pain over the following 12 months. Several cross-sectional studies have demonstrated a link between anxiety and pain in CRPS (Bean et al., 2014b; Bruehl et al., 1996), but this is the first demonstration that anxiety is associated with future pain intensity in CRPS. This provides support for the theory that CRPS represents an aberrant protective response to perceived threat, as anxiety likely primes people to perceive greater threat. There are several mechanisms by which anxiety may be linked to pain. Anxiety activates the sympathetic nervous system, which is thought to play a role in CRPS. It might be that increased levels of catecholamines (suggested to be able to trigger nociception directly (Baron et al., 1999)), or greater levels of sympathetic activity mediate this anxiety-pain link (Schurmann et al., 2000). Another possible mechanism is the inflammatory response. Evidence suggests that anxiety is associated with heightened levels of pro-inflammatory markers, impaired cellular immunity and vulnerability to infection (Salim, Chugh, & Asghar, 2012). It might be that anxiety exacerbates the pro-inflammatory state associated with early CRPS, leading to increased peripheral sensitization and pain. Alternatively, anxiety might influence plasticity in the central nervous system, leading to greater central sensitization and/or cortical re-mapping, or may prevent such neuroplastic changes from reverting back to their former state (Koga et al., 2015). Finally, it is likely that those who are more anxious develop different beliefs and concerns about their symptoms, become more hypervigilant to symptoms, and that anxiety leads to avoidance of activity, as proposed by the fear-avoidance model.

Second, those with lower levels of pain-related fear at baseline were less disabled over the following 12 months. According to the fear-avoidance model, pain-related fear causes a patient to avoid using their painful body-part, leading to disability (Vlaeyen et al., 2012). No prospective studies have previously assessed the influence of pain-related fear on later outcomes in CRPS, but cross-sectional studies have found an association between pain-related fear and disability in chronic CRPS (de Jong et al., 2011), and small treatment trials provide support for the treatment of pain-related fear using exposure therapy (de Jong et al., 2005; Ek et al., 2009; van de Meent et al., 2011). Our results suggest that pain-related fear may also be influential in the acute stages.
Third, those with greater disability at baseline exhibited a poorer recovery in terms of CRPS severity and pain. This effect could be mediated by immobilization, whereby those who stop using the limb (and therefore rate themselves as more disabled) experience more symptoms in the long term. Immobilization has been shown to lead to CRPS-like symptoms, including reduced pain threshold, cold hyperalgesia, skin temperature differences, vascular and trophic changes, increased inflammatory markers, and alterations to the primary somatosensory cortex (Lissek et al., 2009; Pepper et al., 2013; Singh & Davis, 2006; Terkelsen et al., 2008). Interestingly, 93.5% of patients in the present study reported having their limb immobilized in a splint or cast at some stage. This was likely necessary for various injuries that led to CRPS (e.g. fracture), but splinting was common even amongst those who developed CRPS following a minor or soft tissue injury. Our results suggest that instead of limiting limb movement, it might be important to maximise limb movement and reduce disability early in the treatment of CRPS. Another possibility is that disability ratings might reflect a patient’s perceptions of the severity of their condition or their expectations, and expectation has been shown to influence pain and recovery outcomes consistently in experimental settings (Tracey, 2010) and longitudinal studies in other pain conditions (Hallegraeff, Krijnen, van der Schans, & de Greef, 2012).

Fourth, pain intensity was associated with CRPS severity and disability. This was not surprising, as pain intensity has been reported to predict the development of CRPS (Moseley et al., 2014), to be associated with disability in CRPS (Bean et al., 2014b; de Jong et al., 2011), and sensory symptoms have been shown to predict later CRPS outcomes (Wertli et al., 2013). We also found that females experienced greater CRPS severity than males. CRPS is more common amongst females (de Mos et al., 2007), and our data suggests they may also experience a greater number of signs and symptoms.

In contrast with previous studies, we did not find that limb temperature or the presence/absence of allodynia were associated with outcomes in CRPS. We noted that over the study period, limb temperatures changed from predominantly warmer to cooler (Bean et al., In press). A number of the previous studies either assessed limb temperature at later stages of the condition (de Mos et al., 2009b) or did not report the patients’ duration of CRPS at the time of temperature assessments (van der Laan et al., 1998). It is possible that the development of a cooler limb marks a change to chronic symptoms without necessarily being a prognostic indicator in the initial months, but further research would be required to explore this hypothesis. Additionally, limb temperatures in CRPS are known to fluctuate frequently and it could be that measuring temperature at a single time-point is inadequate.
The research has several implications. The psychological variables identified are all modifiable through cognitive and/or behavioural therapies. Research has demonstrated that exposure therapy reduces pain-related fear amongst small samples of patients with chronic CRPS symptoms (de Jong et al., 2005). It would be worthwhile developing and testing such an intervention in the acute stages of CRPS. Such treatments could accompany the medical and physiotherapy approaches that are usually provided to acute CRPS patients. Lower intensity interventions could also be tested amongst acute CRPS patients, aiming to prevent the development of pain-related fear and anxiety about the condition. The research also has implications for understanding CRPS. Results suggest that an integrative biopsychosocial model is more appropriate for understanding CRPS than either a biomechanical model or psychiatric perspective. The results support the theory that CRPS represents an aberrant protective response to threat (Moseley, 2007), and the mechanisms involved in this response would be worthwhile elucidating. For example, it is possible that the psychological constructs measured (based around threat perception) do not have a causal link to outcomes but may correlate with a third set of unmeasured variables. Future research could include a range of physiological measures that might mediate associations between psychological factors and outcomes, such as inflammatory markers, measures of autonomic function and/or neuronal plasticity.

The present results were likely affected by several limitations. Being an observational study, the data cannot demonstrate causation, and associations between independent and dependent variables could be attributed to a third set of unmeasured variables. Also, because the baseline measures were taken up to 12 weeks after CRPS onset (as early as was practically possible), bidirectional relationships between ‘predictors’ and outcome variables could have already occurred by that time. The sample may not have been representative of all early CRPS patients, as they were identified clinically and it is possible that those with mild or transient symptoms of CRPS do not present to healthcare professionals. However our results are more likely applicable to those seeking treatment in clinical settings. The population of the present study also had an over-representation of upper-limb CRPS patients, and although we did not find differences between upper and lower limb CRPS patients in the effects we observed, future studies may wish to replicate the findings amongst those with lower-limb CRPS. We utilised the IASP-Orlando diagnostic criteria for CRPS, rather than the newer Budapest criteria. This was to maximise recruitment, noting that the population of Auckland is not large, so imposing strict diagnostic criteria would have limited sample size. In reality, 89% of participants met the Budapest research criteria, likely because clinicians only diagnosed CRPS when a broad range of signs were present. When we re-analysed the data excluding those who did not meet the Budapest research criteria, the majority of findings remained unchanged, except for the effect of baseline disability on CRPS severity, which was no longer significant. Additionally, the effect of pain-related fear on disability became a non-significant trend (p=.067), likely due to lack of power. We also did not
attempt to control the treatments received by the patients during the study. Although we found that no treatment was associated with better outcomes, it is likely that the treatments received varied in terms of quality and/or dose. This would influence results only if treatments varied according to our independent variables, for example, anxious or fearful patients may have engaged less readily in physiotherapy, or taken fewer tablets. Future studies may wish to replicate the findings amongst a cohort receiving a particular treatment protocol. Additionally, we did not measure participants’ history of other pain conditions or duration of limb pain, which may have influenced recovery.

Conclusions
We found that psychological factors associated with threat perception were associated with poor outcomes in CRPS. Specifically, the present study showed that those who were more anxious, disabled and fearful of pain exhibited greater pain intensity, disability and CRPS severity over a 12-month follow-up. These results support the theory that CRPS represents an aberrant protective response to perceived threat, and suggest that it might be worthwhile testing interventions designed to assist with anxiety reduction and activity involvement early in the course of CRPS.

Acknowledgements
We thank all of the participants of the study for their time and cooperation. We are grateful to the Oakley Mental Health Research Foundation for funding the study. We appreciated the support of the following teams for their involvement with the study: the Auckland Regional Plastic and Reconstructive Hand Surgery Service, The Counties-Manukau Hand Therapy Service, The Auckland Regional Pain Service, Handworks, Moving Hands Rehabilitation, Hands Out West, Paincare, the Counties-Manukau Chronic Pain Service, the Waitemata Orthopaedics Department and Waitemata Pain Management Unit.
Chapter 9: Discussion

Overview
The notion that psychological factors influence pain and physical health outcomes is not a new idea. Research over the past few decades has found that mood, cognitions and behaviours interact with physiological processes in the body, influencing pain and many other health symptoms. CRPS is a condition which, traditionally, was poorly understood. However in recent years, research on CRPS has gained momentum and the physiological abnormalities that accompany the condition are becoming increasingly well documented. However, the possible influence of psychological factors on CRPS symptoms has not been well researched, with much of the research seeking to find psychological causes of CRPS rather than seeking to understand how psychological and physiological processes might interact within the condition. The aims of the work presented in this thesis were to a.) understand the course of symptoms, or outcomes of CRPS, b.) determine whether psychological factors are associated with pain and disability in CRPS, and c.) understand whether psychological factors are associated with the long-term outcomes of CRPS.

Over the following pages, the key findings of the body of research will be summarized. Following-on from this, the findings will be revisited in light of the previous literature on CRPS outcomes, CRPS pathophysiology and on psychological factors in CRPS. The implications of the research for understanding the risk of poor outcomes in CRPS, and for understanding the pathophysiology of CRPS are described. In addition, potential clinical implications and future research directions are addressed. The chapter will conclude with a discussion of the research limitations and suggestions for overcoming some of these limitations in future studies.

Summary of Key Findings
The body of research presented in this thesis has revealed several key findings, related to the outcomes of CRPS, associations between psychological factors, pain and disability in both acute and chronic CRPS, and psychological factors that are associated with the recovery process. First, the systematic review presented in Chapter 3 highlighted the disparities in the literature regarding the outcomes of CRPS: whilst prospective studies based on older criteria for CRPS found that the outcomes are generally favourable and few patients develop chronic symptoms, retrospective and cross-sectional studies (some of which used newer diagnostic criteria) revealed that a significant number of CRPS patients experience long-term pain and disability (Bean et al., 2014a). The review demonstrates that there is significant variability between patients in terms of the course and
outcomes of CRPS. This suggests that there may be a role for screening patients with early CRPS to
determine those at risk of poor outcomes and providing interventions to prevent long-term pain and
disability. This systematic review was followed-up by the study presented in Chapter 7, which
provided an analysis of the extent of change in each of the signs and symptoms of CRPS over the first
12 months of the condition (Bean et al., In press). This revealed that 12 months after developing
CRPS, three-quarters of the sample still experienced pain and two-thirds continued to meet the IASP-
Orlando diagnostic criteria for CRPS. The results are considerably less optimistic than previous
prospective studies, which had utilised different diagnostic criteria for CRPS and different recruitment
methods (for example, screening all patients after fracture). These findings further highlight the
importance of developing adequate early treatments for CRPS to prevent poor long-term outcomes.

Based on research from other pain conditions and a small body of literature in CRPS that has
investigated associations between psychological factors and pain, the thesis also presents a series of
papers aimed at investigating whether psychological factors might play a role in maintaining CRPS.
This is investigated in a cross-sectional study in Chapter 5, which compared CRPS and low back pain
patients, a group where psychological factors are known to influence outcomes. The study found that
compared to those with low back pain, CRPS patients exhibited even stronger relationships between
psychological factors on the one hand and pain and disability on the other. In particular, there was a
stronger association between depression and disability for CRPS patients than low back pain patients,
and there was a link between anxiety and pain which existed only for CRPS patients, not for low back
pain patients. For the two groups, similar relationships existed between pain-related fear and pain
intensity (Bean et al., 2014b). These results suggest that psychological factors interact with outcomes
such as pain and disability at least as much for CRPS as for low back pain, but the study’s cross-
sectional nature could not elucidate cause-and-effect. One possibility was that because the patients
had chronic symptoms, enough time had lapsed for psychological factors, pain and disability to form a
vicious cycle, each influencing each other. Thus examining such relationships amongst a cohort with
recent-onset CRPS was the aim of the manuscript presented in Chapter 6. This revealed that even in
the first 12-weeks of CRPS, those with higher levels of depression were more disabled and more likely
to stop work compared to those with lower levels of depression (Bean et al., 2015a).

These cross-sectional studies were then followed by a prospective study identifying predictors of
recovery from CRPS amongst the same sample of recently-onset CRPS patients who were followed for
one year. This revealed that females, and those with greater pain and disability at baseline
experienced greater CRPS severity over the 12 months. Those who were most anxious and disabled
experienced higher pain levels over the year. Additionally, those with higher levels of pain and pain-
related fear experienced greater disability over the 12 months (Bean et al., 2015b). This suggests that
in addition to the expected influences of pain, those with heightened states of fear and/or anxiety
might be expected to have a poorer recovery from CRPS than those with lower fear and/or anxiety. In addition, the influence of baseline disability on later outcomes suggests that activity avoidance may also exert a negative influence on CRPS.

Integration Into the Broader Literature

CRPS Outcomes

The outcomes of CRPS, or the natural history of the condition, have attracted relatively little high-quality research in the literature to date. The systematic review in Chapter 3 identified only 3 prospective studies conducted with the specific aim of documenting the outcomes of CRPS, and whilst there were a larger number of retrospective studies identified, these are obviously limited by the potential for utilising unrepresentative samples. The previously conducted prospective studies identified that positive outcomes for CRPS patients were the norm, for example, the proportion of patients experiencing pain at 12-13 month follow-up were just 7-18% (Bickerstaff & Kanis, 1991; Zyluk, 1998a). However these prospective studies were based on old diagnostic criteria for CRPS, so may not be relevant to samples recruited today. Moreover, the methodology for recruiting patients in several of these studies was to follow up patients after fracture and determine who met the diagnostic criteria for CRPS. As symptoms normally experienced post-fracture overlap to some degree with the symptoms of CRPS, this may have led the inclusion of a significant number of ‘false-positive’ cases in the samples. For example, Atkins et al. (1989) diagnosed ‘algodystrophy’ in 25% of fracture patients, which is likely a gross overestimation compared to the numbers diagnosed with CRPS using more stringent criteria in more recent studies (3.8%, Moseley et al., 2014).

In contrast with the 3 previous prospective studies included in the systematic review, our results suggest that outcomes for CRPS patients are far less optimistic. These findings are in accordance with a growing body of literature which has utilised stricter diagnostic criteria, and/or recruited patients identified clinically as having CRPS. For example, Beerthuizen et al. (2012) reported that of those who met the Budapest research criteria for CRPS following distal radius fracture, not a single patient was symptom free one year later (this study was not included in the systematic review as assessing outcomes was not its primary aim, but nonetheless it represents a large prospective study). Similarly, de Mos et al. (2009b) found that two-thirds of patients previously diagnosed with CRPS still met the IASP-Orlando criteria for CRPS at a mean of 5.8 years later. Thus it appears that diagnostic criteria and clinical practise have evolved so that CRPS is now identified only amongst those who have a more significant or longstanding condition. These findings on the outcomes of CRPS have important implications and suggest that those with CRPS are likely to experience signs and symptoms in the long-term, and that complete recovery within one year is the exception rather than the rule. This
makes it an even more important and urgent imperative to develop quality treatments for CRPS to prevent long-term pain and disability.

Another finding from the research presented here was that improvements in CRPS symptoms were greatest in the initial stages and plateaued thereafter. This was in line with a popular idea in the literature: that early intervention is essential for CRPS, as improvements are most likely in the few months after the condition develops (Goebel et al., 2012). However to date there has been relatively little research data to support this idea. Harden et al. (2003) found that 13% of patients met the criteria for CRPS three months after total knee arthroplasty, and this was virtually unchanged at 6 months (12.7% met the criteria), suggesting that much of the recovery occurs in the first few months. Several studies have discussed a “window” for intervention and have shown for example that mirror therapy is most effective in the acute stages of CRPS, preferably in the first 8 weeks (McCabe et al., 2003b). Ehrler et al (1995) noted differences in long-term outcomes between those diagnosed and treated prior to the six month mark and those whose diagnosis and treatment was delayed. Overall the data suggests that identifying those with CRPS early, particularly those with a greater risk of poor outcomes, and providing treatments to prevent those poor outcomes would be highly valuable.

Pathophysiology of CRPS

Previous research on the pathophysiology of CRPS has implicated a range of biomedical factors that are associated with and likely contribute to the condition. Such factors include genetic abnormalities, possibly due to abnormalities on the human leukocyte antigen complex (van Rooijen et al., 2012), which has previously been implicated in inflammatory conditions. Neurogenic inflammation is also known to occur in CRPS, with an excess of pro-inflammatory markers noted (Parkitny et al., 2013), and this may contribute to peripheral sensitization and pain. Disturbances in autonomic activity have also been observed in CRPS (Drummond, 2004; Terkelsen et al., 2012), though there is debate as to the importance of sympathetic activity in the condition (Campero et al., 2010). Additionally, maladaptive neuronal plasticity is implicated in CRPS, whereby central sensitization at the level of the spinal cord leads to amplification of nociception and expansion of the painful area (Woolf, 2011). Neuroplastic changes at the level of the brain also occur, with altered representation of the limb on the primary somatosensory and motor cortices amongst other changes (Di Pietro et al., 2013a, 2013b). Whilst the extent to which each of these physiological mechanisms might cause CRPS is a matter of debate, current theories pose that an interaction between all of these factors occurs, leading to the condition. It is interesting to note that many of the physiological changes that accompany CRPS are known to be influenced by psychological factors, yet very little research has sought to uncover such influences in the context of CRPS.
A distinctly different line of research has explored CRPS from a psychological or psychiatric perspective, but has yielded inconsistent results. A number of studies have sought to determine whether those who develop CRPS are psychologically different from those who do not develop CRPS, but these have generally shown that no ‘CRPS-prone’ psychological profile exists (Beerthuizen et al., 2011; Daviet et al., 2002; Harden et al., 2003; Puchalski & Zyluk, 2005). Other studies have explored whether psychiatric conditions are a risk factor for CRPS or noted extremely high rates of psychiatric comorbidity amongst those with CRPS (de Mos et al., 2008; De Vilder, 1992; Rauis, 1999; Szeinberg-Arazi et al., 1993; Van Houdenhove, 1986). There are also a number of studies that have sought to establish whether CRPS is a result of malingering, self-harm or could be considered a factitious disorder (Greiffenstein, Gervais, Baker, Artiola, & Smith, 2012; Taskaynatan et al., 2005). Whilst some studies have concluded in favour of this view, their methods have not justified these conclusions.

Thus the background literature to this thesis revealed two largely unrelated bodies of literature: one viewing CRPS from a biomedical point of view and the other from the psychological perspective. Relatively few studies had sought to identify interactions between psychological phenomena and symptoms or physiological markers, though some do exist. This is surprising, as the health psychology literature from other pain conditions and even from a broad range of health conditions reveals that it is entirely normal for psychological factors such as mood, expectations, beliefs, coping strategies and behaviours to influence health outcomes (Chida & Hamer, 2008; Chida et al., 2008; Knoop et al., 2010; Lichtman et al., 2008; Surdea-Blaga et al., 2012). Instead, it appears that the tendency to seek a psychological cause of CRPS may have prevented research from exploring this track of research in the condition.

Our research clearly indicates that the biopsychosocial model is more suitable for understanding CRPS, as it revealed relationships between anxiety and pain, depression and disability, and pain-related fear and disability. This also forms part of a small but growing body of literature. One theory which may be able to incorporate these findings into the biomedical research is that proposed by Moseley (2007). He proposed that pain in general, and CRPS in particular could be understood as a conscious correlate of implicit perceived (or real) threat to the body tissues. This theory notes that pain does not reflect the degree of tissue damage, but effectively drives protective behaviours, and that all of the other pathological findings in CRPS (inflammation, sensory, vasomotor and sudomotor symptoms, as well as altered autonomic reactivity) could also be considered part of a protective response. Following on from this ‘threat’ hypothesis, it is likely that psychological factors such as anxiety and fear would lead to an increase in perception of pain and other ‘protective’ symptoms.

The support we found for this idea can be roughly divided into two separate findings: 1.) anxiety was prospectively associated with pain in CRPS, and 2.) pain-related fear was prospectively associated
with disability in CRPS. In terms of the association between affective factors and CRPS, we found consistent associations between anxiety and pain intensity between cross-sectional and prospective studies, and we also found several associations between depression and disability. These findings were consistent with two previous studies that identified an influence of mood on pain in CRPS. One used a diary study to show that depression influences pain (Feldman et al., 1999), and the other used a cross-sectional design to demonstrate significant correlations between pain, anxiety and depression (Bruehl et al., 1996). A previous study of acute pain after hand-fracture (a common trigger for CRPS) found that anxiety sensitivity, pain-related anxiety, and pain catastrophising were all associated with different aspects of pain and disability (Keogh, Book, Thomas, Giddins, & Eccleston, 2010). The prospective study presented in Chapter 8 is the first to demonstrate that baseline anxiety is also associated with future pain intensity in CRPS.

Our findings of associations between pain-related fear and outcomes of CRPS also join a small but growing body of literature on the topic. Relatively little previous research has examined the importance of pain-related fear in CRPS, and ours is the first to demonstrate an influence prospectively, but de Jong et al. (2011) reported that the perceived harmfulness of activities was associated with functional limitations. The same group also found that exposure therapy to reduce pain-related fear was highly effective for CRPS patients (de Jong et al., 2005). Several other studies have drawn associations between passive coping, catastrophic thinking and CRPS (Marinus et al., 2013; Moseley et al., 2008b).

There are a number of mechanisms that could mediate associations between psychological factors and pain or disability. First, psychological factors are known to influence the autonomic nervous system, for example anxiety and fear activate the sympathetic nervous system and lead to increased catecholamine release, impaired vasoconstriction and changes in skin blood flow. There is some evidence that sympathetic-afferent coupling might occur in CRPS (Baron et al., 1999), so that catecholamines could directly trigger nociception, and one prospective study found that altered vasoconstriction responses predicted the development of CRPS post-fracture (Schurmann et al., 2000). An alternative is that psychological factors might influence CRPS via their effect on inflammatory processes. There is extensive evidence that stress influences the immune system (Webster Marketon & Glaser, 2008) and some (albeit limited) research on the effects of anxiety on inflammatory processes. Anxiety has been linked to impaired cellular immunity, damage to cellular and humoral immune responses, and risk of infection (Salim et al., 2012). As CRPS is associated with a heightened inflammatory state, and various conditions associated with neurogenic inflammation have been implicated as risk factors for CRPS (de Mos et al., 2008), and various inflammatory markers can increase nociceptor excitability and lead to peripheral sensitization (Sommer & Kress, 2004). Thus inflammatory mechanisms could explain the link between anxiety and pain. It is also plausible that
anxiety and fear alter plasticity of the nervous system. Recent research has suggested that anxiety and pain both occlude a certain type of long-term potentiation and suggest that this mechanism might be at least responsible for the comorbidity of anxiety and pain (Koga et al., 2015). As neuronal plasticity is suggested to play a major role in CRPS, and in particular alterations to the cortex are associated with CRPS pain, this is a further mechanism that may be involved.

Finally, behavioural mechanisms may link psychological factors to the symptoms of CRPS. Much research in other areas of chronic pain has focussed on the fear-avoidance model, which proposes that in the presence of pain, catastrophic thinking leads to fear, avoidance of activity, hypervigilance, disuse, disability and depression, which further reinforce pain (Vlaeyen et al., 2012). After several decades of research on the fear-avoidance model in various pain conditions, a number of suggestions for enhancing the model have been proposed. For example, the model does not presently describe the way in which motivation, competing goals, and other self-regulatory processes might influence disability (Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012). Additionally, it has been noted that many of the relationships that the model assumes to be linear are not so straightforward, and that disability is likely influenced by a cumulative set of risk factors, including catastrophising, pain-related fear and depression (Wideman et al., 2013). Regardless, the present research found that there was a prospective relationship between pain-related fear and disability, and in addition disability itself predicted later pain intensity and CRPS severity, which further supports this model. Thus one possibility is that anxiety and fear lead to avoidance of movement in an effort to protect the painful body part. Not only would this lead to greater disability, but immobilization may then have a range of physiological effects which perpetuate pain. This is further discussed below.

The present studies were not specifically designed to identify which aspects of anxiety or threat perception might be most important in predicting outcomes, whether it be the autonomic arousal associated with anxiety, the cognitive aspects, behavioural avoidance, or a general factor associated with avoidance of unpleasant sensations. One previous study found that after hand fracture, anxiety sensitivity (fear of anxiety-related sensations) was related to disability, pain-related anxiety was associated with pain intensity during task performance, and pain catastrophising (i.e. cognitive aspects) was associated with pain intensity itself (Keogh et al., 2010). The present studies found that pain intensity in CRPS was associated with general measures of anxiety from both the Depression Anxiety Stress Scale 21 (DASS-21) and the Hospital Anxiety and Depression Scale (HADS). Items from both of these scales tend to focus on physiological arousal as well as feelings of fear and panic, with few items about cognitions. In contrast, the pain catastrophising scale, which focuses on cognitions regarding pain, did not show an independent influence on pain in the present studies. The Tampa Scale for Kinesiophobia, which focuses on cognitions regarding exercise, was shown to predict disability prospectively, and was associated with pain cross-sectionally but not prospectively in CRPS.
These findings suggest that the mechanism that links anxiety and pain in CRPS might be more closely related to physiological arousal whilst the influences of fear on disability might be more cognitively driven.

Interestingly, the prospective study presented in this thesis also demonstrated that early disability was associated with future outcomes, which suggests a possible mechanism linking psychological factors to outcomes in CRPS – disuse or immobilization. Immobilization appears to be a contentious issue in CRPS. On the one hand, we found that immobilization was frequently used in the treatment of CRPS or in the treatment of the injury that caused the CRPS, and anecdotally, patients reported that this relieves pain. However limb immobilization has been shown to produce many (though not all) CRPS symptoms, including sensory changes, temperature, vascular and trophic changes (Lissek et al., 2009; Pepper et al., 2013; Singh & Davis, 2006; Terkelsen et al., 2008). The fear-avoidance model proposes that “disuse” is one mechanism by which psychological factors influence pain. Disuse also affects the representation of the body-part on the somatosensory cortex, and alterations in cortical representation of the CRPS limb is known to correlate with pain intensity. Thus it is possible that disuse creates not only local changes in the limb, but could maintain CRPS by exacerbating CRPS-related cortical changes.

Overall, the research presented here supports the idea that once established, psychological factors may exacerbate or contribute to maintaining CRPS. Effects could be mediated by various potential pathways, including autonomic activity, inflammatory processes, altered neuronal plasticity and/or behavioural mechanisms and disuse. The results support the hypothesis that CRPS represents an over-protective response to perceived threat.

**Potential Clinical Implications**

The associations between psychological factors, pain and disability in CRPS have a range of potential clinical implications, though all must be somewhat tempered with caution as no interventions have been tested in the body of research presented here. One possibility raised by the research is that of screening programmes for CRPS patients. If risk factors for poor prognosis in CRPS are known, then it may be possible to use a screening instrument to identify those at risk of poor outcomes. Based on the findings presented here, such a tool might include measures of the number of CRPS signs and symptoms, pain intensity, disability, anxiety, depression and pain-related fear and could also take patient gender into account. Previous research has also identified factors such as the presence of sensory symptoms and cold limb temperature, so these may also be worthwhile including. However, screening is not without risk and debate exists as to the value of screening programmes. If such screening were to be conducted, then it would be essential to have an effective treatment pathway available for those identified as high risk for chronic symptoms, and this would first need to be
developed and tested in future research. If treatment were targeted at the risk factors identified, then it would likely involve a multidisciplinary intervention comprising treatments aimed at maximising limb movement and function to reduce disability, education about pain in CRPS to prevent unnecessary pain-related fear and anxiety, exposure therapy for patients with elevated levels of fear, cognitive behavioural therapies aimed at managing anxiety and/or depression, and medical intervention aimed at reducing pain intensity. The relationship between pain intensity and pain-related fear has been shown to be weaker for those who are more accepting of pain (Crombez, Viane, Eccleston, Devulder, & Goubert, 2013), so such an intervention should also focus on assisting patients to come to a sense of acceptance around their pain. This is supported by qualitative research which found that acceptance of pain and having a sense of control were key processes in treatment for CRPS patients (Rodham, McCabe, Pilkington, & Regan, 2013). Very little research has tested the efficacy of multidisciplinary treatment for CRPS, and it would be worthwhile determining whether such a programme was cost-effective, acceptable to patients and led to reductions in long-term negative outcomes. In other fields of pain medicine, far more extensive bodies of research have established sets of psychosocial risk factors for chronic pain and/or disability (Gatchel, Polatin, Noe, Gardea, Pulliam, & Thompson, 2003), and early-intervention programmes designed to prevent pain-related disability have proven effective (Bergbom, Flink, Boersma, & Linton, 2014; George et al., 2011), so there is good reason to think that such programmes would also prove beneficial in CRPS.

The research also highlights the potential for broader-scale interventions that could be provided to a greater number of patients. It may be possible to develop high quality but low-intensity interventions that could be provided to all patients when initial symptoms of CRPS arise, or even all patients undergoing limb surgery or recovering from a fracture. Such an intervention might aim to emphasize the importance of maintaining function, and the lack of association between pain and tissue damage, and by changing patients’ beliefs and perceptions, may alter behaviour and subsequent outcomes. Such information may help to prevent the development of pain-related fear amongst early CRPS patients. Similar brief education interventions based on modifying patient’s illness perceptions and recovery expectations have been shown to be effective at preventing post-concussion syndrome following mild head injury (Mittenberg, Canyock, Condit, & Patton, 2001) and for preventing long-term pain and disability following whiplash injury (Meeus, Nijs, Hamers, Ickmans, & Oosterwijk, 2012).

Research has also indicated that health care professionals themselves can have elevated levels of pain-related fear, and this influences patients’ outcomes. Two studies showed that health care professionals with high pain-related fear were less likely to advise patients to be active and more
likely to recommend sick leave (Coudeyre et al., 2006; Linton, Vlaeyen, & Ostelo, 2002). There is some evidence that providing biopsychosocially oriented education to healthcare providers could alter their practices (Domenech, Sanchez-Zuriaga, Segura-Orti, Espejo-Tort, & Lison, 2011), making them more likely to recommend an active approach to pain management. It is possible that the signs and symptoms of CRPS induce fear in health practitioners, especially for those working in the community with a broad range of conditions, who may see CRPS only occasionally. If such an intervention were able to decrease health professionals’ fear of pain in CRPS, it may lead to beneficial outcomes for patients.

Limitations and Areas for Future Research

In total, the works described in this thesis have contributed to the literature by highlighting that a.) Long-term symptoms are common in CRPS; b.) Pain and disability in CRPS are associated with elevated psychological distress; and c.) Psychological factors during the acute stage of CRPS are associated with later pain and disability. However, the work is not without its limitations. All of the work presented here is observational in nature, no experimental manipulations were conducted and therefore the research cannot demonstrate cause and effect. All observed effects could be due to a third unmeasured variable, and particularly for the cross-sectional studies, it is likely that symptoms influence psychological state in addition to an influence of distress on symptoms. Future studies could include experimental designs, for example manipulating psychological state amongst CRPS patients and measuring effects on pain and/or symptoms.

There are six main sources of bias that can occur in observational or prognostic studies, relating to: study participation, attrition, measurement of prognostic indicators, measurement of confounding variables, measurement of outcome variables, and analyses (Hayden et al., 2006). Each will be discussed with relation to the studies presented here.

First, it is likely that there were limitations in study participation that influenced results. For example, the study presented in Chapter 5 involved a sample of patients with longstanding CRPS who had attended a multidisciplinary pain centre, which likely means that this sample involved those with the most severe cases of CRPS. Multidisciplinary pain centres are also known for their strong focus on psychological support, so it is also likely that the patients referred to such a centre are more distressed than those who are not referred. Thus it is possible that the study’s findings (of associations between psychological factors and outcomes) were biased by the participation of a distressed, chronic sample of CRPS patients. This was partly remedied by the study presented in Chapters 6, 7 and 8, where the sample recruited were those with recently-onset CRPS and the majority were identified upon consulting orthopaedic, hand surgery, and physiotherapy clinics, thus the sample was less likely to comprise the most disabled or distressed CRPS patients. Clinical staff
members were asked to refer all patients who met the criteria for CRPS for the study, but it is possible that this sample was still not entirely representative. First, those with the mildest CRPS symptoms may not present to healthcare settings at all, and their symptoms may go undiagnosed, and this group would not be included in the studies described here. Second, it is possible that staff were more likely to identify CRPS amongst those with psychological distress or higher levels of disability, when other patients who had features of CRPS but who were managing well were not diagnosed and referred for the study. Additionally, the sample recruited for the prospective study had had their CRPS for up to 12 weeks at the time of the initial assessment, and by this time, bidirectional relationships may have developed between CRPS symptoms and psychological factors which could account for the relationships seen, and very mild cases may have already resolved.

Another factor that limits the representativeness of the sample was the diagnostic criteria used. The studies presented here utilised the IASP-Orlando criteria for CRPS, which is much less strict than the newer Budapest criteria. This use of the older criteria increases the risk of ‘false-positives’, i.e. patients who don’t have CRPS being included in the studies. However we note that in the cross-sectional study presented in Chapter 5, all participants had undergone a 60-90 minute assessment with an experienced pain medicine specialist, and the sample described in Chapters 7-9 were assessed with a detailed physical examination to determine their suitability for the study. Eighty-nine percent of the sample met the Budapest research criteria for CRPS in addition to the IASP-Orlando criteria. However future research should be able to further limit the risk of including ‘false positives’ by utilising the Budapest criteria, which is now widely accepted.

The issue of diagnostic criteria is not unique to the body of research presented in this thesis, but is in fact a limitation or hurdle for all CRPS research. For example, the discrepancy between older and newer studies on the outcomes of CRPS highlights a significant issue pertaining to the condition and diagnostic criteria: the difficulty of defining what is CRPS and what is not CRPS. There are a vast number of names for CRPS and sets of diagnostic criteria that have been used, and these do not agree on the particular signs and symptoms that must be present. Various authors have suggested that in fact CRPS might not represent a discrete condition, but that subtypes of CRPS might exist based on the symptoms experienced or genetic differences (Bruehl, 2009; Bruehl et al., 2002; van Rooijen et al., 2012; Zyluk & Puchalski, 2013). At present no diagnostic test exists for CRPS and the diagnosis is one of exclusion. Thus the best way forward for future researchers will be for all to adopt the same set of diagnostic criteria and make efforts to ensure ‘false positives’ are excluded from studies.

There are some samples that were not included or poorly represented in the studies. First, there was a dearth of lower-limb CRPS patients included in the prospective study. This is likely due to the ease of recruitment from specialist hand clinics for the upper-limb CRPS patients, whilst few specialist foot
clinics exist in the Auckland region. In future, researchers could consider focusing on this population, as it is possible that different factors might be associated with disability given the difficulties lower-limb pain patients have with mobilising. Children were not included in the research studies presented here. CRPS is known to present differently in children to adults, and psychological distress often manifests differently in children to adults as well. Thus, the findings should not be generalised to children, though it may be worthwhile conducting similar research studies in this population. Finally, no patients with CRPS post-stroke were included in the prospective study, and likely only a few in the cross-sectional study in Chapter 5 (though actual numbers were not collected). CRPS does occur post-stroke, but it is possible that a range of other factors play a role in recovery from CRPS in this population, so further research would be valuable to investigate the role of psychological factors in CRPS in this group.

Both adequate recruitment rates and attrition are considered to be significant sources of bias in observational studies, but pleasingly were unlikely to affect the results presented here. The cross-sectional study presented in Chapter 5 represented a consecutive sample of CRPS patients. As it was a review of routinely collected clinical information, participants were not required to give consent to be included in the study and hence all CRPS patients with adequately completed questionnaires and medical records were included in the study. In the prospective study, just two participants out of the 68 eligible declined to participate, and only one was lost to follow-up for both of the 6- and 12-month assessments.

Measurement practices are also known to be a potential source of bias in observational studies, and high quality measures of outcome variables, predictor variables and possible confounding variables is obviously important. This is not entirely straightforward in psychological and/or pain research, where measurement often involves self-report. It is possible that reporting of pain, disability and psychological factors were all influenced by some extraneous factor, such as negative affect. This could lead to an inflation of associations between the constructs. We attempted to limit this possibility by using reliable and well-validated measures and where possible to include measures not biased by self-report, such as work status.

The studies were also limited by the selection of predictor variables included, which focussed on psychological factors previously shown to be associated with chronic pain, and also measures of perceptions of the CRPS limb, which has been shown to be abnormal in CRPS. It is possible that the associations observed were in fact related to a third set of unmeasured variables, such as inflammatory processes or autonomic activity, which led to both CRPS symptoms and anxiety/fear. Thus future studies may wish to include a broader range of predictor variables. Other possible variables to include might be expectations, beliefs about tissue damage, and coping strategies.
the research may have been limited by the measurement of confounding variables. We measured factors such as CRPS duration, CRPS trigger, and the receipt of various treatments. However we did not capture the ‘dose’ or quality of treatment given, and this could have influenced our findings, as the particular treatments that a patient received or engaged with may have varied according to psychological factors. Whilst we suspect that those who were most fearful or anxious would be more likely to seek and attend treatments, and would be more likely to receive medications, future studies would benefit from standardising treatment protocols during the study period or following patients on a particular rehabilitation programme.

Finally, another potential influence on our results could have been the ‘Hawthorne’ effect, whereby the practise of measuring and observing something can alter its outcomes. It is possible that taking part in a study on CRPS either validated patients’ symptoms and relieved anxiety, or alarmed patients by suggesting their condition was serious enough to warrant investigation. Also, though efforts were made not to provide information or ‘intervention’ during the three study assessments, there were times when patients asked questions about the study and it was unavoidable to provide some information about CRPS and the reason for inclusion of various measures.

**Conclusions**

CRPS research has generally focussed on two branches, seldom overlapping: the biomedical branch, which notes the importance of neurogenic inflammation, autonomic activity, genetics and neuroplastic changes in CRPS; and the psychological branch, which has clearly shown that the psychological factors investigated are not a cause of CRPS. In many ways, this body of research contrasts with that of other pain and health conditions, where biopsychosocial research has uncovered multiple bidirectional pathways linking psychological state to pain, symptoms and health outcomes. The body of work presented here has sought to address this imbalance in the CRPS literature, by assessing associations between the psychological factors that normally influence pain, and outcomes in CRPS. In completing this aim, the research also required an investigation of the usual trajectory and outcomes of CRPS, and as such the research presented here has two distinct arms. First, the studies showed that whilst previously conducted prospective studies demonstrate good outcomes for most CRPS patients, utilising a clinically recruited sample (most of whom met much stricter diagnostic criteria), it appears that in reality many CRPS patients are left with chronic pain and symptoms. Thus prevention of poor outcomes is important in CRPS. Second, we demonstrated that in CRPS, relationships exist between depression, disability and work status, between anxiety, pain-related fear and pain intensity, and that prospectively, both anxiety and pain-related fear interact with pain and disability, and are associated with poorer outcomes. The research has implications for understanding CRPS, as it strongly supports the hypothesis that CRPS represents
a protective response to perceived threat. It also has implications for clinical practise, and suggests that targeting pain-related fear, anxiety and depression may be important in order to prevent long-term pain and disability amongst CRPS patients.
### Appendices

**Appendix 1: Table 23: Quality and Relevance Assessment Criteria for Systematic Review**

<table>
<thead>
<tr>
<th>Quality Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sampling method described</td>
<td>Positive if state where and/or how sample was selected.</td>
</tr>
<tr>
<td>2. Sample described</td>
<td>Positive if state age and sex of CRPS patients.</td>
</tr>
<tr>
<td>3. Inclusion/exclusion criteria described</td>
<td>Positive if report inclusion/exclusion criteria.</td>
</tr>
<tr>
<td>4. Diagnostic criteria described</td>
<td>Positive if report diagnostic criteria utilised.</td>
</tr>
<tr>
<td>5. Response rate &gt;75%</td>
<td>Positive if response rate &gt;75%, or in cases of retrospective audit, if it appears all cases have been included.</td>
</tr>
<tr>
<td>6. Representative Sample</td>
<td>Positive if items in methodology don’t suggest the sample is non-representative. Examples of non-representative samples: those with a particular trigger for CRPS (e.g. fracture patients only), those with a positive or negative response to previous treatment, tertiary referral centre samples with chronic duration.</td>
</tr>
<tr>
<td>7. Assembled at common time-point &lt;3mo</td>
<td>Positive if the sample were recruited at a certain time-point, e.g. 6 weeks post-fracture, and that time point was less than 3 months post-CRPS-development.</td>
</tr>
<tr>
<td>8. Follow-up at least 6 months</td>
<td>Positive if follow-up is more than 6 months. N/a for retrospective or cross-sectional studies.</td>
</tr>
<tr>
<td>9. Attrition described</td>
<td>Positive if the number who did not attend follow-up is reported. N/a for retrospective or cross-sectional studies.</td>
</tr>
<tr>
<td>10. Attrition adequate</td>
<td>Positive if attrition is &lt;20%, unless there is an important difference between completers and drop-outs, e.g. those who dropped out were the most or least severe cases.</td>
</tr>
<tr>
<td>11. Information about completers versus dropouts</td>
<td>Positive if baseline differences between those who completed the study and those who dropped out are explored.</td>
</tr>
<tr>
<td>12. Outcomes defined</td>
<td>Positive if outcomes are labelled and clear.</td>
</tr>
<tr>
<td>13. Outcomes objective</td>
<td>Positive if there was at least one objective measure (i.e. not self-report or physician opinion).</td>
</tr>
<tr>
<td>14. Outcomes measured appropriately</td>
<td>Positive if at least one standardized measure or validated questionnaire is used to assess the course of CRPS symptoms (VAS/NRS pain scale included as acceptable measure).</td>
</tr>
<tr>
<td>15. Relevant statistical analysis conducted</td>
<td>Positive if differences in symptom scores between time-points have been assessed with statistical tests. Also for retrospective studies if scores are compared with controls or measures from the unaffected side, or where the statistical significance of correlations between symptoms and CRPS duration is tested.</td>
</tr>
<tr>
<td>16. Analysis Appropriate</td>
<td>Positive if tests selected are appropriate for the question posed.</td>
</tr>
</tbody>
</table>
Appendix 2: Description of the Psychometric Scales
(Supplementary online information accompanying the publication of Chapter 7: Extent of Recovery in Complex Regional Pain Syndrome Type 1: A Prospective Study).

1. **Short-form McGill Pain Questionnaire 2 (SFMPQ2)** (Dworkin et al., 2009): This scale asks participants to rate each of 22 pain descriptors on a scale from 0 (none) to 10 (worst possible). A total score is determined by calculating the average score over all 22 items, giving a minimum score of 0 and a maximum score of 10. The SFMPQ2 has been demonstrated to have excellent reliability and validity (Lovejoy et al., 2012). Reliability was excellent for the present study’s baseline data (Cronbach’s α= .929), as well as at each of the 6 & 12 month follow-ups (Cronbach’s α= .959 & .969).

2. **Disability: Pain Disability Index** (Pollard, 1984): This seven-item scale asks participants to rate their level of disability for seven domains of life on a scale from 0 (no disability) to 10 (total disability). A total disability score out of 70 is calculated by adding the items together. Higher scores represent greater disability. This scale has been shown to have good psychometric properties (Tait & Chibnall, 2005). Reliability was acceptable for the present study’s baseline data (Cronbach’s α=.796), as well as at each of the 6 & 12 month follow-ups (Cronbach’s α=.907 & .920).

3. **Pain-related fear: Tampa scale for Kinesiophobia** (Woby et al., 2005): This is an 11-item scale which asks participants to rate the extent to which they agree or disagree with a range of statements endorsing pain-related fear. Scores are calculated between a minimum of 11 (no pain-related fear) and a maximum of 44 (high levels of pain-related fear). This scale has been demonstrated to have good reliability and validity (Woby et al., 2005). For the present study’s data, reliability was good (Cronbach’s α=.834 (baseline), .875 (6 months), .916 (12 months)).

4. **Catastrophic thinking: Pain Catastrophizing Scale** (Sullivan et al., 1995). This is a 13-item scale which asks participants to rate the extent to which they experience a range of catastrophic thoughts on a 5 point scale from 0 (not at all) to 4 (all the time). A total score out of 52 is calculated by summing all answers together. Higher scores indicate greater levels of pain catastrophising. The scale has been shown to have excellent reliability and validity (Sullivan et al., 1995). Reliability at baseline in the present study was excellent (Cronbach’s α=.955 (baseline), .961 (6 months), .967 (12 months)).
5. **Depression Anxiety Stress Scale 21** (Lovibond & Lovibond, 1995a): This 21-item scale consists of 7 items measuring depression, 7 measuring anxiety and 7 measuring stress. Participants are asked to rate the extent to which they endorse each item on a scale from 0 (did not apply to me at all) to 3 (applied to me very much or most of the time). Items for each of the three subscales are added together to give three scores, each out of 21, with higher scores representing greater distress. The DASS has been shown to have very good reliability and validity (Lovibond & Lovibond, 1995a). Reliability (Cronbach’s α) coefficients were good for the present study’s baseline data (Depression: α=.883 (baseline), .943 (6 months), .941 (12 months); Anxiety: α=.829 (baseline), .878 (6 months), .863 (12 months); Stress: α=.907 (baseline), .901 (6 months), .933 (12 months)).

6. **The Bath CRPS Body Perception Disturbance Scale** (Lewis & McCabe, 2010): This 11-item measure consists of 4 items asking participants to rate the extent to which they feel connected to and aware of their affected limb, 4 items asking participants whether or not they experience discrepancies between sensory and visual information associated with the affected limb, 2 items asking about participants’ desire to amputate their limb, and 1 item assessing the patient’s mental image of their affected and unaffected limbs. This scale is scored from 0-57, with higher scores representing greater body perception disturbance. The scale has been shown to have adequate internal consistency and inter-rater reliability in previous reports (Lewis & Schweinhardt, 2012). However with the present study’s baseline data, the scale’s internal consistency was poor (Cronbach’s α=.533). Subsequent reliability at 6 months was good (Cronbach’s α=.707), and at 12 months was good (Cronbach’s α=.801).

7. **Perceived ownership of the affected limb** (Moseley et al., 2009): Participants were asked “How strong is your sense of ownership over your affected limb?”, and were asked to place a mark on a 100mm visual analogue scale with anchors at each end “very weak – I feel like the limb doesn’t belong to me at all” and “normal – the same as all my other limbs”. Higher scores represent greater ownership over the limb.
## Appendix 3: Table 24. Rates of CRPS Symptoms (Self-Reported) at Baseline, 6 and 12 Months

(Same data displayed in Figure 5)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline (N=66)</th>
<th>6 Months (N=64)</th>
<th>12 Months (N=63)</th>
<th>Cochran’s Q (df), p</th>
<th>MacNemar Post-Hoc tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour difference</td>
<td>62 (93.94%)</td>
<td>45 (70.31%)</td>
<td>33 (52.38%)</td>
<td>30.79 (2) &lt;.001**</td>
<td>T1&gt;T2, T2&gt;T3, T1&gt;T3</td>
</tr>
<tr>
<td>Temperature difference</td>
<td>39 (59.09%)</td>
<td>46 (71.90%)</td>
<td>36 (57.14%)</td>
<td>3.62 (2) .164</td>
<td>ns</td>
</tr>
<tr>
<td>Swelling</td>
<td>62 (93.94%)</td>
<td>41 (64.06%)</td>
<td>30 (47.62%)</td>
<td>33.56 (2) &lt;.001**</td>
<td>T1&gt;T2, T1&gt;T3</td>
</tr>
<tr>
<td>Altered sweating</td>
<td>43 (65.15%)</td>
<td>29 (45.31%)</td>
<td>22 (34.92%)</td>
<td>12.74 (2) .002**</td>
<td>T1&gt;T3</td>
</tr>
<tr>
<td>Reduced range of motion</td>
<td>64 (96.97%)</td>
<td>50 (78.13%)</td>
<td>45 (71.43%)</td>
<td>17.48 (2) &lt;.001**</td>
<td>T1&gt;T2, T1&gt;T3</td>
</tr>
<tr>
<td>Motor changes</td>
<td>62 (93.94%)</td>
<td>57 (89.06%)</td>
<td>45 (71.43%)</td>
<td>13.58 (2) .001**</td>
<td>T2&gt;T3, T1&gt;T3</td>
</tr>
<tr>
<td>Altered hair/nail growth</td>
<td>40 (60.61%)</td>
<td>28 (43.75%)</td>
<td>18 (28.57%)</td>
<td>13.89 (2) .001**</td>
<td>T1&gt;T3</td>
</tr>
<tr>
<td>Allodynia</td>
<td>43 (65.15 %)</td>
<td>23 (35.94%)</td>
<td>17 (26.98%)</td>
<td>23.44 (2) &lt;.001**</td>
<td>T1&gt;T2, T1&gt;T3</td>
</tr>
<tr>
<td>Pain (score &gt; 0 on NRS)</td>
<td>66 (100%)</td>
<td>57 (89.06%)</td>
<td>47 (74.60%)</td>
<td>21.44 (2) &lt;.001**</td>
<td>T1&gt;T2, T1&gt;T3</td>
</tr>
</tbody>
</table>

*p<.05; **p<.01; T1=Time 1, T2=Time 2, T3=Time 3.

MacNemar post-hoc tests were conducted with a Bonferroni correction for multiple testing.
Appendix 4: Table 25. Rates of CRPS Signs (during Physical Examination) at Baseline, 6 and 12 Months
(Same data displayed in Figure 6)

<table>
<thead>
<tr>
<th>Sign</th>
<th>Baseline (N=66)</th>
<th>6 Months (N=64)</th>
<th>12 Months (N=63)</th>
<th>Cochran’s Q (df)</th>
<th>p</th>
<th>MacNemar Post-Hoc tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour difference</td>
<td>59 (89.39%)</td>
<td>39 (60.94%)</td>
<td>27 (42.86%)</td>
<td>29.85 (2)</td>
<td>&lt;.001**</td>
<td>T1&gt;T2, T1&gt;T3</td>
</tr>
<tr>
<td>Temperature difference</td>
<td>37 (56.06%)</td>
<td>24 (37.50%)</td>
<td>25 (39.68%)</td>
<td>5.77 (2)</td>
<td>.056</td>
<td>ns</td>
</tr>
<tr>
<td>Swelling</td>
<td>52 (78.79%)</td>
<td>30 (46.88%)</td>
<td>14 (22.22%)</td>
<td>35.76 (2)</td>
<td>&lt;.001**</td>
<td>T1&gt;T2, T2&gt;T3, T1&gt;T3</td>
</tr>
<tr>
<td>Altered sweating</td>
<td>14 (21.21%)</td>
<td>7 (10.94%)</td>
<td>4 (6.35%)</td>
<td>5.48 (2)</td>
<td>.065</td>
<td>ns</td>
</tr>
<tr>
<td>Reduced range of motion</td>
<td>62 (93.94%)</td>
<td>52 (81.25%)</td>
<td>53 (84.13%)</td>
<td>5.47 (2)</td>
<td>.065</td>
<td>ns</td>
</tr>
<tr>
<td>Motor changes</td>
<td>54 (81.82%)</td>
<td>32 (50.00%)</td>
<td>29 (46.03%)</td>
<td>24.40 (2)</td>
<td>&lt;.001**</td>
<td>T1&gt;T2, T1&gt;T3</td>
</tr>
<tr>
<td>Altered hair/nail growth</td>
<td>44 (66.67%)</td>
<td>23 (35.94%)</td>
<td>11 (17.46%)</td>
<td>31.85 (2)</td>
<td>&lt;.001**</td>
<td>T1&gt;T2, T2&gt;T3, T1&gt;T3</td>
</tr>
<tr>
<td>Mechanical Allodynia</td>
<td>25 (37.88%)</td>
<td>11 (17.19%)</td>
<td>11 (17.46%)</td>
<td>17.04 (2)</td>
<td>&lt;.001**</td>
<td>T1&gt;T2, T1&gt;T3</td>
</tr>
<tr>
<td>Hyperpathia</td>
<td>20 (30.30%)</td>
<td>10 (15.63%)</td>
<td>7 (11.11%)</td>
<td>10.21 (2)</td>
<td>.006**</td>
<td>T1&gt;T3</td>
</tr>
</tbody>
</table>

*p<.05; **p<.01; T1=Time 1, T2=Time 2, T3=Time 3.

MacNemar post-hoc tests were conducted with a Bonferroni correction for multiple testing.
Appendix 5: Ethical Approval for Prospective Study

15 December 2011

Debbie Bean
University of Auckland
Level 12, Support Building
Private Bag 92019
Auckland

Dear Debbie -

Ethics ref: NTY/11/10/099 (please quote in all correspondence)
Study title: A prospective, observational study of the natural history of Complex Regional Pain Syndrome type-1 (CRPS1): Do psychological factors influence outcome?
Principal Investigator: Debbie Bean

This study was given ethical approval by the Northern Y Regional Ethics Committee on 15 December 2011.

Approved Documents
— Participant Information sheet and Consent form version 2 dated 16/11/11
— Participant Questionnaire time 1 version 1 dated 02/09/11
— Participant Questionnaire time 2 & 3 version 1 dated 02/09/11
— Interviewer results sheet version 2 dated 16/11/11

This approval is valid until 30 August 2013, provided that Annual Progress Reports are submitted (see below).

Amendments and Protocol Deviations
All significant amendments to this proposal must receive prior approval from the Committee. Significant amendments include (but are not limited to) changes to:
— the researcher responsible for the conduct of the study at a study site
— the addition of an extra study site
— the design or duration of the study
— the method of recruitment
— information sheets and informed consent procedures.

Significant deviations from the approved protocol must be reported to the Committee as soon as possible.

Annual Progress Reports and Final Reports
The first Annual Progress Report for this study is due to the Committee by 15 December 2012. The Annual Report Form that should be used is available at www.ethicscommittees.health.govt.nz. Please note that if you do not provide a progress report by this date, ethical approval may be withdrawn.

A Final Report is also required at the conclusion of the study. The Final Report Form is also available at www.ethicscommittees.health.govt.nz.

Statement of compliance
The committee is constituted in accordance with its Terms of Reference. It complies with the Operational Standard for Ethics Committees and the principles of international good clinical practice.

The committee is approved by the Health Research Council’s Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990.

We wish you all the best with your study.

Yours sincerely

Amrita Kuruvilla
Northern Y Ethics Committee Administrator
Email: amrita_kuruvilla@moh.govt.nz
Appendix 6: Participant Information Sheet for Prospective Study

16th November 2011

Participant Information Sheet

“A Study of the Course of Complex Regional Pain Syndrome (CRPS)”

Principal Investigator: Debbie Bean
PhD Student
Faculty of Medical & Health Sciences
University of Auckland
Telephone: 373 7599 extn. 82891

Supervisor: Professor Rob Kydd
Faculty of Medical & Health Sciences
University of Auckland
Telephone: 373 7599 extn. 83774

You are invited to take part in a study about recovery from painful limb conditions. Please take your time to think about it and decide whether you wish to take part. Taking part is completely voluntary (your choice). If you do agree to take part in the study, you are free to withdraw from the study at any time, without having to give a reason. If you decide you do not wish to take part, or you withdraw, it will not affect your continuing healthcare in any way.

About the study
We are asking people who are experiencing pain and other symptoms (such as swelling, colour or temperature changes) in an arm, leg, hand or foot to take part in a research project. The aims are to better understand the time course of a condition called Complex Regional Pain Syndrome, and to identify any factors which are associated with a more speedy recovery from this condition. Clinicians involved in treating patients with limb conditions are identifying people with pain and other symptoms, and inviting them to take part. In total, we hope to have 65 participants for the study.

If you decide to participate, the study will involve meeting with the researcher (Debbie Bean) on three occasions: the first meeting will be scheduled as soon as is convenient for you once you have decided whether or not to take part, the second will be scheduled to be in approximately 3-6 months time, and the third will be scheduled in approximately 9-12 months time. Each time, we will ask you to complete some questionnaires about your experiences of pain, will examine your limb, will ask you about any treatments you have received, will ask you to complete a short computer task (identifying pictures of limbs as either a left or right hand/foot), and will measure your heart-rate variability using a comfortable chest strap and Polar watch (this measures the function of the autonomic nervous system). Each appointment should take about one hour, and can be done either at the clinic where you are being seen (if space is available), or at The University of Auckland, or in your own home, whichever is more convenient to you.

Also, if you choose to take part, we will ask the clinicians who are treating you to provide us with a copy of the medical notes relating to your pain condition (how and when it started).
Benefits, risks & safety
The main benefit from participating in the study is that you can contribute to helping us develop a better understanding of complex regional pain syndrome, which we plan to use to help to improve treatments. The study does not involve providing you with any treatment, so the risks are few. It is possible that you may find some of the tasks painful during the three appointments (for example, it may be painful to complete questionnaires if your dominant hand is affected), but in these circumstances, we can help you, you do not have to answer all the questions, and you are welcome to stop at any time. You may have a friend, family or whānau support to help you understand the risks and/or benefits of this study and any other explanation you may require. If you have any questions or concerns, we will be more than happy to discuss these with you.

If you choose to take part, you will be provided with a $50 petrol/gift voucher to compensate you for travel, parking and the inconvenience of taking part.

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact an independent health and disability advocate:
Free phone: 0800 555 050
Free fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

Confidentiality
We will keep all of the information you provide confidential. Once the data collection is complete we will remove all identifying information from it so we will no longer know who the information belongs to. At any time up until we remove identifying information you can withdraw from the study and your data will be removed from the dataset and destroyed.

Results
If you wish, we will keep your name and address on a database so we can send you the findings of the study once the data are analysed. We hope to report the findings of the study in a suitable scientific journal so patients and treatment providers can benefit from improved understanding about complex regional pain syndrome, but this will not include any identifying information about you, only the results from the whole group of participants.

This study has received ethical approval from the Northern Y Regional Ethics Committee. Ethics reference number NTY/11/10/099.

If you have any questions about the study, please do not hesitate to contact us.

<table>
<thead>
<tr>
<th>Debbie Bean</th>
<th>Rob Kydd</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhD Candidate</td>
<td>Head of Department, Psychological Medicine</td>
</tr>
<tr>
<td>University of Auckland</td>
<td>University of Auckland</td>
</tr>
<tr>
<td>Ph 373 7599 extn. 82891</td>
<td>Ph 373 7599 extn. 83774</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malcolm Johnson</th>
<th>Wolfgang Heiss-Dunlop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senior Lecturer</td>
<td>Hand &amp; Upper Limb Surgeon</td>
</tr>
<tr>
<td>University of Auckland</td>
<td>Counties Manukau District Health Board</td>
</tr>
<tr>
<td>Ph 373 7599 extn. 83092</td>
<td></td>
</tr>
</tbody>
</table>

Participant Info Sheet v2 (16.11.11)
Appendix 7: Consent Form for Prospective Study

Consent Form

“A Study of the Course of Complex Regional Pain Syndrome (CRPS)”

Researchers: Debbie Bean (PhD Candidate)
             Professor Rob Kydd (Supervisor)
             Malcolm Johnson (Supervisor)
             Mr Wolfgang Heiss-Dunlop (Orthopaedic Hand & Upper Limb Surgeon)

Contact Phone Number: 09 373 7599 extn 82891

I have read and I understand the information sheet dated 31.08.11 for volunteers taking part in the study designed to assess the course of Complex Regional Pain Syndrome. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.
I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time, and this will in no way affect my continuing health care.
I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.
I have had time to consider whether to take part in the study.
I know who to contact if I have any side effects from the study, or if I have any questions about the study in general.

I wish to receive a copy of the results (please circle)  

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>I wish to receive a copy of the results (please circle)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

I (full name) __________________________________________ hereby consent to take part in this study.

Signature: ___________________________ Date: __________

Project explained by: __________________________

Signature: ___________________________ Date: __________

Thank you very much for volunteering to take part in this study.

Consent Form v1 (31.08.11)
Appendix 8: Participant Questionnaire for Prospective Study

Participant Questionnaire

The University of Auckland
83 Park Rd, Grafton
Private Bag 92019
Auckland
www.health.auckland.ac.nz
Telephone: 64 9 373 7599 extn 82891
Facsimile: 64 9 373 7013
Email: d.bean@auckland.ac.nz

“A Study of the Course of Complex Regional Pain Syndrome”

Thank you for taking the time to participate in this research project. If you would like assistance with completing this questionnaire, we would be happy to help.

Date: __________________________

Code: __________________________
Section A: Pain Intensity

1. Pain
Please circle a number to indicate your average pain level over the last 2 days.

<table>
<thead>
<tr>
<th>No pain</th>
<th>Worst pain you can imagine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

Section B: Pain Descriptors (SF-MPQ-2)

Below is a list of words that describe some of the different qualities of pain and related symptoms. Please circle the numbers that best describe the intensity of each of the pain and related symptoms you felt during the past week. Use 0 if the word does not describe your pain or related symptoms.

1. Throbbing Pain none
<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Shooting Pain none
<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Stabbing Pain none
<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Sharp Pain none
<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Cramping Pain none
<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. Gnawing Pain none
<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. Hot-burning Pain none
<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. Aching Pain none
<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. Heavy Pain none
<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. Tender none
    | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
    |---|---|---|---|---|---|---|---|---|---|---|
    |   |   |   |   |   |   |   |   |   |   |   |
    |   |   |   |   |   |   |   |   |   |   |   |
    | Best possible |

11. Splitting Pain none
    | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
    |---|---|---|---|---|---|---|---|---|---|---|
    |   |   |   |   |   |   |   |   |   |   |   |
    |   |   |   |   |   |   |   |   |   |   |   |
    | Best possible |

12. Tiring-Exhausting none
    | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
    |---|---|---|---|---|---|---|---|---|---|---|
    |   |   |   |   |   |   |   |   |   |   |   |
    |   |   |   |   |   |   |   |   |   |   |   |
    | Best possible |

13. Sickening none
    | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
    |---|---|---|---|---|---|---|---|---|---|---|
    |   |   |   |   |   |   |   |   |   |   |   |
    |   |   |   |   |   |   |   |   |   |   |   |
    | Best possible |

14. Fearful none
    | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
    |---|---|---|---|---|---|---|---|---|---|---|
    |   |   |   |   |   |   |   |   |   |   |   |
    |   |   |   |   |   |   |   |   |   |   |   |
    | Best possible |
Section B: Pain Disability Index

The rating scales below are designed to measure the degree to which several aspects of your life are presently disrupted by pain. In other words, we would like to know how much your pain is preventing you from doing what you would normally do, or from doing it as well as you normally would. Respond to each category by indicating the overall impact of your pain in your life, not just when the pain is at its worst.

For each of the 7 categories of life activity listed, please circle the number on the scale which describes the level of disability you typically experience. A score of (0) means no disability at all, and a score of (10) signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your pain.

1. Family/home responsibilities
   This category refers to activities related to the home or family. It includes chores or duties performed around the house (e.g. gardening) and errands or favours for other family members (e.g. driving the children to school).

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>no disability</td>
<td>total disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Recreation
   This category includes hobbies, sports, and other similar leisure time activities.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>no disability</td>
<td>total disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. **Social Activity**
This category refers to activities which involve participation with friends and acquaintances other than family members. It includes parties, theatre, concerts, dining out, and other social functions.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>no disability</td>
<td>total disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. **Occupation**
This category refers to activities that are a part of or directly related to one’s job. This includes non-paying jobs as well, such as household duties or volunteer work.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>no disability</td>
<td>total disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. **Sexual Behaviour**
This category refers to the frequency and quality of one’s sex life.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>no disability</td>
<td>total disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. **Self-care**
This category includes activities which involve personal maintenance and independent daily living (e.g. taking a shower, driving, getting dressed etc.)

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>no disability</td>
<td>total disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. **Life-support activity**
This category refers to basic life-supporting behaviours such as eating, sleeping, and breathing.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>no disability</td>
<td>total disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Section C: Tampa Scale

With this questionnaire, we measure how you look at pain. Therefore, you are requested to complete all questions by indicating on a 4-point scale to what extent you agree or disagree with each of the statements. This is not a test of your medical knowledge and there are no good or bad answers. We are interested in your opinion, not that of others.

<table>
<thead>
<tr>
<th></th>
<th>Highly disagree</th>
<th>Somewhat disagree</th>
<th>Somewhat agree</th>
<th>Highly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If I were to try to overcome it, my pain would increase</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I can't do all the things normal people do because it's too easy for me to get injured</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. My body is telling me I have something dangerously wrong</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I wouldn't have this much pain if there weren't something potentially dangerous going on in my body</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I'm afraid that I might injure myself if I exercise</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. People aren't taking my medical condition seriously enough</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. My accident has put my body at risk for the rest of my life</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Pain lets me know when to stop exercising so that I don't injure myself</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Pain always means I have injured my body</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. No one should have to exercise when he/she is in pain</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Section D: PCS

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that people may have about pain. Please circle the number to show how much you have these thoughts and feelings when you are experiencing pain.

<table>
<thead>
<tr>
<th>When I'm in pain ...</th>
<th>Not at all</th>
<th>To a slight degree</th>
<th>To a moderate degree</th>
<th>To a great degree</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I worry all the time about whether the pain will end</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I feel I can't go on</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It's terrible and I think it's never going to get any better</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It's awful and I feel that it overwhelms me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I feel I can't stand it anymore</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I become afraid that the pain will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I keep thinking of other painful events</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. I anxiously want the pain to go away</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. I can't seem to keep it out of my mind</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. I keep thinking about how much it hurts</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. I keep thinking about how badly I want the pain to stop</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. There's nothing I can do to reduce the intensity of the pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. I wonder whether something serious may happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
**Section E: DASS Scale**

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you **over the past week**. There are no right or wrong answers. Do not spend too much time on any statement.

*The rating scale is as follows:*

- **0** = Did not apply to me at all
- **1** = Applied to me to some degree, or some of the time
- **2** = Applied to me to a considerable degree, or a good part of time
- **3** = Applied to me very much, or most of the time

<table>
<thead>
<tr>
<th>Statement</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I found it hard to wind down</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. I was aware of dryness of my mouth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. I couldn't seem to experience any positive feeling at all</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. I found it difficult to work up the initiative to do things</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. I tended to over-react to situations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. I experienced trembling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. I felt that I was using a lot of nervous energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. I was worried about situations in which I might panic and make a fool of myself</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. I felt that I had nothing to look forward to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. I found myself getting agitated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. I found it difficult to relax</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. I felt down-hearted and blue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. I was intolerant of anything that kept me from getting on with what I was doing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. I felt I was close to panic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. I was unable to become enthusiastic about anything</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. I felt I wasn't worth much as a person</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. I felt that I was rather touchy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. I felt scared without any good reason</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. I felt that life was meaningless</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section F: Your Views of Your Affected Limb

1. How strong is your sense of ownership over the affected limb?
   Please place a mark on the line.

   Very weak — Normal —
   I feel like the the same as
   limb doesn’t my other limbs
   belong to me
   at all

   Thank you very much for completing this questionnaire
Appendix 9: Interview Record from Prospective Study

Interview & Medical Record Results Sheet

Date: 
Code: 

<table>
<thead>
<tr>
<th>Section One: From medical records:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age</td>
</tr>
<tr>
<td>2. Gender</td>
</tr>
<tr>
<td>3. Circumstance of CRPS onset</td>
</tr>
<tr>
<td>4. Date of onset</td>
</tr>
<tr>
<td>5. Affected Limb</td>
</tr>
<tr>
<td>6. Treatments to date</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section Two: With Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What pain medications do you currently take?</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. What treatments have you tried so far?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weeks in cast:</th>
<th>Weeks in splint:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physiotherapy:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventional Pain Management (injections/nerve blocks etc.):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Are you left or right handed?</th>
</tr>
</thead>
<tbody>
<tr>
<td>L / R</td>
</tr>
</tbody>
</table>
4. Work

How many hours per week are you working in paid work?

Hours: ___________/wk

Or:

- Retired
- Sickness/Invalids Benefit
- Unemployment Benefit
- ACC Weekly Compensation
- Fulltime student
- Other: _______________________

Unpaid work?

Hours: ___________/wk

5. Which ethnic group do you belong to?

Tick the box or boxes that apply

- New Zealand European
- Māori
- Samoan
- Cook Island Māori
- Tongan
- Niuean
- Chinese
- Indian
- Other (such as Dutch, Japanese, Tokelauan)
  Please state: ____________________________________________

T2: Any spreading or other new pain?

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________
6. Bath CRPS Body Perception Disturbance Questionnaire

1) On a scale of 0-10 how much a part of your body does the affected part feel?

   Very much a part = 0__1__2__3__4__5__6__7__8__9__10 = Completely detached

2) On a scale of 0-10 how aware are you of the physical position of your limb?

   Very aware = 0__1__2__3__4__5__6__7__8__9__10 = Completely unaware

3) On a scale of 0-10 how much attention do you pay to your limb in terms of looking at it and thinking about it?

   Full attention = 0__1__2__3__4__5__6__7__8__9__10 = No attention

4) On a scale of 0-10 how strong are the emotional feelings that you have about your limb?

   Strongly positive = 0__1__2__3__4__5__6__7__8__9__10 = Strongly negative

5) Is there a difference between the way your affected limb looks and how it feels to you in terms of the following:

   i.e. does the affected limb ever feel bigger than it actually is when you look at it?
   Does it ever feel hot or cold but then when you touch it, it's a normal temperature?
   Does it ever feel swollen or pressured but then when you look it’s not?
   Does it ever feel heavier than it actually is?

   | Size   | yes no | Comment
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>yes no</td>
<td>Comment</td>
</tr>
<tr>
<td>Pressure</td>
<td>yes no</td>
<td>Comment</td>
</tr>
<tr>
<td>Weight</td>
<td>yes no</td>
<td>Comment</td>
</tr>
</tbody>
</table>

6a) Have you ever had a desire to amputate the limb?  Yes No

6b) If yes, how strong is that desire now?

   Not at all= 0__1__2__3__4__5__6__7__8__9__10 = Very strong

   Desired amputation site..............................................
7) With eyes closed describe a mental image of your affected and unaffected body parts
(drawn by assessor during patient description then verified by the patient)
7. Heart-rate Variability
   Wet sensors. Attach HRV monitor to chest strap.
   Give patient HRV monitor and ask them to put chest strap around chest.
   Start Polar watch to obtain HRV data.
   Press 'Lap' and record for 5 min with patient sitting comfortably.
   Press 'Lap' and have patients stand for 5 min.
   Press 'Lap' and have patient sit again for 5 min.
   Press 'stop'.

8. Laterality Task Performance

<table>
<thead>
<tr>
<th>Trial</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Response time L limbs:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Response time R limbs:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean accuracy L limbs:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean accuracy R limbs:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9. Signs/symptoms in affected limb:

Examine the limb in following order:

1. Look for limb asymmetries in colour, nails/hair growth, sweating
2. Measure temperature with infra-red thermometer, swelling with tape measure
3. Ask patient to flex/extend wrists/ankles, measure range of motion with goniometer, observe speed & co-ordination during repetitive finger/foot tap
4. Brush with cotton wool to test for allodynia
5. Repetitive tap to test for hyperpathia

<table>
<thead>
<tr>
<th></th>
<th>Reported by patient:</th>
<th>Observed by researcher: Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Colour asymmetry</td>
<td>Nil / Mild / Moderate / Severe</td>
<td></td>
</tr>
<tr>
<td>2. Nail/hair asymmetry</td>
<td>Nil / Mild / Moderate / Severe</td>
<td></td>
</tr>
<tr>
<td>4. Sweating asymmetry</td>
<td>Nil / Mild / Moderate / Severe</td>
<td></td>
</tr>
<tr>
<td>5. Temperature asymmetry</td>
<td>Affected:</td>
<td>Unaffected:</td>
</tr>
<tr>
<td></td>
<td>Hot / Cold / Both</td>
<td></td>
</tr>
<tr>
<td>3. Swelling</td>
<td>Nil / Mild / Moderate / Severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A wrist:</td>
<td>U wrist:</td>
</tr>
<tr>
<td></td>
<td>A D1:</td>
<td>U D1:</td>
</tr>
<tr>
<td></td>
<td>Or</td>
<td>Or</td>
</tr>
<tr>
<td></td>
<td>A Ankle:</td>
<td>U Ankle:</td>
</tr>
<tr>
<td></td>
<td>A Midfoot:</td>
<td>U Midfoot:</td>
</tr>
<tr>
<td>6. Range of motion asymmetry</td>
<td>Affected:</td>
<td>Unaffected:</td>
</tr>
<tr>
<td></td>
<td>Extension /</td>
<td>Extension /</td>
</tr>
<tr>
<td></td>
<td>Plantar flexion:</td>
<td>Plantar flexion:</td>
</tr>
<tr>
<td></td>
<td>Flexion / Dorsiflexion:</td>
<td>Flexion / Dorsiflexion:</td>
</tr>
<tr>
<td>7. Motor changes</td>
<td>Nil / Mild / Moderate / Severe</td>
<td></td>
</tr>
<tr>
<td>8. Allodynia</td>
<td>Pain pre-brush: /10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain during brush: /10</td>
<td></td>
</tr>
<tr>
<td>9. Hyperpathia</td>
<td>N/A</td>
<td>Pain pre-tap: /10</td>
</tr>
<tr>
<td></td>
<td>Pain during tap: /10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain post-tap: /10</td>
<td></td>
</tr>
<tr>
<td>Subtotals</td>
<td>/8</td>
<td>/9</td>
</tr>
<tr>
<td>Total</td>
<td>/17</td>
<td></td>
</tr>
</tbody>
</table>
10. Limb Function Tests
   a. Pre function-test pain level on VAS:
      Pain: [ ] mm

   b. Upper limb patients: 9-hole Pegboard Test
      Show patient 9-hole pegboard and pins. Instructions: This is called a 9-hole pegboard. It's used to see how well you can use your arm and hand. What I'd like to ask you to do is that when I start the timer, you need to pull the pins out of the pegboard one at a time and place them on the table. Once you've taken them all out, then you need to put them all back, one at a time. I'll time you to see how long it takes. Is that ok?
      Unaffected Time: [ ] sec  Affected Time: [ ] sec

   Or b. Lower Limb Patients: 15m timed walk test
      One of the things we want to do is to see how well you can use your leg and foot, with a timed walk test. I've mapped out a course in the corridor and what I'd like to ask you to do is to walk, as quickly as is possible for you, from here to (x-point) and back. I'll time you to see how long it takes. Is that ok?
      Time: [ ] sec

   c. Post function-test pain level on VAS:
      Pain: [ ] mm

   c. Post function-test swelling:
      Wrist: [ ] mm
      D1: [ ] mm
      Ankle: [ ] mm
      Foot: [ ] mm
Appendix 10: Completion Report to Ethics Committee for Prospective Study

Department of Psychological Medicine

24 April 2014

Final Report for MOH Ethics Committee

To whom it may concern,

Re: NTY/11/10/099: A prospective, observational study of the natural history of Complex Regional Pain Syndrome Type-1 (CRPS1): Do psychological factors influence outcome?

We have now completed our project investigating the influence of psychological factors on the outcomes of complex regional pain syndrome (CRPS). The study achieved its objectives. We recruited 66 participants and 63 completed both follow-ups (6 & 12 months).

Results were analysed and showed the following:

- All signs and symptoms of CRPS (except for temperature disturbance) showed statistically significant improvements over the 12 months, indicating that the general trajectory was for recovery.
- However, at 12 months, less than 5% of participants were completely symptom free. 75% reported still experiencing at least some pain, and over 80% had measurable restrictions in range of motion.
- We assessed predictors of recovery for 3 dependent variables.
  - CRPS severity scores (number of signs/symptoms of CRPS) were higher over the 12 months for females, those with higher baseline pain scores and higher baseline disability scores
  - Pain intensity was greater over the 12 months for those with higher baseline anxiety scores and those with higher baseline disability scores
  - Disability over the 12 months was greater for those with higher baseline pain scores and for those with higher baseline pain-related fear
- In addition, we analysed the baseline data separately and found that those with early disability was associated with greater depression. Also, sick-leave in the early stages of CRPS was associated with injury-type, physically demanding work, and higher depression scores.

The study results have been written up in three publications:
The results will also be presented in a poster presentation:

In addition, I have arranged to present the results at the New Zealand Pain Society meeting, New Plymouth, April 2016, at the Auckland Regional Pain Service journal club, the University of Auckland Health Psychology seminar series and the Institute of Health Psychology Peer Review.

Yours Sincerely,

Debbie Bean, PhD Candidate
Dept of Psychological Medicine, Faculty of Medical and Health Sciences
The University of Auckland, Private Bag 92019, Auckland
Mobile: 021 150 3131
Email: d.bean@auckland.ac.nz
Appendix 11: Final Report to Participants for Prospective Study

Study Results Report

"The Course of Complex Regional Pain Syndrome: A Prospective Study"

Thank-you so much for the time and effort you put into participating in our research study (The Course of Complex Regional Pain Syndrome). It’s now a long time since I last saw you, but we have had time to analyse the results and write them up. I’m writing to let you know what it is that we found.

In total, there were 66 people who took part in the study, and 63 people completed both of the follow-ups. We found that on average, pain scores and other symptoms (such as colour changes in the limb, swelling, limited movement etc.) all got better over the 12 months, which means that in general, people were getting better. However we also found that even at the end of the study, only 5% of people were completely symptom-free. Around three-quarters of people continued to have at least some intermittent pain and the other commonly reported lasting effect was limitations with movement.

We also assessed whether there were any factors that were associated with a better recovery. We found that males had a better recovery than females, and that those with the lowest levels of pain and those with the fewest limitations at the first appointment had better outcomes over the course of the year. In addition, those who had less anxiety and who felt most confident to get their painful limb moving had better pain scores and reported fewer limitations over the course of the year. This means that in future it would be worthwhile for us to do more research investigating whether or not we can improve recovery by optimising pain management, helping people to get their limbs moving more quickly and develop confidence that it is safe to do so. Hopefully we can run projects such as this in future.

We have also sent the study’s findings to be published in two journal articles in international medical journals, and hope these will be accepted to be published in the near future. This is important so that others who work in the field can also benefit from learning the study results. If you’d like more information, please feel free to contact me.

I’d also like to say a huge thank-you. I thoroughly enjoyed meeting you all during the study and greatly appreciated the time you made to take part. I wish you all the best.

Thanks again so much,

Debbie Bean
PhD Student
Auckland University
Ph 09 923 2891
d.bean@auckland.ac.nz
References


Birklein, F., Kunzel, W., & Sieweke, N. (2001). Despite clinical similarities there are significant differences between acute limb trauma and complex regional pain syndrome I (CRPS I). *Pain, 93*(2), 165-171. doi:10.1016/s0304-3959(01)00309-8


The Royal Australasian College of Physicians, & The Australasian Faculty of Occupational &
outcomes: A position statement. Sydney: The Australasian Faculty of Occupational and
Environmental Medicine, RACP.


Tracey, I. (2010). Getting the pain you expect: Mechanisms of placebo, nocebo and reappraisal effects
in humans. *Nature Medicine, 16*(11), 1277-1283. doi:10.1038/nm.2229


syndrome in adults: Concise guidance. *Clinical Medicine, 11*(6), 596-600. doi:10.7861/clinmedicine.11-6-596

Uceyler, N., Eberle, T., Rolke, R., Birklein, F., & Sommer, C. (2007). Differential expression patterns of


van de Meent, H., Oerlemans, M., Bruggeman, A., Klomp, F., van Dongen, R., Oostendorp, R., & Frölke,
J. P. (2011). Safety of "pain exposure" physical therapy in patients with complex regional pain


van Hilten, J. J., van de Beek, W. J., & Roep, B. O. (2000). Multifocal or generalized tonic dystonia of

aspects of multifocal or generalized tonic dystonia in reflex sympathetic dystrophy. *Neurology, 56*(12), 1762-1765. doi:10.1046/j.1533-2500.2001.1039_34.x

399-406. doi:10.1007/BF02054260

vander Beek, A. J. (2013). Predictors of return to work and employment in cancer survivors: A
systematic review. *European Journal of Cancer Care, 22*(2), 144-160. doi:10.1111/ecc.12033


