Somaesthesia, autonomic dysfunction and the perception of pain in Complex Regional Pain Syndrome and chronic rheumatic disease.

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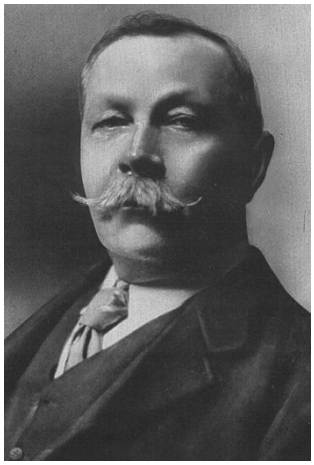

"It is with diffidence that a young medical man must approach a subject upon which so many masters minds have pondered – more particularly when the views which he entertains differ in so many respects from any which he has encountered in his reading."

Upon the vasomotor changes in tabes dorsalis and on the influence which is exerted by the sympathetic nervous system in that disease.

Sir Arthur Conan Doyle

1885.

Thesis (M.D.), Edinburgh University.

Image: *Current History of the War* Vol.I (December 1914 - March 1915). Sir Arthur Conan Doyle [online]. New York: New York Times Company. Available from: http://en.wikipedia.org/wiki/File:Conan_doyle.jpg. [Accessed 18.1.2012].

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List of Abbreviations

AFU	Arbitrary flux units
AL	Affected limb
ANS	Autonomic nervous system
AVS	Ambiguous visual stimuli
B	Blank sheet control figure
BBF	Baseline blood flow
BS	Black square control figure
BSA	Body surface allodynia
C	Control figure
CRPS	Complex Regional Pain Syndrome
CVR	Contralateral vasoconstrictor response
D	Dystonia
DB	Deep breath
DR	Duck/rabbit figure
EEG	Electroencephalogram
ESR	Electrodermal skin response
FME	Full motor extinction
fMRI	Functional magnetic resonance imaging
HC	Healthy control
IQR	Interquartile range
INIM	Initiation impairment
LA	Left arm
LDF	Laser Doppler flowmetry
LL	Lower limb
MEG	Magnetoencephalography
MS	Mental stress task
MVF	Mirror visual feedback
N	Necker cube
OA	Osteoarthritis
OVS	Optokinetic vulnerability scale
PET	Positron emission tomography
PhD	Photograph of a duck (control figure)
PhR	Photograph of a rabbit (control figure)
QST	Quantitative sensory testing
RA	Rheumatoid arthritis / Right arm

RNHRD	Royal National Hospital for Rheumatic Diseases
S	Seconds
SeD	Sensory disturbance
UL	Upper limb / Unaffected limb
V	Valsalva manoeuvre
VAR	Venoarteriolar response
VS	Visual stimuli

Glossary of terms

Acalculia: an acquired impairment characterised by difficulty performing simple mathematical tasks.

Agraphia: an acquired deficiency in the ability to write, regardless of the ability to read, not due to intellectual impairment.

Allochiria: unilateral tactile stimulation perceived only in the analogous location on the opposite limb

Allodynia: pain due to a stimulus which does not normally provoke pain.

Asteroeognosis: the inability to identify an object by touch or to discriminate shape, texture, weight, and size of objects without visual input.

Central pain: pain initiated or caused by a primary lesion or dysfunction in the central nervous system.

Conduction aphasia: a disorder of speech characterised by intact auditory comprehension, fluent speech production, but poor speech repetition.

Constructional apraxia: a form of apraxia characterized by the inability to copy drawings or to manipulate objects to form patterns or designs.

Contralateral vasoconstrictor response: a limb dependency test where in a healthy subject a vasoconstriction response is observed in the non-dependent limb opposite (ie. contralateral) to the limb lowered.

Dysaesthesia: an unpleasant abnormal sensation, whether spontaneous or evoked.

Dysgraphaesthesia: inability to recognize letters or numbers written on the hand.

Dysynchiria (tactile): unilateral non-noxious tactile stimulation perceived bilaterally as noxious

Dystonia: a syndrome of abnormal, involuntary muscle movements due to sustained muscle contractions resulting in twisting and/or repetitive, patterned movements.

Egocentric & alloocentric reference frames: an an egocentric reference frame, locations are represented with respect to the particular perspective of a perceiver, whereas an allocentric reference frame locates points within a framework external to the holder of the representation and independent of his or her position.

Finger agnosia: the inability to distinguish the fingers on the hand.

Hemineglect: a neuropsychological condition in which, after damage to one hemisphere of the brain, a deficit in attention to and awareness of one side of space is observed.

Homologous: having the same relation, relative position, or structure; Origin: Greek homologos ‘agreeing, consistent’, from homos ‘same’ + logos ‘ratio, proportion’

Hyperaesthesia: increased sensitivity to stimulation, excluding the special senses. Note: The stimulus and locus should be specified. Hyperaesthesia may refer to various modes of cutaneous sensibility including touch and thermal sensation without pain, as well as to pain. The word is used to indicate both diminished threshold to any stimulus and an increased response to stimuli that are normally recognized.

Hyperalgesia: an increased response to a stimulus which is normally painful.

Hyperpathia: a painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.

Hypoaesthesia: decreased sensitivity to stimulation, excluding the special senses. Note: Stimulation and locus to be specified. Hypoalgesia was formerly defined as diminished sensitivity to noxious stimulation, making it a particular case of hypoesthesia (q.v.). However, it now refers only to the occurrence of relatively less pain in response to stimulation that produces pain. Hypoesthesia covers the case of diminished sensitivity to stimulation that is normally painful.

Hypoalgesia: diminished pain in response to a normally painful stimulus.

Ideomotor apraxia: a disorder where there is disconnection between the idea of movement and its execution; inability to correctly imitate hand gestures and voluntarily pantomime tool use.

Motor extinction: difficulty initiating movement or impaired use of a limb during bilateral simultaneous movements.

Neuropathic pain: pain initiated or caused by a primary lesion or dysfunction in the nervous system.

Noxious stimulus: a stimulus which is damaging to normal tissues.

Optokinetic: pertaining to visual encoding of movement.

Pain: an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Paraesthesia: an abnormal sensation, whether spontaneous or evoked.

Peripheral neuropathic pain:

Pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system.

Qualia: a term used to describe the subjective conscious experience of sensory stimuli.

Quantitative sensory testing: a standardised technique of assessing and quantifying an individual's response to sensory stimulation that allows comparison to other individuals.

Referred sensation: unilateral tactile stimulation perceived concurrently in another discrete body area.

Right Left Disorientation: inability to distinguish between right and left.

Sensory extinction: bilateral non-noxious tactile stimulation perceived unilaterally

Somaesthesia: the faculty of bodily perception. Origin: somat-+ G. Aisthesis, sensation.

Somatoparaphrenia: a type of monothematic delusion with denial of ownership of a limb or an entire side of one's body.

Sudomotor: a response within the system controlling sweat gland activity.

Valsalva manoeuvre: moderately forceful attempted exhalation against a closed airway.

Vasomotor: a response within the vascular system

Venoarteriolar reflex: a limb dependency test where in a healthy subject a vasoconstriction response is observed in the limb lowered.

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The body of work in this thesis could not have occurred without the collaboration and contribution of the following colleagues. Many thanks to Professors David Blake, Candy McCabe and Dr Nigel Harris who assisted in the design of the studies, Dr Gordon Taylor for statistical support, and Professor Wilfrid Jänig for help with data interpretation, and to all for their assistance with preparation of papers for publication. All other work relating to these studies was conducted by myself.

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And finally to the late Professor.Gregory whose pioneering work continues to inspire me, and to make me question the process of ‘perception’.

Declaration

I declare that this work has been produced by my own endeavour and that no part of this has been carried out by anyone else, except where acknowledged. This work has been completed whilst registered as a post graduate student at the University of Bath.

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List of publications

The following publications have emanated from the work presented in this thesis:

1. Enhanced pain and autonomic responses to ambiguous visual stimuli in chronic Complex Regional Pain Syndrome (CRPS) type I. **Cohen HE**, Hall J, Harris N, McCabe CS, Blake DR, Jänig W. Eur J Pain. 2011 Aug 6. [Epub ahead of print]

2. A case of complex regional pain syndrome with agnosia for object orientation. Robinson G, **Cohen H**, Goebel A. Pain. 2011 Jul;152(7):1674-81.

In submission:

Clinical evidence of parietal cortex dysfunction and correlation with extent of allodynia in Complex Regional Pain Syndrome (CRPS) Type 1. A pilot study.

Cohen H, Harris N, Lewis J, Hall J, Blake DR, McCabe C.

List of conference publications

The following presentations at National or International conferences have emanated from the work presented in this thesis:

1. British Society of Rheumatology (BSR) 2008 - Concurrent Oral Presentation: Labile vasomotor autonomic responses to ambiguous visual stimulation in patients with complex regional pain syndrome (CRPS) type 1.

2. BSR 2009: Clinical evidence of parietal lobe dysfunction in patients with complex regional pain syndrome (CRPS) type 1.

3. BSR 2010: A case of Complex Regional Pain Syndrome with extensive severe allodynia, refferred sensations and clinical evidence of parietal lobe dysfunction: cortical reorganisation contributes to clinical presentation.

4. BSR 2010: Does the degree of cortical reorganisation determine different clinical phenotypes in Complex Regional Pain Syndrome (CRPS)? A sensorimotor study.

5. BSR 2010: Distorting proprioception in patients with rheumatic diseases exacerbates sensory disturbances: Further evidence for central pain mechanisms.

6. European Federation of IASP Chapters (EFIC) 2006: Visual stimulation can elicit pain and asymmetric autonomic skin blood flow responses in complex regional pain syndrome (CRPS) type 1.

7. Second International Congress on Neuropathic Pain (NeuPSIG) 2007: Asymmetric sympathetic autonomic responses to ambiguous visual stimulation in Complex Regional Pain Syndrome (CRPS) Type 1 patients.

8. 12th World Congress on Pain (International Association for the Study of Pain 2008): Anomalous vasomotor autonomic responses and dystonic reactions to visual stimulation in patients with complex regional pain syndrome (CRPS) type1.

9. 13th World Congress on Pain (International Association for the Study of Pain 2010): Different clinical phenotypes in Complex Regional Pain Syndrome (CRPS) may reflect the degree of cortical reorganisation: A sensorimotor study.

Additional publications relevant to the thesis but not forming part of it

The following publications have emanated from work presented in this thesis and are relevant to it, but do not form part of it:

1. Pain and other symptoms of CRPS can be increased by ambiguous visual stimuli – An exploratory study. Jane Hall, Simon Harrison, **Helen Cohen**, Candida S. McCabe, N. Harris, David R. Blake. *European Journal of Pain* 15 (2011) 17–22.

2. McCabe C.S.; **Cohen H.**; Blake D.R. Somaesthetic disturbances in fibromyalgia are exaggerated by sensory motor conflict: implications for chronicity of the disease? *Rheumatology* 2007:46:1587-1592.

Abstract

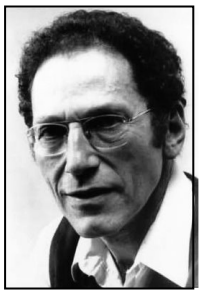
The perception of pain is a complex process involving central integration of nociceptive sensory signals with autonomic, emotional, motor and behavioural cortical networks. The principal aim of this thesis was to explore how this process contributes to the presenting clinical phenotype in complex regional pain syndrome (CRPS), and whether this extends to other chronic pain conditions in rheumatic disease such as osteoarthritis (OA) and rheumatoid arthrits (RA).

The first study established baseline quantitative sensory testing parameters and autonomic function. It found that allodynia was absent in controls, present in some OA and RA patients and most marked in CRPS patients. Autonomic function was normal in controls, with some impairment in OA and RA and most dysfunction in CRPS. The second study used an optokinetic visuo-motor challenge induced by a mirror-whiteboard device. The presence or absence of sensory disturbances and/or new/worsening pain was used to generate a vulnerability scale. Controls were the least vulnerable followed by RA, then OA with CRPS the most vulnerable. Autonomic responses, sensory disturbances and new/worsening pain to a pure visual conflict in the form of ambiguous visual stimuli (AVS) were used for the third study. Sensory disturbances, pain enhancement and abnormal asymmetric autonomic responses occurred only in the CRPS cohort. The final study investigated parietal lobe function in CRPS patients. It showed clinical evidence of parietal lobe dysfunction present in a substantial number of CRPS patients, and that this was reflected both in symptoms and impact upon activities of daily living.

Overall, the thesis findings support the concept that perterbation of central somaesthetic integration may induce cortical network dysfunction, reflected in different patterns of autonomic and pain responses. This might contribute to the differing clinical presentations seen in CRPS. Similar processes may also occur in OA and RA. This work provides an approach to the clinical phenotyping of CRPS and other chronic painful rheumatic diseases. Appreciation of the potential mechanisms described may allow better targeting of therapy.

Chapter 1: Introduction

"I ache for the touch of your lips, dear,
But much more for the touch of your whips, dear.
You can raise welts
Like nobody else,
As we dance to the masochism tango."



Tom Lehrer – *The Masochism Tango*

(A quote illustrating pain as both a sensation and a perception)

(Image available from: http://philosophyofscienceportal.blogspot.com/2008/11/tom-lehrers-elements.html. Accessed 17.1.12.)

1.1. Overview

The definition of 'somaesthesia' is the faculty of bodily perception. Perceptual experiences including bodily sensations are termed 'qualia'. As Daniel Dennett wrote (Dennett, 1988), a qualia is "an unfamiliar term for something that could not be more familiar to each of us: the ways things seem to us." Pain is thus both a sensation and a perception, and therefore an individual personal experience. Pain is an inevitable companion to human experience, and where it is absent in rare conditions such as congenital pain insensitivity, life span is shortened (Drummond and Rose, 1975;Nagasako et al., 2003). Pain is therefore a necessary evil, and an evolutionary survival strategy (Stefano et al., 2005). Fortunately pain is usually self limiting. However in certain pathologic circumstances, it may become chronic.

Chronic pain causes impaired quality of life (Hoftun et al., 2011;Keeley et al., 2008;Nordeman et al., 2011), and is a significant socio-economic burden (Langley et al., 2010;Latham and Davis, 1994). Chronic musculoskeletal pain is common. In a one month period, up to 20% of adults may complain of chronic widespread pain, one third of shoulder pain and up to one half, low back pain (McBeth and Jones, 2007). Chronic pain is commonly encountered in Rheumatological practice among patients with osteoarthritis (OA) and rheumatoid arthritis (RA). Complex regional pain syndome (CRPS) is a rarer, poorly understood chronically painful condition that is occasionally encountered by Rheumatologists. Typically affecting the extremities, it is

characterised by unremitting pain, autonomic disturbances in the control of blood flow and sweating and often marked tactile allodynia (normally non-painful touch is perceived as painful). Thus in some chronic pain conditions, the perception of sensory stimuli can change from non-noxious to noxious.

Chronic non-malignant pain is poorly understood and often difficult to treat. There are likely to be multiple aetiopathogenic mechanisms operating acrosss a spectrum of diseases. Futhermore, even within one disease there are likely to be different patterns of pain mechanisms between patients, and patterns may vary in an individual over time. Therefore to improve the treatment of the chronic pain of an individual patient, better understanding of the pain mechanisms operating in that person at that time are needed.

This thesis sets out to address whether it is possible to identify when certain pain mechanisms are operational in chronically painful rheumatic diseases such as OA, RA and CRPS.

1.2. Pain mechanisms relevant to the thesis (see **Chapter 2** for a fuller discussion)

1.2.1. Central pain in OA and RA

There is increasing evidence of central cortical pain mechanisms in OA and RA (Hendiani et al., 2003). It is a well recognised clinical conundrum that the severity of osteoarthritic changes on plain X-ray films may not correlate with symptoms (Hochberg et al., 2003). Concurrent unrecognised fibromyalgic widespread pain in RA may invalidate the 'inflammatory' DAS (Disease Activity Score) 28 score (Wolfe, 2009). Together with recent neuroimaging studies (Wartolowska et al., 2011) (Rodriguez-Raecke et al., 2009), such features suggest central pain mechanisms may be operational.

1.2.2. Sensory and motor conflict

Sea sickness is a common problem among people undertaking maritime voyages or water based activities. Individuals vary in their susceptibility to motion sickness (Golding, 2006), and it may change with age. A well recognised and accepted explanation is that it arises due to the inability of higher cortical centres to accurately integrate the conflicting sensorimotor, visual and proprioceptive information produced by being a stationary passenger on a moving vehicle (Kohl, 1983). In the case of sea sickness, if a person remains on the vessel for a prolonged period (such as during a

cruise, or as an occupation), they will regain their 'sea-legs' as brain integration improves and the conflict resolves.

Previous research has shown that it is possible to induce sensory disturbances and pain in healthy controls by creating visuo-sensorimotor conflict using a mirror (McCabe et al., 2005). It has been hypothesised that cortical reorganisation (see **1.2.3** below) may cause an individual to be more vulnerable to sensory conflict (Harris, 1999). Vulnerability to mirror induced sensory disturbances and pain is increased in the chronic pain condition of fibromyalgia (McCabe et al., 2007). Enhanced pain in response to a pure visual challenge induced by viewing an optical illusion has been described in CRPS (Hall et al., 2010). Therefore in chronic pain conditions, there may be enhanced vulnerability to visual and sensorimotor conflict.

1.2.3. Central pain in CRPS: the role of cortical reorganisation

Some of the sensory findings in CRPS such as referred sensations (McCabe et al., 2003) and the quality of pain share similarities with another chronic pain condition, phantom limb pain (PLP) in amputees. There is good evidence for the contribution of central mechanisms in PLP, and specifically for the role of cortical reorganisation (Lotze et al., 2001). There is increasing evidence of neuroplastic cortical reorganisation and network dysfunction in CRPS (Swart et al., 2009), and that successsful treatment can reverse both the pain and cortical reorganisation (MacIver et al., 2008;Maihöfner et al., 2004).

1.2.4. CRPS: the role of autonomic dysfunction

The role of sympathetic autonomic dysfunction in pain remains unclear (see **Chapter 2** for a fuller discussion). In CRPS there is often marked sympathetic autonomic dysfunction in the affected limb, which has given rise to the concept of 'sympathetically maintained pain' (Drummond, 2010;Gibbs et al., 2008). Interventional techniques such as chemical and surgical sympathectomies are often performed as a treatment for the pain of CRPS, but the evidence base remains poor (Straube et al., 2010). The mechanisms causing the sympathetic autonomic dysfunction are complex, probably multifactorial and still unclear (Bruehl, 2010).

1.2.5. Role of the parietal cortex

The parietal lobes of the brain are association cortices. They are essential for the integration of allocentric (of the environment) and egocentric (of the person) sensory stimuli with previous experience and knowledge. This allows appropriate behavioural and emotional responses. Parietal lobe lesions can cause a variety of disabling

syndromes including neglect. Neglect-like features hace been reported in CRPS (Galer and Jensen, 1999). There is also evidence for the role of the parietal cortex in the perception of pain (Duncan and Albanese, 2003).

1.3. Principal aims and objectives

The underpinning theme of this thesis is that patterns of autonomic and pain network dysfunction may arise from varying neuroplastic cortical reorganisational changes, which could cause impairment of central somaesthetic integration and be reflected in the presenting clinical phenotype across a spectrum of rheuamatic diseases. In a severe pain condition such as CRPS where it is known that reorganisational changes may exist, there may be more chance of being able to detect such patterns. Similar changes may also occur in other chronic rheumatic pain conditions such as osteoarthritis (OA) and rheumatoid arthritis (RA).

The principal aim of this research was to gain insights into different mechanisms that contribute to chronic pain, and thereby obtain new understanding of the varying patterns and presentations of chronic pain in rheumatic disease. This was done through a series of central integrative sensory challenges investigating how these might contribute to pain in both CRPS and chronic rheumatic disease.

1.4. The four clinical studies

For each study, the questions raised by the literature are given together with an outline of the aims. The specific hypotheses to each study are given in the chapter describing it.

> **Study 1** (**Chapter 4**)**:** Quantitative sensory testing (QST) and baseline sympathetic autonomic function in CRPS and rheumatic disease.
> **Research question addressed:** Is there any evidence of sensory or sympathetic autonomic dysfunction in OA, RA and CRPS compared to healthy controls?

The aim of this study was to define and describe the clinical presentation of sensory and autonomic function in the study populations (healthy controls, OA, RA and CRPS). This would allow comparison of parameters in healthy controls with the patient cohorts. It also establishes a baseline for comparison with the other studies.

Study 2 (**Chapter 5**)**:** Sensory disturbances and vulnerability during a visuo-sensorimotor challenge in CRPS and rheumatic disease.

Research question addressed: Can a mirror induced visuo-sensorimotor challenge cause sensory disturbances and new or enhanced pain in OA, RA and CRPS? If so, are there differences between these cohorts and between healthy controls?

Study 2 investigated vulnerability to sensory and pain responses induced by visuo-sensorimotor conflict using a mirror device. Vulnerability could be compared between and within cohorts, and compared to baseline parameters in Study 1 such as autonomic dysfunction and allodynia.

Study 3 (**Chapter 6**)**:** Sensory disturbances and sympathetic autonomic responses during a pure visual challenge utilising ambiguous visual stimuli in CRPS and chronic rheumatic disease.

Research question addressed: Can a pure visual challenge cause sensory or pain disturbances in healthy controls, OA, RA and CRPS? What is the pattern of concurrent autonomic responses? If abnormalities are found, are there differences between the cohorts?

In this study, vulnerability to sensory and pain disturbances during a pure visual challenge together with concurrent sympathetic autonomic responses were assessed. Vulnerability to a visual challenge could be compared between and within cohorts, and correlated with vulnerability to the visuo-sensorimotor (mirror) challenge (study 2) as well as to baseline autonomic function and sensory parameters (study 1).

Study 4 (**Chapter 7**)**:** Parietal lobe function in CRPS.

Research question addressed: Is there any clinical evidence for parietal lobe dysfunction in CRPS?

The final study investigated whether there was any clinical evidence for parietal dysfunction in CRPS. Findings could then be compared to vulnerability to a pure visual challenge (study 3), a visuo-sensorimotor challenge (study 2) and to baseline autonomic function and allodynia (study 1).

1.5. Structure of thesis

The thesis is presented as a series of four clinical studies (**Chapters 4** – **7**) investigating different potential mechanisms contributing to pain in both CRPS and chronic rheumatic disease. The results from CRPS patients are compared to those of healthy controls and two cohorts of patients with chronic rheumatic pain; osteoarthritis and rheumatoid arthritis. Each study is presented, strengths and weaknesses discussed, and the outcomes of the latter compared to the former such that the fourth study brings together a comparison of all the different contributing mechanisms investigated. **Chapter 2** provides the background to the research questions and reviews the literature against which they are formulated. As each study chapter has a separate methods section specific to that study, **Chapter 3** provides the methods common to each to avoid repetition. **Chapter 8** draws together the findings of each study, and puts them into context against current literature summarising novel findings, clinical implications and potential future research directions.

The overall objective of this body of work is to provide a clearer understanding of some of the pain mechanisms that may be operating in chronic rheumatic pain. It aims to provide a provisional basis for the clinical phenotyping of chronic pain, particularly in CRPS. When an individual patient presents with complex chronic pain, a phenotyping approach will allow for the more prominent pain mechanisms operating to be recognised, and treatment targeted appropriately.

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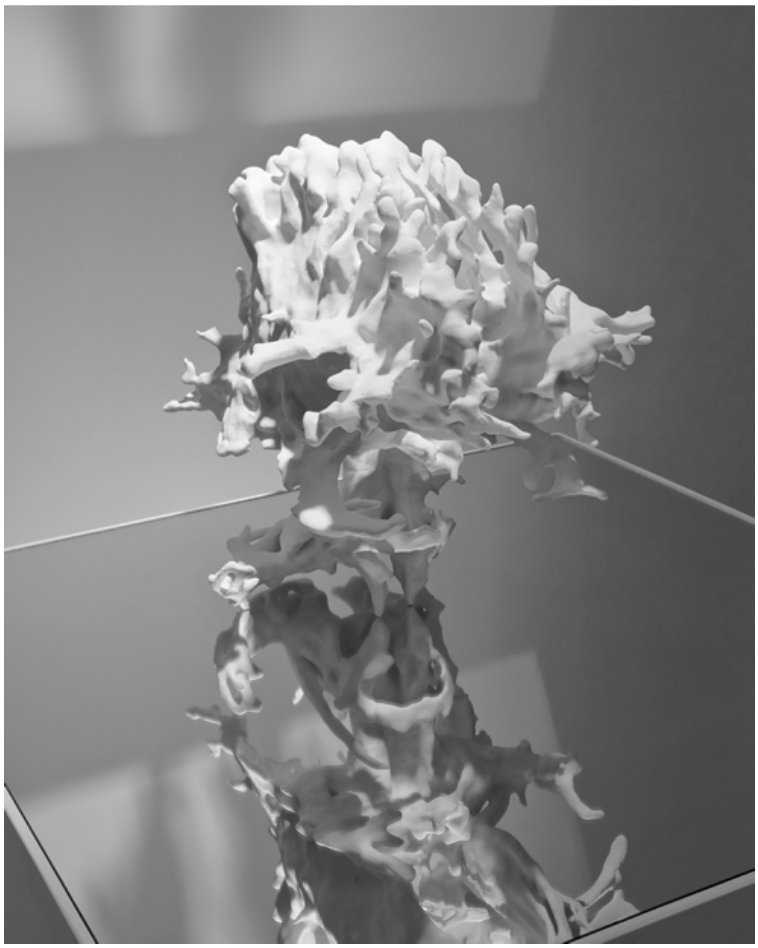
Pleasure/Pain

By artist ANNIE CATTRELL



Pleasure/Pain was made in collaboration with Professor Morten L Kringelbach of Oxford University. Functional Magnetic Resonance Imaging with Diffusion Tensor Imaging was used to create a three dimensional representation of the overlapping cerebral pathways of pleasure and pain.

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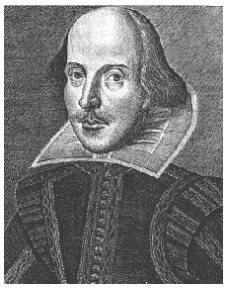
Chapter 2: Literature review



"A wretched soul, bruised with adversity,
We bid be quiet when we hear it cry;
But were we burdened with like weight of pain,
As much or more we should ourselves complain."

William Shakespeare – *The Comedy of Errors* (Act 1, scene 1).

(Image available from: http://shakespeare.mit.edu/. Accessed 17.1.12.)

2.1. Introduction

This chapter will introduce the background literature that provides the basis upon which the thesis questions were formulated and the research constructed. It will begin by outlining current concepts of pain, and pain modulating systems. It will then demonstrate the importance of cortical sensory integration in somaesthesia and the perception of pain, and how this links with visual perception. From here it will move to autonomic nervous system integration with pain and interoception. Finally it will review the problem of pain in chronic rheumatic disease, specifically osteoarthritis (OA) and rheumatoid arthritis (RA), and Complex Regional Pain Syndrome (CRPS) together with a more detailed review of CRPS and potential aetiopathogenic mechanisms.

2.2. Pain

2.2.1. Basic neuroanatomy and physiology

The perception of pain involves sensory (nociceptive), affective (emotional) and cognitive (interpretation, context and meaning) dimensions. The key elements of nociception include activation of peripheral sensory afferent nerves, transmission to the spinal cord, projection to supraspinal structures and regulation of spinal transmission by modulatory ascending and descending facilitatory/inhibitory pathways (McCleane and Smith, 2007).

During a noxious stimulus such as an injury, primary afferent small myelinated A-δ and unmyelinated C-fibre nociceptors transmit impulses to the dorsal horn of the spinal cord. A- δ terminate primarily on neurones in laminas I, V and X, and dorsal root C-fibres in laminas I – V (mainly I and II). Impulses form C-fibres pass to several different second order interneurones. These include the wide dynamic

range (WDR) cell responsive to pain and gentle touch, found in lamina V (and also IV & VI). WDR neurones are responsible for the phenomenon of 'wind-up' in pain. Other second order interneurones include nociceptive specific neurones in lamina I.

Pain is often described as having a 'fast' component which is a sharp, well localised sensation, then followed by a 'slow' pain described as dull, diffuse and unpleasant. 'Fast pain is subserved by the faster conducting A-δ fibres, and the 'slow' by the slower unmyelinated C-fibres.

Nociceptive impulses ascend by two main pathways: the primitive spino-reticulo-diencephalic tract in the posterolateral cord, and the more modern neospinothalamic anterolateral system (including the lateral spinothalamic tract) which takes most of its fibres from laminas I and V. Higher ascending pathways project to many cortical areas including the thalamus, reticular system, hypothalamus, periaqueductal grey, S1, S2 and cingulate cortex, collectively known as the 'pain matrix'. The phylogenetically older spino-reticulo-diencephalic tract ends in the reticular system of the brainstem, with other connections to the thalamus and (via the reticular system) hypothalamus. These connections allow for integration of the autonomic components of pain. Thalamic connections to many cortical areas including limbic and anterior cingulate mediate the affective/emotional aspects of pain. The spinothalamic tracts pass to the lateral thalamus with connections to the sensory cortex allowing the localisation of pain. Damage to this pathway can cause a severe pain syndrome known as the 'thalamic syndrome'.

2.2.2. Descending control of pain

The original descending inhibitory 'gate theory' of Melzack and Wall (Melzack and Wall, 1965) has been superseded by newer understanding of pain modulation mechanisms. Descending control arises from supraspinal areas, including the midline periaqueductral gray-rostral ventromedial medulla (PAG-RVM) system, and the dorsal reticular nucleus (DRt) and ventrolateral medulla (VLM). These systems can be inhibitory or facilitatory. The PAG-RVM inhibitory system suppresses C-fibre input preferentially to the more rapidly conducting A-δ fibres preserving sensory discrimination. Within the PAG-RVM system there are populations of neurones, ON-cells and OFF-cells. These are differentially recruited by higher structures during fear, psychological stress and illness causing enhancement or inhibition of pain. Persistent nociception can activate both descending inhibition and facilitation (Heinricher et al., 2009).

In models of inflammation, descending inhibition attenuates primary hyperalgesia and descending facilitation enhances secondary hyperalgesia. Descending facilitation from the PAG-RVM is believed to contribute to the hyperalgesia and allodynia of neuropathic pain (Vanegas and Schaible, 2004). PAG-RVM connections are serotoninergic (Heinricher et al., 2009). Axons descend in the dorsolateral funiculus to lamina II where synapses are enkephalinergic.

The DRt-VLM are connected with nociceptive dorsal horn laminae. Studies suggest that the role of the DRt is primarily facilitatory. The VLM exerts a tonic inhibitory control of dorsal horn nociception but may also exert a facilitatory influence, as neurons with features of ON and OFF cells have been identified in this region (Heinricher et al., 2009;Tavares and Lima, 2002). There is another noradrenergic descending inhibitory pathway that projects from the nucleus raphe magnus (NRM) and locus coeruleus in the pons (Jones, 1991).

2.2.3. Sensitisation

In chronic neuropathic pain, sensitisation occurs such that thresholds are lowered so that stimuli that would normally not produce pain now begin to (allodynia), and responsiveness is increased, so that noxious stimuli produce an exaggerated and prolonged pain (hyperalgesia).

Peripheral sensitisation refers to a reduction in the threshold and increase in the responsiveness of peripheral nociceptor endings. Sensitisation occurs through the action of inflammatory mediators (for more details, see **2.7.6.1. '**Facilitated neurogenic inflammation'), and contributes to hyperalgesia.

Central sensitization occurs when there is increased excitability of CNS neurones such that normal inputs produce abnormal responses. Activity in low threshold sensory fibres produced by light touch may activate ascending nociceptive pathways, and can produce allodynia.

2.2.4. Neuroplasticity

After peripheral tissue or nerve injury, hyperalgesia may develop which is related to changes at the site of injury and to CNS hyperexcitability that leads to long term CNS changes, termed 'plasticity' (Pillemer S, 1997).

Somatosensory cortical representation of limbs can show plastic changes. The reading fingers of Braille readers have been shown to have larger areas of representation (Pascual-Leone A, 1993;Sterr A, 1998). In focal hand dystonia (Bara-Jimenez et al., 1998;Elbert et al., 1998) disordered topographical cortical

somatosensory representation has been shown, with fusion of digital areas. This has also been demonstrated in a monkey model of repetitive strain injury (Byl et al., 1996). Among Braille readers with disordered cortical topography, they were found to frequently misperceive which finger was being touched by a light tactile stimulus (Sterr A, 1998).

In patients with phantom limb pain (Flor et al., 1998) and patients with chronic back pain (Wiech K, 2000), alterations in the somatotopic organisation of the primary somatosensory cortex have been demonstrated, whereby the site of origin of the pain has a relatively larger allocation. In upper limb amputees, the reorganisational changes in the sensory cortex are such that the face lying next to the hand on the Penfield homunculus may now expand into the area formerly occupied by the hand. This is the explanation behind 'referred sensations' in amputees. In an upper limb amputee with these neuroplastic changes, touch on the face may be felt simultaneously in a specific location on the phantom hand (Ramachandran et al., 1992)(**Fig.2.1**).

Fig.2.1.

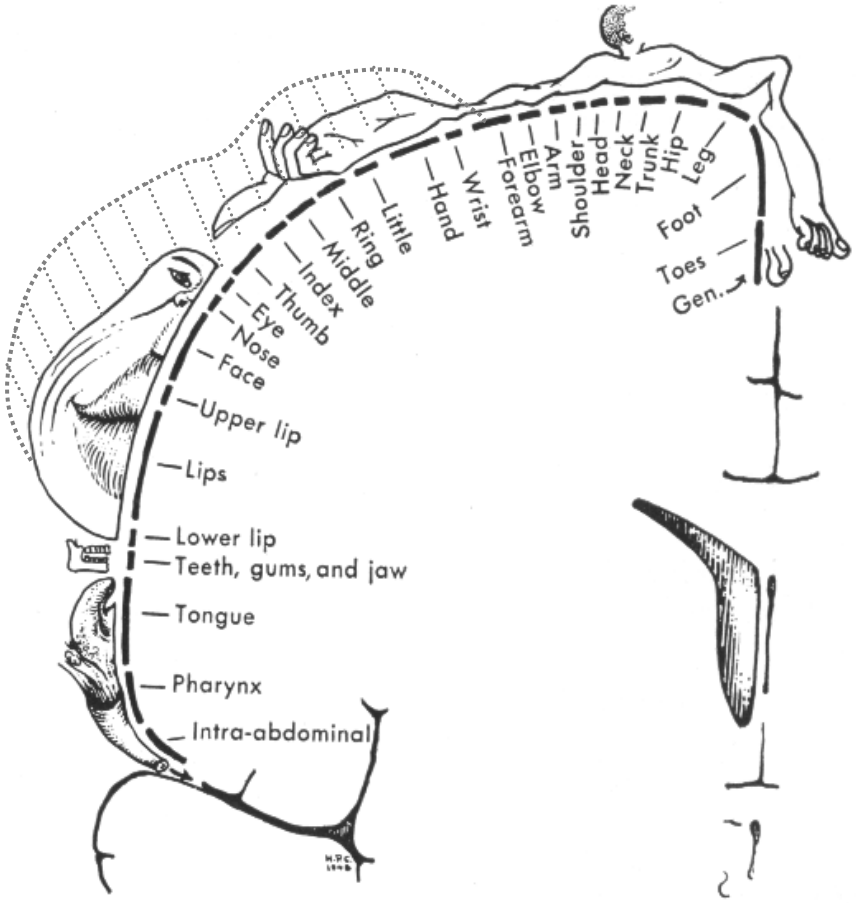


Fig.2.1. The sensory Penfield homunculus. The grey dashed area around the face represents the neuroplastic cortical reorganisation that may occur in an upper limb amputee with referral of sensations from the face to the phantom hand.

Illustration based upon an original image available from:
http://www.neurobiography.info/teaching/teaching.php?mode=view&lectureid=1&slide=24. [Accessed 17.1.12.]

Neuroplasticity and its role in CRPS are discussed below in ***2.7.6.3***. 'Neuroplastic changes within the CNS'.

Thus chronic stimulation, or loss of sensory input of a body part can cause plastic changes in cortical somatosensoy representation leading to enlargement and/or topographical disorder. How might this type of disorder contribute to pain? One theory is through consequent sensorimotor conflict.

2.2.5. Sensorimotor conflict and pain

Fink (Fink et al., 1999) investigated the neural consequences of conflict between intention and the senses by PET scanning subjects performing Luria's bimanual

coordination tasks. This required healthy volunteers to open and close their hands repetitively either in phase or out of phase with each other, always looking towards the left hand. A mirror was then introduced to alter the visual feedback from the left hand by showing a reflection of the right hand in its place. This allowed a condition to be created where visual feedback was rendered non-veridical and incongruent ie. the subjects intention and proprioceptive feedback indicated out of phase movements, while visual feedback indicated in phase movements via the mirror image reflecting the right hand. A second study repeated the same protocol but manipulated visual feedback from the right hand rather than the left. A third study removed motor intention by moving the hand passively therefore creating conflict between proprioception and vision only. It was shown that a ventral right lateral prefrontal region was primarily activated by discrepancies between signals from sensory systems, while a more dorsal area in right lateral prefrontal cortex was activated when actions had to be maintained despite conflict between intention and sensory outcome. Feelings of peculiarity were greatest in the incongruent conditions.

From his work on patients with left neglect and parietal lobe syndrome (Ramachandran, 1995), Ramachandran proposed the existence of a unilateral right cortical centre monitoring incongruence of sensation (CIS). He suggests that as a Darwinian defence mechanism, there is a need to impose a ‘decision’ where a sensory conflict offers different possibilities and the potential for vacillation. The CIS therefore has a role to “detect anomalies or discrepancies, and to generate a paradigm shift if the discrepancy is too large.”

Harris (Harris, 1999) suggested that incongruent sensorimotor feedback may be generated as a consequence of cortical reorganisation, be detected by the CIS and result in pain not only in phantom limb pain, but also in a variety of chronic pain conditions where cortical reorganisation occurs. He hypothesised that the right dorsal lateral prefrontal cortex activated by conflict generated in the incongruent conditions of Fink's study (Fink et al., 1999) could be the CIS equivalent proposed by Ramachandran (Ramachandran, 1995). Sensory conflict can generate unpleasant somaesthetic experiences in healthy individuals. It is a well recognised explanation of motion sickness (Warwick-Evans et al., 1998). Our group has shown that it is possible to induce a range of unpleasant somaesthetic percepts including pain in healthy controls by using an optokinetic system (mirror/whiteboard) to generate conflict between the visual and proprioceptive senses (McCabe et al., 2005). Furthermore, the susceptibility to this is increased in a chronic pain cohort of fibromyalgia patients (McCabe et al., 2007).

Newer models of sensorimotor integration offer further insights. The motor control system manages the relationships between motor commands and sensory feedback, ensuring that goal directed movements are achieved accurately and smoothly. Each time a movement is undertaken, motor commands are transformed into efferent motor actions and then into reafferent sensory feedback. State variables such as proprioceptive information about body configuration, joint angles, kinaesthetic information and the state of the body system prior to implementation of a movement provide a basis for internal models of the motor system. When a sequence of motor commands is issued, on the basis of the state variables and the internal model, it is possible to 'predict' the subsequent behaviour of the motor system and sensory feedback arising from that behaviour. 'Predictors' model aspects of the external world and of the motor system in order to capture the forward or causal relationship between actions and their outcomes. 'Controllers' provide the motor commands necessary to achieve a desired outcome. 'Controllers can compare the desired state with the motor commands needed to achieve it, and a forward model, or 'efference' copy of the motor command is issued (Frith et al., 2000). The forward model is often a rough prediction. Any difference between actual and predicted sensory feedback can be used to modify the current state of the system and correct the state estimates from the forward model (Wolpert et al., 1995) (**Fig.2.2**).

Cortical reorganisation due to chronic pain could lead to the production of impaired efferent motor command copies, which will produce conflict between motor intention and sensory feedback. From the Harris hypothesis (Harris, 1999), this would be predicted to cause pain, or worsening pain where it already exists.

Fig.2.2.

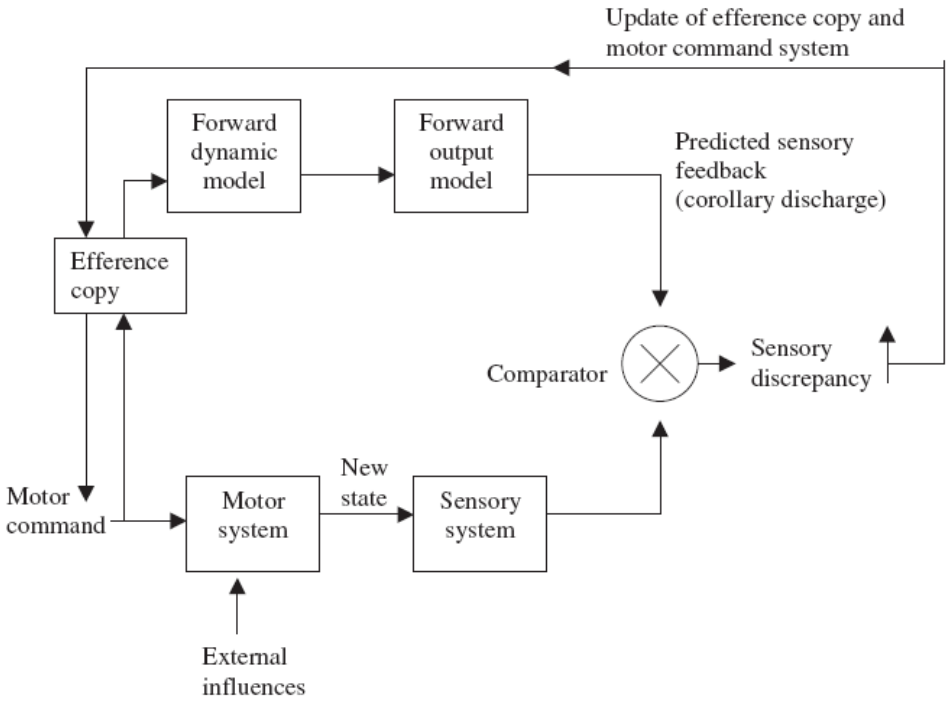


Fig.2.2. Schematic diagram depicting the role of the efference copy in the motor control system.

Information from current state variables (e.g. joint position sense) is used to create a prediction of the sensory consequences of any motor command. This prediction, or efference copy, is compared (comparator) with the actual sensory consequences of that new activity. When a discrepancy is noted this information is fed back to the motor command system to update the state variables and thereby inform future efference copies.

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2.2.6. Conclusion

The perception of pain is a complex interplay of peripheral and central mechanisms, which is highly variable depending upon the individual and the circumstances. Neuroplastic change and sensory conflict can induce a variety of unpleasant somaesthetic sensations including pain in chronic pain patients. Sensory conflict can induce similar sensations in susceptible healthy individuals. The effect of sensory conflict in patients with rheumatic chronic pain and in CRPS is little known.

Having demonstrated that the integration of body sensory information ie. 'somaesthesia' can be perturbed by neuroplastic changes and sensory conflict, the next section expands upon this process.

2.3. Somaesthesia; the integration of sensation with body schema

2.3.1. Somatosensory integration

The feeling of body ownership refers to the special perceptual status of one's own body. This makes bodily sensations, or 'somaesthesia' unique to oneself, and is a fundamental aspect of self-consciousness. Disturbance of body schema and ownership of body parts may occur after brain damage including parietal lesions (Braun et al., 2007). Alien hand syndrome is characterised by autonomous motor activity perceived as involuntary and purposeful, with a feeling of foreignness and failure to recognise ownership of the affected limb. It has been described with lesions of the copus callosum, frontal lobes and after parietal damage (Carrilho et al., 2001;Kikkert et al., 2006). A right parietal stroke may produce left sided weakness and left neglect syndrome (for more details on neglect, see **Chapter 7**). Braun proposes that the psychic tonus model of hemispheric specialisation incorporates the representation of body schema in the parietal lobes, whereby the left hemisphere is a 'booster' of internal experience and behaviour, and the right a 'dampener' (Braun et al., 2007).

2.3.2. When somatosensory integration is disrupted; body schema illusions

Illusions of body schema can occur in the intact brain. Regional anaesthesia can induce body image distortions (Paqueron et al., 2003), a phenomenon which anyone who has had a local injection when undergoing dental treatment can verify. Vibration applied to a tendon across a joint can induce illusory movement. If the vibration is applied to the wrist, it will cause illusory movement of the hand. If vibration is applied while the hand is in contact with the nose, the nose can appear to elongate or shrink depending on which tendon is manipulated. If the hands are in contact with the waist, illusory shrinkage can occur (Ehrsson et al., 2005b). Some healthy controls may experience not only vibration induced illusory movement, but also feelings of peculiarity, swelling and foreignness (Moseley et al., 2006), or it may cause disruption in a motor imagery task (McCormick et al., 2007). Moseley's group postulate faulty proprioceptive input as a potential mechanism for the illusory movement and of the abnormal sensations perceived (McCormick et al., 2007;Moseley et al., 2006).

In the 'rubber hand illusion', viewing a rubber hand being brushed at the same time as the person's hidden hand is brushed can cause a feeling of 'ownership' of the rubber hand. The mechanisms are unclear, but it is likely that the illusion occurs within a hand-centred reference frame updated with changes in body posture (Costantini and Haggard, 2007). It is also unclear whether vision (Farne et al., 2000)

or multisensory feedback from one's own body (Ehrsson et al., 2005a) is dominant in the generation of the illusion.

Functional neuroimaging techniques have been employed during the rubber hand illusion in which normal subjects may perceive a fake rubber hand as part of their body, allowing insight into brain areas active in body ownership and somaesthesia. Ehrsson (Ehrsson et al., 2004) found multisensory integration in the premotor cortex provides a mechanism for body self-attribution. Tsakiris et al (Tsakiris et al., 2007) utilised positron emission tomography (PET) and showed that body ownership was related to activity in the right posterior insula and right frontal operculum, and conversely non-attribution to contralateral parietal activity. Another study using transcranial magnetic stimulation suggested that the right temperoparietal junction is involved in maintaining a coherent sense of body ownership (Tsakiris et al., 2008).

In phantom limb phenomena in amputees, while the brain is structurally intact the body integrity has been disturbed. Phantom limb phenomena can provide insights into the mechanisms underlying bodily awareness and ownership. Giummarra suggests involvement of body schema and the body-self neuromatrix, mirror neurons, and cross-callosal and ipsilateral mechanisms in phantom limb phenomena. Within this model, phantom limb pain is proposed to be a maladaptive failure of the neuromatrix to maintain global bodily constructs (Giummarra et al., 2007).

2.3.3. When visual integration is disrupted; optical illusions (see also **Chapter 6**)
"The key notion of cognitive psychology, since the collapse of behaviourism, is that we build *brain-descriptions* of the world of objects, which give perception and intelligent behaviour. Perceptions are not regarded as internal pictures or sounds, but rather as language-like descriptions coded, we suppose, by brain structures of what may be out there." (Gregory, 1998)

Gregory suggests that visual perception utilises predictive hypotheses of the external world and of the self. Simple figures or objects can be ambiguous and spontaneously change orientation (**Fig.2.3A**,) or into other objects (**Fig.2.3B**.). A change in the predictive hypothesis causes a change in perception. Thus optical illusions operate by conflicting predictive hypotheses alternating in predominance, and a failure of normal visual integration. For a more detailed review of the background literature, see **Chapter 6**.

Fig.2.3A. **Fig.2.3B.**

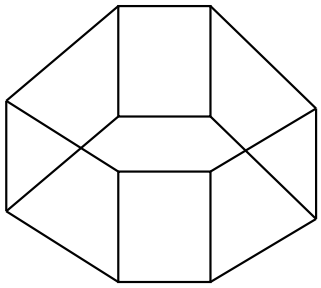

Fig.2.3. Examples of optical illusions that **A.** spontaneously change orientation, and **B.** spontaneously change into other objects (young woman / old lady).
A: H.Cohen 2011; B: Origin anonymous

2.3.4. The parietal cortices (see also **Chapter 7**)

The parietal cortex is central to the construction of a unified body image and determining its relevance to the external world via allocentric and egocentric cues. It receives sensory information and integrates it with past sensory experiences. The parietal lobes are association cortices, involved in higher order processing of sensory information necessary for perception and movement initiation. Anatomically they can be divided into the primary somatosensory area (Brodmanns' areas 1, 2 and 3), superior (Brodmanns' areas 5 and 7) and inferior (Brodmanns' areas 39 and 40) parietal lobules. The superior parietal lobule is involved with the interpretation of general sensory information and for the conscious awareness of the contralateral half of the body. The inferior parietal lobule: interfaces between the somatosensory cortex and the visual and auditory association cortices of the occipital and temporal lobes respectively, and in the dominant hemisphere contributes to language functions.

The parietal cortex has a role in selective attention, behaviour and sensory discrimination through its associative functions (Freund, 2001). It is involved with motor control and parietal lesions can produce unusual motor syndromes (Timsit et al., 1997) and difficulty integrating body schema (see below)(Ghika et al., 1998;Pause et al., 1989). Parietal lesions can also cause apraxia (loss of the ability to execute or carry out learned purposeful movements) (Freund, 2003) and significant problems in numeracy and written / spoken language including alexia (word blindness) and acalculia (difficulty performing simple mathematical tasks) (Tucha et al., 1997). It has been argued that there is sufficient weight of human pain research to establish a role for the parietal lobes in the perception of pain (Duncan and Albanese, 2003).

2.3.5. Parietal and limbic interaction

As a result of its integrative function, the parietal cortices have many cortical projections including limbic (Hok et al., 2005) and hippocampal (Habler et al., 1997;Save and Poucet, 2000b;Save and Poucet, 2000a). The hippocampus, amygdala, limbic lobe, hypothalamus and anterior nucleus of the thalamus comprise the limbic system, one of the phyllogenetically oldest parts of the brain. It is concerned with instinctive and emotional behaviour, memory and endocrine and autonomic system integration. It appears to be important in down regulating the stress response (McEwen, 2001). Hippocampal place cells are sensitive to environmental perceptual cues (Hines and Whishaw, 2005;Rotenberg and Muller, 1997). More recent work shows that the hippocampus is involved with body scheme and orientation within the environment (Whishaw and Maaswinkel, 1998), and has a major role in the integration of motor planning (Hok et al., 2005;McNaughton et al., 1996;Poucet et al., 2004). Hippocampal-parietal cortical interactions are hypothesised to be involved in spatial cognition (Save et al., 2005;Save and Poucet, 2000b;Save and Poucet, 2000a).(Save and Poucet, 2000b) Head directional cells are located in the hippocampus and have also been found in the posterior parietal cortex (Poucet et al., 2001).

2.3.6. Conclusion

The integration of vision, sensorimotor information and body schema is essential for the perception of the ‘self’. Optical illusions generate deliberate visual conflict and can provide insights into how the brain integrates visual information into allocentric and egocentric parameters. The parietal lobes play an important role, and damage can produce abnormalities in body schema. Parietal and limbic interactions are also involved in environmental body schema orientation and emotional and neuroendocrine responses to stress. Sensorimotor conflict is able to produce illusory changes to body schema, which can be associated with feelings of peculiarity, swelling and foreignness in healthy subjects. CRPS patients often describe feelings of ‘foreignness’ of the affected part (see below), suggesting impairment of body ownership and somaesthesia. Therefore dysfunctional parietal networks may be implicated in CRPS. Clinical parietal testing may be abnormal in CRPS patients and is worthy of further investigation.

We have seen that somaesthesia is a complex process involving the integration of allocentric (of the environment) and egocentric (of the person) sensory qualia with behavioural, emotional and autonomic responses. The next section

focuses on the role of the autonomic nervous system and its intimate involvement with pain.

2.4. The autonomic nervous system and pain

2.4.1. Basic neuroanatomy and physiology

The nervous system has two components: the somatic which is under voluntary control and regulates mainly the skeletal muscles, and the autonomic which is for the most part not subject to voluntary control and is the principle regulatory system of internal bodily functions concerned with organ function and homeostasis. It is organised on the basis of the reflex arc, involving an autonomic and/or somatic afferent limb and then autonomic and somatic efferent limbs. Impulses from afferent visceral or pain receptors are relayed to the central nervous system, integrated within it at various levels including cortical, and transmitted via efferent pathways to visceral effectors. The autonomic nervous system is divided into two divisions on the basis of anatomical and functional differences, through which homeostatic function is achieved: the sympathetic which responds to and prepares the body for fear, fight or flight, and the parasympathetic which is concerned with conservation and restoration of energy (**Fig.2.4**). Sympathetic and parasympathetic axes provide neural input into every major body system (Brading, 1999) (**Table 2.1**). Impending or actual pain activates the sympathetic nervous system.

Fig.2.4.

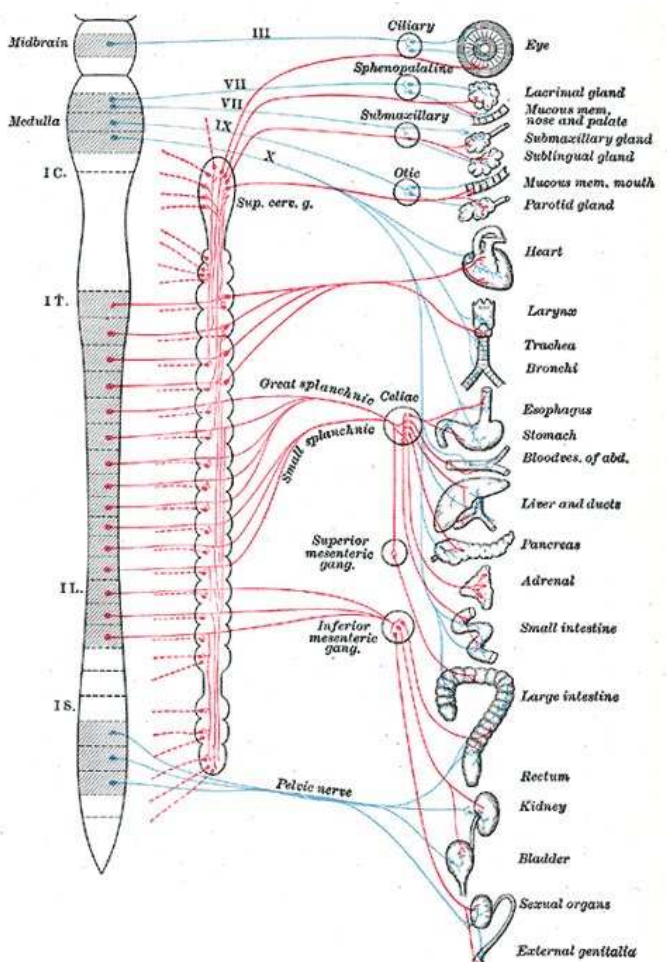

Fig.2.4. Human autonomic nervous system showing sympathetic nerve fibres in red and parasympathetic in blue.

Image available from: http://www.daviddarling.info/encyclopedia/A/autonomic_nervous_system.html. [Accessed 17.1.12.]

Table 2.1. Differential actions of the sympathetic and parasympathetic autonomic nervous system on vascular structures.

Target	**Sympathetic** (adrenergic)	**Parasympathetic** (muscarinic)
vascular smooth muscle	α: contracts; β2: relaxes	M3: relaxes
renal artery	α1: constricts	---
larger coronary arteries	α1 and α2: constricts	---
smaller coronary arteries	β2:dilates	---
arteries to viscera	α: constricts	---
arteries to skin	α: constricts	---
arteries to brain	α1: constricts	---
arteries to erectile tissue	α1: constricts	M3: dilates
arteries to salivary glands	α: constricts	M3: dilates
hepatic artery	β2: dilates	---
arteries to skeletal muscle	β2: dilates	---
Veins	α1 and α2: constricts β2: dilates	---

2.4.2. Autonomic nervous system integration

The autonomic nervous system is continually active and responds to a wide range of internal and external environmental stimuli. It is therefore constantly responding to sensory stimuli, both physical and emotional, and is involved in the integration of a coordinated response to those stimuli through a variety of effector organs. For example, response to a painful stimulus may include somatic reflex motor actions (eg. withdrawal), and a variety of autonomic responses coordinated via the sympathetic nervous system such as emotional responses (eg. surprise, fear, anger), hormonal (eg. activation of adrenal glands and release of endogenous cortisol and catecholamines) and unconscious autonomic responses (eg. elevation of heart rate and blood pressure).

The integration of peripheral autonomic activity with central autonomic responses is a complicated and poorly understood. There appear to be many function-specific peripheral autonomic pathways with characteristic signal transmission which the central nervous system is able to distinguish and to differentially activate. This allows for precise autonomic system function throughout the behavioural repertoire (Jänig, 2006).

Pain unpleasantness is often but not always closely linked to pain intensity, and reflects the contribution of several sources including nociception, arousal, autonomic and somatomotor responses in relation to the meaning and context of the pain (Wells and Ridner, 2008). Nociceptive and autonomic systems interact at peripheral, spinal, brainstem and cortical levels. In a review by Bennarroch (2001), it relates how pain and viscerosensory pathways provide converging information in the dorsal horn of the spinal cord, brainstem and cerebral cortex, which in turn project to many other cortical areas involved in reflex, homeostatic and behavioural control of autonomic outflow, endocrine function and nociception. In order to understand the complex pathophysiology of chronic pain, these interactions need to be taken into account (Benarroch, 2001). A more detailed account follows.

Afferent interoceptive (ie. arising from the body) information is proposed to have a central role in the expression of emotional feeling states (Price, 2000). A-δ and C primary afferent fibres innervate all body tissues and convey physiological information including the mechanical, thermal, chemical, metabolic and hormonal status of skin, muscle, joints, teeth and viscera. They terminate in lamina one of the spinal and trigeminal dorsal horns. Lamina 1 neurons project to autonomic columns forming spino-spinal loops, and to pre-autonomic sites in the brainstem forming spino-bulbo-spinal loops for somato-autonomic reflexes. A major target of lamina 1 projections is the parabrachial nucleus (PB) in the upper brain stem which is a main

integration site for autonomic activity. In turn the PB projects densely to the periaqueductal grey (PAG) and hypothalamus guiding goal-directed autonomic, neuroendocrine and behavioural activity including nociception. Integrated homeostatic afferent information from PB reaches the anterior cingulate (ACC) and insular cortices by way of the medial thalamic nuclei and the basal ventral medial nucleus (VMb) of the thalamus. The ACC and the insula (limbic sensory cortex) provide descending control of brainstem homeostatic integration sites (Craig, 2003). These include the rostral ventrolateral medulla (RVLM), a primary regulator of sympathetic nervous system activity and the ventromedial medulla (VMM), both areas involved in the descending control of nociception (Heinricher et al., 2009). See **Fig.2.5**. Further activity in the limbic system is involved in emotional, behavioural and neuroendocrine responses.

The ascending homeostatic sensory afferent pathway terminates in the posterior insula, and is re-represented and integrated in the mid-insula, and then the anterior insula (Craig, 2003). Activation in the anterior insula correlates with subjective body and emotional feelings, which would allow it to provide a model for human awareness and subjectivity (Craig, 2011). Recent work demonstrates somatotopic organisation of the human insula to painful stimuli (Brooks et al., 2005). Convergent functional imaging findings show concurrent activation of the anterior insula and anterior cingulate cortices during human emotion (Craig, 2010).

Fig.2.5.

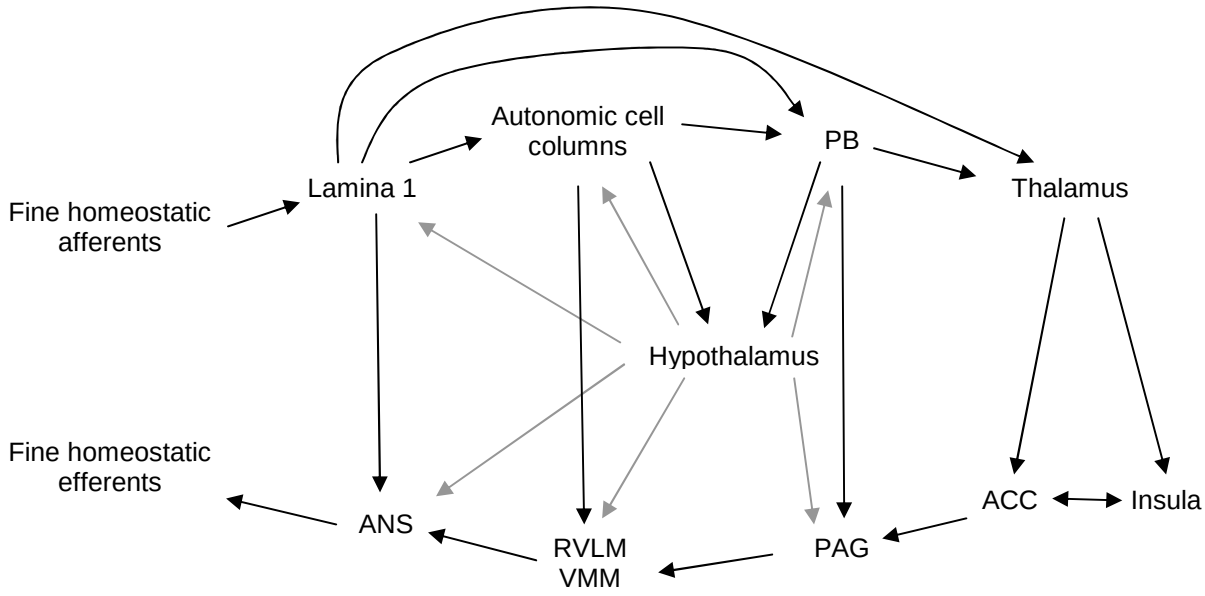

Fig.2.5. A simplified diagram of the homeostatic afferent system (based upon Craig 2003).

PB = parabrachial nucleus, ACC = anterior cingulate cortex, PAG = periaqueductal grey, RVLM = rostral ventrolateral medulla, VMM = ventromedial medulla, ANS = autonomic nervous system
Grey lines = hypothalamic modulation

2.4.3. Conclusion

Interaction between the insula and anterior cingulate cortices provide an integrational network for homeostatic autonomic and somaesthetic afferent information providing a platform for efferent emotional, affective and autonomic responses. The insula has a somatotopic organisation which hypothetically could be subject to neuroplastic reorganisational changes in chronically painful conditions akin to that demonstrated in S1.

Thus in the investigation of responses to different sensory stimuli in subjects with chronic pain, there is clear interaction between cognitive, emotional and autonomic responses. Therefore the investigation of involuntary autonomic sympathetic responses during such stimuli can provide insights into these complex mechanisms.

2.5. Rheumatic disease: Osteoarthritis

2.5.1. Overview of symptoms

OA typically presents as a painful, stiff joint. There may be swelling, deformity, weakness, instability and complaints of clicking and grinding. Signs include altered gait, tenderness, crepitus and limitation of range of movement.

2.5.2. Diagnostic criteria

There are diagnostic criteria for OA (see **Chapter 3** and **Appendix 4**), which are generally reserved for research use.

2.5.3. Mechanisms

OA is a degenerative disorder resulting from the breakdown of articular hyaline cartilage. The modern view of OA is of a disease entity involving the whole joint organ including subchondral bone and synovium. Similarly, it is no longer thought of as simply 'wear and tear', and involves many pathogenic mechanisms including inflammatory (Goldring and Otero, 2011), oxidative stress (Yudoh et al., 2005), mechanical (Henriksen et al., 2011;Horak et al., 2011), impaired proprioception (Knoop et al., 2011) and genetic factors (Meulenbelt et al., 2011).

2.5.4. Treatment

Treatment is aimed at reducing pain and minimising disability. Pharmacologic therapies include analgesics such as non-steroidal anti-inflammatory drugs (NSAID's), non-opiates and opiates. Intra-articular agents include corticosteroids and hyaluronoc acid derivatives. Non-pharmacologic approaches include patient education on exercise and weight reduction. Physiotherapy to improve proprioceptive acuity may be useful (Fitzgerald et al., 2011;Tunay et al., 2010). Joint replacement surgery may eventually become necessary.

2.5.5. Pain in OA

Pain is the most common symptom in OA. However it is often diffuse and poorly localised. It is well recognised that severity of X-ray appearances may not correlate with clinical symptoms and signs (Hochberg et al., 2003).

There are many potential sources for the pain in OA. The articular cartilage is not one of them, as it lacks nerve endings. However cartilage debris may induce inflammatory responses. Damaged cartilage may cause mechanical stress, and exposed subchondral bone pain. The synovium contains nerve fibres that may be stretched by fluid, impinged by osteophytes or activated by inflammatory mediators. Muscle spasm may also cause pain. There is also increasing evidence for central

mechanisms in OA pain (for more details, see **Chapter 5**). OA patients have been found to have hypoaesthesia with mechnical allodynia over the knees (Hendiani et al., 2003) and higher pressure pain thresholds compared to controls (Gerecz-Simon et al., 1989).

2.6. Rheumatic disease: Rheumatoid arthritis

2.6.1. Overview of symptoms

The peak onset of RA is in the 4th and 5th decades of life. It typically presents as a diffuse painful symmetric inflammatory polyarthritis often affecting the small joints. Morning stiffness can be marked and of variable duration. There can be associated fatigue and malaise. Symptoms may be impacting upon ability to perform activities of daily living.

In established disease, there is progressive erosion and damage to joints resulting in typical rheumatoid deformities. These may include swan-neck and Boutonniere deformities in the fingers with metacarpophalangeal subluxation and ulnar deviation of the fingers, 'wind-swept' deformity, rheumatoid foot changes with halux valgus, over-riding toes, metatarsal subluxation and callous formation, and hindfoot deformity. Depending upon disease activity, there may be active, warm, tender synovitis and joint effusions. As joints become damaged, the range of motion decreases. RA is a systemic disease and may have extra-articular manifestations.

2.6.2. Diagnostic criteria

There are diagnostic criteria for RA (see **Chapter 3** and **Appendix 4**), which are generally reserved for research use.

2.6.3. Mechanisms

RA is an autoimmune generated systemic inflammatory disease. The cause of RA is still unknown. Cellular immune mechanisms remain unclear (Firestein, 2005), and both T cells and B cells are involved although the relative contribution may vary between patients (Panayi, 2005;Scrivo et al., 2007). The intimal lining of the synovium develops an expanded cell population with massive infiltration by T cells, B cells and macrophages. Inflammatory mediators such as pro-inflammatory cytokines, prostaglandins and leukotrienes are key to the perpetuation of rheumatoid synovitis.

2.6.4. Pain in RA

One of the main sources of pain in RA is inflammation. Therefore the thrust of modern treatment is aimed at inhibiting the inflammatory response thereby reducing pain and progressive joint damage. Secondary OA may contribute to pain.

There is also evidence for central mechanisms of pain in RA (Lee et al., 2011). They have been found to have lower pressure pain thresholds than controls (Gerecz-Simon et al., 1989), hyperalgesia (Gaston-Johansson and Gustafsson, 1990), hypoaesthesia and allodynia over knee joints (Hendiani et al., 2003) and allodynia over inflamed joints with pressure allodynia in non-painful areas in longer duration RA (Leffler et al., 2002). A recent fMRI study has shown the presence of increased grey matter content in the basal ganglia of RA patients. The basal ganglia have a role in motor control and pain processing, and the study links the findings to prolonged changes in motor control and pain processing in RA patients (Wartolowska et al., 2011). Furthermore many RA patients may have concurrent widespread pain and/or fibromyalgia syndrome (FMS) (Ranzolin et al., 2009), which has a well established central pain component (Smith et al., 2011).

2.6.5. Treatment

The main treatment for RA is early intervention with immune suppressing medication to inhibit inflammatory activity and prevent disease progression. Disease modifying anti-rheumatic drugs (DMARD) therapy reduces the frequency and severity of flares, but it does not stop them all, and they are not a cure. Therefore RA patients need ongoing access to analgesic medications. NSAID's, non-opiates and opiates are often used. Non-pharmacologic treatments such as physiotherapy and occupational therapy are essential for the integrated care of RA. Many RA patients may need surgical intervention. Procedures vary from arthroscopic synovectomies to open procedures, tendon repair, arthrodesis and joint replacement surgery.

2.6.6. Conclusion

Pain in OA is largely thought to be mechanical, and in RA inflammatory. However there is emerging evidence for the role of central pain mechanisms in both conditions which warrants further investigation.

2.7. Complex Regional Pain Syndrome (CRPS)

2.7.1. Nomenclature

First clearly described by Silas Weir Mitchell et al in injured soldiers of the American Civil War (Mitchell et al., 1864), CRPS has been known by a variety of different names. Mitchell called it causalgia. Sudeck described a similar syndrome with accompanying osteoporosis, with this later becoming the eponymous syndrome (Sudeck, 1900). In 1946, Evans described it as 'reflex sympathetic dystrophy' (Evans, 1946). The International Association for the Study of Pain (IASP) held a series of consensus workshops culminating in the development of diagnostic criteria published in 1995, and the new umbrella term 'Complex Regional Pain Syndrome' (Stanton-Hicks M et al., 1995).

CRPS may develop in the presence (type 2) or absence (type 1) of a clear nerve injury (Stanton-Hicks M et al., 1995). Clinical presentation is similar, except where in the presence of a defined nerve lesion there may be a typical distribution of sensory and motor impairment. Symptoms and signs in CRPS type 1and 2 are usually non-dermatomal and do not follow patterns consistent with a specific peripheral nerve injury.

2.7.2. Epidemiology

2.7.2.1. Incidence and prevalence

There are only two major epidemiological studies; Sandroni et al (Sandroni et al., 2003) and de Mos et al (de Mos et al., 2007). The former was a population based study in Olmsted County, Minnesota with a population in 1990 of 106,470. The latter was a retrospective cohort study was conducted during 1996-2005 using a general practice research database with electronic patient record data from 600,000 patients throughout the Netherlands. The incidence of CRPS type 1 varies from 5.46 per 100,000 person-years at risk with a prevalence of 20.57 per 100,000 (Sandroni et al., 2003), to 26.2 per 100,000 person-years (de Mos et al., 2007). CRPS may occur in approximately 4% of peripheral nerve injuries (Veldman et al., 1993).

2.7.2.2. Age and gender

There is a middle aged peak in onset of CRPS with a median age of onset 46 years (Sandroni et al., 2003). Other studies suggest a mean of 42 (Allen et al., 1999;Veldman et al., 1993) to 53 years (de Mos et al., 2007). Older people can be affected. The highest incidence in the de Mos study was among the 61- to 70-year-old group. The age range affected was up to 85 years old in the Veldman (Veldman

et al., 1993) paper. CRPS is rarer in children. In the Veldman study, only 12 patients were younger than 14 years. Children with diabetes have a higher incidence of CRPS as compared to non-diabetic children although the reasons are unclear (Schiller, 1989).

2.7.2.3. Precipitating events

CRPS can may occur after trauma (Allen et al., 1999;de Mos et al., 2007) such as fracture (Atkins et al., 1990;Lee and Nandi, 2011;Veldman et al., 1993) or operative interventions (Atkins et al., 1990;Lai et al., 2006;Li et al., 2010). Both the Sandroni (Sandroni et al., 2003) and Veldman (Veldman et al., 1993) studies confirmed that fractures and sprains were the most common precipitating events and that CRPS more commonly affects the upper extremities. CRPS may occur after 30-40% of fractures (Atkins, 2003). CRPS may happen after spinal cord injury (Akkoc et al., 2008;Sutbeyaz et al., 2005), stroke (Chae, 2010;Pertoldi and Di Benedetto, 2005), myocardial infarction (Ahmed, 2003), amputation (Odderson and Czerniecki, 1990) and in association with multiple sclerosis (Schwartzman et al., 2008). It may also be associated with immobilisation (Allen et al., 1999;Schwartzman and Kerrigan, 1990) or excessively tight casts (Field et al., 1994).

2.7.2.4. Psychological factors

The role of psychological factors in CRPS remains controversial. A minority opinion holds that CRPS is “a common clinical avenue for somatoform expression” (Ochoa and Verdugo, 1995). Although the literature is conflicting, overall studies do not support the concept of a ‘CRPS personality’ or a predisposing psychological profile (Ciccone et al., 1997;de Mos et al., 2008;Lesky, 2010;Puchalski and Zyluk, 2005;Reedijk et al., 2008;van der Laan et al., 1999).

Psychological issues may develop in patients with chronic severe pain, including CRPS patients. As a consequence of chronic pain, CRPS patients have been shown to have higher levels of depression (Rommel et al., 2005), anxiety (Rommel et al., 2001a) and personality disorder (Monti et al., 1998). Psychological risk factors for the development of CRPS may include anxiety (Dilek et al., 2011) and antecedent psychological stress (Bruehl and Carlson, 1992;Field and Gardner, 1997;Geertzen et al., 1998;Harden et al., 2003). These factors may exacerbate pain through a variety of different mechanisms (Bruehl and Chung, 2006). These include influence on psychoneuroendocrine stress responses (Kaufmann et al., 2007), systemic catecholamines (Harden et al., 2004) and pain seeking behaviour (Rodham et al., 2009).

2.7.2.5. Impact on quality of life

CRPS has a severe impact upon quality of life. In a self-reported questionnaire survey of 31 patients, substantial interference was reported in 9 of the 10 modified Brief Pain Inventory activity items by the majority of patients. Significant sleep disturbance was found in 80%, and 97% described weakness at some time during the course of their CRPS (Galer et al., 2000).

2.7.3. Overview of symptoms

(Allen et al., 1999;Atkins, 2003;de Mos et al., 2009a;de Rooij et al., 2010;Moses MA et al., 1990;Schwartzman et al., 2009;Veldman et al., 1993) (Goebel, 2011)

CRPS is characterised by severe, constant pain often seemingly out of proportion to any precipitating injury and can occur in the absence of injury. There is often marked hyperalgesia and allodynia. Autonomic vasomotor and sudomotor instability is common causing variable, often florid colour changes together with temperature changes, sweating abnormalities and oedema in the affected area. The affected area may be warmer or colder, with increased sweating or no vasomotor activity and dry skin. Trophic changes of hair, skin and nails may develop. Nails may grow faster or more slowly and become brittle and discoloured. Hair can become thicker and dark, or fall out. Motor impairment may develop including tremor, myoclonus, dystonia, bradykinesia and decreased range of motion/paresis. Other features may include feelings of foreignness towards the affected limb (Forderreuther et al., 2004), neglect-like features (Galer and Jensen, 1999a), amputation desire and body dysmorphia (Lewis et al., 2007).

2.7.3.1. Assessment of symptoms

The ability of physicians to accurately assess the presence of clinical symptoms in patients with CRPS has been assessed by comparing judgments against assessments using quantitative measurements with regard to presence and severity of pain, temperature and volume asymmetry, and reduction in active range of motion(Perez et al., 2005). Measurements included Visual Analog Scales and McGill (number of words chosen total) for pain, infrared thermography for temperature differences, water displacement volumeters for volume differences, and hand-held goniometers for active range of motion. The study concluded that except for temperature and volume asymmetries, establishing the presence of CRPS Type 1

symptoms and monitoring of disease progression could be performed by clinical judgment.

However, the pattern of symptoms and clinical signs are variable between and within patients which can make diagnosis difficult. This has led to the development of different diagnostic criteria. These criteria continue to develop and to be revised. The commonly used criteria are now presented.

2.7.4. Diagnostic criteria

2.7.4.1. Veldman's criteria (Veldman et al. 1993)

The 1993 Veldman criteria (Veldman et al., 1993) are based upon the presence of 4 out of 5 symptoms and signs at the first examination.

1. 4or 5 of:	Unexplained diffuse pain
	Difference in skin colour relative to the other limb
	Diffuse oedema
	Difference in skin temperature relative to the other limb
	Limited active range of motion
2. Occurrence or increase of above signs and symptoms after use	
3. Above signs and symptoms present in an area larger than the area of primary injury or operation and including the area distal to the primary injury	

These criteria do not allow for the fluctuation of symptoms and signs in CRPS, and could therefore miss many cases. The IASP 1994 criteria do allow for this (Stanton-Hicks M et al., 1995).

2.7.4.2. IASP 1994 criteria (Merskey and Bogduk, 1994)

CRPS type 1	**1.** The presence of an initiating noxious event, or a cause of immobilization. **2.** Continuing pain, allodynia or hyperalgesia, not limited to the territory of a single peripheral nerve, with which the pain is disproportionate to the inciting event. **3.** Evidence at some time for oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain. **4.** This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.
CRPS type 2	**1.** Develops after a nerve injury. **2.** Continuing pain, allodynia or hyperalgesia, not necessarily limited to the territory of the injured nerve. **3.** Evidence at some time for oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain. **4.** This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Bruehl et al (Bruehl et al., 1999) worked upon the validation of these criteria, and calculated a high sensitivity (0.98) but low specificity (0.36). Therefore to minimise false positive rates and the potential of over-diagnosis and inappropriate treatment, the criteria were revised.

2.7.4.3. IASP revised 'Bruehl' (Budapest) criteria (Bruehl et al., 1999;Harden et al., 2007;Harden and Bruehl, 2005)

General definition: CRPS describes an array of painful conditions characterised by a continuing (spontaneous and/or evoked) regional pain seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor and/or trophic findings. The syndrome shows variable progression over time.

Clinical Criteria:

1. Continuing pain which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories

Sensory: reports of hyperesthesia and/or allodynia

Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry

Sudomotor/oedema: reports of oedema and/or sweating changes and/or sweating asymmetry

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 (only counted if observed at the time of diagnosis) at the time of evaluation in two or more of the following categories:

Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)

Vasomotor: evidence of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry

Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry

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

Research Criteria:

1. Continuing pain which is disproportionate to any inciting event

2. Must report at least one symptom in each of the four categories

3. Must display at least one sign (only counted if observed at the time of diagnosis) at the time of evaluation in two or more of the categories:

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

The ‘Budapest’ criteria have been recently validated (Harden et al., 2010), and the clinical criteria shown to retain a high sensitivity (0.99) but an improved specificity (0.68). The 'Budapest' research criteria were used throughout this study.

2.7.4.4. Conclusion

There is considerable variability of symptoms and signs within and between patients with CRPS. This is reflected in the ongoing debate as to what should and should not be included in diagnostic criteria. The variability is likely to reflect different phenotypes, which in turn depend upon different aetiopathogenic mechanisms.

2.7.5. CRPS Diagnosis

There is no gold standard diagnostic test for CRPS. It remains a diagnosis of exclusion which may be supplemented by the use of diagnostic criteria. Therefore while different investigations may show changes consistent with CRPS (Schurmann et al., 2007), they are used to primarily exclude the presence of other conditions that might account for the symptoms and signs.

2.7.5.1. Investigations

Plain X-ray (**Fig.2.5**) may show marked osteopaenic changes in some patients (Rho et al., 2002).

Fig.2.6.

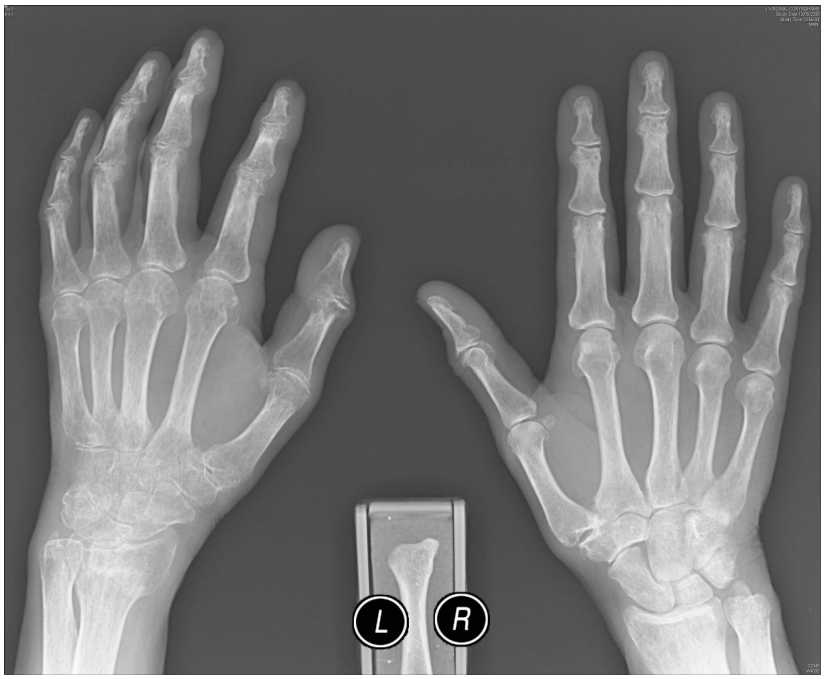

Fig.2.5. Example of osteopaenia in the affected limb of a patient with left arm CRPS.

Three phase isotope bone scanning can be helpful in the exclusion of other diagnoses (Nitzsche, 2011) and may show a typical pattern of uptake throughout the three phases (blood pool, blood phase, scan phase). MRI scanning may also detect changes in CRPS affected limbs and is useful to exclude or to diagnose other conditions (Poll et al., 2010). Other tests used include electromyography, sweat testing and diagnostic sympathetic blocks (Rho et al., 2002).

Thermography may show a significant temperature difference in the affected area (Rho et al., 2002)(**Fig.2.6**). No widely accepted temperature threshold has been defined for the normal range of systematic temperature differences between affected and unaffected limbs (Schurmann et al., 2007). While there may be moderate bilateral temperature differences under thermoneutral conditions, differences can increase dramatically under heat or cold stress in CRPS I patients (Niehof et al., 2006;Wasner et al., 2001) demonstrating that the vascular abnormalities leading to bilateral temperature differences are dynamic. Although reliability and repeatability can be low, thermography can distinguish between healthy controls and CRPS patients (Niehof et al., 2007).

Fig.2.6.

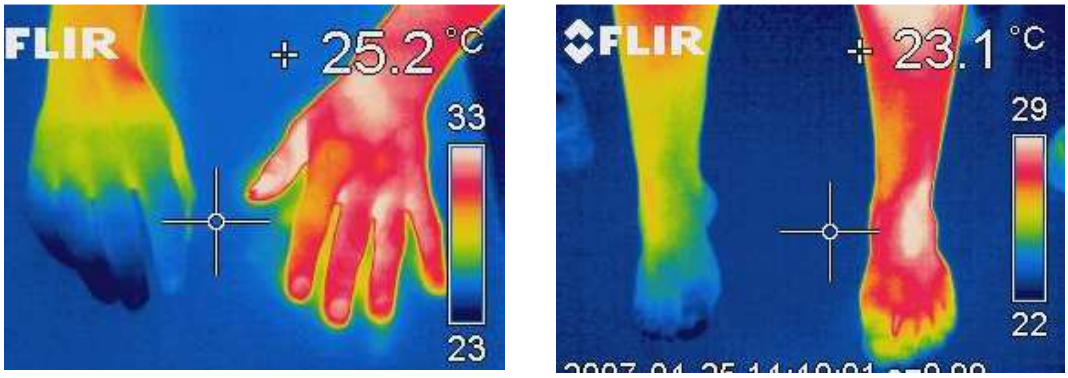

Fig.2.7. Examples of thermographic images of CRPS affected right hand and right lower limb. Black and blue represent the lowest temperatures ranging through green, yellow, orange and red to the warmest in white.

2.7.5.2. Conclusion

There is no diagnostic test for CRPS due to the variability of the condition, and it remains a diagnosis of exclusion. This fact again suggests that there are a wide variety of pathogenic mechanisms operating in different patients and at different stages of the condition.

2.7.6. Mechanisms

Several pathophysiological concepts have been proposed to explain the complex symptoms of CRPS. Three major areas include facilitated neurogenic inflammation, autonomic dysfunction and neuroplastic changes within the central nervous system (CNS) (Maihofner et al., 2010b). The review will now focus on these areas, and other significant postulated mechanisms.

2.7.6.1. Facilitated neurogenic inflammation

Calor, dolor, rubor, tumor and functio laesa: Heat, pain, redness, swelling and loss of function. These four classical signs of inflammation were originally recorded by Celsus in the 1st century A.D, with Galen adding the term 'functio laesa'. Sudeck first proposed a role for inflammation as a major mechanism in CRPS (Sudeck, 1902;Sudeck, 1931). Inflammation is known to be a complex process of interacting mechanisms proceeding via a cascade of inflammatory mediators. Inflammation can play a pivotal role in health and disease, and there is extensive ongoing research aiming to improve understanding of the process.

The skin is innervated by afferent somatic nerves containing fine myelinated A-δ, unmyelinated C-fibres and postganglionic autonomic fibres. During a noxious stimulus such as an injury, primary A-δ and C-fibre nociceptors transmit impulses to the dorsal horn of the spinal cord. Both fibre types respond to a range of stimuli including heat, cold, mechanical distension and nociception. Upon stimulation, they release an array of neuropeptides into the microenvironment triggering an inflammatory cascade. These include calcitonin gene-related peptide (CGRP), neuropeptide Y NY), atrial natriuretic peptide, vasoactive intestinal peptide (VIP) and tachykinins substance P (SP) and neurokinin A (NK-A) (Steinhoff et al., 2003). In addition to classic neurotransmitters, autonomic fibres can release CGRP, NY and VIP (Roosterman et al., 2006). These inflammatory mediators act on mast cells and other target cells via paracrine, juxtacrine and endocrine pathways continuing the inflammatory process. Mast cells have a role in mediation of antidromic nerve responses through degranulation and the products thereby released. CGRP causes arteriolar dilatation and hyperaemia, and SP acts upon post capillary venules to induce increased vascular permeability, extravasation and oedema, as well as acting upon mast cells causing degranulation. Additionally, sensory nerve endings are sensitised by VIP. Nerves in inflamed areas upregulate expression of NGF (Donnerer et al., 1993) which can cause mast cell degranulation and sensitise nerve endings by increasing expression of CGRP and SP (Donnerer et al., 1992).

Afferent nerve fibres express receptors for neuropeptides as well as prostaglandins, histamine, neurotrophins and cytokines allowing interaction in the process. Most cells expressing neuropeptides also release neuropeptide denaturing enzymes such as such as neutral endopeptidase (NEP) or angiotensin converting enzyme (ACE) so that the process can be stopped.

What evidence is there for a role of facilitated neurogenic inflammation in CRPS?

Electrically induced neurogenic vasodilatation via intradermal microdialysis capillaries allowing simultaneous measurement of protein extravasation as a means to assess neuropeptide release, has been studied in CRPS patients and healthy controls. Transcutaneous electrical stimulation provoked protein extravasation only in the patients with a time course similar to that observed following application of exogenous substance P (Weber et al., 2001). Similar work has demonstrated enhanced release of SP in both the affected and unaffected limbs of CRPS patients (Leis et al., 2003). There is evidence for enhanced CGRP release (Leis et al., 2004)l, and elevated levels in the serum of CRPS patients with reduction after therapy (Birklein et al., 2001). Blister fluid studies have shown elevation of inflammatory mediators such as endothelin-1 (Groeneweg et al., 2006), IL-6 and tumour necrosis factor (TNF)-α (Groeneweg et al., 2006;Huygen et al., 2002) and reduction of anti-inflammatory cytokines IL-4 and IL-10 (Uceyler et al., 2007). However the levels of IL-6 and TNF-α are not correlated with CRPS characteristics suggesting other factors are involved (Wesseldijk et al., 2008). Synovial biopsies have demonstrated hypervascularity (Renier et al., 1983) and radiolabelled immunoglobulins shown enhanced uptake demonstrating increased vascular permeability, especially in early (< 5 months) disease (Oyen et al., 1993).

Elevated blood levels of inflammatory monocytes (CD14(+) CD16(+)) have been found in patients with complex regional pain syndrome. The percentage of proinflammatory CD14(+) CD16(+) monocyte/macrophage subgroup was elevated compared to controls, and individuals with a high percentage of CD14(+) and CD16(+) demonstrated lower plasma levels of the anti-inflammatory cytokine IL-10 (Ritz et al., 2011). Further evidence is provided by reports of the successful use of anti-TNF-α biologic medications (Huygen et al., 2004). These are monoclonal derived pharmacologic agents that work by blocking the pro-inflammatory cytokine TNF- α and thereby reducing systemic inflammation.

2.7.6.2. Conclusion

Facilitated neurogenic inflammation may be a mechanism involved in the pathogenesis of CRPS, especially in early disease. However levels of inflammatory mediators do not correlate with the disease characteristics and other mechanisms are involved.

2.7.6.3. Sympathetic autonomic dysfunction

The vasomotor and sudomotor changes observed in CRPS have been associated with presumed sympathetic autonomic dysfunction since the pioneering work of Leriche at the beginning of the 20th century (Leriche, 1916).

2.7.6.3A. Sympathetically maintained pain (SMP)

Previously the concept of sympathetically maintained pain (SMP) was synonymous with CRPS, but has undergone considerable debate in recent years (de Mos et al., 2009b). Patients with autonomic signs and symptoms can be divided into two groups by the positive or negative effect of selective blockade of the sympathetic nervous system or blockade of α-adrenoceptors (Arner, 1991;Maier and Gleim, 1998;Raja et al., 1991) into those with SMP and those with sympathetically independent pain (SIP). However the evidence for clinical effectiveness of sympathetic blockade and surgical sympathectomy is poor (Straube et al., 2010). Furthermore, neuralgia can occur after sympathectomy (Kramis et al., 1996;Mailis and Furlan, 2003;Straube et al., 2010). SMP is now defined as a symptom in a subset of patients with neuropathic disorders and not a clinical entity (Wilsey et al., 2001), and is not essential for the diagnosis of CRPS (Jänig and Baron, 2003). When considering the SMP component, allowance should be made that it is likely to vary over the time course of the CRPS (Michaelis et al., 1996;Schattschneider et al., 2006).

2.7.6.3B. Pain and sympathetic nerve activity

Can pain enhance sympathetic activity?

Electrophysiological studies in the cat have demonstrated nociceptor driven segmental sympathetic reflexes (Janig, 1985). Conversely, painful stimuli in one leg of human subjects did not show any difference in recording of sympathetic nerve activity from the skin compared to the other non-painful limb. Similarly, bilateral recordings from patients with CRPS did not show a difference between the affected and unaffected limbs (Elam, 2001). In another CRPS patient with marked skin vasoconstriction, intraneural recording from skin fascicles showed normal

sympathetic nerve activity (Casale and Elam, 1992). The techniques used in these studies do not provide information about the numbers of active fibres in the recorded nerve fascicle at rest, so do not allow for a proportional activity difference (Elam, 2001). Further studies show that sympathetic nerve discharge does not affect afferent polymodal c-fibre firing (Campero et al., 2010;Elam et al., 1999) and reduced rather than increased myelinated cutaneous afferent firing (Elam and Macefield, 2004). Other research shows plasma concentrations of noradrenalin are similar in affected and unaffected limbs (Drummond et al., 1991), or even reduced (Harden et al., 1994). A Positron Emission Tomography study of sympathetic neurocirculatory function in CRPS showed decreased perfusion of the affected limb, symmetrical sympathetic innervation and norepinephrine synthesis and variably decreased release and turnover of norepinephrine in the affected limb (Goldstein et al., 2000). Thus there is little evidence for increased sympathetic nerve activity to pain suggesting other mechanisms are operational.

Can a physiological increase in sympathetic activity enhance pain?
Injection of noradrenalin around the stump neuroma of an amputated limb can cause intense pain (Chabal et al., 1992). When injected into a neuralgic symptomatic skin area, it may rekindle spontaneous pain and dynamic mechanical hyperalgesia or allodynia that had been relieved by sympathetic blockade (Torebjork et al., 1995) and induce activation of nociceptive fibres (Jorum et al., 2007). Baron et al (Baron et al., 2002) used whole body cooling in CRPS patients identified by prior blocks as having SMP or SIP, to maximise sympathetic vasoconstrictor activity to the affected limb. They found that pain and the area of dynamic mechanical hyperalgesia or allodynia increased in those with SMP but not in subjects with SIP. Therefore there may be an increased sensitivity to adrenergic substances in some CRPS patients.

2.7.6.3C. Proposed mechanisms of SMP (Gibbs et al., 2008)

1. Direct coupling between the sympathetic neurons and sensory neurons in the dorsal root ganglion.

Evidence provided for:

- Sympathetic nerve sprouting in the dorsal root ganglion (DRG) (McLachlan et al., 1993) with electrically enhanced activity (Devor et al., 1994).
- Aberrantly innervated DRG cell bodies may develop increased spontaneous firing activity (Devor et al., 1992).

- The proportion of DRG neurons responsive to noradrenaline increases after chronic nerve injury (Petersen et al., 1996) and the proportion expressing α2A-adrenoceptor immunoreactivity birder increases after complete or partial peripheral nerve transaction (Birder and Perl, 1999).

2. Chemically mediated coupling between the sympathetic and sensory neurons in the skin.

Evidence provided for:

- Aberrant migration and sprouting of non-perivascular sympathetic fibres in rat skin following chronic nerve injury (Grelik et al., 2005;Yen et al., 2006).
- Newly sprouted aberrant sympathetic fibres may wrap around sensory fibres forming novel associations (Yen et al., 2006).

3. α-adrenoceptor mediated supersensitivity of nociceptive fibres.

Evidence provided for:

- No increase in sympathetic outflow (Casale and Elam, 1992), venous noradrenaline concentrations (Drummond et al., 1991) or reflex vasoconstrictor response in the affected limb (Rosen et al., 1988).
- Sensitisation of nociceptors by inflammatory mediators (Schim and Stang, 2004).
- Greater constriction of superficial dorsal hand veins to increasing doses of noradrenaline, particularly in the affected limb in CRPS patients compared to controls (Arnold et al., 1993).
- Greater axon reflex sweating to iontophoresis of phenylephrine in CRPS patients compared to controls or resolved CRPS (Chemali et al., 2001).
- A close physical relationship between sympathetic and nociceptive fibres in normal skin (Gibbs et al., 2008).

There remains a vocal group that refute the role of the sympathetic nervous system in CRPS (Ochoa and Verdugo, 2001;Ochoa, 2007;Ochoa and Verdugo, 1995;Ochoa, 1999).

2.7.6.4. Conclusion

The evidence for the mechanism of sympathetic autonomic dysfunction contributing to or causing pain in CRPS remains contradictory, and may vary over time but it is likely to play a role in some patients.

2.7.6.5. Neuroplastic changes within the CNS

2.7.6.5A. CRPS as a disease of the CNS

Certain clinical features of CRPS are consistent with it being a disease of the CNS. Many patients demonstrate motor impairment including weakness (Birklein et al., 2000;Veldman et al., 1993), impaired dexterity (Maihöfner et al., 2007), impaired finger identification (Förderreuther et al., 2004), tremor (Deuschl et al., 1991;van Hilten, 2010) and dystonia (Cooper, 2011;Schwartzman and Kerrigan, 1990;van Hilten, 2010).

Body perception disturbances may be evident. Some CRPS patients report feelings of foreignness towards the affected limb (Förderreuther et al., 2004), body dysmorphia (Lewis et al., 2007) and neglect-like features (Frettlöh et al., 2006;Galer and Jensen, 1999b). Moseley et al have shown that in CRPS there is a deficit in tactile processing that is defined by the space in which the affected limb normally resides, not by the affected limb itself and suggest that CRPS may involve a type of spatial neglect (Moseley et al., 2009). There is also evidence for impaired upper limb proprioception in a pointing accuracy task (Lewis et al., 2010). For more details on body perception, integration and neglect, see **Chapter 7**.

Agnosia for object orientation (Robinson et al., 2011), hemisensory patterns of tactile impairment (Rommel et al., 1999;Rommel et al., 2001b) and decreased tactile acuity of the affected limb (Maihofner and DeCol, 2007) have been reported. For more details on sensory abnormalities in CRPS, see **Chapter 4**.

2.7.6.5B. Evidence from neuroimaging

One of the first studies to demonstrate evidence of representational change in CRPS utilised whole-head magnetoencephalography (MEG) responses to tactile stimulation of the fingertips. It showed stronger S1 responses from the affected painful limb, shorter distances between the thumb and little finger in the hemisphere contralateral to the painful limb and altered reactivity of the 20-Hz motor cortex rhythm to tactile stimuli (Juottonen et al., 2002). Maihofner's group used magnetic source imaging to investigate the cortical representation of the hand in the primary somatosensory cortex (S1) of patients with CRPS (Maihöfner et al., 2003a). They found significant shrinkage of the cortical hand representation for the CRPS affected side, with the

centre of the hand shifted toward the cortical representation of the lip. Furthermore the cortical reorganization correlated with the amount of CRPS pain and the extent of mechanical hyperalgesia. Similar shifts in hand representation have been shown in another study using a whole-scalp neuromagnetometer (Vartiainen et al., 2008). Other studies have confirmed that expansion of hand representation correlates with mean pain intensity (Pleger et al., 2004b), tactile impairment (Pleger et al., 2006) and that plastic cortical changes are reversible with treatment and improvement of the CRPS (Maihöfner et al., 2004;Pleger et al., 2005;Pleger et al., 2006).

Cortical processing of stimuli on the affected limb can also change. This has been demonstrated with fMRI studies showing a complex cortical network activated during pin-prick hyperalgesia in CRPS comprising areas not only involved in nociceptive, but also in cognitive and motor processing (Maihöfner et al., 2005). Allodynia has been shown to activate many areas including contralateral S1 and motor cortex (M1), parietal association cortices (PA), bilateral S2, insula, frontal cortices, and both anterior and posterior parts of the cingulate cortex (aACC and pACC); and can also cause deactivations detected in the visual, vestibular, and temporal cortices (Maihöfner et al., 2006). Another MEG study demonstrated that brushing the affected side produced stronger magnetic fields and more laterally located corresponding equivalent current dipoles, consistent with the presence of cortical reorganisation (Maihöfner et al., 2003b). An fMRI study in children has also confirmed changes in processing of stimuli in affected and unaffected limbs (Lebel et al., 2008). A recent fMRI study suggests an abnormal activation pattern of cerebral areas belonging to the descending opioid pain suppression pathway. Ten CRPS patients with left sided symptoms underwent electrical stimulation of both index fingers during a task to suppress the feeling of pain under constant painful stimulation. The periaqueductal grey (PAG) and cingulate cortex were activated significantly less during suppression of pain, regardless of whether the symptomatic or asymptomatic hand was stimulated (Freund et al., 2011). Another study using electrical stimulation of the hands in CRPS patients provides some support to this concept. It showed decreased pain adaptation and increased pinprick hyperalgesia in both affected and unaffected limbs compared to healthy controls implying a shift from inhibition towards facilitation of nociceptive input in CRPS patients (Seifert et al., 2009).

Neuroimaging also provides evidence of impaired motor function. An MEG study showed abnormal motor cortex reactivity (Kirveskari et al., 2010). An fMRI study investigating motor dysfunction during target reaching and grasping and finger tapping using kinematic analysis showed significant prolongation of the target phase

with a pattern of motor impairment, consistent with disturbed integration of visual and proprioceptive inputs in the posterior parietal cortex. Subsequent analysis demonstrated that activations of the posterior parietal cortices, supplementary motor area (SMA) and primary motor cortex were correlated with the extent of motor dysfunction (Maihöfner et al., 2007). When fMRI was performed during imagined movements of the affected hand in CRPS patients with dystonia, compared to controls there was contralaterally reduced activation in the inferior parietal and adjacent primary sensory cortex (Gieteling et al., 2008).

Other studies suggest parietal lobe involvement. A positron emission tomography (PET) study of cerebral glucose metabolism in CRPS demonstrated bilateral increases in several brain areas including the parietal cortex (Shiraishi, Kobayashi, et al. 2006 212 /id). Another PET study of a CRPS patient before and after successful treatment showed increased cerebral blood flow in the right parietal and left frontal lobes, which decreased after treatment (Wu, Fan, et al. 2006 213 /id). Vartiainen showed that MEG responses during tactile processing of hyperaesthetic CRPS subjects demonstrated defective posterior parietal cortex (PPC) activation, and suggested that this might be associated with neglect-like symptoms (Vartiainen et al., 2008). For further discussion of the role of the parietal cortex, see **Chapter 7**.

2.7.6.6. Conclusion

There is increasing evidence for a variety of cortical mechanisms operating in CRPS which challenge the view that CRPS is entirely a somatoform illness seen in malingerers (Ochoa and Verdugo, 1995). Different contributions of varying cortical mechanisms may account for some of the clinical patterns that present in patients with CRPS.

2.7.6.7. Hypoxia

The hypoxia hypothesis proposes an ischemia-reperfusion injury which produces a microvascular injury characterised by slow-flow/no-reflow in the capillaries. This phenomenon initiates and maintains deep-tissue ischemia and inflammation, leading to the activation of muscle nociceptors, and the ectopic activation of sensory afferent axons due to endoneurial ischemia and inflammation (Coderre and Bennett, 2010). A rat model has been developed with some animals displaying a CRPS-like syndrome (Coderre et al., 2004). Tissue hypoxia (Koban et al., 2003) and diminished nitric oxide levels have been demonstrated in blister fluid from patients with cold CRPS (Groeneweg et al., 2009a) which would be consistent with this model. However topical application of the nitric oxide donor isosorbide dinitrate did not show an

improvement of the regional blood distribution suggesting that there may be other central or peripheral factors contributing to the disturbed vasodynamics in cold chronic CRPS that are not influenced by nitric oxide substitution (Groeneweg et al., 2009b)

2.7.6.8. Conclusion

There is limited evidence for a role of tissue hypoxia in some CRPS patients.

2.7.6.9. Other mechanisms

2.7.6.9A. Autoimmunity

Autoimmunity is a newer postulated mechanism in CRPS (Blaes et al., 2007). Anti-neuronal antibodies have been demonstrated in CRPS patients (Blaes et al., 2004;Goebel et al., 2005b;Kohr et al., 2009). In mice, the passive transfer of patient serum immunoglobulin G (IgG) antibodies has shown a functional effect causing abnormal behaviour and motor function (Goebel et al., 2011). Intravenous immunoglobulin is used as a treatment in a variety of autoimmune mediated diseases. It has demonstrated a therapeutic effect in some patients with CRPS (Goebel et al., 2005a;Goebel et al., 2010).

2.7.6.9B. Muscle pathology

Muscle specimens from the amputated limbs of patients with severe CRPS have demonstrated histopatholgic changes (van der Laan et al., 1998). Hulsman et al describe fatty degeneration, atrophy of both type 1 and type 2 fibres without selective type 2 fibre atrophy and nuclear clumping unrelated to duration of CRPS prior to amputation (Hulsman et al., 2009). In another study, mitochondria obtained from muscle tissue of amputated CRPS limbs showed reduced mitochondrial ATP production and substrate oxidation rates (Tan et al., 2011). Skeletal muscle MRI abnormalities in the acute phase of CRPS include changes consistent with muscular oedema, interstitial oedema, and vascular hyperpermeability, which may implicate haemodynamic abnormalities. Chronic phase abnormalities indicated the presence of muscle atrophy and fibrosis or fatty infiltration of the affected muscle (Nishida et al., 2009).

2.7.6.9C. Peripheral nerve damage

Small fibre loss has been demonstrated in histopathological studies of tissue from skin biopsies of CRPS patients (Oaklander et al., 2006) and skin (Albrecht et al., 2006) and nerves (van der Laan et al., 1998) from amputated limbs.

2.7.6.9D. Genetic predisposition

Several potential genetic associations have been described. These include HLA DR2(15) (Mailis and Wade, 1994) and HLA DQ1 (Kemler et al., 1999;van de Beek et al., 2000). The dystonic pattern of CRPS has been linked with HLA DR13 (van Hilten et al., 2000), and HLA B62 and HLA DQ8 (de Rooij et al., 2009b).

A recent study suggests that some cases of CRPS after distal radial fracture may be associated with mutations in genes encoding for alpha 1a-adrenoceptors (Herlyn et al., 2010). Familial cases have also been reported (Shirani et al., 2010), and may be associated with a younger onset (de Rooij et al., 2009a).

2.7.6.10. Overall conclusions

There are likely to be many different mechanisms operating in CRPS and they are likely to vary both between and within patients. Different mechanisms may be more active at different times over the course of the disease. An understanding of which mechanisms are facilitated and when would lead to better understanding and treatment of the varying presentations of CRPS. Therefore there needs to be development of a clinical phenotyping approach in the evaluation of the new patient with CRPS.

2.7.7. Stages

(See **Chapter 6**, section **6.4.10.**)

CRPS is often considered as having three different stages, or as having a ‘warm’ acute, ‘intermediate’ (warm or cold) and a ‘cold’ chronic stage (Vaneker et al., 2005;Veldman et al., 1993;Wasner et al., 2001). The three stages were first described by Steinbrocker (Steinbrocker et al., 1948), with further elaboration by Bonica (Bonica, 1953).

The first (acute) stage is characterised by constant burning pain with oedema, warmth, erythema and often dry skin. In the second (dystrophic) stage there is onset of trophic changes with cold and often moist skin. The third (atrophic) stage is marked by development of atrophy of skeletal muscle and bone, with joint contractures. The pain is usually an aching character, and the limb cold, pale with glossy skin.

Is there any difference in prognosis for ‘warm’ or ‘cold’ CRPS? Vaneker et al reviewed a cohort of 47 CRPS patients with one upper limb affected 8 years after their diagnosis. Those diagnosed as having ‘cold’ CRPS had poorer clinical pain outcomes and showed persistent signs of central sensitisation correlating with disease progression, which was not the case for warm CRPS 1 patients (Vaneker et

al., 2005). Perez et al found that there was a difference in the pattern of response of CRPS type 1 patients treated with free radical scavengers N-acetyl cysteine or dimethyl sulfoxide (DMSO)(Perez et al., 2003).

It has been questioned whether staging is a valid concept, as many patients do not pass through all stages (Jänig and Baron, 2003;Veldman et al., 1993). Additionally, some patients present with a primarily 'cold' CRPS rather than the more common 'warm' pattern.

2.7.7.1. Conclusion

In some CRPS patients, the stages described may reflect varying aetiopathogenic mechanisms operating at different time points over the course of the condition.

2.7.8. Treatment

There is a bewildering array of treatments for CRPS. The evidence base is poor, and effectiveness highly variable. This again probably reflects that there are different combinations of mechanisms operating in different patients at different stages of their disease. Treatment modalities include pharmacologic, interventional and non-pharmacologic. A summary (comprehensive but not exhaustive) is provided in **Table 2.2**. A list of recent reviews of treatment in CRPS is given in **Table 2.3**. The only common theme is that the evidence is poor and more research is required.

Table 2.2. Summary of therapeutic modalities used in the treatment of CRPS.

Pharmacologic	NSAID's Corticsteroids Opiates Tricyclic antidepressants Gabapentin / pregabalin Memantine Baclofen Calcitonin Bisphosphonates Ketamine IV/topical Lignocaine IV/topical Capsaicin topical Dimethyl sulfoxide (DMSO) N-acetyl cysteine IV Botulinum toxin Mannitol IV Immunoglobulin IV Anti-TNF Thalidomide Tadalafil Isosorbide dinitrate topical Magnesium IV Phentolamine IV Vitamin C Hyperbaric oxygen
Interventional	Sympathectomy
	IV regional infusion Guanethidine Bretylium Ketanserine
	Intrathecal infusion Baclofen Morphine Clonidine Ziconatide Glycine
	Stellate ganglion block Neuroablation Spinal column stimulation Amputation
Non-pharmacologic	Physiotherapy Occupational therapy Psychological interventions Graded motor imagery Mirror visual feedback therapy Graded pain exposure therapy Chiropractic Tai Chi

NSAID’s = Non-steroidal anti-inflammatory drugs

Table 2.3. List of recent published reviews of treatment for CRPS.

Pharmacologic	Rowbotham,M.C. (2006). Pharmacologic management of complex regional pain syndrome. Clin.J.Pain *22*, 425-429. Kingery,W.S. (1997). A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. Pain *73*, 123-139. Maihofner,C., Seifert,F., and Markovic,K. (2010a). Complex regional pain syndromes: new pathophysiological concepts and therapies. Eur J Neurol *17*, 649-660. Perez,R.S., Zollinger,P.E., Dijkstra,P.U., Thomassen-Hilgersom,I.L., Zuurmond,W.W., Rosenbrand,K.C., and Geertzen,J.H. (2010). Evidence based guidelines for complex regional pain syndrome type 1. BMC.Neurol. *10*, 20. Atkins,R.M. (2003). Complex regional pain syndrome. J.Bone Joint Surg.Br. *85*, 1100-1106. Goebel,A. (2011). Complex regional pain syndrome in adults. Rheumatology.(Oxford). Tran,d.Q., Duong,S., Bertini,P., and Finlayson,R.J. (2010). Treatment of complex regional pain syndrome: a review of the evidence. Can.J.Anaesth. *57*, 149-166.
Interventional	Nambi-Joseph,P., Stanton-Hicks,M., and Sferra,J.J. (2004). Interventional modalities in the treatment of complex regional pain syndrome. Foot Ankle Clin. *9*, 405-417. Nelson,D.V. and Stacey,B.R. (2006). Interventional therapies in the management of complex regional pain syndrome. Clin.J.Pain *22*, 438-442.
Non-pharmacologic	Harden,R.N., Swan,M., King,A., Costa,B., and Barthel,J. (2006). Treatment of complex regional pain syndrome: functional restoration. Clin.J.Pain *22*, 420-424. Daly,A.E. and Bialocerkowski,A.E. (2009). Does evidence support physiotherapy management of adult Complex Regional Pain Syndrome Type One? A systematic review. Eur.J.Pain *13*, 339-353.

2.7.8.1. Conclusion

Effective treatment of CRPS remains a challenging problem, and the evidence base is poor. Pharmacologic and interventional approaches work best when combined with physical rehabilitation and pain management approaches (Goebel, 2011). There is limited evidence that rTMS (Picarelli et al., 2010;Pleger et al., 2004a) and ECT (Fukui et al., 2002;Wolanin et al., 2007) may have a beneficial effect in CRPS, supporting the role of central pain mechanisms in CRPS. The fact that there are so many different treatments of varying efficiency is again suggestive that there are many different pathologic mechanisms operating in CRPS. Treatment would be more effective if they could be identified and targeted appropriately.

This thesis uses a series of simple, non-invasive techniques to investigate whether sympathetic autonomic and cortical mechanisms could be identified in a group of CRPS patients. This might begin to form the basis of a clinical phenotyping approach.

2.8. Summary

Multiple pain mechanisms operate across the spectrum of rheumatic disease and CRPS, and may account for the different clinical manifestations observed among patients. Key mechanism areas include autonomic disturbances and central pain mechanisms with particular reference to neuroplasticity and sensorimotor conflict causing central integrational impairment, and the function of the parietal lobes.

This thesis explores the clinical presentation of patients with OA, RA and CRPS investigating baseline autonomic function and sensory testing parameters. It then applies a series of sensorimotor challenges while measuring autonomic responses and monitoring pain responses. Finally, it investigates parietal lobe function in a group of patients with CRPS, and correlates this with the findings from the previous studies. The final aim is to provide a phenotyping approach to CRPS which weighs different contributions from the key mechanistic areas, and may allow a more targeted approach to treatment. The same approach may be applicable in rheumatic disease such as OA and RA.

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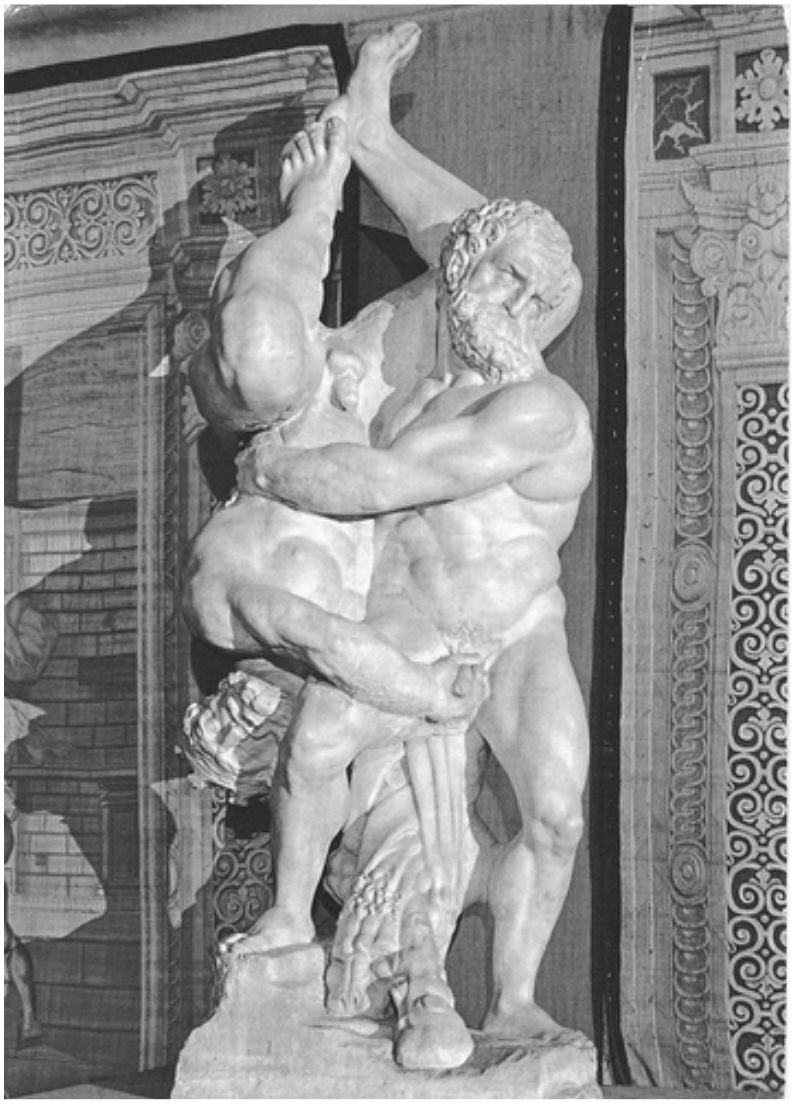

Autonomic indifference to severe visceral pain

Hercules and Diomedes

V. dei Rossi (16th century) - Palazzo Vecchio, Florence

Image available from: http://www.sculpturegallery.com/sculpture/hercules_and_diomedes.html. [Accessed 17.1.12.]

Chapter 3: Methods

"It's odd that you can get so anesthetized by your own pain or your own problem that you don't quite fully share the hell of someone close to you."

Lady Bird Johnson

Image: Tames,G., 2007. Lady Bird Johnson [online]. New York: Time Magazine. Available from: http://www.time.com/time/specials/2007/personoftheyear/article/0,28804,1690753_1691759_1695063,00.html. [Accessed 18.1.2012].

3.1. Experimental design

The experimental method employed was a multifactorial comparison between non-equivalent groups (a 'between-within' design), utilising a semi-purposive sampling strategy. As CRPS is a rare condition, a non-probability sampling strategy was required.

All CRPS and rheumatology patients were recruited from the RNHRD. This is a small, specialist foundation trust. The RNHRD has become nationally renowned for the specialist CRPS service, and therefore many patients are late stage, long disease duration, complex cases. Therefore my CRPS population will not reflect that of the wider population. However, as the aim of the research is to investigate novel pain mechanisms secondary to cortical remapping, this is more likely in the long disease duration cohort (see **Chapter 2**).

Most general rheumatology patients are from the local area and will reflect the wider general rheumatology population characteristics. However, it is possible that a similar bias may exist for a minority of patients who come from out of the local catchment area to be treated at a specialist rheumatology hospital. Therefore the same sampling strategy was utilised for the other comparison groups in order to minimise between group sampling bias.

3.2. Ethical approval

The study was conducted in accordance with the Declaration of Helsinki(1996). Informed written consent was obtained from all subjects (See **Appendix 2** - **3**), and local ethics committee (Bath Local Ethics Committee) approval obtained. See **Appendix 1**.

3.3. Subject recruitment

Healthy controls

Healthy volunteers, who responded to an advertisement and who met the inclusion criteria were recruited from staff and visitors to the RNHRD. Subjects were recruited by word of mouth and via recruitment posters that had been scrutinised and approved by the local ethics committee. Individuals were invited to participate, verbal and written information about the study provided and their written consent was taken. Time was allocated for participants to ask questions prior to consent and participation.

CRPS, osteoarthritis and rheumatoid arthritis patients

Adult patients who met the IASP 'research' diagnostic criteria for CRPS type 1(Harden et al., 2007) were recruited from consecutive attendees of the weekly CRPS outpatient clinic and the CRPS in-patient programme of the Royal National Hospital for Rheumatic Diseases (RNHRD), Bath. Patients meeting American College of Rheumatology criteria for the diagnosis of osteoarthritis (Altman et al., 1986;Altman et al., 1990;Altman et al., 1991) and rheumatoid arthritis (Arnett et al., 1988) were similarly recruited. In addition to the recruitment posters, clinicians were asked to identify possible subjects from among their outpatients and in-patients.

3.4. Inclusion and exclusion criteria

Controls were excluded if they had ever had CRPS or any other chronic pain syndrome, any rheumatological disease or any significant cardiovascular, cerebrovascular or microvascular disease. Participants also had to have no known proprioceptive disorder (including medication that may cause proprioceptive impairment), and no significant visual or hearing impairment. Furthermore, there had to be no visible disfigurement or tattoos on the limbs. These factors may have caused difficulty participating in the studies and/or have confounded any results obtained. The same exclusion criteria were applied to OA, RA and CRPS patients. See **Table 3.1**.

Table 3.1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Subjects	
Healthy controls	
• ≥ 18yrs • male or female • Co-operative • No rheumatological disorders • Matched for age (within 5 yrs) and sex with subjects	• Co-morbidity that may affect proprioception • Asymmetrical visible disfigurement on upper and lower limbs • Significant visual or hearing impairment • Significant cardiovascular, cerebrovascular or microvascular disease
Osteoarthritis	
• Participants meet ACR criteria for osteoarthritis of the hip, knee or hand (Altman et al., 1986;Altman et al., 1990;Altman et al., 1991) • ≥ 18yrs • male or female • symmetrical OA • Co-operative	• Diagnosis of any other rheumatological condition • Co-morbidity that may affect proprioception • Asymmetrical visible disfigurement on upper and lower limbs • Significant visual or hearing impairment • Significant cardiovascular, cerebrovascular or microvascular disease
Rheumatoid arthritis	
• Participants meet the ACR criteria for rheumatoid arthritis (Arnett et al., 1988) • ≥ 18yrs • male or female • symmetrical disease • RA under stable control with no major flares for the last 6 months • Co-operative	• Diagnosis of any other rheumatological condition • Co-morbidity that may affect proprioception • Any asymmetrical visible disfigurement additional to that caused by RA on upper and lower limbs • Significant visual or hearing impairment • Significant cardiovascular, cerebrovascular or microvascular disease
Complex regional pain syndrome	
• Participants meet the IASP revised criteria for CRPS (Harden et al., 2007) • ≥ 18yrs • male or female • Co-operative • Upper limb CRPS	• Diagnosis of any other rheumatological condition • Co-morbidity that may affect proprioception • Any asymmetrical visible disfigurement additional to that caused by CRPS on upper and lower limbs • Significant visual or hearing impairment • significant cardiovascular, cerebrovascular or microvascular disease

3.5. Sample size:

CRPS is considered to be a rare diagnosis, and throughout the literature, evidence is lacking due to difficulty in recruiting significant numbers of patient. Papers are usually based upon small numbers. The methodology of **Chapter 5** is based upon McCabe et al 2005, which used 41 healthy volunteers.

A semi-purposive sampling strategy was used, and the sample size was based upon the number of subjects available within the data collection period aiming for at least 40 subjects in each cohort. It is recognised that the generalisation of findings may be limited by employing this method.

3.6. Ethical considerations

Ethics

The study protocol and all other appropriate documentation has been submitted and approved by the Local Research Ethics Committee and by the RNHRD Research and Development Committee.

Informed consent

Prior to recruitment to the research, all participants had the nature, scope and possible consequences of the study explained to them in a written and verbal form that they were able to understand. Time was permitted for subjects to ask questions and written and verbal consent was gained prior to commencement of assessment in accordance with the Declaration of Helsinki guidance (1996).

Confidentiality

Participants were informed that all study findings would be stored on computer and handled confidentially. The data were stored for the purpose of data analysis and will be destroyed within the designated time frame. Anonymity of participants was preserved and all data stored on a password-protected computer kept on locked hospital premises.

Visit details

All subjects were requested to make at least two visits for assessments. Reimbursement of travel expenses was offered to all participants. There was no financial incentive.

3.7. Assessment methods

3.7.1 Quantitative Sensory Testing and the assessment of allodynia: see **Chapter 4**.
3.7.2 Assessment of autonomic sympathetic responses: see **Chapter 4**.
3.7.3 Assessment of optokinetic induced vulnerability: see **Chapter 5**.
3.7.4 Assessment of responses to ambiguous visual stimuli: see **Chapter 6**.
3.7.5 Assessment of parietal lobe function: see **Chapter 7**.

3.8. Data analysis

The LDF readings and ESR measurements were captured via a Cambridge Electronics Division (CED) Electrophysiological Response Recording System, recorded on a notebook computer and analysed using CED Spike Data Analysis software.

3.9. Statistical analysis

Demographic data were analysed using descriptive statistics. Cumulative frequency histograms of autonomic response data were not normally distributed, demonstrating a negative skew (**Fig.3.1**). Data transformation was unhelpful and therefore non-parametric statistical analysis techniques were used. Data are presented as median + interquartile range (IQR). For comparison between cohorts, Mann Whitney-U and Kruskal Wallis tests were used. Chi squared test was used for analysis of frequency data of categorical variables, and Spearman's rho for correlation.

Symmetry ratio data showed marked homogeneity of variance particularly in the CRPS cohort, with grouping of extreme high and low values. For comparison of data across cohorts, a Siegel-Tukey test was used. This is a non-parametric sum of ranks procedure for relative spread in unpaired samples.

Fig.3.1

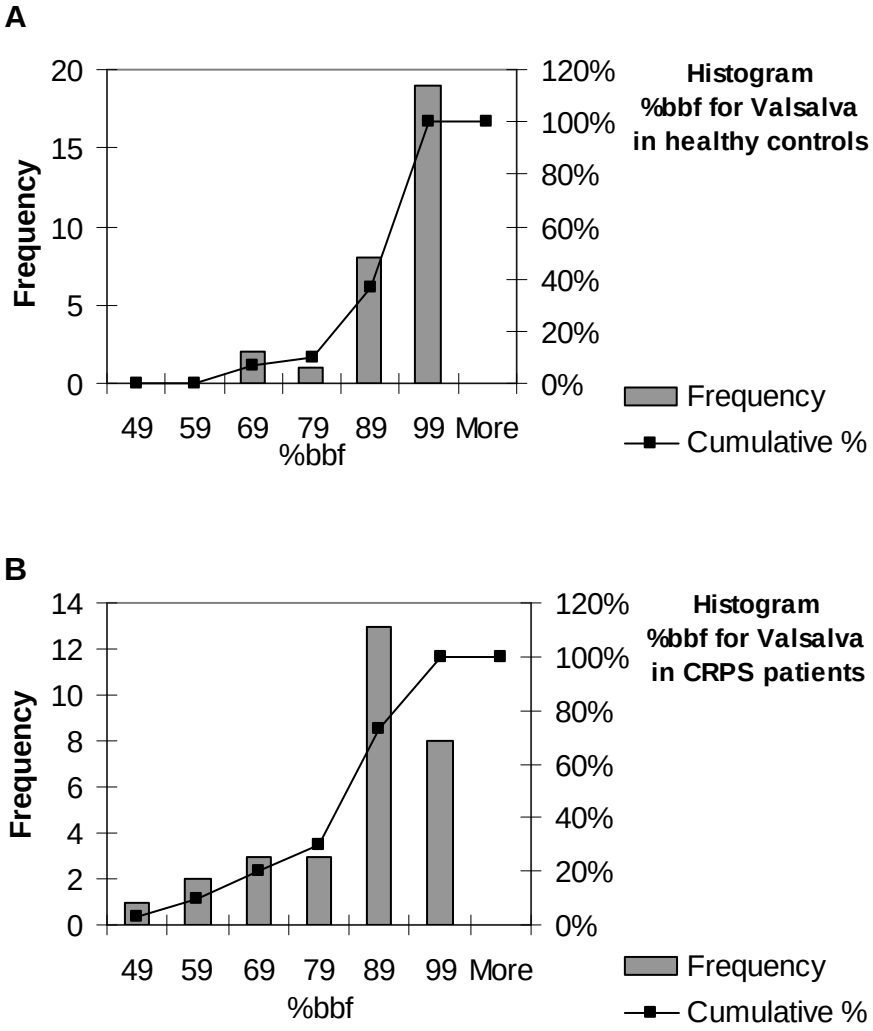

Fig.3.1. Histograms showing cumulative frequency of percentage change from baseline blood flow (%bbf) for the Valsalva manoeuvre in (**A**) healthy controls and (**B**) CRPS patients.

3.10. Qualitative assessments

Qualitative data generated from participants' descriptors of temperature, pain and other sensations on movement and at rest was collected and analysed. Pain was rated using simple verbal scales. For further details, see **Methods** sections of **chapters 5** and **6,** and **Appendix 3**.

3.11. References

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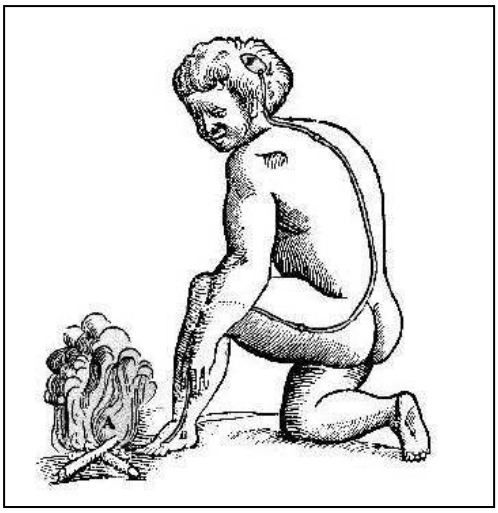


When things were simpler:
The ‘Descartes’ model of pain

Image: Illustration of the pain pathway in René Descartes' Traite de l'homme (Treatise of Man) 1664. Available from: http://en.wikipedia.org/wiki/File:Descartes-reflex.JPG

Chapter 4:

Quantitative Sensory Testing and baseline sympathetic autonomic function in CRPS and rheumatic disease

"..to know them was merely to know their ailments, and the ailments were almost invariably rheumatism. Some, of course, had other bodily infirmities, but they always had rheumatism as well."

Saki (H.H.Munro), *from 'The Toys of Peace'*

Image: Hoppé, E.O., 1913. Hector Hugh Munro aka Saki [online]. San Francisco: Wikimedia Foundation. Available from: http://en.wikipedia.org/wiki/File:Hector_Hugh_Munro_aka_Saki,_by_E_O_Hoppe,_1913.jpg. Accessed 17.1.12.)

4.1. Introduction

Chapter 1 outlined some of the challenges in pain research, key among them being the problem of pain being both a sensation and a perception and therefore not directly comparable between subjects. It introduced quantitative sensory testing (QST) as an approach to allowing comparison of some quantifiable aspects of sensory perception and pain between different persons. **Chapter 2** focussed on current concepts of the complexity of pain and that there are many mechanisms contributing to the experience of pain. Furthermore, it showed that different diseases causing chronic pain have varying pain pathologies that may account for the spectrum of clinical presentation. Allodynia is a common distressing symptom in complex regional pain syndrome (CRPS) and is seen less often in osteoarthritis (OA) and rheumatoid arthritis (RA) patients.

Chapter 2 also introduced the role of the autonomic nervous system in pain. It was shown to be both responsive to painful stimuli, and that sympathetic autonomic dysfunction may be a pain mechanism. Autonomic responses are often thought of as simple peripheral spinal reflexes. However the central integration of the autonomic nervous system with nociception and the consequent behavioural, emotional and neuroendocrine responses are a vital part of interoception, homeostasis and survival.

This chapter describes the baseline assessment of quantitative sensory testing parameters and sympathetic autonomic function in healthy controls, and patients with chronic painful rheumatic disease; OA, RA and CRPS. The subsequent studies build upon this baseline data.

4.1.1. Aims

To establish and compare baseline quantitative sensory testing (QST) parameters and sympathetic autonomic function in healthy controls, complex regional pain syndrome (CRPS), osteoarthritis (OA) and rheumatoid arthritis (RA) patients.

4.1.2. Hypotheses

1. There will be no allodynia present in healthy controls.
2. Allodynia will be present in some osteoarthritis (OA) and rheumatoid arthritis (RA) patients and most marked in CRPS patients.
3. Baseline sympathetic autonomic function will be normal in healthy controls, OA and RA patients and impaired in CRPS patients.

4.2. Methodological considerations

4.2.1. Establishing the model to investigate allodynia

4.2.1.1. Quantitative Sensory Testing and the assessment of allodynia: review of literature and methodological considerations

CRPS is characterised by disturbances of sensory function in the affected area. Allodynia is a frequent and disabling occurrence. The incidence is unclear and has been reported from 5 – 30% (Birklein et al., 2000;Huge et al., 2011). CRPS patients may also develop a hemi-sensory impairment characterised by decreased temperature and pinprick sensation ipsilateral to the CRPS affected limb (Rommel et al., 1999), and there was a high incidence of allodynia in this group (58%). A follow-up study reported that patients with this pattern of impairment were more likely to have mechanical allodynia and hyperalgesia, and tended to have longer duration of CRPS (Rommel et al., 2001).

Quantitative sensory testing techniques and protocols are variable depending on whether they are being utilised clinically or in research and clinical trials settings. The German DFNS (German Research Network on Neuropathic Pain) guidelines (Rolke R et al., 2006;Topp and Byl, 1999) outline a standardised approach suitable for research and clinical trials. It details seven tests covering 13 different parameters. However, it is time consuming (three hours per subject) and requires specific, expensive equipment. It uses the modified method of limits procedure which involves

applying stimuli in decreasing order of intensity until the stimulus is no longer perceived to obtain the subthreshold measure. The stimuli are then presented in increasing intensity until the stimulus is perceived again to obtain the suprathreshold measure. This whole procedure is repeated in five 'runs'. The EFNS (European Federation of Neurological Societies) guidelines (Cruccu G et al., 2004;Cruccu et al., 2010) are more suited for clinical use. They recommend the use of simple, easily obtainable tools for bedside testing. Detection and pain thresholds are determined by applying stimuli to the skin in an ascending and descending order of magnitude but they do not specify a number of 'runs' or times to repeat.

Patients with allodynia may demonstrate marked 'wind-up' and subsequent lowering of detection and pain thresholds to repetitive stimuli (temporal summation). After the single application of a stimulus, the sensation perceived may last for several seconds. Keizer et al (Keizer D et al., 2007) used at least ten seconds between successive applications of a stimulus to avoid this phenomenon. They allocated the allodynic threshold as when 2 out of 3 stimuli were perceived as painful. Stimuli were applied using the method of limits which involves applying successively stronger stimuli until the threshold was reached.

4.2.1.2. Specific methodological considerations

The severity of the CRPS in this cohort and the florid nature of the allodynia rendered repeated 'runs' of testing inappropriate due to the wind-up phenomenon. Pilot work demonstrated many patients quickly developed wind-up with worsening pain and lowering of tactile thresholds. Therefore only one 'run' of testing was used to avoid wind-up and lowering of thresholds. Consequently this data cannot be directly compared to studies using the standard 'method of limits' approach, but a modified approach was required for patient tolerability.

While Keizer et al applied the stimuli for 2-3 seconds, in my pilot studies this was too long, also precipitating wind-up. The application of stimuli for approximately 0.5 seconds was found to be better. Tighter threshold delineation was required, and therefore the allodynic threshold used was when at least 3 out of 4 stimuli were perceived as painful.

4.2.1.3. Method:

4.2.1.3-1. Participants

For full details of inclusion/exclusion criteria, ethical considerations etc, see **Chapter 3**.

4.2.1.3-2. Apparatus

- Semmes-Weinstein monofilaments ('Touch-test', USA. Standard set covering 0.008 – 300g target force)
- Somedic Senselab brush
- Body map mannequin – see **Appendix 4**
- 'Lund and Browder' burns chart– see **Appendix 5**

4.2.1.3-3. Outcome measures

- Tactile thresholds
- Percentage of body surface area allodynia (BSA) calculated from a 'Lund and Browder' burns chart (Lund CC and Browder NC, 1944)
- Other sensory disturbance patterns observed

4.2.1.3-4. Assessment of baseline pain levels

A common method to assess pain levels is the use of a verbal rating scale where 0 = no pain and 10 = worst possible pain. This is a modified Likert scale (Likert, 1952), which has been shown to reliably measure changes in pain (Oppenheim AN, 1992). However in pilot work, most CRPS patients put their baseline pain levels at 8, 9 or 10 and some rated it >10, or 'off the scale' giving little scope to understand how pain might change if it worsened. Therefore a simple verbal scale was used where patients were asked if their pain was unchanged or mild, moderate or severely worse or better than baseline.

4.2.1.3-5. Tactile threshold

The participant was positioned comfortably upon an examination couch dressed in underclothes only, with a covering blanket as tolerated and was asked to close their eyes during testing. If there were any difficulties in keeping the eyes closed, or compliance issues, a blindfold was used. The testing area was quiet and heated to a

comfortable temperature. The examiner explained that a series of filaments of differing stiffness would be applied to the skin, and the participant would be asked to indicate when they could feel it touching their skin. They would be asked additionally to either point to where it was felt, or describe where it was detected so that the stimuli could be differentiated from spontaneous sensations. The verbal explanation was followed by a physical demonstration on an unaffected area. Different grades of Semmes-Weinstein monofilaments were used in the standard way (pressure applied until the hair starts to bend). The body surface area was visually divided into discrete testing areas: upper limbs, lower limbs, head and neck and torso. In CRPS patients, testing started in the area furthest away from the affected limb to gain their confidence, and avoid wind-up at the start of the testing protocol. Tactile thresholds were mapped onto the corresponding area of a mannequin.

4.2.1.3-6. Mechanical allodynia

During the above protocol, subjects were also asked to indicate if any abnormal sensations were perceived. If it was perceived as abnormal, they were asked to describe how it felt (ie. unpleasant, painful etc). Allodynic areas were mapped onto the corresponding area of a mannequin on a Lund and Browder burns chart.

4.2.1.3-7. Brush-evoked allodynia

The same experimental conditions as above were utilised. The examiner explained that a soft brush would be applied to the surface of the skin and that the participant would be asked to indicate if the sensation evoked was different to that expected, and how. An unaffected area was used as the testing standard. The stimulus was a standardised ‘Somedic Senselab’ brush brushed gently over the surface of the skin for a distance of approximately 2 cm over 2 seconds. This produces a pressure of approximately 200 - 400mN. The body surface area was visually divided into discrete areas that were tested for the presence of brush evoked allodynia. Allodynic areas were mapped onto the corresponding area of a mannequin on a Lund and Browder burns chart.

4.2.1.3-8. Pressure allodynia

The same experimental conditions as above were utilised. The examiner assessed for the presence of pressure allodynia at wrists, elbows, shoulders, axial spine, hips, knees, ankles, metacarpophalangeal, metatarsophalangeal and distal interphalangeal joints. The standard technique for joint tenderness employed during

a rheumatological DAS28 score was utilised (gentle but firm pressure applied to medial and lateral, and anterior and posterior aspects of the joint). For axial spine, the three finger alignment over dorsal vertebral prominences was used. If an allodynic area was found, the same pressure on the contralateral uninvolved joint, or if that joint was involved, a point on the mid-forearm was used to confirm. Allodynic areas were mapped onto the corresponding area of a mannequin on a Lund and Browder burns chart.

4.2.2. Establishing the model to investigate sympathetic autonomic function

4.2.2.1. Assessment of autonomic sympathetic responses: review of literature and methodological considerations

Sweating and skin blood flow are vital components of thermoregulation. The central control of thermoregulation is in the preoptic/anterior hypothalamus of the brain. Information on core and surface temperature converge here, and appropriate efferent responses are coordinated via the sympathetic autonomic nervous system (Charkoudian, 2003). Emotion, pain and environmental temperature and humidity induce sympathetic autonomic responses and therefore any testing protocol has to control as much as possible for these potential confounding factors.

There are a wide variety of techniques and equipment available for the assessment of autonomic nervous system integrity. The particular method of assessment chosen will depend upon the homeostatic mechanism being investigated, and the body system that it controls. For example, assessment of lower oesophageal sphincter competence might utilise oesophageal manometry, where as investigations of cardiac electrical rhythm control would employ electrocardiographic techniques. Cognitive effort, mental stress and pain cause sympathetic autonomic arousal and therefore a technique was required that could monitor sympathetic activity.

Cutaneous blood vessels and eccrine sweat glands are innervated by post ganglionic sympathetic fibres which cause vasoconstriction and sweating when stimulated (Charkoudian, 2003). There is no parasympathetic innervation, making cutaneous blood flow and sweating activity a good index of sympathetic activity. There are several techniques described to continually assess cutaneous vasomotor and sudomotor activity. As this thesis concerns the sympathetic control of microvascular peripheral cutaneous blood flow and sweating, the discussion will be confined to autonomic assessment of these parameters.

Measurement of autonomic responses in a severely allodynic population is challenging, due to: i. non-tolerance of tactile stimuli ii. induction of pain by tactile stimuli, which would therefore confound the study. Some autonomic assessment techniques considered but rejected are now described.

4.2.2.2. Rejected autonomic function assessment techniques

Peripheral sympathetic autonomic function can be investigated by invasive and non-invasive means. Invasive methods such as microelectodes for microneurography or microdialysis techniques were rejected as the allodynic CRPS cohort would be unable to tolerate this. Sympathetic autonomic function can also be assessed by detailed measurement of cardiovascular function. The reliability and reproducibilty of heart rate variability as a method of autonomic assessment continues to be a debated issue (McNames and Aboy, 2006). Beat to beat heart rate variability measured by a finger blood pressure cuff as utilised by the Portapress system was considered but rejected due to concerns with tolerability within the allodynic cohort.

Sudomotor function can be assessed using the Quantitative Sudomotor Axon Reflex Test (QSART). However, this requires the use of an iontophoresis chamber affixed to the skin surface, and while it can demonstrate the presence of dysfunction it cannot show dynamic sudomotor responses to central stimuli. Similarly, the silastic imprint test of sweating was rejected due to the inability to demonstrate dynamic responses and the requirement of application and removal of a material to the skin over a period of time.

4.2.2.3. Selected techniques: laser Doppler blood flow recording

Laser Doppler Flowmetry (LDF) provides simple non-invasive measurement of blood flow within the microcirculation, and is becoming increasingly used as an investigative technique in rheumatic diseases (Murray et al., 2004). The technique relies on the Doppler effect, described by Christian Doppler in 1842 (Doppler, 1842). The first report of the use of the Doppler effect to measure microvascular blood flow was by Riva et al in 1972 (Riva et al., 1972). When coherent (laser) light is directed towards the skin at a depth of about 1mm, photons are scattered by moving red blood cells causing the Doppler effect and a shift in photon frequency. The reemitted light is directed towards a photodetector producing a stochastic photocurrent. Analysis of this provides information on the velocity of the skin blood flow in arbitrary flux units (AFU) (Humeau et al., 2007). LDF systems can be separated into two categories: laser Doppler perfusion monitoring and laser Doppler perfusion imagers.

4.2.2.3-1. Laser Doppler perfusion imaging

Skin blood perfusion can be assessed using a Laser Doppler imager, which uses a motorised mirror to reflect laser light and scan it across a defined area of skin. Depending on the size of the skin area, this may take one to several minutes. Whilst this is useful where changes in skin blood flow occur slowly, it cannot be used to study dynamic changes or if that part of the body is moving. As both the latter conditions apply to these studies, perfusion imaging was rejected.

Stimulated microvascular skin blood flow to iontophoresed acetylcholine and sodium nitroprusside has been studied in 17 CRPS patients using laser Doppler imaging, and compared to healthy controls. No differences were found between affected and unaffected limbs or between CRPS patients and healthy controls (Gorodkin et al., 2004).

4.2.2.3-2. Laser Doppler perfusion monitoring

A Laser of known frequency is conducted down a fibre optic cable to a small probe attached to the surface of the skin, and the light is measured as it is reflected back. This provides a continuous spot measurement. The Doppler signal is proportional to the concentration and velocity of red blood cells within the tissue. Blood flow is expressed in arbitrary 'flux units'. Pulsatile flow is observed under steady state conditions, the amplitude of the signal being dependant on diameter of the arterioles under the control of the sympathetic nervous system. Glabrous skin is used to record from rather than hairy skin as it is innervated only by sympathetic vasoconstrictor nerves and it contains arteriovenous anastomoses (Charkoudian, 2003). Hairy skin in comparison is innervated by sympathetic vasoconstrictor and vasodilator nerves and has few if any arteriovenous anastomoses (Johnson JM and Proppe DW, 1996). These are major contributors to the vasoconstrictor component of vasomotor reflexes in glabrous skin of warm subjects (Krogstad et al., 1995).

The technique of laser Doppler perfusion monitoring was selected to provide continuous measurement of the skin blood flow of glabrous skin. As this is under pure sympathetic autonomic control, it provides a continuous measurement of dynamic sympathetic autonomic function.

In order to simplify the terminology, laser Doppler perfusion monitoring will be hereafter referred to as laser Doppler flowmetry (LDF).

4.2.2.3-3. Laser Doppler flowmetry analysis

There is no consensus on the analysis of laser Doppler flowmetry data. Previously described parameters include absolute values such as blood flow in arbitrary flux units, time to peak response, intrinsic perfusion variation expressed as absolute value +/- 2 standard deviations, quotient of intervals, ratio comparing blood flow between affected and unaffected limbs and percentage change from baseline blood flow (Valley et al., 1993). Schurmann used percentage change, absolute values and quotient of intervals in his series of papers (Schürmann et al., 1996;Schürmann et al., 1999;Schürmann et al., 2000) with CRPS patients, and found the most reliable parameter to be the percentage change from baseline mean after stimulation. There is also no consensus on whether the data obtained is parametric or non parametric with statistical tests differing and results being variably expressed as means +/- SDs or medians +/- interquartile ranges. Ide (Ide et al., 1997) used a ratio of the percentage change in the affected limb compared to the unaffected in CRPS patients, and percentage change of the left compared to the right limb in healthy controls in response to an inspiratory gasp. They compared CRPS patients before and after successful treatment and concluded that the parameters were of value in the diagnosis and management of CRPS. Low (Low et al., 1983) used both a quantitative and qualitative approach to analysis of the results of laser Doppler flowmetry in suspected dysautonomia.

4.2.2.3-4. Selected Laser Doppler outcome measures:

Blood flow through finger pulps were measured in arbitrary flux units (AFU).
Three outcome measures were utilised.

1. Responses were quantified by calculating the mean percentage change from baseline skin blood flow (Δ%bbf) in response to a stimulus as follows: Δ%bbf = (baseline mean – minimum) / baseline mean x 100 (**Fig.4.1**). No response to stimulus is highly relevant to this study, which investigates sympathetic autonomic activity in response to different stimuli. Therefore non-response is part of the possible activity spectrum from nil to maximal. It was recorded as zero and included in the analysis.

Fig.4.1.

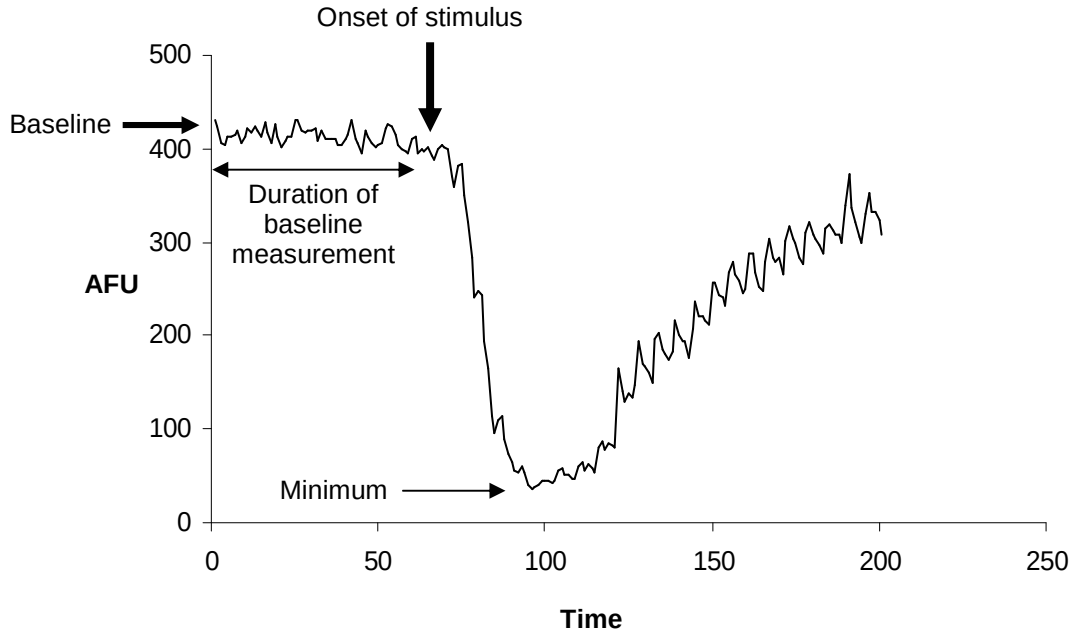


Fig.4.1. Calculation of mean percentage change from baseline blood flow (Δ%bbf) in response to a stimulus. Δ%bbf = (baseline mean – min)/baseline mean x 100. AFU = arbitrary flux units.

2. Quantitative symmetry of Laser Doppler responses: The symmetry ratio (SR) of the magnitude of vasomotor responses between the limbs was calculated as follows: Δ%bbf limb A / Δ%bbf limb B, where A was the larger of the two responses. The range of SR values were from 1 – 5, where a value of 1 shows complete symmetry and >1 indicates increasing asymmetry. A maximum cut-off value of 5 was utilised. Thus, the SR was 5 in patients showing no changes of skin blood flow on one of the limbs and a good response on the other.

3. Qualitative homology of Laser Doppler responses: Responses to stimuli were classified as:

i) homologous response if there were bilateral sympathetic vasoconstrictor responses (**Fig.4.2A**)

ii) asymmetric response if there was vasoconstriction in one limb but no response or vasodilation in the other limb (**Fig.4.2B**).

Where applicable, responses were also categorised as:

iii) no response (homologous) if there was no vasoconstriction to stimuli in either limb

iv) excessive vasoconstriction if the skin blood flow remained <150 AFU at a room temperature of 23-25°C despite acclimatisation time.

In the latter group, response homology or asymmetry was noted but to avoid inflation of error, if any small responses were present they were not quantified

Fig.4.2.

Fig.4.2A

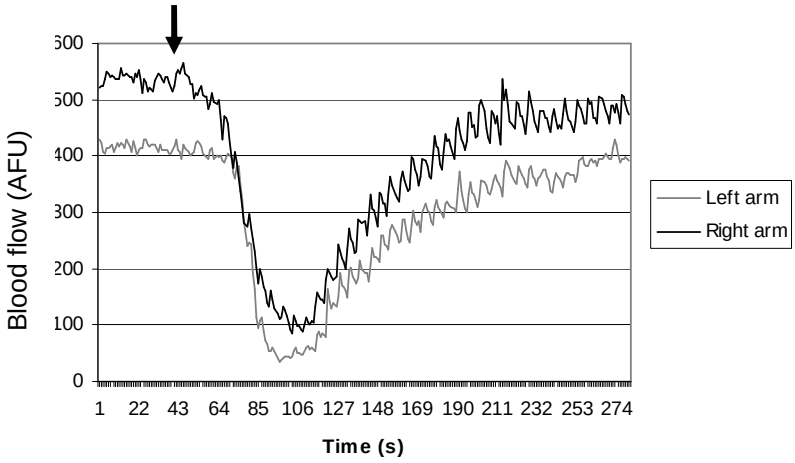


Fig.4.2B

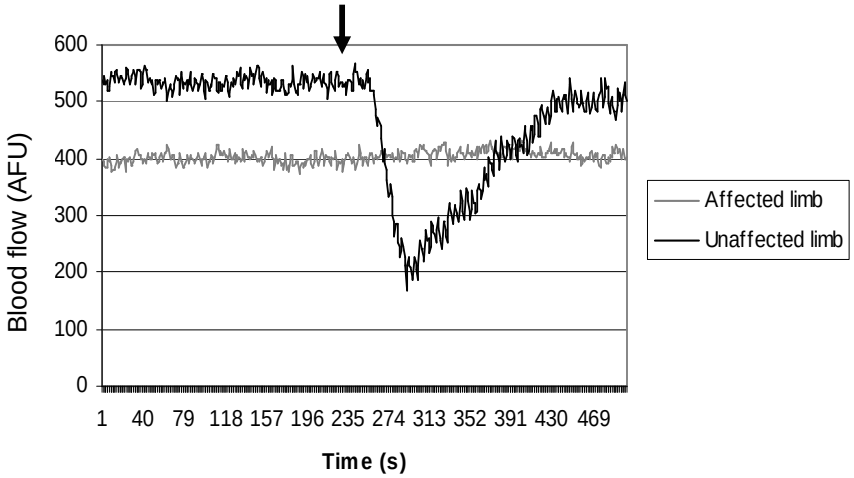


Fig.4.2. Example of (**A**) an homologous bilateral sympathetic vasoconstrictor response to a Valsalva manoeuvre in a healthy control and (**B**) an anomalous asymmetric sympathetic vasomotor response while viewing an ambiguous visual stimuli (AVS) in a CRPS patient. Blood flow is measured in arbitrary flux units (AFU).

↓ = onset of stimulus

4.2.2.4. Electrodermal skin response

The electrodermal skin response (ESR) is a measure of electrodermal activity in response to stimuli from the skin surface. Sympathetic activity is closely linked to emotion, and ESR is a widely used sensitive index of emotion-related sympathetic activity (Critchley et al., 2000;Critchley, 2002). Féré first discovered a drop in electrical resistance of the skin to an applied current in 1888 (Féré C, 1888), and Tarchanoff described changes in the potential difference between two areas of the body surface in 1890 (Tarchanoff J, 1890). There are several different pseudonyms in use including galvanic skin response which refers to skin resistance, and sympathetic skin response which utilises changes in potential difference across the skin. All techniques record the pattern of change in the electrical conductance, resistance or potential difference across the skin surface caused by changes in sweat gland activity. Increasingly, skin conductance (ie. the reciprocal of skin resistance) is being used. Skin conductance is directly proportional to the number of active sweat glands (Montagu and Coles, 1966). The SI derived unit of skin conductance is the 'Sieman', which replaced the previously used 'mho' in 1971. Electrodermal skin response can be measured in response to a variety of sympathetic, psychological and electrical stimuli. Commonly used stimuli include an electrical square wave pulse, startle stimuli such as auditory clicks and 'internal' stimuli such as a cough or deep inspiration (Kucera et al., 2004). Electrical stimuli were not used in this research as it was thought allodynic patients would be highly unlikely to tolerate this.

ESR has been validated and used extensively to investigate sympathetic responses in animal and human studies(Critchley et al., 2000;Habler et al., 1997;Hay et al., 1997a). All normal subjects less than 60 years of age demonstrate electrodermal responses (Arunodaya and Taly, 1995;Gutrecht, 1994). As age increases, responses may not be elicitable particularly in the very elderly. ESR amplitudes are consistently higher in the upper limbs than the lower limbs (Arunodaya and Taly, 1995;Montagu and Coles, 1966) and are more often absent from the foot than the hand (Gutrecht, 1994). The wave form is variable within and between subjects. Typical morphology is biphasic or triphasic and less commonly monophasic (Arunodaya and Taly, 1995;Gutrecht, 1994;Kucera et al., 2004). Several factors influence ESRs. Habituation is a decrease in amplitude observed after repetitive stimulation although some groups report that latency is unaffected (Hoeldtke et al., 1992). Therefore adequate time must be allowed between stimuli, and irregular application of stimuli is

recommended (Kucera et al., 2004). ESRs are also affected by age (Drory and Korczyn, 1993;Hay et al., 1997a), gender, modality of stimulation and body temperature (Kucera et al., 2004). Gutrecht (Gutrecht, 1994) reports that ESRs are not recordable at skin temperatures of <30℃. A temperature controlled room between 22-26℃ (Gutrecht, 1994;Kucera et al., 2004) is suggested with skin temperature being maintained at >32℃ (Gutrecht, 1994). Thus a tight protocol is required to allow comparison within and between subjects.

4.2.2.4-1. Electrodermal skin response analysis

There is still no consensus about the evaluation and processing of ESRs (Arunodaya and Taly, 1995;Gutrecht, 1994;Kucera et al., 2004). While quantitative approaches are being developed, there are inherent difficulties. Amplitude is variable and affected by habituation. Latency may be less variable but there are difficulties marking the exact onset of the ESR to the stimulus. Response averaging is influenced by habituation of responses and ESR shape variation. Most groups advocate a qualitative approach, with absence of a response being abnormal (Arunodaya and Taly, 1995). Some groups include asymmetry of amplitude and asynchrony of response (Evans BA et al., 1988;Johns DR and Young RR, 1986;Raszewa et al., 1991).

ESR has been validated and used to investigate sympathetic responses in human studies investigating the cortical generation of sympathetic autonomic responses (Critchley et al., 2000) and with autonomic dysfunction in different diseases (Fusina et al., 1999;Gozke et al., 2003;Hay et al., 1997a;Karatas et al., 2002;Magnifico et al., 1998;Navarro et al., 1990;Pereon et al., 1995;Raszewa et al., 1991;Thomaides et al., 1993). Few studies have been done investigating CRPS, and they have described abnormalities in the electrodermal skin response (Drory and Korczyn, 1995;Rommel et al., 1995).

This series of research studies utilise skin conductance. Therefore galvanic skin response and sympathetic skin response are inappropriate terminology. The more generic term, ‘electrodermal skin response’ has been used throughout this thesis.

4.2.2.4-2. Selected electrodermal skin response outcome measures:

1. Qualitative analysis.

Responses were classified as:

i. Normal (bilateral symmetric responses)

ii. Abnormal (responses present but either unilateral, or abnormal waveform)

iii. Absent

See **Fig.4.3.**

Fig.4.3.

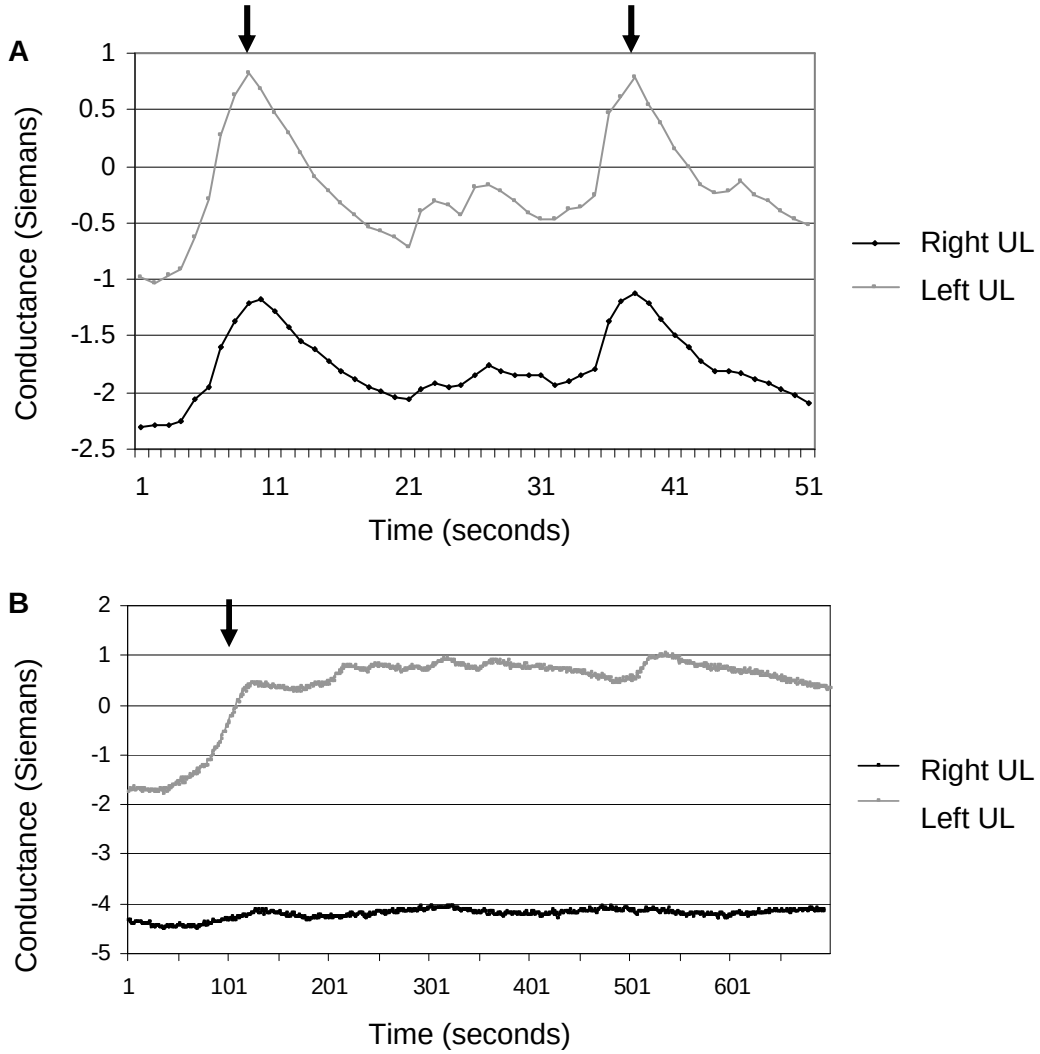


Fig.4.3. Examples of (**A**) normal symmetric responses to two Valsalva manoeuvres and (**B**) abnormal asymmetric unilateral electrodermal skin responses during mental stress. UL = upper limb

↓ = onset of Valsalva manoeuvre / mental stress task

4.2.2.5. Sympathetic stimuli

The protocol established uses standard autonomic provocative tests for both peripheral and centrally coordinated sympathetic autonomic responses.

The integrity of sympathetic vasomotor control is assessed using known sympathetic stimuli. A variety of standard pressor tasks (eg. mental stress, cold pressor challenge, isometric exercise, hyperventilation) (Mathias, 2000) can be utilised to test for autonomic integrity. Robust dynamic responses are elicited by an inspiratory gasp, the Valsalva manoeuvre, the venoarteriolar reflex (moving the upper limb from heart level to a dependent position) and mental arithmetic. The Valsalva manoeuvre was described in 1704 by the anatomist Antonio Maria Valsalva in *De aure humana tractatus*. The original Valsalva manoeuvre is forced expiration against a closed glottis. A modified version where expiration is with an open glottis against a known expiratory pressure, is commonly used in physiological research (Korner PI et al., 1976). The inspiratory gasp/deep breath is a reliable, repeatable and sensitive sympathetic stimulus (Allen et al., 2002;Oberle et al., 1988;Valley et al., 1993) in common use for autonomic testing and has been used with laser Doppler flowmetry in the assessment of CRPS patients (Schürmann et al., 1996;Wasner et al., 1999). When a series of inspiratory gasps are used, provided that adequate time is allowed to elapse between each stimulus, the preceeding vasoconstrictions do not influence the observed change in cutaneous blood flow (Mueck-Weymann and Rauh, 2002). The venoarteriolar reflex is a robust sympathetic stimulus mediated by local vasomotor control (Johnson, 2002). It has also been used in laser Doppler studies with CRPS patients (Birklein et al., 1998;Kurvers et al., 1996). Mental stress induced by a mental arithmetic task is a cortically generated vasoconstrictor stimulus and can induce intense regional vasoconstriction detected by laser Doppler flowmetry in healthy controls (Silverman et al., 1996) and CRPS patients (Birklein et al., 1998;Drummond et al., 2001). Sympathetic responses are known to vary within and between individuals; therefore each subject was used as their own internal control.

4.2.2.5-1. Specific methodological considerations

A standard Valsalva manoeuvre is forced expiration against a closed glottis, and relies heavily on subject comprehension, compliance and voluntary effort for reproducibility. A modified Valsalva manoeuvre was therefore introduced. This was done by asking the subject to blow as hard as possible down the barrel of a 10ml

syringe pressed to the lips, into an anaeroid sphygmomanometer. The investigator noted the maximum reading, and asked the subject to repeat this, but holding the sphygmomanometer reading at ¾ of maximal value for 5 seconds. The two techniques were tested on two cohorts of healthy controls; an original pilot group and the current (new) group. It showed improved reproducibility with the modified technique compared to the standard technique (see **Table 4.1**).

Table 4.1 Healthy controls: Current (new) cohort compared to Pilot group

Healthy Controls (SE)			
Stimulus	Measurement	New (N=17)	Pilot (N=12)
VM	M%ch-R	88 (2)	118 (5)
	M%ch-L	88 (2)	111 (6)

SE = (standard error), VM = Valsalva manoeuvre, M%ch = mean % change from baseline blood flow, R = right upper limb, L = left upper limb

The difference in magnitude of the Valsalva manoeuvre reflects the different techniques employed. In the pilot group, subjects were told how to perform it but there was no method of ascertaining the degree of voluntary effort. In the new cohort, the modified technique was used as described above, which allows some control over the amount of voluntary effort used.

4.2.2.6. Repeated LDF assessments in healthy controls

In healthy controls, autonomic measurements performed under steady state conditions are similar, and repeated assessments by laser Doppler flowmetry have shown good reliability and reproducibility (Allen et al., 2002;Low et al., 1983;Schürmann et al., 1996). It is unknown whether autonomic measurements under steady state conditions in CRPS patients would show similar reliability, or as seems more probable, fluctuate with the pain levels on those days. In previous studies of healthy controls, the reproducibility data were based on repeated measurements from 3-15 subjects on 2-10 occasions.

4.2.2.7. Repeated LDF assessments in CRPS patients

To assess this issue in CRPS, repeated measurements were performed on a subgroup of 12 CRPS patients. These patients had between 2-4 repeat assessments over a duration of 6 months to 2 years. Some patients had no response to some of the sympathetic stimuli (SR = 1); 2 with deep breaths, 3 with mental stress task and 1 with the Valsalva manoeuvre.

Some patients had intermittent marked asymmetric responses. When responses were of a symmetric homologous vasoconstrictor pattern, the symmetry ratios were similar (see **Fig.4.4**). For the mean percentage change from baseline skin blood flow (Δ%bbf), the mean difference between repeated assessments for deep breath was 21%, for mental stress was 28% and for the Valsalva manoeuvre was 15%. Therefore while more fluctuant than healthy controls, when the responses are not markedly asymmetric, they show reasonable reproducibility.

There has not been any previous published work on reproducibility of LDF responses to sympathetic stimuli in long duration CRPS patients. It is possible that the markedly asymmetric responses correlate to worse periods of pain. However, this repeated measures data was pilot work and not intended as a specific research project. Whether asymmetry to baseline sympathetic stimuli relates to pain levels or disease activity over time is a separate issue to this body of work, and one that should be addressed by further appropriate research.

Fig.4.4.

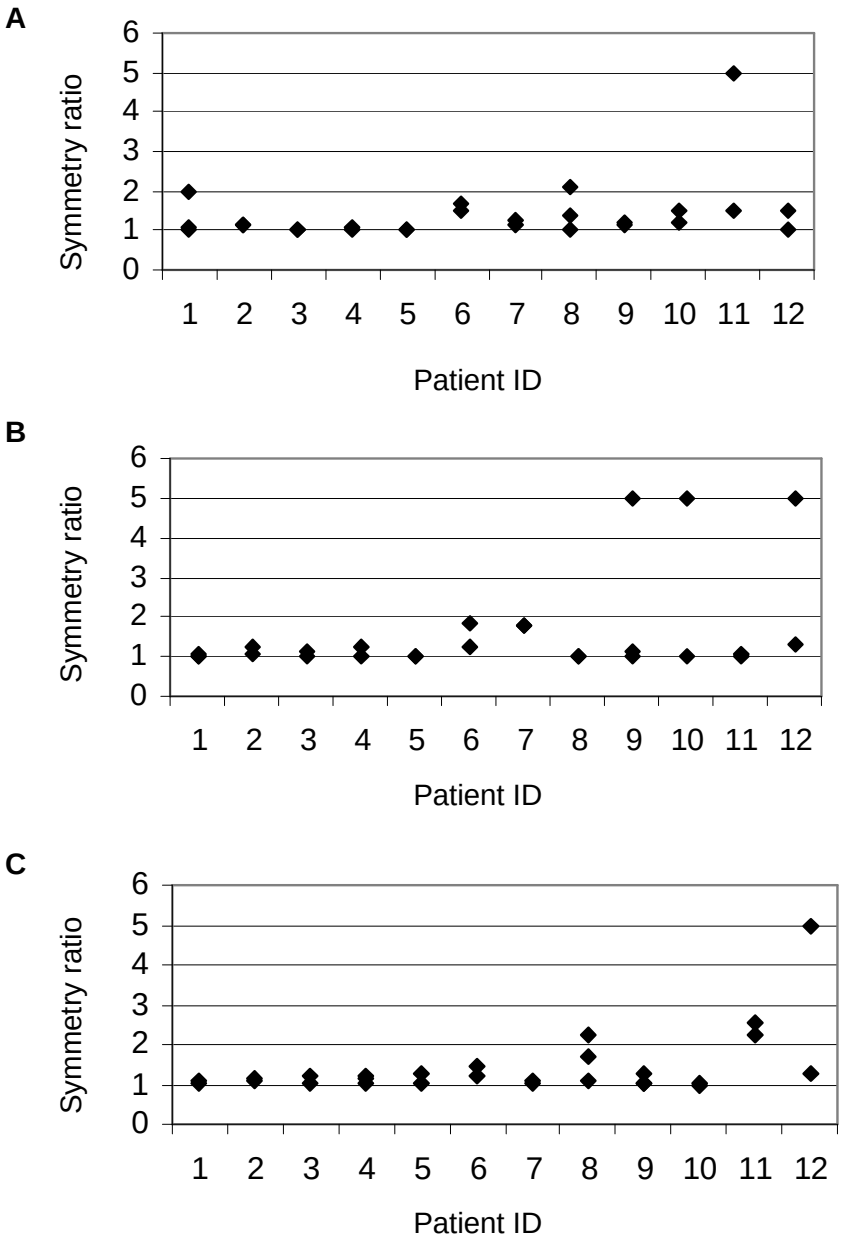


Fig.4.4. Repeated LDF symmetry ratios for baseline sympathetic stimuli done on 2-4 occasions over a duration of 6 months to 2 years in a cohort of CRPS patients.

A = deep breath, **B** = mental stress and **C** = Valsalva manoeuvre.

4.2.2.8. Location of LDF recording probes

There is almost no literature available upon the reliability or reproducibility of LDF recordings from the feet, and from feet compared to the hands. Limb dependency tests are technically more difficult as the patient has to be assessed while lying

supine to avoid gravitational effects on skin perfusion. Pilot work demonstrated that CRPS affected lower limbs often did not acclimatise as expected even after 1 hour at 25℃, remaining cold. Four out of 11 lower limb CRP S patients had flux values from the feet of <150 arbitrary flux units despite prolonged acclimatisation. Therefore, only data from patients with upper limb +/- lower limb involvement recorded from the hands is presented here.

4.2.2.9. LDF recording environment

The autonomic testing was performed in a quiet, temperature and humidity controlled room. There were no pictures or ornamentation in the room to avoid arousal of emotional responses.

4.2.2.10. Use of Laser Doppler flowmetry and electrodermal skin response in this research

Electrodermal skin response and LDF were recorded concurrently from the hands or feet. LDF and ESR readings were recorded from three protocols:
i. responses to graded sympathetic stimuli for assessment of baseline sympathetic function.
ii. responses to optokinetic induced allocentric/egocentric mismatch.
iii. responses to ambiguous stimuli.

4.3. Method

4.3.1. Participants

For full details of inclusion/exclusion criteria, ethical considerations etc, see **Chapter 3**.

4.3.2. Acclimatization

Patients were tested between therapy sessions when rested and their pain was at usual baseline levels. All subjects were asked to refrain from smoking or caffeine for at least 2 hours prior to recording. Subjects were acclimatised for 30 minutes, sitting still in a temperature controlled room maintained at 25 ºC. For recordings taken from

the hands, subjects were seated with the forearms resting at heart level on the arm rests of the chair. CRPS subjects were allocated further acclimatisation time if probe and electrode attachment had altered baseline pain, until this had settled back to baseline levels.

The study did not commence until stable baseline blood flow traces were established, and subsequent stimuli were not administered until a stable baseline was re-obtained.

4.3.3. Electrodermal skin response (ESR)

4.3.3-1. Apparatus

- CED (Cambridge Electronic Design) 2502 skin conductance units x 2
- CED 1902 electrophysiological Response Recording System
- Laptop computer with CED Spike signal data analysis software
- Disposable 'Biotab' electrocardiogram (ECG) electrodes

4.3.3-2. ESR recording:

ESR measurements were made from the palms of the hands or soles of the feet using 1cm^2 disposable 'biotab' ECG electrodes 1 cm apart on the hypothenar eminence of the palms of the hands or arch of the foot. Prior to electrode placement, the skin was prepared with an isopropyl alcohol 'steret' skin cleansing swab and assessed for conditions such as psoriasis, eczema, dermatitis, vitiligo, inflammatory arthritis, or scarring over the region of interest. If present, the electrodes were moved to matching unaffected areas. Recordings were made in silence, with time allocated at the end of each study for qualitative aspects and subject feedback.

4.3.4. Laser Doppler flowmetry (LDF)

4.3.4-1. Apparatus

- Laser Doppler Flowmeter system (Moor Instuments FloLAB server with satellite module, Moor Instruments, U.K.) with a near-infrared laser wavelength 780nm. A bandwidth of 15 kHz and time constant of 0.02s were used.
- Optical probes x 2
- Double-sided adhesive discs for probe attachment

4.3.4-2. LDF recording:

The subject was sat comfortably with the forearms resting horizontally at approximately heart level on the arms of the chair. Probes were attached to the palmar aspect of the middle finger tip of each hand. Prior to probe placement, the skin was prepared with an isopropyl alcohol 'steret' skin cleansing swab and assessed for conditions such as psoriasis, eczema, dermatitis, vitiligo, inflammatory arthritis, or scarring over the region of interest. If present, the probes were moved to a non affected area.

Recordings were made in silence, with time allocated at the end of each study for qualitative aspects and subject feedback. LDF data were recorded on a notebook computer and analysed using CED (Cambridge Electronics Design) signal data processing software.

Baseline mean LDF flux values at rest are optimal between 250 – 550 flux units, and acceptable at not less than 150 flux units. If this had not been achieved after acclimatisation, then another 15 minutes of acclimatisation occurred before repeat baseline readings were taken. If baseline readings were still <150, the study was abandoned.

4.3.5. Testing Protocol: autonomic sympathetic responses to graded sympathetic stimuli

A continuous LDF and ESR recording was made during the following series of sympathetic stimuli. Each stimulus was followed by a resting period of 1 – 5 minutes to allow the trace to return to baseline.

Condition/Stimulus	[$]Stimulus duration
Relaxed (eyes closed)	1 min
Relaxed (eyes open)	1 min
Deep breath	N/A
Dependent right arm	1 min
Bring right arm back	1 min
Dependent left arm	1 min
Bring left arm back	1 min
*Congruent movements	1 min
*Incongruent movements	1 min
#Mental stress	1 min
Valsalva	1 min

*Congruent and incongruent movements are the same as those used for the testing of optokinetic induced allocentric/egocentric vulnerability but with no mirror or whiteboard present (see **Chapter 5**). This was done on a cohort of 10 CRPS and 10 control patients, which showed no significant vasoconstrictor response. It was therefore dropped from further studies.

$Patients were asked to continue for as long as they could manage without distress, so in some instances (especially with CRPS patients) the stimulus duration was less.

#Mental stress comprised a mental arithmetic task of serial subtractions of 7 from 100, with answers being given aloud. If this was completed quickly and easily, subjects were asked to verbalise the alphabet backwards complimented if necessary by a spelling task.

The investigator explained and demonstrated a modified Valsalva manoeuvre, and asked the subject to replicate this, and practice another few times if necessary.

4.3.6. Baseline Autonomic function: Outcome measures LDF/ESR.

To summarise from above, the following outcome measures were used:

4.3.6-1. Quantitative

- Mean percentage change from baseline skin blood flow (Δ%bbf) in response to a stimulus as follows: Δ%bbf = (baseline mean – minimum) / baseline mean x 100
- The symmetry ratio (SR) of the magnitude of vasomotor responses between the limbs was calculated as follows: Δ%bbf limb A / Δ%bbf limb B, where A was the larger of the two responses.

4.3.6-2. Qualitative

- For LDF: Responses to stimuli were classified as
    - i. homologous response if there were bilateral sympathetic vasoconstrictor responses
    - ii. asymmetric response if there was vasoconstriction in one limb but no response or *vasodilation in the other limb.

    - iii. absent

* Vasodilation is a descriptive term referring to an increase in skin blood flow in response to a stimulus; it is not used as a mechanistic term (ie. it does not imply activation of vasoconstrictor / vasodilatory nerves).

- For ESR: Responses were classified as
    - i. 'normal' if there were bilateral symmetric responses
    - ii. 'abnormal' if responses were present but either unilateral, or abnormal non-sinusoidal waveform
    - iii. 'absent'

4.3.6-3. Overall composite autonomic function (ANS) score

This comprises the presence or absence of a sympathetic response on laser Doppler flowmetry and galvanic skin response, in each upper limb to each of the 5 sympathetic autonomic stimuli (deep breath, Valsalva manoeuvre, limb dependency (ipsilateral and contralateral vasoconstrictor responses) and the mental stress task). The maximum possible score was 20.

4.3.7. Data analysis

4.3.7.1. Sample size

CRPS is considered to be a rare diagnosis and the literature is sparse. Papers are often based upon small numbers using different diagnostic criteria. The methodology of **Chapter 5** is based upon McCabe et al 2005, which used 41 healthy volunteers.

A semi-purposive sampling strategy was used, and the sample size was based upon the number of subjects fulfilling inclusion criteria available within the data collection period, aiming for at least 40 subjects in each cohort.

4.3.7.2. Statistical analysis

Demographic data were analysed using descriptive statistics. Cumulative frequency histograms of the mean percentage change from baseline blood flow (Δ%bbf) data and symmetry ratio (SR) data demonstrated a negative skew. Therefore data are presented as median + interquartile range (IQR). Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) v.16 software. Non-parametric statistics (Mann-Whitney *U*-test and Kruskal-Wallis test) were used. Symmetry ratio data showed marked homogeneity of variance particularly in the

CRPS cohort, with grouping of extreme high and low values. For comparison of data across cohorts, the Siegel-Tukey test (a non-parametric sum of ranks procedure for relative spread in unpaired samples) was used.

4.4. Results

The total number of CRPS patients recruited was 56 (overall cohort). Forty healthy controls, 40 patients with osteoarthritis and 40 patients with rheumatoid arthritis were recruited for comparison cohorts. Most of the CRPS had severe baseline pain and many patients had severe allodynia and body dysmorphia. Some were unable to participate in all arms of the research due to fatigue and pain. Where comparisons are made to the overall CRPS cohort, the numbers for this study are as follows:

- 44/56 has baseline QST.
- 54/56 had baseline autonomic function testing (overall CRPS cohort);
- 31/54 had upper limb (UL) involvement. One subject had a previous sympathectomy and was therefore excluded from analysis. Therefore for the UL cohort, n = 30. Autonomic function testing data for UL affected CRPS patients is presented (See **4.2.2.8. Location of LDF recording probes**).
- 40 healthy controls (HC) had baseline autonomic function testing (overall HC cohort). From the overall HC cohort, 30 were matched for gender and age (to within 10 years) to the UL-CRPS cohort, forming the 'matched HC' cohort.

Please also note:

- Comparison of QST data for the UL-CRPS cohort (n = 30) with the overall-CRPS cohort (n = 54) is given in section **4.4.3.9.**
- For healthy controls, the autonomic function testing data presented is taken from the overall HC cohort, and compared to the other cohorts.
- In a subgroup analysis, autonomic data from the matched HC cohort is compared to the UL cohort (**4.4.3.5.**). The matching reduces potential bias from gender and age differences. Comparison of the matched and unmatched HC data (**4.4.3.1C.**) provides an indication of potential confounding effects from these factors.

4.4.1. Demographic data

Demographic data is presented below in **Table 4.2**. A schematic flow chart of the location of the CRPS among the CRPS patient cohort is given in **Fig.4.5**.

None of the healthy controls had any baseline pain or were on any analgesic medication. The male:female ratio was similar among controls, osteoarthritis (OA) and rheumatoid arthritis (RA) patients. Among CRPS patients, there was a greater female preponderance.

The mean disease duration for OA was 15 years, and for RA 17 years. For CRPS, the mean disease duration of the overall cohort was 5.2 years and for the UL cohort was 5.7 years.

Table 4.2. Demographic data for CRPS, osteoarthritis and rheumatoid arthritis patients and for healthy controls.

	Healthy controls N = 40	CRPS N = 56	Osteoarthritis N = 40	Rheumatoid arthritis N = 40
Age (years)	38	43	61	57
range	22-64	20-71	42-75	27-77
Disease duration (years)	~	5.2	15	17
range	~	0.5-18	2-40	0.5-40
Gender: male	12 (30%)	10 (18%)	10 (25%)	10 (25%)
Genger: female	28 (70%)	46 (82%)	30 (75%)	30 (75%)
Hand dominance: right	35 (87.5%)	44 (79%)	34 (85%)	34 (85%)
Hand dominance: left	4 (10%)	10 (18%)	5 (12.5%)	6 (15%)
Hand dominance: ambidextrous	1 (2.5%)	2 (3%)	1 (2.5%)	0
Smoker	2 (5%)	16 (28%)	1 (2.5%)	5 (12.5%)
Baseline pain level				
Nil	40 (100%)	1 (2%)	8 (20%)	8 (20%)
Mild	~	3 (5%)	22 (55%)	24 (44%)
Moderate	~	38 (69%)	9 (22.5%)	8 (20%)
Severe	~	13 (24%)	1 (2.5%)	0
Medication				
No analgesics	40 (100%)	3 (5%)	2 (5%)	2 (5%)
Neuromodulatory	0	36 (64%)	8 (20%)	5 (12.5%)
Non-opiate +/- neuromodulatory	0	14 (25%)	19 (47.5%)	23 (57.5%)
Opiate	0	38 (68%)	19 (47.5%)	16 (40%)
Neuromulatory + opiate	0	26 (46%)	6 (15%)	3 (7.5%)
Neuromodulatory + opiate + non-opiate	0	17 (30%)	5 (12.5%)	1 (2.5%)

Age & disease duration = group means; all other figures represent the actual numbers in the group, with the percentage of the group that it represents bracketed.

Full demographic data for the overall CRPS cohort is given below in **Table 4.3**.

Table 4.3. Demographic data for overall CRPS patient cohort

Patient ID	Gender	Age (yrs)	Handed	CRPS loc'n	CRPS dur'n (yrs)	Baseline pain
1*	F	38	R	LA	0.5	Moderate
2*	F	34	R	LA	4	Moderate
3	M	46	R	RL,LL	7	Moderate
4	F	39	L	LL,RL	17	Moderate
5*	M	55	R	LA	2	Moderate
6	F	49	R	RL	4	Moderate
# 7	F	33	R	LA	17	Moderate
8*	F	55	L	LA LL	8	Moderate
9*	F	54	R	RA	15	Moderate
10*	F	46	R	LA	0.7	Moderate
11*	F	46	L	LA	10	Severe
12*	F	35	L	LA	1	Moderate
13*	M	50	R	RA	11	Moderate
14	F	56	R	LL	3.5	Moderate
15*	F	62	R	LA	10	Moderate
16*	F	59	R	RA	18	Moderate
17*	F	43	R	RA	4	Moderate
18	F	29	R	LL	0.7	Moderate
19*	M	39	L	RA	4	Severe
20	M	44	R	LL	10	Moderate
21*	F	47	R/L	LA,LL	2	Moderate
22*	F	42	R	RA RL	8	Mild
23	F	36	R	RL	2	Severe
24	F	50	R	LL	2	Severe
25*	F	55	R	LA	0.75	Moderate
26	F	46	L	RL	3	Severe
27*	F	36	R	RA	4	Mild
28	M	52	L	LL	7	Severe
29*	F	22	R	RA	1.5	Moderate
30	M	56	R	RA	2	Severe
31*	F	44	R	RA	1	Moderate
32	F	47	R	RL	2	Moderate
33	F	28	R	LL	3	Moderate
34	F	58	R	LL	1	Severe
35*	F	39	R	LA,RL	16	Severe
36*	F	66	R	RA	0.7	Moderate
37	M	20	R	LL	2.5	Moderate
38*	F	22	R	RA,RL	2.5	Moderate
39*	F	28	L	LA,LL	8	Severe
40*	F	42	R	LL RL LA	8	Moderate
41*	F	63	R	RA	1	Moderate
42	F	43	R/L	LL	1	Severe
43	F	27	L	RL	8	Moderate
44	F	33	R	LL	10	Moderate
45	F	21	R	LL	6	Severe
46*	F	50	L	LA	3	Mild
47*	M	46	R	LA	7	Severe
48*	F	33	R	RA,RL	3	Moderate
49*	F	40	R	RA	4	Moderate
50	F	39	R	LL	6	Moderate
51	F	41	R	RL	3	Moderate
52	M	24	R	RL,LL	6	Moderate
53	F	42	R	RL	2	Moderate
54*	F	71	R	LA	1	Nil
55	F	34	R	RL	5	Moderate
56	F	30	R	RA	2	Severe

Table 4.3. Demographic data for the overall CRPS patient cohort.

Age and CRPS duration are given in years.

F = female, M = male, R = right, L = left, RA = right arm, LA = left arm, RL = right leg, LL = left leg, dur'n = duration.

☐ = QST performed * = patient in the upper limb (UL) CRPS cohort

4.4.1.2. Medication

The term 'neuromodulatory' medication is used as a pharmacological group description, referring to anticonvulsant or antidepressant medications used in neuropathic pain. Examples include anticonvulsants such as gabapentin, pregabalin, tricyclic antidepressants (eg. amitriptyline, sertraline), serotonin specific reuptake inhibitors (eg. fluoxetine), and serotonin / noradrenaline reuptake inhibitors (eg. venlafaxine). The term 'opiate' medications refers to weak opioids (eg. codeine, tramadol) and strong opioids (eg. morphine, fentanyl, oxycodone). Both 'neuromodulatory' medications and opiate medications have central effects. 'Non-opiates' incudes paracetamol and non-steroidal anti-inflammatory drugs (NSAID's).

When medication use was compared, more CRPS patients were using neuromodulatory (64%) and opiate (68%) medication compared to OA (20%, 47.5%) and RA (12.5%, 40%) respectively. Among CRPS patients, 30% were on a combination of non-opiate, opiate and neuromodulatory medications compared to 12.5% of OA and 2.5% of RA patients.

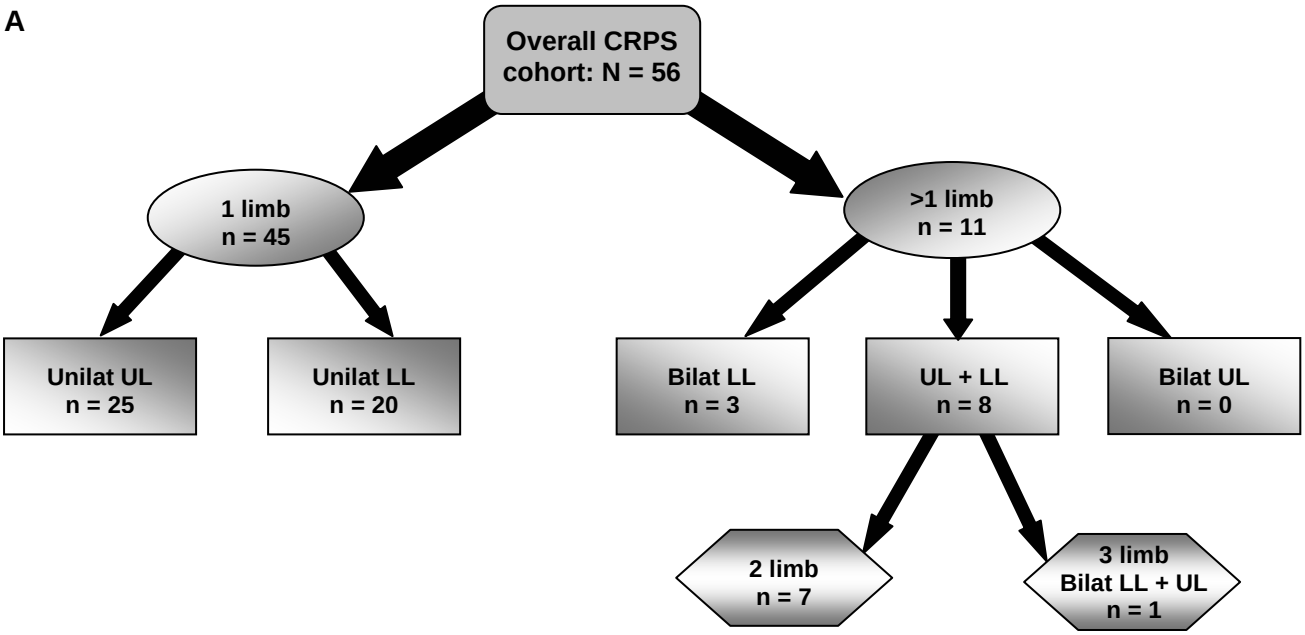
4.4.1.3. Location of CRPS

Comparing location of CRPS (overall cohort, n = 56): 45 had one limb involvement and 11 had >1 limb involvement. 25 had unilateral upper limb, none had bilateral upper limb, 20 had unilateral lower limb, 3 had bilateral lower limb CRPS and 8 had upper and lower limb CRPS (7 had 2 limb CRPS; one had 3 limb involvement ie. bilateral lower limb and unilateral upper limb). Of the 10 patients with two limb involvement, 6 had ipsilateral or contralateral disease and 1 had diagonal disease.

For the UL CRPS cohort (n = 30), 22 had unilateral upper limb CRPS and 8 had >1 limb involvement. See **Table 4.3** and **Fig.4.5**.

Fig.4.5.

A



B

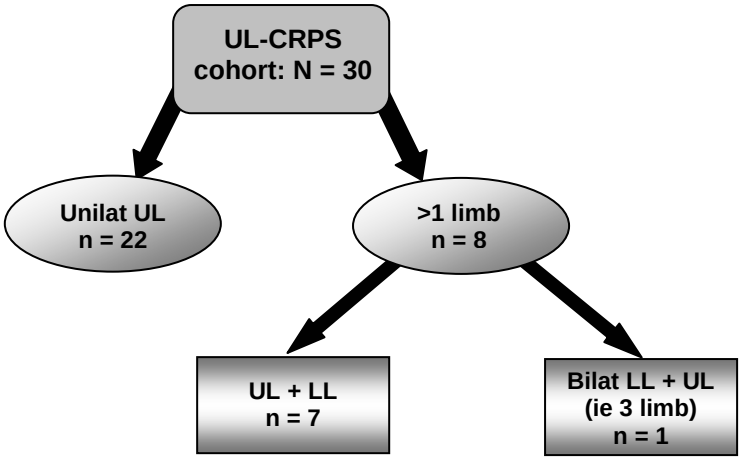


Fig.4.5. Schematic flow chart of CRPS location demographics. **A** shows the overall CRPS cohort, and **B** the upper limb CRPS cohort.

UL = upper limb, LL = lower limb, unilat = unilateral, bilat = bilateral

4.4.2. Quantitative sensory testing

4.4.2.1. Healthy controls

None of the 40 healthy control subjects demonstrated static or dynamic mechanical allodynia. The tactile detection threshold and two point discrimination parameters were uniformly consistent and therefore 25/40 controls underwent QST. The mean (median) tactile detection threshold was 0.039 (0.04) g and mean two point discrimination 2.4 (2) mm. See **Table 4.4**.

Table 4.4. Results of quantitative sensory testing.

A. QST findings in CRPS, healthy controls, osteoarthritis (OA) and rheumatoid arthritis (RA) patients.

	CRPS (n=44)	HC (n=25)	OA (n=40)	RA (n=40)
Tactile allodynia: mean %BSA	14.3	0	1.1	1.4
%BSA range	0 - 83	~	0 - 2	0 - 2
2 pt D (SE)	2.3 (0.18)	2.4 (0.09)	2.7 (0.08)	2.6 (0.11)
Tactile threshold (mean SWF)	0.231	0.039	0.043	0.042
SWF range	0.008 - 4	0.02 - 0.04	0.02 - 0.07	0.02 - 0.07
Median filament rank	4	3	3	3

%BSA = % of body surface area affected, 2 pt D = mean two point discrimination (mm), SE = standard error, SWF = Semmes-Weinstein filament (g).

B. Ranking order and target force of the Semmes Weinstein filaments.

Semmes Weinstein Filaments			
Filament rank	Target force (g)	Filament rank	Target force (g)
1	0.008	11	4
2	0.02	12	6
3	0.04	13	8
4	0.07	14	10
5	0.16	15	15
6	0.4	16	26
7	0.6	17	60
8	1	18	100
9	1.4	19	180
10	2	20	300

Target force is given in grams.

4.4.2.2. Osteoarthritis and rheumatoid arthritis

All of the OA (n = 40) and RA (n = 40) subjects had QST performed. The mean (median) tactile detection threshold for OA was 0.043 (0.04) g and for RA was 0.042 (0.04) g. The mean two point discrimination distance for OA was 2.7 (3) mm and for RA was 2.6 (2) mm. Pressure allodynia was present in 60% of OA and 52.5% of RA patients. The mean (median) percentage of body surface area (BSA) affected by pressure allodynia was 4.8 (3.2) %BSA in OA with a range of 0.1 – 25%, and was 2.2 (1.7) %BSA in RA with a range of 0.5 – 7%. Three OA patients had tactile allodynia of 0.3, 1 and 2% BSA and 4 RA patients of 0.3, 0.3, 2 and 3% BSA. See **Table 4.4**.

4.4.2.3. CRPS

Forty-five CRPS patients had QST performed. The mean disease duration for the QST cohort was 5.3 years. CRPS patients displayed an overall lower (ie. hyperaesthetic) tactile threshold compared to the other cohorts, with a mean (median) threshold of 0.023 (0.07) g. There was a wide range from 0.008 – 4g, with 47% being hyperaesthetic and 24% hypoaesthetic on the affected compared to the unaffected limb. On the affected limb, 12 (27%) could detect the normally undetectable finest Semmes-Weinstein filament (0.008g), and for all except one it was noxious. Among CRPS patients, 73% had tactile and pressure allodynia coexisting together (**Table 4.4**). The mean (median) %BSA was 14 (7.2) %, with a range of 1-83%. The area of allodynia extended beyond one limb in 36% (16).

There was a moderate correlation between the duration of CRPS and %BSA ie. longer duration, larger %BSA (r = 0.31, $p<0.05$, two-tailed). Only 10 CRPS patients had two point discrimination tested, and it was similar to the other cohorts (mean 2.3, median 2 mm).

Several unusual sensory patterns were discovered in CRPS affected areas. With eyes closed:

- Nineteen (42%) demonstrated referral of sensation (tactile stimulation felt concurrently in the area stimulated, and in another discrete area).
- Eight (18%) subjects had allochiria (unilateral tactile stimulation perceived only in the analogous location on the opposite limb).
- Three (7%) showed sensory extinction (concurrent bilateral tactile stimulation perceived only in one limb).
- Four (9%) displayed tactile dysynchiria (unilateral non-noxious tactile stimulation is perceived bilaterally as noxious. The area of sensory impairment extended beyond the affected limb in 16 (36%).

4.4.2.4. Comparison of cohorts

There was a significant difference in the mean %BSA affected by tactile allodynia between the CRPS patients compared to controls, OA and RA (Kruskal-Wallis, $p<0.001$, post hoc Mann-Whitney *U*-test with Bonferroni correction). See **Table 4.4**. There was no statistically significant difference for the other parameters.

4.4.3. Baseline sympathetic autonomic function

4.4.3.1A. Healthy controls (overall cohort n = 40)

All 40 subjects demonstrated good baseline skin blood flow. The group median flow in the right upper limb was 404 AFU and in the left 434 AFU. The subjects had homologous bilateral symmetric LDF responses to all sympathetic stimuli. Nine subjects had absent ESR responses in one or both limbs to limb dependency; there were normal bilateral symmetric ESR responses to all other sympathetic stimuli.

The median Δ%bbf (IQR) for deep breath (DB), mental stress (MS) and the Valsalva manoeuvre (V) were 77 (28), 66 (49) and 84 (18) respectively. The median SR (IQR) for DB, MS and V were 1.1 (0.34), 1.13 (0.72) and 1.09 (0.19)The mean (median) composite ANS score was 19.2 (20). See**Table 4.5**.

4.4.3.1B. Matched healthy controls (n = 30)

The group median flow in the right upper limb was 417 AFU and in the left 445 AFU. Seven subjects had absent ESR responses in one or both limbs to limb dependency; there were normal bilateral symmetric ESR responses to all other sympathetic stimuli.

The median Δ%bbf (IQR) for deep breath (DB), mental stress (MS) and the Valsalva manoeuvre (V) were 82 (20), 77 (25) and 88 (13) respectively. The median SR (IQR) for DB, MS and V were 1.05 (0.14), 1.1 (0.21) and 1.05 (0.07). The mean (median) composite ANS score was 19.2 (20). See**Table 4.5**.

4.4.3.1C. Comparison of overall and matched control cohorts

Comparison of the qualitative response trace pattern frequencies and quantitative autonomic response data does not show any significant differences between the overall and matched cohorts.

4.4.3.2. Osteoarthritis and rheumatoid arthritis

All subjects demonstrated good baseline skin blood flow. The group median flow in the right upper limb was 492 AFU and in the left 470 AFU in patients with osteoarthritis (OA), and 438 AFU right upper limb and 425 AFU left upper limb in patients with rheumatoid arthritis (RA).

Among OA patients, 9 (17.5%) had absent LDF responses to one or more stimuli; 1 was of an asymmetric pattern (to mental stress). For RA patients, 13 (32.5%) had absent LDF responses; none were of an asymmetric pattern. All other LDF responses to the remaining sympathetic stimuli among the OA and RA groups were present and normal.

Comparing ESR responses, 23 OA patients had absent responses but only 1 OA patient had an abnormal ESR form. Nineteen RA patients had absent responses; 2 RA patients had absent ESR responses throughout. All other ESR responses to the remaining sympathetic stimuli among the OA and RA groups were present and normal.

The mean (median) composite ANS score was 17.7 (19) for OA and 17.4 (18.5) for RA. Data for Δ%bbf and SR to stimuli are given in **Table 4.5B**.

4.4.3.3. CRPS (UL cohort, n = 30)

All subjects demonstrated good baseline skin blood flow. The group median flow of the affected limb (AL) was 390 AFU, and in the unaffected limb (UL) 423 AFU. CRPS subjects could be divided into 'warm' (overall baseline mean blood flow of >250 arbitrary flux units) and 'cold' (overall baseline mean blood flow of 150 - 250 arbitrary flux units) types. Twenty four patients had 'warm' CRPS, and six subjects had 'cold'.

In the CRPS cohort, 14 (43%) had absent LDF responses; 11 patients had asymmetric responses – 5 of these were to >1 sympathetic stimulus. The mean (median) composite ANS score was 15.4 (16). See **Table 4.5A**.

Two patients with CRPS did not demonstrate an LDF response to deep breath (one bilaterally, one unilaterally in the unaffected limb (UL). Six had no response to mental stress (2 bilaterally and 4 unilaterally in the UL), and one to the Valsalva manoeuvre in the UL. Four demonstrated unilateral vasodilation LDF responses: all four to limb dependency, 2 to MS (1 in the affected limb (AL), 1 in the UL) and 1 to Valsalva in the UL. One subject had unilateral vasodilation LDF responses to all stimuli in the UL.

Thirteen (47%) had absent ESR responses to one or more sympathetic stimuli, with 5 (17%) having abnormalities of ESR trace form. Data for Δ%bbf and SR to stimuli are given in **Table 4.5B**.

Table 4.5. Summary of baseline autonomic testing function parameters.

A. Composite autonomic score: numbers of subjects with abnormal results (score <20 overall) with breakdown for presence/absence of response or qualitatively abnormal trace.

	ANSscore<20	ESR<10	ESR abnormal	LDF<10	LDF asym
HC (N=40)	9	9	0	0	0
OA (N=40)	23	23	1	7	1
RA (N=40)	22	19	0	13	0
CRPS (N=30)	21	13	5	14	5

ESR = electrodermal skin response, LDF = laser Doppler flowmetry response

ESR<10 = absent ESR response to ≥1 stimuli in protocol, LDF<10 = absent LDF response to ≥1 stimuli in protocol, ESR abnormal = qualitative trace abnormality present, LDF asym = qualitatively asymmetric trace.

B. Quantitative data (medians and interquartile range, IQR) for baseline sympathetic autonomic testing.

	Cohorts							
Sympathetic stimulus	CRPS UL (n = 30)		Healthy controls (n = 40)		Osteoarthritis (n = 40)		Rheumatoid arthritis (n = 40)	
	Δ%BBF (IQR)	SR (IQR)	Δ%BBF (IQR)	SR (IQR)	Δ%BBF (IQR)	SR (IQR)	Δ%BBF (IQR)	SR (IQR)
Deep breath	77 (28)	1.1 (0.34)	86 (16)	1.05 (0.1)	79 (36)	1.07 (.26)	70 (26)	1.07 (0.19)
Valsalva	84 (18)	1.09 (0.19)	89 (11)	1.05 (0.07)	76 (25)	1.06 (0.15)	79 (30)	1.05 (0.16)
Mental stress	66 (49)	1.13 (0.72)	80 (27)	1.09 (0.17)	59 (39)	1.14 (0.39)	54 (31)	1.19 (0.44)
ANS score / 20 : mean	15.4		19.2		17.7		17.4	
: median	16		20		19		18.5	

	Cohort	
Sympathetic stimulus	Age & gender matched HC (n=30)	
	Δ%BBF (IQR)	SR (IQR)
Deep breath	82 (20)	1.05 (0.14)
Valsalva	88 (13)	1.05 (0.07)
Mental stress	77 (25)	1.1 (0.21)
ANS score / 20 : mean	19.2	
: median	20	

HC = healthy controls

Δ%BBF = group median value for mean percentage change from baseline blood flow, SR = symmetry ratio, ANS score / 20 = composite ANS score (mean & median values displayed).

4.4.3.4. Comparison of all cohorts

Comparing healthy controls with OA, RA and CRPS cohorts, there was a significant difference for the ANS composite score (Kruskal-Wallis, p<0.001, post hoc Mann-Whitney *U*-test with Bonferroni correction)(**Fig.4.6**).

Comparing Δ%bbf of controls for DB, MS and V with OA, RA and CRPS cohorts (**Fig.4.7**), there was a significant difference for MS and V between HC and OA and RA (Kruskall-Wallis, p<0.001, post hoc Mann-Whitney *U*-test with Bonferroni correction). Comparing the SR of controls for DB, MS and V with OA, RA and CRPS cohorts (Siegel-Tukey test; see **4.5.3.**) while there was a difference in variability between the limbs, it was not statistically significant difference. (**Fig.4.8**).

Fig.4.6.

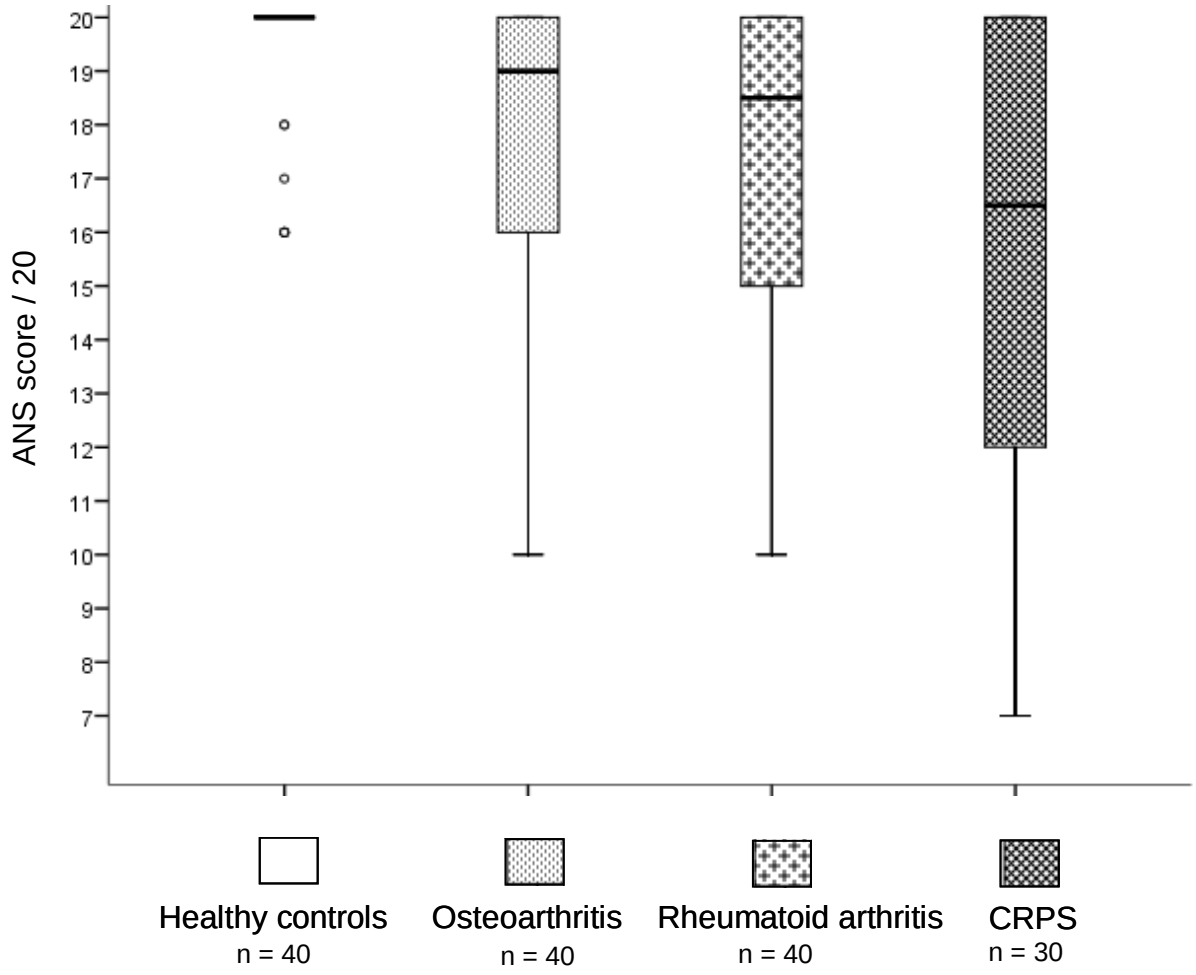


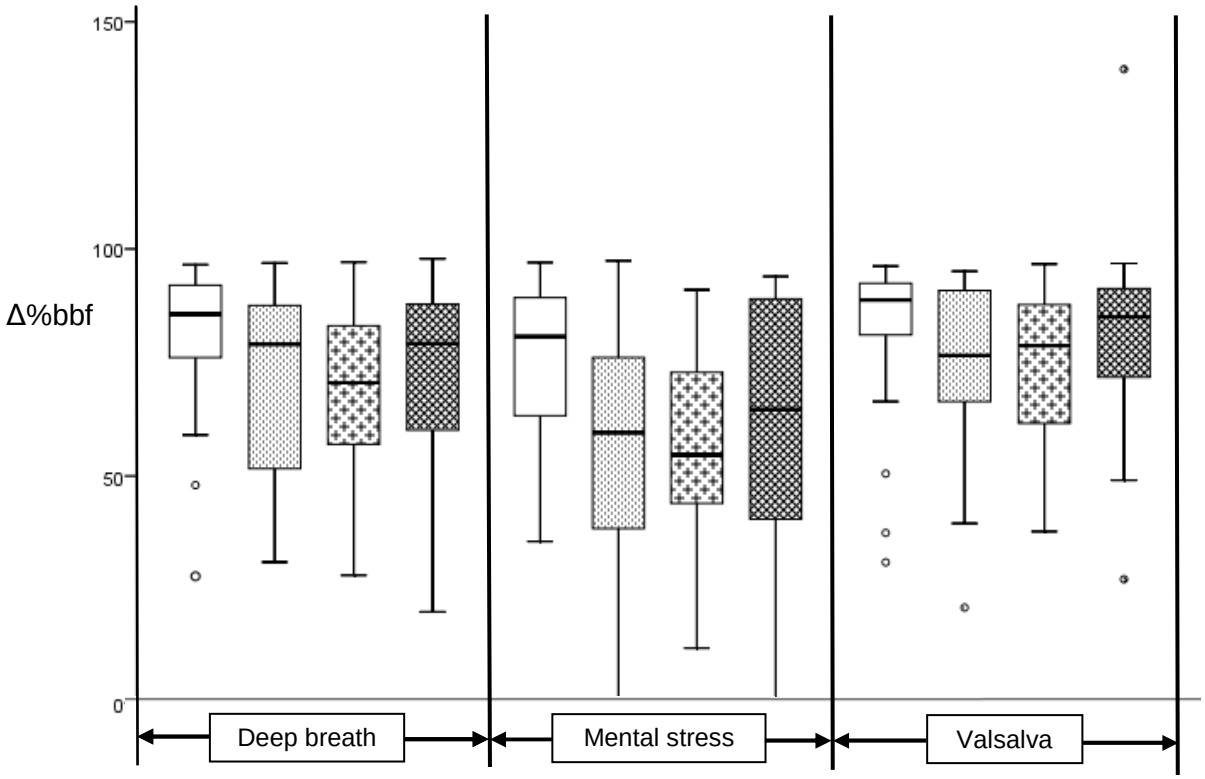
Fig.4.6. Box plots showing the composite autonomic (ANS) score for healthy controls (overall HC cohort, n = 40), osteoarthritis, rheumatoid arthritis and CRPS patients.

4.4.3.5. Comparison of CRPS with matched healthy controls

When the matched HC cohort were compared to the CRPS cohort, there was still a significant difference for the ANS composite score (Mann-Whitney $p<0.001$, $U = 211$, $Z = -4.121$).

When matched controls were compared to the CRPS patients (**Fig.4.8**), the SR of blood flow responses to DB was significantly larger in CRPS patients compared to the control subjects (median + IQR: 1.1 [1.04 - 1.38] vs 1.05 [1.02 - 1.16], $p<0.05$ Mann-Whitney *U*-test) but not for MS or V ($p>0.05$, Mann-Whitney *U*-test).

Fig.4.7.



Healthy controls (n = 40)

Osteoarthritis (n = 40)

Rheumatoid arthritis (n = 40)

Complex Regional Pain Syndrome (n = 30)

Fig.4.7. Mean percentage change from baseline blood flow (Δ%bbf) in response to sympathetic stimuli for healthy controls (overall cohort), osteoarthritis, rheumatoid arthritis and CRPS patients.

Box plots comparing mean percentage change from baseline blood flow (Δ%bbf) between healthy controls (overall cohort), osteoarthritis, rheumatoid arthritis and CRPS patients for deep breath, mental stress and Valsalva manoeuvre.
AFU = arbitrary flux units

Fig.4.8.

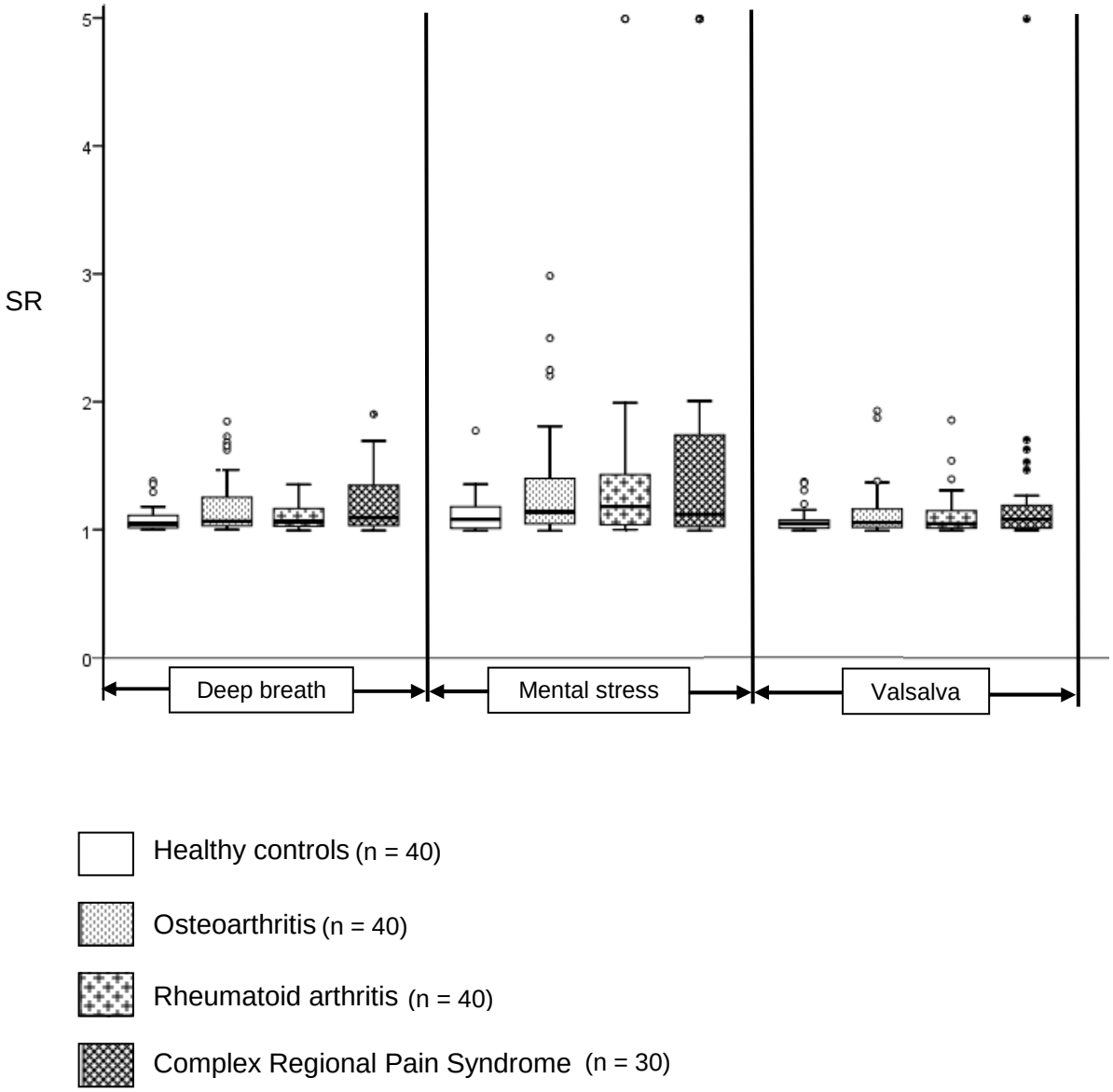


Fig.4.8. Symmetry ratio (SR) of healthy controls (overall cohort), osteoarthritis, rheumatoid arthritis and CRPS patients in response to sympathetic stimuli.

Box plots showing the median, IQR and range for deep breath, mental stress and Valsalva manoeuvre. There is (non-significant) increased variability comparing the SR of controls for DB, MS and V with OA, RA and CRPS cohorts.

Fig.4.9.

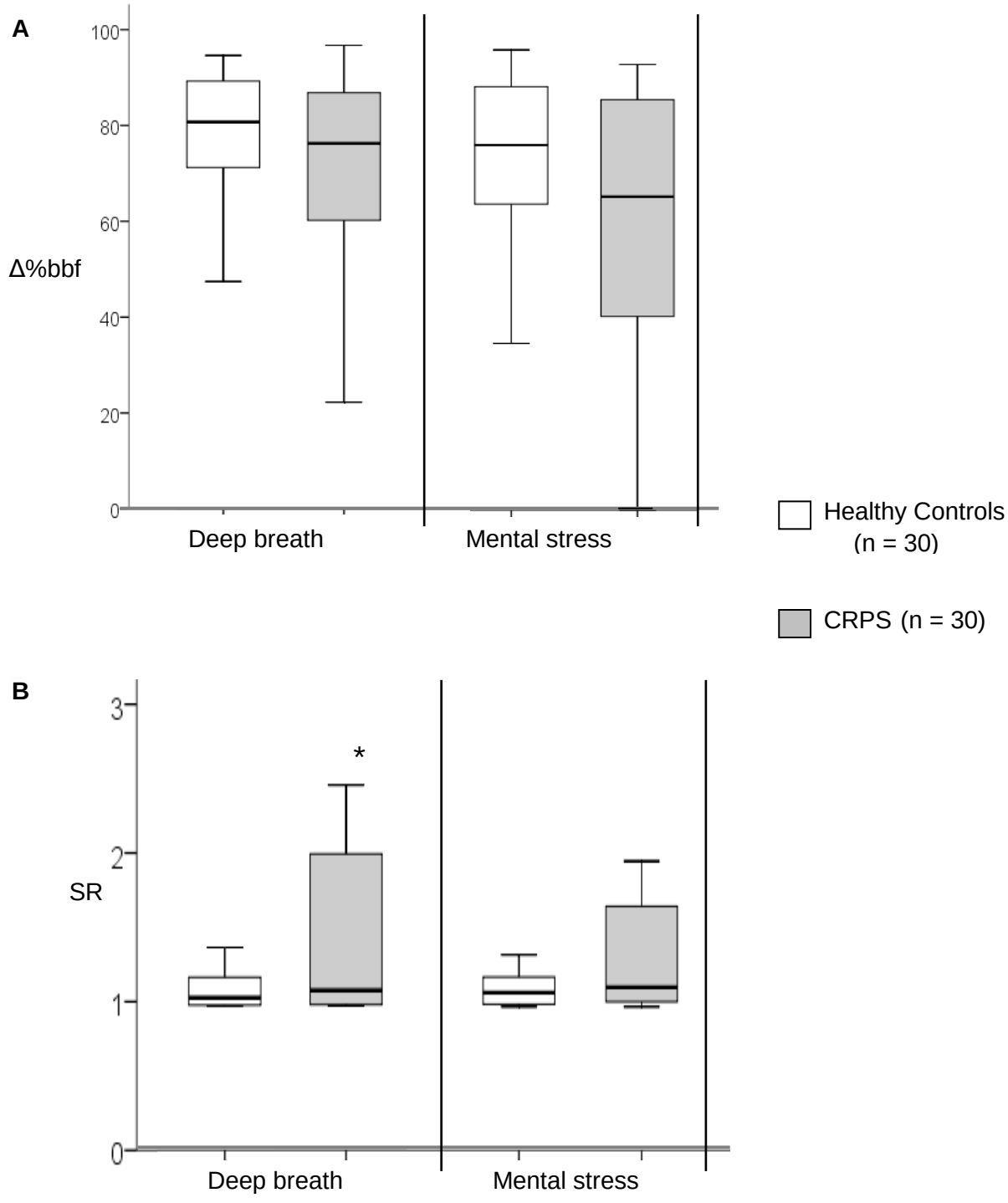


Fig.4.9. Mean percentage change in baseline blood flow (Δ%bbf)(**A**) and symmetry ratio (SR)(**B**) in healthy controls (age & gender matched cohort, n = 30) and CRPS subjects for deep breath and mental stress task.

Box plots showing the median, IQR and range are illustrated. There is a statistically significant greater SR for a deep breath in CRPS subjects compared to healthy controls, demonstrating greater variability in the magnitude of response between the limbs (*, $p<0.05$ Mann Whitney U-test).

4.4.3.6. Comparison of unilateral upper limb CRPS and CRPS involvement of >1 limb.

Comparing UL only (n = 22) with >1 limb involvement (n = 8), there was no statistically significant difference (Mann-Whitney *U*-test) between Δ%bbf and SR for any baseline autonomic function parameters. The characteristics of baseline pain were not markedly different either.

4.4.3.7. Comparison of 'cold' and 'warm' CRPS.

The mean disease duration of cold CRPS was 2.6 years. Comparing the 'cold' and 'warm' groups, there was no statistically significant difference (Mann-Whitney *U*-test) between Δ%bbf and SR for any baseline autonomic function parameters.

4.4.3.8. Comparison of QST and baseline sympathetic autonomic function.

Comparing the composite ANS score across the cohorts with %BSA, there was a low to moderate negative correlation (Spearman's rho = -0.256, $p<0.01$) (ie. higher %BSA, more baseline autonomic abnormality).

4.4.3.9. Comparison of UL-CRPS cohort (n = 30) with overall CRPS cohort (n = 44).

Comparing UL and overall cohort QST data, the mean (median) tactile thresholds were 0.103 (0.055)g / 0.023 (0.07) g respectively. Comparing %BSA, it was 15.8 (9.5)% / 14 (7.2)% respectively.

4.5. Discussion

4.5.1. Epidemiology

Epidemiological studies demonstrate that there is a female preponderance in CRPS of between 3 - 4:1 (de Mos et al., 2007;Sandroni et al., 2003). Data from this cohort is similar with a male:female ratio of 1:4.6. Of patients with two limb CRPS with an upper and a lower limb involved, the majority (6/7) had ipsilateral or contralateral disease. This is consistent with previous epidemiological research of the pattern of CRPS spread (van Rijn et al., 2011;Veldman and Goris, 1996) showing that diagonal spread is unusual and often trauma related.

4.5.2. Quantitative sensory testing (QST)

QST demonstrated that none of the healthy controls had allodynia, consistent with hypothesis 1. Patients with osteoarthritis, rheumatoid arthritis and CRPS were shown to have allodynia consistent with hypothesis 2. In OA and RA, tactile allodynia was unusual and confined to small areas while pressure allodynia was more common and involved slightly larger areas (mean %BSA of 4.8% and 2.2% respectively). In CRPS, tactile and pressure allodynia coexisted together, in larger areas (mean %BSA of 14%).

Several unusual sensory patterns were noted in CRPS patients including referred sensations, allochiria, tactile dysynchiria and sensory extinction. For a full review, see discussion of **Chapter 7**.

Lower pain thresholds to pressure algometry compared to healthy controls have been described in OA (O'Driscoll and Jayson, 1974) and RA (Gerecz-Simon et al., 1989;Huskisson and Hart, 1972). Kosek et al described statistically (parametric) significant pressure allodynia in OA hip patients compared to age and sex matched healthy controls, with no difference between the groups for tactile thresholds (Kosek and Ordeberg, 2000). The mean duration of OA was 7 yrs, which is half the duration of this cohort. No tactile allodynia was noted. Another paper from this group examined QST parameters in age and sex-matched healthy controls and RA and found statistically (parametric) significant pressure allodynia over inflamed joints and additionally over a non-inflamed area in patients with > 5 years duration of disease, but no tactile allodynia (Leffler et al., 2002). Compared to age and sex-matched healthy controls, significant tactile hypoaesthesia was noted. In comparison, my data demonstrates a non-significant trend towards higher tactile thresholds and hypoaesthesia in OA and RA compared to healthy controls. However, these cohorts were not age and sex-matched and parametric statistical analysis was not used, which may account for the apparent differences.

Studies utilising QST techniques in CRPS have shown pain at rest (Birklein et al., 2000), pressure hyperalgesia (Birklein et al., 2000;Vaneker et al., 2005) and mechanical allodynia (Rommel et al., 1999;Rommel et al., 2004) in the affected limb in differing combinations in different patients. Changes in warm and cold thresholds (Birklein et al., 2000;Huge et al., 2008;Huge et al., 2011))(Rommel et al., 2004) and sensory thresholds (Eberle et al., 2009);(Huge et al., 2011))(Rommel et al., 1999) have been noted. Similar findings of changes in warm and cold thresholds with cold allodynia and mechanical allodynia have been reported in children with CRPS (Sethna et al., 2007). Rommel et al (Rommel et al., 1999) described a subgroup

(33%) of CRPS patients with hemisensory impairment characterised by decreased temperature and pinprick sensation ipsilateral to the CRPS affected limb. The overall prevalence of mechanical allodynia was 58% and mean disease duration 4 years. Other studies report allodynia prevalence of 30% (Birklein et al., 2000) and 11% (de Mos et al., 2009), with mean disease durations of 6 months and 6 years respectively. In a follow-up study, Rommel et al (Rommel et al., 2001) confirmed that 30% of CRPS patients had hemisensory impairment. They were more likely to have mechanical allodynia and hyperalgesia, and tended to have longer duration of CRPS.

The prevalence of mechanical allodynia for this cohort that underwent QST assessment was 73% and mean disease duration was 5.3 years, range from 0.5 – 18 years. Like Rommel and colleagues, a similar percentage of these patients (36%) were found to have sensory abnormalities extending beyond the affected limb. CRPS patients demonstrated large areas of tactile allodynia with mean %BSA of 14%. Furthermore, the disease duration correlated with the extent of allodynia. However, the fact that this is a long duration disease cohort with severe clinical features needs to be taken into consideration when comparing to the CRPS literature.

Tactile hypoaesthesia is reported more frequently in CRPS. Rommel et al (Rommel et al., 2001) reported that of 40 CRPS patients, 85% had sensory impairment with higher tactile thresholds on the affected limb compared to the unaffected. The mean disease duration was 43 months. Huge et al investigated sensory and motor function in 118 chronic CRPS patients with a mean disease duration of 42 months (Huge et al., 2011). They found that comparing side to side differences, only 11% had hypoaesthesia and 30% had hyperalgesia. My cohort has substantially longer disease duration (68 months), and also demonstrated a higher proportion with hyperaesthesia (47%) compared to hypoaesthesia (24%). Huge et al suggest that their sensory QST findings support a role for small fibre loss of A-δ and c-fibres combined with central sensitization contributing significantly to the pathophysiology of the chronic CRPS. However they do not discuss how this proposed combination of mechanisms account for their patients displaying hyperaesthesia. Hypoaesthesia could be a manifestation of both small fibre loss and altered central sensory processing of sensory afferent input. The greater degree of hypoaesthesia and hyperaesthesia in my longer duration cohort may reflect the potential role for both of these processes.

4.5.3. Baseline sympathetic autonomic function

Baseline sympathetic autonomic function was normal in healthy controls, OA and RA patients and impaired in CRPS patients consistent with hypothesis 3. Stimuli such as a deep breath (Allen et al., 2002) and mental stress (Silverman et al., 1996) are known to produce consistent vasoconstrictor responses in the glabrous skin of the fingers. In agreement with previous studies (Allen et al., 2002), robust vasoconstrictor responses were demonstrated in the control group to standard stimuli (Low et al., 1983;Valley et al., 1993). All 40 controls in this study had robust LDF responses to a deep breath. In healthy controls, a mean reduction of baseline skin blood flow of 60% to a deep breath, and 73% to a Valsalva manoeuvre have been reported (Mundo et al., 2002), compared to 86% and 89% respectively in this study. The lack of standardisation of effort for the deep breath and Valsalva is likely to account for the observed difference. Silverman et al (Silverman et al., 1996) report a Δ%bbf of 37 +/- 18% for mental stress using serial seven subtraction in 7 healthy males aged 22-30 years. In comparison, this work found a Δ%bbf for the same mental stress task of 80%; however my healthy control group comprised 40 males and females aged 22-64 years.

The venoarteriolar (VAR) response is cutaneous vasoconstriction in response to limb dependency, and occurs as a response to venous congestion (Crandall et al., 2002). The mechanisms remain unclear and include contributions from a myogenic reflex (Okazaki et al., 2005) and non-adrenergic neurally mediated local mechanisms (Crandall et al., 2002). The VAR has been used as a means to investigate very early skin VAR dysfunction using LDF (Stoyneva, 2004). In healthy controls it has been shown to be less reliable compared to an inspiratory gasp which was present in all the subjects tested (Feger and Braune, 2005), which is in agreement with this work.

Previous work shows that ESR responses to a deep breath are consistently present in healthy controls (Mundo et al., 2002). Hay et al (Hay et al., 1997b) reported that 56/58 healthy controls had ESR responses to an inspiratory gasp while Shahani et al (Shahani et al., 1984) found inspiratory gasp responses to all 30 controls tested. In this work, ESR responses to a deep breath were present in all the healthy controls tested. Arousal such as mental arithmetic also produced ESR responses in healthy controls, similar to previous work (Critchley, 2002). No references in the literature could be found for use of ESR in assessment of VAR, suggesting that this is novel work.

4.5.4. Baseline sympathetic autonomic function & rheumatic disease

There is a paucity of literature assessing autonomic function in rheumatic disease (Stojanovich, 2009). There is even less using LDF and probably none utilising ESR other than as a means of 'stress' assessment in research papers (Fujita et al., 2001;Geenen et al., 1998). LDF has been used to assess the skin blood flow over the small joints of the hand in OA (Ng et al., 2003), and in RA to assess inflammation (Ferrell et al., 1996;Ferrell et al., 2001). Meyer compared LDF over PIP joints in RA and OA, reporting a lack of difference (Meyer et al., 2005). LDF has been used to assess endothelial function in RA and the relationship to inflammatory activity (Foster et al., 2010;Meyer et al., 2007;Sandoo et al., 2011), and for the assessment of cutaneous sensory and autonomic axon reflexes in RA utilising responses to intradermal capsaicin (Jolliffe et al., 1995). Autonomic function assessment in RA was assessed by Bidikar et al (Bidikar and Ichaporia, 2010). They used orthostatic, sustained hand grip and cold pressor tests in 50 RA patients, reporting sympathetic autonomic dysfunction in 26%. Toussirot et al (Toussirot et al., 1993) found 30/50 (60%) RA patients had autonomic dysfunction using heart rate variability analysis of orthostatic, deep breathing and Valsalva manoeuvre testing. We found that 32.5% of RA patients had LDF abnormalities to a series of sympathetic autonomic stimuli, or 55% using the composite ANS score of LDF and ESR responses. However it is not possible to directly compare the studies as all used different test parameters.

4.5.5. Baseline sympathetic autonomic function, CRPS & LDF

Impaired LDF responses to a deep breath have been reported in early CRPS (Wasner et al., 1999) and after trauma (Gradl and Schürmann, 2005;Schürmann et al., 1996;Schürmann et al., 1999;Schürmann et al., 2000), with recovery of vasomotor function on resolution of the CRPS (Gradl and Schürmann, 2005;Wasner et al., 1999). Sympathetic blockade (Rosen et al., 1989) or sympathectomy (Baron and Maier, 1996) of the affected limb can improve skin blood flow.

Altered responses to limb dependency (Rosen et al., 1988), mental stress (Birklein et al., 1998) and Valsalva manoeuvre (Bej and Schwartzman, 1991) have also been shown. Birklein et al (Birklein et al., 1998) used VAR, inspiratory gasp, cold pressor and mental arithmetic (serial seven subtraction) as sympathetic stimuli and noted that 7/21 controls and 6/20 patients had vasodilation in at least one test (5/6 patients to mental arithmetic with vasodilation on the unaffected limb). These subjects were excluded from analysis. No healthy control in our data demonstrated a

vasodilation pattern, and 4/30 CRPS patients had vasodilation to at least one stimulus, 2/4 to mental stress.

Dayan et al investigated venoarteriolar (VAR) and venoarteriolar-myogenic (VMR) responses in upper and lower limb CRPS patients by measuring the reactive hyperaemic response (Dayan et al., 2008). They found an impaired balance in CRPS affected limbs between the vascular regulation systems responsible for vasoconstriction and vasodilation. Whilst this pattern was found for an ischaemic stimulus, my results suggest that a similar imbalance may occur with the baseline sympathetic stimuli used in this protocol.

The pattern of autonomic dysfunction in CRPS varies over time. Ide et al (Ide et al., 1997) investigated 20 CRPS patients subdivided into Steinbrocker's stages 1 and 2 (Steinbrocker and Argyros, 1958). They used a symmetry ratio of Δ%bbf affected / unaffected limb to an inspiratory gasp, and found decreased blood flow with a stronger vasoconstrictor response in the affected hand of later stage 2 patients compared to stage 1, with a mean SR of 1.56. When the SR for a deep breath is calculated the same way, data from our work showed a SR of 1.09. However, the mean duration of symptoms for the 9 stage 2 patients was 9.4 months, where as almost all of the CRPS cohort from our study had much longer duration disease and were Steinbrocker stage 3. Wasner et al (Wasner et al., 2001) report three distinct vascular regulation patterns identifiable using whole body warming and cooling related to the duration of CRPS; warm/early, intermediate, cold/chronic. The duration of disease was 1.5 – 48 months. Kurvers et al (Kurvers et al., 1995) describe similar findings in 120 patients meeting Veldman criteria (Veldman et al., 1993) for CRPS of increased skin blood flow in early/warm CRPS and reduced in intermediate and cold stages. The mean duration of patients with 'cold' CRPS was 33 months. Therefore the CRPS patients comprising the cohort for our study have much longer duration disease, and there is almost no data available for comparison.

4.5.6. Baseline sympathetic autonomic function, CRPS & ESR

There is even less literature on ESR in CRPS than LDF. Impairment of ESR responses has been reported in CRPS. Rommel et al describe differences in waveform between sides, and differences in amplitude or latency in 'severe' cases for sympathetic skin response (SSR) to single square wave electrical stimuli. (Rommel et al., 1995), and confirmed the findings and correlation with disease severity in a follow up report (Rommel et al., 1996). Other studies confirm changes in

amplitude and latency (Bolel et al., 2006;Clinchot and Lorch, 1996;Drory and Korczyn, 1995). Pankaj (Pankaj et al., 2006) studied sympathetic skin response to electrical stimulation in CRPS patients with abnormal 3-phase bone scintigraphy. SSR was absent in 29% of CRPS patients. Furthermore, 79% of 14 patients with disease duration of greater than 6 months had abnormalities of SSR compared to 11% presenting within 3 months. Our data demonstrated abnormal ESR responses to sympathetic stimuli in 47%. However, the studies use different protocols and ESR techniques so are not directly comparable.

4.5.7. Study strengths

As previously discussed (**4.2.3.3.**, **4.2.4.1.**) there is no consistent method of analysis of LDF or ESR responses. The approach of combining the two techniques to provide a qualitative composite ANS score appears to be new in the literature. LDF responses are more consistent across the groups, with no healthy control demonstrating an LDF abnormality to the sympathetic testing protocol. The ESR responses are more variable, with 9/40 (22%) controls having one or more abnormality to the sympathetic testing protocol. Thus on its own the ESR responses are not a good method to compare autonomic function across different cohorts. However, when combined with the LDF responses to produce a composite ANS score, a potentially more useful measure is produced. It would be suitable for use in allodynic patient populations, and for the assessment of dynamic sympathetic responses to stimuli.

4.5.8. Study limitations and future directions

The QST was detailed, involving use of an official 'Somedic' brush and a full set of twenty Semmes-Weinstein filaments for assessment of static allodynia and tactile thresholds. The filaments are expensive, and not practically easily available to therapists working in district general hospitals. However, simple methods such as use of a disposable 4g filament (used by diabetes nurses to test for loss of protective sensation) for assessing static allodynia, a pain or pastry brush for dynamic allodynia, a disposable 'neurotip' for sharp sensation /hypoaesthesia should be used concurrently. This would help to establish the reliability of a simpler, more easily administered version compared to the full version used in the study.

The CRPS cohort has long duration disease. Future research needs to include early onset disease, and to repeat assessments longitudinally. This will help to understand the evolution of the disease over time. It will ascertain reliability and

tolerability of the autonomic function assessment protocol and whether repeated exposure causes learned responses or a biofeedback effect.

The rheumatoid arthritis patients all had stable disease. Further work could investigate whether autonomic responses change during flares of disease.

The sympathetic testing protocol used five sympathetic stimuli. More investigation could be done on which of the stimuli are most robust and reliable, aiming to reduce the number of stimuli needed. In terms of quantitative assessment of LDF responses, the ΔBBF is a simple but blunt measure. The current method is also laborious and time consuming, being done by hand. Further work should look into different types of quantitative assessment eg. area under the curve, and subtraction as a measure of symmetry. More work on the software script could improve accuracy, reduce observer bias with automatic peak/trough finding, and markedly speed up the analysis process.

4.5.9. Clinical Implications

QST is able to delineate patterns in CRPS, including hypoaesthesia and hyperaesthesia. It is helpful to establish the presence and extent of allodynia, and to look for other more unusual sensory patterns. Severe allodynic CRPS requires a different therapy approach to that of hypoaesthesia.

This work has established a practical, non-invasive means of assessing baseline sympathetic autonomic function, applicable to CRPS and other chronic pain conditions. It has the major advantage of being tolerable to patients with severe, extensive allodynia. This may be applicable in research where assessment of sympathetic function is needed in an allodynic patient population.

4.6. Summary

The hypotheses postulated were proven:

- There was no allodynia present in healthy controls.
- Allodynia was present in some osteoarthritis (OA) and rheumatoid arthritis (RA) patients and most marked in CRPS patients.

Mechanical allodynia was present in 60% of OA and 52.5% of RA patients, in 73% of CRPS patients and in none of the healthy controls. Several unusual sensory patterns were noted in CRPS patients including referred sensations, allochiria, tactile dysynchiria and sensory extinction. A moderate correlation was found between the

duration of CRPS and percentage of body surface allodynia (%BSA) ie. longer duration, larger %BSA.

The third hypothesis was partially proven.

- Baseline sympathetic autonomic function was normal in healthy controls, and did show some impairment in OA and RA patients with most impairment in CRPS patients.

Abnormalities of baseline sympathetic autonomic function were found in OA, RA and CRPS patients compared to healthy controls, with a significant difference in composite ANS score impairment between patient groups and healthy controls, and age and sex matched healthy controls compared to CRPS. There was a significant difference for Δ%bbf mental stress between HC and OA and RA patients, and non-significant increased variability of SR between the limbs for different stimuli. When age and sex matched healthy controls were compared to CRPS patients, SR of blood flow responses to DB was significantly larger in CRPS patients. There was no difference in baseline autonomic parameters comparing unilateral upper limb CRPS and CRPS involvement of >1 limb, or 'cold' and 'warm' CRPS.

4.7. Conclusion

Allodynia does not occur in healthy controls, but is present in patients with OA, RA and CRPS. The autonomic testing protocol described is novel, and is able to delineate differences in baseline autonomic function in patients with CRPS and chronic rheumatic disease compared to healthy controls in keeping with previous studies. Several unusual sensory patterns were discovered in CRPS affected areas including allochiria, referral of sensation, sensory extinction and tactile dysynchiria.

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Chromolithograph by Hughes Litho.Co., Chicago, 1889.

Image available from: http://en.wikipedia.org/wiki/File:Hamlin's_Wizard_Oil_poster.jpg

Chapter 5:

Sensory disturbances and pain responses during optokinetic challenge in complex regional pain syndrome (CRPS) and rheumatic disease

"Mirrors present the opposite of blindness – sight without touch. As the mirror world is not checked by touch, or any of the other senses, it is less than a complete copy of the world we call reality. But it is also more, for our visual imagination is not constrained by counter-evidence."

Professor Richard Gregory *from 'Mirrors in Mind'*

Image: The Royal Institution, 2010. Professor Richard Gregory [online]. London: The Royal Institution of Great Britain. Available from: http://www.rigb.org/contentControl?action=displayContent&id=00000004163 [Accessed 18.1.2012].

5.1. Introduction

The background literature upon which the study and this chapter are based is covered in **Chapter 2**, sections 2.2 - 2.3. An outline is presented here with the reader being referred to the appropriate section of **Chapter 2** where fuller details can be found.

This study builds upon the previous work described in **Chapter 4** by assessing vulnerability to sensorimotor conflict in CRPS, chronically painful rheumatic disease (osteoarthritis (OA), rheumatoid arthritis (RA)) and healthy controls, and relating the findings to baseline assessment of quantitative sensory testing and allodynia.

The concept of conflicting sensory stimuli generating nociceptive sensations is relatively new. From his work on patients with left neglect and parietal lobe syndrome (Ramachandran, 1995), Ramachandran proposed the existence of a unilateral right cortical centre monitoring incongruence of somaesthetic sensation (CIS). He suggests that sensory (including visual and sensorimotor) conflict offers different interpretive possibilities and the potential for vacillation. In evolutionary terms, this is a potential survival disadvantage. The CIS has a role to detect anomalies and to

generate a paradigm shift if the discrepancy is too large, enabling a rapid behavioural response. A positron emission tomography (PET) study of incongruence between motor intention and sensory feedback by Fink (Fink et al., 1999) showed a right dorsolateral prefrontal area differentially activated by sensorimotor conflict. Harris (Harris, 1999) suggested that incongruent sensorimotor feedback may be generated as a consequence of cortical reorganisation, be detected by the CIS and result in phantom limb pain in amputees and in other chronic pain conditions. For full details, see **Chapter 2**; section *2.2.5. 'Sensorimotor conflict and pain'.*

Sensory conflict can generate unpleasant somaesthetic experiences in susceptible healthy individuals. It is a well recognised explanation of motion sickness (Warwick-Evans et al., 1998). Our group has shown that it is possible to induce a range of unpleasant somesthetic percepts including pain in healthy controls by using an optokinetic system (mirror/whiteboard) to generate conflict between the visual and proprioceptive senses (McCabe et al., 2005b). Furthermore, the susceptibility to this is increased in chronic pain patients eg. fibromyalgia (McCabe et al., 2005a;McCabe et al., 2007).

Cortical reorganisation in sensory and motor areas has been demonstrated in CRPS patients (Maihöfner et al., 2003;Maihöfner et al., 2007), with resolution in those who recover (Maihöfner et al., 2004). The extent of somatotopic shift has been shown to correlate with the incidence and severity of phantom limb pain (Lotze et al., 2001). Therefore CRPS patients may have increased susceptibility to sensorimotor conflict. There is also increasing evidence for central pain mechanisms in the chronic pain of osteoarthritis (OA) and rheumatoid arthritis (RA) (for full details, see **Chapter 2**, sections 2.5.6 and 2.6.6.), so these groups may also have enhanced susceptibility to sensorimotor conflict. However extensive areas of cortical reorganisation have not been demonstrated thus far in OA and RA patients, who may therefore have less susceptibility to sensorimotor conflict compared to CRPS patients. A better understanding of such mechanisms would potentially improve their treatment.

I postulate that vulnerability to somaesthetic sensory conflict arises from a lowered threshold for detecting sensorimotor discrepancy and subsequent failure of central integration of those detected sensory discrepancies (for full details, see **Chapter 2**, section 2.3., 'Somaesthesia; the integration of sensation with body schema'). Where there is enhanced susceptibility to sensory (including visual and sensorimotor) conflict such as in chronic pain patients with cortical reorganisation, there will be an increased likelihood of enhanced pain and abnormal somaesthetic sensation.

This study uses an optokinetic device to create visuo-sensorimotor conflict in healthy controls, and patients with chronic pain due to CRPS, OA and RA and assesses whether any somaesthetic sensory disturbances are generated. It then relates those findings back to the baseline assessments of quantitative sensory testing.

5.1.1. Aims

To assess vulnerability to the generation of new or exacerbation of current pain, and other sensory perceptions via sensorimotor conflict using an optokinetic challenge in healthy controls and in patients with chronic pain due to CRPS, RA and OA.

5.1.2. Hypothesis

1. During an optokinetic challenge, sensory disturbances and pain responses will be more common in CRPS patients compared to healthy controls and patients with rheumatoid or osteoarthritis.

5.2. Methodological considerations

5.2.1. Assessment of optokinetic induced vulnerability

The protocol is based upon the work of McCabe et al (McCabe et al., 2005b) The optokinetic device is a framed mirror 150 x 80 cm, with a non-reflective whiteboard on the obverse side. Assessments were conducted in a quiet room heated to a comfortable ambient temperature. In the original study with healthy controls, the order of limb assessment was randomised. During pilot work, it was quickly apparent that in many CRPS patients, incongruent movements particularly while viewing the mirror resulted in worsening of CRPS pain. A randomised order may have precluded recovery time, requiring the assessment to be abandoned. In order for CRPS patients to be able to complete the assessment, the order of assessment was not randomised. The order used was with congruent movements followed by incongruent starting with the right upper limb on the whiteboard side, progressing to the mirror side. The procedure was repeated for the left upper limb. This avoided starting with incongruent movements and allowed for recovery time between incongruent phases, avoiding wind-up pain. The same order was maintained for healthy subjects and subjects with OA and RA (**Fig.5.1**). As there were a mixture of right and left handed

subjects, dominant and non-dominant affected limbs, any order effect of hand dominance was diluted.

5.2.2. Assessment of pain

In pilot work and McCabe's original study, when painful sensations were reported the subject was asked to rate it on a verbal rating scale where 0 = no pain and 10 = worst possible pain. This is a modified Likert scale (Likert, 1952), which has been shown to reliably measure changes in pain (Oppenheim AN, 1992). However most patients put their baseline pain levels at 8, 9 or 10 giving little scope to understand how the pain had changed if it increased. Therefore a simple verbal scale was used where patients were asked if their pain was unchanged or mild, moderate or severely worse or better than baseline.

5.2.3. Participants

For full details of inclusion/exclusion criteria etc, see **Chapter 3**.

5.2.4. Ethical considerations

It was possible that the optokinetic challenge might result in somaesthetic disturbances including pain in some healthy subjects, and worsening of pain in some CRPS, OA and RA patients. Clinical experience both personally and within our group had shown that sensations in healthy controls are short lived and resolve completely, and in CRPS patients their pain returns to baseline levels within minutes to 4 - 6 hours. The effect in OA and RA was unknown. All participants were forewarned of this possibility. The patient and healthy volunteer information sheet contained advice about what to do if pain was experienced together with contact details if participants did experience problems and required further advice (see **Appendix 2**). Subjects were advised that if they did experience an exacerbation of pain to take their usual analgesia. Full ethical approval was granted by the local ethics committee.

5.2.5. Apparatus

- Optokinetic mirror whiteboard device (150 x 80cm mirror in a wooden frame with a whiteboard backing) (**Fig.5.2**)

5.3. Method:

5.3.1. Subject preparation and protocol

Prior to undergoing assessments participants were asked to remove their watch, any jewellery on hands and wrists, shoes and socks.

All participants (Subjects and Controls) were seated with a mirror/ whiteboard in front of them positioned at waist height and at right angles to the subject's body (**Fig.5.2**). The participant was requested to put one limb either side of the whiteboard. All participants were asked to look to one side of the device so that one limb was hidden behind it, and one was visible. They were instructed to flex and extend both limbs in a congruent manner whilst attending to the visible limb on the whiteboard side for a timed 60 seconds. This exercise was repeated with:

- the limbs being moved in an incongruent manner whist viewing the visible limb on the whiteboard side.

On completion of the above, the optokinetic device was turned around so that the same limb could be assessed in the same manner viewing the mirror side. This exercise was repeated with:

- the participant viewing the visible limb on the mirror side with limbs moved in a congruent manner.
- the participant viewing the mirror side with limbs moved in a incongruent manner.

After this, the above stages were repeated with the other limb visible. The protocol was performed in a quiet temperature controlled room with no pictures on the walls to avoid distraction.

5.3.2. Control Condition

The control condition for upper and lower limb assessments was congruent and incongruent movements as detailed above without the mirror/whiteboard device between the limbs. This provided a baseline for movement without visuomotor distortion (**Fig.5.2**).

For all subjects, flexion and extension from the elbow for upper limb and of the knee for the lower limb for up to 60 seconds as tolerated was used.

Healthy controls OA and RA subjects were tested on the upper limbs. CRPS patients were assessed on the affected and contra-lateral limbs (which included included upper and lower limbs).

Fig.5.1

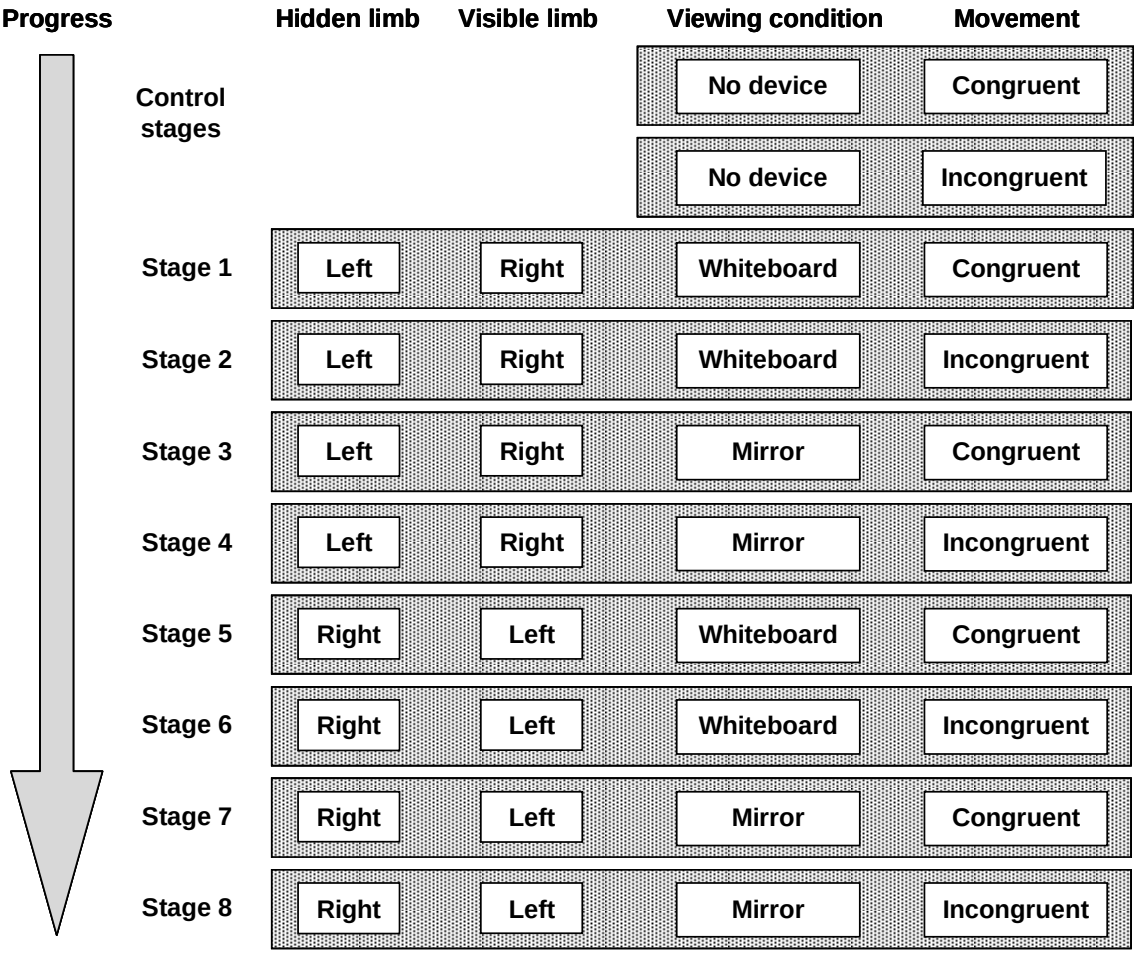

Fig.5.1. Flow chart showing the stages of the optokinetic protocol. Each subject performed the same protocol progressing through the stages in sequential order.

Fig.5.2.

Fig.5.2. Optokinetic mirror/whiteboard apparatus demonstrating incongruent movement whilst viewing the mirror side.

5.3.3. Qualitative assessments

These were made throughout by a series of open questions. As far as possible, no specific direct enquiry was made about possible sensory changes to prevent leading the subject and creating bias. Specific prompts were used if necessary as follow-up to positive responses to open questions, or where it was clear that the subject did not understand the question (see **Appendix 5**). Where painful sensations were reported, the subject was asked to rate it on a simple verbal rating scale as described above.

5.3.4. Vulnerability to optokinetic induced sensorimotor mismatch

The degree of sensorimotor conflict escalates moving through the stages. The stage with least conflict is whiteboard (WB) congruent (no visual input and congruent proprioception). WB incongruent and mirror congruent are intermediate levels of conflict (no visual input and incongruent proprioception in the former, and 'false' congruent visual input with congruent proprioception in the latter). Conflict is maximal with the mirror incongruent stage ('false' conflicting visual input with conflicting proprioception).

Based upon McCabe et al (McCabe et al., 2005b), 'vulnerability' classifications were allocated. Subjects were assigned to the following vulnerability classification according to how many of the four stages generated sensory disturbances (SeD):

High	Sensory disturbance all stages
Moderate	Sensory disturbance ≥3 mirror +/- 3 whiteboard (WB) stages
Mild	Sensory disturbance ≤2 mirror +/- 2 WB stages
Minimal	Sensory disturbance 1 mirror +/- 1 WB stage
Nil	No sensory disturbances

5.3.5. Optokinetic vulnerability score

Having created a vulnerability classification, a score could then be assigned between 0 – 4 (where none = 0, minimal = 1, mild = 2, moderate = 3 and high = 4) to create an optokinetic vulnerability score (OVS). This ordinal level ranking system allowed for statistical comparisons to be made.

5.3.6. Data analysis

5.3.6.1. Sample size

The sample size was based upon McCabe's original paper (McCabe et al., 2005b). This detailed the results of an optokinetic challenge in 41 healthy controls.

5.3.6.2. Statistical analysis

Only symptoms additional to, or as an exacerbation to baseline symptoms were included in the data analysis. The data is presented as percentages (actual number of subjects), mean and median values. Statistical analysis was performed on Statistical Package for the Social Sciences (SPSS) v.16 software and utilised non-parametric tests. For comparison between cohorts, the Mann-Whitney or Kruskal-Wallis test were used and for correlation analysis, the Spearman's Rho test. Where categorical data is compared, the chi-squared test was used. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated where appropriate.

5.4. Results

Forty healthy controls, 40 OA, 40 RA and 55 CRPS patients underwent assessment of vulnerability to sensorimotor conflict using the optokinetic mirror whiteboard system. For details of demographics, see **Chapter 4**.

5.4.1. Sensory disturbances

Sensory disturbances during baseline testing (no mirror/whiteboard device) were reported in only 1 control, 2 OA, 1 RA and 3 CRPS subjects.

Abnormal somaesthetic sensations additional to baseline were perceived throughout different stages of the protocol by some participants in all the cohorts. Twenty-two (55 %) of controls, 27 (67.5%) of RA, 36 (90%) of OA and 50 (91%) of CRPS subjects perceived abnormal sensations (see **Table 5.1**, **Fig.5.3**). Comparing the cohorts, there was a statistically significant difference in the frequency of subjects with abnormal somaesthetic sensations (χ^2 (3) = 22.893, p<0.001) and an association between cohort and likelihood of abnormal somaesthetic sensations (Cramer's V = 0.362). The odds ratio (95%CI) for perceiving abnormal somaesthetic sensations compared to a healthy control was 8.2 (2.7;24.8) in a CRPS subject, 7.4 (2.2;24.6) in OA and 1.7 (0.7;4.2) in RA.

Table 5.1. Optokinetic vulnerability: distribution by cohort.

		Vulnerability				
Cohort	N	High	Moderate	Mild	Minimal	Nil
CRPS (%)	55	17 (31)	19 (34.5)	11 (20)	3 (5.5)	5 (9)
HC (%)	40	0	7 (17.5)	11 (27.5)	4 (10)	18 (45)
OA (%)	40	8 (20)	14 (35)	12 (30)	2 (5)	4 (10)
RA (%)	40	2 (5)	12 (30)	8 (20)	5 (12.5)	13 (32.5)

CRPS = complex regional pain syndrome, HC = healthy controls, OA = osteoarthritis, RA = rheumatoid arthritis.

Fig.5.3.

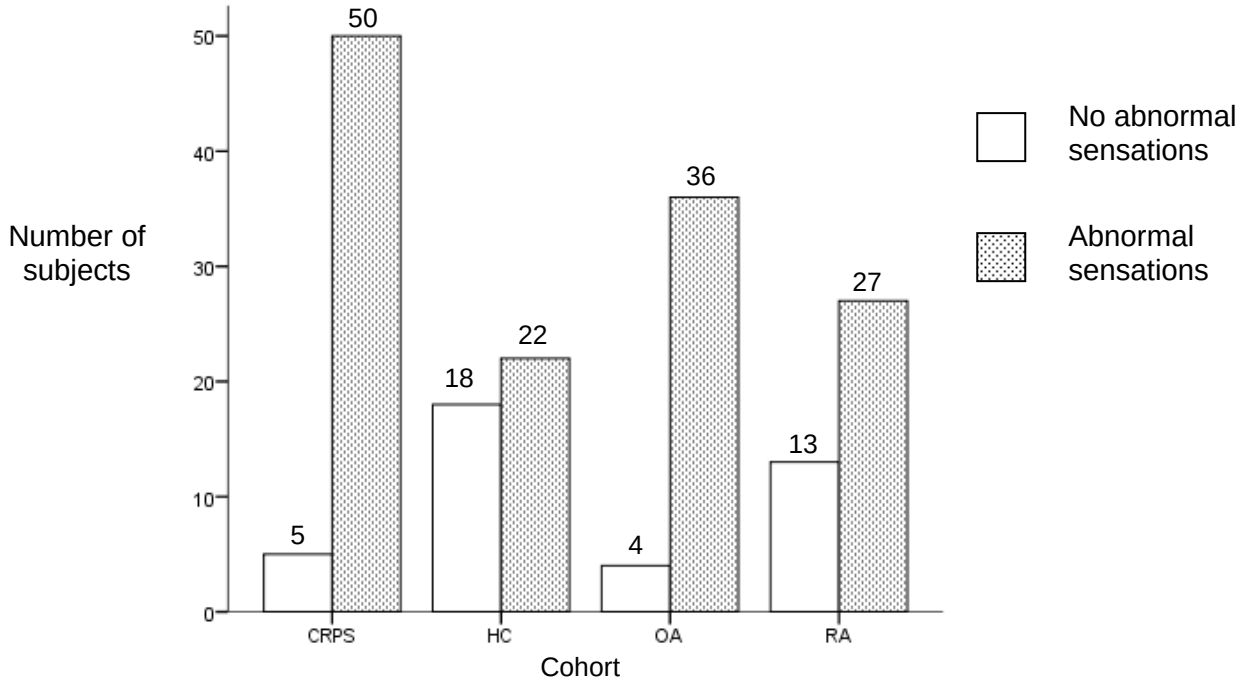

Fig.5.3. Comparison of the numbers of subjects perceiving abnormal sensations in addition to baseline at any stage in the protocol, and those that did not by cohort. CRPS = complex regional pain syndrome, HC = healthy controls, OA = osteoarthritis, RA = rheumatoid arthritis.

In all participant groups, altered or exacerbated sensory disturbances were predominantly reported in the hidden limb and faded rapidly after limb movement had ceased and the hidden limb could be directly visualized by the subject. There were a variety of abnormal sensations perceived which are detailed in **Table 5.2**.

5.4.1.1. Sensory disturbances and degree of sensorimotor conflict

Overall, subjects more often had abnormal sensations when looking at the mirror (62%) rather than the whiteboard (34%), and with incongruent (55%) rather than congruent movements (41%).

When the least conflicting stage (whiteboard congruent) was compared with the most (mirror incongruent), overall there was a statistically significant increased frequency of abnormal sensations (χ^2 (3) = 8.528, $p<0.05$). Compared to healthy controls, the odds ratio (95%CI) for perceiving abnormal sensations in the most conflicting stage was 5.3 (2;14.1) for CRPS, 6.3 (2.1;19.5) for OA and 1.5 (0.5;3.1) for RA subjects. This was also statistically significant within each cohort; χ^2 (1) = 12.511, $p<0.001$ (CRPS), 22.029, $p<0.001$ (HC), 23.226, $p<0.001$ (OA), 14.907,

p<0.001 (RA). All stages of the protocol generated a higher frequency of report in the CRPS, OA and RA cohorts than that of the maximum report in the HC population.

When the intermediate conflict level stages (whiteboard incongruent and mirror congruent) are compared, in every cohort there were higher frequencies of sensory disturbances in the mirror congruent compared to the whiteboard incongruent stage. See **Table 5.2**.

5.4.2. Pain responses

During the optokinetic protocol, new onset of pain was felt in 3 (7.5%) of control subjects. Fourteen (35%) of RA, 20 (50%) of OA and 44 (80%) of CRPS subjects had exacerbation of their usual pain (see **Table 5.3**, **Fig.5.4**). Comparing cohorts, there was a statistically significant difference in the frequency of subjects with pain (χ^2 (3) = 51.619, p<0.001) and an association between cohort and odds of having pain (Cramer's V = 0.543). The odds ratio (95%CI) for perceiving pain compared to a healthy control was 50 (12.8;190.2) in a CRPS subject, 12.5 (3.3;46.7) in OA and 6.7 (1.7;25.5) in RA.

5.4.2.1. Pain and degree of sensorimotor conflict

Overall, subjects more often had pain when looking at the mirror (37%) rather than the whiteboard (23%), and with incongruent (34%) rather than congruent movements (26%). Comparing the least conflicting stage (whiteboard congruent) with the most (mirror incongruent), overall there was no statistically significant difference in frequency of pain reports compared to baseline. The odds ratio (95%CI) for perceiving new or additional pain for the most compared to least conflicting stage was 2.9 (1.8;4.8). Within the cohorts, there was an increased frequency of new or enhanced pain. In the CRPS group this was statistically significant (χ^2 (1) = 21.008, p<0.001), and was non-significant in the OA, RA and control groups. The OA group showed a more even distribution across the conflict gradient compared to the other cohorts (**Fig.5.4**).

Table 5.2. Details of the incidence of symptoms reported in addition to baseline at each stage of the protocol in relation to the study populations.

	CRPS				Healthy controls			
	WB		Mirror		WB		Mirror	
Sensation perceived	C	IC	C	IC	C	IC	C	IC
Pain	17 (31%)	27 (49%)	32 (58%)	41 (74%)	0	0	1 (2.5%)	3 (7.5%)
Weight change of limb	12 (22%)	8 (14%)	14 (25%)	22 (40%)	2 (5%)	2 (5%)	2 (5%)	7 (17.5%)
Loss or gain of limb	2 (4%)	2 (4%)	5 (9%)	10 (18%)	0	0	1 (2.5%)	9 (22.5%)
Nausea	2 (4%)	4 (7%)	10 (18%)	12 (22%)	0	0	1 (2.5%)	3 (7.5%)
Tingling, pins & needles	2 (4%)	3 (5%)	2 (4%)	8 (14%)	0	0	1 (2.5%)	2 (5%)
Feeling of peculiarity	1 (2%)	0	8 (14%)	13 (24%)	0	1 (2.5%)	4 (10%)	7 (17.5%)
Headache	1 (2%)	1 (2%)	4 (7%)	9 (16%)	0	0	0	0
Dizziness	1 (2%)	2 (4%)	1 (2%)	3 (5%)	0	0	0	1 (2.5%)
Foreigness	0	0	0	0	0	0	0	1 (2.5%)
Tiredness	0	1 (2%)	0	1 (2%)	0	0	0	2 (5%)
Temp change	2 (4%)	4 (7%)	4 (7%)	5 (9%)	0	0	0	3 (7.5%)
Stiffness	0	0	1 (2%)	1 (2%)	0	0	0	0
Phantom swelling	1 (2%)	0	1 (2%)	4 (7%)	0	0	0	0
Total no. any sensation	30 (54.5%)	36 (65%)	37 (67%)	47 (85%)	2 (5%)	3 (7.5%)	9 (22.5%)	21 (52.5%)

	Osteoarthritis				Rheumatoid Arthritis			
	WB		Mirror		WB		Mirror	
Sensation perceived	C	IC	C	IC	C	IC	C	IC
Pain	12 (30%)	12 (30%)	16 (40%)	16 (40%)	5 (12.5%)	7 (17.5%)	9 (22.5%)	12 (30%)
Weight change of limb	12 (30%)	12 (30%)	11 (27.5%)	12 (30%)	4 (10%)	6 (15%)	9 (22.5%)	12 (30%)
Loss or gain of limb	0	0	7 (17.5%)	24 (60%)	0	0	4 (10%)	15 (37.5%)
Nausea	1 (2.5%)	1 (2.5%)	2 (5%)	4 (10%)	1 (2.5%)	1 (2.5%)	0	4 (10%)
Tingling, pins & needles	0	1 (2.5%)	1 (2.5%)	3 (7.5%)	3 (7.5%)	1 (2.5%)	2 (5%)	4 (10%)
Feeling of peculiarity	1 (2.5%)	1 (2.5%)	2 (5%)	2 (5%)	0	0	2 (5%)	4 (10%)
Headache	0	0	0	1 (2.5%)	0	0	0	0
Dizziness	0	1 (2.5%)	0	3 (7.5%)	1 (2.5%)	1 (2.5%)	0	1 (2.5%)
Foreigness	0	0	0	5 (12.5%)	0	0	0	1 (2.5%)
Tiredness	0	0	2 (5%)	1 (2.5%)	0	0	0	0
Temp change	0	0	2 (5%)	2 (5%)	0	0	0	1 (2.5%)
Stiffness	2 (5%)	1 (2.5%)	2 (5%)	1 (2.5%)	0	0	1 (2.5%)	0
Phantom swelling	0	0	0	0	0	0	0	0
Total no. any sensation	14 (35%)	13 (32.5%)	24 (60%)	35 (87.5%)	8 (20%)	12 (30%)	18 (45%)	25 (62.5%)

	At any stage in the protocol			
Sensation perceived	CRPS	HC	OA	RA
Pain	44 (80%)	3 (7.5%)	20 (50%)	14 (35%)
Weight change of limb	27 (49%)	7 (17.5%)	16 (40%)	17 (42.5%)
Loss or gain of limb	12 (22%)	9 (22.5%)	25 (62.5%)	16 (40%)
Nausea	12 (22%)	3 (7.5%)	5 (12.5%)	4 (10%)
Tingling, pins & needles	11 (20%)	3 (7.5%)	4 (10%)	6 (15%)
Feeling of peculiarity	15 (27%)	8 (20%)	4 (10%)	5 (12.5%)
Headache	9 (16%)	0	1 (2.5%)	0
Dizziness	4 (7%)	1 (2.5%)	3 (7.5%)	1 (2.5%)
Foreigness	0	1 (2.5%)	5 (12.5%)	1 (2.5%)
Tiredness	2 (4%)	2 (5%)	3 (7.5%)	0
Temp change	9 (16%)	5 (12.5%)	2 (5%)	1 (2.5%)
Stiffness	1 (2%)	0	3 (7.5%)	1 (2.5%)
Phantom swelling	4 (7%)	0	0	0
Total no. any sensation	50 (91%)	22 (55%)	36 (90%)	27 (67%)

CRPS = complex regional pain syndrome, HC = healthy controls, OA = osteoarthritis, RA = rheumatoid arthritis.

WB = whiteboard, C = congruent movement, IC = incongruent movement; Total no. any sensation = total number of subjects experiencing any sensation.

Table 5.3. Optokinetic vulnerability distribution and perception of pain by cohort.

		Pain			
		Vulnerability (% of total with pain)			
Cohort	Total with pain	High	Moderate	Mild	Minimal
CRPS	n = 44	16 (36)	18 (41)	8 (18)	2 (5)
HC	n = 3	0	2 (67)	1 (33)	0
OA	n = 20	8 (40)	10 (50)	1 (5)	1 (5)
RA	n = 14	2 (14)	8 (57)	4 (29)	0

CRPS = complex regional pain syndrome, HC = healthy controls, OA = osteoarthritis, RA = rheumatoid arthritis.

Fig.5.4.

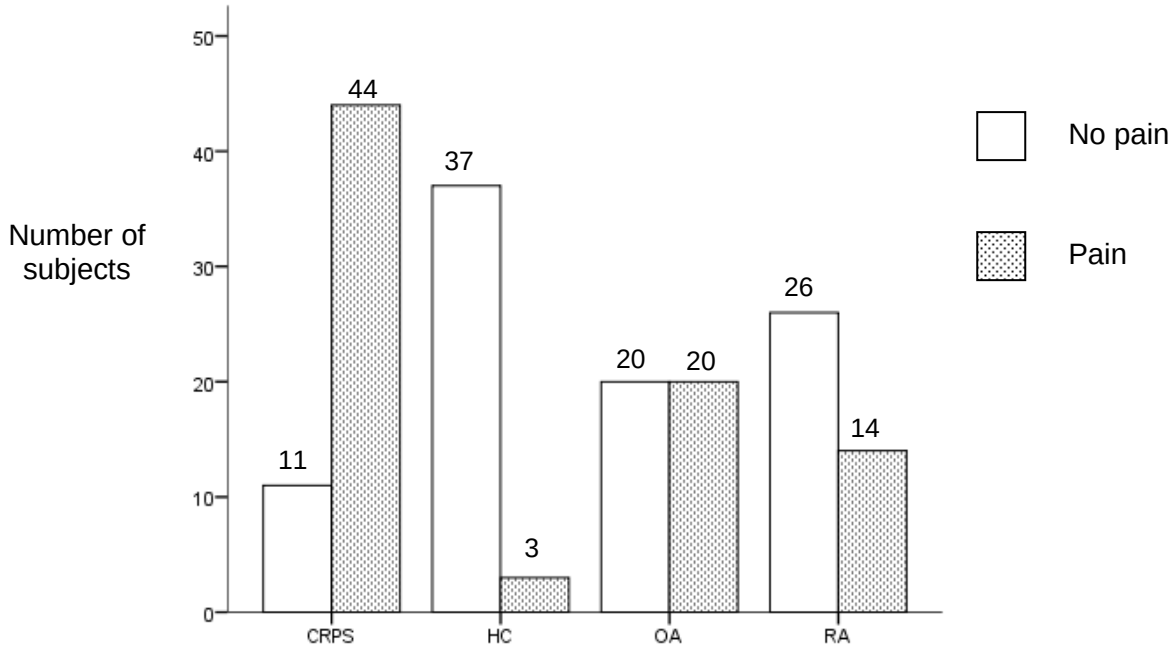

Fig.5.4. Comparison of the numbers of subjects with pain (new pain or exacerbation of existing pain) in addition to baseline at any stage in the protocol, and those that did not by cohort.

CRPS = complex regional pain syndrome, HC = healthy controls, OA = osteoarthritis, RA = rheumatoid arthritis.

5.4.2.2. Pain and optokinetic vulnerability classification

When the frequency of subjects with new or exacerbated pain is compared by optokinetic vulnerability classification, there was a significant difference (χ^2 (3) = 39.649, p<0.001) and a strong association between vulnerability and pain (Cramer's V = 0.542).

Comparison of the optokinetic vulnerability score (OVS) between cohorts demonstrates a significantly higher score (Kruskall Wallis test p<0.001, post-hoc Mann-Whitney *U*-test with Bonferroni correction) for CRPS (median = 3) and OA (median = 3) compared to RA (median = 2) and controls (median = 1).

5.4.3. Comparison of vulnerability classification with quantitative sensory testing and autonomic composite score.

i. Between cohorts

There was a moderate positive correlation between optokinetic vulnerability score (OVS) and percentage of body surface allodynia (%BSA) (Spearman's rho = 0.346, p<0.05). There was a low to moderate negative correlation between OVS and autonomic (ANS) composite score (ie. higher vulnerability, lower (ANS) composite score and more autonomic impairment) (Spearman's rho = -0.165, p<0.05).

ii. Within CRPS cohort

Abnormal sensations and pain, allodynia and tactile threshold perturbations were more common in the high and moderate vulnerability subjects (see **Table 5.4**).

For the overall CRPS cohort (n = 55), there was a strong negative correlation between OVS and Semmes-Weinstein filament threshold of the affected limb (ie. higher vulnerability and lower threshold) (Spearman's rho = -0.542, p<0.001) (see **Fig.5.5**). There were moderate positive correlations between OVS and baseline pain score (mild = 1, moderate = 2, severe = 3) (Spearman's rho = 0.319, p<0.05), and for OVS and %BSA (Spearman's rho = 0.306, p<0.05). These correlations were not significant in the CRPS upper limb (UL) cohort (n = 30).

In the CRPS UL cohort (n = 30), correlation of optokinetic vulnerability score (OVS) with disease duration was statistically significant (rho = 0.523, p<0.01). Disease duration was also significantly correlated with %BSA (rho = 0.571, p<0.01). This did not hold for the overall CRPS cohort where the numbers are larger.

Table 5.4. Vulnerability classification for CRPS patients with enhanced pain and quantitative sensory testing findings.

	Optokinetic vulnerability				
n = 44	**High**	**Mod**	**Mild**	**Min**	**Nil**
Vulnerability classification	14	16	9	4	1
Allodynia present	13	11	4	4	0
No allodynia	1	5	5	0	1
Mean % BSA allodynia	21.7	9.25	9.5	4	~
ATvsTT higher (hypoaesthesia)	3	5	0	2	~
ATvsTT lower (hyperaesthesia)	7	5	3	1	~
% ATvsTT lower	77	40			
%TT = SW-1	54	13			
Mean CRPS duration (yrs)	7.3	4.6			

ATvsTT = allodynic threshold vs tactile threshold

Fig.5.5.

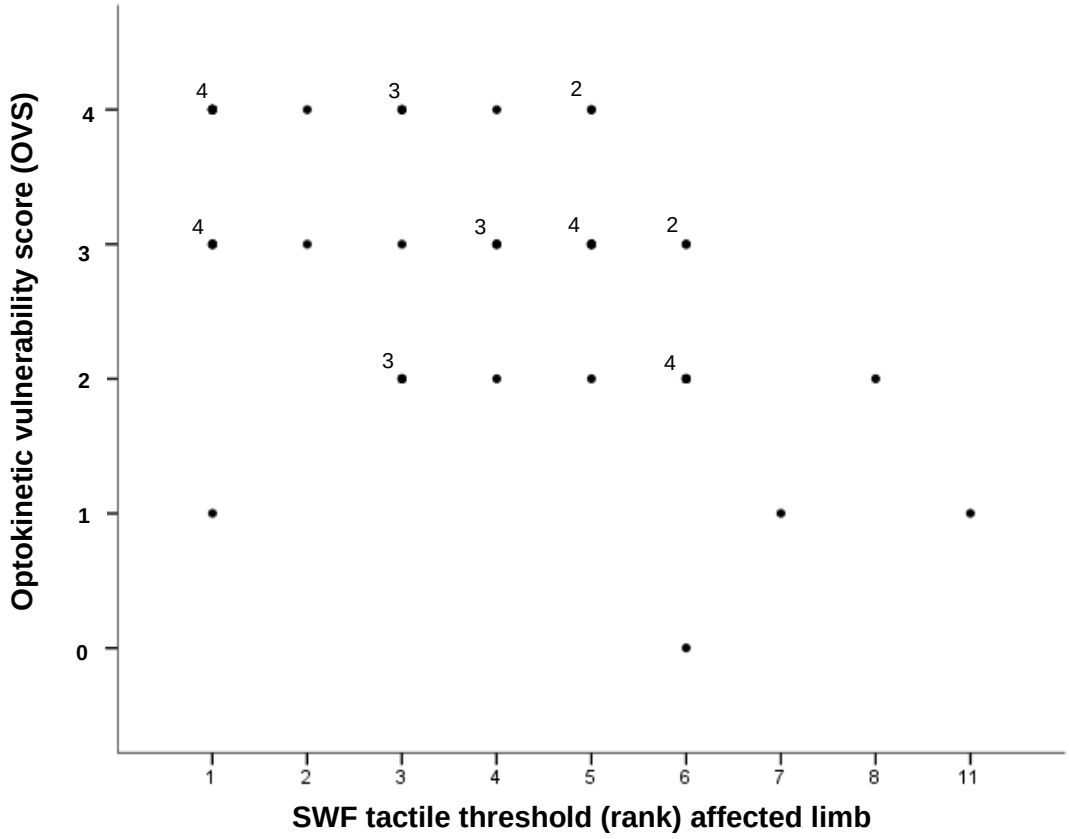

Fig.5.5. Scatterplot of optokinetic vulnerability score (OVS) against Semmes Weinstein tactile threshold of the affected limb.

NB. Where some data points represent more than one subject, the number of subjects is indicated by a numeral beside the plot point.
The finest hair is ranked 1 (target force 0.008g) through to the heaviest filament ranked 20 (target force 300g). Filament 11 = 4g. See **Table 4.4.B.**
SWF = Semmes Weinstein filament

5.4.4. Other findings: motor impairment and motor extinction

An unexpected observation was the finding of motor impairment and motor extinction in some subjects while undertaking the optokinetic challenge. When asked to perform bilateral movements, many CRPS patients were unable to initiate motor action in the hidden limb without the visual feedback of the limb, or displayed much reduced movement in the hidden limb. Many demonstrating extinction were unaware that the hidden limb was not moving, and expressed great surprise.

Motor extinction is defined as difficulty initiating movement or impaired use of a limb during bilateral simultaneous movements (Freund et al., 2011). As this is the closest analogy to this clinical finding, it has been termed 'motor extinction'. Subjects demonstrated the full spectrum from inability to initiate any movement, to impaired movement in one limb.

Subjects were classified as having:

1. Full motor extinction (FME) when they were unable to initiate movement

2. Initiation impairment (INIM) where there was hesitancy, 'false starts' or difficulty in starting movement

3. Motor 'lag' where movement did occur in the limb but at reduced amplitude with impaired rhythm. Subjects with lag all demonstrated loss of the usual smooth coordinated movements, and had jerky movement.

There was no motor extinction in any cohort during baseline testing. During the sensorimotor challenge, no healthy control subject demonstrated any form of motor extinction. Among OA patients, one had FME and 5 had INIM &/or lag and in RA subjects there were none with FME and 2 with INIM &/or lag. Among CRPS patients, 37 (67%) had evidence of motor extinction; 23 had FME – 4 of these subjects were completely unable to initiate movement in the hidden limb at any stage of the optokinetic protocol. There were combinations of INIM and/or lag with and without FME at different stages of the protocol (see **Table 5.5**). Thirty two out of 37 showed evidence of motor extinction in both the affected and unaffected limbs, 3 in the hidden affected limb only and 2 in the hidden unaffected limb only.

Comparing the CRPS patients with and without extinction, there was a significant difference in OVS (Mann-Whitney *U*-test, $p<0.001$), with the median OVS for CRPS with extinction = 4 and median OVS with no extinction = 2. There was also a significant difference in Semmes-Weinstein filament (Mann-Whitney *U*-test,

$p<0.05$), with the median tactile threshold of the affected limb in a patient with extinction = 0.16g compared to 0.04g in a patient without extinction.

5.4.5. Other findings: dystonia

Eight CRPS patients developed a dystonic reaction in the affected limb at some stages of the protocol characterised by sustained muscular contraction at the wrist and/or fingers, tremor or muscular jerks. All of these subjects experienced worsening pain and all demonstrated evidence of motor extinction. See **Table 5.5**.

5.4.6. Comparison of vulnerability between OA and RA

There was a significant difference in OVS (Mann-Whitney *U*-test, $p<0.01$) between OA (median OVS = 3) and RA (median OVS = 2).

5.4.7. Comparison of vulnerability classification with parietal lobe testing

See **Chapter 7**.

Table 5.5. Motor extinction and dystonia during optokinetic protocol.

CRPS patients

Patient ID	FME	INIM / Lag	Dystonia
2	Y		
3	N	L,INIM	
6	N	L	
8	N	INIM	
9	Y	L,INIM	
10	Y	L,INIM	
11	N	L,INIM	
12	N	L,INIM	
13	N	L	
15	Y	L	D
16	Y	L	
17	Y	INIM	
18	N	L,INIM	
19	Y		D,Tr
21	N	L	
22	Y	L	Tr
23	Y	L,INIM	J
26	Y	INIM	
27	Y	L,INIM	
28	Y	L,INIM	D
29	N	L	
32	Y	L	
33	Y	INIM	J
34	Y	L,INIM	
35	Y		D,J
36	N	L	
39	Y		
40	Y		
42	Y	L,INIM	
43	N	L,INIM	
44	Y	L,INIM	
46	Y		
48	Y	L	D,Tr
49	N	INIM	
50	N	L,INIM	
51	N	L,INIM	
53	N	L	

OA patients

Patient ID	FME	INIM / Lag	Dystonia
2	Y	L,INIM	
4	N	L,INIM	
9	N	L	
21	N	L	
23	N	INIM	
35	N	L,INIM	

RA patients

Patient ID	FME	INIM / Lag	Dystonia
1	N	L,INIM	
2	N	L,INIM	

OA = osteoarthritis, RA = rheumatoid arthritis, FME = full motor extinction, INIM = initiation impairment, Y = yes & present, N = no & absent, L = lag, D = dystonia, Tr = tremor, J = jerk

5.5. Discussion

During a sensorimotor challenge, sensory disturbances and pain responses were more common in CRPS patients, and they had a higher optokinetic vulnerability compared to healthy controls and patients with rheumatoid or osteoarthritis, supporting the hypothesis. Unexpectedly, it was also found that osteoarthritis patients have a higher incidence of sensory disturbances and pain, and higher optokinetic vulnerability compared to patients with Rheumatoid Arthritis and healthy controls.

5.5.1. Comparison with previous studies

In McCabe's original paper investigating the consequences of sensorimotor conflict by using a mirror to create an optokinetic challenge among healthy volunteers (McCabe et al., 2005b), 66% reported at least one anomalous sensory symptom and 17% reported pain at some stage in the protocol. A subsequent study (McCabe et al., 2007) reported 48% of controls had sensory disturbances and 14% reported pain utilising the same protocol. Another recent study of professional violinists by Daenen et al (Daenen et al., 2010) found that 60% had sensory changes at some stage in the same protocol. The frequency of sensory disturbances in these studies is similar to the frequency in this work, which found that 55% of healthy controls reported sensory disturbances. However there was a lower frequency (7.5%) of reported pain among controls.

A recent study of 113 HVs found only 2% reported pain and no difference between reported frequencies of sensory disturbances or pain across the stages (J.Foell, personal communication). The authors suggest that the McCabe group may have overestimated the incidence of pain due to questionable methodology, and that the lack of difference of report frequencies for pain and sensory disturbances (except for gain of a limb) does not support the Harris cortical model of pain. However there were some important study methodology differences. A metronome was used for participants to keep a steady movement rhythm, and the elbows of the participants were kept resting upon a table. Both of these conditions provide the subjects with additional non-visual sensory feedback cues reducing the level of sensory discrepancy. The metronome would also provide a significant auditory distraction.

Among fibromyalgic patients with chronic pain, the frequency of sensory disturbance (90%) and pain (62%) has been shown to be higher (McCabe et al., 2007) compared to controls. Daenen's study of violinists (Daenen et al., 2010) found that those with baseline symptoms (pain, tension, fatigue, tingling, discomfort or swelling) reported significantly more sensory changes compared to those without

baseline symptoms. Data from my work confirms that patients with chronic pain due to rheumatoid arthritis (67.5%), osteoarthritis (90%) and CRPS (91%) are more likely to report sensory disturbances than healthy controls. It also demonstrates that patients with chronic pain are more likely to report new or enhanced pain; 35% rheumatoid arthritis (RA), 50% osteoarthritis (OA) and 80% CRPS.

5.5.2. Degree of sensorimotor conflict, sensory disturbances and pain

Ramachandran's proposed right cortical centre monitoring incongruence of sensation (CIS) together with the Harris hypothesis (that incongruent sensorimotor feedback may be generated as a consequence of cortical reorganisation and be detected by the CIS) would predict incongruent mirror movement to be the stage most likely to produce sensory disturbance and/or pain. This stage of the protocol induces the greatest degree of visual and proprioceptive conflict.

In McCabe's original study (McCabe et al., 2005b), healthy volunteers (HV) demonstrated the greatest frequency of sensory disturbances during the mirror stages, and most during maximal sensorimotor conflict, the mirror incongruent stage (66%) compared to the mirror congruent stage (41%). Deanen et al (2010) also found that the mirror incongruent stage produced the highest frequency of sensory changes (55%). However in fibromyalgia (FMS) patients there was no difference in frequency of report across the intervention stages (McCabe et al., 2007). It was suggested that FMS patients may have a reduced threshold to sensory–motor discrepancies as compared with HVs and therefore any degree of conflict is sufficient to trigger detection of feedback anomalies, and cause somaesthetic disturbances.

In this study, all the cohorts show an increased frequency of sensory disturbances in the stage with highest conflict compared to the stage with lowest. However there was a different pattern observed for pain reports where controls, OA and RA patients demonstrated no difference in frequency of pain reports across the intervention stages, and CRPS patients had a significantly greater frequency in the highest conflict stage compared with the lowest.

Can this be explained within the context of the sensory discrepancy model? I suggest that during the process of central integration, when a feedback discrepancy is detected there are separate mechanisms and thresholds that may trigger sensory disturbances or pain. In the majority of healthy controls and among many patients with chronic pain, a moderate level of sensorimotor conflict is required to exceed the sensory-motor discrepancy threshold and initiate sensory disturbances. The pain mechanism is separate and cannot usually be triggered by activation of the sensory-motor disturbance threshold. However in 'vulnerable' subjects, the threshold is lower

still and can activate pain networks. This would result in a similar frequency of pain reports across all the stages.

Among CRPS patients where frequencies of sensory disturbances and pain are highest in all stages compared to the other cohorts, the degree of conflict does have an effect on perceived pain with maximal reports in the highest conflict stage. This may be due to additional activation of top-down networks, possibly activated through impaired motor pathways and disrupted body schema. 'Vulnerability' may be conferred by the presence of cortical reorganisation, rendering a subject more susceptible to sensory incongruence. An alternative explanation may lie with a genetic predisposition to lower thresholds, abnormal connectivity or neuronal firing and subsequent impaired central integrative network responses.

5.5.3. Osteoarthritis & rheumatoid arthritis patients

An unexpected finding was that OA patients were highly vulnerable to sensory disturbance and/or pain compared to RA patients or healthy controls. Proprioception is thought to decline with age (Pai et al., 1997;Skinner et al., 1984), which might explain higher vulnerability compared to healthy controls, but not compared to the RA cohort who were of a similar age (mean age OA =61 years , mean age RA = 57 years). However, there is increasing evidence for pain in osteoarthritis having significant centrally generated components (Mease et al., 2011).

A study of patients with hip OA found significantly lower threshold perception to punctate stimuli and hyperalgesic to the noxious punctate stimulus in areas of referred pain (Gwilym et al., 2009). Functional brain imaging of these patients illustrated significantly greater activation in the brainstem in response to punctate stimulation of referred pain areas compared with healthy controls, and the magnitude of the activation positively correlated with the extent of neuropathic-like elements to the patient's pain. Another study using fMRI volumetric analysis in hip OA found a characteristic gray matter decrease in patients compared with controls in the anterior cingulate cortex (ACC), right insular cortex and operculum, dorsolateral prefrontal cortex (DLPFC), amygdala, and brainstem. A subgroup of 10 patients after total hip replacement surgery were completely pain free, and repeat imaging showed gray matter increase in the DLPFC, ACC, amygdala, and brainstem (Rodriguez-Raecke et al., 2009).

Central pain may also be present in RA (Lee et al., 2011;Ranzolin et al., 2009), and could make validity of the 'inflammatory' DAS 28 score questionable when it is present (Wolfe, 2009). A recent fMRI study has shown the presence of increased grey matter content in the basal ganglia of RA patients. The study

suggests that RA is associated with changes in the subcortical grey matter rather than with cortical grey matter atrophy and links the findings to prolonged changes in motor control and pain processing in RA patients (Wartolowska et al., 2011).

Why do OA patients apparently have higher vulnerability to sensory conflict than RA? One possible explanation is that in RA, there is usually a more peripheral inflammatory pain compared to OA, where there may be a larger central contribution. Extrapolating from the Harris hypothesis (Harris 1999), the OA group may have a greater degree of cortical reorganisation and central pain. Another explanation could be that while in RA there may be grey matter increase, in painful OA there is grey matter decrease and therefore neuronal or glial loss may be more associated with pain.

5.5.4. Vision and sensory conflict mechanisms

Side effects of mirror visual feedback therapy including confusion, dizziness and irritation have been reported in phantom limb pain patients (Casale et al., 2009). Some healthy control and fibromyalgic subjects reported similar sensory disturbances to congruent mirror feedback, and to congruent /incongruent movements during whiteboard stages (one limb hidden with no visual feedback) (McCabe et al., 2005b;McCabe et al., 2007). This demonstrates that low levels of visual feedback discrepancy may be responsible for sensory disturbances, and may partially account for the reported side effects. My work suggests that visual feedback may be dominant over proprioceptive feedback. In this study when comparing the intermediate conflict stages (whiteboard incongruent and mirror congruent), there were higher reports of sensory disturbances during the mirror congruent stage. Therefore the 'false' visual feedback but congruent proprioception appears to be dominant compared to the whiteboard incongruent stage of no visual feedback but conflicting proprioception.

Vision is an important human sensory modality and can dominate other senses such as touch (Gibson J.J, 1962) and proprioception (Farne et al., 2000;Rock and Victor, 1964). It can also significantly affect proprioception. Healthy subjects can 'feel' touch during the rubber hand illusion (Ehrsson et al., 2004), and demonstrate skin conductance responses when the illusory rubber hand is threatened (Armel and Ramachandran, 2003). They can also be made to experience having three arms not only using MVF (McCabe et al., 2005b;McCabe et al., 2007), but also by incorporating a third rubber arm into the body image (Guterstam et al., 2011).

When performing visually guided actions such as drawing under conditions of perturbed visual feedback, e.g., in a mirror or a video camera, there is a spatial

conflict between visual and proprioceptive information. Repetitive transcranial magnetic stimulation (rTMS) over the somatosensory cortex contralateral to the hand has been shown to reduce proprioceptive acuity and enhanced mirror drawing performance (Balslev et al., 2004). A study utilising brain event-related potentials demonstrated activity in the motor cortex of the hidden hand during congruent and incongruent MVF (Touzalin-Chretien et al., 2010). The effect was greatly reduced when the task was executed in the dark with hand position represented by small lights fixed on the moving hand, with no motor activity being recorded in the cortical area of the hidden hand, demonstrating the dominance of vision over motor programming. Furthermore, visual stimuli do not have to reach visual awareness in order to guide rapid motor responses (Schenk et al., 2005).

A study of hand positions during observed movement in healthy controls showed that incompatible (but not compatible) movements elicited higher fMRI activation of the left dorsolateral prefrontal cortex and inferior parietal cortex bilaterally (Pilgramm et al., 2009). The authors suggest that this demonstrates the tight interaction between body representation and action observation. Data from my study shows that sensorimotor conflict generated by incompatibility may be a contributory mechanism. Cortical reorganisation may enhance the susceptibility to sensorimotor conflict and have a disruptive effect on the interaction between body representation and action observation in patients with chronic pain.

In my work, the incongruent stages of the protocol are used to generate sensorimotor conflict. There is little research in this area. However the congruent stages can be used therapeutically to reduce sensorimotor conflict, in mirror visual feedback (MVF) techniques. The evidence base for MVF is poor (Rothgangel et al., 2011) but there is growing literature in this area. As it embraces the congruent stages of the protocol, it is of relevance to the study.

5.5.5. Reducing sensory conflict as a therapeutic treatment: MVF

MVF is used therapeutically in CRPS (Karmarkar and Lieberman, 2006;McCabe et al., 2003) and in an increasing number of other clinical conditions (Grünert-Plüss et al., 2008;Ramachandran and Altschuler, 2009) including phantom limb pain (Chan et al., 2007;Ramachandran, 2005), stroke (Michielsen et al., 2011), fibromyalgia (Ramachandran and Seckel, 2010) and cerebral palsy (Smorenburg et al., 2011b;Smorenburg et al., 2011a). A study of MVF on arm control in children with Spastic Hemiparetic Cerebral Palsy found that it was most effective when viewing mirror feedback from the less impaired arm, suggesting that improved congruence

improves outcome. MVF has been used successfully prior to amputation to reduce post-operative phantom sensations (Hanling et al., 2010).

If the basis of the therapeutic effect is by improving sensory integration, then is there evidence for enhanced benefit by combining MVF with other sensory modalities? It has been demonstrated that effectiveness may be improved when combined with auditory feedback in phantom limb pain (Wilcher et al., 2011) and with graded motor imagery (Moseley, 2006) lenses (Ramachandran et al., 2009) and the use of prisms (Bultitude and Rafal, 2009) in CRPS.

5.5.6. Mechanisms of mirror visual feedback: the role of mirror neurones

The mechanisms operational during MVF will also be active in the congruent stages of my work, but how MVF achieves a beneficial effect is unclear. Ramachandran postulates that in phantom limb pain and stroke, restoring congruence between vision and motor output is able to compensate and aid recovery from 'learnt' paralysis (every time a motor command is sent to the intact arm, visual and proprioceptive feedback informs the brain that the limb is not moving) (Ramachandran and Altschuler, 2009). There are likely to be several potential mechanisms, some of which may involve mirror neurones.

Mirror neurones are a subset of motor neurones discovered by Rizolatti et al (Di Pellegrino et al., 1992) that fire when a person watches another individual perform a movement. They allow the individual to integrate the allocentric (environment outside the person) action into an egocentric (of the person) framework. This permits inference of action and learning of motor skills. Mirror neurones integrate multiple sensory modalities including vision, proprioception and motor commands. Use of MVF may stimulate mirror neurones helping to overcome 'learned' paralysis, and may stimulate previously dormant mirror neurones (Ramachandran and Altschuler, 2009).

Another potential mechanism is the role of ipsilateral corticospinal tracts. Little is known of their function, but there is evidence that they are involved in the timing of muscle recruitment (Davare et al., 2007) and in the pathology of congenital mirror movement (unintended and unnecessary movements accompanying voluntary activity in homologous muscles on the opposite side of the body) (Papadopoulou et al., 2010).

Mechanisms such as those described are also operational during an optokinetic mirror challenge, and abnormal activity may be involved in the origin of sensory disturbance and/or pain.

5.5.7. Motor extinction

An unusual finding was that of motor extinction during the optokinetic challenge. When asked to perform bilateral movements, many CRPS patients were unable to initiate motor action in the hidden limb without the visual feedback of the limb. Many demonstrating extinction were unaware that the hidden limb was not moving, and expressed great surprise. Motor extinction is usually seen after a stroke affecting the right parietal cortex, and is often associated with left hemispatial neglect. It is difficult to disentangle the motor neglect from the hemiparesis (Punt and Riddoch, 2006). However in the CRPS patient population, none had ever suffered from a stroke or had clinical symptoms or signs suggestive of a stroke. Therefore in this population, the motor extinction is most likely to be secondary to a neglect-like phenomenon rather than a cortical lesion causing a hemiparesis. Furthermore, neglect-like phenomena have been reported in CRPS (Galer and Jensen, 1999). For a fuller discussion of parietal cortex and neglect, see **Chapter 7**.

For the overall CRPS cohort, there was a strong negative correlation between the OVS vulnerability score and tactile threshold (ie. higher vulnerability, lower tactile threshold). However among CRPS patients with motor extinction compared to those without extinction, there was a higher OVS score but higher tactile thresholds. Patients with extinction therefore appear to have impairment in either sensory fibre function or central processing of afferent tactile information compared to those without extinction. Whether this is cause or effect remains unclear, and may be worthy of future research.

5.5.8. Dystonia

See discussion of **Chapter 6**.

5.5.9. Study strengths

This work was able to confirm findings from previous studies, and to enlarge upon research in the field by expanding it to include patients with OA and RA.

Use of a mirror to create an optokinetic challenge is a simple, non-invasive and practical means of patient assessment. It can also be used therapeutically. If a patient is suitable for mirror visual feedback, they are likely to have a mirror at home that they could use, or could easily obtain one.

The optokinetic vulnerability score (OVS) provides an insight into patterns of sensorimotor integration difficulties that a CRPS patient may experience. This can be used to inform the therapy approach. For example, if motor extinction is present then graded motor imagery might be more suitable.

5.5.10. Study limitations and future directions

Similar work needs to be done on a larger scale and in other patient cohorts with chronic pain. Not all protocols for MVF emphasise congruent movement, and therefore it is important to understand if congruence/incongruence has similar or different outcomes in these patients. In particular, similar work in patients with stroke and phantom limbs, where there is an absent or immobile limb, would be revealing. There needs to be better understanding of what cortical areas are active during an optokinetic challenge, and concurrent autonomic responses.

Further research should combine an optokinetic challenge with neuroimaging and autonomic assessment. There are alternatives to an optokinetic mirror device including the use of prism spectacles (Bultitude and Rafal, 2009;Walsh and Bannister, 2010) and augmented virtual reality (Cole et al., 2009;Henderson et al., 2007;Merians et al., 2002). Future work could use these technologies to create a similar optokinetic challenge, and establish whether similar types and rates of sensory disturbance and/or pain are seen in controls and patient cohorts. If this were the case, then there would be a strong case for similar mechanisms operating in visuo-sensorimotor incongruence rather than differences in the techniques used to create it.

Vulnerability is not confined to CRPS, and is higher in RA and OA than healthy controls. Future research should address the identification of central pain in OA and RA, and whether alternative treatment approaches (eg. pharmacologic, MVF) would be beneficial.

5.5.11. Clinical Implications

A direct consequence of this work is that the optokinetic challenge is now used to screen CRPS patients for the presence of motor extinction for the following reasons:

- If a subject is unable to perform congruent movements without visual input from both limbs, they will actually be performing incongruent mirror movements. The data has demonstrated that this is likely to cause sensory disturbances and/or pain.
- A patient with motor extinction requires a different approach for physical rehabilitation, as the therapist has to allow that motor action is non-existent or poor without visual input.

Some OA and RA patients have a high vulnerability to sensorimotor conflict. This group may have a larger central pain component and may benefit from different therapeutic strategies. Further research into these areas is required.

5.6. Summary

The hypothesis postulated was proven:

- During an optokinetic challenge, sensory disturbances and pain responses were more common in CRPS patients compared to healthy controls and patients with rheumatoid or osteoarthritis.

Some participants in all the cohorts experienced abnormal somaesthetic sensations and/or pain during the optokinetic challenge. There was a statistically significant difference between the cohorts, with a higher incidence of abnormal sensations and pain in the RA and OA cohorts, with the highest in the CRPS cohort. There was a strong association between optokinetic vulnerability and pain, with a high vulnerability subject more likely to experience pain than a minimally vulnerable subject. Within the CRPS cohort, optokinetic vulnerability was correlated with BSA, and negatively correlated with tactile threshold (higher vulnerability, lower tactile threshold).

Abnormal sensations were significantly more frequent in the stage of highest conflict (mirror incongruent movement) in all the cohorts. This stage also demonstrated significantly higher frequencies of enhanced pain among CRPS patients, and non-significantly increased rates for OA, RA and healthy control subjects. Motor impairment / extinction was noted in six OA and two RA patients, none of the healthy controls and in 67% of CRPS patients. CRPS patients with extinction had higher optokinetic vulnerability and higher tactile thresholds compared to CRPS patients without extinction. Unexpectedly, OA patients demonstrated higher vulnerability and a higher incidence of sensory disturbance and/or pain during an optokinetic challenge than RA or healthy control subjects.

5.7. Conclusions

It is suggested that in the majority of healthy controls and among many patients with chronic pain, a moderate level of sensorimotor conflict is required to exceed the sensory-motor discrepancy threshold and initiate sensory disturbances. The pain mechanism is separate and cannot usually be triggered by activation of the sensory-motor disturbance threshold. However in ‘vulnerable’ subjects, the threshold is lower and can activate pain networks which may be due to additional activation of top-down networks, possibly activated through impaired motor pathways and disrupted body schema. Cortical reorganisation may contribute to vulnerability.

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Chapter 6:

Sensory disturbances, pain responses and autonomic function while viewing ambiguous visual stimuli in complex regional pain syndrome (CRPS) and rheumatic disease

"Illness is the doctor to whom we pay most heed; to kindness, to knowledge, we make promise only; pain we obey."

Marcel Proust

Image: Unknown, 2011. Marcel Proust in 1900 [online]. Available from: http://en.wikipedia.org/wiki/File:Marcel_Proust_1900-2.jpg. [Accessed 18.1.2012].

6.1. Introduction

(Work from this study has been published as 'Enhanced pain and autonomic responses to ambiguous visual stimuli in chronic Complex Regional Pain Syndrome (CRPS) type I. Cohen HE, Hall J, Harris N, McCabe CS, Blake DR, Jänig W. Eur J Pain. 2011 Aug 6. [Epub ahead of print]'. See **Appendix 11**)

It has been hypothesised that disturbances in sensory and motor systems may cause sensorimotor conflict, generating pain and other sensory anomalies (Blake et al., 2000;Harris, 1999;Ramachandran et al., 1992). Specifically, conflicting visual information can worsen the pain in CRPS patients (Cohen HE et al., 2006;Hall et al., 2010). A functional MRI study has demonstrated that pain can impact on visual processing (Bingel et al., 2007). What has not been reported to date is the relationship between the responses of the autonomic nervous system, pain and visual processing.

Chapter 5 looked at how a visuo-sensorimotor conflict induced by an optokinetic challenge influenced somaesthesia and perception of pain. This study builds upon **Chapter 5** by investigating how stimuli causing a pure visual conflict - optical illusions (hence referred to as ambiguous visual stimuli (AVS)) might influence somaesthesia and pain in healthy controls and in patients with complex regional pain syndrome (CRPS), osteoarthritis (OA) and rheumatoid arthritis (RA). In **Chapter 4**, laser Doppler flowmetry was used to assess sympathetic autonomic function.

Previous work has demonstrated it to be a reliable and repeatable means to assess cutaneous microvascular blood flow (Bonelli and Koltringer, 2000;Low et al., 1983). Previous studies have demonstrated sympathetic abnormalities in CRPS (Wasner et al., 1999;Wasner et al., 2001) but the pattern of responses during painful stimuli in CRPS and patients with chronic rheumatic disease, and the possible contribution to pain is less known (Baron et al., 2002).

In this chapter, laser Doppler flowmetry is used to 1) investigate the dynamic sympathetic autonomic responses produced by a pure visual conflict in healthy controls, and patients with OA, RA and CRPS and 2) relate the autonomic response patterns to the somaesthetic disturbances induced by the visual stimulus.

6.1.1. Aims

To investigate sensory disturbances, pain responses and autonomic function while viewing ambiguous visual stimuli (AVS) in healthy controls (HC) and patients with OA, RA and CRPS.

6.1.2. Hypotheses

1. Viewing ambiguous visual stimuli (AVS) will cause sensory disturbances and enhanced pain responses in CRPS patients but not in healthy controls and patients with rheumatoid arthritis (RA) or osteoarthritis (OA).
2. Healthy controls, OA and RA patients will have homologous symmetric sympathetic autonomic responses in the upper limbs while viewing AVS.
3. Some CRPS patients will have abnormal (absent or asymmetric) sympathetic autonomic responses while viewing AVS compared to other CRPS patients with homologous symmetric sympathetic responses.
4. Abnormal sympathetic autonomic responses in CRPS patients while viewing AVS will be associated with enhancement of pain.

6.2. Methodological considerations

6.2.1. Assessment of responses to ambiguous visual stimuli: review of literature

"An adequate theory of visual perception must explain how the fleeting patterns of light upon the retinas give knowledge of surrounding objects. The problem of how the brain 'reads' reality from images is acute, because images represent directly but few, and biologically unimportant, characteristics of objects."
Professor Richard Gregory (Gregory, 1968).
Viewing certain optical illusions gives rise to systematic visual processing errors, which provide insights into how the brain resolves the problem of what objects are represented by which images. Professor Gregory argues that perceptions are predictive hypotheses whereby bottom-up (stimulus driven) signals from the eyes are read or interpreted with top-down (conceptually driven) knowledge of objects and with general sideways rules to generate perceptions of the external world (Gregory, 1998). He suggests that illusions can be classified by appearance and causes (Gregory, 1997).

The ambiguous visual stimuli selected for this study were a duck/rabbit figure and a Necker cube (**Fig.6.3**). These stimuli have different visual processing biases. The Necker cube is an example of an ambiguous depth illusion which can be used to demonstrate the presence of a central size scaling mechanism (Gregory, 1968). The duck/rabbit is a content-reversal type of ambiguous figure. The relative contribution from top-down and bottom-up processing to the reversals is debated and probably different between the two. There is electroencephalogram (EEG) evidence of a crucial role for early neural activity in Necker cube reversals consistent with bottom-up influences (Kornmeier and Bach, 2004). Another EEG study showed differences in top-down influences on voluntary reversal rate of the structural perspective Necker cube compared to the meaningful content duck/rabbit figure. Top-down moderation of reversal rate (subjects were asked to speed up or slow down the reversal rate) was less effective for the Necker cube figure (Struber and Stadler, 1999). A further investigation by the same group suggested that speeding up reversal rate needs attentional shift and may be supported by automatic bottom-up processes while slowing down the rate requires focus of attention and more top-down influences (Mathes et al., 2006). Other groups suggest a hybrid model in which both processes are coordinated and their effects integrated to determine conscious perceptual

experience (Kornmeier and Bach, 2006;Long and Toppino, 2004). For the Necker cube, eye position may also be a factor (Einhauser et al., 2004) which may suggest a visual dorsal stream bias (see below).

Retinal stimuli are conducted along the optic nerves to the lateral geniculate body, and then stream posteriorly via the optic radiation to the primary visual area in the occipital lobes. From here, information is conveyed by a phylogenetically older tract, the dorsal pathway, superiorly to the parietal lobe and visual areas which are concerned with orienting self to the object and its location in extrapersonal space. This pathway is mainly unconscious, and is sometimes referred to as the 'where' pathway. Visual information is also conveyed to parietal areas by the tectal pathway via the superior colliculi and is also unconscious, associated with orientation of the eyes to an object in space. Information is conveyed laterally along a phylogenetically more recent pathway, the ventral pathway, to the temporal lobe. This pathway is a conscious one and concerned with the discrimination of the characteristics of the object, the 'what' pathway (Goodale et al., 2005;Goodale and Milner, 1992;Goodale and Westwood, 2004;Westwood and Goodale, 2011).

Therefore, the Necker cube and duck/rabbit are likely to differentially stimulate these pathways. A study which combined functional magnetic resonance imaging (fMRI) and EEG while viewing the Necker cube suggested a dorsal stream spread of activation with additional top down processing (Schoth et al., 2007).

There is increasing evidence from neuroimaging studies for the role of the parietal cortex in having distinct patterns of causal influence upon functional activity in the human visual cortex (Ruff et al., 2008). Specifically during misperception such as decision making under visual uncertainty (Summerfield et al., 2006), during ambiguous apparent motion (Williams et al., 2003) and while viewing ambiguous figures (Hirsch et al., 2004). An fMRI study has demonstrated that right parietal cortex brain activity precedes perceptual alternations of the Necker cube (Britz et al., 2008).

There are many different versions of the duck/rabbit figure from the original in 'Fliegende Blätter' in 1892, the Jastrow (Jastrow, 1899) and Wittgenstein (Wittgenstein, 1998) (**Fig.6.1**) versions, and many others since. The duck/rabbit figure selected **Fig.6.3**) was Jastrow's original drawing where the ears/bill are orientated horizontally. A study has suggested that of the many versions, this one is truly ambiguous and not markedly either duck or rabbit dominant (Brugger, 1999). Necker's original cube (Necker, 1832) was a rhomboid. An open cube is the modern

standard version. For this study, the Necker cube and the non-reversible control figure had a visual fixation point located centrally (**Fig.6.3**).

Fig.6.1.

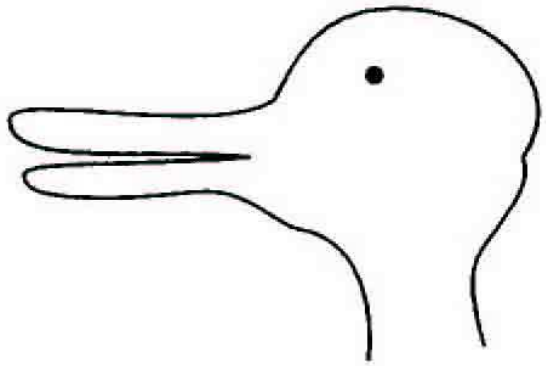


Fig.6.1. The Wittgenstein duck rabbit figure

6.2.2. Control figure

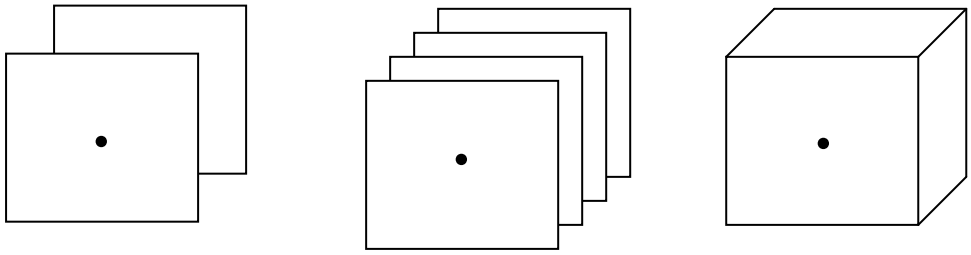
A non-reversible control figure was required as a comparator for the ambiguous visual stimuli. In pilot work with healthy controls and CRPS patients, it was quickly apparent that simple geometric designs, such as **Fig.6.2A**, were described as "moving" by some in both groups. The next control figures tried were a white blank page, and a black square. For some subjects (CRPS and controls), the blank page was described as making 'floaters' more apparent which then "danced" across the sheet. A black square was described as having "the corners curling up". Others described a variety of emotions associated with these. Word used to describe the blank page included "calming", "relaxing" and "pure", and for the black square, "depressing", "a dark hole", and "like a coffin – it reminds me of death". As the geometric shapes did not generate many emotional descriptions, the next design used was a simple square with a central fixation dot. This was not described as transforming into any other shape or design, and did not generate emotional responses, and was therefore used as the minimally ambiguous non-reversible control figure (C), (**Fig.6.3**).

Control images were also piloted among control and CRPS subjects for the duck/rabbit figure. A photograph of a duck's head and a rabbit's head as similar as possible to the percept of the duck or rabbit on the duck/rabbit ambiguous figure were used **Fig.6.2B**). While these images were not reported as moving, there were

emotive descriptions eg. “what a cute rabbit”, “it reminded me of the Easter bunny”, “the duck’s head looks removed from the body; it’s quite unsettling”. Many subjects describe being distracted by trying to see a duck when looking at the photograph of the rabbit and vice-versa.

Fig.6.2.

A



B

Fig. 6.2. Illustrations of pilot control figures for **A**: the Necker cube and **B**: the duck/rabbit figure

6.2.3. Autonomic responses to pilot control figures in healthy controls

As mentioned in **Chapter 4**, absence of a LDF response to a stimulus is highly significant. **Table 6.1** demonstrates that the rate of ‘no response’ to the chosen control figure (C) is similar to that of the blank page (B) and the black square (BS), but markedly different to those of the photograph of a duck (phD) or rabbit (phR). The group median value of the mean percentage change from baseline skin blood flow (Δ%bbf) showed a similar pattern. Therefore the photographs were not utilised. As the control figure needed to avoid emotional responses if possible, the blank page and black square were also eliminated. The simple square with a central fixation dot was selected as the control figure for the study.

Table 6.1. Laser Doppler flowmetry (LDF) autonomic responses among healthy controls to viewing different proposed control figures.

No response	C (n = 40)	B (n = 22)	BS (n = 22)	phD (n = 10)	phR (n = 10)
Number	11	6	5	4	5
%	27.5	27.3	22.7	40	50
Δ%bbf	57	44	60	33	21

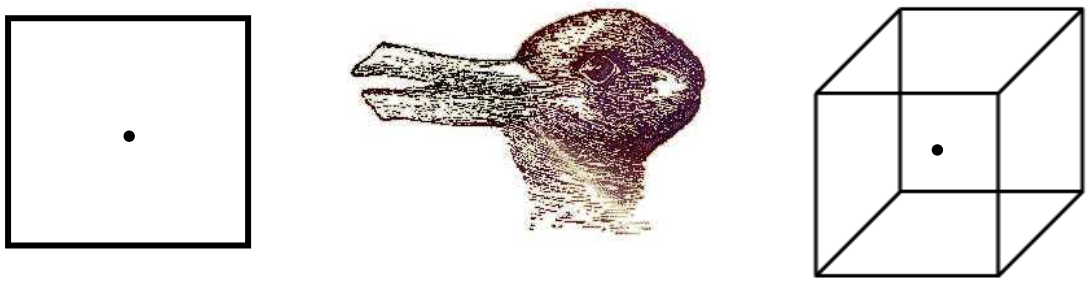
C = minimally ambiguous control figure, B = blank page, BS = black square, phD = photograph of a duck, phR = photograph of a rabbit, Δ%bbf = group median value of the mean percentage change from baseline skin blood flow.

6.2.4. Stimulus presentation order

Initially, the order of presentation was randomised. It was quickly apparent that there was a clear gradation of the stimuli likely to induce abnormalities of sensation or pain in the CRPS patients. Therefore, as with the optokinetic challenge, the order was standardised to allow for a gradual increase in challenge, with the non-reversible control figure presented first before the ambiguous figures. This order was maintained for healthy controls and subjects with OA and RA.

The order was: control figure, duck/rabbit, Necker cube. The figures used are illustrated in **Fig.6.3**.

Fig.6.3.



Non-reversible figure Duck/rabbit Necker cube

Fig.6.3. The visual stimuli utilised

6.2.5. Communication and language considerations

Extreme care was taken with the choice and style of language used to explain the tasks, and for qualitative assessments. This was necessary to avoid leading subjects or introducing bias. Qualitative assessments were made throughout by a series of open questions. As far as possible, no specific direct enquiry was made about possible sensory changes to prevent leading the subject and creating bias. Specific prompts were used if necessary as follow-up to positive responses to open questions, or where it is clear that the subject did not understand the question. For full details, see **6.3.1. Subject preparation/instruction** below.

6.2.6. Assessment of pain

Qualitative assessments of pain were made before and after exposure to AVS. A verbal assessment was selected over a written one, as viewing an additional shape (i.e. line bisection test) might interfere with the assessment. In addition, many subjects had CRPS of the upper limb, and if the subject experienced disorientation or an increase in pain then a written assessment would be difficult to perform and lack accuracy. An 11 point verbal Likert scale (Likert, 1952), was utilised in pilot work. However, most CRPS patients put their baseline pain levels at 8, 9 or 10 giving little scope to understand how the pain had changed if it increased. Therefore a simple verbal scale was used where patients were asked if their pain was unchanged or mild, moderate or severely worse or better than baseline.

6.2.7. LDF recording environment

The autonomic testing was performed in a quiet, temperature and humidity controlled room. There were no pictures or ornamentation in the room to avoid arousal of emotional responses or diversion of attention.

6.2.8. Participants

For full details of inclusion/exclusion criteria etc, see **Chapter 3**.

6.2.9. Ethical considerations

It was possible that viewing the ambiguous visual stimuli might result in abnormal somaesthetic sensations, amounting to pain in some healthy subjects, and worsening of CRPS pain in some patients. However, from clinical experience both personally and within our group such sensations in healthy controls are short lived and resolve

completely, and in CRPS patients their pain returns to baseline levels within minutes to a few hours. All participants were forewarned of this possibility, and it was detailed in the patient information together with contact details if participants did experience this and required further input (see **Appendix 2**). This was accepted by the local ethics committee.

6.2.10. Apparatus

- Set of A4 sized laminated pictures
- Stopwatch
- LDF and ESR recording equipment

6.3. Method

6.3.1. Subject preparation/instruction

All subjects were informed that the purpose of the study was to investigate whether people with chronic pain differ from healthy controls in processing visual signals due to the attentional demands of pain, and that this could affect nerves controlling skin blood flow. The explanation met the criteria for informed consent as outlined by the approving ethics committee but was considered sufficiently vague not to induce a source of bias. Subjects were told that they would first do two simple tasks known to affect skin blood flow, a deep breath and mental stress test. They were instructed that after this, they would be viewing a series of pictures for one minute per picture, with the possibility that some of these pictures could be viewed in more than one way so that different images were perceived. After viewing the pictures, subjects would be asked to describe what they had seen and if they noticed any change in the way they felt. However, subjects were informed that it was normal for some people not to see an alternative image and if this were the case, then the investigator would explain the alternative percept and rerun the session for that image. In order to avoid leading or conditioning the subjects, no further descriptions of the pictures or how they might be seen was given. Subjects were not told at any time point that they might experience any concurrent somesthetic sensations, and were only asked how they had felt at the end.

A single investigator (HC) conducted the intervention and collected the autonomic recordings. Information on somesthetic or pain responses was gained via

open ended questions from a prepared script to ensure uniformity across subjects. All responses were recorded verbatim and additional notes were made by the investigator on any observable physical responses or reactions.

6.3.2. Visual stimulus exposure

A standardised sequence of three visual stimuli used: a control figure (C), and two ambiguous visual stimuli - the duck/rabbit (DR) figure and the Necker cube (N).

The visual stimuli were printed in black and white on A4 sized laminated white cardboard and presented to seated subjects at a distance of 1 metre approximating reading distance. The visual subtended angle was approximately 5° (this figure is approximate as the participants were invited to view the images from a comfortable, rather than precisely determined position). Subjects used their usual visual aids for reading if required and were asked to view each picture for a maximum of one minute, or as long as tolerated. Subjects had a 2 minute rest period between each visual stimulus when the pictures were hidden from view. If needed, subjects could have a further 1 minute up to a maximum of ten minutes rest time.

6.3.3. Pain and somesthetic assessment

Baseline pain levels and changes in pain levels to stimuli were assessed using a verbal four point Likert scale (Likert, 1952) covering a range of none, mild and moderate to severe. For changes in pain, subjects were asked to rate whether this was mild, moderately or severely worse or better compared to their baseline pain. If subjects reported any changes in how they felt, the responses were recorded verbatim.

6.3.4. Frequency of changes in image percept

Subjects were asked to report approximately how many times the visual stimuli had reversed, or ‘flipped’. Subjects had not been forewarned of this question to avoid participants counting reversal changes which would bring in additional undesired attentional demands.

6.3.5. Autonomic response assessment

6.3.5-1. Autonomic sympathetic responses upon exposure to ambiguous stimuli

Continuous Laser Doppler flowmetry (LDF) and electrodermal skin response (ESR) recordings were taken while viewing ambiguous visual stimuli. The full details of the autonomic assessment method are given in **Chapter 4**. Each stimulus was followed by a resting period of 1 – 5 minutes to allow the trace to return to baseline.

6.3.5-2. Laser Doppler Flowmetry analysis

To summarise from **Chapter 4**, the following outcome measures were used:

Quantitative

For LDF:

- Mean percentage change from baseline skin blood flow (Δ%bbf) in response to a stimulus as follows: Δ%bbf = (baseline mean – minimum) / baseline mean x 100
- The symmetry ratio (SR) of the magnitude of vasomotor responses between the limbs was calculated as follows: Δ%bbf limb A / Δ%bbf limb B, where A was the larger of the two responses.

Qualitative

For LDF: Responses to stimuli were classified as

- i. "homologous" response if there were bilateral sympathetic vasoconstrictor responses
- ii. "asymmetric" response if there was vasoconstriction in one limb but no response or vasodilation in the other limb.
- iii. "absent" if there was no response

For ESR: Responses were classified as

- i. "normal" response if there were bilateral symmetric responses
- ii. "abnormal" if responses were present but either unilateral, or abnormal non-sinusoidal waveform
- iii. "absent" if there was no response

6.3.6. Data analysis

6.3.6.1. Sample size

CRPS is considered to be a rare diagnosis and the literature is sparse. Papers are often based upon small numbers using different diagnostic criteria. Therefore, it was not possible to make an accurate sample size calculation.

A non-random sampling strategy was used, and the sample size was based upon the number of subjects available within the data collection period.

6.3.6.2. Statistical analysis

The same approach was used as described in **Chapter 4**. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) v.16 software. For comparisons, non-parametric statistics were used (Mann-Whitney *U*-test and Kruskal-Wallis test), and for frequency analysis, Fisher's exact test. For comparison of SR data across cohorts, the Siegel-Tukey test (a non-parametric sum of ranks procedure for relative spread in unpaired samples) was used. Odds ratios (OR) and 95% confidence intervals (%% CI) are calculated where appropriate.

6.4. Results

Terminology:

Visual stimuli (VS): collective term for all three of the visual stimuli utilised.

Ambiguous visual stimuli (AVS): refers to the ambiguous visual stimuli used ie. the duck/rabbit (DR) and the Necker cube (N)

6.4.1A. Demographic data

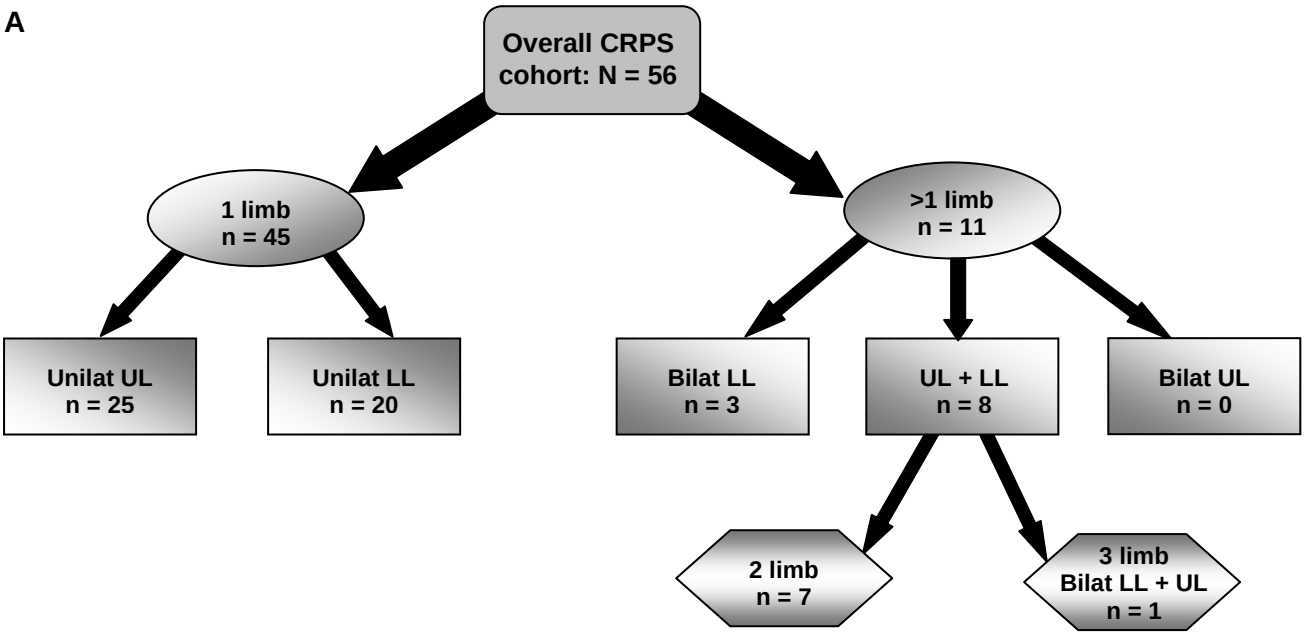
Forty healthy controls, 40 OA, 40 RA and 54 CRPS patients underwent assessment of sensory disturbances and autonomic function testing while viewing visual stimuli (VS). For details of demographics, see **Chapter 4**, section **4.4.1.**

6.4.1B. Location of CRPS

For schematic flow chart of data presented, see **Fig.6.4** (reproduced from **Chapter 4** for ease of reference).

Fig.6.4.

A



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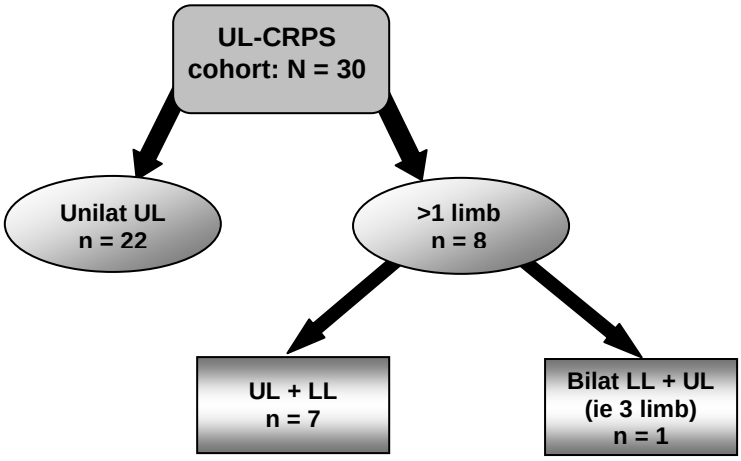


Fig.6.4. Schematic flow chart of CRPS location demographics. **A** shows the overall CRPS cohort, and **B** the upper limb CRPS cohort.

UL = upper limb, LL = lower limb, unilat = unilateral, bilat = bilateral

6.4.2. Sensory disturbances

6.4.2.1. Healthy controls, OA and RA

None of the healthy controls (n = 40), OA or RA subjects developed sensory disturbances while viewing any of the visual stimuli (VS).

6.4.2.2. CRPS

In contrast, 8 (27%) of the UL CRPS cohort experienced sensory disturbances while viewing ambiguous visual stimuli (AVS). These were described as heaviness, tingling/pin & needles, feelings of swelling/tightness or sensations of changing temperature in the upper limbs (ie. limb feeling subjectively warmer or colder). Six experienced this while viewing both AVS and 2 only while viewing the Necker cube (N).

6.4.3. Visual stimuli exposure and pain

6.4.3.1. Healthy controls

None of the healthy controls (n = 40) experienced pain while viewing either the non-reversible control figure or the ambiguous visual stimuli (AVS) for the full 60 seconds. The mean ambiguous figure reversal rate was 14 times per minute for the duck/rabbit (DR) and 12 for the Necker cube (N).

6.4.3.2. Osteoarthritis and rheumatoid arthritis patients

None of the OA or RA subjects experienced pain while viewing either the control figure or the ambiguous visual stimuli (AVS) for the full 60 seconds. Among OA patients, the mean ambiguous figure reversal rate was 9 times per minute for the duck/rabbit and 8 for the Necker cube while for RA it was 9 times per minute for the duck/rabbit and 6 for the Necker cube.

6.4.3.3. CRPS

In contrast, 19 (61%) of the UL-CRPS cohort experienced enhancement of their pain within seconds of viewing the VS (**Table 6.2**). Eighteen (60%) had worse pain viewing the Necker cube and 16 (53%) viewing the duck/rabbit figure. Unexpectedly, 6 (20%) had worsening pain viewing the control figure. Pain severity ratings for individual patients were similar across the types of inciting visual stimuli. For details of numbers with mild, moderate or severely worsening pain, see **Table 6.2A**.

Nine (47%) were unable to view the VS for the full 60 seconds. The mean duration of the viewing time for patients with enhanced pain during VS was 43 seconds (s), range 5 – 60s. The pain exacerbation lasted for 30 minutes to several hours. All the patients that had enhanced pain with the control figure found it unstable, with the central fixation dot and box edges described as “moving”. Eleven subjects described an extremely high reversal rate of images, as “too fast to count”. Patients with pain were significantly more likely to describe reversal rates as ‘too fast to count’ (Fisher’s exact test, $p<0.05$). For further breakdown, see **Table 6.2B**. The odds ratio showed that a patient with pain while viewing AVS was 13.7 (95%CI 1.5;120) times more likely to report a reversal count as ‘too fast to count’ than a patient without pain.

Table 6.2. Changes in pain, reversal rates and time of viewing tolerated while looking at visual stimuli.

A. Changes in pain

	Cohort			
Change in pain	UL-CRPS (n = 30)	HC (n = 40)	OA (n = 40)	RA (n = 40)
None	11 (36.5%)	40 (100%)	40 (100%)	40 (100%)
Mild	2 (7%)	0	0	0
Moderate	9 (30%)	0	0	0
Severe	8 (26.5%)	0	0	0

UL = upper limb, HC = healthy controls, OA = osteoarthritis, RA = rheumatoid arthritis

B. Time of viewing and reversal rates

	Viewing duration			Reversals			
	Time (secs)			Mean no. reversals		Reversals 'too fast to count'	
	C	DR	N	DR	N	DR	N
HC (n = 40)	60	60	60	14	12	0	0
OA (n = 40)	60	60	60	9	8	0	0
RA (n = 40)	60	60	60	9	6	0	0
UL-CRPS (n = 30)	50	46	42	14	11	7 (23%)	10 (33%)
UL-CRPS & pain (n = 19)	50	46	42	16	14	7 (37%)	9 (47%)

UL-CRPS & pain = CRPS patients with pain while viewing visual stimuli

Reversals 'too fast to count' = number of patients reporting this phenomenon

6.4.4. Autonomic responses during visual stimuli exposure

For autonomic testing, please also note (summarised from **Chapter 4**):

1.1. 31/54 CRPS patients had upper limb (UL) involvement. One subject had a previous sympathectomy and was excluded from analysis. Therefore for the UL cohort, n = 30. Autonomic function testing data for UL affected CRPS patients is presented (See **4.2.2.8. Location of LDF recording probes**).

1.2. Comparison of UL-CRPS cohort (n = 30) with the overall-CRPS cohort (n = 54) is given in section **6.4.10.**

2.1. 40 healthy controls (HC) had autonomic function testing while viewing AVS (overall HC cohort). From the overall HC cohort, 30 were matched for gender and age (to within 10 years) to the UL-CRPS cohort, forming the 'matched HC' cohort.

2.2. For healthy controls, the autonomic function testing data presented while viewing VS is taken from the overall HC cohort, and compared to the other cohorts.

2.3. In a subgroup analysis, data from the matched HC cohort is compared to the UL cohort (**6.4.6.**). The matching reduces potential bias from gender and age differences. Comparison of the matched and unmatched HC data (**6.4.4.1C.**) provides an indication of potential confounding effects from these factors.

6.4.4.1. Healthy controls

6.4.4.1A. Healthy controls (overall cohort n = 40)

Qualitative analysis of the LDF responses showed that 35 (87.5%) had "normal" and 5 (12.5%) had "absent" responses while viewing VS. See **Fig.6.5**.

Of the normal responses, viewing VS resulted in either homologous LDF vasoconstrictor responses to all stimuli in 24 (60%) matched HC subjects or 'mixed' homologous vasoconstrictor responses to some of the visual stimuli in 11 (27.5%). For details, see **Table 6.3** and **Fig.6.6**.

The median Δ%bbf (IQR) for the C, DR and N stimuli were 59 (78), 56 (62) and 59 (64). The median SR (IQR) for the C, DR and N visual stimuli were 1.06 (0.24), 1.07 (0.23) and 1.06 (0.16)(**Fig.6.7** & **6.8**). See **Table 6.4**.

ESR responses while viewing VS were normal in 24 (60%) and absent in 15 (37.5%). One subject had no discernable trace.

6.4.4.1B. Matched healthy controls (n = 30)

Qualitative analysis of the LDF responses showed that 27 (90%) had normal and 3 (10%) had absent responses while viewing VS.

Of the normal responses, viewing VS resulted in either homologous LDF vasoconstrictor responses to all stimuli in 17 (57%) matched HC subjects or 'mixed' homologous vasoconstrictor responses to some of the visual stimuli in 10 (33%).

The median Δ%bbf (IQR) for the C, DR and N stimuli were 57 (78), 52 (78) and 64 (88). The median SR (IQR) for the C, DR and N visual stimuli were 1.07 (0.22), 1.06 (0.22) and 1.07 (0.15)(**Fig.6.9**). See **Table 6.4**.

ESR responses were normal in 18 (60%) of matched controls, and were absent to viewing visual stimuli in 11 (37%). One subject had no discernable trace.

Table 6.3. Qualitative autonomic testing data: breakdown of frequency of responses while viewing visual stimuli.

				'Mixed' responses						
		R-all VS	NR-all VS	NR-C			R-C			NDT
				R-AVS	R-DR	R-N	NR-AVS	R-DR	R-N	
ESR	HC (n = 40)	21	15	0	0	1	2	0	0	1
	OA (n = 40)	7	20	4	2	3	2	0	1	0
	RA (n = 40)	5	22	0	3	1	1	4	2	2
	CRPS (n = 30)	19	4	0	0	3	4	0	0	0
LDF	HC (n = 40)	24	5	4	1	1	1	2	2	0
	OA (n = 40)	12	15	5	2	2	2	1	1	0
	RA (n = 40)	15	12	1	4	2	2	2	2	0
	CRPS (n = 30)	17	3	1	1	2	0	2	0	4

R = response, NR = no response, ESR = electrodermal skin response, LDF = Laser Doppler flowmetry, NDT = no discernable trace

VS = visual stimuli, C = control, DR = duck/rabbit, N = Necker cube, AVS = ambiguous visual stimuli (ie. DR & N), HC = healthy controls, OA = osteoarthritis, RA = rheumatoid arthritis CRPS = complex regional pain syndrome

NB. This breakdown shows frequency of response (present, absent) to viewing VS. Among the CRPS cohort, it does not differentiate whether responses are homologous or abnormal.

Fig.6.5.

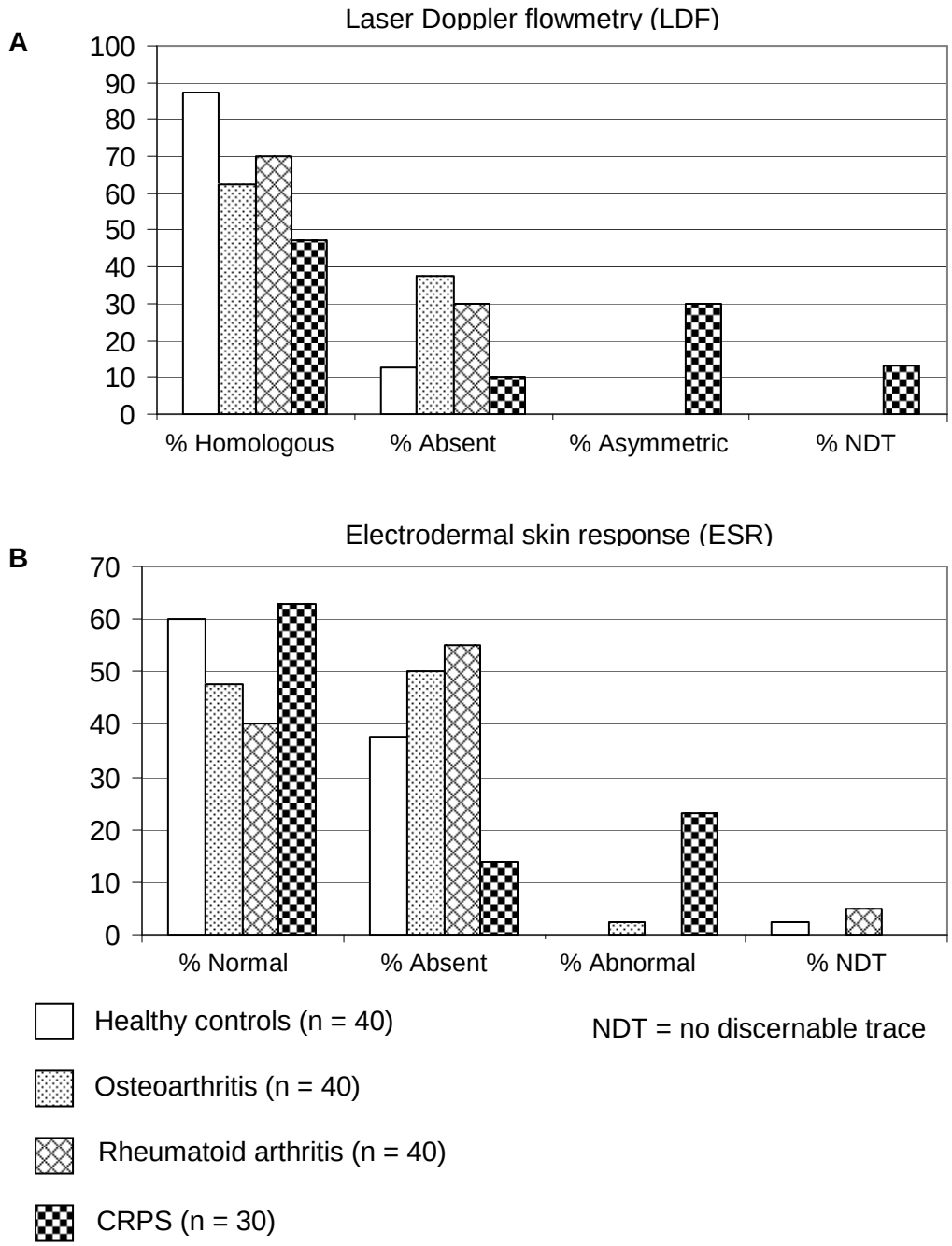
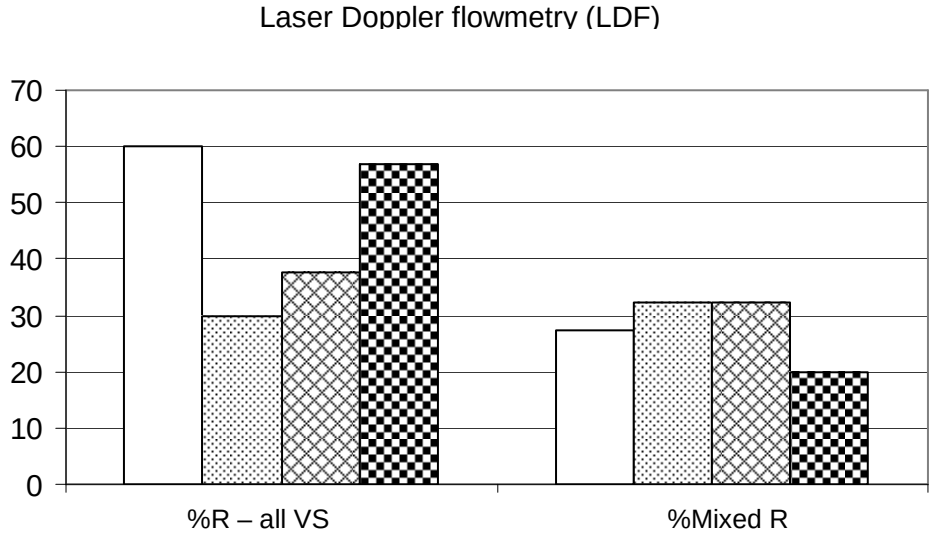


Fig.6.5. Qualitative analysis of **A.** LDF responses and **B.** ESR responses for viewing all visual stimuli.

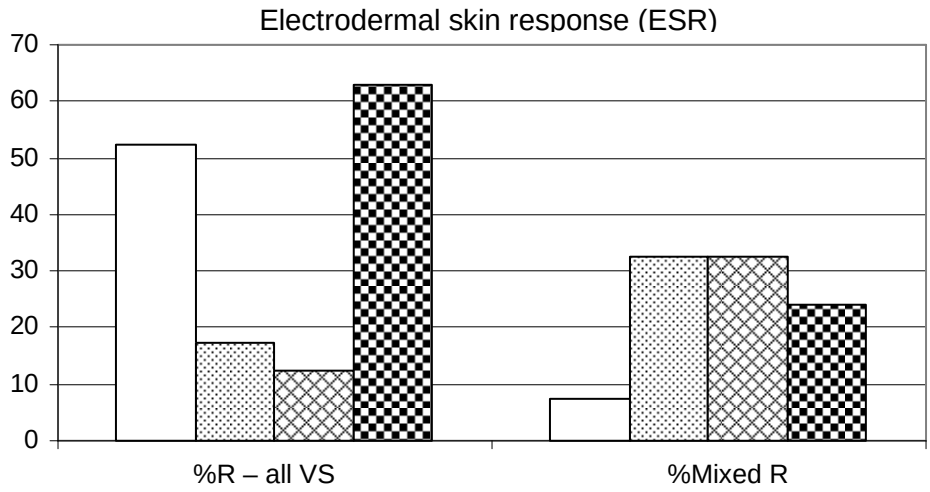
Percentages of responses classified as **A.** homologous, absent, asymmetric or NDT and **B.** normal, absent, abnormal or NDT are illustrated.

Fig.6.6.

A



B



Healthy controls (n = 40)

Osteoarthritis (n = 40)

Rheumatoid arthritis (n = 40)

CRPS (n = 30)

%R = response to all VS

%Mixed R = responses to some VS

VS = visual stimuli (control, duck/rabbit and necker cube)

Fig.6.6. Qualitative autonomic testing data: breakdown of **A.** LDF and **B.** ESR traces recorded in response to all VS or to some of the VS.

6.4.4.1C. Comparison of overall and matched control cohorts

The mean ambiguous figure reversal rate was the same for the overall and matched HC groups, at 14 times per minute for the duck/rabbit (DR) and 12 for the Necker cube (N).

Comparison of the qualitative response trace pattern frequencies and quantitative autonomic response data does not show any significant differences between the overall and matched cohorts.

6.4.4.2. Osteoarthritis and rheumatoid arthritis

LDF responses were "normal" in 25 (62.5%) OA / 28 (70%) RA, and "absent" in 15 (37.5%) OA / 12 (30%) RA. One OA subject had an "abnormal" LDF trace while viewing all VS (no discernable trace in the right upper limb) (**Fig.6.5**).

Of the normal responses, viewing VS resulted in either homologous LDF vasoconstrictor responses to all stimuli in 12 (30%) OA / 15 (37.5%) RA subjects or 'mixed' homologous vasoconstrictor responses to some of the visual stimuli in 13 (32.5%) OA / 13 (32.5%) RA. For details, see **Table 6.3** and **Fig.6.6**.

The median Δ%bbf (IQR) among subjects with OA for the C, DR and N stimuli were 0 (29), 9 (50) and 8 (39). The median SR (IQR) for the C, DR and N visual stimuli were 1.0 (0.14), 1.02 (0.31) and 1.01 (0.3). Among RA patients, the median Δ%bbf (IQR) for the C, DR and N stimuli were 25 (51), 19 (46) and 7 (48). The median SR (IQR) for the C, DR and N visual stimuli were 1.0 (0.15), 1.04 (0.29) and 1.01 (0.25). See **Table 6.4**.

ESR responses were normal in 19 (47.5%) OA and 16 (40%) of RA subjects. They were absent to viewing visual stimuli in 20 (50%) of OA and 22 (55%) of RA subjects (**Fig.6.5**). There was one abnormal trace in an OA patient (asymmetric impedance between limbs) and 2 RA patients had completely flat non-reactive traces.

6.4.4.3. CRPS (UL cohort, n = 30)

LDF responses while viewing VS were "normal" in 14 (35%), "absent" in 3 (10%), "abnormal" asymmetric responses (see **Fig.6.5** and **6.7**) in 9 (30%) and non-discernable in 4 (13%) (see below).

There were 17 (57%) CRPS patients with LDF responses to all the VS and 'mixed' homologous vasoconstrictor responses to some of the visual stimuli in 6 (20%). For details, see **Table 6.3** and **Fig.6.6**. There was excessive vasoconstriction with skin blood flow <150 AFU at a room temperature of 23-35°C in 4 subjects, and therefore undiscernable 'absent' traces. Variability was evident within individuals as

to which of the visual stimuli that induced enhancement of pain also caused asymmetric responses (see **Table 6.5**).

The median Δ%bbf (IQR) for the C, DR and N stimuli were 30 (55), 35 (61) and 37 (53). The median SR (IQR) for the C, DR and N visual stimuli were 1.24 (1.5), 1.11 (1.29) and 1.32 (3.4). See**Table 6.4**.

ESR responses were normal in 19 (63%) of UL-CRPS subjects. They were absent to viewing visual stimuli in 4 (13%) and abnormal in 7 (23%) (**Fig.6.8**). Five of the 7 abnormal traces were in patients with pain while viewing visual stimuli, and 3/7 were in subjects with asymmetric LDF traces.

Table 6.4. Quantitative autonomic testing data (medians and interquartile range, IQR) while viewing visual stimuli (VS).

	Cohorts							
Visual stimulus	CRPS UL (n = 30)		Healthy controls (n = 40)		Osteoarthritis (n = 40)		Rheumatoid arthritis (n = 40)	
	Δ%BBF (IQR)	SR (IQR)	Δ%BBF (IQR)	SR (IQR)	Δ%BBF (IQR)	SR (IQR)	Δ%BBF (IQR)	SR (IQR)
Control	30 (55)	1.24 (1.5)	59 (78)	1.06 (0.24)	0 (29)	1.0 (0.14)	25 (51)	1.0 (0.15)
Duck/rabbit	35 (61)	1.11 (1.29)	56 (62)	1.07 (0.23)	9 (50)	1.02 (0.31)	19 (46)	1.04 (0.29)
Necker	37 (53)	1.32 (3.4)	59 (64)	1.06 (0.16)	8 (39)	1.01 (0.3)	7 (48)	1.01 (0.25)

	Cohort	
Visual stimulus	Age & gender matched HC (n = 30)	
	Δ%BBF (IQR)	SR (IQR)
Control	57 (78)	1.07 (0.22)
Duck/rabbit	52 (78)	1.06 (0.22)
Necker	64 (88)	1.07 (0.15)

HC = healthy controls

Δ%BBF = group median value for mean percentage change from baseline blood flow, SR = symmetry ratio.

Fig.6.7.

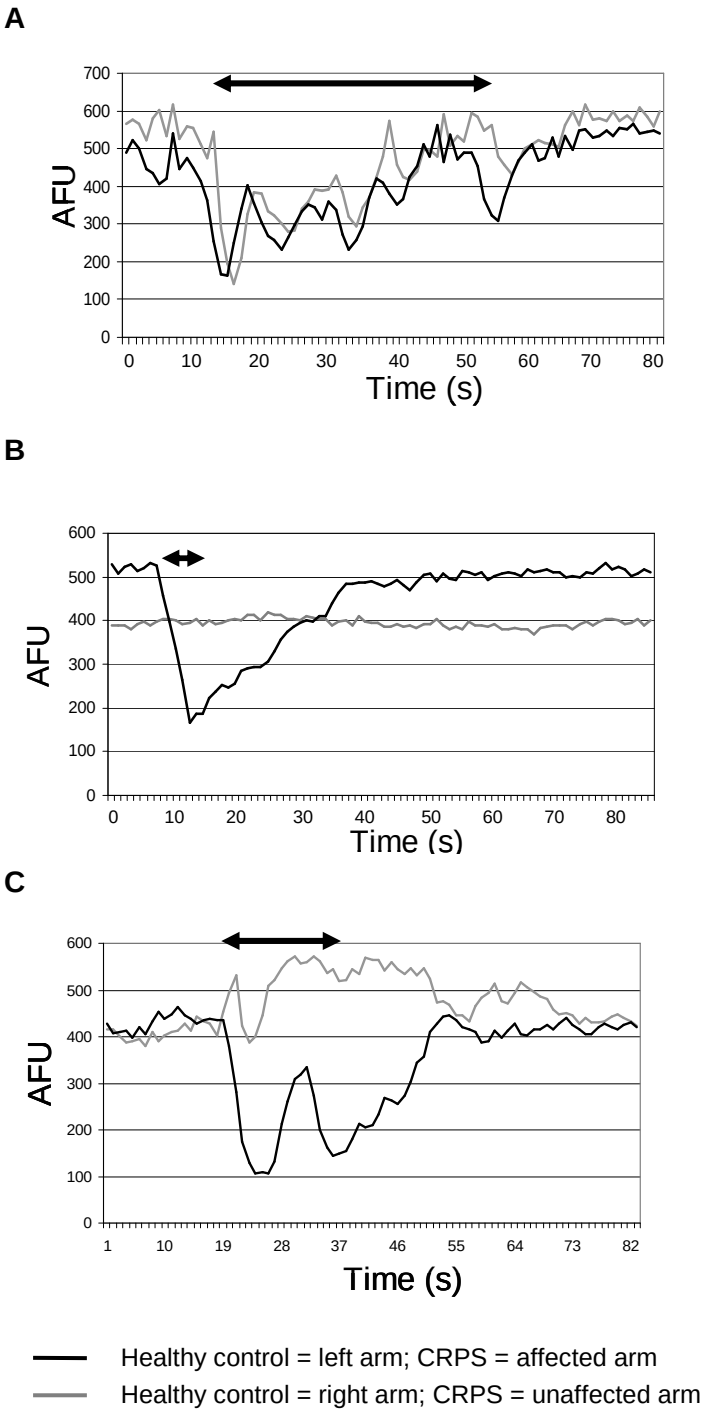


Fig.6.7. A-C: Examples of LDF vasomotor responses while viewing AVS from three different CRPS patients.

A: Example of homologous laser Doppler traces from a CRPS patient while viewing AVS (duck/rabbit). **B,C**: Examples of asymmetric vasomotor responses while viewing AVS (B = Necker cube, C = duck/rabbit).

Time is in seconds is on the X axis, and blood flow in arbitrary flux units (AFU) is on the Y axis. The vertical arrow shows onset of the stimuli, and the horizontal arrows the duration of visual stimulus exposure. LDF = laser Doppler flowmetry.

Fig.6.8.

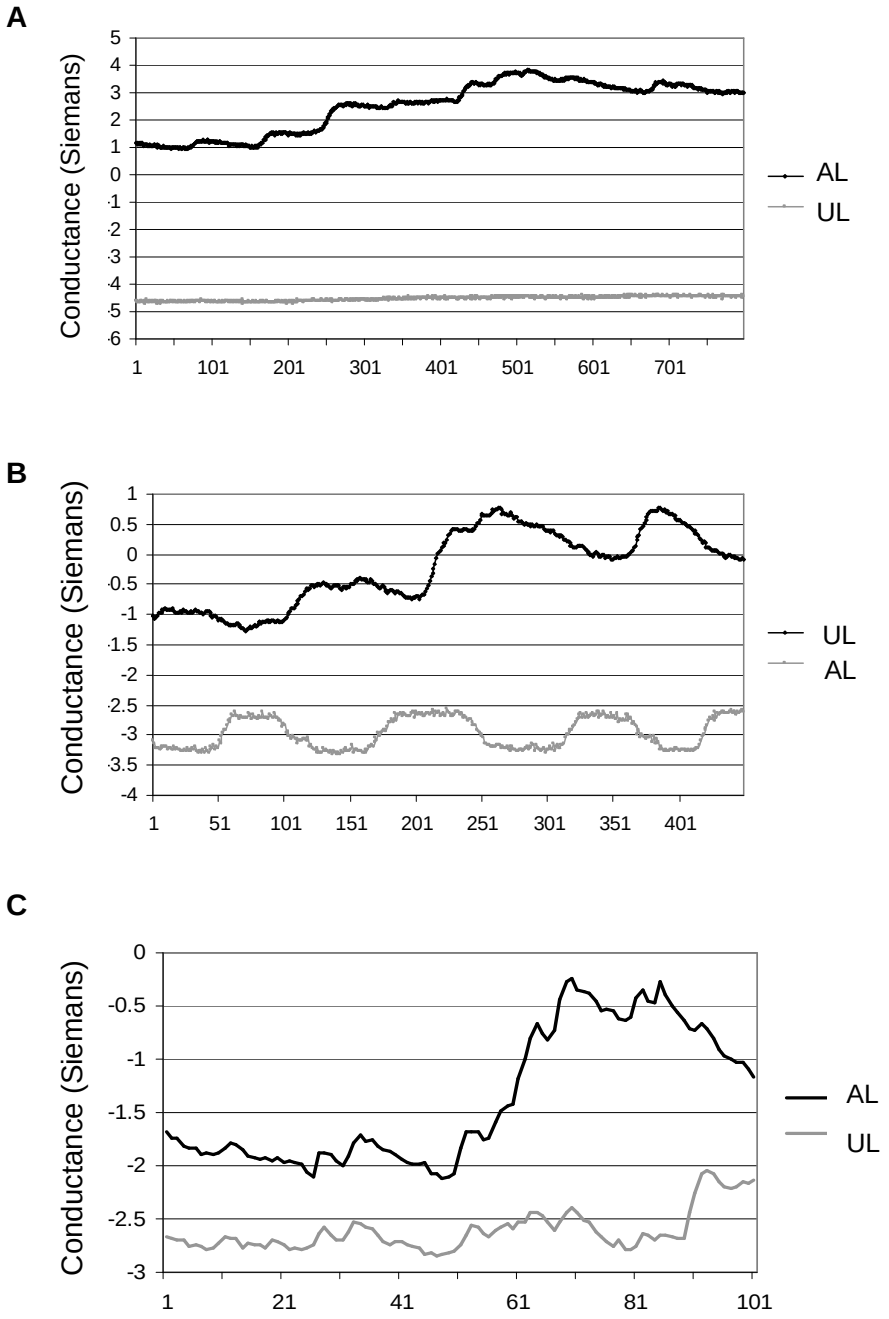


Fig.6.8. A-C: Examples of abnormal asymmetric electrodermal skin responses (ESR) while viewing AVS from three different CRPS patients.

A,B: Examples of asymmetric ESR from a CRPS patient while viewing a duck/rabbit figure.
C: Examples of asymmetric ESR while viewing a Necker cube.

Time is in seconds is on the X axis, and skin conductance in Siemans is on the Y axis. The vertical arrow shows onset of the stimuli, and the horizontal arrows the duration of visual stimulus exposure. AL = affected limb, UL = unaffected limb.

6.4.8. Dystonia during visual stimuli

Ten (33%) in the UL-CRPS cohort developed acute dystonic reactions in the affected limb (**Table 6.5**). The dystonia was characterised by involuntary flexion of the fingers and wrist in the affected limb and / or tremor. Eight subjects had enhanced pain and dystonic reactions; 5 while viewing all the VS, two viewing AVS and 1 while looking at the Necker cube only. Two subjects had no pain and dystonia; 1 viewing AVS, and 1 to the Necker cube only.

Fig.6.9. demonstrates the relationship between enhancement of pain, asymmetric vasomotor responses and dystonia. In CRPS patients showing enhanced pain during VS (group 2 and group 3 patients), the incidence of anomalous asymmetric autonomic vasomotor responses and/or dystonia was significantly higher than in CRPS patients not showing enhancement of pain (group 1 patients)($p<0.02$ χ^2-test).

Fig.6.9.

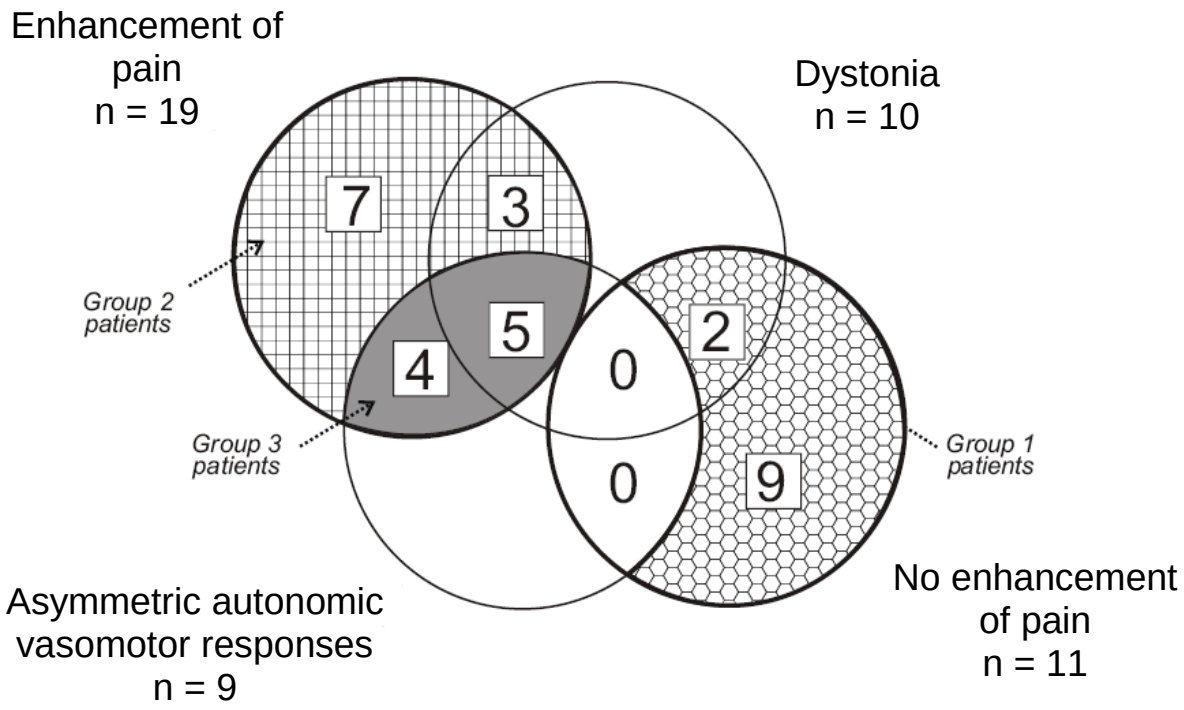


Fig.6.9. A modified Venn diagram illustrating the relationship between pain, dystonic reactions and asymmetric blood flow responses while viewing visual stimuli.

Numerals refer to the number of patients with those clinical features

6.4.5. Comparison of all cohorts

For the comparison of cohorts, age and sex matched data were available only for controls and CRPS, as OA and RA cohorts tended to be older. Therefore unmatched data from the overall healthy control cohort (n = 40) was used.

Comparing Δ%bbf of healthy controls (overall cohort, n = 40) for C, DR and N with OA, RA and CRPS cohorts (**Fig.6.10**): there was a significant difference for C, DR and N between HC and OA, and for C and N with RA (Kruskall-Wallis, $p<0.001$, post hoc Mann-Whitney *U*-test with Bonferroni correction). Comparing the SR of healthy controls for the different visual stimuli (Siegel-Tukey test; see **4.5.3.**), there was a statistically significant difference in variability between the limbs for the Necker cube ($W = 420$, $p = 0.005$) (**Fig.6.11**) among CRPS patients.

6.4.6. Comparison of CRPS with matched healthy controls

The Δ%bbf for AVS was diminished though not statistically significantly different for CRPS patients compared to healthy controls (**Fig.6.12A**). The SR of blood flow responses while viewing the Necker cube was significantly greater in CRPS patients compared to the control subjects (median + IQR: 1.32 [1.0 - 4.4] vs 1.07 [1.0 - 1.15], $p<0.02$ Mann Whitney U-test), but not for the control or duck/rabbit stimuli (**Fig.6.12B**). There was variability within individuals to which of the visual stimuli that induced enhancement of pain also caused asymmetric responses.

Fig.6.10.

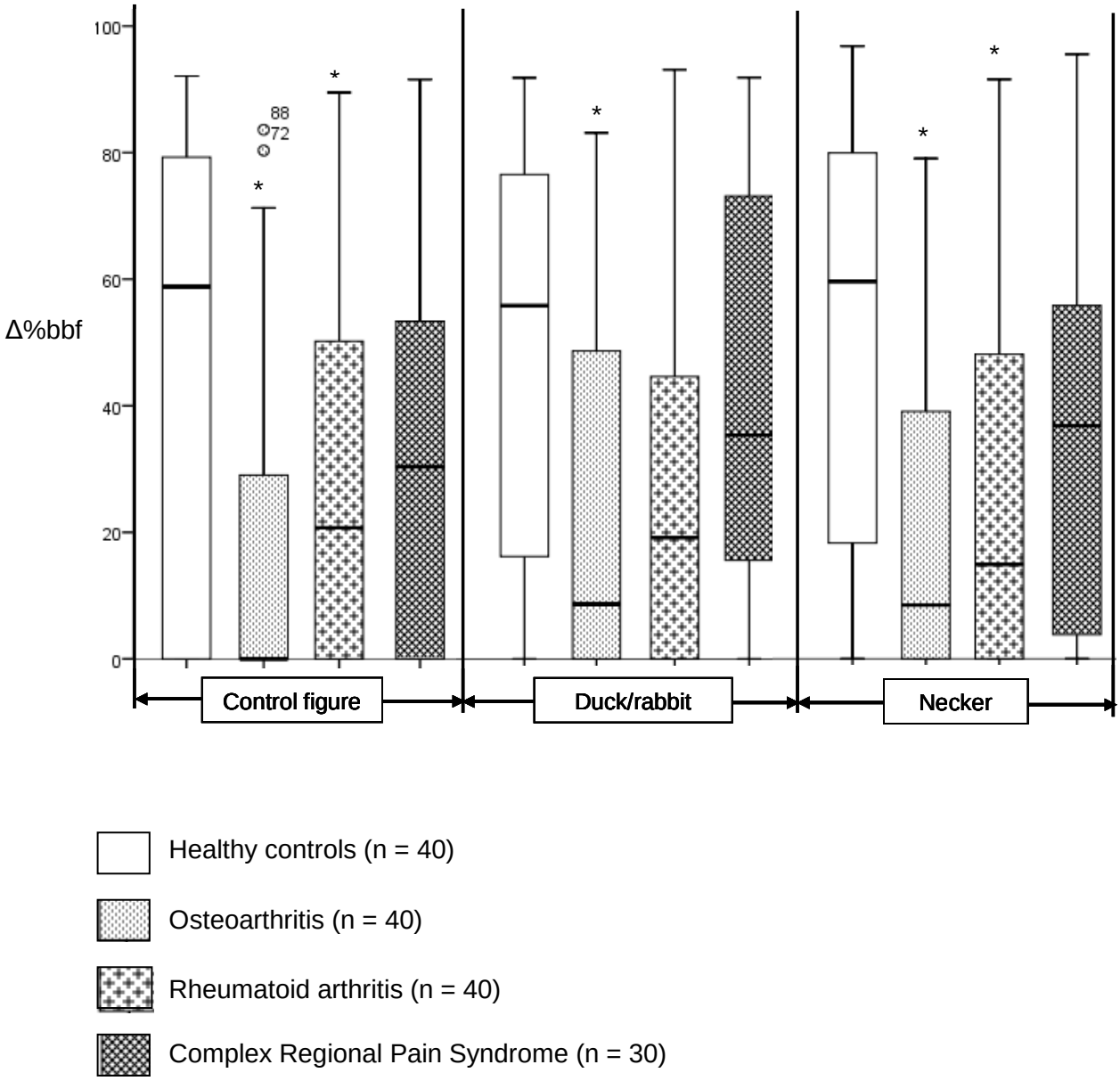
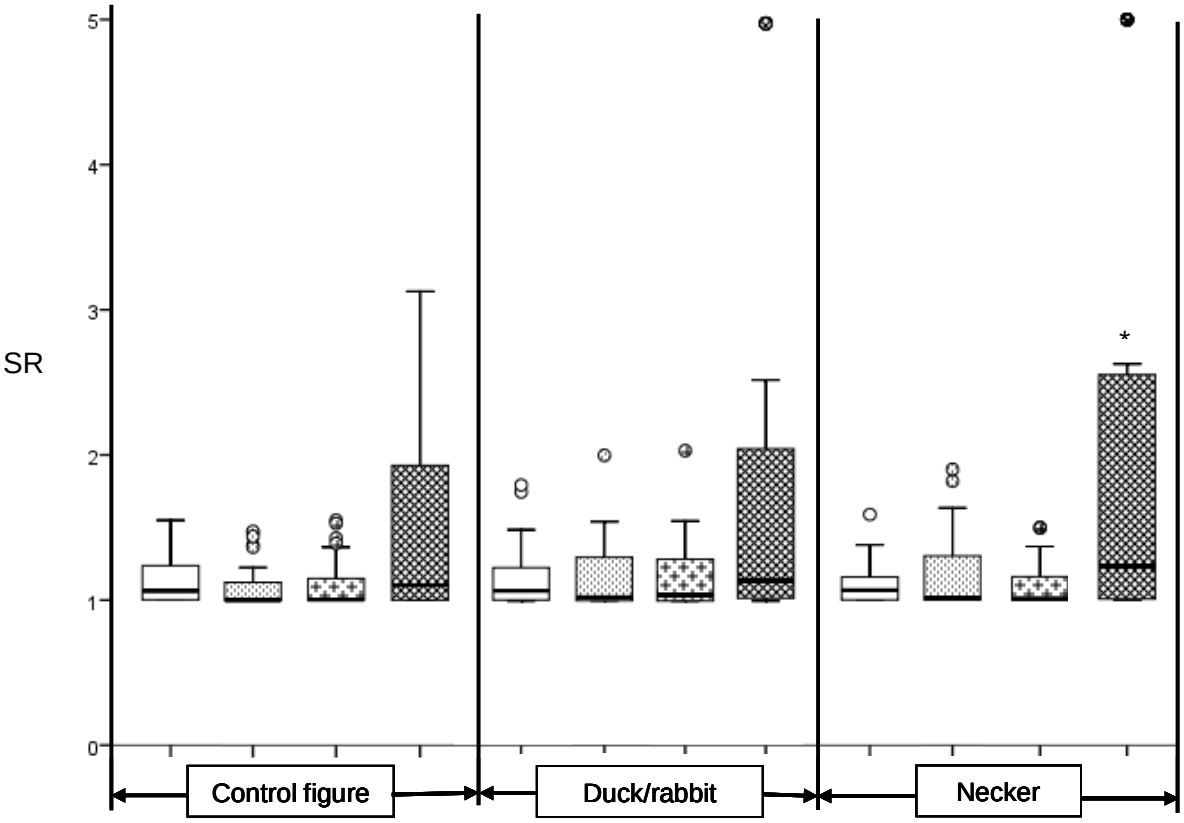


Fig.6.10. Group median values for mean percentage change from baseline blood flow (Δ%bbf) between healthy controls (overall cohort), osteoarthritis, rheumatoid arthritis and CRPS patients while viewing visual stimuli. * indicates statistically significant difference compared to healthy controls.

Box plots showing the median, IQR and range are illustrated.
AFU = arbitrary flux units

Fig.6.11.



Healthy controls (n = 40)

Osteoarthritis (n = 40)

Rheumatoid arthritis (n = 40)

Complex Regional Pain Syndrome (n = 30)

Fig.6.11. Symmetry ratio (SR) of healthy controls (overall cohort), osteoarthritis, rheumatoid arthritis and CRPS patients while viewing visual stimuli.

Box plots showing the median, IQR and range are illustrated. Comparing the SR of controls for the Necker cube, there is significantly increased variability* among CRPS patients.

Fig.6.12.

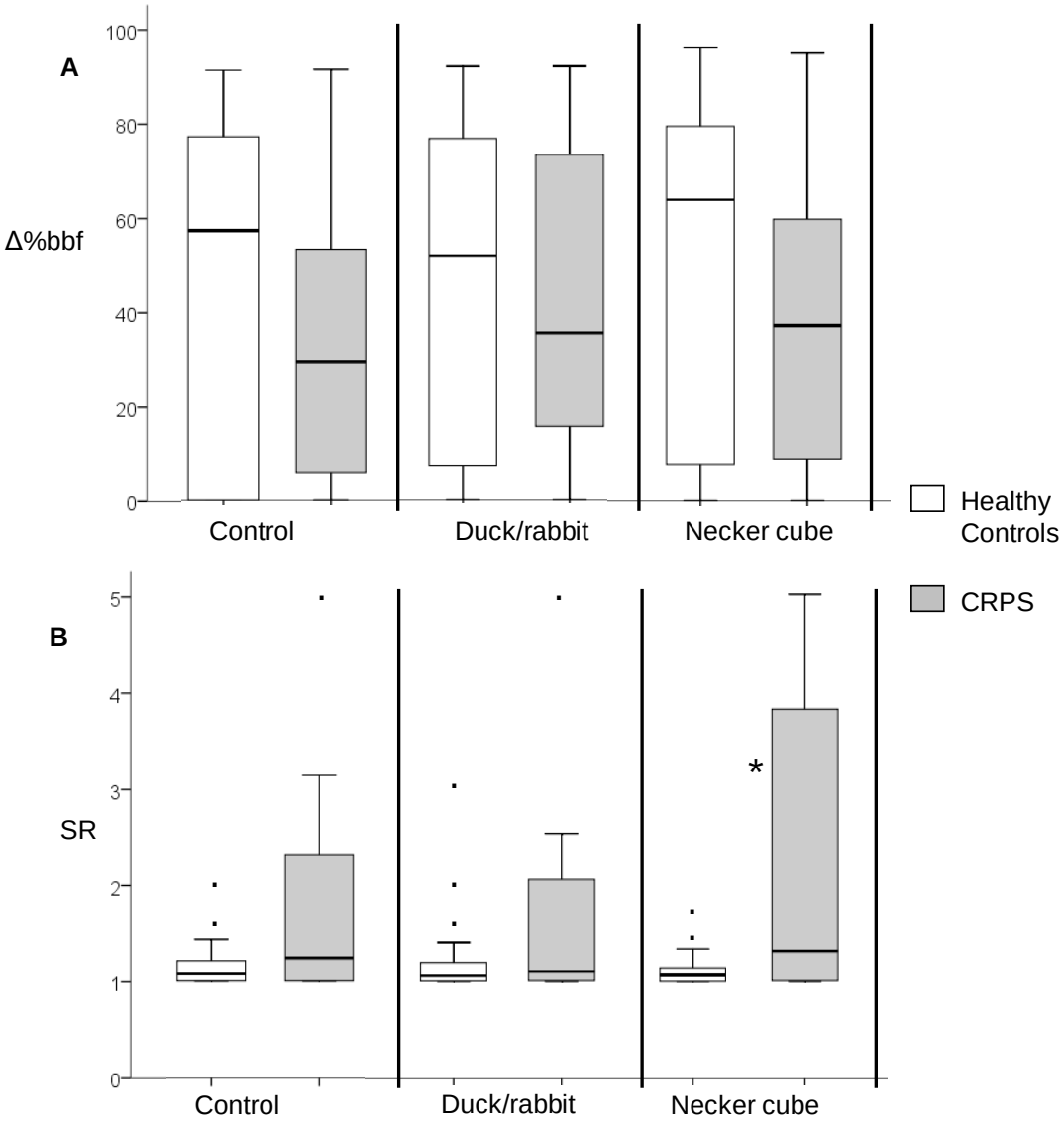


Fig.6.12. Group median values for mean percentage change in baseline blood flow (Δ%bbf) (**A**) and symmetry ratio (SR) (**B**) in healthy controls (age & gender matched cohort, n = 30) and CRPS subjects for viewing visual stimuli: control figure, duck/rabbit and Necker cube.

Box plots showing the median, IQR and range are illustrated. There is a statistically significant greater SR for viewing the Necker cube in CRPS subjects compared to healthy controls, demonstrating greater variability in the magnitude of response between the limbs (*, p<0,02, Mann Whitney U-test).

6.4.7. CRPS subgroup comparison by homology of autonomic response

Distinct patterns emerged when comparing the frequencies of homologous responses, of asymmetric responses or of no response between CRPS patients and control subjects. During the presentation of VS the CRPS patients demonstrated either homologous vasoconstrictor responses to all visual stimuli (n=12, 40%), homologous responses to only one of the AVS (n=2, 7%), no response to all AVS (n=3, 10%), excessive vasoconstriction with skin blood flow <150 AFU at a room temperature of 23-35°C (n=4) or asymmetric vasomotor responses (n=9, 30% **Fig.6.7B**,**C** & **Table 6.5**). The distribution of vasomotor responses to VS in CRPS patients was significantly different from the distribution of vasomotor responses to VS in the matched control subjects, which showed homologous responses in 26 (87%) subjects (18 / 60% subjects to all VS and 8 / 27% subjects to one of the AVS) or no response to any AVS in 4 / 13% subjects (χ^2-test, $p<0.002$).

Using the pain responses and the vasomotor response to AVS the CRPS patients were divided into three groups (**Table 6.5**).

Group 1. Subjects 1 – 11, no pain viewing AVS with homologous vasoconstrictor responses

Group 2. Subjects 12 – 21, pain enhancement viewing AVS with homologous vasoconstrictor responses.

Group 3. Subjects 22 – 30, pain enhancement viewing AVS with asymmetric mixed vasomotor responses. The asymmetric responses were: vasoconstriction in the affected limb (AL) with no response in the unaffected limb (UL) (n = 4; **Fig.6.7B**), vasodilation in the AL with no response in the UL (n = 3), vasodilation in the AL with vasoconstriction in the UL (n = 1, **Fig.6.7C**), initial vasodilation followed immediately by vasoconstriction in the AL with no response in the UL (n = 1).

Table 6.5. Pain responses and dystonic reactions among CRPS patients grouped according to qualitative homology of Laser Doppler responses (homologous or asymmetric).

Patient ID	BF change during VS	Enhancement of pain to VS	VS causing pain enhancement	Dystonia during VS
Group I patients: no pain to visual stimuli, homologous BF responses				
1	homologous	Nil	~	#
2	homologous	Nil	~	***D***
3*	homologous	Nil	~	#
4	homologous	Nil	~	#
5^	homologous	Nil	~	#
6	homologous	Nil	~	#
7	homologous	Nil	~	#
8	homologous	Nil	~	#
9	homologous	Nil	~	#
10	homologous	Nil	~	***D***
11	homologous	Nil	~	#
Group II patients: pain enhancement to visual stimuli, homologous BF responses				
12*	homologous	Severe	C,DR,N	***D***
13^	homologous	Moderate	DR,N	***D***
14*	homologous	Moderate	N	#
15	homologous	Moderate	DR,N	#
16	homologous	Severe	C,DR,N	#
17	homologous	Severe	C,DR,N	***D***
18	homologous	Severe	N	#
19*	homologous	Mild	DR,N	#
20	homologous	Moderate	DR,N	#
21^	homologous	Moderate	DR	#
Group III patients: pain enhancement to visual stimuli, asymmetric BF responses				
22	asymmetric	Moderate	***DR,N***	***D***
23	asymmetric	Moderate	***C,DR,N***	***D***
24	asymmetric	Severe	***DR*** ,N	#
25	asymmetric	Severe	***C,DR,N***	***D***
26	asymmetric	Severe	***DR,N***	#
27	asymmetric	Moderate	DR***,N***	#
28	asymmetric	Severe	***C,*** DR***,N***	***D***
29	asymmetric	Moderate	***N***	***D***
30	asymmetric	Mild	***DR,*** N	#

Pain: Enhancement of pain on the verbal Likert rating scale as none, mild, moderate or severe. BF = blood flow; VS = visual stimulus: C, control figure; DR, duck/rabbit; N, Necker cube ; * = excessive vasoconstriction with skin blood flow <150 arbitrary flux units (AFU) at a room temperature of 23-25°C despite acclimatisation time; ^ = no response; ~ = not applicable; ***bold/italic*** = visual stimulus causing asymmetric BF response; D = dystonic reaction present; # = no dystonic reaction.

There were no major differences in the demographic data between groups 1 – 3: mean age 38, 40 and 40 years, and mean disease duration 7, 7 and 6 years, respectively. Medication profiles were similar.

When pain responses were compared between the CRPS subgroups, half of the patients who rated their baseline pain as ‘severe’, and half of the subjects that had a dystonic reaction while viewing visual stimuli were in group 3. This group experienced worsening pain while viewing at least two of the three visual stimuli. Furthermore, the only subjects to experience pain viewing the control figure were in this group, and they did not perceive it as a stable object. There were more subjects reporting reversal rates as ‘too fast to count’ in group 3 (**Table 6.6**).

Table 6.6. Reversal rates ‘too fast to count’ by CRPS group homology.

	Reversals 'too fast to count'	
Grp	DR	N
1	0	1 (8%)
2	3 (33%)	3 (33%)
3	4 (44%)	6 (67%)

Grp = group, DR = duck/rabbit, N = Necker cube.

Compared between matched healthy controls (n = 30) and the CRPS subgroups, group 3 patients were significantly different for the SR of the Necker cube ($p<0.05$, Kruskal-Wallis test, post hoc Mann Whitney U-test with Bonferroni correction) (**Fig. 6.13**).

Fig.6.13.

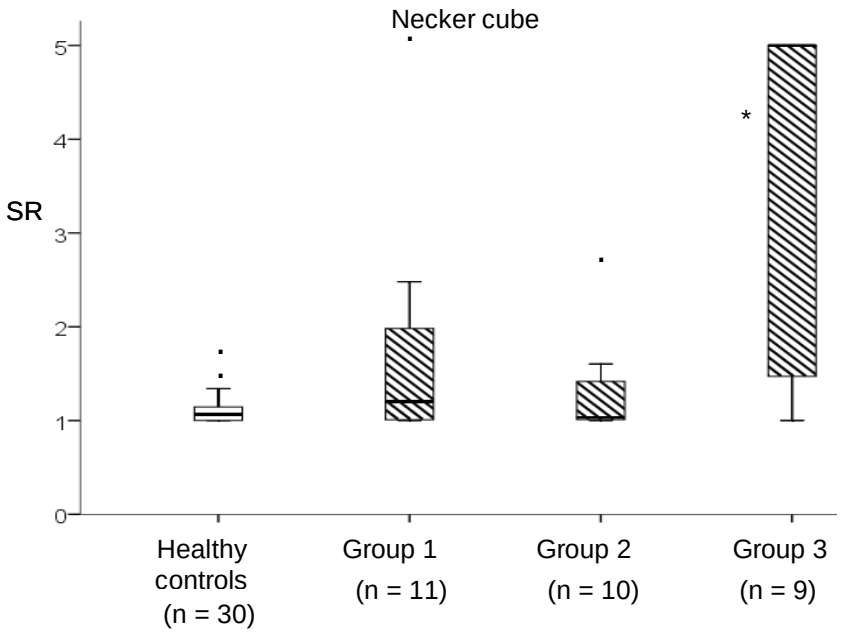


Fig.6.13. Blood flow response symmetry ratios (SR) for CRPS subgroups for the while viewing the Necker cube.

Box plots showing medians, IQR and range are illustrated. The CRPS subgroups demonstrate greater variability in magnitude of response between the limbs than the control subjects. The greatest (statistically significant) variability is in group 3.

Group 1: no pain viewing visual stimuli, symmetric vasomotor responses
Group 2: pain enhancement viewing visual stimuli, symmetric vasomotor responses
Group 3: pain enhancement viewing visual stimuli, asymmetric mixed vasomotor responses

6.4.9. Comparison of unilateral upper limb CRPS and CRPS involvement of >1 limb.

Comparing UL only (n = 22) with >1 limb involvement (n = 8), there was no statistically significant difference (Mann Whitney U-test) between Δ%bbf and SR for any baseline autonomic function parameters or while viewing AVS. The characteristics of baseline pain were not markedly different either. However the >1 limb group all experienced enhanced pain while viewing ambiguous +/- control visual stimuli (compared to 50% of UL only) and were more likely to have severely enhanced pain while viewing those stimuli (50% compared to 18% of UL only) (**Table 6.7**). Autonomic response patterns of subjects with enhanced pain while viewing the VS were not different between the two groups: 53% of UL only and 50% of >1 limb had homologous blood flow responses while 47% of UL only and 50% of >1 limb had asymmetric blood flow responses.

Table 6.7. Comparison of pain and dystonic responses in patients with unilateral upper limb CRPS involvement and >1 limb (unilateral upper limb + lower limb) CRPS involvement

	Limb Involvement	
	Unilateral Upper Limb n = 22 (73%)	>1 limb n = 8 (27%)
Baseline pain		
Nil	1 (4.5%)	0
Mild	1 (4.5%)	1 (12.5%)
Moderate	16 (73%)	5 (62.5%)
Severe	4 (18%)	2 (25%)
Pain enhancement viewing VS		
Nil	11 (50%)	0
Mild	0	2 (25%)
Moderate	7 (32%)	2 (25%)
Severe	4 (18%)	4 (50%)
Dystonic response viewing VS	8 (36%)	2 (25%)

Comparison of subjects with unilateral upper limb CRPS only and subjects with CRPS involving >1 limb. In the latter group, 7 patients had unilateral upper limb plus one lower limb involvement, and 1 patient had unilateral upper limb plus both lower limbs involved. Data for the numbers (%) of subjects with nil, mild, moderate or severe baseline pain and for nil, mild, moderate or severe pain enhancement while viewing AVS are shown. The incidence of dystonic responses while viewing VS is also displayed.
VS = visual stimuli (control, duck/rabbit, Necker cube)

6.4.10. Comparison of 'cold' and 'warm' CRPS.

(See **Chapter 2**, section **2.7.7.**)

CRPS subjects could be divided into 'warm' (overall baseline mean blood flow of >250 arbitrary flux units) and 'cold' (overall baseline mean blood flow of 150 - 250 arbitrary flux units) types. Twenty four patients had 'warm' CRPS, and six subjects had 'cold'.

The mean disease duration of cold CRPS was 2.6 years. Comparing the 'cold' and 'warm' groups, there was no statistically significant difference (Mann Whitney U-test) between Δ%bbf and SR for any baseline autonomic function parameters or while viewing AVS. Five out of the six 'cold' subjects had no pain while viewing AVS, and all six had homologous symmetric vasoconstrictor responses.

6.4.11. Comparison of baseline autonomic function with pain and autonomic responses while viewing AVS

The change in pain was allocated a score, where none = 0, mild = 1, moderate = 2 and severe = 3. There was no significant correlation between the baseline composite autonomic score and change in pain while viewing AVS.

The presence of abnormal or absent LDF sympathetic autonomic responses to baseline testing did not predict asymmetric responses to viewing visual stimuli. The sympathetic autonomic responses to the mental stress task (maths or spelling) are generated by higher central mechanisms, but also did not predict abnormal response to visual stimuli. See **Table 6.8**. A patient with a previous sympathectomy was still able to generate a peripheral response to AVS (**Table 6.8**).

Comparing between matched healthy controls (n = 30) and the CRPS subgroups, group 3 patients were significantly different for both the Δ%bbf and the SR (all effects reported at $p<0.05$, Kruskal-Wallace test, post hoc Mann Whitney U-test with Bonferroni correction) of the baseline mental stress task (**Fig. 6.14**).

Fig.6.14.

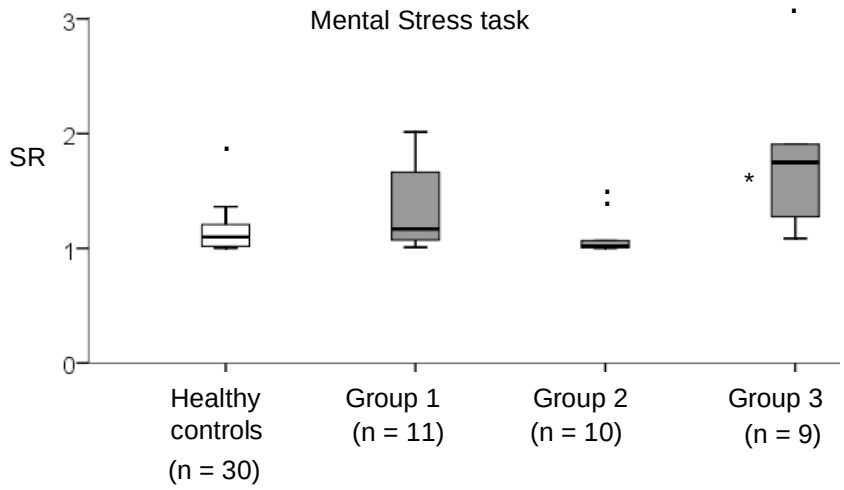


Fig.6.14. Blood flow response symmetry ratios (SR) for CRPS subgroups for the Mental stress task.

Box plots showing medians, IQR and range are illustrated. The CRPS subgroups demonstrate greater variability in magnitude of response between the limbs than the control subjects. The greatest (statistically significant) variability is in group 3.

Group 1: no pain viewing visual stimuli, symmetric vasomotor responses
Group 2: pain enhancement viewing visual stimuli, symmetric vasomotor responses
Group 3: pain enhancement viewing visual stimuli, asymmetric mixed vasomotor responses

Table 6.8. Comparison of baseline autonomic blood flow responses to sympathetic stimuli with responses to visual stimuli.

Pt ID	Baseline sympathetic autonomic testing											Visual stimuli		
	LDF													
	DB		VAR		CVR		MS		V					
	A	U	A	U	A	U	A	U	A	U		C	DR	N
Group 1: no pain to visual stimuli, homologous BF responses														
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
#	■	Y	Y	Y	■	Y	Y	Y	Y	Y		▒	Y	▒
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
3*	Y	Y	Y	▒	Y	■	Y	■	Y	Y		■	■	■
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
5^	Y	Y	■	■	■	■	Y	■	Y	Y		■	■	■
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		■	Y	■
7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	■
11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
Group 2: pain enhancement to visual stimuli; homologous BF resonses														
12*	Y	Y	▒	Y	Y	▒	Y	Y	Y	Y		■	■	■
13^	Y	Y	Y	■	■	■	■	■	Y	Y		■	■	■
14*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		■	■	■
15	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
16	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
17	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
18	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
19*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		■	■	■
20	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
21^	Y	▒	Y	▒	Y	▒	Y	▒	Y	▒		■	■	■
Group 3: pain enhancement to visual stimuli, asymmetric BF responses														
22	Y	Y	Y	Y	■	Y	Y	Y	Y	Y		Y	▒	▒
23	Y	Y	▒	Y	■	Y	▒	Y	Y	Y		▒	▒	▒
24	Y	■	Y	■	■	■	Y	■	Y	■		Y	▒	■
25	Y	Y	Y	■	■	■	Y	Y	Y	Y		▒	▒	▒
26	Y	Y	■	■	■	■	Y	Y	Y	Y		■	▒	▒
27	Y	Y	Y	■	■	Y	Y	Y	Y	Y		■	■	▒
28	Y	Y	Y	Y	Y	Y	■	■	Y	Y		▒	Y	▒
29	■	■	■	■	■	■	Y	■	Y	Y		Y	Y	▒
30	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	▒	Y

Y Homologous response

▨ Vasodilation response

■ Absent response

▩ Asymmetric response

Pt ID = patient/subject identification, LDF = laser Doppler flowmetry, DB = deep breath, VAR = venoarteriolar response, CVR = contralateral vasoconstrictor response, MS = mental stress, Val = Valsalva manoeuvre, C = control figure, DR = duck/rabbit, N = Necker cube, A = affected limb, U = unaffected limb.
= patient with previous sympathectomy & excluded from further analysis
* = excessive vasoconstriction with skin blood flow <150 arbitrary flux units (AFU) and therefore non-discernable absent trace
^ = no response to any VS.

6.4.12. Comparison of optokinetic vulnerability with pain, dystonia and autonomic responses while viewing AVS

There was a moderate positive correlation between optokinetic vulnerability score and change in pain while viewing AVS in UL-CRPS cohort (Spearman's rho = 0.449, $p<0.05$). There was no significant correlation with the composite baseline autonomic score. Comparing dystonic responses, 3/10 patients with dystonia viewing VS also had dystonia during an optokinetic challenge.

6.4.13. Comparison of UL-CRPS cohort (n = 30) with overall CRPS cohort (n = 54).

Comparing sensory disturbances, 33% of the overall CRPS cohort, and 27% of the UL CRPS cohort experienced sensory disturbances while viewing VS.

Comparing enhancement of pain while viewing VS, 61% of the UL-CRPS cohort and 63% of the overall CRPS cohort experienced enhancement of their pain within seconds of viewing the Necker cube and/or the duck/rabbit figure (**Table 6.2**). Six in the UL-CRPS cohort, and 10 (including the 6 from the UL-CRPS cohort) in the overall CRPS had worsening pain viewing the control figure. The mean duration of the viewing time for patients with enhanced pain during AVS was 43 seconds (s), range 5 – 60s for UL-CRPS (overall CRPS = 51s, range 4-60s). In the overall cohort, 35% subjects described an extremely high reversal rate ("too fast to count") compared to 37% UL-CRPS. Patients with pain were significantly more likely to describe reversal rates as 'too fast to count' in both groups (overall CRPS cohort: χ^2 (1) = 6.631, $P<0.01$; UL-CRPS cohort: Fisher's exact test, $p<0.05$).

Comparing dystonic reactions while viewing VS, 33% (n = 10) in the UL-CRPS cohort and 28% (n = 15) in the overall CRPS cohort developed acute dystonic reactions in the affected limb.

There was a moderate positive correlation between optokinetic vulnerability score and change in pain while viewing AVS in both the overall and UL-CRPS cohorts (Spearman's rho = 0.491, $p<0.001$ / rho = 0.449, $p<0.05$ respectively).

6.5. Discussion

The study has shown that healthy controls and patients with OA and RA do not experience sensory disturbances or new / enhanced pain while viewing AVS, supporting hypothesis 1. Using LDF and ESR to record sympathetic autonomic responses while viewing AVS, this work has demonstrated that healthy controls and

patients with OA and RA have either symmetric homologous responses bilaterally, or no detectable response consistent with hypothesis 2. In contrast, some CRPS patients have enhanced pain while viewing AVS supporting hypothesis 1, and abnormal asymmetric autonomic responses supporting hypothesis 3. Furthermore all asymmetric autonomic responses were among CRPS patients with enhancement of pain while viewing AVS supporting hypothesis 4.

6.5.1. Comparison with previous work

After extensive review of the literature, there appears to be only one similar previous study investigating sensory responses while viewing a control and an ambiguous visual stimulus among controls and patients with chronic rheumatic pain. Hall et al (2010) recorded qualitative changes in somatosensation and frequency of percept changes among 45 healthy controls, 30 CRPS patients and 33 patients with rheumatic disease (mostly OA and RA). Their study used the duck/rabbit figure as a familiarisation image to establish the bistable nature of the image, and did not specifically look for whether this produced any somaesthetic changes. A control figure and reversible Necker cube were then displayed.

They also found that none of the controls had pain but 3 had sensory disturbances. Two rheumatology patients reported a minor increase in pain, and 5 sensory disturbances viewing AVS. Twelve of the rheumatology group reported a decrease in pain, which was not observed in my study. Among CRPS patients, 73% had enhanced pain and/or sensory disturbances (43% pain, 50% somaesthetic disturbances viewing the Necker cube) and one reported amelioration of symptoms. Reversal rates for the Necker cube during the 1 minute exposure were 9 for controls, 8 for rheumatology patients and 10 for CRPS, with 4 CRPS subjects reporting rates as too fast to count. These figures are similar to my study.

The Hall paper was primarily a qualitative exploratory study, which may explain the wider variety of somatosensory findings such as reduction in symptoms due to distraction. The use of the DR as a familiarisation task may have introduced several confounding factors. The bistable DR could have started to induce sensory changes before the control and reversible figure were subsequently shown. This might prime cortical pathways and cause higher reporting rates compared to my work. Subjects had been informed that they would be viewing bistable images, and to indicate changes in percept by pressing a button. This introduces an attentional bias, both looking for percept changes, and directing attention towards pressing a button.

6.5.2. Visual stimuli and somaesthetic responses

Sensory disturbances and enhanced pain responses to viewing VS were only present in the CRPS cohort. These responses were absent in controls or patients with OA and RA. Explanations include that different pain mechanisms are operational in CRPS. An alternative is that the sensory discrepancy threshold is much reduced in CRPS compared to in OA or RA, such that a pure visual conflict is adequate to activate Ramachandran's proposed right cortical centre monitoring incongruence of sensation (CIS) and generate sensory disturbances and activate pain networks (see **Chapter 5**, **5.5.2**). Application of Occam's razor would favour the latter, simpler suggestion.

The visual system processes the Necker cube as a three dimensional object (Bisiach et al., 1999;Kornmeier and Bach, 2004) utilising spatial cues (Long and Toppino, 2004) and with a dorsal-parietal visual stream bias (Lehky and Sereno, 2007). The duck/rabbit illusion is an object recognition dependent visual illusion (ie. the subject has to have seen a duck or a rabbit previously in order to be able to recognise a pictorial representation of either), and has a ventral pathway bias (Shen et al., 1999). Work using fMRI in healthy subjects demonstrated how pain could modulate visual object processing in the ventral visual stream (Bingel et al., 2007). Their data suggest that the source of modulation for pain could be attributed to activation of the rostral anterior cingulate cortex whereas for a working memory task, this was observed in the parietal cortex.

Among CRPS patients with enhanced pain while viewing VS, few arose from viewing the control figure (n=6, 20% in the UL-CRPS cohort (n = 30)). There was little difference in the frequency of enhanced pain induced by the Necker cube (n=18, 60%) or the duck/rabbit figure (n=16, 53%). Therefore the visual processing pathway differences do not appear to be significant factors in generating pain, and the role of visual conflict seems more important. The enhancement of pain is unlikely to represent an attentional effect induced by viewing any kind of picture, as there is a clear frequency difference for the control compared to the AVS, again suggesting that the visual conflict is significant. Furthermore, all the CRPS patients that had enhanced pain viewing the control figure described it as unstable and 'moving' which infers visual fixation instability for a normally stable object and thus visual conflict. Cortical network changes secondary to chronic pain affecting visual processing areas such as the V5 cortex (motion) may account for how apparently stable objects such as the control figure can become unstable and seem to move.

6.5.3. Autonomic responses and visual processing

Comparison of the quantitative autonomic response data between the overall healthy control cohort (N = 40) and the matched healthy control cohort (N = 30) did not show any significant differences between the cohorts. However the matched cohort were all taken from the overall cohort, and the numbers are small which could obscure differences.

Visual stimuli are centrally processed in higher cortical areas. The process of perception interacts with affective areas to generate emotion, which in turn will cause autonomic and neuroendocrine responses (Craig, 2003;Critchley, 2005). Centrally generated autonomic responses are detectable peripherally. Peripheral autonomic pathways need to be intact to detect either peripheral or centrally generated autonomic responses using LDF or ESR. Therefore, the symmetric responses obtained from OA and RA subjects suggest that there have not been significant changes to peripheral or central efferent and afferent pathways.

One of the CRPS patients had undergone a previous surgical sympathectomy of the affected upper limb. The baseline autonomic testing demonstrates a lack of response to the more peripheral/spinal sympathetic stimuli such as deep breath on the affected limb, but bilateral sympathetic responses to the centrally processed mental stress task and to one of the AVS (the duck/rabbit figure). The mechanism remains unclear. Possible explanations might be an incomplete procedure, axonal regeneration or the presence of putative ipsilateral sympathetic projections (personal communication). It is interesting to note that it was the 'top-down' mental stress task and the more 'top-down' object recognition duck/rabbit stimulus that generated bilateral responses rather than the more 'bottom-up' Necker cube.

A reversal rate described as ‘too fast to count’ while viewing AVS was significantly higher in patients with enhanced pain responses. It was also higher in CRPS patients with pain and asymmetric autonomic responses. A potential explanation is that some CRPS patients are especially vulnerable to visual conflict, possibly through top-down processing of conflicting visual stimuli abnormally activating pain networks and other aberrant visual processing pathways. This could cause marked instability of a bistable object resulting in a very fast reversal rate, and further increased activation of autonomic and pain pathways.

Comparing autonomic responses among cohorts, there were greater 'no response' rates while viewing VS among OA (ESR = 20, LDF = 15) and RA (ESR = 22, LDF = 12) patients, and fewer among CRPS (ESR = 4, LDF = 3) patients and

healthy controls (ESR = 15, LDF = 5). There may be an age effect, as the mean age of healthy controls (38 years) and CRPS (43 years) is younger compared to OA (61 years), RA (57 years). Could there also be a pain effect? Another possible explanation is that OA and RA patients have chronic pain and may have chronic sympathetic autonomic activation. They could have therefore developed an autonomic tolerance/damping effect. However this effect is not as marked in CPRS patients, where there is evidence for compensatory up-regulation of peripheral adrenergic receptors (Bruehl, 2010).

6.5.4. Autonomic responses and pain

Previous work has demonstrated LDF to be a reliable and repeatable means to assess cutaneous microvascular blood flow (Bonelli and Koltringer, 2000;Low et al., 1983). Previous studies have demonstrated sympathetic abnormalities in CRPS (Wasner et al., 1999);(Wasner et al., 2001), but the pattern of responses during painful stimuli in CRPS and the possible contribution to pain is less known (Baron et al., 2002).

This research has demonstrated that anomalous asymmetric mixed sympathetic autonomic responses to viewing VS can identify a group (group 3) of CRPS patients with vulnerability to enhanced pain and concurrent dystonic reactions, supporting hypothesis 3. Furthermore, all the patients in this group experienced worsening pain viewing VS (AVS +/- C) consistent with hypothesis 4. When the CRPS subgroups were compared to each other and to matched healthy controls, there was a significant difference for the SR of the Necker cube in group 3. More group 3 CRPS subjects described reversal rates as 'too fast to count' for the Necker cube (n=6) than the duck/rabbit (n=4). The dorsal parietal visual processing stream bias of the Necker cube may be a contributing factor to visual conflict, instability and enhanced pain in this more vulnerable group. However the numbers are small and require confirmatory findings in a larger study.

There is one study by Ackerman et al using laser Doppler imaging to evaluate pre and pot-operative sympathetic function and recurrence of CRPS in patients undergoing carpal tunnel release (Ackerman, III and Ahmad, 2008). Thirty-four patients had sympathetic function tested by reflex-evoked vasoconstrictor responses to sympathetic stimuli recorded from both hands 5-7 days before and 19-22 days after surgery or 20-22 days after resolution of CRPS. They were assigned to two groups on the basis of pre-operative results: group 1 (11 subjects) – abnormal results; group 2 (23 subjects) – normal results. In group 1, 73% (8/11) had

recurrence of CRPS and 13% (3/23) in group 2. All the recurrent CRPS cases were treated 'successfully' with sympathetic blockade, occupational therapy and pharmacologic modalities. Repeat LDI after resolution of recurrent CRPS was abnormal in all 8 group 1 patients and in 1 of the 3 group 2 patients. The authors concluded that the technique might be able to identify individuals who would benefit from post-operative therapies.

It is interesting to note that all eight group 1 patients with 'successfully' treated recurrent CRPS had sympathetic blockade, and continued to have abnormal testing. Many would classify these patients as having 'sympathetically maintained pain', and yet they continued to have abnormal sympathetic responses throughout despite sympathetic blockade. This strongly suggests that the role of the detected sympathetic autonomic abnormalities are unclear, but that they do select a group of CRPS patients with an increased likelihood of recurrence. It could be argued that the sympathetic block may not have had any effect, and the other components of therapy were the therapeutic element. This could be investigated by repeating the study and omitting or substituting the sympathetic blockade with placebo in some, and comparing to others who received the block.

6.5.5. Dystonia and visual processing

Ten patients (UL-CRPS, n = 30) had concurrent dystonic responses in the affected limb while viewing VS implicating involvement of motor areas. This is unlikely to represent an attentional phenomenom as there is a distinct distribution of dystonic responses, being least in group 1 and highest in group 3 CRPS patients. There was no dominant VS associated with dystonic responses suggesting that the visual conflict itself is more significant. However, the numbers are small and require larger scale study confirmation.

CRPS patients with dystonia have been demonstrated to have altered cerebral activation patterns during imagined movements of the affected limb (Gieteling et al. 2008). This was postulated to reflect an interface between pain-associated circuitry and higher order motor control, and a specific mechanistic pathophysiology. Results from this study suggest that visual conflict may also operate at this interface. In a susceptible group of CRPS patients visual conflict may be sufficient for the consequent pain network activity to induce an efferent motor response and dystonic reactions, supporting the concept of a specific pathophysiologic mechanism in this group.

6.5.6. Role for cortical reorganisation?

The Harris hypothesis (Harris, 1999) suggests that subjects with chronic pain are more likely to have cortical reorganisation rendering them more susceptible to sensory incongruence. OA and RA subjects did not experience sensory disturbances or pain viewing AVS. One explanation would be that they have less neuroplastic reorganisation than in a neuropathic pain syndrome such as CRPS.

It could also be argued that patients with OA and RA are more stoic than CRPS patients or less psychologically distressed. However the data also showed that patients with CRPS of >1 limb (and therefore probable greater extent of cortical remapping) all had enhanced pain while viewing VS (AVS +/- C) compared to 50% of unilateral upper limb CRPS patients. Such a pattern would not be expected if CRPS patients were less 'stoic' although the psychological explanation could not be excluded. There is no data in the literature to support the latter argument, and future work could address this specific point.

6.5.7. Central and autonomic nervous system organisation

It has been postulated that the three divisions of the motor system (somatic, autonomic and neuroendocrine) are hierarchically organised and integrated within the central nervous system (Jänig, 2006). Activity of the motor system is dependent on inputs from the sensory systems, the cortical system and the behavioural state system (controlling attention, arousal, sleep/wakefulness and circadian timing). Changes within the input systems are reflected by changes in autonomic regulation and therefore autonomic pathway activity (Jänig and Baron, 2006). Neuroplastic cortical reorganisation resulting in functional changes of somatic (Maihöfner et al., 2003) and autonomic (Geha et al., 2008) divisions may occur in chronic pain conditions such as CRPS. Peripheral changes (including inflammatory responses, changes to nociceptive and other afferent nerve fibres and sympathetic afferent coupling) may alter sensory inputs, changing afferent inputs to the central systems (Jänig, 2006). Thus changes in peripheral and central input systems to the motor hierarchies are reflected in somatomotor pathway activity, autonomic pathway activity and autonomic regulation.

This work has demonstrated that in a group of CRPS patients, a stimulus causing central arousal via visual pathways can generate pain and asymmetric peripheral vasomotor sympathetic responses. Pain and anomalous responses while viewing VS could not be predicted from baseline autonomic function or from responses to non-painful central stimuli activating the sympathetic system (e.g. in the

mental stress task). These findings suggest that anomalous responses while viewing VS cannot be explained by abnormalities of peripheral mechanisms and autonomic spinal reflexes alone, and that supraspinal cortical interactions are involved.

6.5.8. Asymmetric sympathetic autonomic responses

The concept of the autonomic nervous system as one of 'mass action' has been challenged in recent years (Drummond, 2006;Jänig, 2006). Changes in peripheral and central input systems (such as that induced by chronic pain) can disrupt central integration causing disturbance of the usually precise autonomic outputs (Jänig, 2006). Asymmetric responses of cutaneous vasoconstrictor neurons to ipsilateral noxious skin stimulation has been described in animals (Horeyseck and Jänig, 1974) Some healthy subjects can be trained to simultaneously change the skin temperature of both hands in opposite directions by biofeedback techniques (Roberts et al., 1975) or hypnosis (Maslach et al., 1972;Zachariae et al., 1994), demonstrating that central cognitive processes are able to cause asymmetric autonomic skin responses. Sustained noxious stimulation of one forearm in healthy subjects with mustard oil generates the presence of sympathetic reflex asymmetry that is specific for the nociceptive afferent input, with consistently smaller vasoconstrictor responses on the contralateral hand than on the ipsilateral one (Magerl et al., 1996). Immersion of the hand in painfully cold ice water induces asymmetric vasodilation in the temples of healthy subjects with less response on the contralateral side (Drummond, 2006).

The contribution of sympathetic autonomic dysfunction to pain is unclear. Baron et al (Baron et al., 2002) used whole body warming and cooling combined with pain measures before and after sympathetic blockade to investigate the contribution of sympathetically maintained pain mechanisms. Their results suggest a relationship between sympathetic vasoconstrictor activity and pain. Drummond et al report that pain can increase during sympathetic arousal in patients with CRPS (Drummond et al., 2001).

These observations suggest that nociception is able to cause a differentiated sympathetic response with separate control of discrete reflex pathways on each side of the body. Data from my research suggest that in some CRPS patients, abnormal brain processing of visual information can cause further disruption of central autonomic integration resulting in asymmetric peripheral responses.

It has been proposed that in chronic pain syndromes, sensory feedback has lost its precise temporal and spatial coordination with cortical sensory maps, central

autonomic and somatic motor programmes (Jänig, 2009). Drawing on data from this study, the following mechanism is proposed: In a subgroup of CRPS patients, in addition to remapping in sensory-motor areas there may be neuroplastic reorganisation of parietal and central autonomic pathways. Visual sensory conflict could activate pain pathways via dorsal parietal routes, which interact with disrupted central autonomic and motor programmes producing pain, dystonia and asymmetric sympathetic responses.

6.5.9. Study strengths

This work has established a practical, non-invasive means of assessing short duration dynamic sympathetic autonomic responses to pain, applicable to CRPS and other chronic pain conditions. It has the major advantage of being tolerable to patients with severe, extensive allodynia.

6.5.10. Study limitations and future directions

Further studies are needed on patients with early disease to investigate whether similar mechanisms are operational. Whilst there was no clear effect of disease duration, longitudinal studies are required to assess both this, and whether responses change with worsening or resolution of CRPS. Functional imaging studies would provide further exploration and validation of these findings.

Further work in CRPS patients at varying stages and disease duration may provide more insight into whether this pattern of sensory conflict vulnerabilty develops early or late, and if it remits with resolution of disease. Comparison of patients with type 1 and type 2 CRPS and with other neuropathic pain conditions such as post herpetic neuralgia or spinal cord injury may differentiate whether this is specific to type 1 CRPS, or exists in other neuropathic pain states.

Only two ambiguous visual stimuli were used. Different types of optical illusion are postulated to work in different ways (Gregory, 1997). Repeating the study using different types of illusion might provide further insight into pain mechanisms in CRPS.

The visual stimuli were used in a graded consistent order. Randomisation of order has been used in OA and RA (Cohen HE et al., 2006). Further work should randomise the order of visual stimuli with larger numbers of CRPS patients to assess whether this is feasible, or not (as suggested by pilot work).

OA and RA subjects had a similar, higher non-response rate while viewing AVS compared to HC and CRPS. As non-response was an important finding, it was

included in analysis. However, this makes the mean and median values of OA and RA lower in comparison, and produces wider variability. Another approach to analysis of quantitative LDF data would be to separate out non-responses, and compare the magnitude of responses between cohorts. In future work, with larger numbers, it would be useful to compare both types of analysis.

A major challenge remains that of separating attentional bias. It proved impossible to find a single true control figure. Therefore, several control figures need to be used within and between cohorts. One figure might control for emotion, and another for stability. This would allow better separation in the subsequent analysis of results.

Finally, the study should be repeated with investigators blinded to the subject (ie whether control or patient).

6.5.11. Clinical Implications

One particular phenotype of CRPS appears to be characterised by enhanced vulnerability to sensory conflict which may explain some pain behaviours observed among CRPS patients. Anecdotal descriptions of avoidance of flashing images, difficulty with looking at passing rows of road cones, dislike of complex geometric forms in art or on external surfaces of buildings become understandable in this context. Patients have described being confused why this apparently made their pain worse, and had not volunteered such information before for fears of being thought ‘crazy’. Some subjects found a normally stable object (the control figure) unstable, and were able to relate this to difficulty with reading describing the words as ‘moving around’ on the page. For those with marked symptoms, they may need to be cautioned against driving.

The outcome of this research supports the concept that sympathetic autonomic baseline testing may provide a potential approach to the identification of subgroups of CRPS patients with particular patterns of problems, assisting in novel clinical phenotyping and treatment approaches for CRPS.

6.6. Summary

The hypotheses postulated were proven:

- **i.** Viewing ambiguous visual stimuli (AVS) caused sensory disturbances and enhanced pain responses in CRPS patients but not in healthy controls and patients with rheumatoid arthritis (RA) or osteoarthritis (OA).
- **ii.** Healthy controls, OA and RA patients had symmetric sympathetic autonomic responses in the upper limbs while viewing AVS.
- **iii.** Some CRPS patients had abnormal sympathetic autonomic responses while viewing AVS.
- **iv.** Abnormal sympathetic autonomic responses in CRPS patients while viewing AVS were associated with enhancement of pain.

Among healthy controls (HC), osteoarthritis (OA) and rheumatoid arthritis (RA) patients there were no sensory disturbances or new / enhanced pain while viewing any visual stimuli (VS). In contrast, 27% of CRPS patients experienced sensory disturbances, and 63 % enhanced pain. Among those that had worsening pain, 20% had mild, 42% moderate and 38% severely worse pain compared to baseline pain. The reversal rate of the AVS was significantly more likely to be reported as 'too fast to count' in patients with enhanced pain while viewing AVS. Some CRPS subjects found the control figure appeared unstable and also caused enhanced pain. Others (33%) had a concurrent dystonic reaction in the affected limb. CRPS patients with >1 limb affected all experienced pain viewing AVS.

Laser Doppler flowmetry (LDF) and electrodermal skin response (ESR) recordings of sympathetic autonomic responses while viewing visual stimuli were homologous bilateral symmetric responses, or there was no detectable response among controls, OA and RA subjects. CRPS patients also demonstrated these responses, but others had abnormal asymmetric LDF responses (30%) and ESR responses (23%). Comparing CRPS patients to a selected age and sex matched cohort of controls, there was a statistically significant difference in symmetry ratio (SR), showing increased variability of blood flow response between the limbs while viewing the Necker cube. Among both the overall and UL-CRPS cohorts, there was a moderate positive correlation between OK vulnerability and enhanced pain viewing AVS (ie. higher vulnerability, higher pain rating while viewing AVS). CRPS patients with asymmetric responses and enhanced pain while viewing AVS were more likely to find the control figure unstable, report the reversal rate as 'too fast to count',

experience severely worse pain and to have a dystonic reaction. Asymmetry while viewing AVS was not predictable from the baseline sympathetic autonomic testing.

6.7. Conclusion

Viewing AVS does not cause sensory disturbances or pain among healthy controls or patients with OA or RA, but can induce pain, dystonic reactions and abnormal asymmetric sympathetic autonomic responses among some CRPS patients. In these CRPS patients, higher visual processing of conflicting stimuli may cause abnormal pain network activation which disrupts normal autonomic integration, causing asymmetric sympathetic responses. Cortical reorganisation involving parietal areas may be a predisposing factor.

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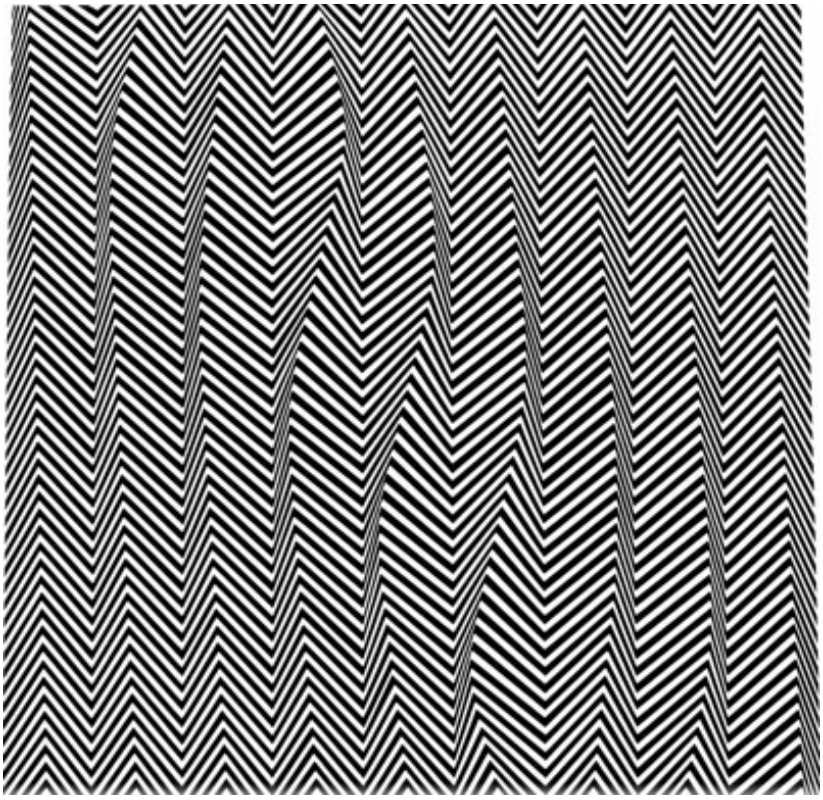


Bridget Riley

Descending,

1965

Image available from: http://www.karinsanders.com/bridgetriley.html.

Accessed 25.101.12.

Chapter 7: Parietal lobe function in CRPS

"The brain is our engine of understanding. There is nothing closer to our intimate experiences, yet the brain is less understood and more mysterious than a distant star."

Professor Richard Gregory *from 'Eye and Brain: The Psychology of Seeing'*

Image: Haswell,M., 2011. Professor Richard Gregory [online]. Bristol: University of Bristol. Available from: http://www.bris.ac.uk/news/2011/7737.html [Accessed 18.1.2012].

7.1. Introduction

(Data from this study has been published; see **Appendix 10**, or submitted for publication; see **Appendix 11**)

In the previous three studies, baseline autonomic function and somaesthesia in healthy controls, and patients with OA, RA and CRPS has been established. All four cohorts have been exposed to different forms of sensorimotor conflict. Their vulnerability to sensory disturbances and/or pain arising from these challenges has been assessed, and sympathetic autonomic responses recorded. It has been shown that CRPS patients are more vulnerable to visuo-motor or pure visual conflict, and that those who experience enhanced pain are particularly vulnerable and may have concurrent abnormal sympathetic autonomic responses and dystonic reactions. It is postulated that in vulnerable subjects there may be lower sensory disturbance detection thresholds and activation of pain networks together with motor and autonomic integrational dysfunction. Cortical reorganisation may predispose to vulnerability.

There is increasing evidence for the role of central mechanisms in CRPS. Several studies show evidence of neuroplastic cortical reorganization in CRPS (Juottonen et al., 2002;Maihöfner et al., 2003;Pleger et al., 2004;Schwenkreis et al., 2009), with the extent of reorganization linking to characteristics of CRPS pain (Maihöfner et al., 2003;McCabe et al., 2003;Pleger et al., 2006). Rommel et al (Rommel et al., 2001) have demonstrated that CRPS patients may have a hemisensory pattern of impairment and that this group are more likely to have

mechanical allodynia (pain due to a tactile stimulus which does not normally provoke pain) and hyperalgesia (an increased response to a stimulus which is normally painful). They concluded that hemisensory impairment may be a clinical correlate of subcortical brain plasticity. Furthermore, resolution of reorganizational changes upon recovery from CRPS have been observed (Maihöfner et al., 2004;Pleger et al., 2005). This is in keeping with extensive work demonstrating clear reorganizational changes in phantom limb pain (Flor et al., 1998;Karl et al., 2001;Ramachandran et al., 1992), and with the degree of remapping correlating to the severity of pain (Flor et al., 1995). Other studies in CRPS have confirmed that expansion of hand representation correlates with mean pain intensity (Pleger et al., 2004) and tactile impairment (Pleger et al., 2006).

It has been recognised that CRPS patients often complain of apparently bizarre symptoms such as feelings of 'foreigness' (Förderreuther et al., 2004) of the affected limb, and body dysmorphic features (Lewis et al., 2007) whereby the affected limb feels grossly distorted in size, shape and weight. They may demonstrate clinical signs such as neglect-like phenomena (Galer and Jensen, 1999) and finger misidentification (Förderreuther et al., 2004). This constellation of clinical symptoms and signs is reminiscent to those seen in patients with parietal lobe lesions eg. hemineglect and somatoparaphrenia (denial of ownership of a limb or an entire side of one's body) after parietal cerebrovascular accident.

Evidence is emerging for the role of the parietal cortex in the neurocognitive dysfunction observed in CRPS (Maihofner and Peltz, 2011). A study investigating motor dysfunction in CRPS, using kinematic analysis, showed significant prolongation of the target phase during target reaching and grasping with a pattern of motor impairment consistent with disturbed integration of visual and proprioceptive inputs in the posterior parietal cortex. Subsequent functional magnetic resonance imaging (fMRI) analysis demonstrated that activations of the posterior parietal cortices, supplementary motor cortices and primary motor cortex were correlated with the extent of motor dysfunction (Maihöfner et al., 2007). When fMRI was performed during imagined movements of the affected hand in CRPS patients with dystonia, there was contralaterally reduced activation in the inferior parietal and adjacent primary sensory cortex compared to healthy controls (Gieteling et al., 2008). A Positron Emission Tomography (PET) study of cerebral glucose metabolism in CRPS demonstrated bilateral increases in several brain areas including the parietal cortex (Shiraishi et al., 2006). Another PET study of a CRPS patient before and after successful treatment showed increased cerebral blood flow in the right parietal and left frontal lobes, which decreased after treatment (Wu et al., 2006). Vartiainen

showed that magnetoencephalography (MEG) responses during tactile processing of hyperaesthetic CRPS subjects demonstrated defective posterior parietal cortex (PPC) activation, and suggested that this might be associated with neglect-like symptoms (Vartiainen et al., 2008).

A possible underlying explanation for these otherwise apparently bizarre symptoms is abnormal central sensorimotor integration involving the parietal areas with activation of dysfunctional cortical networks, causing unusual symptoms and signs that have often been regarded as psychological or malingering. Cortical reorganisation extending beyond S1 may be a predisposing factor. Based upon the literature reviewed above, such patients would be conjectured to have severe pain, mechanical allodynia and hyperalgesia in extensive areas.

This study builds upon the previous ones by assessing a series of CRPS patients for clinical evidence of parietal lobe dysfunction, which if present would be suggestive of abnormal higher central sensorimotor integration, and of reorganisation extending beyond S1.

7.1.1. Aims

The aim of this clinical study was to assess whether patients with CRPS Type 1 demonstrate objective signs of parietal lobe dysfunction on detailed clinical testing, and whether this was related to Quantitative Sensory Testing (QST) findings.

7.1.2. Hypotheses

The hypothesis was that:

- Some CRPS patients will demonstrate evidence of parietal lobe dysfunction when assessed by detailed clinical bedside testing.

The secondary hypothesis was that:

- CRPS patients with parietal dysfunction will have more extensive areas affected by mechanical allodynia compared to patients who have no parietal dysfunction.

7.2. Methodological considerations

7.2.1. Assessment of parietal lobe function

The clinical assessment of parietal lobe function is complex, and often needs detailed neuropsychological assessment as well as clinical testing. If a parietal lobe lesion is suspected, the 'standard' bedside clinical test is usually a brief part of the formal neurological examination and can only detect gross dysfunction. **Fig.7.1** is a typical example.

Fig.7.1

Cortical sensations should be tested whenever a parietal lesion is suspected from the screening examination or patient history. These additional tests include:

- **number identification (graphesthesia).** Examiner traces a number in patient's palm with patient's eye closed and asks the patient to identify the number. Repeat in the other palm.
- **double simultaneous stimulation.** Examiner touches the patient on left upper limb, then right upper limb, then both upper limbs simultaneously while the patient's eyes are closed. Ask the patient. where they feel the touch.
- **two point discrimination.** Examiner can use special calipers or open up a paper clip for this maneuver.
- **stereognosis.** This tests object recognition without the use of vision. Ask the patient to close their eyes, then examiner places a familiar object in the patients palm (i.e., – a coin, key, paper clip) and asks them to identify the object by touch.

Fig.7.1. A typical example of a standard bedside test of parietal function taken from the Loyola University Medical Education Network for medical students (LUMEN [online] ((2010).

In order to establish not only whether parietal dysfunction was present, but what pattern (eg. left Vs right parietal lobe), a more detailed assessment was required. A series of clinical tests were constructed encompassing ten different aspects of parietal lobe function, based upon the testing parameters used in previously published papers clinically examining parietal function in detail (Moo et al., 2003;Tucha et al., 1997). The ten categories of function tested are listed below in **7.3.2**, and the testing protocol and data collection sheet are reproduced in **Appendix 8** and **9**.

7.2.2. Apparatus

For *Parietal testing*

See **Appendix 8**.

For *Quantitative sensory testing:*

As per **Chapter 4.**

7.2.3. Subjects

Twenty-two consecutive CRPS patients attending a two week in-patient rehabilitation programme at the Royal National Hospital for Rheumatic Diseases (RNHRD), Bath UK were invited to participate. All patients fulfilled IASP diagnostic criteria for CRPS (Harden et al., 2007). No patient had any other concurrent pathology that might impair sensation or higher central perception of sensory stimuli (eg. peripheral neuropathy, multiple sclerosis, prior history of cerebrovascular accident) or significant visual impairment.

All admitted patients undergo a full clinical examination which includes a neurological assessment. The parietal testing was done as part of the neurological examination which while more detailed than a standard neurological screen, was not beyond that performed by a Neurologist or neuropsychologist and was appropriate as part of their clinical appraisal. Therefore ethics approval for this part of the overall research project was not sought. All patients had consented to participate in the broader research project which had full local ethics approval. All subjects were informed that they did not have to undergo the more detailed neurological assessment, and that refusal would not impact upon their current or future care.

7.3. Methods

7.3.1. Parietal testing

All the clinical testing was done by one examiner (HC). The subject was seated comfortably, and told that they were undertaking a series of tests to explore how well a particular part of the brain was working. It was explained that as this brain area is involved with putting a variety of different sense information together to make sense of our surroundings, it would involve testing language, numeracy, drawing, touch and sense of body location. The subject was reassured that if they were found to have difficulties, that this would be used to help with individualising their rehabilitation programme.

Each testing category comprised two or more tests administered on each upper limb. Some tests required a series of stimuli (certain tests within the conduction and nominal aphasia, agraphia /alexia, acalculia, astereognosis, finger agnosia, dysgraphaesthesia, right/left disorientation categories) when each limb was presented with 3 stimuli in succession. The tests were performed in the same sequence for each patient, with gaps of 2 – 5 minutes (or more as required by the patient) between each category of testing. Each test was performed first with the unaffected limb, and then with the affected limb. When an abnormal result was obtained, the subject was asked to describe in more detail what had happened, and contemporaneous notes of the qualitative descriptions were taken. The full testing took approximately two hours per patient. Where the testing significantly worsened pain, it was broken into two testing sessions of one hour on consecutive days.

7.3.2. Categories of parietal function tested

For full testing protocol details, see **Appendix 8**.
Each subject performed a testing battery for each of the following categories:

- Interlocking fingers screen (Moo et al., 2003)
- Ideomotor apraxia
- Conduction & nominal aphasia
- Agraphia / alexia
- Acalculia
- Astereognosis
- Finger agnosia
- Dysgraphaesthesia
- Right/left disorientation
- Constructional apraxia

7.3.3. Scoring

For each normal test, a score of one point was allocated. The maximum total possible score was 116 points. During clinical appraisal of parietal lobe function, healthy controls do not make consistent mistakes across multiple categories of testing. Minor infrequent errors may occur due to distraction. The patient groups all had chronic pain and therefore potentially more impaired attention and distractibility. Allowance needed to be made for this. Healthy controls did not make more than one error in any one testing category (see below). Therefore in order to fail a test where a

series of stimuli were given, patients were allowed 3 mistakes in total before being deemed to have failed that test. This allowed for mistakes due to distraction or loss of concentration. A subject that failed one or more tests within a category was classified as having failed that category.

7.3.4. Verification of testing validity in healthy subjects

i. Healthy subjects should not have any difficulty performing clinical tests of parietal function such as these. In order to establish that the parietal testing protocol was performed easily without error in healthy controls, a shortened version of the protocol was performed on 15 healthy subjects (**Fig.7.2**). Two tasks were selected from each test category. Where the test required a series of stimuli, the subject was allowed 3 mistakes in total before being deemed to have failed. All subjects completed the test protocol quickly and easily. No subject made more than one error in any stimulus series test, and no subject failed any of the ten categories.

ii. Dyslexia can cause difficulties with written tasks including letter ordering within a word. However healthy subjects with dyslexia do not have an organic parietal lesion causing these problems, and would not be expected to fail any of the testing categories. Therefore the full testing protocol was done on a healthy control subject with a diagnosis of dyslexia. This subject did not fail any of the ten testing categories.

Fig.7.2.

Interlocking fingers screen **1** **2** **3** **4**

Ideomotor Apraxia
Motor act to command (wave goodbye; salute; thumbs up; hammer a nail; turn a doorknob; stub out a cigarette) **R** **L**

Conduction & Nominal Aphasia
Repetition of: Sentences
Confrontation naming of: Objects
Parts of objects
Clothing
Body

Agraphia / Alexia
Write down: Sentence of own **R** **L**
Dictated words/sentence **R** **L**

Acalculia
Copy numbers **R** **L**
Write dictated numbers **R** **L**

Asteroeognosis
Identify objects by touch **R** **L**
Texture series **R** **L**

Finger Agnosia
Point to named: Own fingers **R** **L**
Examiners fingers **R** **L**
Eyes closed; examiner touches a finger:
Name finger **R** **L**
Move finger **R** **L**

Dysgraphaesthesia
Letters **R** **L**
Numbers **R** **L**

Right Left Disorientation
Crossed commands; Eyes open, on self
Touch named part **R** **L**
Point to named part **R** **L**

Constructional Apraxia
Draw a named shape to command (house, triangle, square etc) **R** **L**
Copy a shape **R** **L**

Fig.7.2. The shortened parietal function testing protocol used on healthy volunteers. The tests and the data collection sheet are shown. Tasks were performed with both the right and left hands. R = right, L = left.

7.3.5. Quantitative sensory testing:

Semmes Weinstein filaments were used to assess tactile thresholds and body areas affected by allodynia. Areas were mapped onto a 'Lund and Browder' burns chart to allow for quantification of the percentage of body surface area (%BSA) affected by allodynia. For the full protocol, see **Chapter 4.** For ease of reference, the Semmes Weinstein filament rank order and their target force is repeated below from **Chapter 4** (**Table 7.1**):

Table 7.1. Semmes Weinstein filament ranking order.

Semmes Weinstein Filaments			
Filament rank	Target force (g)	Filament rank	Target force (g)
1	0.008	11	4
2	0.02	12	6
3	0.04	13	8
4	0.07	14	10
5	0.16	15	15
6	0.4	16	26
7	0.6	17	60
8	1	18	100
9	1.4	19	180
10	2	20	300

Target force is given in grams.

7.3.6. Data analysis

7.3.6.1. Sample size

CRPS is considered to be a rare diagnosis and the literature is sparse. Papers are often based upon small numbers using different diagnostic criteria. Therefore, it was not possible to make an accurate sample size calculation.

A non-random sampling strategy was used, and the sample size was based upon the number of subjects available within the data collection period.

7.3.6.2. Outcome measures

1. QST

The percentage body surface area affected by allodynia was calculated from the mapped mannequin using a Lund and Browder burns chart.

2. Parietal testing

Two outcomes were recorded: 1. Total test score (for each test performed without error, a score of one point was allocated. The maximum total possible score accumulated across all ten categories was 116 points); 2. Category score / 10 (the number of testing categories passed). Patients were classified as having parietal dysfunction if they failed one or more of the 10 testing categories.

7.3.6.3. Statistical analysis

The data is presented as percentages (actual number of subjects), mean and median values and interquartile range (IQR). Statistical analysis was performed on Statistical Package for the Social Sciences (SPSS) v.16 software and utilised non-parametric tests. For comparison between subjects with and without parietal dysfunction, the Mann-Whitney test was used and for correlation analysis, the Spearman's Rho test. Odds ratios (OR) and 95% confidence intervals (CI) are calculated where appropriate.

7.4. Results

7.4.1. Patient demographics

Seventeen female and 5 male patients admitted for a CRPS specific rehabilitation programme at the Royal National Hospital for Rheumatic Diseases, Bath UK were assessed as part of routine clinical examinations during their two week hospital stay. The mean age was 45 yrs, range 27 – 63 yrs and mean CRPS duration 6.8 yrs, range 1 – 18 yrs (see **Table 7.2**).

Nine subjects had CRPS in an upper extremity, 9 in a lower extremity and 4 in an upper and lower extremity. Ten had CRPS on the right side, 11 on the left and one on both sides. Six were left handed, 15 right handed and 1 ambidextrous. Of the total cohort, 64% (n = 14) were on opiate medication, 64% (14) on neuromodulatory / antidepressant drugs and 41% (9) on both.

Table 7.2. CRPS patient demographic data.

Patient ID	CRPS dur'n	CRPS loc'n	Handed	Age (yrs)	Gender	Medication
1	8	RA	R	43	F	Op, BZ, NSAID, O
2	2	RA	R	56	M	NO,NSAID,Op,NA
3	10	LA	L	47	F	NO, NA, O
4	18	LA RL	R	41	F	NA,O
5	8	LA LL	L	29	F	Op, NSAID
6	2	RL	R	42	F	NO
7	17	LA	R	44	F	NO, Op, NA, MR, O
*8	8	RA RL	R	42	F	Op
9	2	LL	R	50	F	NO,NSAID,Op,NA,O
10	11	RA	R	50	M	NO, Op, NA, O
11	8	RL	L	27	F	Op, NO, O
12	4	RA	L	30	M	NA, O
13	1	RA	R	63	F	Op, NSAID, NO, O
14	2	RL	R	46	F	NA, Op
15	8	LA LL	L	55	F	NO, NSAID, NA
16	1	LL	R	58	F	Op, NSAID, NA
17	9	LA	R	63	F	NO,NA,O
*18	2	RA	R	30	F	Op, NA
19	1	LL	R/L	43	F	NIL
20	10	LL	R	33	F	Op, NSAID, NA, NO
*21	7	LL	L	52	M	Op, NO, NA, O
22	10	LL	R	44	M	NSAID, BZ, O

Table 7.2. Details of the CRPS, handedness of subject and medication is displayed. The patient cohort was taken from subjects attending an in-patient rehabilitation programme; the disease duration is therefore skewed towards long duration (mean 7 years).

Dur'n = duration (yrs), loc'n = location, RA = right arm, LA = left arm, RL = right leg, LL = left leg, R = right handed, L = left handed, F = female, M = male
NO = non-opioid, Op = opioid, NSAID = non-steroidal anti-inflammatory drug, NA = neuromodulatory/antidepressant, BZ = benzodiazepine, MR = muscle relaxant, O = other
* = dyslexia

7.4.2. Parietal function in CRPS patients

Only 32 % (n = 7) of CRPS patients performed within normal parameters on all ten test batteries, with 68% (15) failing 1 or more test category. The number and percentage of the cohort failing each testing category is as follows (**Fig.7.3**, **Table 7.3**):

- astereognosis 64% (14)
- finger agnosia 59% (13)
- dysgraphaesthesia 36% (8),

- constructional apraxia 32% (7)
- dyscalculia 27% (6)
- dysgraphia 27% (6)
- conductional dysphasia 14% (3)
- Right /Left (R/L) disorientation 9% (2)
- ideomotor apraxia 4% (1)

None failed the interlocking fingers screen. Dyscalculia, dysgraphia, constructional apraxia, R/Ldisorientation and conductional dysphasia were associated with multiple category failures. Six (27%) failed 6 or more test categories. Five out of six (83%) left handed and 7/12 (58%) right handed subjects failed one or more battery. Eleven of the 15 patients with parietal dysfunction (73%) had CRPS affecting their dominant side. All the patients with >1 limb involvement (n = 4) failed one or more testing categories. There was no statistically significant correlation between disease duration and parietal score (Spearman's rho = -0.213, p=0.34, NS).

Only 32 % (n = 7) performed within normal parameters on all ten test batteries. The majority of subjects with normal parietal function (n=7) were right handed (n = 5, 71%), 1 was left handed and 1 ambidextrous. Five had unilateral involvement of a lower limb and 2 unilateral upper limb involvement (29%). Only 1/7 (14%) had CRPS affecting the dominant upper limb.

Fig.7.3.

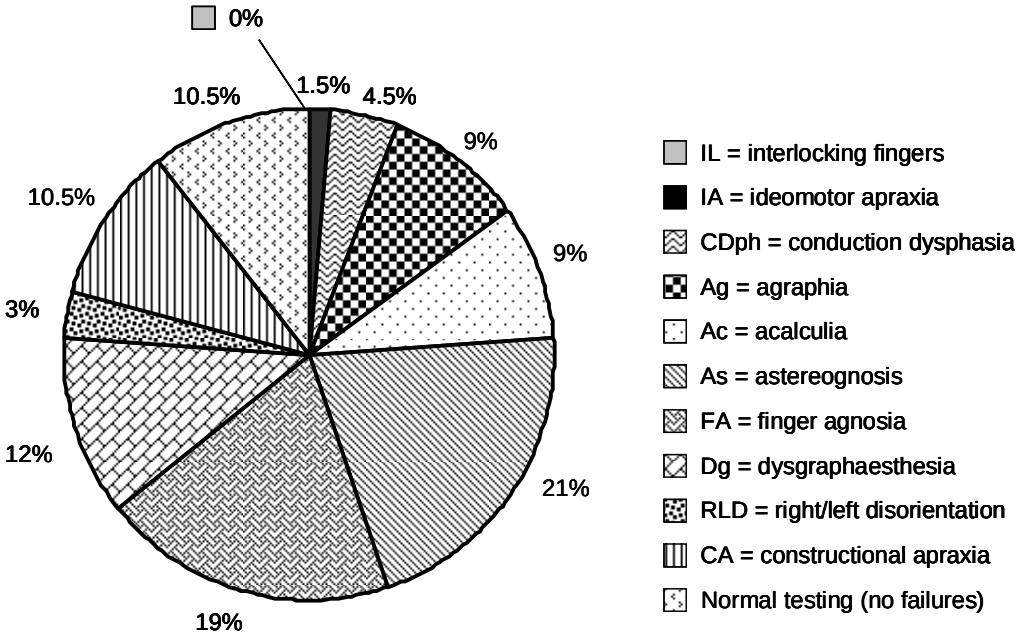


Fig.7.3. Pie chart showing the distribution of normal testing and category failures among CRPS patients.

Table 7.3. Parietal lobe testing results.

Patient ID	Handed	Total score %	Category score/10	Category failed
1	R	45	1	IA,CDph,Ag,Ac,As,FA,Dg,RLD,CA
2	R	47	1	CDph,Ag,Ac,As,FA,Dg,CA
3	L	59	3	Ag,Ac,As,FA,Dg,RLD,CA
4	R	62	4	Ag,Ac,As,FA,Dg,CA
5	L	75	4	Ag,Ac,As,FA,Dg,CA
6	R	75	4	CDph,Ag,Ac,As,FA,CA
7	R	85	7	As,FA,CA
8	R	86	7	As,FA,Dg
9	R	89	8	As,FA
10	R	90	8	FA,Dg
11	L	91	8	As,FA
12	L	93	8	As,Dg
13	R	95	8	As,FA
14	R	95	8	As,FA
15	L	96	9	As
16	R	97	10	
17	R	97	10	
18	R	98	10	
19	R/L	98	10	
20	R	98	10	
21	L	99	10	
22	R	99	10	

Table 7.3. The results of parietal testing are tabulated showing the parietal testing score as a percentage of total score, number of testing categories that tested normally out of ten and which categories were failed. The handedness of the subjects is indicated (grey shading, left handed). 83% of left handed and 58% of right handed subjects failed one or more parietal testing categories.

IL = interlocking fingers, IA = ideomotor apraxia, CDph = conduction dysphasia, Ag = agraphia, Ac = acalculia, As = astereognosis, FA = finger agnosia, Dg = dysgraphaesthesia, RLD = right/left disorientation, CA = constructional apraxia
R = right handed, L = left handed

7.4.3. Quantitative sensory testing

There was mechanical allodynia in 82% (n = 18) of CRPS patients. The percentage of body surface area affected by allodynia (%BSA) ranged from 3 - 57.5%, with the median %BSA = 16%. The area of sensory impairment was confined to the affected limb in 41% (9) and extended beyond the limb in 59% (13). There was no significant correlation between %BSA and disease duration.

The tactile threshold on the affected limb compared to the tactile threshold on the unaffected limb was lower (hyperaesthesia) in 59% (13), higher (hypoaesthesia) in 27% (6) and the same in 14% (3) (**Table 7.4**).

Several unusual sensory patterns were discovered in CRPS affected areas (**Table 7.4**, **Fig**.**7.4**). With eyes closed:

- Twelve (54%) demonstrated referral of sensation (tactile stimulation was felt concurrently in the area stimulated, and in another discrete area bi-directionally) (**Fig.7.4.A,B,D**).
- Five (23%) subjects had allochiria (unilateral tactile stimulation was perceived only in the analogous location on the opposite limb) (**Fig**.**7.4.C,D**).
- Three (14%) showed sensory extinction (concurrent bilateral tactile stimulation was perceived only in one limb).
- Three (14%) displayed tactile dysynchiria[#] (unilateral non-noxious tactile stimulation on the unaffected limb perceived bilaterally, and as noxious on the affected limb).

[#]Synchiria is defined as bilateral sensations in response to unilateral tactile stimulation (Medina and Rapp, 2008). The most appropriate term for this clinical sign would therefore be *dysynchiria.*

Table 7.4. Findings of Quantitative Sensory Testing.

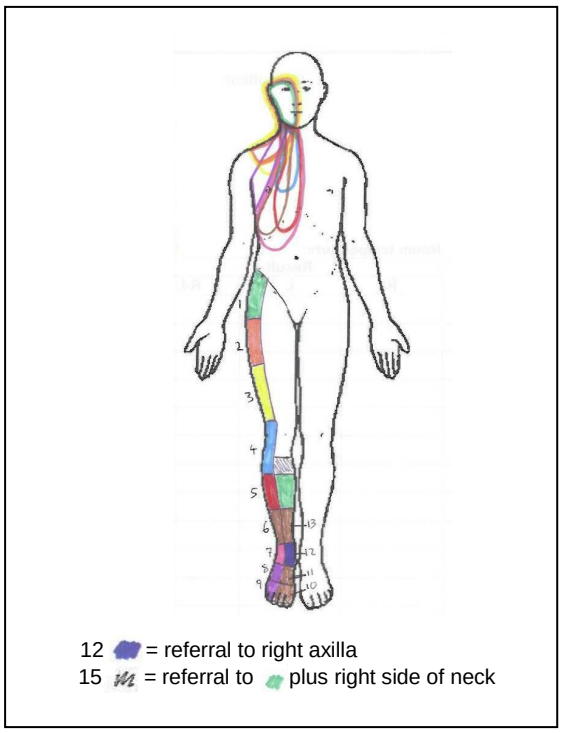
Patient ID	%BSA	TT:AL (g)	TT:UL (g)	TT:AL vs UL	Somaesthesia
1	47.75	0.07	0.04	H	R
2	57.5	0.008	0.02	L	R
3	16	0.008	0.02	L	R,AC,SE
4	35	0.008	0.04	L	R,AC
5	36	0.008	0.008	S	R,AC,D,SE
6	8.25	0.6	1	L	R,AC
7	19	0.4	0.6	L	
8	32	0.04	0.16	L	R
9	26	0.04	2	L	R
10	11.5	0.008	0.008	S	D
11	40.25	0.04	0.02	H	R,D
12	18	0.008	0.07	L	SE
13	0	0.07	0.04	H	
14	0	0.4	0.16	H	
15	29	0.16	0.04	H	R
16	0	0.16	0.16	S	R
17	0	0.02	0.04	L	
18	15.25	0.008	0.4	L	R,AC
19	4	0.008	0.16	L	
20	16.5	0.07	0.4	L	D
21	3.5	0.008	0.04	L	
22	3	4	0.16	H	

Table 7.4. Quantitative Sensory Testing findings for each patient are shown. Tactile thresholds on the affected and unaffected limbs were assessed using Semmes-Weinstein filaments; the target force (in grams) is given. The tactile thresholds between the affected and unaffected limb are compared, and details of any abnormal somaesthetic patterns found are indicated.

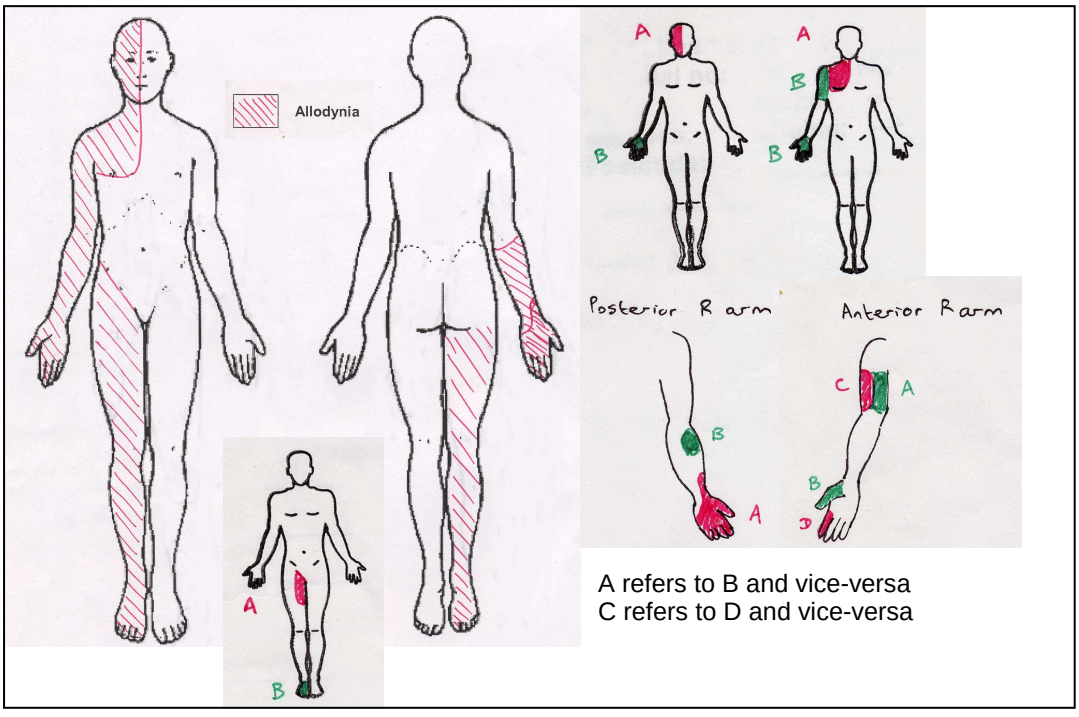
%BSA = percentage of body surface allodynia.
TT = tactile threshold, AL = affected limb, UL = unaffected limb.
TT:AL vs UL = tactile thresholds of affected limb compared to the unaffected limb.
H = AL higher tactile threshold than UL (hypoaesthesia), L = AL lower tactile threshold than UL (hyperaesthesia), S = tactile threshold AL same as UL.
Somaesthesia = pattern of abnormal sensory findings; R = referred sensations, AC = allochiria, SE = sensory extinction, D = dysynchiria

Fig.7.4.

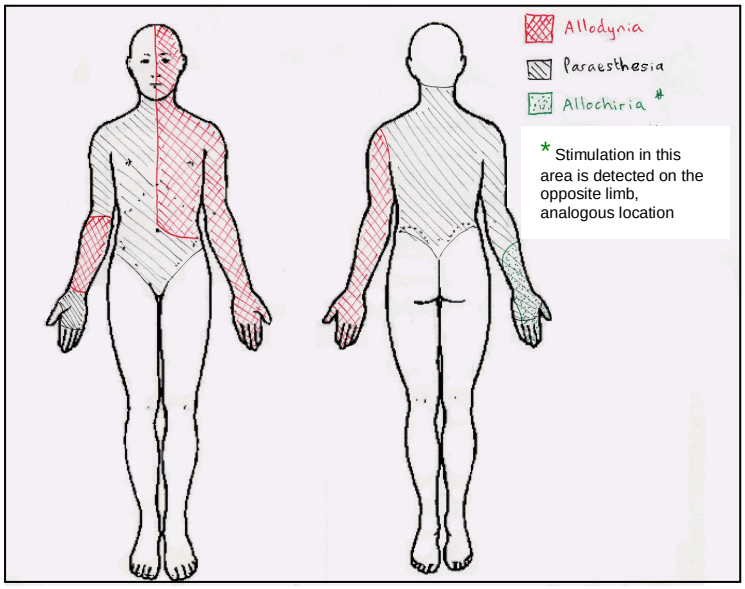
A. Patient 2.



B. Patient 8.



C. Patient 3.



D. Patient 18.

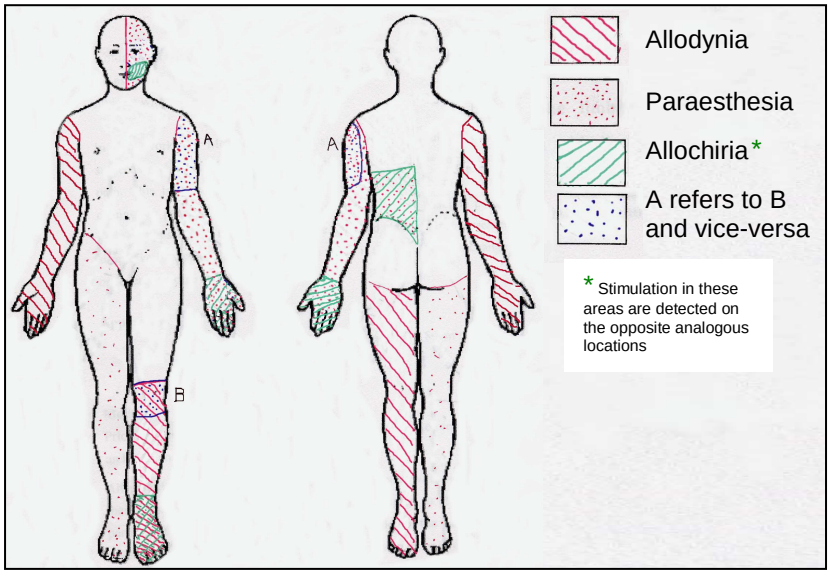


Fig.7.4. Quantitative sensory testing: examples of referred sensation (**A**, **B**) and allochiria (**C**,**D**).

A: The colour coding on the right leg denotes that tactile stimulation in this areas was also perceived on the right side of the face, neck and chest wall in the same coloured areas. **B:** This patient had right upper limb CRPS and a hemi-sensory allodynic pattern with referred sensation in the upper limb and ipsilateral lower limb. **C:** Left upper limb CRPS with bilateral upper limb and left upper quadrant allodynia, and well demarcated allochiria. **D:** Right upper limb CRPS with allodynia in the contralateral lower limb, and allochiric areas on the left side of the face, left lower back, left arm and left leg.

7.4.4. Within group comparison (normal/abnormal parietal function): allodynia

Comparing subjects, there was a significantly greater %BSA in those who failed one or more categories compared to those who performed normally on parietal testing (median (IQR) = 26% (11.5, 36) vs median 3.5% (0, 15.2) respectively; Man Whitney test: U = 13, z = -2.45, p<0.05). There was a strong negative correlation between a low parietal testing score (greater parietal dysfunction) and the extent of BSA (Spearman's rho = -0.674, p=0.001) (ie. low score, greater extent of allodynia, **Fig.7.5**). Some examples of abnormal testing patterns are given in **Fig.7.6**.

Fig.7.5.

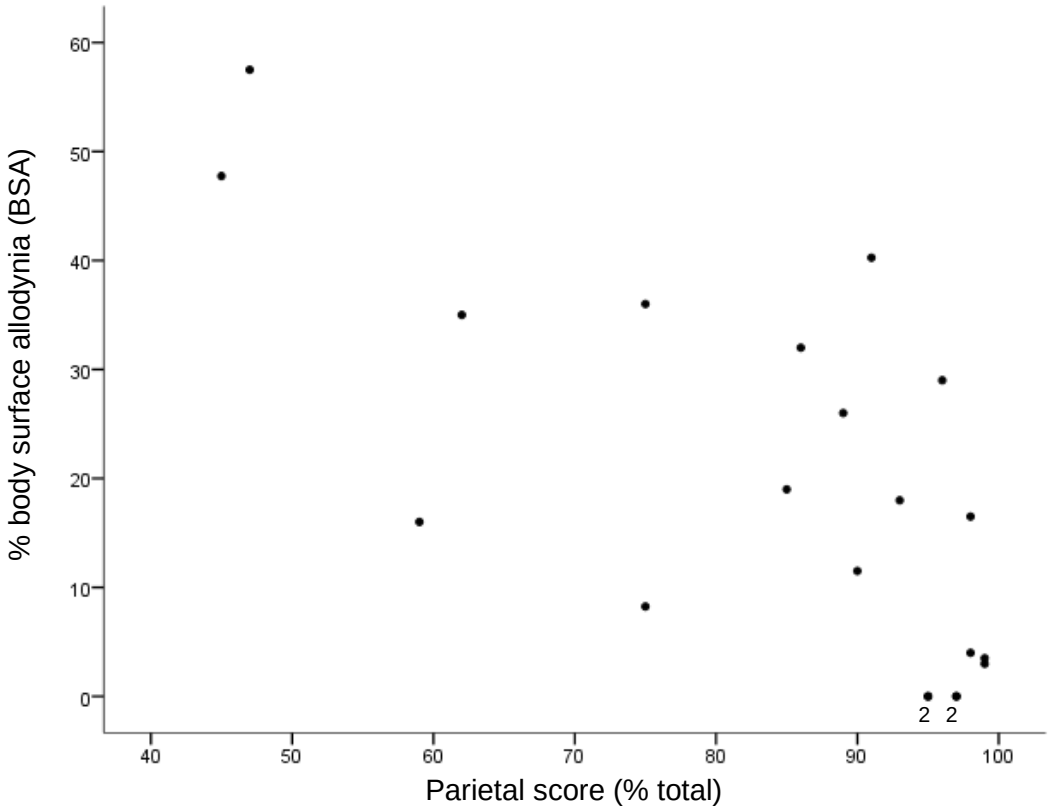
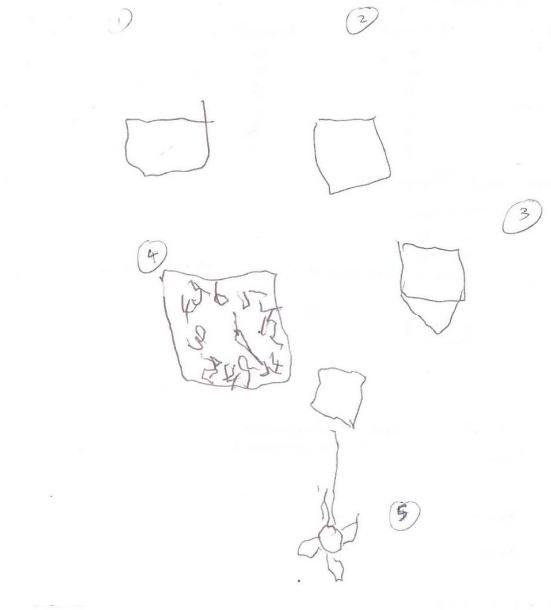


Fig.7.5. Scatterplot of the parietal score as a percentage of the total against the extent of body surface allodynia.

Declining parietal score indicates worsening parietal function. Where data points coincide, the number of data points is given below. There is a significant strong negative correlation (rho = -0.674, p=0.001) indicating that a low parietal score is associated with a greater extent of body surface allodynia.

Fig.7.6.

A. Patient 2



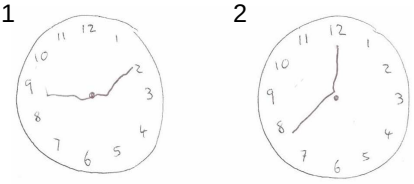
Draw the following shapes: 1 = triangle, 2 = circle, 3 = house, 4 = clock face with the time of 4.30, 5 = copy this picture (flower pot)

Copying numbers

Actual	Reproduced
982	298
6347	4736
110,022	22,010
521	125
1952	2579

Put the following times on to these pre-drawn clock faces: 1 = 7.45, 2 = 6.20

1 2



Examples of writing to dictation (unaffected hand).

1.The cat sat on the mat

2.Shop

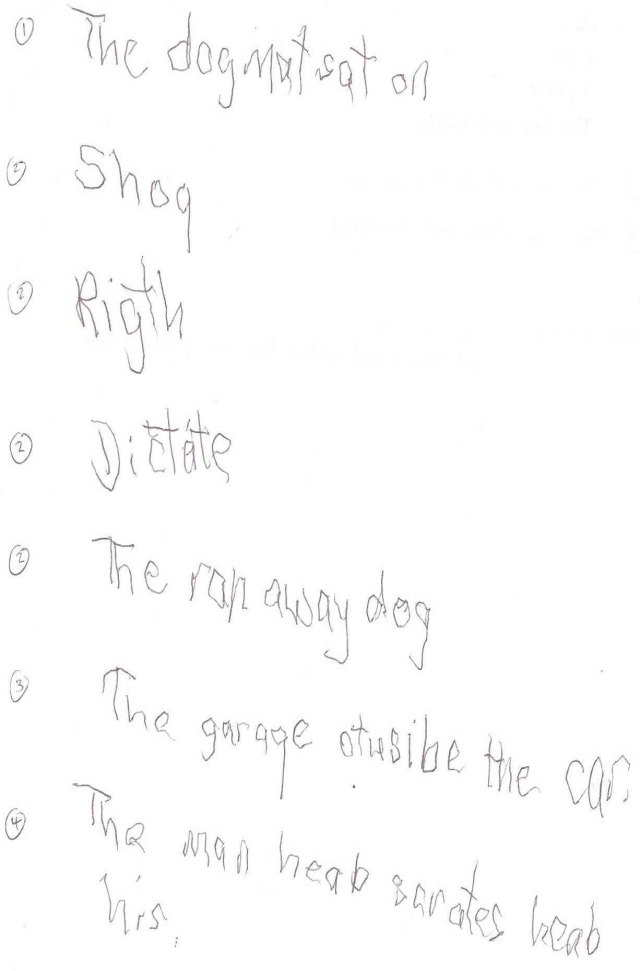
3.Right

4.Dictate

5.The dog ran away

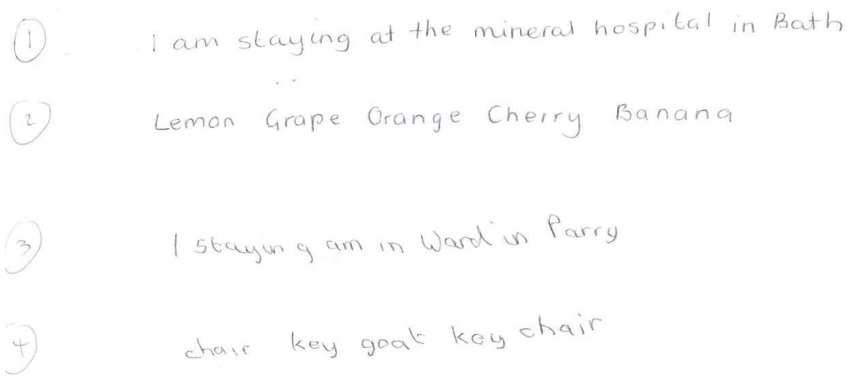
6.The car outside the garage

7.The man scratches his head



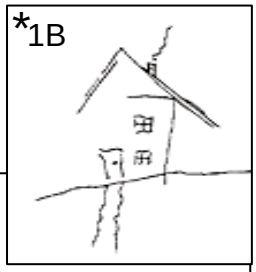
B. Patient 3

1. Write a sentence (unaffected)
2. Write down 5 pieces of fruit (unaffected)
3. Write a sentence (affected) (I am staying in Parry ward)
4. Write down 5 things in the kitchen (affected)



C. Patient 5

*1B



Draw these pictures (affected limb):

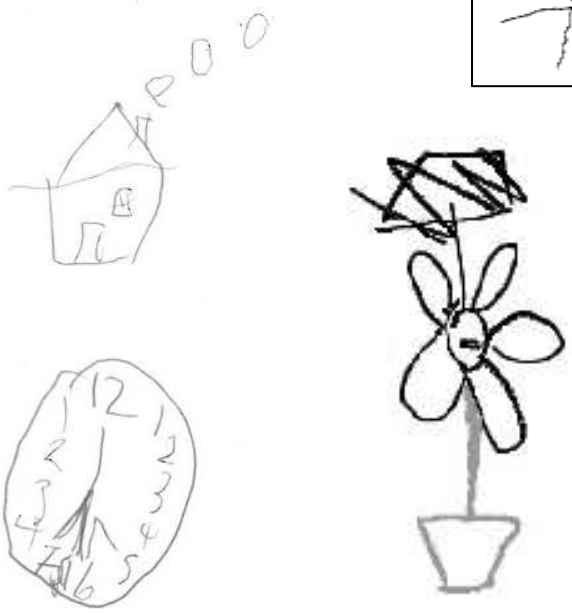
1.House

2.Clock with the numbers

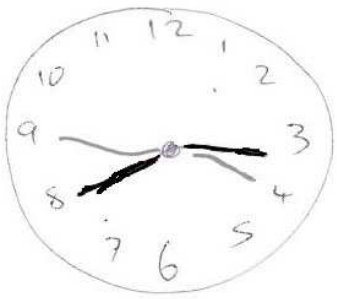
3.Copy this picture of a flowerpot

Black = 'what it wants to do'

Grey = correction



Put the time in on this pre-drawn clock face (affected limb): 4.45
Black = 'what it wants to do'
Grey = correction



D.

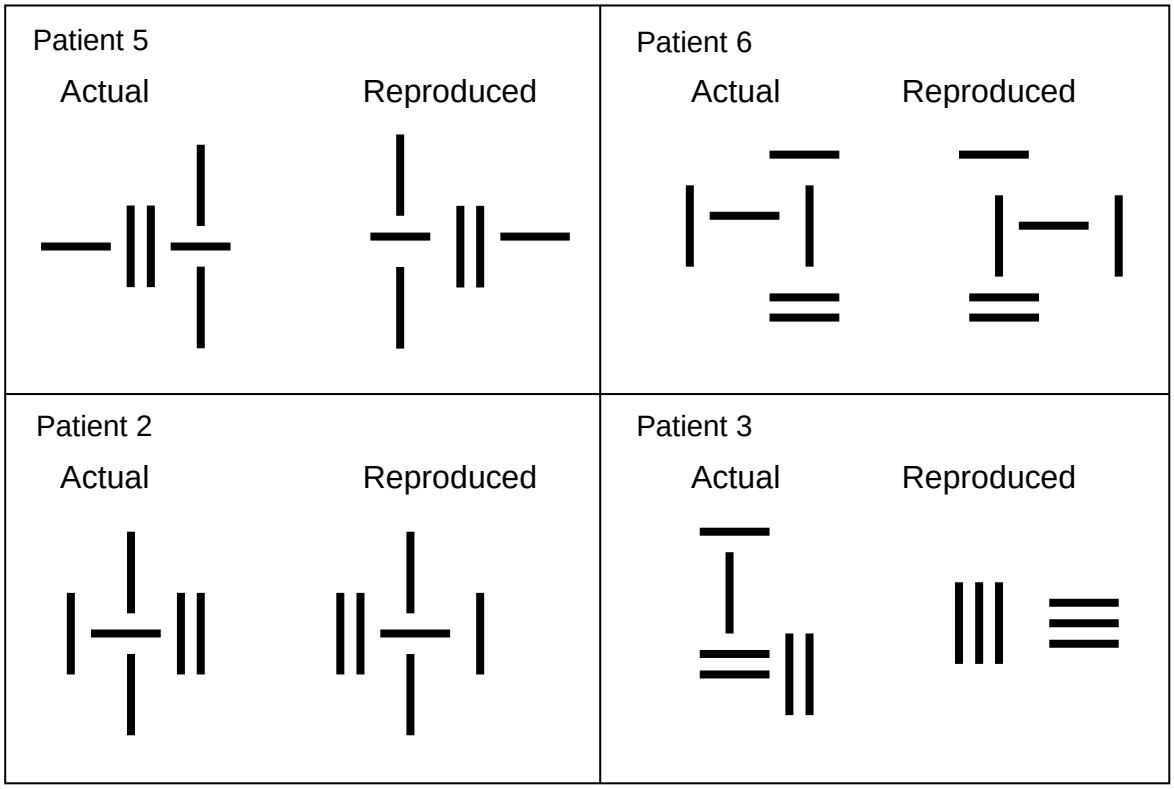


Fig.7.6. Examples of abnormal parietal testing.
When subjects demonstrated dysgraphia, dyscalculia and constructional apraxia, all except one (patient 5) were unable to recognise the mistakes until asked to close their eyes for a few seconds, and then look back at what they had just done.

A. Examples of constructional apraxia, dyscalculia and dysgraphia from patient 2. This was the only patient to demonstrate signs bilaterally. The other subjects had signs only on the affected side. Note the incorrect word use in the first dictated sentence (‘dog’ for ‘cat’), errors in word order and lateral inversion of both letters and clock hands on the pre-drawn clock faces.

B. Examples of normal writing from the unaffected limb and dysgraphia from the affected limb in patient 3.

C. Examples of constructional apraxia from patient 5. Note the lack of a left hand side window in the drawing of the house (1), similar to drawings done by stroke patients with neglect (1B)*. There is also lateral inversion of the clock hands. This patient was able to recognise errors that she was making, and corrected them.

D. Examples of constructional apraxia when copying a random geometric figure using matchsticks. All subjects copied a different figure easily and correctly using the unaffected hand.

* Thomas, Nigel J.T., "Mental Imagery", *The Stanford Encyclopedia of Philosophy (Winter 2011 Edition)*, Edward N. Zalta (ed.). Available from: http://plato.stanford.edu/archives/win2011/entries/mental-imagery/representational-neglect.html. Accessed 02.01.2012.

7.4.5. Within group comparison (normal/abnormal parietal function): tactile thresholds and abnormal sensory findings

Comparing tactile threshold testing, there was no significant difference between tactile thresholds among patients with parietal dysfunction and patients with normal testing.

Comparing abnormal sensory findings, 83% (n = 10/12) of referred sensations, 75% (n = 3/4) with dysynchiria, and 100% of those with allochiria (n = 5) and sensory extinction (n = 3) were found in the parietal dysfunction group.

7.4.6. Clinical observations

During written and drawing tasks, most patients were unaware that any mistakes had been made. Four out of the five subjects that demonstrated constructional apraxia were unable to see the errors made until their attention was distracted and then refocused upon the drawings they had made. A typical comment was 'that is not what I did' with the patient explaining that they were 'doing it right in my head' and confused by what they saw on the page. Only one (patient 5) could recognise that errors were being made during execution of the task, and corrected these (**Fig.7.6C**).

Many patients expressed great surprise at the difficulties that the testing revealed. They were then able to relate how these problems had been manifesting themselves in activities of daily living. The following details four examples.

Patient 5 (**Fig.7.6C**) had persistent tactile mislocalisation from the index to middle finger of the affected hand. When this was explained to her, she related an incident that occurred at home. She had cut the index finger of her affected hand with a knife while chopping vegetables, and put a plaster on her finger. She could not understand why it kept on bleeding until her husband examined her hand and told her that she had put the plaster on her uninjured middle finger.

Patient 18 (**Fig.7.4D**) had areas of allochiria on the unaffected left side of the body. Tactile stimulation in these areas were perceived as painful in the analogous location on the affected side. Once this phenomenon had been explained, she began to cry as she related how she repeatedly scolded her young daughter for touching her 'bad' side. Her daughter would often say "but Mummy, I touched your good side."

Patient 2 (constructional apraxia, agraphia, acalculia, **Fig.7.6**) stated that he could now understand why his wife had banned him from writing cheques or doing the family accounts, and his son declined his help with homework.

Patient 3 (**Fig.7.6B**) said that her family and friends sometimes complained of her using the wrong words in conversation although she was unaware of any error.

She gave a recent example, when she had confused her sister by asking her several times to “feed the table” rather than to “feed the dog.”

It was noted that our patients complained of language difficulties such as inability to find and/or use the correct word. They mentioned written language problems in everyday tasks (such as a shopping list) noticing incorrect word usage, erroneous word and letter ordering (‘writing nonsense’), and spontaneous reversals of letters ‘like mirror writing’. This could be observed clinically on samples of writing such as a shopping list (‘shopping list sign’)*. They reported similar difficulties with numbers, some complaining that they were unable to write cheques anymore (seen clinically on written tasks such as a cheque, the ‘cheque sign’)*, inability to use a credit/debit card due to inability to type the pin number in the correct order (‘swallowed card sign’)* and similar difficulty dialling telephone numbers correctly (‘wrong number sign’)*.

* terminology for these new clinical signs

7.4.7. Cross study analysis: Parietal function in context of data from the preceding thesis studies.

Autonomic function, pain, optokinetic vulnerability and responses while viewing ambiguous visual stimuli: comparison within parietal tested cohort (n = 22) and between the upper limb and overall CRPS cohorts*.

***** Overall CRPS cohort n = 56. Where comparisons are made to the overall CRPS cohort, the numbers for each study are as follows (see Chapter 1):

- 45/56 has baseline QST
- 54/56 had baseline autonomic function testing
- 55/56 had optokinetic vulnerability testing
- 42/56 had responses to ambiguous visual stimuli assessed

7.4.7-1. Study 1: Baseline Autonomic function

The overall composite autonomic function (ANS) score comprises the presence or absence of a sympathetic response on laser Doppler flowmetry and galvanic skin response, in each upper limb to each of the 5 sympathetic autonomic stimuli (deep breath, Valsalva manoeuvre, limb dependency (ipsilateral and contralateral vasoconstrictor responses) and the mental stress task. The maximum possible score was 20. For full details, see **Chapter 4**.

For the parietal tested cohort (n = 22), the overall mean composite autonomic function (ANS) score was 14.9 (median 16) / 20. There was a non significant (Mann-Whitney *U*-test, p>0.05) lower ANS score between the CRPS patients with parietal dysfunction (mean ANS score = 14.4, median = 16) and those who performed normally (mean ANS score = 16.4, median = 17). The mean ANS score of the overall CRPS cohort (n = 54) was 15.7 (median 17), and of the upper limb CRPS cohort (n = 30) was 15.4 (median 16.5) (**Fig.7.7**).

Baseline pain

The baseline pain levels for the patients with and without parietal dysfunction are detailed (**Fig.7.8**) below as pie charts.

Fig.7.7

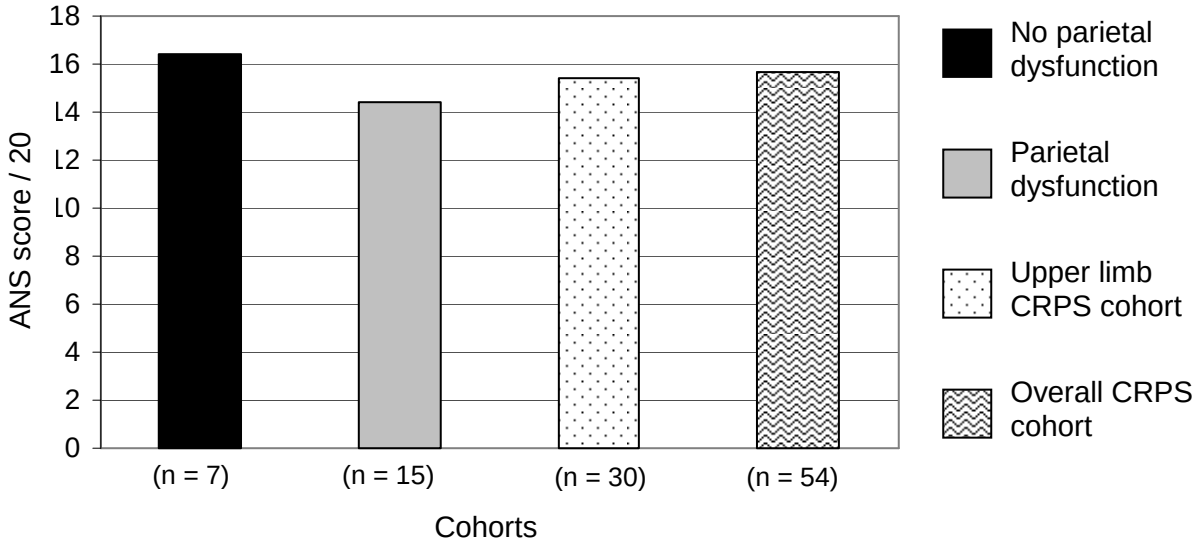


Fig.7.7. Baseline autonomic function score of CRPS patients with and without parietal dysfunction, and compared to the baseline autonomic function score upper limb and overall cohorts.

ANS score / 20 = mean composite autonomic function score (out of a possible maximum score of 20)

Fig.7.8.

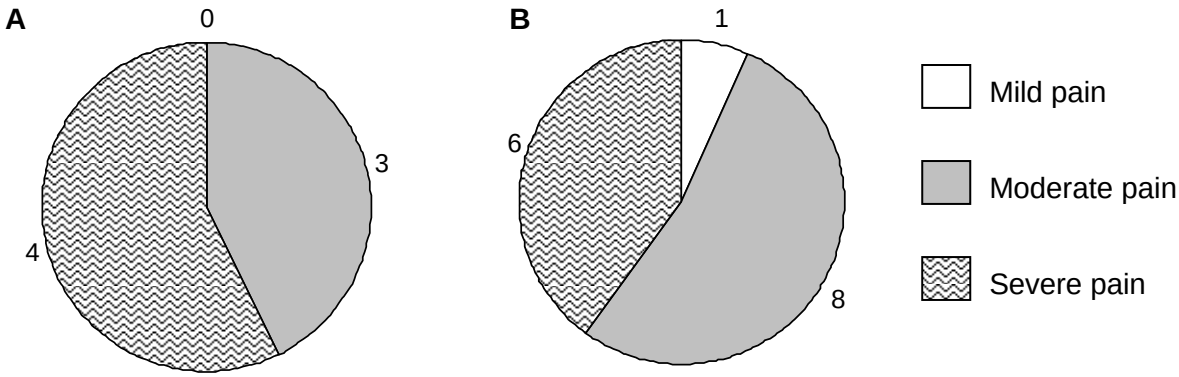


Fig.7.8. Pie charts showing baseline pain levels among CRPS patients without (**A**) and with (**B**) parietal dysfunction.

n = numbers of patients.

7.4.7-2. Study 2: Vulnerability and pain responses during optokinetic challenge

Vulnerability during the optokinetic testing protocol was classified as none, minimal, mild, moderate or high. A score could then be assigned between 0 – 4 (where none = 0, minimal = 1, mild = 2, moderate = 3 and high = 4). For full details, see **Chapter 5**.

All of the parietal tested cohort (n = 22) were vulnerable to optokinetic testing, experiencing worsening of their usual pain. Eleven demonstrated motor extinction, 6 in the parietal dysfunction group and 5 in the normal testing group.

There was a non significant (Mann-Whitney *U*-test, p>0.05) higher mean optokinetic vulnerability score (OVS) among patients with parietal dysfunction (OVS = 3.4) compared to those without (OVS = 3.1). The mean OVS for the CRPS upper limb cohort was 2.9, and for the overall CRPS cohort 2.7 (see **Fig.7.9**). The median OVS was the same for all groups (median OVS = 3).

Fig.7.9.

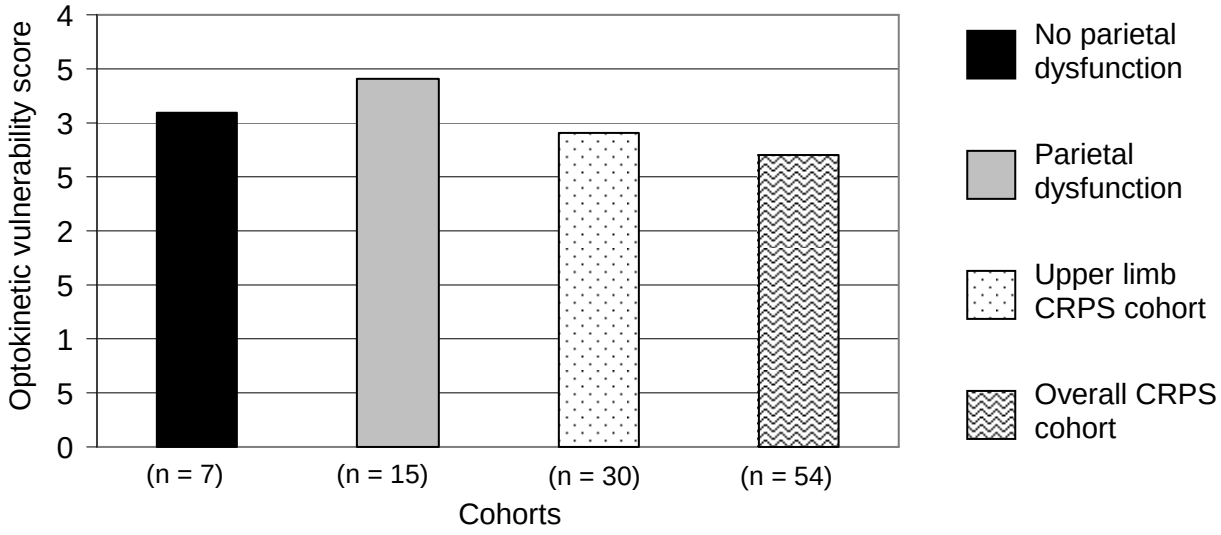


Fig.7.9. Mean optokinetic vulnerability scores of CRPS patients with and without parietal dysfunction, and compared to optokinetic vulnerability scores of the upper limb and overall cohorts.

Vulnerability: none = 0, minimal = 1, mild = 2, moderate = 3 and high = 4

Within the parietal tested cohort (n = 22), there was a significant strong negative correlation (Spearman's Rho = -0.734, p<0.001) between the Semmes Weinstein tactile threshold (rank) of the affected limb and the optokinetic vulnerability score (ie. the lower the tactile threshold, the higher the optokinetic vulnerability) (**Fig.7.10**).

Fig.7.10

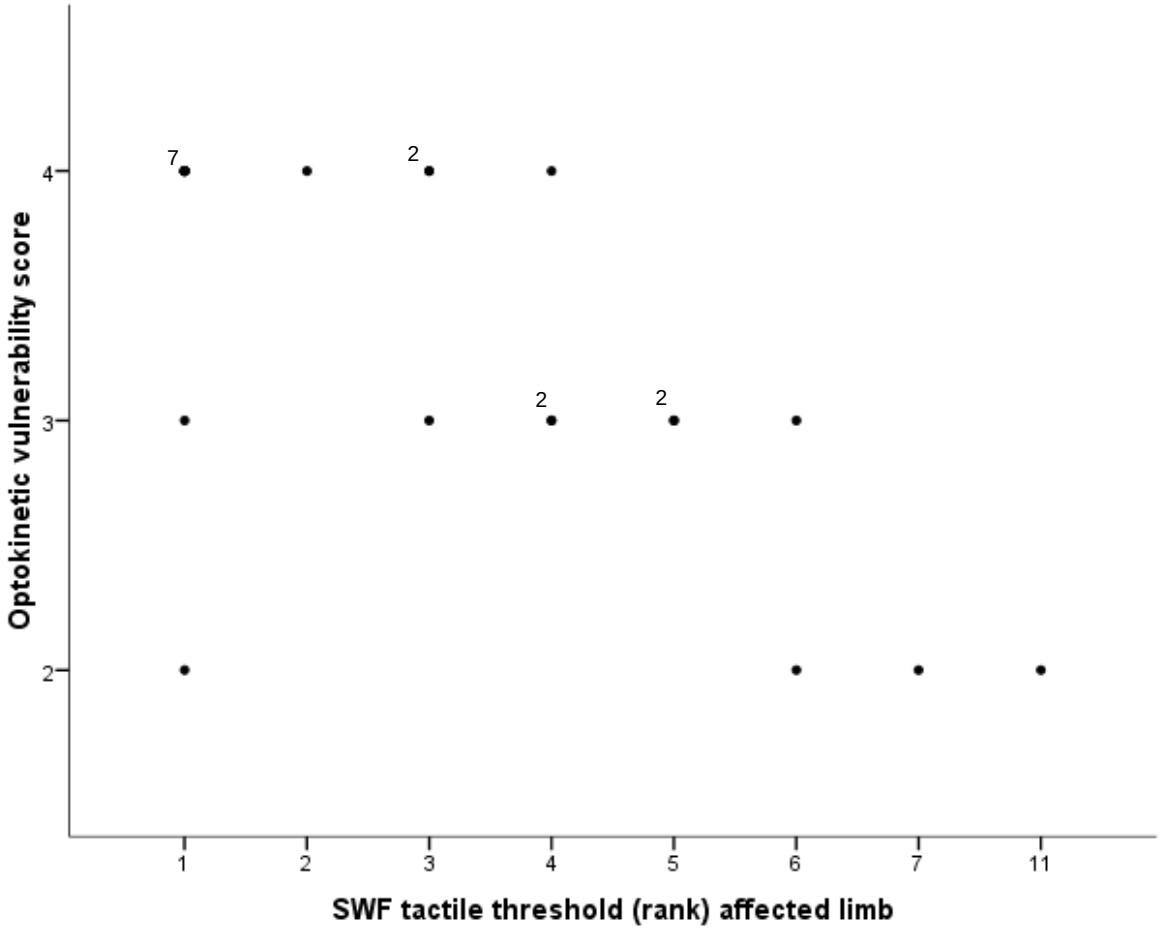


Fig.7.10. Scatterplot of optokinetic vulnerability score (OVS) against Semmes Weinstein tactile threshold of the affected limb.

NB. Where some data points represent more than one subject, the number of subjects is indicated by a numeral beside the plot point.
The finest hair is ranked 1 (target force 0.008g) through to the heaviest filament ranked 20 (target force 300g). Filament 11 = 4g. See **Table 7.4**.
SWF = Semmes Weinstein filament

7.4.7-3. Study 3: Pain responses and autonomic function while viewing ambiguous visual stimuli in CRPS.

For details of the full protocol, see **Chapter 6**.

7.4.7-3i. Pain responses

While viewing ambiguous visual stimuli (AVS), 90% of the parietal tested cohort (n = 20/22) had enhancement of pain. Only two patients (one each of normal/abnormal

parietal testing groups) did not have enhancement of pain while viewing AVS. Among the upper limb CRPS cohort, 63% had enhancement of pain.

7.4.7-3ii. Autonomic function: homology

Autonomic sympathetic laser Doppler flowmetry (LDF) and electrodermal skin responses (ESR) can be qualitatively analysed in terms of homology and pain response while viewing AVS (see **Chapter 6**). These groups were: Group 1= no pain and homologous symmetric responses, Group 2 = pain and homologous symmetric responses and Group 3 = pain and anomalous asymmetric responses. For the abnormal parietal function cohort with autonomic function data (n = 15), 1 (6%) was in group 1, 7 (47%) were in group 2 and 7 (47%) in group 3 (see **Table7.5**). Compared to the upper limb cohort, patients with parietal dysfunction were eight times less likely to be in group 1 (odds ratio (OR) = 0.123, 95% CI:0.01;1.07) and twice as likely to have group 3 type responses (OR = 2.04, 95% CI:0.6;7.3).

For patients with normal parietal testing and autonomic function data (n=6), 1 (16.5%) was in group 1, 4 (67%) in group 2 and 1 (16.5%) in group 3.

Table 7.5. Autonomic function: homology and pain responses while viewing ambiguous visual stimuli.

	Cohort		
Group	PD	UL CRPS	Overall CRPS
Group 1	1 (6%)	11 (37%)	20 (37%)
Group 2	7 (47%)	10 (33%)	23 (42.5%)
Group 3	7 (47%)	9 (30%)	11 (20.5%)

Table 7.5. Pain and autonomic response homology classified by group while viewing ambiguous visual stimuli for CRPS patients with parietal dysfunction (PD) (n = 15/22), upper limb (UL) CRPS (n = 30) and overall CRPS (n = 54) cohorts.

Group 1= no pain and homologous symmetric responses, Group 2 = pain and homologous symmetric responses and Group 3 = pain and anomalous asymmetric responses.

7.5. Discussion

Data from this work supports the primary hypothesis that some CRPS patients demonstrate evidence of parietal lobe dysfunction when assessed by detailed clinical bedside testing. It also provides evidence supporting the secondary hypothesis that CRPS patients with parietal dysfunction have more extensive areas affected by mechanical allodynia compared to patients who had no parietal dysfunction.

I propose that in CRPS, a clinical phenotype associated with extensive allodynia and distinct symptoms and signs can be identified, and that parietal lobe network involvement may be a factor. Further studies are required to validate these clinically based hypotheses, in a larger cohort combined with detailed neuropsychological testing and neuroimaging.

7.5.1. Parietal dysfunction & CRPS

Previously described clinical features in CRPS such as digit misidentification (Förderreuther et al., 2004), agnosia for object orientation (Robinson et al., 2011) and neglect-like phenomena (Galer and Jensen, 1999;Lewis et al., 2007) are suggestive of parietal lobe dysfunction in CRPS, with neuroimaging studies providing further evidence of parietal involvement (Gieteling et al., 2008;Lebel et al., 2008;Maihöfner et al., 2007;Shiraishi et al., 2006;Vartiainen et al., 2008;Wu et al., 2006). A previous PET study of brush evoked allodynia in healthy volunteers given intradermal capsaicin demonstrated activation of the posterior parietal cortex (Witting et al., 2001). Specific activation was seen in the contralateral Brodmann area 5/7 suggesting the importance of this area to the processing of allodynia due to its multisensory input, role in conscious pain perception and its neuroplastic properties. Reorganization in parietal areas other than S1 have been proposed as contributing to synchiria in hands rendered anaesthetic by stroke or neurosurgery (Sathian, 2000), and referral of sensation in phantom limb patients (Flor et al., 2000;Grusser et al., 2004).

Using detailed sensory and neurological testing, it has been demonstrated for the first time that there is clinical evidence of parietal lobe dysfunction in some CRPS type 1 patients. Furthermore, the extent of the body surface area affected by tactile allodynia strongly correlated with the degree of parietal dysfunction observed, suggesting that there may be greater cortical reorganization in these patients. Neuroimaging studies are required to investigate this further. The parietal tested cohort was taken exclusively from patients admitted to the in-patient rehabilitation

programme. Therefore it is likely that this cohort is a particularly severe phenotype with long duration disease. However, five patients with disease duration of 2 years or less demonstrated parietal dysfunction. This work needs to be extended to larger numbers including early CRPS, which may allow for further clinical phenotyping. If some patients develop a 'parietal' phenotype early in the disease, they might benefit from early identification and aggressive rehabilitation (which opens further potential avenues of clinical research). Such rehabilitation might include techniques usually used in brain injury and stroke rehabilitation for patients with parietal compromise. Treatments that aim to improve visual exploration of extrapersonal space in neglect may prove fruitful if applied to extrapersonal space around the affected limb.

7.5.2. Neurological abnormalities and organic brain lesions

The neurological abnormalities described in this series of patients cannot be accounted for by a focal cortical lesion such as an infarct, or neurodegenerative disorders for the following reasons:

i. All subjects performed normally on standard neurological testing.
ii. None of the patients had any of the self-reported difficulties subsequently found prior to onset of their CRPS, corroborated by their families.
iii. Twelve patients had undergone brain imaging as part of their work up prior to referral to our centre, which did not demonstrate any significant abnormality (11/12 scans were in the parietal dysfunction group).
iv. The pattern of parietal abnormalities in the severely affected group (ie. more than three categories failed) is unusual and suggestive of both right and left parietal dysfunction.

Furthermore, there was no obvious impairment in memory, reasoning or emotional responses. Clusters of neurocognitive deficits such as these would be more typical in localized brain damage or neurodegenerative disorders. Future work would need to include formal neuropsychological appraisal of such areas of cognition.

7.5.3. Mechanical allodynia

The prevalence of mechanical allodynia for this cohort was 82% and mean disease duration was 7 years. Rommel and colleagues (Rommel et al., 1999;Rommel et al., 2001;Rommel et al., 2004) described that in 30-33% of CRPS patients, sensory abnormalities extend beyond the affected limb in a hemisensory pattern. The mean disease duration was 43 months. We demonstrated that in this severe, long duration

CRPS cohort 59% had sensory abnormalities extending beyond the affected limb. However, we found no correlation between disease duration and extent of allodynia. This may be due to the small sample size.

7.5.4. Sensorimotor dysfunction and parietal testing

The parietal testing protocol required patients to use their upper limbs, so it is unsurprising that 11 out of the 15 with dysfunction had CRPS affecting an upper limb. However 4/15 CRPS patients with parietal dysfunction had unilateral lower limb involvement showing that impaired testing is unlikely to be an artefact of a protocol that needs subjects to use their upper limbs.

Higher order testing such as stereognosis, apraxia etc ideally require that the performance is not influenced by the presence of sensory or motor impairment. However such testing is often undertaken in patients with sensorimotor involvement such as stroke patients, allowances being made for any baseline impairments. A similar approach was used testing CRPS patients. However sensory and motor impairment in the affected upper limb may have been a confounding factor and affected performance of stereognosis testing. Patients with astereognosis were unable to detect the weight, size, shape or volume of objects. These judgements are the result of higher order integration of different lower order sensory modalities. The system may fail when one or more lower order components perturb the complex process of higher order integration, or when higher order integration is disturbed (such as posterior parietal lobe damage) despite intact lower order components. Further work should include more detailed QST including two point discrimination.

7.5.5. Referral of sensations

Referral of sensation (Maihofner et al., 2006;McCabe et al., 2003;Robinson et al., 2011) has been previously documented in CRPS patients. Only one previous study (Förderreuther et al., 2004) has looked for sensory extinction in a cohort of CRPS patients (n = 114) and did not find any. However this was an early CRPS cohort with a mean disease duration of 6 months. While dysynchiria in CRPS has been reported (Acerra and Moseley, 2005), it was a type of visuotactile dysynchiria induced by watching a reflected image of the unaffected limb being touched and feeling pain or paraesthesia at the corresponding site on the affected limb. We have not found any previously published reports of allochiria (mislocation of sensory stimuli to the corresponding opposite half of the body) (Meador et al., 1991) or pure tactile dysynchiria in CRPS.

7.5.6. Right or left parietal dysfunction

The pattern of parietal disturbance is unusual, and probably involves both the right and left parietal cortices, and superior and inferior lobules. Left parietal dysfunction can include finger agnosia, asteroegnosis, dysgraphaesthesia, conduction aphasia, R/L disorientation and agraphia. Right parietal dysfunction often causes constructional apraxia. Among subjects with three or more category failures, both right and left sided dysfunctions are apparent. This cannot be accounted for by an anatomical lesion and is more likely to reflect a maladaptive failure of the parietal cortices to maintain associative functional integrity. A similar maladaptive failure in another parietal function, the maintenance of global body constructs (Giummarra et al., 2007) has been proposed to explain the complexity of phantom limb pain and body schema distortion described in CRPS (Lewis et al., 2010).

A possible contributing mechanism may be disruption in normal right-left hemispheric communication. Side to side hemispheric asymmetry in primary somatosensory cortical representation of the affected hand in upper limb CRPS patients has been described, with the affected hand having significantly smaller representation compared to the healthy hand (Pleger et al., 2004). A sustained shift leading to hemispheric representational asymmetry might perturb transcallosal cross-referencing and interhemispheric communication. There has been a case report of a CRPS patient with mirror-like spread of pain and neurophysiologic evidence of altered inter-hemispheric conduction, lending credence to both this concept, and its possible involvement in pathologic chronic pain (Forss et al., 2005). Hand dominance is associated with hemispheric lateralisation (ie. right handedness with left hemisphere dominance). Some subjects with CRPS affecting the dominant limb may become more reliant upon the non-dominant limb over time. This could have an effect on hemispheric dominance, and effective inter-hemispheric communication.

Some of the findings from this study are consistent with these concepts. Thirteen subjects had CRPS in an upper limb. For 9/13 (69%) subjects, it was in their dominant hand; eight out of 9 (89%) had parietal dysfunction. When numbers of patients with CRPS affecting their dominant side are reviewed (n = 13), there were a similar proportion (11/13, 85%) with parietal dysfunction. Seven CRPS patients had CRPS affecting their non-dominant side; just over half (4/7, 57%) had parietal dysfunction.

In this study, there was a higher than expected incidence of left handed subjects (27% vs UK prevalence of 3-15% (Postnote, 2004;Miles TR, 2004), and proportionally more (83%) demonstrated parietal dysfunction compared to right

handed subjects (67%). Further studies are needed to investigate the role of handedness and hand switching upon parietal function.

7.5.7. Constructional apraxia and allochiria

Right parietal lesions can cause left neglect and impaired visual-spatial perceptual functioning. Constructional apraxia (CA) may occur after unilateral right or left sided parietal lesions. Possible explanations include that both parietal lobes are required for drawing, or that there is a strong influence of cerebral laterality (Makuuchi et al., 2003). With constructional tasks, the ability to perceive (or care) that errors have been made is usually compromised (Joseph, 1990). Four out of the five subjects that demonstrated CA were unable to see the errors made until their attention was distracted and then refocused upon the drawings they had made. A typical comment was 'that is not what I did' with the patient explaining that they were 'doing it right in my head' and confused by what they saw on the page. One subject demonstrated left neglect when drawing a simple house (**Fig.7.6C**). The term 'allochiria' has also been applied to transpositional construction errors observed in drawing tasks, usually in patients with right parietal lesions and left hemi-spatial neglect. Halligan et al (Halligan et al., 1992) describe a patient with 'visual' allochiria who transposed details when copying a drawing from the left to the right. This subject was also unable to notice the errors. The lateral inversions produced in the matchstick task (**Fig.7.6D**) may represent a form of visual allochiria.

Visual allochiria can be elicited by some tasks but not others, and is rarely consistent even in the same cognitive domain (Lepore et al., 2003). It remains unclear whether neglect and allochiric phenomena are theoretically unrelated disorders or part of the same spectrum (Grossi et al., 2004;Halligan et al., 1992). A recent study in CRPS patients (Moseley et al., 2009) found evidence of deficits in tactile processing defined by the space in which the affected limb normally resides and not by the affected limb itself, suggesting that chronic CRPS may involve a type of spatial neglect. There may be both representational (Bisiach et al., 1981;Mijovic, 1991) and attentional (Di Pellegrino, 1995) aspects to allochiria, and it is likely that there are different types of spatial transposition (Lepore et al., 2004). Patients 2 and 5 demonstrated an unusual type of transposition characterised by both vertical and lateral inversions. Patient 2 was reviewed by a neuropsychologist and found to have agnosia for object orientation (Robinson et al., 2011). This may provide an alternative explanation for the drawings and matchstick patterns. Further studies including detailed neuropsychological testing are needed to investigate patterns of

constructional apraxia / visual allochiria in CRPS, and to attempt to disentangle representational from attentional components.

7.5.8. Dysgraphia

Different types of parietal dysgraphia are caused by lesions in different anatomical substrates including the angular gyrus, superior parietal lobule and intraparietal sulcus. Features may include difficulty in forming letters (apraxic agraphia), substitutions, omissions, inversions and distortions (Sakurai et al., 2007)(Fig 4). Some people are able to write fluent laterally inverted text, or 'mirror writing' spontaneously (Schott, 2007). It can also occur after a stroke (Pflugshaupt et al., 2007).

Mirror writing is associated with being left handed (Schott and Schott, 2004), as is dyslexia (Goez and Zelnik, 2008) in which letter inversions are often seen. Traumatic injury rendering the preferred right hand useless and causing a switch to the left hand has been reported to be associated with mirror reversal of letters and mirror phenomena in daily tasks (Schott, 1980). While left handedness might produce characteristic patterns on a full neuropsychological assessment (Gregory and Paul, 1980), it would not be expected to produce abnormal clinical neurological parietal testing results. Pilot work included performing full testing on a left handed dyslexic subject who tested normally throughout all categories. As mentioned above, there was a higher than expected incidence of left handedness in the study cohort, which could influence some of the written tasks. Further studies are needed to investigate the role of handedness, mirror writing and parietal function.

7.5.9. Parietal cohort compared to overall and upper limb CRPS cohort

The parietal tested cohort was taken exclusively from patients admitted to the in-patient rehabilitation programme, where as the other cohorts also included some subjects treated as out-patients. The RNHRD has become a National centre for the treatment of CRPS and therefore tends to draw severe, longstanding cases. Those patients with incapacitating functional difficulties due to pain and motor impairment are offered an in-patient rehabilitation programme which runs over two weeks. While there was no intentional selection bias, not all admitted patients could be tested for parietal dysfunction. One to two were selected from among admitted patients (between 1-4 patients per programme) in consecutive programmes over 6 months. Therefore it is likely that the parietal tested cohort is a particularly severe phenotype, and generalisation of findings to other CRPS cohorts is therefore limited.

7.5.10. Parietal function and sensory testing, optokinetic vulnerability and autonomic function.

There was a strong negative correlation between the Semmes Weinstein tactile threshold (rank) of the affected limb and the optokinetic vulnerability score, with lower the tactile thresholds correlating with higher optokinetic vulnerability. A previous MEG study of tactile stimulation in hyperaesthetic CRPS patients demonstrated increased activation of S1 on the affected hand compared to the unaffected, suggesting increased central sensitisation to touch (Vartiainen et al., 2008). Other research has indicated that tactile impairment appears to be linked to the amount of cortical reorganisation (Pleger et al., 2006), and that reversal of tactile impairment is associated with restoration of cortical map size and reduction in pain (Pleger et al., 2005). Therefore hyperaesthetic CRPS patients with lower tactile thresholds in my study may have a greater degree of cortical reorganisation, and this is linked with higher optokinetic vulnerability. The numbers are small and need verification with a larger study.

CRPS patients with parietal dysfunction were more likely to have enhanced pain and asymmetric responses while viewing ambiguous visual stimuli compared to the overall cohort. In chapter 5 it was proposed that in a subgroup of CRPS patients, visual sensory conflict could activate abnormal pain pathways which interact with disrupted central autonomic and motor programmes producing pain, dystonia and asymmetric sympathetic responses. It was suggested that neuroplastic reorganisation involving parietal areas could be a predisposing factor. This study provides further support for this as a potential mechanism.

7.5.11. Study strengths

This work is the first to demonstrate clinical evidence of parietal lobe dysfunction in severe, long duration CRPS which is not detectable by typical limited routine neurological testing. It shows correlation between parietal dysfunction and extent of allodynia, suggesting cortical reorganisation may be a contributing mechanism. It also provides an explanation for symptoms that might otherwise be labelled as psychological or malingering.

7.5.12. Study limitations and future directions

Most of the parietal testing tasks involved use of the upper limbs. In this study there were 9 patients with CRPS in an upper limb (UL), 9 in a lower limb (LL) and 4 with upper and lower limb involvement. The parietal testing protocol required patients to use their upper limbs, so it is unsurprising that 11 out of the 15 with dysfunction had CRPS affecting an upper limb. However 4/15 had unilateral lower limb involvement

confirming that impaired testing is not an artefact of a protocol that needs subjects to use their upper limbs. Future work needs to address whether the testing protocol reliance on use of the upper limbs has a bias on the outcome parameters. Further work should expand numbers of UL and LL affected patients and introduce other neuropsychiatric testing techniques which do not require use of the upper limbs.

Having demonstrated that clinical parietal dysfunction can be observed in severe long duration CRPS, the research needs to be extended to earlier, less severe cases and to be combined with neuroimaging techniques. By utilising this clinical phenotyping work with functional imaging techniques, it may offer new insights into dysfunctional cortical network mechanisms in CRPS. This may allow for better targeting of rehabilitation treatments.

The major limitation is the lack of confirmatory functional neuroimaging work. However, the data provides some insights into possible mechanisms and suggests that future neuroimaging studies should further investigate the role of the parietal cortex.

7.5.13. Clinical Implications

When the results of parietal dysfunction testing are combined with optokinetic vulnerability and sympathetic autonomic function testing at baseline and while viewing AVS, a particular severe phenotype is seen to emerge. Compared to the overall cohort, a CRPS patient with parietal dysfunction is more likely to have abnormal baseline testing, optokinetic vulnerability with lower tactile thresholds on the affected limb and is more likely to experience pain while viewing AVS with asymmetric sympathetic responses in the limbs (and therefore higher chance of experiencing a dystonic reaction in the affected limb). This is highly relevant to understanding the pattern of clinical symptoms and signs, and therefore utilisation of the most appropriate rehabilitation techniques.

Extent of allodynia appears to be linked to the degree of dysfunction, and should prompt clinicians to look for symptoms and signs of parietal dysfunction in patients with extensive allodynia. New clinical signs have been described, and the presence of >1 in a CRPS patient is suggestive of parietal lobe involvement and should prompt further clinical assessment.

On a practical level, patients with constructional apraxia, agraphia or acalculia may not be able to perceive mistakes made. They should be advised to ask someone else to check written work or tasks involving numeracy. They may need to avoid writing cheques and consider using a ‘chip and signature card’ rather than a ‘chip and PIN’ number card[†]. Use of the speed dial facility on telephones may overcome

problems with correctly dialling a number sequence. Those with digit misidentification should be warned to check injuries carefully. Above all, the patient and their family need reassurance that these phenomena can occur, and that they are not 'going mad'.

[†]More information available on the Royal National Institute for the Blind website: http://www.rnib.org.uk/livingwithsightloss/yourmoney/moneymattersguide/Pages/chipandpin.aspx. Accessed 12.1.12.

7.6. Summary

The hypotheses postulated were proven:

- Primary hypothesis: Some CRPS patients demonstrate evidence of parietal lobe dysfunction when assessed by detailed clinical bedside testing.
- Secondary hypothesis: CRPS patients with parietal dysfunction have more extensive areas affected by mechanical allodynia compared to patients who had no parietal dysfunction.

Sixty eight percent of the CRPS patients tested demonstrated evidence of parietal lobe dysfunction when assessed by detailed clinical bedside testing, confirming the primary hypothesis. Compared to subjects with normal testing, those with parietal dysfunction were more likely to be left handed, or to have CRPS affecting >1 limb and/or the dominant upper limb. Furthermore, CRPS patients with parietal dysfunction had significantly more extensive areas affected by mechanical allodynia compared to patients who had no parietal dysfunction, confirming the secondary hypothesis. There was a strong negative correlation between a low parietal testing score (greater parietal dysfunction) and the extent of allodynia. Quantitative sensory testing revealed some unusual patterns of sensory impairment across the cohort including referred sensations, allochiria, dysynchiria and sensory extinction.

All of the parietal tested cohort were vulnerable to optokinetic testing, experiencing worsening of their usual pain. There was a significant correlation between lower tactile threshold on the affected limb and higher optokinetic vulnerability. While viewing AVS, patients with parietal dysfunction were unlikely to

have no pain and homologous symmetric autonomic responses, and more likely to have pain and asymmetric autonomic responses.

7.7. Conclusion

Clinical evidence of parietal lobe dysfunction has been demonstrated in CRPS patients, which is not detected with standard neurological testing. Furthermore, the extent of the body surface area allodynia strongly correlated with the degree of parietal dysfunction observed suggesting that maladaptive neuroplasticity and cortical network disruption may be a potential mechanism. Parietal lobe dysfunction could account for many of the unexplained, apparently ‘bizarre’ symptoms and signs encountered in CRPS.

7.8. References

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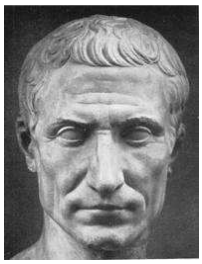
Freda Kahlo

The Broken Column, 1944.

Image available from: http://www.museum-reproductions.com/cgi-bin/modern.pl?fid=1022581321&cgifunction=form. Accessed 25.101.12.

Chapter 8: Discussion & conclusions



"It is easier to find men who will volunteer to die, than
to find those who are willing to endure pain with patience."

Julius Caesar

(Image available from: http://www.facebook.com/people/Julius-Cesar/100002204135581. Accessed 25.01.12.)

8.1. Introduction

The underpinning theme of the thesis is that patterns of autonomic dysfunction and pain may arise from activation of aberrant cortical networks which in turn may occur from varying neuroplastic reorganisational changes. This is reflected in the presenting clinical phenotype. The primary thesis aim was to gain insights into different mechanisms that contribute to chronic pain, and thereby obtain new understanding of the varying patterns and presentations of chronic pain in rheumatic disease. This was achieved through a series of four clinical studies which collectively provide evidence for the emergence of specific patterns of CRPS, including a group with enhanced vulnerability to sensory conflict and abnormal asymmetric sympathetic responses. It also demonstrated that OA and RA patients have higher vulnerability to sensory conflict compared to healthy controls, and that similar mechanisms of pain network dysfunction may operate across a spectrum of chronic pain in rheumatic disease.

An overall summary of the study findings and their context in current literature are discussed below in relation to each hypothesis. Study strengths, limitations, clinical implications and future directions were discussed in each study (**Chapters 4** – **7**).

8.2. Study 1 (**Chapter 4**)

8.2.1. Accepted hypotheses:

- There was no allodynia present in healthy controls.
- Allodynia was present in some osteoarthritis (OA) and rheumatoid arthritis (RA) patients and most marked in CRPS patients.

8.2.2. Summary of findings

The first study establishes a baseline of quantitative sensory testing parameters and sympathetic autonomic function in helathy controls, patients with CRPS, and two other chronic rheumatic pain comparator cohorts; patients with OA and stable RA. There was no allodynia in healthy controls. Allodynia was present in some OA and RA patients, and most marked in CRPS patients. Among CRPS subjects, unusual patterns of sensory impairment including referred sensations, allochiria, dysynchiria and sensory extinction were noted. Baseline sympathetic autonomic function was normal in controls, with some impairment in OA and RA, and most impairment in CRPS patients.

8.2.3. Current literature context and novel findings

Allodynia was present in OA and RA patients consistent with previous work (Kosek and Ordeberg, 2000) (Leffler et al., 2002). In CRPS, referred sensations have been previously described (McCabe et al., 2003) although one patient in paticular demonstrated this on a large scale "(see (Robinson et al., 2011); for details see **Chapter 7** and ***Appendix 10***. The findings of allochiria, tactile dysynchiria and sensory extinction appear to be new in the CRPS literature. These are more commonly seen as sequelae of a parietal lobe stroke and provide support for the concept of the activation of abnormal cortical networks influencing clinical presentation. A future research project would be to combine this type of clinical phenotyping with neuroimaging.

There was autonomic impairment in some OA and RA patients. The literature is sparse, with varying methodologies. Autonomic dysfunction has been reported in RA (Bidikar and Ichaporia, 2010;Stojanovich, 2009;Toussirot et al., 1993), and postulated as a Darwinian phenoptosis (programmed death of organisms akin to apoptosis at a cellular level) selection mechanism in OA (Yun et al., 2006). The results of this study add to the evidence for low level autonomic dysfunction in OA and RA, and provide a quick, non-invasive means of assesment.

8.3. Study 2 (**Chapter 5**)

8.3.1. Accepted hypothesis

- During an optokinetic challenge, sensory disturbances and pain responses were more common in CRPS patients compared to healthy controls and patients with rheumatoid or osteoarthritis.

8.3.2. Summary of findings

The second study explores the concept that cortical reorganisation may render a subject more vulnerable to sensory disturbances and pain through sensorimotor conflict, by investigating reponses to an optokinetic challenge. Sensory disturbances and pain responses were most common in CRPS patients compared to controls or patients with OA and RA. OA patients demonstrated a higher rate of sensory disturbances than RA. There was a strong association between vulnerability and pain response. Relating back to the first study, vulnerability within the CRPS cohort was correlated with extent of allodynia and negatively with tactile threshold.

8.3.3. Current literature context and novel findings

Some healthy controls are vulnerable to an optokinetic visuo-motor challenge, developing sensory disturbances and/or pain. This study found 55% were vulnerable which is consisent with previous work showing rates of 48-66% (McCabe et al., 2005;McCabe et al., 2007). While similar work has been done with fibromyalgic patients (McCabe et al., 2007) and symptommatic professional violinists (Daenen et al., 2010), it has not been applied previously to OA or RA, and in limited numbers to CRPS. The findings demonstrate that OA and RA patients are more vulnerable compared to healthy controls, but from previous work, not as vulnerable as fibromyalgia patients. CRPS patients are the most vulnerable, with associations between pain response, extent of allodynia and tactile threshold. Some of the CRPS patients demonstarted motor extinction, another clinical sign usually seen in parietal lobe stroke. This provides more evidence for the activation of abnormal cortical networks with possible underlying cortical reorganisation influencing clinical symptoms and signs in CRPS.

All the cohorts show an increased frequency of sensory disturbances in the stage with highest conflict compared to the stage with lowest, a pattern previously

seen in healthy controls (McCabe et al. 2005). Other similar work with fibromyalgia (McCabe et al., 2007) showed an even distribution of sensory disturbance reports across the stages. However there was a different pattern observed for pain reports where controls, OA and RA patients demonstrated no difference in frequency of pain reports across the intervention stages, and CRPS patients had a significantly greater frequency in the highest conflict stage compared with the lowest. I suggest that in healthy controls and patients with rheumatic disease, a moderate degree of sensorimotor conflict is required to exceed the sensory discrepancy threshold, and cannot usually activate pain networks. However in vulnerable subjects, the threshold is lower and can trigger pain networks producing even reports of sensory disturbances and pain across the conflict stages. In CRPS patients, activity in top-down networks may be initiated by disrupted motor pathways and corrupted body schema and therefore the degree of conflict does have an effect on pain and sensory disturbance. The presence of cortical reorganisation may confer vulnerability.

The OA cohort had higher levels of vulnerabilty than the RA cohort suggesting mechanistic differences. There is neuroimaging work showing loss of grey matter in patients with OA pain (Rodriguez-Raecke et al., 2009), and increased grey matter content in the basal ganglia of RA patients (Wartolowska et al., 2011). Thus although imaging work supports the role of a central pain component in both OA and RA (Mease et al., 2011), the mechanisms may differ. Data from this study lends further credence to this concept.

8.4. Study 3 (**Chapter 6**)

8.4.1. Accepted hypotheses

- Viewing ambiguous visual stimuli (AVS) caused sensory disturbances and enhanced pain responses in CRPS patients but not in healthy controls and patients with rheumatoid arthritis (RA) or osteoarthritis (OA).
- Healthy controls, OA and RA patients had symmetric sympathetic autonomic responses in the upper limbs while viewing AVS.
- Some CRPS patients had abnormal sympathetic autonomic responses while viewing AVS.
- Abnormal sympathetic autonomic responses in CRPS patients while viewing AVS were associated with enhancement of pain.

8.4.2. Summary of findings

The third study used a pure visual conflict induced by an ambiguous visual stimulus (AVS) – an optical illusion, and looked at qualitative outcomes, and sympathetic autonomic responses. It found that viewing AVS caused sensory disturbances and enhanced pain in CRPS patients but not in controls, OA or RA subjects. A subgroup of CRPS patients were found to have asymmetric autonomic responses and enhanced pain responses with dystonic reactions. Asymmetry could not be predicted from baseline autonomic function testing.

8.4.3. Current literature context and novel findings

There has only been one previous study investigating somaesthetic responses while viewing an ambiguous visual stimulus (Hall et al., 2010). This work also found that viewing AVS did not cause pain in healthy controls or patients with rheumatic disease, and that CRPS patients were vulnerable to enhancement of pain. The investigation of dynamic sympathetic autonomic responses while viewing AVS is novel. A subgroup of CRPS patients had enhanced pain and distinctive asymmetric autonomic responses. They also were more likely to have a cluster of other features including dystonic reactions in the affected limb, instability of the control figure and an AVS reversal rate described as ‘too fast to count’. This clustering of symptoms and signs is suggestive of a consistent pattern of pain network dysfunction. Based upon current concepts of visual processing (Goodale et al., 2005) and CRPS neuroimaging literature (Swart et al., 2009), this may be affecting dorsal parietal visual processing and other parietal-motor and visual integrational areas.

Reports of asymmetric autonomic responses are unusual, and the mechanisms poorly understood. Previous work using noxious mustard oil (Magerl et al., 1996) and cold immersion (Drummond, 2006) has shown that pain is able to cause a differentiated sympathetic response with separate control of discrete reflex pathways on each side of the body. This study demonstrates that a non-noxious visual stimulus can enhance pain and cause centrally rather than peripherally triggered asymmetric sympathetic responses.

8.5. Study 4 (**Chapter 7**)

8.5.1. Accepted hypotheses

- Some CRPS patients demonstrate evidence of parietal lobe dysfunction when assessed by detailed clinical bedside testing.
- CRPS patients with parietal dysfunction have more extensive areas affected by mechanical allodynia compared to patients who had no parietal dysfunction.

8.5.2. Summary of findings

The final study investigated whether ***abnormal cortical network activation*** could extend to parietal areas by assessing detailed clinical measures of parietal function in a series of CRPS patients. Of those tested, 68% were found to have parietal dysfunction not apparent with a standard neurological screen. The severity of dysfunction correlated with the extent of allodynia. Patients with parietal dysfunction were all vulnerable to an optokinetic challenge with enhanced pain, and were more likely to have pain and asymmetric responses viewing AVS.

8.5.3. Current literature context and novel findings

This is also a novel study reporting novel findings. One of the patients from the parietal cohort was reviewed by a neuropsychologist and found to have agnosia for object orientation, conjectured to have arisen from cortical reorganisation secondary to chronic severe CRPS pain, affecting parietal areas (Robinson et al., 2011). Previous neuroimaging research has suggested parietal involvement that may account for some of the motor impairments found in CRPS (Maihöfner et al., 2007). Data from this study supports the concept, and provides evidence for much more extensive parietal disruption evident clincially. Extent of allodynia appears to be linked to the degree of dysfunction, and should prompt clinicians to look for symptoms and signs of parietal dysfunction in patients with extensive allodynia. The fact that all the patients with parietal dysfunction were vulnerable to sensory conflict supplies further credence to the activation of abnormal cortical networks, possibly secondary to underlying cortical reorganisation, producing specific patterns of somaesthetic integrational dysfunction and pain.

8.6. Unanswered questions

The CRPS cohort were selected from a tertiary centre specialising in rehabilitation of CRPS. Therefore, this was a severely affected group often with long duration disease (overall mean disease duration 6 years). Therefore this research cannot answer whether similar findings are present in earlier cases, and further work is needed.

The research utilised simple clinical and qualitative methods combined with autonomic function testing to explore potential central cortical mechanisms of pain. While it provides good evidence for this, it still need to be combined with neuroimaging techniques for further elucidation and validation.

8.7. Final conclusions

Taken together, in patients with CRPS these research findings provide evidence for abnormal pain networks and central autonomic integration in a subgroup of vulnerable patients. However allowance should be made for many of the findings being made through post-hoc analysis, and further validation is required.

Abnormal cortical network activation and reorganisation extending beyond S1 to parietal areas may be a contributory factor. This may account for some of the motor difficulties and unusual symptoms encountered in CRPS. The extent of allodynia is correlated with severity of parietal dysfunction, which suggests that the extent of abnormal cortical network activation and reorganisation may be greater in these patients. It may also involve cortical areas responsible for autonomic integration, as evidenced by abnormal responses in a particularly vulnerable subgroup. Similar changes may occur at a lower level in OA and RA, where enhanced vulnerability to an optokinetic challenge and impaired baseline sympathetic autonomic function compared to healthy controls was demonstrated.

The thesis findings provide an approach to the clinical phenotyping of CRPS, which may help to improve treament approaches. It opens new research questions about central brain mechanisms operating across a wide spectrum of chronic pain conditions.

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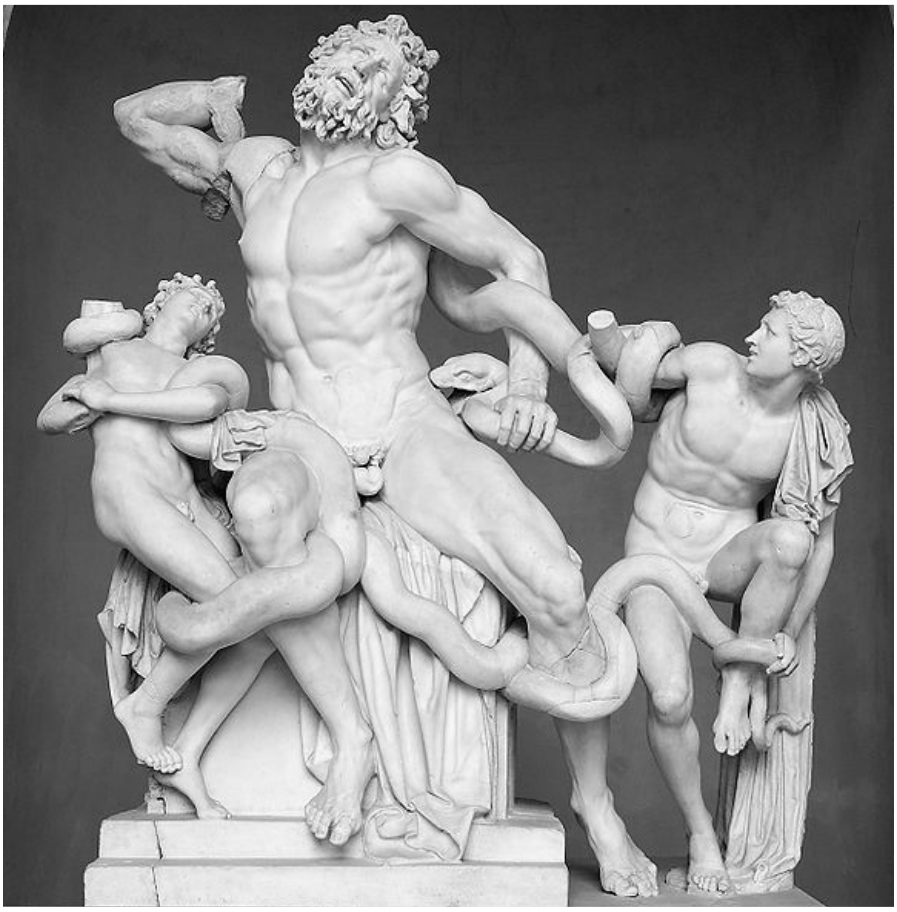

Laocoön and his sons, also known as the Laocoön Group. Marble, copy after an Hellenistic original from ca. 200 BC. Found in the Baths of Trajan, 1506. Museo Pio-Clementino, Vatican City.

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