The cortical integration of tactile sensation in complex regional pain syndrome

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The cortical integration of tactile sensation in complex regional pain syndrome

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Much is still unknown about sensory and perceptual changes in the cortex associated with complex regional pain syndrome (CRPS). This PhD aimed to investigate cortical integration of tactile sensation of the hand specifically the fingers, and how this might be altered in CRPS.

A match-paired cross-sectional design was used in a series of neuroimaging and psychophysical studies on patients with unilateral upper limb CRPS (n=21). Clinical characteristics were described and compared with age, gender and hand dominance matched controls (Chapter 2). Methodological improvements for fine-grained fingertip mapping in the primary somatosensory cortex were piloted (n=1) in two separate experiments (Chapter 3). Single fingertip stimulation versus bilateral simultaneous fingertip stimulation was compared using phase encoded functional magnetic resonance imaging (fMRI). Fine-grained fMRI maps of the fingertips in S1 in CRPS were described. Structural morphometry measures underlying the functional S1 fingertip maps including cortical thickness were analysed with step-wise mixed modelling with *a priori* hypothesised effects including hand dominance and medication. Patient characteristics including pain- related measures were correlated with morphometry measures (Chapter 4). A new finger illusion experiment was applied for the first time in patients with CRPS (Chapter 5).

The pilot found that bilateral tactile stimulus was most suitable for use in CRPS and had superior time efficiency. Disordered S1 functional fingertip maps in CRPS with no distinct pattern were found using this stimulus, when compared to the orderly homogenous map pattern in healthy controls. These functional imaging observations were strengthened by the key finding that increased cortical thickness underlying these maps together with hand dominance predicted group (CRPS versus healthy controls) membership. An abnormal finger illusion response in CRPS compared to controls, also suggests a disruption to normal efficiencies of bimanual hand representation cortically, not previously reported.

In conclusion, disruption to cortical integration of tactile sensation in CRPS is suggested from the results. These changes also suggest cortical representation of differences in hand dominance rather than CRPS-sided-differences predicted those with CRPS in this study. Future directions to test these suggested cortically mediated changes in CRPS were explored.

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ORIGINALITY STATEMENT

'I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at UNSW or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at UNSW or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.'

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Presentations and Achievements during Candidature

Invited Oral Presentations

Changes in a "finger' illusion in complex regional pain syndrome (CRPS)", Postgraduate Research Seminar Day, Prince of Wales Clinical School, Faculty of Medicine, October 2015.

Changes in a "finger' illusion in complex regional pain syndrome (CRPS)", NeuRA Sensorimotor Seminar presentation, July 2015.

"The functional organisation of finger maps in the primary somatosensory cortex (S1) in complex regional pain syndrome (CRPS)", Invited speaker (PhD plenary session) for Australian Pain Society 35th Annual Scientific Meeting, Brisbane, Queensland, with travel award, March 2015.

"Complex regional pain syndrome", NeuRA Sensorimotor Seminar presentation, April 2014.

"The function of the primary somatosensory cortex (S1) and brain neural networks in complex regional pain syndrome (CRPS)". Invited speaker (PhD plenary session) for Australian Pain Society 34th Annual Scientific Meeting, Hobart, Tasmania, with travel award, March 2014.

"Recognising CRPS and research directions" - South East Sydney and Illawarra Area Health Service Public Hospital Hand Network Seminar, Royal Prince Alfred Hospital, Sydney, February 2014.

Poster Presentations

Wang A P , Butler A, Schira M M, McAuley J H, Rae C D, Gandevia S and Moseley G L (2016). A novel illusionary experiment in complex regional pain syndrome (CRPS): Are my hands that close together? 2016 Postgraduate Research Seminar Day, Prince of Wales Clinical School, Faculty of Medicine, University of New South Wales. 28th October 2016 - *Best Poster prize.*

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Wang A P, Mancini F, Schira M M, McAuley J H, Isherwood Z J, Iannetti G, Rae C D and Moseley G L (2014). Developing a time efficient tactile paradigm for fingertip representation in the primary somatosensory cortex in pathological pain. First CiiNet Pain Neuroscience conference, Osaka, Japan.

Wang A P, Schira M M, McAuley J H, Isherwood Z J, Rae C and Moseley GL (2014). Finger representation in the primary somatosensory cortex using visual field mapping techniques: a pilot study, Finalist for Poster presentation at Pain Adelaide.

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Wang A P, Schira M M, McAuley J H, Isherwood Z J, Rae C and Moseley G L (2013). Finger representation in the primary somatosensory cortex using visual field mapping techniques: a pilot study. Poster abstract No: P51, EFIC Satellite Symposium, Neural Circuits Underlying Nociception and Pain and Their Plasticity, Heidelberg, Germany.

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Supplementary Part A - Functional fingertips maps

(file name: Thesis_SupAmaps.pdf)

Supplementary Part B- Functional fingertips maps

(file name: Thesis_SupBmapsU.pdf)

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Acronyms

AI	Anterior Insula
ap	Anterior posterior
BA	Brodmann area
BFP	Bilateral Finger Paradigm
BOLD	Blood Oxygen Level Dependent
CI	Confidence interval
CNS	Central Nervous System
CRPS	Complex Regional Pain Syndrome
D1	Thumb
D2	Index finger
D3	Middle finger
D4	Ring finger
D5	Little finger
DCML	dorsal column-medial lemniscal pathway
DLPFC	dorsolateral prefrontal cortex
DTI	diffusion tensor imaging
EHI	Edinburgh Handed Inventory
EPI	echo planar imaging
FC	laterofrontal cortex
FFT	Fast Fourier Transform
fh	feet-head
FM	Dr. Flavia Mancini
fMRI	functional magnetic resonance imaging
FOV	field of view
GM	grey matter
GMD	grey matter density
GMI	Graded Motor Imagery
HRF	Haemodynamic Response Function
Hz	Hertz. The standard unit of frequency; equal to cycles per second.
IASP	International Association for the Study of Pain
IBS	irritable bowel syndrome
LCD	Liquid Crystal Display
LM	Professor Graham Lorimer Moseley
M1	primary motor cortex
MEG	magnetoencephalography

MR	magnetic resonance
NAc	nucleus accumbens
nocte	at night
OA	osteoarthritis
p.r.n	as when required (pro re nata)
RHI	rubber hand illusion
rl	right-left
S1	primary somatosensory cortex
S2	secondary somatosensory cortex
SBA	Surface based analysis
SENSE	Sensitivity coding - Phillips vendor-specific parallel imaging technique for controlling susceptibility artefacts common to EPI sequence.
SFP	Single Finger Paradigm
SNR	Signal to noise ratio
CNR	Contrast to noise ratio
T1	longitudinal relaxation time
T2	transverse relaxation time
TE	The variation of echo time from one RF pulse to the next.
Tesla (T)	The unit of magnetic flux density. One tesla is equal to 10,000 gauss.
TMD	temporomandibular disorder
TN	trigeminal neuralgia
TR	repetition time
TR	The variation of repetition time from one RF pulse to the next.
VBM	voxel-based morphometry
VMPFC	ventromedial prefrontal cortex

Complex Regional Pain Syndrome

1 Introduction

Complex Regional Pain Syndrome (CRPS) is a chronic pain condition that develops following an injury. It has a significant social, personal and economic impact. Compared to other chronic pain conditions, CRPS is associated with poorer quality of life (van Velzen et al., 2014), especially in the physical domains and with younger sufferers. Patients with CRPS are at increased risk of suicide; estimates are that 1 in 20 patients with chronic CRPS have either reported suicidal ideation or made an attempt (Braden and Sullivan, 2008, Smith et al., 2004). A diagnosis of CRPS is made after exclusion of other medical conditions, leaving patients with delayed access to appropriate help and support (Allen et al., 1999). The percentage of CRPS study participants incapable of work was 31% in a Dutch cohort (de Mos et al., 2009) and 80% in a Korean cohort (de Mos et al., 2009, Kang et al., 2012). Estimated annual income loss due to chronic pain including CRPS exceeded $1 billion in the US (Kemler and Furnee, 2002).

This chapter is presented in three sections. First, a definition of CRPS and a review of the evidence for the epidemiology and outcomes associated with CRPS will be provided. Secondly, theories of pain, maladaptive neuroplasticity in CRPS, neuroimaging in CRPS, evidence of altered perception and sensory discriminative symptoms of CRPS, will be reviewed. In the final section, research on the organisation of touch and perceptual dysfunction in CRPS will be presented.

1.1 Definition of Complex Regional Pain Syndrome

CRPS is characterised by a continuing (spontaneous and/or evoked) pain that appears disproportionate in time or degree to the usual course of any known trauma or lesion. The pain is regional (not confined to a specific nerve innervation or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings (Harden et al., 2007). Pain in response to non - noxious stimuli such as light touch (allodynia) is often reported (Shenker et al., 2015). Other symptoms reported in CRPS include: dystonia (muscle spasms and contractions that fix the limb in an awkward posture), discolouration of the skin, swelling, excessive growth of nail and hair. Fractures in the peripheral limbs including the wrist, ankle, and foot (de Mos et al., 2007) or surgery, injections and infusions (Veldman et al., 1993) are often reported as precipitating injuries for CRPS.

CRPS can be sub classified according to whether the precipitating injury involved damage to a nerve. If the precipitating event did not include any major nerve damage, the diagnosis is often referred to as CRPS Type 1. If major nerve damage occurred before the condition developed, then the diagnosis is classified as CRPS Type 2 (Harden et al., 2007). The claim that CRPS Type 1 contains no neuronal involvement is controversial. For example, nociceptive small-diameter fibre axonal degeneration in the peripheral nervous system was identified in patients with CRPS Type 1 (Oaklander et al., 2006, Oaklander and Fields, 2009). It is likely that fractures and other types of injuries, commonly reported precipitating injuries prior to the development of CRPS, might inevitably involve some form of peripheral nerve injuries; making this distinction between CRPS Type 1 and Type 2 not useful (Marinus et al., 2011). Given this controversy, CRPS was not sub-classified into Type 1 or 2 in this thesis.

CRPS is a broad diagnostic term that covers a range of historically used diagnoses. Previously, patients with similar clusters of CRPS symptomology could be diagnosed with algodystrophy, Sudeck atrophy, reflex sympathetic dystrophy or causalgia (Bickerstaff and Kanis, 1994, Schott, 2007a). However, these diagnoses were limiting; causalgia only referred to heat and pain, and reflex sympathetic dystrophy emphasised the involvement of the sympathetic nervous system. Any diagnoses that included the word “atrophy or dystrophy” indicated the condition included limb shrinkage or disuse, at diagnosis. Although an involved limb is often swollen at diagnosis, signs of atrophy are often presented only when the condition is prolonged (Veldman et al., 1993, Otake et al., 1998, Schasfoort et al., 2003). A consensus meeting of expert researchers and clinicians in 1993 proposed the umbrella term of Complex Regional Pain Syndrome or CRPS (Veldman et al., 1993) which captured the range of symptomology without making inferences on an unknown mechanism.

Currently, a diagnosis of CRPS is made on the presence or absence of signs or symptoms, contained in the International Association for the Study of Pain (IASP) diagnostic criteria for CRPS (Harden et al., 2010). The IASP criteria require all four symptom categories in Table 1-1 to be present for the diagnosis. Further progress was made from the IASP 1994 criteria and replaced by the Budapest 2010 recommendations for CRPS diagnosis for the clinic and research. The reasons why this progression to the Budapest criteria was deemed necessary was detailed in the paper by Harden et al. (2007). The CRPS Budapest 2010 clinical criteria require at least three of four symptom categories (in Table 1-2) and at least two of four sign categories. The CRPS Budapest 2010 research decision rules are stricter and require all four symptom categories and at least two of four sign categories.

This Budapest set of criteria were validated in an international, multi-site, between-subjects study in 2010 (Harden et al., 2010). Evidence for validity of the criteria was obtained by comparing the ability of the IASP and Budapest criteria to distinguish between CRPS Type 1 and non-CRPS neuropathic pain. The research criteria were shown to have a sensitivity of 0.78 and the highest specificity of all the criteria at 0.79. The Budapest clinical criteria had a sensitivity and specificity of 0.99 and 0.68 respectively, which compared favourably to the IASP criteria, which had a sensitivity of 1.00 and specificity of 0.41. Currently, the Budapest criteria are the most widely accepted and used diagnostic criteria for both clinical and research purposes.

Table 1-1: IASP diagnostic 1994 criteria for complex regional pain syndrome (CRPS).

1. The presence of an initiating noxious event, or a cause of immobilisation.†
2. Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event.
3. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain (can be sign or symptom).
4. This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction.

Table 1-2: The Budapest 2010 diagnostic criteria for complex regional pain syndrome (CRPS).

(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 at 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 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.

Note: CRPS Budapest research decision rules require CRPS characteristics present in all four symptom categories and at least two of four sign categories. The CRPS Budapest clinical criteria requires CRPS characteristics present in at least three of four symptom categories and at least two of four sign categories.

The next section reviews the evidence on the incidence, prevalence, risk factors and prognosis of CRPS.

1.1.1 Incidence and prevalence of CRPS

Population-based estimates of CRPS vary. As part of a large US-based epidemiological study Sandroni et al. (2003), reported that the incidence of CRPS was 5.46 per 100,000 person years, whereas a retrospective cohort study in the Netherlands reported an incidence rate almost four times larger at 26.2 per 100,000 person years (de Mos et al., 2007). Variable incidence rates may reflect differences in study methodology such as management of loss to follow-up (Dijkstra et al., 2003), diagnostic criteria (Harden et al., 2010) and sampling methods (Demir et al., 2010).

The incidence of CRPS has also been investigated in specific patient populations, most commonly in patients post-fracture, the most common precipitating injury. In a multi-centre prospective study conducted over four years, patients with a single fracture of the wrist, scaphoid, ankle, or fifth metatarsal were followed up for one year. Of the 596 participants recruited, 42 (7.0%) were diagnosed with CRPS Type 1 according to the Budapest research criteria, 289 (48.5%) according to the IASP criteria and 127 (21.3%) according to the Veldman criteria (Beerthuizen et al., 2012). A large prospective cohort study of a consecutive sample of 1549 patients presenting with wrist fractures in hospital-based clinics used the criteria from Bruehl et al. (1999) and reported an incidence rate for CRPS of 3.8% at the 4 month follow-up (Moseley et al., 2014). Studies with smaller samples have reported significant variability in the incidence of CRPS post-fracture or surgery. For example, Dijkstra et al. (2003) reported an incidence of 1%, Rewhorn et al. (2014) reported 4.4%, Zyluk and Mosiejczuk (2012) reported 8.4%, Puchalski and Zyluk (2005) reported 18% and Dilek et al. (2012) reported 26%.

Some of the variation may be explained by the lack of an agreed time post the precipitating event at which a diagnosis should be made (Beerthuizen et al., 2012). For example, a study on patients post total knee arthroplasty reported that the proportion of patients who fulfilled the criteria for CRPS was highest at 1-month postoperatively (21%) and this reduced over time to 12.6% at 6 months (Harden et al., 2003). These data suggest that the application of the same diagnostic criteria at different time points produces different incidence estimates. Different routes of fracture management might also result in missing cases of patients who subsequently develop CRPS. For example, in Australia, not all fractures are managed by orthopaedic specialists; some patients with fractures who present to emergency departments may be subsequently managed by their local general practitioner.

1.1.2 Risk factors for CRPS

Identifying risk factors for CRPS may assist in diagnosis, early intervention and prevention of disability. To date, few epidemiological studies have been able to identify risk factors for CRPS in the general population; most have focused on a specific clinical population or sub-group such as post fracture (Dijkstra et al., 2003, Beerthuizen et al., 2012, Moseley et al., 2014, Wang et al., 2015, de Mos et al., 2007). The risk factors identified from these studies included demographic factors such as gender and age, psychological factors and factors associated with the pathology of the inciting event such as type of fracture (Dilek et al., 2012, Beerthuizen et al., 2011).

The systematic review by Pons et al. (2015) attempted to summarise the evidence for risk factors for CRPS Type 1 despite the inconsistent use of the Budapest Criteria for diagnosis and high risk of bias across multiple or homogeneous studies. They argued that post-menopausal women, distal fractures, immobilisation and higher than usual pain intensity were potential risk factors for CRPS. Some of these factors were also found by several studies. For example, de Mos et al. (2007) conducted a large retrospective population - based study (source population of 217, 653 persons) in The Netherlands. Their study found that the development of CRPS was associated with the following factors: any fracture, involvement of the upper extremity, the age group of 61 - 70 years. Beerthuizen et al. (2012) showed that patients (n = 596) who developed CRPS Type 1 were more likely to have had an intra-articular fracture, fracture dislocation, rheumatoid arthritis, or musculoskeletal co-morbidities. Moseley et al. (2014) argued that reported pain intensity scoring of five or more out of a 10-point numerical rating scale elevated the risk in wrist fracture patients of developing CRPS from their large (n = 1549) prospective hospital-based cohort study.

Much controversy still remains about the psychological risk factors in the development of CRPS. Smaller studies have claimed a relationship between anxiety and/or depression and the risk of developing CRPS (Dilek et al., 2012, Van Houdenhove et al., 1992, Bruehl and Carlson, 1992, Rommel et al., 2005). Other observational studies have not detected significant associations between psychological factors and CRPS (Puchalski and Zyluk, 2005, Reedijk et al., 2008, Ciccone et al., 1997). Beerthuizen et al. (2009) concluded that the available evidence did not support a major role for psychological factors in the development of CRPS from their systematic review of research published from 1980 to 2007. Large cohort studies have shown no such association either (Beerthuizen et al., 2011, de Mos et al., 2008). In any case, it has been argued that any psychological factors associated with CRPS are related to the outcome of living with the condition (Bean et al., 2015), rather than a risk factor for the development of CRPS

(Beerthuizen et al., 2011). The answer to whether psychological factors are involved in the development of CRPS might be answered in the future by larger epidemiological studies (TREND, 2013).

1.1.3 Prognosis of CRPS

There is limited high quality evidence concerning the prognosis of CRPS. The available evidence suggests that CRPS has a poor outcome (Schwartzman et al., 2009, Bean et al., 2014). In a large retrospective cohort of patients with CRPS, assessed in Dutch general practitioner clinics, 64% still fulfilled IASP criteria at an average of 5.8 years following onset with persistent impairments and 31% (95% CI: 19 - 43) were incapable of working (de Mos et al,. 2009). In a later Dutch prospective study, all patients diagnosed with CRPS at four months post fracture had unresolved symptoms at one year (Beerthuizen et al., 2012).

CRPS is associated with worsening of symptoms for a significant proportion of patients. In the study by de Mos et al. (2009), 16% (95% CI: 9-22) of patients with CRPS reported their symptoms had worsen 2 years following diagnosis. Worsening of CRPS is also reflected by symptoms spreading to other body parts as well as a proximal increase in symptoms from the localised area of the affected limb. In a retrospective hospital-based study by van Rijn and colleagues, 53% had multiple limb involvement of CRPS, and within this group, 92% reported the CRPS involvement had spread from one to two limbs (van Rijn et al., 2011). Based on current evidence, the prognosis for many patients with CRPS is poor as the symptoms not only persist but can also affect other body parts.

Prognostic factors or patient characteristics associated with poor outcome in CRPS were recently reviewed by Wertli et al. (2013). Out of a range of possible prognostic factors, the authors found evidence that sensory disturbances, cold skin temperature and pain intensity were associated with poor outcome. They concluded that many of the currently used prognostic factors are weak and suggested that larger, high quality prospective studies aimed at identifying predictors of recovery are required for the development of new treatment strategies. Bean et al. (2015) addressed this deficit in the literature and identified prognostic factors associated with recovery in 66 patients with the condition, with follow-up for up to one year. They concluded that high fear of movement and re-injury, pain, anxiety, disability, a greater number of total symptoms and being female at the start of the study were associated with poor recovery from the condition.

1.1.4 Treatments in CRPS

Many individual studies have attempted to address the efficacy of treatments developed from pain theories. O'Connell et al. (2013) conducted a systematic review of systematic reviews on the effectiveness of therapeutic interventions for CRPS and found a lack of high quality evidence and consensus. The authors identified six Cochrane reviews and 13 non-Cochrane systematic reviews that included evidence related to a broad range of treatments, from drugs to surgical procedures, rehabilitation and alternative therapies. Their updated review (Smart et al., 2016) emphasised that until larger treatment trials were undertaken, finding robust evidence for the efficacy of treatments to manage CRPS remains elusive.

Several reviews (Daly and Bialocerkowski, 2009, Smart et al., 2016, O'Connell et al., 2013) have agreed that the best available non-pharmacological treatment for CRPS is graded motor imagery (GMI). The review by Daly and Bialocerkowski (2009) also supported graded exposure therapy and sensorimotor retraining besides GMI. GMI is a three-stage, six-week program involving hourly training sessions, commencing with left or right judgements of pictured limbs, progressing to imagined limb movements and then mirrored movements, in which patients view the unaffected limb in the mirror while they perform bilateral limb movements. About 50% of patients treated with GMI experience symptomatic and functional improvements of greater than 50% (Moseley et al., 2008a, Moseley, 2012, Moseley, 2006, Moseley, 2004a). The exact mechanism underlying the effect of GMI is unknown.

Graded exposure is another type of therapy focussing on reducing the threat value of pain for patients with CRPS (de Jong et al., 2005, den Hollander et al., 2016). The treatment aims to correct the misinterpretations and misconceptions that have occurred during the development of pain-related fear. The treatment uses psychology with behavioural components to increase patients' engagement in activities, movements and scenarios they have been avoiding for a long time. The most essential step of graded exposure is for the patient to 'expose' themselves to situations that they had erroneously identified as 'dangerous' or 'threatening' (Vlaeyen et al., 2002a, Vlaeyen et al., 2002b). To facilitate independence and to promote generalisation, the presence of the therapist is gradually withdrawn, and contextual practice opportunities are created to mimic those of the home situation (de Jong et al., 2005, de Jong et al., 2012). Detailed descriptions of the *in vivo* exposure treatment are available (Vlaeyen et al., 2002a, Vlaeyen et al., 2002b) but the underlying mechanisms for these treatments are poorly understood at present.

Sensorimotor retraining including tactile acuity retraining is another treatment program recommended for CRPS. Poor tactile acuity is a known deficit associated with CRPS (Pleger et al., 2006, Moseley and Wiech, 2009, Reiswich et al., 2012, Lewis and Schweinhardt, 2012). Studies have shown treatments that specifically target improvement of tactile acuity appear effective at reversing this deficit in CRPS (Moseley and Wiech, 2009, Pleger et al., 2005). This finding was also supported by a recent literature review by Parianen Lesemann et al. (2015). They concluded that tactile stimulation is a promising treatment option for several disorders associated with maladaptive plasticity or disrupted synaptic connectivity including CRPS and phantom limb, by citing work from Pleger et al. (2005) and (Flor et al., 2001) respectively.

Pharmacological treatments for pain relief in CRPS have also been reviewed (Stanton et al., 2013, Wertli et al., 2014). A systematic review by Stanton et al. (2013) found that there was insufficient evidence that local sympathetic blockade (LASB) was better than placebo in reducing pain. It also did not provide additional pain relief when added to rehabilitation. Then, a network meta–analysis by Wertli et al. (2014) concluded that only bisphosphonates, *N*-methyl-D-aspartate (NMDA) analogues, and vasodilators showed better long-term pain reduction than placebo. They recommended that pharmacological treatment of pain should consider bisphosphonates in early CRPS Type 1 and a short-term course of calcitonin in later stages (Wertli et al., 2014).

1.2 Theories of pain

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey and Bogduk, 1994).

The cardinal symptom of CRPS is severe debilitating pain. Theories of pain have developed since Descartes (1662) proposed the original concept of noxious pain processing via nerves into the brain. The most influential pain theories are: i) the gate control theory at the spinal cord level (Wall, 1978, Melzack and Wall, 1965); ii) the neuromatrix theory with the central nervous system processing of pain signals (Melzack, 2001); and iii) the combinational coding theory with peripheral mechanisms (Moayedi and Davis, 2013, Prescott et al., 2014). These theories often emphasise the physical and physiological components of pain but newer hypotheses including the central sensitisation theory and imprecision hypothesis incorporate processes that involve the transition from acute noxious pain to chronic pathological pain state. Patterns of change in pain processing following central sensitisation and its associative cognitive processes in the imprecision hypothesis contribute new ideas about the on-going generation of the chronic pain experience.

1.2.1 Gate control theory and Neuromatrix pain theories

The gate control theory of pain (Wall, 1978, Melzack and Wall, 1965) proposed that:

i. Information about the presence of injury is transmitted to the central nervous system by peripheral nerves. Certain small diameter fibres respond only to injury while others with lower thresholds increase their discharge frequency if the stimulus reaches noxious levels
ii. Cells in the spinal cord or fifth nerve nucleus that are excited by these injury signals are also facilitated or inhibited by other peripheral nerve fibres carrying information about innocuous events
iii. Descending control systems originating in the brain modulate the excitability of the cells transmitting information about injury.

Therefore, the brain receives messages about injury by way of a gate controlled system influenced by: i) injury signals; ii) types of afferent impulses; and iii) descending control mechanisms.

Melzack (2001) later revised the gate control theory to propose that higher mechanisms in the brain were responsible for features in chronic pain**.** Melzack (2001) proposed an anatomical substrate of the body-self, consisting of a large, widespread network of neurons that loops between the thalamus and cortex, and between the cortex and limbic system. He labelled the entire network a 'neuromatrix'. The spatial distribution and synaptic links of the neuromatrix are initially determined genetically and are shaped by sensory inputs subsequently. The loops diverge to permit parallel processing in different components of the neuromatrix and converge repeatedly to permit interactions between outputs.

The repeated cyclical processing and synthesis of nerve impulses through the neuromatrix imparts a characteristic pattern: the neurosignature. The neurosignature shapes all nerve impulse patterns that flow through it, producing patterns of synaptic connections across the entire neuromatrix. All inputs from the body undergo cyclical processes and synthesis so that characteristic patterns are impressed upon them in the neuromatrix. Specialised portions of the neuromatrix process information related to major sensory events (such as injury, temperature change, and stimulation of erogenous tissue) and are labelled as neuromodules that impressed sub-signatures upon the larger neurosignature (Melzack, 2001).

The neurosignature, modulated by ongoing inputs, projects continuously to areas in the brain (shown in Figure 1-1), where nerve impulses are converted to fluctuating levels of awareness of

pain. The neurosignature patterns might then activate related neural networks to produce movement. The patterns divide: proceeding to the sentient neural hub (to be converted into the experience of movement); and also to neural networks that drive activity in spinal cord neurons to produce muscle patterns for complex actions. In summary, the four components of the nervous system conceptual model are: 1) the body-self neuromatrix; 2) cyclical processing and synthesis in which the neurosignature is produced; 3) the sentient neural hub, which conducts the flow of neurosignatures into the flow of pain awareness; and 4) the activation of an action neuromatrix that provides the pattern of movements towards a desired goal (Melzack, 2001).

Figure has been removed due to copyright restrictions

Figure 1-1: Factors that contribute to the inputs and outputs of the body self-neuromatrix (Melzack, 2001).

1.2.2 Combinatorial coding theory

Pattern based theories require input from peripheral afferent neurons (PAN) before the expression of pain or other types of perception in the central neurons in the brain. Both the gate control theory for pain and the specificity theory are pattern-based theories (Moayedi and Davis, 2013). The gate control theory proposes that low and high-threshold afferents converge on unspecialized central neurons and sufficiently strong activation of these central neurons codes for pain. Specificity theory holds that nociceptors, classified as a type of PAN, are uniquely activated by noxious stimulation and that their activation ultimately codes for pain. Other pattern theories fall between specificity theory and gate control theory, as they do not necessarily have the strict criteria of unspecialised central neurons with specialised afferent neurons found in the gate control theory (Prescott et al., 2014).

Prescott and colleagues (2014) argued that many different patterns are conceivable but evidence points towards co-activation of PANs, described within a population called 'combinatorial coding theory'. Combinatorial coding states that perception is dependent on what combination of PAN subtypes was activated and in what proportion. In contrast, specificity theory posits that final perception of sensation including pain is dependent on what PAN subtype was activated and to what degree. Combinatorial coding involves differential activation of different PAN types and, therefore, meaningful co-activation patterns cannot occur without PAN specialization. PAN specialisation would mean that a neuron responds preferentially to a certain stimulus feature, not that a stimulus preferentially activates a certain type of PAN. A combinatorial code cannot be decoded unless central neurons receive input from more than one type of co-activated PAN. Both coding strategies require PAN specialisation but do not exclude co-activation of different PANs (Prescott et al., 2014). This would argue against exclusive synaptic connectivity or labelled lines, but would be consistent with pre- and post-synaptic neurons being equivalently tuned under most conditions and thus often operating as if they were labelled lines under most conditions.

Co-activation patterns hold information beyond what is available from individual PAN activation levels, but that extra information becomes irrelevant unless central circuits can decode it. This is where specificity theory and combinatorial coding theory differ. Combinatorial coding requires some degree of interaction or crosstalk between otherwise labelled lines, whereas specificity theory regards crosstalk as a 'design fault'. According to combinatorial coding theory, crosstalk is a necessary design feature because it enables information carried by co-activation patterns to be used. Prescott and colleagues (2014) argued that this "design" has computational benefits and works so well as to be unapparent unless the

system is tricked (as during an illusion) or perturbed (as in neuropathic pain conditions). An example of crosstalk is illustrated by tactile allodynia, characteristic of CRPS and neuropathic pain. In both spinal and trigeminal lamina 1 relay pathways, more than 80% of the neurons are nociceptive specific and do not receive direct input from non-nociceptive PANs. After injury, central disinhibition unmask existing interconnections between separate sensory pathways (Miraucourt et al., 2007). Hence, it is thought that nociceptive specific neurons then start to receive direct input from non-nociceptive PANs. The consequence of this new process is a conversion to responsiveness to innocuous touch (Keller et al., 2007), known as allodynia, a common symptom of CRPS.

1.2.3 Central sensitisation

The widely held hypothesis of central sensitisation (Woolf, 2011, Herrero et al., 2000, Latremoliere and Woolf, 2009) is used to explain the change from acute to chronic pain states including CRPS. This hypothesis attempts to link how the information about dysfunctional proprioceptive afferent feedback from the affected tissue is modified, through supra-spinal mechanisms, into subcortical and cortical centres. These higher order centres affects how a body part is perceived, corresponding to changes in the regulation of somatosensory, motor and visceromotor responses. These regulatory responses are hypothesised to have a major role in the mechanisms that underlie CRPS (Gierthmühlen et al., 2014).

1.2.4 An imprecision hypothesis

An alternative hypothesis to central sensitisation is the imprecision hypothesis. Moseley and Vlaeyen (2015) reviewed the chronic pain literature and proposed this hypothesis to explain the development of chronic pain conditions, including CRPS. Their hypothesis focuses on the encoding of the precision of multisensory information (temporal, proprioceptive and spatial) of a painful event. This encoding and how it is represented in the brain determines the degree that the painful response subsequently generalises to similar events. The authors argue against the currently held view of central sensitisation in chronic pain, specifying that central sensitisation has been attributed to entirely non-associative mechanisms. Even when considering the phenomenon of allodynia, where non-nociceptive input triggers pain, central sensitisation theory, they argued, did not give any emphasis to the previous association between nociceptive and non-nociceptive input. Indeed, central sensitisation attributes it either to the sprouting of non-nociceptive primary neurons induced by death of nociceptive neurons (for example after peripheral nerve injury), and / or, heterosynaptic facilitation induced by ongoing primary nociceptor input through descending facilitation. The fact that non-noxious stimuli come to

trigger nociceptive input (manifested in allodynia, hyperalgesia, and spreading of receptive fields) is thought to be dependent on the sprouting of primary non-nociceptive afferents or sustained activation of the spinal nociceptor, not on the association between nociceptive and non-nociceptive input. Importantly, associative learning and central sensitisation are not necessarily mutually exclusive, but both would manifest in clinical signs such as allodynia and hyperalgesia (Moseley and Vlaeyen, 2015).

In summary, modern pain theories continue to evolve since the gate control theory was first proposed by Melzack and Wall (1965). Pathological pain including CRPS is a continual health problem with no objective biomarker, and has no authoritative theory on pain pathophysiology, limiting pain treatment discoveries. At present, pain treatment discoveries focus on different pain theories and their effect on different components of pain.

1.3 Theories of pathophysiology underlying CRPS

Theories about the pathophysiology of CRPS remains debated. Three major biological pathways are proposed to contribute major roles to the pathophysiology underlying CRPS: aberrant inflammatory mechanisms and processes (Birklein and Schmelz, 2008, de Boer et al., 2011, Parkitny et al., 2013a), vasomotor dysfunction (Mailis-Gagnon et al., 2014, Ostergaard et al., 2014), and maladaptive functional neuroplasticity (Marinus et al., 2011, Goebel, 2011). The role of maladaptive functional neuroplasticity in contributing to the pathophysiology of CRPS is briefly discussed below (as vasomotor and inflammation is not the focus of this work).

1.3.1 Maladaptive neuroplasticity

Central nervous system involvement is widely accepted as part of the pathophysiology of CRPS. Clinical and quantitative sensory testing of the nociceptive system has demonstrated hemi-sensory impairment and hyperalgesia that frequently extends far beyond the area affected by spontaneous pain, indicating changes in central afferent processing of these systems (Wasner et al., 2003). Dystonia and tremor symptoms reported by patients with CRPS are associated with altered sensorimotor dysfunction (van der Laan et al., 1998, Mugge et al., 2013, Schott, 2007b). Imagined movements of the affected limb (motor imagery) has been shown to increase pain and swelling of the affected limb (Moseley et al., 2008c).

Evidence of maladaptive neuroplasticity in CRPS was found in experiments investigating perceptual and vasomotor changes (Moseley et al., 2012a, Moseley et al., 2013). Patients with CRPS perceive their affected hand to be about 7% larger than it is (Moseley, 2005a), and that an increase in hand size estimation correlated significantly with the duration of the condition, neglect score and with decrease of the difference in two point discrimination tests (Peltz et al., 2011). The evidence from several studies (Moseley et al., 2013, Hall et al., 2011), proposes that conflicting sensory information in CRPS could be a source of pain (Moseley et al., 2013, Knudsen and Drummond, 2014).

1.4 Neuroimaging and CRPS

Neuroimaging is a non-invasive method available to investigate possible supraspinal mechanisms of pain and to test ideas from pain theories. Neuroimaging techniques- both functional and structural - are relatively new tools for studying the central nervous system in chronic pain (Handwerker, 2007), and have made significant technological advances in recent times. The blood oxygenation level dependent (BOLD) response in functional magnetic resonanace imaging (fMRI) is able to provide an indirect index of neural activity by measuring a change in local deoxyhaemogloblin from a combination of hameodynamic response, blood flow changes, venous blood volume and metabolic responses to the change in oxygen metabolism (Buxton, 2012, Ogawa et al., 1990). Phase encoded fMRI imaging uses this BOLD response with an appropriate stimulus to acquire better spatial and temporal resolution fMRI data. T1-weighted structural MRI images are mainly processed with volume based neuroimaging methods in an attempt to quantify voxel by voxel differences in brain morphometry in chronic pain conditions. However, the analysis of structural data has improved from these volume based methods such as voxel-based morphometry or VBM (Apkarian et al., 2009, Mechelli et al., 2005) to surface-based methods (Fischl et al., 1999a, Pereira et al., 2012, Fischl, 2012) that hold more faithfully to the actual topography of the brain surfaces of subcortical structures, sulci and gyri (Greve, 2011). These techniques discussed in Chapter 3 and Chapter 4 facilitate the quantification of structural and functional neuroplastic changes in clinical conditions such as CRPS.

1.4.1 Functional imaging

Cortical changes in the motor (Di Pietro et al., 2013a) and somatosensory cortices (Di Pietro et al., 2013b) are said to be involved in CRPS (Gieteling et al., 2008, Di Pietro et al., 2015). For example, reduced fMRI cortical signals in S1 and the secondary somatosensory cortex (S2) in CRPS have been reported to be related to poor tactile acuity and increased pain intensity. The

functional representation of the index fingers in those areas were mapped using index finger electrical stimulation in an fMRI study in patients with CRPS Type1 (n = 17). The study tested two-point discrimination thresholds on the tip of both index fingers as a marker of tactile perception. Cortical signals within S1 and S2 were significantly reduced contralateral to the CRPS-affected index finger as compared to the ipsilateral side, and to healthy controls. The results found this was correlated with increased thresholds for two-point discrimination and mean sustained CRPS pain (Pleger et al., 2006).

Di Pietro and colleagues (2013a, 2013b) reviewed and identified that there were several shortcomings in the literature with the measurement of the spatial representation of the CRPS hand in S1. One of the earliest studies was the study by Maihöfner et al. (2003). In this study, the authors measured the spatial representation of the CRPS affected hand using current dipole localizations for the thumb and little finger from magnetoencephalography (MEG). The Euclidian distance between these two locations was reduced on the painful affected side, with a mean of 0.80 cm for the affected side and 1.37 cm for the unaffected side.

In this study, the centre of the hand representation was found to be shifted toward the cortical representation of the lip. The hand representation was measured as the mid-point of the cortical representation of the thumb and little finger, with this change relative to the lip representation considered a somatotopic map shift. The mean Euclidian distance of 1.95 cm between the cortical representation of the hand and the lip was decreased on the affected CRPS side compared to the unaffected side, at 2.76 cm. This cortical reorganisation correlated with the amount of CRPS pain, as measured by the McGill Pain Questionnaire, and the extent of mechanical hyperalgesia. Although the authors acknowledged the limitations of using MEG including that dipole localisation only corresponds to the centre of the cortical electrical activity, and does not reflect the whole cortical representation of a distinct skin area, but justified their findings as being a comparative study of both sides and that this bias was measured in both sides. Maihöfner et al. (2004) concluded that following effective CRPS therapy, cortical reorganisation reversed corresponding to clinical improvement of pain intensity. The authors suggested that this was supported by the increase in the same Euclidian measurement to 1.45cm a year later using the same methods.

Di Pietro et al. (2015) sought to improve on identified spatial resolution issues of MEG in the previous study, by using fMRI. They used a vibrotactile stimulus on the thumb (D1) and little finger (D5) as a measure of hand representation in S1, by calculating the Euclidian distance between D1 and D5. In CRPS participants, this D1 - D5 distance was smaller for the affected hand (15.02 ± 5.08 mm) than it was for the healthy hand (19.98 ± 7.14 mm; t (11) =

2.02, p = 0.03). However, the main finding from their analyses showed that when comparing between the healthy and CRPS group, that the D1 - D5 distance in the unaffected CRPS hemisphere was larger when compared with the non-dominant (12.21 ± 3.91 mm) hemisphere of control groups (U = 25.0, p = 0.02, r = 0.50), but not their dominant (18.09 mm ± 4.45) hemisphere (t(20) = 0.73; p = 0.48). This mean D1 to D5 Euclidian distance of the dominant hand in controls reported by Di Pietro et al. (2015) was comparable to the 17.2 ± 2.0 mm D1 to D5 distance in the right dominant hand of healthy controls (n=17) reported by van Westen et al. (2004). Their finding was novel as it focused attention on a maladaptive change in the unaffected hemisphere in CRPS (Di Pietro et al., 2015). This finding is different from the previously accepted conclusion of a shrunken hand representation in the affected S1 hemisphere from a large body of literature (Di Pietro et al., 2013b).

Patterns of cortical activations have been found to overlap for CRPS participants who experienced noxious hyperalgesia or non-noxious allodynia. Tactile changes of brush and cold allodynia were found to be correlated with cortical activations using fMRI in both adults and children with CRPS (Lebel et al., 2008, Seifert and Maihöfner, 2007, Maihöfner et al., 2006b). An fMRI study on 12 patients with CRPS used mechanical hyperalgesia (pin prick) on their affected side and compared it to their unaffected side. Mechanical hyperalgesia on the affected side was related to a significantly increased activation of the contralateral S1, bilateral S2, bilateral insula, contralateral associative-somatosensory cortices, frontal cortices and parts of the anterior cingulate cortex (Maihöfner et al., 2005). Another fMRI study from the same research group used innocuous brushing to elicit allodynia on the affected upper limbs of CRPS participants and compared it to their unaffected side. The results found allodynic associated cerebral activations included the S1, S2, insular cortices and posterior parts of the cingulate cortex (Maihöfner et al., 2006a).

In a case-control study of 21 CRPS participants using Diffusion Tensor Imaging (DTI) and voxel-based morphometry, clinical features of CRPS were assessed and correlated to the changes in grey matter and re-organisation of white matter connectivity (Geha et al., 2008). The density of regional grey matter was found to be negatively correlated to pain duration and average pain intensity. The strength of white matter connectivity between ventromedial prefrontal cortex (VMPFC) and nucleus accumbens (NAc) was related to the heightened anxiety reported by CRPS participants. The study concluded that CRPS patients had a concentrated region of grey matter atrophy with associated anatomical changes in white matter. This reorganisation of white matter connectivity in these regions was characterised by branching fibre pattern alterations. Specifically increased VMPFC to insula connectivity, and decreased VMPFC to basal ganglion connectivity (Geha et al., 2008).

Methodological limitations are often acknowledged to create bias in the functional neuroimaging studies in CRPS (Di Pietro et al., 2013b, Di Pietro et al., 2013a). Sampling limitations reported includes: small group sizes including from loss of data; technical issues such as obtaining no supra threshold cluster activations with the vibrotactile stimulus used and implausible spurious activations (Di Pietro et al., 2015). Another known limitation involves pre-processing spatial smoothing (Gustin et al., 2010, Di Pietro et al., 2015, Maihöfner et al., 2005) which adjusts for residual between-subject neuroanatomic differences that persist following normalisation (Bowman, 2014). This smoothing is useful for meeting the assumptions of the underlying random field theory analysis but comes at a cost for spatial accuracy. To balance this cost, it has been recommended that the smoothing be avoided at the pre-processing level (Bowman, 2014). For example, activation in the somatosensory cortex is in less than 2 mm thickness of grey matter (Fischl and Dale, 2000), spatial smoothing in a small area may result in mislocalisation or the functional activation being missed altogether (Lindquist, 2008, Weibull et al., 2008). Furthermore, if the participants are not homogeneous in their clinical pain characteristics (Maihöfner et al., 2005, Gustin et al., 2010, Di Pietro et al., 2015), inter-individual variability (Van Essen et al., 2012) might confound the conclusions from the spatial modelling and estimation (Bowman, 2014).

The current state of the research using functional imaging for identifying changes in the brains of patients suffering with CRPS has raised more questions than answers. Previous research has theorised that nociceptive feedback mechanisms can alter the response profiles of cortical sensory neurons in CRPS and other painful conditions (Pleger et al., 2004, Dhond et al., 2012). Therefore, this makes it difficult to disentangle whether cortical changes in CRPS are actually related to the condition or merely the consequence. A more spatially precise method such as phase-encoded fMRI, which would yield fine grained maps of individual digits may assist in providing a more comprehensive description of the biological mechanism of cortical reorganisation (Brett et al., 2002, Di Pietro et al., 2013b, Sanchez-Panchuelo et al., 2014).

1.4.2 Structural imaging in chronic pain using surface based methods

Previous reviews (Wager et al., 2013, Mutso et al., 2014, Schwedt et al., 2015) strongly suggest the use of technological advances in structural morphometry measurement and functional imaging. These advances include surface based techniques that are more faithful to the cortical folds (Fischl et al., 1999a, Cardinale et al., 2014), accounts for inter-subjective morphometry variability (Anticevic et al., 2008), and implicates the underlying cytoarchitecture of the brain (Borsook et al., 2010, Wagstyl et al., 2015). These advances might even have the potential to identify candidate biomarkers for chronic pain conditions (Woo and Wager, 2015);

where robust subjective assessments of pain is nigh impossible e.g. in neonates (Ranger et al., 2013) and in severe cognitive impairments (Woo and Wager, 2015, Poldrack, 2012, Lee and Tracey, 2013). Further details of structural imaging in chronic pain are covered in Chapter 4.

1.4.3 Literature review on surface-based cortical morphometry measures in chronic pain [1]

Borsook and colleagues (Borsook et al., 2013) reviewed the literature on altered brain morphology and chronic pain. They concluded that grey matter changes might be driven by repeated nociceptive drive with different consequences for cortical and sub-cortical structures. For example, patients with persistent migraine were found to have cortical thickening in the somatosensory cortex (Maleki et al., 2012) and insula (Maleki et al., 2015) , alongside a reduction in grey matter volume in the sub-cortical structure, the hippocampus (Maleki et al., 2013). The authors proposed that recurrent migraine attacks may drive increased cortical thickness in brain regions involved in sensory aspects of pain processing, similar to that found in menstrual pain (dysmenorrhea). However, not all brain areas of chronic pain participants show increased cortical thickening. For example, the somatosensory cortices showed no thinning in chronic trigeminal neuropathy participants (DaSilva et al., 2008) and reduced cortical thickness was found in chronic pancreatitis participants (Frokjaer et al., 2012). It has been argued that chronic pain could lead to abnormal synaptic activity, resulting in an imbalance of brain networks and connectivity. This would lead to microscopic dendritic spine changes, seen more globally as macroscopic volumetric changes in grey matter, with increases in some brain regions and reductions in other regions.

May (2008) proposed that once chronic pain is treated, all structural changes should be reversible. Some support for this was found by Teutsch et al. (2008) in their experimental pain exposure study, where exposure to pain led to rapid alterations in brain structure that rapidly receded once the painful stimulation had stopped. However, in other studies, structural changes in the brain's grey matter have persisted beyond the resolution of the episode of pain. This occurred in participants who experienced repeated pain followed by times of no pain during their menstrual cycles (Tu et al., 2010). It also occurred in surgery patients whose osteoarthritis (OA) hip pain was relieved post-operatively (Rodriguez-Raecke et al., 2013).

Controversy therefore exists, about the exact pattern of change in brain structures to expect in chronic pain conditions and during any progression or treatment of the condition. Some of the inadequacies may lie with the techniques and methods used, or with the use of small sample sizes. Both are understandable given the financial costs of these new techniques. Most recent

[1] For the literature search strategy, please see Appendix to Chapter 1 for full details.

studies use a combination of voxel-based morphometry and the newer surface-based morphometry measures for structural brain changes. The pain conditions studied to date include CRPS, migraine, gut related pain, low back pain, temporomandibular disorder, trigeminal neuralgia and generalised musculoskeletal pain including fibromyalgia (For further details, please see the Appendix to Chapter 1 for a review). In many studies, the conclusions can only be applied to that particular study sample. At best, there are a few publications that have studied the same chronic pain condition. Overall, the current state of knowledge about the cortical morphometry of participants with chronic pain is lacking. Research has barely embarked on the quantification of different types of pain states, let alone, responses to traditional treatments, or responses to the various treatments currently used in chronic pain.

1.4.3.1 CRPS

To best knowledge, there is a single published study in CRPS that measured cortical thickness (Lee et al., 2015). There was reduced cortical thickness in the right dorsolateral prefrontal cortex (DLPFC) and the left VMPFC. This was associated with a decline in neurocognitive function performance but not psychiatric symptoms. Correlations with handedness were also not investigated but they did account for age as a co-variate in their analysis of multi-limb clinical CRPS participants. A limitation was that associated functional changes in neurocognitive dysfunction were unable to be temporally correlated with their structural changes found in the analysis. Another limitation was a heterogeneous CRPS study sample (n=25; 13 patients had multi-site CRPS) that was assessed using the CRPS diagnosis criteria from Galer et al. (1998) rather than the most up-to-date criteria by Harden et al. (2010).

Two other studies have attempted to quantify subcortical structures in CRPS that although important, are not the focus of this thesis. Pain duration and intensity were reported to be related to reduced volumetric changes (n=30) in right anterior insula and VMPFC using VBM (Geha et al., 2008). A reduction was also found in the overall volume of the sub-cortical hippocampus structure, similar to low back pain but not to osteoarthritis pain (Mutso et al., 2012). These studies and the study by Lee et al. (2015) illustrates there is little information about the underlying structural morphometry in CRPS in S1 and M1 unlike that found in functional imaging of the corresponding areas.

In summary, little attention has been paid to the use of surface-based cortical morphometry measurements in neuroimaging research in CRPS. No one directional change of these measurements are apparent but instead appear largely dependent on the function of the task assessed in the studies on various chronic pain conditions reviewed herein. These studies in

chronic pain and others in healthy controls have emphasised clarity in the reporting of analysis methods, software processing issues and the interpretation of neuroimaging results. The results from cortical morphometry measurements should also consider the known confounders of age and gender (Salat et al., 2004, Van Essen et al., 2012, Ruigrok et al., 2014). A review of this literature has identified a critical knowledge gap; detailed investigations of structural cortical morphometry in CRPS would ideally be synchronised with functional imaging. For further details, please see Background to the volume and surface-based methods, Appendix for Chapter 4)

1.5 The primary somatosensory cortex and the sensory-discriminative aspects of pain

Touch and pain are highly related in the sensory cortex. Neuroimaging and electrophysiological studies have shown that the processing of these two stimuli occur in the S1 and S2 (Coghill et al., 1994, Zhang et al., 2012, Ploner et al., 2004, Chen et al., 2002). The cortical representation of tactile and nociception were shown to be overlapped within the S1 in healthy participants (Mancini et al., 2012). Research has identified the S1 cortex to be involved in the sensory-discriminative aspects of pain (Schnitzler and Ploner, 2000, Ogino et al., 2005).

The overlap between touch and pain was investigated by Mancini et al. (2012) using phase-encoded functional magnetic resonance imaging (fMRI). Healthy participants had their fingers exposed to either laser or air puffs, as a source of pain and light touch stimulus respectively. Results showed that the fine-grained spatial finger maps in the primary somatosensory cortex were largely overlapped and highly aligned for both the nociceptive and touch stimulus in healthy participants, suggesting comparable cortical representations for, and possible interactions between, mechanoreceptive and nociceptive signals (Mancini et al., 2012).

The processing of touch and pain can be influenced by prior knowledge of painful touch. An experimental fMRI study of healthy participants investigated whether prior experience of experimental allodynia was able to alter central processing of normal tactile sensation (Kramer et al., 2008). The study used a light touch stimulus to the left hand and imagined allodynia with a stimulus to the right hand. The authors compared brain activations in healthy participants who had prior knowledge and experience of allodynia in pain studies, to entirely naïve healthy participants. They demonstrated that the contralateral S1 and bilateral S2 were activated in both groups during light touch stimulus. The allodynia-experienced group had additional brain regions activated including contralateral thalamus, anterior cingulate cortex, and the amygdala

during the imagined allodynia stimulus. Furthermore, there were bilateral activations of S1, S2, the insular cortex and prefrontal cortices in the same participants.

The perception of touch and pain can be conditioned in the short term to change subsequent perception of touch in temporarily. Klein et al. (2004) showed that high frequency but not low frequency electrical stimulation of the skin caused pain to light tactile stimuli in adjacent skin (allodynia) in healthy participants for a few hours after conditioning in the first hour. Two patterns of conditioning pulse trains were used in the experiment; high-frequency stimulation trains of 100 Hz for 1 sec repeated five times at 10 sec intervals to induce long term potentiation, and low-frequency stimulation at 1 Hz with stimulus trains of 1000 pulses to induce long term depression. Their results led them to postulate that one possible mechanism for experimentally induced allodynia was through long term potentiation of synaptic strength and plasticity in cutaneous afferents, likely from the convergence of A- and C-fibre nociceptors on nociceptive spinal neurons and influenced by sub-cortical or cortical structures feedback such as the thalamus.

The processing of touch is hierarchically organised compared to pain in healthy participants, demonstrated in the two studies that will be discussed. Ploner et al. (2000) used whole-head MEG to compare cortical responses to stimulation of tactile and nociceptive afferents of the dorsum of the hand in healthy participants with the purpose of exploring the strength of association between touch and pain in the somatosensory cortex. The authors found that the nociceptive S1 source was located 10 mm medially than the early tactile S1 response arising from cytoarchitectonical area 3b and corresponded spatially to the later tactile S1 response. Considering a mediolateral location difference between the hand representations of cytoarchitectonical areas 3b and 1, the results demonstrated a generation of the single nociceptive response in area 1, whereas the tactile response activated sequentially peaking sources in areas 3b and 1. They concluded that the pattern of responses showed the difference in the organisation of both modalities in S1, that pain perception requires reactions to and avoidance of harmful stimuli compared to tactile stimuli (Ploner et al., 2000).

In a follow–up study, Ploner et al (2004) used MEG and selective nociceptive cutaneous laser stimulation to investigate the effect of phasic painful conditioning stimuli on cortical processing of tactile test stimuli applied to the same skin site. The authors found that having a painful stimulus applied 500 ms prior to the tactile stimulus facilitated the later stages of tactile processing but did not facilitate the earlier stages. This facilitation applied to cortical responses later than 40 ms originating from S1 and S2 somatosensory cortices but not to earlier S1 responses. They found that phasic pain facilitated tactile processing in S1 and S2, and this may

represent a physiological correlate of the alerting function of pain (Ploner et al., 2004). Therefore, the growing evidence from several studies now indicate that the processing of these two sensations appears to be tightly linked in healthy participants.

Research for the involvement of cortical processes in S1 and pathological pain has steadily increased but remains inconclusive about causality. Patients with neuropathic pain (Gustin et al., 2012, Youssef et al., 2014), including CRPS, display cortical reorganisation and associated changes in somatosensory cortical activity. The most recent systematic review by Di Pietro et al. (2013b) on the role of the primary somatosensory cortex function in CRPS identified high risk of bias and a lack of consensus across the CRPS neuroimaging literature. Aside from consistent demonstration of a smaller S1 representation of the CRPS-affected part, results varied between studies (Di Pietro et al., 2013b).

To address the shortcomings of current neuroimaging evidence, an effective tactile stimulus paradigm was developed for phase encoded functional imaging of S1 suitable for pathological pain with minimal participant burden (Chapter 3). This technique was used to describe individual fine-grained fingertip maps of both hands in CRPS using the highest spatial and temporal resolution. In addition, cortical morphometry measurements quantified the neuronal architecture underlying high spatial and temporal resolution fMRI data to comprehensively compare any differences between CRPS participants to healthy participants in Chapter 4.

1.6 The organisation of touch sensation

1.6.1 Touch organisation and processing in the primary somatosensory cortex

Allodynia and abnormal responses to touch in CRPS are thought to be related to maladaptive neuroplasticity in the sensory cortices. The somatosensory areas of the cortex lie in the parietal lobe and consist of three major divisions: the primary somatosensory cortex, secondary somatosensory cortex and the posterior parietal cortex. The anatomical location of the primary somatosensory cortex is at the anterior part of the parietal lobe. The borders of its location start from central sulcus into the post central gyrus, extending posteriorly into the post central sulcus, from the medial wall of the hemisphere to the cingulate gyrus (Kandel et al., 2013).

The primary somatosensory cortex is made up of four distinct cytoarchitectonic regions: Brodmann area (BA) 3a, 3b, 1 and 2, shown in Figure 1-2. The secondary somatosensory cortex is located on the upper bank of the lateral sulcus and comprises of BA 43. There are two further somatosensory regions in the posterior parietal cortex of BA 5 and 7b (McGlone and Reilly, 2010). Neurons from the thalamus project afferent information into these four distinct regions of S1, which hierarchically projects into the posterior parietal cortex and S2 (Kandel et al., 2013)

The neurons in BA 3a respond to muscle stretch, BA 3b and 1 are involved in sensing surface texture and superficial touch and BA 2 for sensing size and shapes of objects. The neurons in BA 2 integrate information from touch and muscle inputs, about hand posture, grip force, tactile information produced by an object, which allowed this integrated information to be processed in BA 2 in order to recognise the object that a person is interacting with (Kandel et al., 2013). In summary, BA 3a and 2 are involved in limb position sense and shape discrimination versus BA 3b and 1 are the receiving areas for superficial touch and texture.

In general, based on data from primate studies, BA 3a, 3b, 1, 2 and 5 are each associated with information processed from: the muscle spindles; slow adapting type 1 (SA1) and rapid adapting type 1 (RA1) receptors and rapid adapting type 2 (RA2) receptors, detecting complex touch and proprioception, and active touch (Kandel et al., 2013, McGlone et al., 2014). Active touch mechanisms activate medial neurons in BA 5 and process postural information from the upper limb joints, skin and associated information about arm movements from muscle spindles. Lateral neurons in BA 5 integrate tactile and postural information from the hand, in anticipation of actions that require planning like grasping. Neurons in BA 7 integrate tactile and visual information, and become more active when visual information during manipulation of the hand during a task is available, compared to when manipulating an object in the dark or by simply observing an object (Kandel et al., 2013).

During hand movements such as reaching and grasping, neural activity in the posterior parietal cortex coincides with neural activity in the motor and pre-motor areas of the frontal cortex, preceding activity in S1. Strong evidence exists for BA 5 to receive convergent central and peripheral signals and compare central motor commands with peripheral sensory feedback. Sensory feedback is then used to confirm the goal of planned action, thereby re-inforcing a previously learnt skill or correcting those plans when errors occur (Kandel et al., 2013, Mountcastle, 2005). In two experiments with 10 participants each, Hlushchuk and Hari (2006) demonstrated that unilateral stimulation of the fingers can be accompanied by prominent activations of contralateral S1 cortex in the parietal operculum (S2 region) of both hemispheres and activation of ipsilateral BA 2, with deactivation of BA 3b in ipsilateral S1 cortex and of the primary motor cortex (M1) in both hemispheres (Hlushchuk and Hari, 2006). They used balloon diaphragms driven by compressed air, eliciting mechanically based-light touch stimuli. Both left and right sided stimulation of fingertips elicited tonic activation in the contralateral S1, whereas phasic deactivations were observed in the ipsilateral S1 and in the MI cortices of both hemispheres. The authors observed that activation in the ipsilateral post central sulcus, likely BA 2, agreed with previous monkey single-neuron recordings indicating bilateral hand representation in this region. For further details of similar studies on neuroanatomical connections and mechanisms involving the sensory cortex, please see Appendix for Chapter 1.

Touch information from different mechanoreceptor types provide afferent feedback to S1 (detailed in the Appendix to Chapter 1) using known pathways such as the dorsal column-medial lemniscal (DCML) pathway, as shown in Figure 1-2 (Wing et al., 1996, Chapman, 1994, Chapman et al., 1996). Light touch and pressure have specialised primary sensory receptors and neurons, whilst nociception is detected mainly by the free nerve endings of these primary sensory neurons. Both the thermal and mechanical nociceptors are associated with Aδ (group III) myelinated fibres. Polymodal nociceptors can be activated by mechanical, chemical or thermal stimuli. They usually conduct information more slowly through C (group IV) unmyelinated fibres. All this information is processed eventually in the primary sensory cortices (Kandel et al., 2013, Wing et al., 1996, Patestas and Gartner, 2009).

Figure has been removed due to copyright restrictions

Figure 1-2: The general organisation of the dorsal column-medial lemniscal pathway. This involves the transmission of tactile information from the skin receptors into the contralateral S1 hemisphere. Adapted from page 331 by Chapman et al. (1996).

The cortical representation of touch in S1 is tightly linked with the perception of touch. The sensory homunculus shows that the relationship is not one to one for touch sensation but depends on the receptive field of the skin responsible for touch. First, the lips and fingertips have a larger representation in the primary somatosensory cortex compared to the back (Penfield and Boldrey, 1937). Second, the perception of touch is associated with the temporal and spatial quality of touch. Finally, the spatial quality is intrinsically associated with body representation and top-down processes of proprioception and touch. However, it is not easy to quantify the spatial perception of proprioception in S1 and its distribution. Longo and Haggard (2010) measured the spatial perception of proprioception of the hand in S1 in an attempt to capture the properties of the sensory homunculus from the work by Penfield and Boldrey (1937). The implicit maps of the mental representation of hand size and shape were massively distorted, in a reliable and characteristic fashion, featuring shortened fingers and broadened hands, similar for touch sensation. Their experiment therefore demonstrated a similar homunculus organisation for the hand's metric properties.

In summary, the sensory and motor functions of the hand interact. The tactile sensation is supported by many mechanisms including those responsible for spatial perception. This thesis has focussed on the sensory function of the hand specifically the fingertips and how this might be altered in complex regional pain syndrome (CRPS).

1.7 The mental body representation of the hand and fingers

The sensory perception of touch is closely associated with how the brain holds a mental representation of the body area responsible for touch. This representation is critical for distinguishing the body from the external environment and optimising function (Longo and Haggard, 2010). This mental body representation involves spatial, temporal components of perception of the body part and its interaction with the external environment. It is reflected in overlapping yet distinct concepts of body schema, body model and body ownership, and is implicated in pain states (Schwoebel et al., 2002, Moseley et al., 2008c, Tsay et al., 2015).

The notion of 'body schema' requires some internal representation(s) of the body's current posture and spatial extension (Maravita et al., 2003). The phrase 'body schema' stems from the original observations made by Head and Holmes which they coined the word 'postural schema' and introduced the idea of plasticity within this schema which could be updated with new information from posture and movement. They identified how this schema was disrupted in their observations of pathological medical cases (Head and Holmes, 1911). These disruptions

often manifest as perceptual changes of sensation including cutaneous and proprioceptive information about body parts.

The spatial representation of our body, its posture and the interaction of our sense of self with our environment are inextricability linked to higher order brain mechanisms and influenced by attitudes and beliefs about body image, contributing to the overall body model and ownership (de Vignemont, 2010, Longo and Haggard, 2010, Longo et al., 2010). A body model contains spatial position sense and localisation in external space including information about how each segment of the body connects at the joint with the size and shape of each segment (Longo and Haggard, 2010). This stored body model is continuously updated, creating probable scenarios that make sense, with the input of sensory signals (Longo and Haggard, 2010).

Body-ownership refers to the special perceptual status of one's own body, which makes bodily sensations seem unique to oneself, that is, the feeling that "my body" belongs to me, and with the cognitive sense of self (Tsakiris, 2010). A sense of ownership over a body part can be manipulated as seen with various body illusions including the rubber hand illusion, where an artificial hand can be perceived as a person's own hand. In contrast, there have been conceptual arguments against the use of "sense of ownership" of a body part in relation to the rubber hand illusion and an alternative concept of a "sense of embodiment" instead, which includes ownership as part of the concept of a sense of embodiment. Much controversy about these concepts are discussed in the work by Longo et al. (2008); Carruthers (2008); Carruthers (2013) and Braun et al. (2014). Hence, this chapter has not separated the concept of body ownership and embodiment, but has accepted both concepts as interchangeable until confirmatory evidence disproves one concept for another.

Body ownership can be modified by a single sensory channel (Heroux et al., 2013) when congruent information arises from anatomical sites, converging via this channel (Ehrsson et al., 2005, Petkova et al., 2011). In an experiment to induce the symptomatic effect of incongruent proprioceptive input without vision, the illusion of perpetual wrist flexion was evoked by vibration of the wrist tendons, while the hand was held in a fixed posture. These sensory disturbances arising from incongruent proprioceptive information were described as feelings of foreignness, fatness and swelling in healthy participants, indicating disruption to central proprioceptive representation. Although pain and discomfort were not reported, body ownership changes were described in healthy participants (Moseley et al., 2006), similar to those reported in neuropathic pain and CRPS (Forderreuther et al., 2004). Interestingly, the manipulation of congruent proprioceptive information, using the RHI, was not able to induce analgesic effects in healthy participants during experimental pain (Mohan et al., 2012).

Congruency of information may have a further role in the real-time updating of the sense of a body model or ownership, which contributes to the overall concept of body representation. Kennett et al. (2002) investigated accuracy and reaction times to detect whether a digit was judged to be up or down in an unseen hand posture. They were interested to test whether a non-informative visual cue aided the accuracy and reaction times and if improvement was associated with the space being tested or with the actual hand. To tease out this component, the experiment was repeated with hands crossed over the midline. Their results demonstrated that the pairing of stimulation in the same visual field and matching space will always lead to the most efficient performance, in crossed hands or uncrossed hands posture. The authors discussed that tactile–visual links in exogenous covert spatial attention do not reflect a fixed mapping. Instead, the cross-modal cuing affects remapping across changes in the current unseen posture, implicating a modulatory role for proprioception in real-time (Kennett et al., 2002). They proposed that proprioceptive information in the tested space aided remapping of body representation and kept visual cues congruent with the tested space. Therefore, visual cues exert an influence only on space being tested and the proprioceptive information processed by the brain.

In a recently reported study on healthy participants, the authors demonstrated by the introduction of incongruence between seen and actual positions of the right hand that, the participants were more inaccurate at hand localisation as they relied on visual weighted information. Over time, weighting of information switched from vision to proprioceptive information and the perceived location became closer to the actual position. A modulatory effect appeared to have occurred once visual information was deemed less reliable, then a preference for proprioception information that was prolonged and more stable occurred in healthy participants, allowing a return to improved hand localisation. This increase in accuracy of hand localisation process could be induced quicker when vision was removed immediately prior to hand localisation (Bellan et al., 2015). This study and others (Kennett et al., 2002, Azañón and Soto-Faraco, 2008) have confirmed that current hand posture relies influences tactile judgement tasks when all other types of somatosensory information were irrelevant or when deemed unreliable to the task.

Congruency of information has also probable influence of body ownership ratings in healthy participants (Walsh et al., 2011, Heroux et al., 2013). In an illusion experiment involving an artificial finger by Heroux et al. (2013), “simply grasping the artificial finger was not enough to induce perceived ownership over the artificial finger.” However, further details of the level of ownership agreement from this study reveals subtle differences in the median ratings (For further details, please refer to Figure 4, original article by Heroux et al. (2013)). Specifically, the study results showed that healthy subjects who experienced congruent movement of both

index fingers had a median rating of “somewhat disagree” and that when the healthy subjects experienced incongruent movement, a median rating of “ disagree” was reported. This level of disagreement between congruent and incongruent movement conditions were accentuated when participants’ index fingers were anaesthetised whilst grasping the artificial finger. Incongruence of information for the finger illusion (Walsh et al., 2011, Heroux et al., 2013) might have implications for how people with unilateral upper limb CRPS might rate their perception of ownership during an illusionary experiment .

1.8 Perception of bodily illusions in healthy participants

There is a wide array of illusion experiments researched in healthy participants but the most well-known is the rubber hand illusion (RHI). The RHI manipulates the brain's predisposition for congruent multisensory input such that, by synchronously stroking a rubber hand held in view and the real hand, held out of view, the participant quickly attains the sense of feeling touch on the rubber hand (Botvinick and Cohen, 1998). The effects of the RHI is confirmed by healthy participants who, when asked to point without visual feedback, typically give proprioceptive estimations that were shifted or integrated (Fuchs et al., 2016) towards the embodied rubber hand compared to their estimations before the stimulation (Holmes and Spence, 2004). Furthermore, the majority of participants reported perceiving touch as if it was coming from the rubber hand, and reported the rubber hand as being part of their own body (Reinersmann et al., 2013, Ehrsson et al., 2005, Ehrsson et al., 2007)

The RHI is known to have a number of physiological effects including a physiological cooling of 0.25°C (Moseley et al., 2008b) and the induction of an inflammatory response in the real hand (Barnsley et al., 2011). In addition, threat-related cortical responses were activated when participants observed brisk stabbing movements of a hypodermic needle, moving toward the index finger of their embodied rubber hand (Ehrsson et al., 2007). The RHI illusion can clearly disrupt spatial transformation of the stimulus and perception but surprisingly this was not adequate for producing analgesic effects of experimentally induced heat pain in healthy participants (Mohan et al., 2012)

The RHI requires a body representation that might include prior knowledge of 'anatomical plausibility' (Ide, 2013). A variation of the RHI study is the self-touch RHI, which is elicited when the participant with their eyes closed, administers brushing to a prosthetic rubber hand and a researcher administers congruent brushing to the participant's actual hand. The experimental manipulation consisted of the misalignment of the prosthetic hand relative to the actual hand by 0°, 45°, 90°, 135° and 180°. The results showed that if the prosthetic hand was grossly misaligned at and after 135° relative to their actual hand, the embodiment of the rubber hand was diminished but interestingly, misalignment up to and including 90° continued to elicit a compelling embodiment of the rubber hand (White et al., 2015). The RHI appears to be robust to moderate levels of spatial misalignment and can elicit very real perception of threat, concepts that are reported by patients with pathological pain. The first potential usage of the RHI, as a of treatment for pain, did not translate to inducing analgesia in experimental pain in healthy participants (Mohan et al., 2012) and therefore, is unlikely to be of clinical benefit. However,

spatial alignment in illusions might inform us more about the perception of pathological pain and provide a potential target for treatment.

The mechanisms behind bodily illusions including the RHI are attributed to the presence of correlated spatial and temporal sensory signals from vision, touch, movement and proprioception (Ehrsson et al., 2005, Heroux et al., 2013, Botvinick and Cohen, 1998, Petkova et al., 2011). This results in the perception of the artificial hand feeling as if it was the participant's own. Other body parts have been the subject of investigation in the RHI. These illusions have included the whole body (Petkova et al., 2011, Maselli and Slater, 2013) , an extra arm (Guterstam et al., 2011) and other body parts such as an artificial finger (Heroux et al., 2013, Walsh et al., 2011). In summary, versions of illusion experiments involving various body parts have demonstrated how easily body perception and ownership can be disrupted (Maselli and Slater, 2013, Moseley et al., 2012b, Kilteni et al., 2015) and the effects of these manipulations on physiological regulation. Experiments involving the use of these illusions provide a method for investigating the mechanisms underpinning perceptual discriminative aspects of touch and pain in CRPS.

1.9 Functional anatomy of illusory sensations

The neural substrates of illusory sensations have been investigated in humans using different illusions including the rubber hand illusion. As background, the RHI was briefly described in Section 1.8 and in the seminal paper by Botvinick and Cohen (1998). This illusion requires synchronicity of vision and touch unlike the novel finger illusion by Heroux et al. (2013), described in Chapter 5. The literature on illusions including the RHI demonstrates an increasingly clear separation of its components namely proprioceptive drift (body location) and body ownership (Fuchs et al., 2016, Rohde et al., 2011, Abdulkarim and Ehrsson, 2016). Most fMRI studies have referred primarily to the body ownership component of the illusion.

As mentioned, there appears to be a behavioural and anatomical dissociation between the degree to which the rubber hand feels like part of one's body (ownership), and the perceived location of one's body (Ehrsson et al., 2004, Longo et al., 2008, Kammers et al., 2009). The functional imaging literature in the RHI has focussed on the subjective ratings of ownership during the RHI in the MRI scanner (Ehrsson et al., 2004, Ehrsson et al., 2005, Ehrsson et al., 2007). The phenomenon was reported to be associated with neuronal activity in several multisensory areas, which included the premotor cortex, the intraparietal cortex and the cerebellum (Ehrsson et al., 2005, Ehrsson et al., 2004) .

The study by Ehrsson et al. (2004) used fMRI to describe the neurological activations of the RHI in detail. Specifically, Ehrsson et al. (2004) proposed three steps and brain activation patterns from prior to when the experimenter starts to brush the seen rubber hand and the hidden real hand to during the RHI. These three steps included:

1. During the initial period prior to the illusion, awareness of the felt position of their real hand hidden under the table is conflicted with the seen position of the rubber hand. During this period the inter-sensory conflict is possibly resolved by a re-calibration of a proprioceptive representation of the arm in a reaching circuit involving the intraparietal cortex, the dorsal premotor cortex, the supplementary motor area, and the lateral cerebellum

2. During the illusion, the contralateral extrastriate cortex, the contralateral intraparietal cortex, and the left and medial cerebellum most probably receive visual information about the position of the seen rubber hand via the detection of the synchronous visual and tactile brushstrokes. The parietocerebellar regions are inferred to have a role in the integration of these types of multisensory information.

3. Finally, when the illusion occurs, the premotor cortex then plays a key role in the self-attribution of the seen rubber hand. The proprioceptive representation of the RHI probably leads to changes in the body-centered reference frames, most notably in the premotor cortex through integrating visual and somatosensory signals.

Ehrsson et al. (2005) extended his fMRI study to investigate a somatic RHI without vision, to address the concerns of the first study. As in their previous study (Ehrsson et al., 2004), this study reported activity associated with the illusion of touching one's own hand was detected in the ventral premotor cortex, intraparietal cortex and cerebellum. Cortices lining the intraparietal cortex are also known to be connected to visual, somatosensory, and premotor areas (Rizzolatti et al., 1981b, Rizzolatti et al., 1981a, Iwamura et al., 2002), and neurons in this region have been shown to integrate visual, tactile, and proprioceptive information from the hand (Wise et al., 1997, Graziano, 1999, Graziano et al., 2000, Graziano, 2006). They suggested that the posterior parietal cortex was involved in the process of multisensory integration during the illusion. This was a logical conclusion as the ventral premotor cortex (Bekrater-Bodmann et al., 2012, Schmalzl et al., 2014) is anatomically connected to visual and somatosensory areas in the posterior parietal cortex and to frontal motor areas.

Another illusion that has previously demonstrated the involvement of the pre motor cortex is the vibration based arm illusion (Naito et al., 1999, Naito and Ehrsson, 2001). The authors vibrated the tendons of the relaxed right wrist extensor (flexor carpi ulnaris) muscle which elicited a vivid illusory palmar flexion. Their study described the involvement of motor cortices (using PET) including the supplementary motor area extending into the caudal cingulate motor area, area 4a extending into the dorsal premotor cortex and area 4p, as associated with the illusion of kinesthesia. The authors also found activations in the somatosensory cortex but that the primary driver for the illusion could be best explained by the pre motor cortices.

Illusory mechanisms clearly have a role for the motor cortex in the interpretation of the illusion or perhaps the kinaesthetic sense related to movement rather than the kinaesthetic sense/ joint position sense in space. Naito et al. (2002b) had a follow-up experiment where the rate of vibrations transferred via the ulnar styloid did not evoke an illusion but vibration of the flexor carpi ulnaris did to create the illusion of wrist flexion. This illusion was transferable to the non-vibrated flexor carpi ulnaris of the control hand. Again, pre motor cortex fMRI activations were found to be associated with the kinaesthesia sense of wrist flexion. Naito et al. (2002b) clearly concluded that that the experience of the illusion was dependent on the activation of the M1 but not dependent on the sensory input from the muscle spindles due to the ability to transfer the illusion to the control hand. However, it is possible that the brain activation areas merely reflects imagined wrist flexion movements rather than a transference of the illusion, as found in a previously study by the same author (Naito et al., 2002a). Besides the activity of M1, there were cortical activity found in the two supplementary motor areas, the two frontal opercular areas, the right dorsal premotor area, the right area 8, the right cytoarchitectonic area 2, and the right supramarginal gyrus (Naito et al., 2002b). This distribution of cortical activity suggests that activation of M1 is crucial for the perception of movement but the conjoined activity of all these areas is necessary for the subjects to experience the sensation of limb motion during the illusion.

Another illusion that can dissociate tactile perception from physical stimulation is the classic cutaneous rabbit illusion (Geldard and Sherrick, 1972, Blankenburg et al., 2006, Miyazaki et al., 2010). Repeated rapid stimulation at the wrist, then near the elbow, can create the illusion of touches at intervening locations along the arm, as if a rabbit hopped along it. Blankenburg et al. (2006) investigated this illusion using functional magnetic resonance imaging (fMRI). When brain activity in humans using fMRI were examined and compared with control stimulation at the same skin sites (but in a different order that did not induce the illusion), illusory sequences activated contralateral primary somatosensory cortex, at a somatotopic location corresponding to the filled-in illusory perception on the forearm. Moreover, the amplitude of this

somatosensory activation was comparable to that for veridical stimulation which included the intervening position on the arm. The illusion additionally activated areas of premotor and prefrontal cortex. These results provide direct evidence that illusory somatosensory percepts can affect primary somatosensory cortex in a manner that corresponds somatotopically to the illusory percept but also involve previously mentioned cortical areas (Christensen et al., 2007, Blankenburg et al., 2006, Theorin and Johansson, 2007).

1.10 Perceptual dysfunction in CRPS

CRPS is a pathological pain condition thought to have both perceptual-discriminative and affective-motivational components (Auvray et al., 2010, Melzack and Casey, 1968). Although influences on affective–motivational components in CRPS are supported by research (Coghill et al., 1994, Treede et al., 2000) these components are not investigated in this thesis. Instead, the studies from this thesis focus on the perceptual and sensory-discriminative aspect of pain and touch in CRPS as current evidence indicates maladaptive reorganisation in S1 cortex, which is associated with the sensory-discriminative aspects of pain and touch (Schnitzler and Ploner, 2000, Apkarian et al., 2005).

Any disruption to the processing of the touch and nociceptive information might produce or maintain altered pain perception and processing in pathological pain, as outlined previously (in the 'Theories of pain' section). Altered processing of touch and perception over time has been reported in CRPS (Reiswich et al., 2012, Pleger et al., 2006). For example, patients with CRPS reported altered tactile processing and spatial awareness; this was shown to worsen when their affected limb was cooled (Moseley et al., 2009). This is proposed to be related to an incongruence between the actual body location and the cortical sensory and motor maps, but deciphering exactly what contributes to this phenomenon requires careful experimentation (Moseley and Gandevia, 2005). Careful experimentation to investigate reported perceptual and sensory-discriminative changes in CRPS can involve the use of bodily illusions (Moseley et al., 2012b, Reinersmann et al., 2013) and comparing these responses with those of healthy participants.

1.10.1 Altered perception of illusions in CRPS

There are limited studies investigating body perception using illusions in CRPS. Reinersmann et al. (2013) used the rubber hand illusion in CRPS and reported that some patients with unilateral CRPS with significant neglect-like characteristics had weaker embodiment of the RHI compared to other patients with CRPS. However, the authors'

generalised conclusion was that there appeared to be intact multisensory integration in CRPS participants linked with the intact ability to perceive illusory ownership with the RHI using congruent visual-tactile stimuli (Reinersmann et al., 2013). The study specifically mentioned that CRPS patients were able to perceive bilateral illusory ownership over an artificial hand, when compared to healthy participants or patients with upper limb pain, as confirmed by both subjective and objective illusion strength measurements. Additionally, the study used another cue of a needle near the rubber arm for habituation. In this situation, there was a significant difference between CRPS Type 1 (affected side) and healthy (dominant side) participants on their ratings of a subjective questionnaire item - "The penetration of the needle on the prosthesis frightened me". However, there was no significant difference between healthy participants and pain (not CRPS pain) patients, presumably because the needle was placed close to each hand's RHI and there was no difference in the strength of illusion in either hand. The subjective questionnaire statement implies a sense of 'threat' experienced in CRPS patients but this did not translate to a physical change in the objective measurement of skin conductance in this study.

The study design was unable to account for whether this illusion was present in the affected or unaffected space in CRPS, with different body postures, the effect of the RHI on skin conductance in CRPS pre and post illusion or to separate visual-tactile components and its effect on the RHI. The study results indicated that tactile incongruent sensation in unilateral CRPS participants did not appear to influence the overall RHI experience. This leaves unanswered the question of how spatial components of an illusion in the condition contribute to the realism of an illusion? Of relevance, a recent study of healthy participants concluded that gross spatial misalignment prevented a compelling experience of self-touch illusion of the RHI but moderate levels of spatial misalignment did not disturb the strength of the illusion (White et al., 2015).

1.10.2 Body representation disturbances in CRPS

A review by Tsay et al (2015) expanded on the concept of altered body representation had a role in pain states. The authors concluded that a distorted mental body representation was implicated in persistent pain conditions but that body maps or body schema disruption did not fully explain an altered body representation. They proposed using psychophysical methods including illusions (please refer to 1.8) to interrogate the quality of this body representation in the context of proprioception, interoception or awareness of bodily sensations (Craig, 2002) and the relationship with exteroception (monitoring the external environment) whilst acknowledging overlap in these systems (Tsay et al., 2015). (For further details, Table 7-2 illustrates the

complexity and contribution of sensory modalities that result in conceptual overlaps between body schema and peri-personal space, which is part of exteroception).

There is a growing body of evidence that CRPS participants have an altered multi-sensory integration of their body representation, ownership and pain (Moseley, 2005b, Moseley, 2005a, Moseley et al., 2012a). The results of one such experiment showed a reduced ability at laterality tasks for patients with upper limb CRPS. The authors reported that patients misidentified digits and were unable to feel part of their hand or digit or even whole sections of their affected limb (McCabe et al., 2005).

An altered perception of body in CRPS (Turton et al., 2013) has been reported in several experiments. In one such experiment, CRPS participants with one affected upper limb were asked to pick subtly different sized pictures of their own hand. These participants chose pictures that indicated that they perceived their painful limb to be larger than it actually was, with a mean of 105% (Moseley, 2005a). In another study of CRPS participants, touching the unaffected extremity while viewing it in a mirror induced pain or parenthesis at the corresponding site on the affected hidden limb (Acerra and Moseley, 2005). Interestingly, Moseley and Wiech (2009) manipulated this altered perception to improve tactile discrimination in the affected limb by having participants watch their unaffected limb in a mirror.

In a further study about positioning and error judgement in CRPS, Lewis and colleagues (2010) compared unilateral affected upper limb CRPS participants with healthy controls. The accuracy with which participants could position their arm horizontally was measured, and the error between the target position and actual position was significantly greater in the CRPS than the control group. This greater error occurred whether measurements were included for the affected limb only or for both limbs combined. Vision aided accuracy of limb positioning for the affected but not the unaffected arm. The authors proposed that the exact relationship between CRPS pain and limb position deficits requires further exploration but that their study raised further evidence towards a spatial deficit and processing problem in CRPS (Lewis et al., 2010).

Another series of studies investigated how the CRPS affected limb was associated with a deficit in tactile processing and was cooler than the unaffected limb. These studies defined the affected space as that in which the affected limb normally resides, rather than the actual position of the affected limb (Moseley et al., 2012a, Moseley et al., 2009). The first study used stimulus onset asynchronicity that meant participants should be equally likely to choose one limb over the other. However, when participants crossed their hands over the midline, the CRPS

participants prioritised stimuli from the unaffected limb and the unaffected space. If both hands were placed in the midline, the stimuli to both hands were only perceived as simultaneous, only if the stimulus to the affected limb was volleyed 25ms earlier than to the unaffected limb (Moseley et al., 2009).

A second study showed that CRPS participants had an impaired spatial perception which modulated temperature of the limbs, tactile processing, spontaneous pain and a sense of ownership over the hands (Moseley et al., 2012b). The third study used a manipulation of visual feedback. In this study, CRPS participants wore prism glasses that distorted the actual position of their limb. When their affected limb appeared to be in the unaffected space, their limb temperature warmed up. Conversely, when their unaffected limb was viewed as if it was in the affected space, the unaffected limb's temperature cooled (Moseley et al., 2013). Other studies have found similar results, using different methods to manipulate the involvement of the visual system (Lewis et al., 2010, Moseley, 2005a).

In summary, there is a growing body of research that suggests spatial deficits are associated with the affected side in CRPS (Reinersmann et al., 2012). Therefore, targeted rehabilitation should consider affected and unaffected spaces, as had been trialled in other neurological conditions affecting tactile sensation (Stevens et al., 2012, Coslett and Lie, 2004). Conflicting sensory information in CRPS (Knudsen and Drummond, 2014) and altered sensory processing about the position of the affected limb in space (Moseley et al., 2013) could also be a source of pain (Moseley et al., 2013, Hall et al., 2011). These maladaptive neuroplastic changes appear to have far reaching effects on both the sensory and motor systems in the central nervous system. Much research is still lacking on the concept of a disrupted body representation in CRPS and its suggested effects on supraspinal mechanisms.

The spatial component of proprioceptive drift and ownership in CRPS was investigated by adapting the experiment of the finger illusion on healthy controls. This adapted experiment novelly investigated if CRPS participants perceived the finger illusion in their affected limb differently from their unaffected limb and in different spaces, in Chapter 5.

This thesis focuses on tactile sensory processing of painful non - noxious touch in CRPS and how touch sensation is integrated in the cortex.

The specific questions that were addressed in this thesis included:

1. Do patients with CRPS have distorted functional somatotopic maps of the fingertips in the primary somatosensory cortex compared to healthy controls?
2. Is there an association between the cortical representation of the fingertips in S1 with clinical characteristics of CRPS?
3. Do patient with CRPS have tactile proprioceptive dysfunction in CRPS compared to healthy controls?

2 Overview of the Study Sample

Rarely do neuroimaging and experimental studies on CRPS participants describe their sampling methods and source population adequately (Di Pietro et al., 2013b, Bean et al., 2014). This makes it difficult to compare results between studies to a wider population of people with CRPS. Here, this work attempts to address this by providing a comprehensive overview of the general characteristics of the current study sample of CRPS participants.

This aim of this chapter is to outline the study methodology, inclusion and exclusion criteria, participant recruitment procedures and participant characteristics that are common to *Chapters 3, 4 and 5*. The characteristics of this study sample were compared to the characteristics of patients with chronic pain (Nicholas et al., 2008) and to the characteristics of CRPS patients from the CRPS - UK Registry (Shenker et al., 2015).

2.1 General Methodology

2.1.1 Study Design

The study design was cross-sectional, with cases compared to age and gender matched non-pain controls.

2.1.2 Ethics

Ethical approval was granted from the University of New South Wales Human Research Ethics Committee (HREC) HC 13214 and from South Eastern Local Health District HREC 10/051. The Scientific Management Committee at NeuRA provided ethical approval for the imaging parameters.

2.1.3 Inclusion Criteria

2.1.3.1 General Inclusion Criteria

To be included, all participants had to:

- be aged between 18 to 89 years.
- have sufficient command of written and verbal English language.
- fulfil all requirements of the NeuRA Imaging Facility MRI safety checklist (please see Appendix for Chapter 2).

2.1.3.2 Specific inclusion criteria for healthy non-pain controls

Controls were included if they:

- were pain-free at that time.
- had no prior history of a significant chronic pain or medical disorder.
- had no history of excessive medication or substance abuse.

2.1.3.3 Specific inclusion criteria for participants with CRPS

Cases were included if they received a diagnosis of CRPS of either one hand or the upper limb, made according to the Budapest criteria (Harden et al., 2010).

2.1.4 Exclusion Criteria

Any participant was excluded if they were:

- Pregnant.
- Had any significant neurological or psychiatric disorders.

2.1.5 Participant Recruitment Procedures

2.1.5.1 Recruitment and participant selection

An Australian-wide convenience sample of participants were recruited into the study and from a concurrent Sydney-based study investigating recovery following wrist and hand fractures (Parkitny et al., 2013b). Recruitment from community dwelling people with CRPS used convenience sampling techniques including widespread online and public advertisements. These included: a CRPS information seminar to hand therapists at tertiary referral hospital in Sydney (Royal Prince Alfred); an email flyer to all hand therapists in New South Wales (NSW); distribution of study advertisement flyers at a national pain conference with medical doctors and allied health representatives from each state; online advertisements in the Australian Pain Society newsletter, on Facebook support groups for CRPS, the Body in Mind website (http://www.bodyinmind.org/) and on the research participant recruitment site run by Neuroscience Research Australia (https://www.neura.edu.au/volunteer/). The study was also discussed during a research profile talk on national radio (Dr. James McAuley). Interested medical and health professionals who contacted the study were sent information and consent forms that they could distribute to potential participants.

2.1.5.2 Procedure

When a potential participant contacted the research team the information sheet and consent form were sent by mail or email for the potential participant to read. If the participant was recruited via the fracture cohort study (Parkitny et al., 2013b), information about the study and contact details were given before initial contact with the researcher. All participants were given at least 24 hours to consider the information.

If a potential participant was interested in the study, screening for eligibility was performed in two stages. The first stage aimed to determine whether the participant had CRPS or not. This stage was conducted by the researcher using a telephone questionnaire to assess the potential participant's reported symptoms of CRPS. This telephone questionnaire and tool was used to assess whether the potential participant met the study inclusion criteria and fulfilled the research criteria (Budapest) for the diagnosis of CRPS.

The second stage involved the assessment of: exclusion criteria for all participants, the specific inclusion criteria for non-pain controls and the specific inclusion criteria for participants with unilateral upper limb or hand CRPS. This second stage also included the telephone questionnaire checks by a research doctor who was blinded and had no subsequent recruitment involvement in the study. Unless there was disagreement between the primary researcher who performed the first stage of screening and the research doctor regarding fulfilment of CRPS criteria, the potential participant was then asked to complete and sign the consent form, the Edinburgh Handedness Inventory (EHI) to determine hand dominance (Oldfield, 1971) and the NeuRA Imaging Facility MRI safety checklist.

2.1.5.3 Diagnosis of CRPS

Potential cases of CRPS had to be diagnosed with either one hand or upper limb; by the researcher according to the Budapest criteria (see Table 1-2). Exceptions were made if the participant had been diagnosed by their medical consultant using the Budapest criteria.

If the CRPS case had not been assessed against the Budapest criteria, the assessment was made prior to the experimental test day during an assessment visit. A physical examination by an assessor, blinded to hand dominance or suspected diagnosis of CRPS, was performed and a *pro forma* with Budapest criteria completed. A second assessor (LM) who had no contact with any participants reviewed the *pro forma* and decided if the Budapest criteria were met. If the criteria were met, the participant was invited for a testing day. If not, they exited the study.

2.1.5.4 Healthy matched controls

Non-pain controls were age, gender and hand dominance matched to a CRPS case. Age matching was within two years of their year of birth.

Included participants were given an appointment for a test day that included the neuroimaging scan, psychophysical tests and questionnaires. They were asked to minimise the use of any pain medication if possible at least 48 hours prior to their scan date to limit the immediate effects of pain medication on the haemodynamic response in the fMRI scan. They were asked to document their medication usage during this 48 hour period and any changes to their usual medication prior to their test day since screening.

2.1.5.5 Test day

On the day of testing, each participant had a half day of assessments and a series of experiments including: medical history and objective assessment, and medication information; psychophysical tests of tactile acuity and finger illusion experiment (Chapter 2); an MRI scanning experiment of one hour and questionaries. The objective assessment included an assessment of any signs and symptoms of CRPS according to the Budapest criteria. This assessment consisted of clinical observations and tests to detect hand differences in pressure sensation, brush evoked allodynia, swelling, sweating and trophic changes such as hair and skin colour changes. As part of the clinical assessment, pressure pain threshold (PPT) using a digital pressure algometer, FDX® (Wagner instrument, Greenwich, USA) was assessed on two sites on each hand by a research assistant. PPT was measured as an average of two sites on each hand and the units measured were kg/cm^2. The two sites on each hand were at the third interphalangeal joint of the index finger and the thenar eminence. Data from the PPT was used in the correlations of neuroimaging measures (Chapter 4). The result from every objective assessment was evaluated by an expert in the field of CRPS (LM) in a blinded fashion to confirm or refute the diagnosis of CRPS or non-pain control. For a flowchart of the two stages of screening and the test day, please refer to Figure 8-1.

2.1.5.6 Financial reimbursement for participation in the study

Each participant was given $60 compensation for their time and travel expenses to NeuRA, Barker Street, Randwick, New South Wales.

2.1.6 Data collection

Data were collected on the following variables using a study *pro forma*:

- Age
- Gender
- Date of symptoms occurring
- Date of diagnosis, if CRPS
- Relevant history of injury or precipitating event for CRPS
- Self- reported co-morbidities including any blood disorders, cancer, loss of weight or appetite, lung or heart diseases
- Work history: previous and current
- Social and family support: previous and current
- Subjective evaluation of average hand usage over a week prior and post diagnosis of CRPS
- History of any other pain sites
- Medication used

Questionnaires were used to assess hand function and ability to perform daily activities (quickDASH and PRWE), mood (DASS-21), self-efficacy (PSEQ), and pain catastrophising (PCS). The Edinburgh Handedness Inventory (EHI) and pain intensity before experimentation, pre and post tests (PI-NRS) are described here. The clinimetrics of questionnaires are described in detail in Appendix for Chapter 2.

Age, gender, handedness, pain intensity scores, pressure pain threshold (taken from the clinical examination), CRPS pain duration and age on onset of CRPS, opioid and non-opioid medication history were used in latter analysis including in Chapter 4. These variables were chosen from the previous literature on CRPS(Di Pietro et al., 2016, Di Pietro et al., 2015, Di Pietro et al., 2013b, Bean et al., 2010, Bean et al., 2014, Reinersmann et al., 2013, Beerthuizen et al., 2012) and neuroimaging recommendations of influences on results(D'Esposito et al., 2003, Woo et al., 2014, Woo and Wager, 2015). Therefore, neuroimaging changes associated with chronic pain such as CRPS should not be considered in isolation from factors related to analysis, pain duration, demographics, pain resolution and opioid medication (as also discussed in Chapter 4.1 paragraph 5 and last paragraph, Section 4.1.2, Section 4.1.1).

2.1.6.1 Edinburgh Handedness Inventory (EHI)

Hand dominance is assessed using the Edinburgh Handedness Inventory Questionnaire (Oldfield, 1971). The EHI consists of 20 items. Subjects with CRPS were asked to fill in the EHI based on how they were using their hands prior to having a diagnosis of CRPS. A laterality quotient was calculated by the addition of '+'s for each hand, subtracting the sum for the left from that of the right, divide the this number by the sum of both and multiply by 100. A negative laterality quotient indicated left handedness and a positive laterality quotient right handedness. Sex composition influence on the laterality quotient was discussed in the original article.

The original EHI still provides a sufficient "handedness" factor but has been suggested to be shortened with subsequent psychometric analysis. The factor analysis by Williams (1986) showed that most of the items had a loading factor of 0.79 to 0.89 except opening a box lid (0.59) and using a broom with the upper hand (0.60). This led to a suggestion that the ten items could be shortened to eight. In another study by Büsch et al. (2010), they used item response theory models to test the construct validity of the EHI on an item level and confirmed similar findings. By carrying out mixed-Rasch analyses, the authors demonstrated that after eliminating Items 8 (Broom [upper hand]) and 10 (Opening box [lid]) and reducing the response categories from five to either four or three, the best model can be confirmed as a two-class solution (left- vs right-handers) with quantitative differences between the persons within both of the classes. On the one hand, the examination verifies the idea of reducing the numbers of the items by other authors (Williams, 1986; Dragovic, 2004) and on the other hand, the reduction of the response categories permits a more unambiguously classification of the preferred handedness.

2.1.6.2 Pain Intensity Numerical Rating Scale (PI-NRS)

The aims of the pain intensity assessment were to monitor the impact of the day of testing and each component of testing on any subjective change in pain intensity reports. A numeric rating scale (NRS), on an 11-point Likert scale was used in pain intensity questionnaires administered in this study. The questionnaires were investigated in a written format. The 11-point Likert scale consisted of ratings of pain intensity from where zero was 'no pain' to ten was like 'worse pain imaginable' like 'a red hot poker through your eye'. The first pain questionnaire assessed each subject's rating of their average pain over the last 7 days, the last 48 hours and on the day. The wording of this questionnaire was similar to the pain intensity component of the Brief Pain Inventory (BPI), with the exception of different time periods (Internal consistency for BPI Cronbach's α coefficient = 0.80 - 0.92 (Cleeland et al., 1994), Test– retest ICC = 0.83 - 0.88 (Mendoza et al., 2006)). The pre and post pain questionnaire,

used the same NRS scale, and asked the subjects to rate their average pain during and after the test or MRI scan.

The NRS is equally good at detecting current pain intensity and change in baseline pain. The NRS and the well-known Visual Analogue Scale (Revill et al., 1976) for assessment of pain intensity have good agreement and are equally sensitive in assessing acute pain intensity (Breivik et al., 2008). On average, a reduction of approximately two points or a reduction of approximately 30% in the NRS represented a clinically important difference. The relationship between percent change in NRS and the patient's global impression of change had good consistency for baseline pain, while higher baseline scores required larger raw changes to represent a clinically important difference. Percentage change in NRS had a sensitivity and specificity ranging from 76.8% to 81.5% (Farrar et al., 2001). The graphical version of the NRS have been shown to be valid and reliable measures of pain (Bijur et al., 2003, Gagliese et al., 2005, Herr et al., 2004, Williamson and Hoggart, 2005, Hjermstad et al., 2011, Ferraz et al., 1990) and been used across a variety of age groups (de C. Williams et al., 2000, Herr et al., 2004).

2.1.7 CRPS participants compared to the characteristics of other samples.

Characteristics of our study sample were also compared to chronic pain data from the study by (Nicholas et al., 2008) and CRPS data from the CRPS- UK Registry which included multi-limb involvement of CRPS (Shenker et al., 2015).

The normative data from chronic pain measures (Nicholas et al., 2008) were derived from 6,124 chronic pain patients attending the Pain Management and Research Centre at the Royal North Shore Hospital, Sydney from June 1994 to May 2004. Of the 6,124 patients, 5,941 (97%) patients in the sample completed a series of commonly used questionnaires that assess different dimensions of pain including self-efficacy and DASS. Basic demographic data on age and gender as well as pain duration was also included. The numbers of patients varied for different measures, as changes were made in the measures used over the data collection period and not all patients completed all measures in the assessment. The remaining 183 (3%) did not provide any data for the study (Nicholas et al., 2008).

The CRPS-UK Registry (Shenker et al., 2015) was established in 2008 by a group of rheumatologists, anaesthetists, allied health professionals and researchers interested in CRPS. This 35-year project intends to complement other international registries, provide prognostic information for a cohort of patients diagnosed with CRPS in the United Kingdom and provide a

resource for studying this condition. The Registry includes people with CRPS who fulfil the Budapest clinical criteria. In July 2013, the Registry had collected 37 variables from people with CRPS (n = 240). The recruitment to the Registry was from four centres throughout the United Kingdom: Department of Rheumatology, Royal National Hospital for Rheumatic Diseases, Bath; Department of Pain Medicine, Walton Centre NHS Foundation Trust, Liverpool; Department of Rheumatology, Addenbrooke's Hospital, Cambridge; and Pain Clinic, Department of Anaesthetics, Derriford Hospital, Plymouth (Shenker et al., 2015).

2.2 Results

2.2.1 Characteristics of complex regional pain syndrome participants

Forty-two participants; 21 CRPS cases and 21 matched healthy controls, were included in the study (Table 2-1). Study recruitment flow is shown in the chart of participant recruitment (Figure 2-1).

The source of CRPS participants was from: the fracture clinic study (4); online strategies (8); an information leaflet from their private practitioner (2) or pain clinic (5); self - referral after reading an internet advert (2). The source of healthy volunteers was: word of mouth from an internet advert (12); an internet advert on NeuRA website and volunteer database (8) or a physical advertisement (1). The impact of internet based advertisement or online strategies and word of mouth was the main recruitment method. Physical advertisements appeared to have the least impact in recruitment of participants with a rare condition like CRPS.

Patients with CRPS that participated in the study came from:

- NSW - Sydney city areas (8)
- NSW - regional areas (6)
- Queensland - regional areas (4)
- Victoria - Melbourne city area (2)
- South Australian regional area (1)

All healthy volunteers came from the Sydney city areas except one volunteer was from a NSW-regional area.

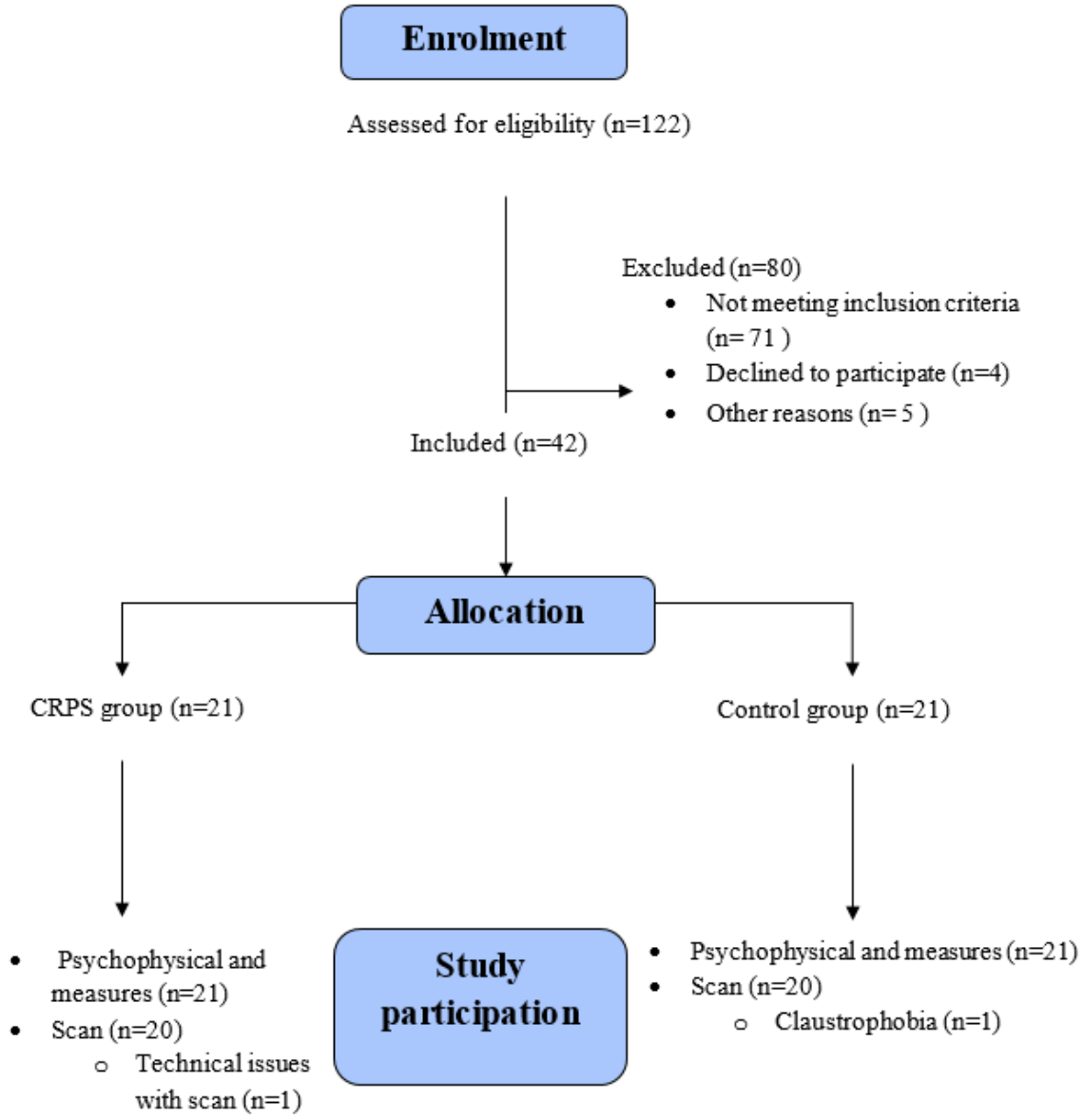


Figure 2-1: Flow chart of participant recruitment

Table 2-1: Basic demographics and clinical information of individual CRPS participants (n = 21).

ID #	Gender	Age at scan date, years	CRPS Upper Limb	Original Hand dominance	CRPS Duration, years.	Pain intensity On day [NRS11]	Incident at onset of CRPS	Type of Opioid medication	Other medication
2	Male	38	Left	Right; 84.62	4.7	8	Hand injury	Endone;Tramadol	Endep 25mg p.r.n; Gabapentin 200mg/ day. Uses 900-1000mg/day; Paracetamol
3	Female	53	Right	Right; 100.00	4.5	7	Shoulder injury	None reported	Salbutamol nocte
6	Female	42	Left	Right; 50.00	1.2	8	Wrist fracture	Prodeine forte 1000mg/ 6 hourly	Amantadine HCL 100mg 2x/day; Orphenadrine 100mg 2x/day; Lyrica 75mg 2x/day; Allergron 25mg nocte
8	Female	38	Left	Right; 85.71	0.4	5	Hand and wrist injury	None reported	Endep 10mg 1x/day
9	Female	43	Right	Right; 83.33	0.9	2	Wrist injury	None reported	Multivitamins and supplements

12	Female	56	Left	Right; 83.33	0.5	9	Frozen shoulder	Targin 40mg 2x/day; Codeine phosphate 15mg p.r.n;	Epilim 400mg 3x/day; supplements
13	Female	38	Left	Right; 91.30	1.0	7	Suspected haemorrhagic stroke - undetected via investigations.	Paracetamol 500mg + codeine phosphate 30mg 4x/day	Endep 25mg; Sotalol 40mg 2x/day; Mefenamic acid 500mg 3x/day; Pregabalin 150mg 2x/day; Aspirin 100mg p.r.n
14	Female	45	Left	Ambidextrous(Right) 4.35	3.8	8	Hand surgery	Targin 5mg 3/day; Endone 10mg p.r.n;	Valium 10mg p.r.n; Mefenamic Acid p.r.n; Paracetamol p.r.n
15	Female	73	Right	Right; 55.56	0.5	8	Arm injury	None reported	Paracetamol 665mg p.r.n
17	Female	52	Right	Right 89.47	0.4	3	Hand injury	None reported	Pamidronate disodium infusion; Panafcortelone 5mg;Gabapentin 300mg 3x/day; Oss max 70mg 1x/ week; Micardis 40mg 1x/day; Escitalopram 10mg 1x/day; Paracetamol p.r.n
18	Female	35	Right	Right 73.33	2.9	5	Hand fracture	None reported	None reported

19	Male	49	Right	Right 100.00	2.6	4	Wrist fracture and surgery	None reported	Hypertensive medication; Chinese herbal remedy
20	Female	47	Right	Right; 66.67	7.5	3	Shoulder injury	Endone 5mg p.r.n	Neurontin 900mg 3x/day; Allergron 45mg nocte, paracetamol p.r.n
23	Female	67	Left	Right; 73.91	0.4	4	Hand injury and infection	None reported	Endep 25mg 2x/day; Paracetomal 665mg 6x/day; Tristase 2.5mg 1x/day; Celbrex 200mg 1x/day; Lipitor 20mg 1x/day
24	Female	57	Right	RH 100.00	14.6	3	Arm injury	None reported	Symbicort ; Hormone based medication
25	Female	27	Right	Left; -66.67	1.9	7	Wrist fracture	Paracetamol with codeine phosphate	Sertaline; Voltaren 50mg 1x/week; Naprosen ; Mersyndol; Alprazolam
26	Female	48	Left	Right; 100.00	4.1	2	Hand surgery	Tramadol 200mg; Endone	Lyrica 150mg 2x/day; Lexipro 20mg 2x/day; Amitryptiline 200mg 2x/day; Paracetamol 500mg; Neurofen 200mg
28	Female	42	Left	Right;	14.8	5	Hand trauma injury	Fentanyl 12mcg/L	Maxalon 10mg p.r.n;

				100.00				patches; Durotram 200mg nocte; Endone 5mg p.r.n	Baclofen 25mg 3x/day; Gabapentin 300mg 3x/ day;
29	Female	29	Left	Left; -100.00	1.8	7	Hand injury	Tramadol p.r.n; Endone 5mg p.r.n; Norspan patch 5mg p.r.n.;	Versatis patches 5mg p.r.n
33	Male	21	Right	Right; 100.00	2.6	4	Wrist and Hand trauma injury with surgery	None reported	12 Cigarettes/ day; > 72 units of alcohol/week
41	Female	45	Right	Right; 64.71	18.3	9	Road traffic accident	Endep 50mg nocte; Endone 5mg p.r.n	Hydrotone 25mg 1x/day; Cipramil 20mg 3x/day; Calcitrol 0.25mg 2x/day

Note: Edinburgh Handedness Inventory HI +ve is Right Hand, -ve is Left Hand with the range from +100.00 to -100.00

Clinical characteristics of each CRPS participant are given in Table 2-1. The signs assessed at recruitment are shown in Table 2-2. Motor weakness was the most prevalent sign, followed by allodynia. Dystonia was the least prevalent sign found in this current study. In the CRPS-UK Registry, the most prevalent sign was reduced range of motion, followed by allodynia, and the least prevalent sign was also dystonia.

Table 2-2: The presence of signs in the CRPS study sample is compared to the CRPS-UK Registry.

Signs	CRPS n (%)	CRPS-UK Registry† n (%)
Sensory		
Allodynia	20 (95.2)	205 (86.5)
Vasomotor		
Temperature asymmetry	20 (95.2)	147 (61.8)
Skin colour asymmetry	20 (95.2)	160 (66.9)
Oedema	18 (85.7)	137 (58.5)
Sweating asymmetry	17 (81.0)	88 (37.3)
Motor		
Reduced ROM	18 (85.7)	208 (87.0)
Weakness	21 (100)	198 (83.2)
Tremor	18 (85.7)‡	67 (28.3)
Dystonia	11 (52.4)	60 (25.4)
Trophic	17 (81)^	
Hair changes		66 (28.1)
Nail changes		72 (30.4)
Skin changes		91 (38.2)

†Adapted from page 126, Table 4: Symptoms and signs at recruitment to the CRPS-UK Registry, n = 240 (Shenker et al., 2015). ‡Based on assessment of intention tremor. ^ Trophic changes of either hair, nail or skin changes were accepted as a sign in our study, n = 21.

2.2.1.1 Demographics and Hand dominance

Pain duration, age, gender, work history and hand dominance are reported in Table 2-3 and Table 2-5. Data from (Nicholas et al., 2008) and Shenker et al. (2015) are provided for comparison, where relevant.

2.2.1.2 Characteristics of our study sample compared to normative chronic pain data and to the CRPS-UK Registry

The mean age of CRPS participants were 44.9 ± 10 years. The gender composition were 18 females (85.7%) and 3 males (14.3%). This was similar to the CRPS-UK national Registry at 43 ± 12.7 years with 174 (72.5%) females and 66 males (27.5%). Mean pain duration for our study cohort, 25.4 months was similar to the 29 months from the Registry. Chronic upper limb pain participants attending a tertiary pain clinic had longer mean duration of symptoms than participants in the current study; mean pain duration for CRPS participants was 25.4 months compared to 41.1 months participants (Nicholas et al., 2008). The median pain intensity ratings for the one week period, 48-hour period and 24-hour period were six, six and five respectively.

Table 2-3: Demographics of study participants and other pain populations.

	CRPS (n=21)	Controls (n=21)	Chronic Pain*	Chronic UL Pain*	CRPS-UK Registry†
Pain duration (months)	25.4 ± 51	0	80.2 ± 111.2 n = 5285	41.1 ± 70.4 n = 513	29 [IQR 39.7] n = 237
Mean **age** (years)	44.9 ± 10	44.0 ± 11.2	47.3 ± 15.6 N = 2528	46.2 ± 15.4 n = 566	43 ± 12.7^ n = 239
Gender					
-Male	3 (14.3%)	3	NA	NA	66 (27.5%)
-Female	18 (85.7%)	18			174 (72.5%) n=240
Original Hand Dominance					
Right	19 (90.5%)	19			133 (83.1%)
Left	2 (9.5%)	2			27 (16.9%)
Employment (hours/week)					
Previous	32.5 ± 17.0	29.4 ± 14.2			
Current	14.9 ± 19.2	29.4 ± 14.2			

^ refers specifically to age at onset of symptoms rather than mean age at recruitment. Data from chronic pain and chronic upper limb pain were found in Nicholas et al. (2008). † Data from CRPS-UK Registry were found in Shenker et al. (2015)*

The results of the Edinburgh Handedness Questionnaire (Oldfield, 1971) revealed there were 19 original right handed and 2 original left handed CRPS participants. CRPS affecting dominant hands were 10 participants and those affecting non-dominant hands were 11 participants of a total of 21 participants with CRPS. Generally, most participants with CRPS had reduced working hours or were no longer able to work due to their condition, compared to their matched controls (Table 2-3).

There were more original right handed CRPS patients (85%) than original left handed CRPS patients (10%), and one CRPS patient (5%) had considered themselves ambidextrous (but was classified by the EHI as right handed). The Registry had a similar percentage of original right handed CRPS patients (83.1%) and had a larger percentage of patients who were originally left handed (16.9%). Our study cohort at recruitment had similar left handed CRPS participants at 9.5% than the expected prevalence seen in a large UK population-based (n = 255,000) internet survey study; which reported 12.8% prevalence of left-handedness for males and 10.6% for females (Peters et al., 2006). Subjective reported hand dominance of all participants in this study was shown in Table 2-4, with a classification of their unilateral upper limb affected by CRPS and their original hand dominance.

Table 2-4: Hand dominance based on subjective assessment of hand usage prior to CRPS diagnosis.

Hand Type	CRPS (%)	CRPS-UK Registry (%) †
Right hand dominant	17 (85%)	133 (83.1%)
Right hand affected	9	
Left hand affected	8	
Left hand dominant	2 (10%)	27 (16.9%)
Right hand affected	1	
Left hand affected	1	
Ambidextrous-(Right)	1 (5%)	
Left hand CRPS	1	
Total	20	160

Note: Handedness was defined by Edinburgh Handedness Questionnaire where left to right scores ranged from -100 to 100. For the Ambidextrous category, the CRPS subject scored 4.35 and their matched control scored 12.50. †Data from CRPS-UK Registry were found in the research article by Shenker et al. (2015) .

2.2.2 Psychological characteristics and upper limb disability

Table 2-5 provides a summary of our study sample and compares the results from psychological and disability questionnaires from normative chronic pain and chronic upper limb data. The CRPS participants in the current study had lower levels of self - efficacy, higher levels of stress, anxiety and depression compared to the controls. The current study's questionnaire results were comparable except for depression, which appeared to be lower to that found in the chronic pain and chronic upper limb study data (Nicholas et al., 2008).

CRPS participants had higher catastrophising scores than healthy controls. Mean and standard deviation for total PCS was 19.8 (10.0) in CRPS participants, which was at the 50th percentiles on the PCS raw scores and percentiles in the user manual guide provided by Sullivan (available from *sullivan-painresearch.mcgill.ca/pcs.php)*. Participants who score between the 50th and 75th percentiles on the PCS are considered at moderate risk for the development of chronicity of pain. CRPS participants in this study mainly had features of helplessness and rumination, compared to magnification.

Quick DASH mean and standard deviation scores in CRPS participants were 60.4 (19.9) compared to controls at 2.5 (3.8). The higher score by CRPS participants indicated CRPS participants had increased issues with disability in their upper limb. The patient wrist and hand evaluation questionnaire (PRWHE) total score (mean and standard deviation scores) was 70.7 (15.6) compared to controls at 1.4 (3.3). CRPS participants had high levels of pain and dysfunction as assessed by the PRWHE with a mean and standard deviation of 38.3 (6.9) and 32.4 (11.0).

Table 2-5: The comparison of the functional and psychological characteristics of the study sample.

	CRPS n=21	Controls n=21	Chronic Pain*	Chronic UL Pain*
Self-Efficacy(PSEQ)	28.4 (13.6)	59.4 (1.2)	25.5 (13.8) n= 4645	26.1 (14.0) n=418
DASS-Stress	14.5 (8.7)	4.5 (3.6)	16.3 (11.2) n=2440	16.1 (11.1) n=192
DASS-Anxiety	9.9 (7.8)	0.8 (1.8)	9.3 (8.7) n=2421	8.7 (8.4) n=192
DASS-Depression	8.4 (8.7)	1.3 (2.2)	14.3 (11.9) n=2445	13.8 (11.7) n=192
Catastrophising(PCS)	19.8 (10.0)	3.6 (4.0)	NA	NA
PCS-Rumination	7.4 (3.9)	1.4 (1.8)		
PCS-Magnification	3.4 (2.4)	0.6 (0.8)		
PCS-Helplessness	9.0 (5.0)	1.6 (1.9)		
quick DASH	60.4 (19.9)	2.5 (3.8)	NA	NA
PRWHE-Total	70.7 (15.6)	1.4 (3.3)	NA	NA
PRWHE-Pain	38.3 (6.9)	1.3 (3.0)		
PRWHE-Function	32.4 (11.0)	0.1 (0.5)		

PSEQ= Pain Self Efficacy Questionnaire; PCS= Pain Catastrophising Questionnaire; Quick DASH=Disability Arm Shoulder Hand Questionnaire, DASS= Depression, Anxiety and Stress Scale; PRWHE=Patient-Rated Wrist and Hand Evaluation. Data from chronic pain and chronic upper limb pain were found in Nicholas et al. (2008)*

2.3 Discussion and Conclusion

The current study sample had a larger percentage of original right handed than left handed participants similar to the CRPS-UK Registry which included patients with CRPS of any limb. However, the Registry had more CRPS patients who were left handed compared to the number of left handers in a typical Western industrialised population (Peters et al., 2006, McManus, 2009). In contrast, the proportion of right and left-handers in our study compared well to a typical population (Peters et al., 2006, McManus, 2009).

The demographic data for age, gender and pain duration from the current study shared more characteristics with the Registry compared to the chronic upper limb data (Nicholas et al., 2008). The CRPS study sample displayed similar psychological characteristics as those in the chronic pain data. The current study participants with CRPS reported more depressive symptoms than controls but less depressive symptoms than those with chronic pain. However, no data for psychological variables were available to compare from the Registry sample.

The study sample seemed to report more symptoms and signs of CRPS compared to the Registry sample. This was unsurprising as the Registry includes CRPS participants who fulfilled the less strict clinical Budapest criteria (see Table 1-2). Additionally this CRPS sample was homogenous due to the strict research inclusion criteria of including only unilateral upper limb CRPS versus the heterogeneity of the Registry which included multi-limb involvement of CRPS.

In summary, the current study suggests that the characteristics of the CRPS participants reflect the average patient with upper limb CRPS pain and reported hand dominance similar to that expected in a general adult population. Further, the CRPS sample reported similar characteristics to the CRPS-UK Registry compared to that found in the study by Nicholas et al. (2008).

3 The development of a highly efficient and optimised tactile stimulus suitable for Complex Regional Pain Syndrome (CRPS) using phase encoded functional magnetic resonance imaging

3.1 Introduction

3.1.1 Background to technique application in CRPS

Complex regional pain syndrome (CRPS) is a debilitating chronic pain condition with poorly understood multi-factorial pathophysiology that frequently affects the upper limb and hand. CRPS was one of the earliest chronic pain conditions to be investigated with neuroimaging (Maihöfner et al., 2003, Flor, 2003), allowing insights to the role of the cortex in its pathophysiology. Maihöfner et al. (2003) reported that the cortical representation of the affected hand was smaller in the primary somatosensory cortex (S1), which reversed (in the same patients in their follow-up study) after CRPS symptoms abated (Maihöfner et al., 2004). A systematic review on the function of S1 in CRPS by Di Pietro et al. (2013b) supported the observation of a maladaptive cortical representation of the affected hand in S1, but cautioned that the risk of biases were high across studies assessed; mainly from unclear sampling methods, methodological issues in analysis and inconsistent application of diagnostic criteria for CRPS.

The observation that CRPS is associated with a maladaptive cortical representation, including a smaller S1 representation of the affected hand (Di Pietro et al., 2013b) and changes to the primary motor cortex (M1) has not been replicated in recent studies (Di Pietro et al., 2013a). For example, Di Pietro et al. (2015) argued that CRPS seems to be associated with an enlarged representation of the healthy hand, not a smaller representation of the affected hand. Although the hand representation in S1 had a smaller Euclidian distance (from thumb to little finger) for the affected CRPS hand than for the healthy hand, the same measure was larger in the healthy hand in CRPS compared to both healthy hands in controls. Similarly, the MRI study by van Velzen et al. (2016) failed to replicate structural brain changes of increased grey matter density in the prefrontal and motor cortex using voxel based morphometry in CRPS previously reported by Pleger et al. (2014). For further details, please see the section on Neuroimaging and CRPS in Chapter 1.

More robust imaging in CRPS would progress the understanding of how central mechanisms contribute to the maintenance or pathophysiology of CRPS (Handwerker, 2007). One approach to address inconsistencies in the neuroimaging CRPS literature is to improve the acquisition and processing parameters of the fMRI neuroimaging data (Bennett and Miller, 2010). Further, Weibull et al. (2008) suggested that an optimal tactile stimulus, together with high spatial

resolution data acquisition in fMRI and less, smarter or no smoothing during analysis should be used in future studies of brain plasticity changes following hand and finger disorders such as CRPS.

Research has shown that high-resolution fMRI has characteristically higher efficiency than low resolution fMRI. While the potential for increased precision and discrimination through higher resolution fMRI is obvious, it has to be acknowledged that these more challenging techniques may result in a loss of statistical power (Petersson et al., 1999). Techniques suggested to countenance this possibility include cluster-level thresholding (Glasser et al., 2016, Dubois and Adolphs, 2016), a stricter thresholding cut-off to avoid spurious activations (Thirion et al., 2007) or to confine the analysis to the known anatomy (Moore et al., 2000, Mancini et al., 2012, Pfannmöller et al., 2016). While the reduced voxel volume of smaller voxels or the absence of smoothing suggests a significant signal decrease, it has been demonstrated that this MRI signal (SNR, signal to noise) decrease does not simply translate to less statistical power (Hagler et al., 2006, Bennett and Miller, 2010). This is because smaller voxels more precisely sample the source of BOLD changes fMRI relies on (CNR, contrast to noise), while sampling less surrounding inactive tissue (Triantafyllou et al., 2006, Triantafyllou et al., 2011, Preibisch et al., 2003). This increases the differentiation between functional localisation in the grey matter versus white matter. The specific costs and benefits of resolution frequently depend on the task and the anatomy of the investigated brain region. Consequently, it is important to test the specific experimental paradigm and scanning protocol to conclude if it yields sufficient CNR (Bennett and Miller, 2010).

The current study aimed to develop a novel phase encoded fMRI design, which can increase temporal and spatial resolution, to investigate the cortical representation of the hand in S1 in patients with CRPS. For further details about phase encoded fMRI and the basics of the BOLD response, please see the Appendix for Chapter 3.

3.1.2 Finger somatotopy and optimising stimulus parameters in the primary somatosensory cortex

Finger mapping in S1 in healthy participants have made recent improvements partly due to the rise in automated tactile stimulus devices (Graham et al., 2001) and advanced imaging parameters with an increased magnetic field strength (Kurth et al., 1998, Gelnar et al., 1998, Overduin and Servos, 2004, van Westen et al., 2004, Nelson and Chen, 2008, Sanchez-Panchuelo et al., 2014, Schweisfurth et al., 2014). Results of these studies suggest that the somatotopic distribution of all digits (or fingers) of the hand are ordered, whereby the thumb is

represented most lateral, anterior, and inferior and the fifth finger is most medial, posterior, and superior (van Westen et al., 2004, Nelson and Chen, 2008).

Successful finger mapping (Graham et al., 2001, Ingeholm et al., 2006) is heavily influenced by the delivery and type of tactile stimulus (Francis et al., 2000, Krause et al., 2001). Mechanised devices, including those that deliver air puffs, electrical or vibrotactile mechanical stimuli, have been used for fMRI studies (Ingeholm et al., 2006). However, the advantages of consistent and precise mechanised stimulus devices may not generalise to CRPS patients. First, the skin physiology of CRPS patients is different compared to healthy controls due to varying levels of pain, sweating and oedema (Veldman et al., 1993, Juottonen et al., 2002, Marinus et al., 2011). These skin changes are often accompanied by fixed dystonic hand postures in CRPS (Munts et al., 2011, van Rijn et al., 2007, Schrag et al., 2004, Schott, 2007b). Second, automatic devices are unable to adapt to dystonic hand postures, changes in skin thickness or changes in force required in CRPS patients which is necessary to maintain the appropriate level of tactile stimulation throughout the experiment. These may have consequences for the final BOLD signal. Hence while a researcher providing manual stimulation including brushing with a plastic brush (Gustin et al., 2012) is less consistent than a mechanical device, the human ability to adapt manual brushing to the variable skin texture and hand posture of each CRPS participant may be more important. Therefore, manual tactile stimuli and delivery might confer an advantage in fMRI studies where participants have highly variable skin physiology such as those with CRPS.

Van der Zwaag and colleagues (2015) compared activations elicited by both mechanical stimulation and manual brushing and found them highly co-localised within BA 3b and 1 of S1. However, a higher BOLD signal intensity (with less habituation) was observed throughout the entire post-central sulcus in S1 induced by manual brushing made it a consistently more powerful stimulus (van der Zwaag et al., 2015) even in healthy participants. The explanations proposed for these differences include that manual brushing responses were more salient to motion and perception compared to vibro-tactile mechanical stimulations. The latter were likely to limit recruitment to smaller subpopulations of somatosensory neurons. Therefore, it has been proposed that stimulus paradigms that mimic natural experiences like manual brushing are best suited for fMRI experiments in the primary cortices (Malinen et al., 2007, Martuzzi et al., 2014).

Somatotopic finger maps can be influenced by the pattern, frequency, intensity of finger stimulation because of how the brain processes the tactile information and the varying density of tactile receptors (Krause et al., 2001, Hlushchuk et al., 2015). Pattern consistency in finger

stimulation is required for anatomical consistency in functional finger brain mapping. Anatomical inconsistency in the finger map can occur with a phase reversal order effect, as reported by Overduin and Servos (2004) in their phase-encoded fMRI experiments on somatotopic mapping of the fingers in BA 3b and 1 in S1. In this controlled experiment, an ordered finger map was produced by a proximal to distal stimulus delivered to the volar aspect of each fingertip. This map was compared, with all other fMRI parameters held constant, to the opposite distal-to-proximal stimulus stimulation direction. Each phase colour and digit identity was reversed compared to the controlled finger map because the direction of stimulation had caused different phase values to be associated with the same finger location. These results have consequences in neuroimaging experimental design for pathological pain; there might be a risk of falsely concluding disordered finger maps are due to the studied pathology without careful control of the chosen tactile stimulation.

The outcome of finger somatotopy can be influenced by how the stimulus is delivered. Functional imaging studies on the primary (Kurth et al., 1998) and secondary somatosensory cortices (Ruben et al., 2001) used alternate single finger stimulations to demonstrate a consistent somatotopic organization of the somatosensory hand area including: i) visualising the distinct cortical representations of single fingers within S1; ii) its representations in the different cytoarchitectural subdivisions of S1; iii) and their sequential medial-to-lateral arrangement from the fifth finger to the thumb. Dechent and Frahm (2003) used the pattern of simultaneous stimulation of finger tapping in two different fingers. They claimed that this revealed more segregated and somatotopically ordered activations of the fingers in M1. However, Ruben et al. (2006) demonstrated a reduction in BOLD responses in the finger areas of S1, when comparing simultaneous electrical stimulation applied to the second and third finger of the right hand to single finger stimulation. The authors argued their results found suppressive interaction effects in the brain during simultaneous versus single finger stimulations. Thus, much remains unknown about the potential of simultaneous stimulation of the fingers to refine finger somatotopy in S1.

The repetitious nature of a stimulus can lead to adaptation of the cortical fMRI responses-affecting the BOLD contrast for mapping and in the long term, structural neuroplasticity changes. Frequent repetition of the same stimulus paradigm, seen during experiments in children (Qin et al., 2004) and adults (Driemeyer et al., 2008, Tomasi et al., 2004, Qin et al., 2003), have demonstrated these effects. However, repetitive stimulation alone is unlikely to generate an observed decrease in stimulus (adaptation) response (Ruben et al., 2006) if adequate care is taken to prevent anticipation of the stimulus sequence by the participant. Therefore,

habituation and adaptation of cortical signals to the chosen stimulus should also be considered in the design of fMRI studies.

A further influence on finger mapping responses is how attention is biased during a stimulus. Attention of the participant during the tactile stimulus influenced the level of receptor responses measured with positron emission tomography (Drevets et al., 1995) and fMRI in S1 (Arthurs et al., 2004, Ackerley et al., 2012). Drevets et al. (1995) first investigated blood flow changes using positron emission tomography (Siemens /CTI 953B/ 31 tomography with septa inserted, 40-60 mCi of $H_2(15)O$ and a 40 second scan) in the human somatosensory cortex during anticipated stimulation. They stimulated the skin of the toes, fingers and face and found that actual and anticipated stimulation produced similar blood flow patterns in all areas of the somatosensory cortex. Conversely, distraction during tactile stimulus produced a reduction in the BOLD response in S1 (Arthurs et al., 2004). Ackerley et al. (2012) demonstrated attentional drive differences between the two types of touch stimulus - active and passive touch - also influenced the BOLD responses in S1. Active self-tactile stimuli had consistent positive BOLD activation of the contralateral S1 hemisphere. Passive touch activated this same response but also activated a negative BOLD signal in the ipsilateral S1 area. Together, these findings highlight the importance to minimise distractions and have consistent instructions to participants for tactile stimulation to reduce their effects on the BOLD signal in fMRI experimentation.

Apart from the factors described above, challenging logistics issues arise when using phase-encoded fMRI in the investigation of patients, particularly pathological pain conditions such as CRPS. The magnetic resonance (MR) environment is inherently noisy, claustrophobic and confined for many patients with pathological pain, including CRPS. Therefore, careful consideration of these factors, an appropriate stimulus and optimising the acquisition parameters (Bennett and Miller, 2010, Howseman and Bowtell, 1999) to minimise the scanning time are required for the successful acquisition of images in the chosen MR modality without causing unnecessary distress to CRPS patients.

3.2 Motivation and outline of this chapter

Recent research has provided inconsistent results for the representation of the hand in S1 for patients with CRPS. Advanced fMRI neuroimaging techniques might improve the accuracy of the finger or hand maps. The aim of this pilot study was to develop the parameters required for the highest feasible spatial resolution of fingertip maps within the S1 within the constraints for imaging CRPS patients.

Key considerations from the literature reviewed on tactile stimulus and neuroimaging research on healthy participants assisted in the development of a suitable method. The key features are: i) increasing the saliency of the stimulus by the use of manual brushing and familiar materials to human touch; ii) consistency in direction and delivery frequency of stimulus; iii) minimisation of distractions to the participant but not to the extent that an inadequate amount of attention is paid to the actual finger brushing stimulus. Stimulus time at the start of the EPI protocol (Appendix for Chapter 3:Table 9-1) should also account for the natural delay in haemodynamic response function rise from its baseline post stimulus (Bandettini et al., 1993, Boynton et al., 1996, Handwerker et al., 2012).

Patients with CRPS change posture or position to get comfortable in a scanner to a greater extent than healthy controls (Schasfoort et al., 2003, Schasfoort et al., 2006). Therefore, a balance of scanning parameters for high spatial resolution data acquisition was guided by the general tolerance of being in the scanner. The chosen scanning parameters included a short repetition time of 2 seconds, field of view (FOV) confinement to S1 area, matrix sizes and slice thickness. The precedent for this method and voxel size chosen are found in the phase encoded fMRI work in the somatosensory cortex (Mancini et al., 2012, Kolasinski et al., 2016a, Kolasinski et al., 2016b).

This first experiment in this pilot study aimed to develop an efficient, robust tactile stimulus technique to provide a strong and consistent BOLD signal for improved differentiation of finger somatotopy. A manual tactile stimulus using a plastic brush was piloted. This study protocoled quality control procedures including the requirement that the tactile stimulus was brushed in the correct anatomical order; consistent instructions were given to the participant to be aware of the tactile stimulus but remain relaxed within the MR environment and improving lying tolerance by allowing minimal movements. The second experiment aimed to concurrently minimise patient burden in the MR environment, while acquiring the highest possible spatial resolution fingertip maps within S1 feasible within these constraints. This study aimed to optimise the protocols further by comparing the single finger stimulus to the bilateral finger stimulus which the literature suggests might refine the BOLD contrast. Any time savings would provide scope for further improvements to the final spatial resolution acquisition parameters. The specific aims, methods and results of each preliminary experiment are described separately, followed by a discussion and conclusion of both experiments together.

3.3 First experiment

3.3.1 Aim

The main aim was to test the performance of a manual tactile paradigm using phase-encoded functional magnetic resonance imaging that would result in activations of the four fingers in the primary somatosensory cortex. During the first pilot a finger tapping paradigm was tested, but it was not used later and hence will not be reported further here.

3.3.2 Methods:

Participant: A healthy 47 year old male participated in a single scanning session of 90 minutes, where this experiment accounted for about half the time.

Task specification: The participant was asked to be awake, relaxed but aware during the tactile stimulus. The participant viewed a 19-inch liquid crystal display (LCD) screen via a mirror mounted on the head coil at a viewing distance of 1.5 m during the structural scan (a short cartoon clip as a distractor) and no screen during the tactile paradigm.

Design: A phase encoded functional MRI design was used for increased temporal and spatial resolution (Engel, 2012), and based the tactile stimulus on visual mapping techniques from previous work (Schira et al., 2009).

Each finger brushing cycle consisted of brushing sequentially each fingertip from: D2; D2 and D3; D3 and D4; D4 and D5 - of the left hand for 3 seconds each time (leading to a 6 second stimulation for each digit), a break of 5 seconds to allow the researcher to swap to the other side of the participant, followed by brushing each fingertip on the right hand (again, D2; D2 and D3; D3 and D4; D4 and D5), another 5 second break to swap sides. This was repeated for 5 cycles per run. Two plastic brushes used as the stimulus, were attached at one end with a bolt to allow each brush to operate like an adjustable calliper. A single researcher was cued to brush at 2Hz with a visual and audio metronome cued through Presentation program-version 17 (Neurobehavioral Systems, Inc.; California, USA, https://www.neurobs.com). The brushing pressure applied was as firm as possible on the end of the fingertips with the plastic calliper tool.

Anatomical scan collection and processing were based on procedures used and tested in previous work (Schira et al., 2009, Isherwood et al., 2016). The somatosensory cortex, posterior to the central sulcus, was the specific brain area of interest for the tactile brushing paradigm. To achieve high resolution and speed and to minimise distortions, a SENSE (Weiger et al., 2005,

Pruessmann et al., 1999) accelerated echoplanar imaging (EPI) sequence was used for functional data.

3.3.2.1 Data acquisition

For the tactile paradigm, all MRI data were acquired using a 3T Phillips (Achieva TX) scanner with a SENSE 32 channel RX head coil and an eight-channel multi-transmit body coil.

3.3.2.2 Structural imaging

Whole brain T1- weighted anatomical scans were acquired with 250 sagittal slices at 0.727 mm x 0.727 mm x 0.75 mm voxel size, with an MP-RAGE sequence (Mugler and Brookeman, 1991) for anatomical registration. Scan resolution was with a 352 x 352 matrix. T1 acquisition took 316 s and EPI factor was 1. Field of view was 256 x 256 x 187.5 mm with a flip angle of 8°.

3.3.2.3 Functional imaging

Whole brain EPI (functional) images were acquired in 43 transverse slices at voxel size of 2 x 2 mm^2 in plane with 2.5 mm slice thickness. Scan resolution was with a 96 x 96 matrix (ascending acquisition). EPI factor of 23. The field of view (ap, fh, rl) was 192 x 107.5 x 192 mm. Flip angle was 82 °. Volume repetition time was 2000 ms. There were 150 volumes per run resulting in a total time of 306 s (including 6 s of dummy scans).

3.3.2.4 Optimisation

All four tactile runs with 5 cycles per run were used to determine the somatotopic arrangement of each finger in the primary sensory cortex.

3.3.2.5 Data analysis

Functional data were motion corrected with a rigid body transform with 6 degrees of freedom using SPM8 and slice scan-time corrected using SPM8 (SPM software package; http://www.fil.ion.ucl.ac.uk/spm), then imported into the mrVista-Toolbox (Stanford University, Stanford, CA; http://white.stanford.edu/software/) for further processing and traveling-wave analysis. No spatial smoothing was applied during the analysis. The cyclic mapping data was analysed using a Fast Fourier Transform (FFT) based correlational analysis.

This estimates a coherency value for each voxel in the cortex as a ratio between power at stimulus frequency and noise.

Functional EPI data was directly aligned to the anatomical T1 images. This is possible as high resolution EPI data provides significant structural information and results in reliable alignment with superior precision than afforded by through the use of an inplane T1 localiser scan typically employed in low resolution fMRI designs, (Schira et al. 2009). It also renders such T1 localiser scans unnecessary. Specifically, the mean EPI image of the motion corrected EPI data was aligned through a 6 degree of freedom, affine projection, through the use of rxAlign tool of the mrVISTA package with manual blink comparison for quality control (Sereno and Huang, 2006, Mancini et al., 2012, Kolasinski et al., 2016).

The somatotopic location of each voxel is determined by the phase value at the stimulus frequency (Engel et al., 1994, Engel, 2012, Isherwood et al., 2016). Each phase (which represents each fingertip somatotopic location) can be denoted by a colour, using a colour map. The hue denotes the phase and the saturation denotes the strength of the stimulus response. A mixture of components denoting the somatotopic location of fingers physically far apart such as D2 and D5 are implausible and would not be adequately modelled by a phase encoded experimental design. . Mixtures between neighbouring fingers such as D2 and D3 however are very possibly well modelled through a phase encoded analysis and are displayed using intermediate colours.

These phase encoded fMRI maps were then overlaid onto the 3D-meshes of the brain surface, as in Figure 3-1. These 3D-meshes were generated by the segmentation of each participant's structural data using mrMesh, from the mrVista-toolbox.

3.3.3 Results of first experiment

The tactile paradigm was found to be an effective, efficient, robust technique that provided stronger and more consistent BOLD signals via the phase mapping technique for improved differentiation of the fingertip somatotopy. This is comparable to studies (Kurth et al., 1998, Francis et al., 2000, McGlone et al., 2002) that have attempted somatotopic finger mapping in S1 using fMRI only (Appendix for Chapter, Section 9.1). The averages of all four runs produced activations at expected locations in the post central gyrus in S1 with some spreading into the precentral gyrus (motor cortex). Some emergence of individual finger mapping could be observed (Figure 3-1). This was despite somatotopic locations from the individual fingers that overlapped.

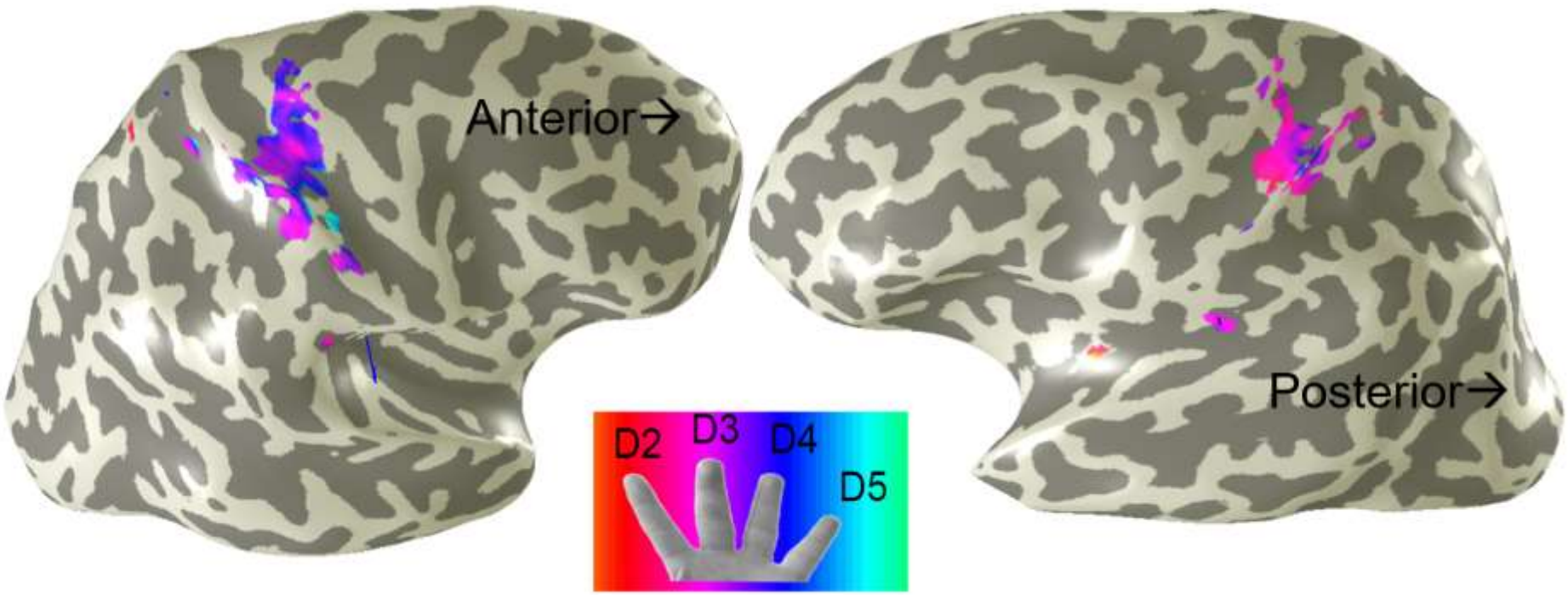


Figure 3-1: Overlapping and individual fingertip somatotopy observed in the primary somatosensory cortex.

Exemplars from the tactile paradigm (simultaneous stimulation of the adjacent fingertips in left hand only is shown) using phase encoded fMRI data are visualised over smoothed brain surface. The right hemisphere is shown on the left and the left hemisphere on the right side of the figure. Sulci and gyri are depicted on the smoothed brain surface in dark grey and light grey respectively. Maps were thresholded at corr > 0.40. The colour bars for each phase location of individual fingers are shown.

This first experiment provided practical experience of the tactile paradigm and identified feasibility issues with the fMRI protocol. The plastic brush calliper was an effective tool for producing adequate tactile stimulation for simultaneous brushing of the digits. The angle of the calliper required some adjustment to ensure each fingertip set had adequate contact with the brush. This was feasible with the healthy participant who had a normal hand posture, but may not be feasible for CRPS patients with hand-related dystonia (which is a reported symptom in CRPS, please see Chapter 2).

Quality control procedures within the protocol were successfully trialled. This included consistent instructions to the participant to be aware of the tactile stimulus but remain relaxed within the MR environment and improving lying tolerance by allowing minimal movements in the breaks. The visual and auditory cues from Presentation assisted the 2 Hz brushing speed and the correct order of fingertips of each digit to be brushed.

3.4 Second experiment

3.4.1 Aim

The overall aim of the second experiment was to further optimise the fingertip tactile brushing paradigm. The feasibility of the required minimum parameters for working with CRPS patients was tested so that time in the scanner was limited. Two paradigms were compared. Firstly, a single finger paradigm (similar to the first experiment) and secondly, a bilateral finger paradigm. After determining which paradigm was more effective for producing fine-grained fingertip mapping, the reliability was estimated through a repeated measurement analysis using bootstrapping.

3.4.2 Methods

Participant: A 20 year old, healthy, right-handed male took part in the two hour fMRI session.

Design: The paradigm was based on visual field mapping techniques. Based on the experience from the first experiment, two well-practised researchers applied the manual tactile stimulation. Each researcher was only responsible for one hand during a run, swapping hands between runs. The start position of each researcher was randomised prior to the first run. Two paradigms were trialled: Single Finger Paradigm (SFP) and Bilateral Finger Paradigm (BFP). The paradigms used tactile, non-noxious stimulation with a plastic brush. The use of the adjustable calliper plastic brush was ceased and no overlapping stimulus to adjacent fingertips

was performed. This was because the technique with the calliper brush was deemed unfeasible for patients with CRPS after the first experiment.

Each paradigm consisted of a tactile stimulus delivered to the respective fingertip of each hand on: the index finger (D2), middle finger (D3), ring finger (D4) or little finger (D5). Specifically, the direction of the brushing was applied proximal to distal to the volar aspect of the fingertips. The brushing aspect of the tactile stimulus was refined to just perceivable manual pressure that would create adequate skin indentation. This would then bring capillary blood flow back to skin after the pressure was released and prevent adaptation effects to the stimulus as suggested in previous research (Chung et al., 2014, Chung et al., 2015).

3.4.2.1 Single Finger Paradigm (SFP)

During the single finger paradigm, each fingertip was brushed for 6 seconds sequentially from D2 to D5 for the left hand (24 seconds for all four digits), followed by brushing in the same pattern for the right hand. Therefore it took 48 seconds to complete a single 'cycle' for both hands. After completing a cycle with brushing D5 of the right hand, the experiment continued with repeating the cycle with brushing D2 of the left hand and so forth. The researcher was cued to brush at 2Hz with a visual and audio metronome (cued through the Presentation program). Each run consisted of seven cycles of the single finger brushing paradigm with a total of 6 minutes and 36 seconds (or a total duration of 7 times 48 seconds).

3.4.2.2 Bilateral Finger Paradigm (BFP)

In the BFP, each respective fingertip on both hands was brushed simultaneously. The sequential pattern of brushing was from D2 to D5 on both hands simultaneously and each fingertip brushing lasted 6 seconds (hence approx. 12 strokes over the 6 seconds). This resulted in 24 seconds of stimulation over the four digits on both hands simultaneously, followed by a 6 second rest period where no digit was brushed; resulting in a completed 12 cycles per run within 6 minutes of the BFP. Identical to the SFP brushing at 2Hz, cues for brushing were controlled with a visual and audio metronome (fed through the Presentation program). Detailed layouts of the exact timings of the BFP are in Table 9-1 (in Appendix for Chapter 3).

Figure 3-5 illustrates the phase encoding task digit order and compares the increased density of the Bilateral Finger Paradigm (BFP) to the Single Finger Paradigm (SFP). *Anatomical scan collection and processing, and task specification* were performed as in the first experiment.

3.4.2.3 Data acquisition

Data acquisition were performed as in the first experiment and the acquisition parameters are described below.

3.4.2.4 Structural imaging

Whole brain T1-weighted anatomical scans were acquired with 250 sagittal slices at 0.75 mm x 0.727 mm x 0.727 mm voxel size, with an MP-RAGE sequence (Mugler and Brookeman, 1991) for anatomical registration. Scan resolution was with a 352 x 352 x 120 matrix. T1 acquisition took 390 s. Field of view was 256 x 256 x 187.5 mm with a flip angle of 8 °.

3.4.2.5 Functional imaging

EPI images covered the whole brain. Functional data were acquired in 43 transverse slices with 2.5 mm slice thickness, voxel size of 2 x 2 mm^2 in plane, with a 96 x 96 matrix (ascending acquisition). The field of view (ap, fh, rl) was 192 x 192 x 107.5 mm. Flip angle was 82°. The SENSE factor was three. TR was 2000 ms. Echo time was 25 ms. Both paradigms were repeated for seven runs each.

3.4.2.6 Data analysis

To estimate the quantity of data required to reliably produce finger maps, a simple boot strapping approach was used. Bootstrapping is a form of data resampling, where random subsamples are accessed as the underlying distribution is unknown and cannot be assumed to be normally distributed (Efron, 1979, Cheng and Yeager, 2007, Bland and Altman, 2015).

Firstly, all seven runs of each paradigm were averaged and analysed (see Results of second experiment for more details). Given the high number of repetitions afforded through seven repeated runs (with seven cycles per run for the SFP or 12 cycles per run for the BFP respectively) these grand averaged data provided excellent finger mappings from both paradigms BFP and SFP. This was achieved through the amalgamation of all seven runs providing the gold standard. However, a suitable numeric metric for quality measurement is problematic. Human pattern judgment is still the gold standard and used (Moore et al., 2000, Pfannmöller et al., 2016, Mancini et al., 2012).

As good agreement had been determined between the paradigms, and the BFP was deemed superior (Please see Results of second experiment and Discussion for justification). While some

runs were of good quality and the average of two runs or even the results from a single run resulted in fine grained fingertip maps, other runs provided less clear fingertip maps. Hence, it was deemed necessary to estimate how many runs would reliably result in sufficiently fine grained fingertip maps.

A simple boot-strapping approach was used for this reliability analysis. Ten sets of two, three and four runs of the seven runs were generated from random permutations (using Matlab R2014b, 64-bit V8.4.0.150421). Second, each of these random subsets, were then averaged and analysed using the FFT based correlation analysis. Fingertip maps for each hemisphere were generated for each averaged set, the threshold was set at 0.35 and visualised on a 3-D rendering of the inflated brain surface (using mrMesh). Last, the quality of the activations and delineation of each averaged set's fingertip maps were visually evaluated, compared to the 'gold standard' generated from the grand average, and rated as 'poor', 'moderate' or 'good'. Specifically, if there were no clear fingertip maps, it was rated poor. Clear delineations of fingertip maps were rated as good. Fingertip maps were rated moderate if reasonable fingertip maps could be delineated, but required a lower threshold or the data displayed spurious activations that were deemed unrelated to the BFP finger mapping. Figure 3-6 illustrates exemplars of poor, moderate and good maps.

3.4.3 Results of second experiment

Each paradigm with seven full runs (grand average) was successfully completed. The fingertip maps were confined to the posterior bank of the central sulcus (post central gyrus) and had a sequential and orderly inferolateral-to-superomedial somatotopic arrangement of D2 to D5 illustrated by the grand average results from the seven runs of BFP in Figure 3-2. The grand averages of each paradigm provided fine-grained polar angle mapping of the 4 digits, illustrated by Figure 3-3 (SFP) and Figure 3-4 (BFP). The SFP was compared with different levels of statistical thresholds on each highlighted section of the brain surface over the primary sensory cortex in Figure 3-3 and the same procedure applied to the results of the BFP, illustrated in Figure 3-4. These different statistical thresholds were used to illustrate the different levels of statistical reliability demonstrated by the two paradigms. The results were of similar quality and in agreement with each other. However, the BFP was found to be more time efficient, as discussed later. Further, it was found that the dominant hand had larger overlaps in the activation clusters compared to the non-dominant hand, specifically larger significant activations were found beyond the primary S1 cluster in SFP compared to BFP finger maps.

The BFP allowed a substantial improvement in data collection in a very similar amount of scanning time to the SFP (Figure 3-5). The BFP collected more cycles (hence simultaneous repetitions) with almost the same amount of time as SFP (As mentioned previously BFP: 12 cycles per run of 180 volumes compared to SFP: 7 cycles per run of 168 volumes). This time for the SFP would be substantially increased if collecting the same amount of data found in the BFP. The reduced scan time for the BFP was considered superior than the SFP when scanning CRPS participants for reasons previously mentioned (in the Introduction).

The simple boot-strapping approach was used to determine the number of repetitions required for reliable mapping of S1 with BFP. It was found that three runs should result in acceptable finger mappings while four runs demonstrated reliable results. Specifically, using two run scan averages resulted in: 10/20 hemisphere with poor ratings for fingertip maps, 8/20 with moderate ratings and 2/20 with good ratings. Using three runs scan averages resulted in: 4/20 poor ratings, 6/20 moderate ratings and 10/20 good ratings. Using four runs scan averages resulted in: 1/20 poor rating, 3/20 moderate ratings and 16/20 good ratings. The details of scan averages used for the boot-strapping optimisation procedure is shown in Table 3-1 .Two exemplars of BFP fingertip maps for each rating are shown in Figure 3-6.

Key: D2= Index finger, D3= Middle finger, D4= Ring finger and D5 = Little finger

Figure 3-2: 3D - brain surface map of the right hemisphere showing the location of the central sulcus, and the fMRI maps in native subject space resulting from the BFP.

The semi-flattened view of sulci (dark grey) and gyri (light grey) with clear ordered separation of each fingertip somatotopy corresponding to each colour (derived from the colour bar for each phase location) on the post central gyrus of the left hand, is shown in the highlighted section. This figure illustrates an optimal finger mapping result obtained from the average of all 7 BFP runs; thresholded at corr > 0.40.

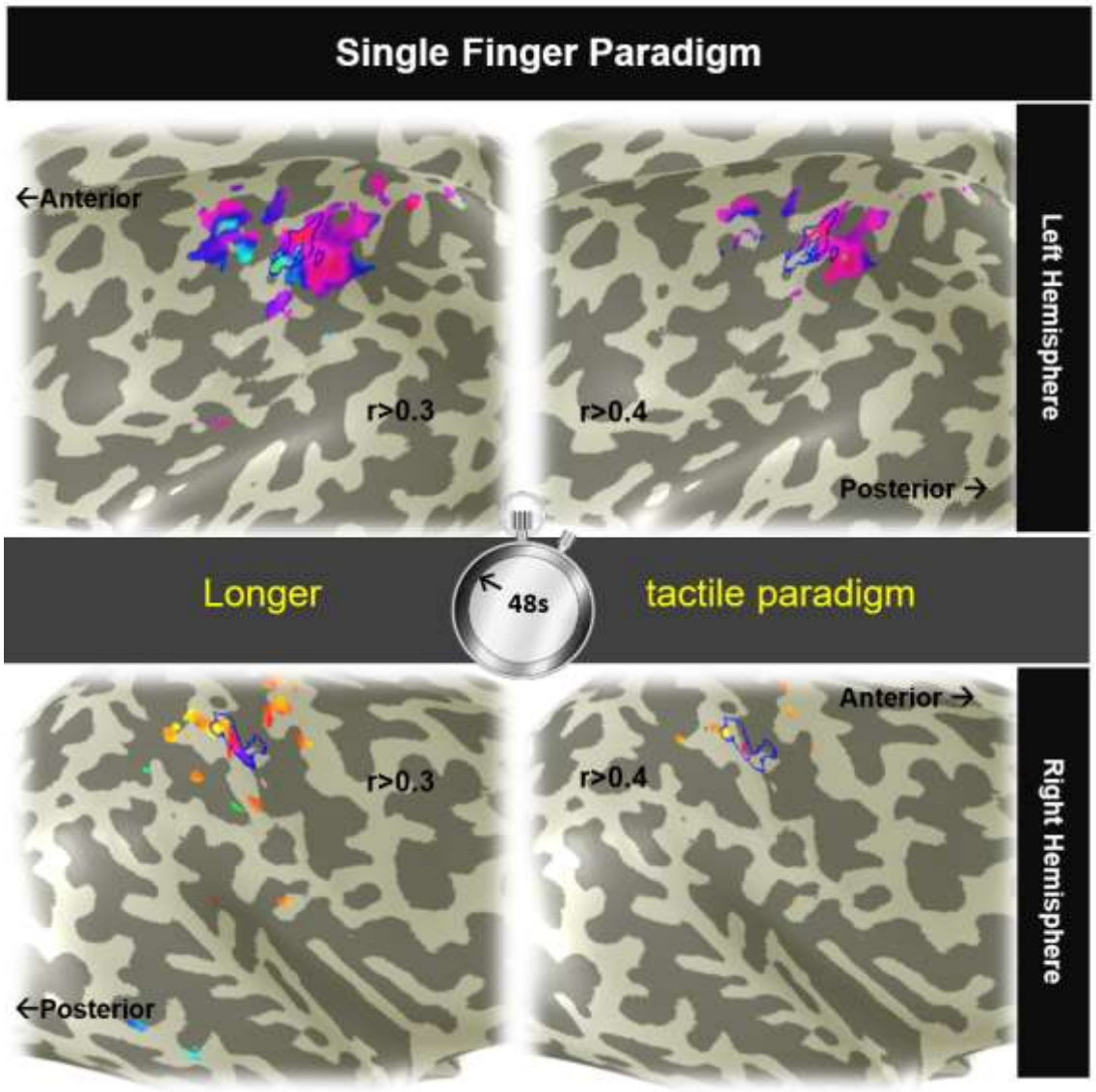


Figure 3-3: Highlighted brain section of fingertip mapping for four digits in native subject space on the corresponding contralateral hemisphere using the single finger tactile paradigm.

For images on the left of the figure, n= 1176, $r \geq 0.30$, $p < 10^{-5}$ and for images on the right $r \geq 0.40$, $p < 10^{-5}$. The regions marked in blue outline correspond to the location of activity found for the BFP demonstrated in Figure 3-2.

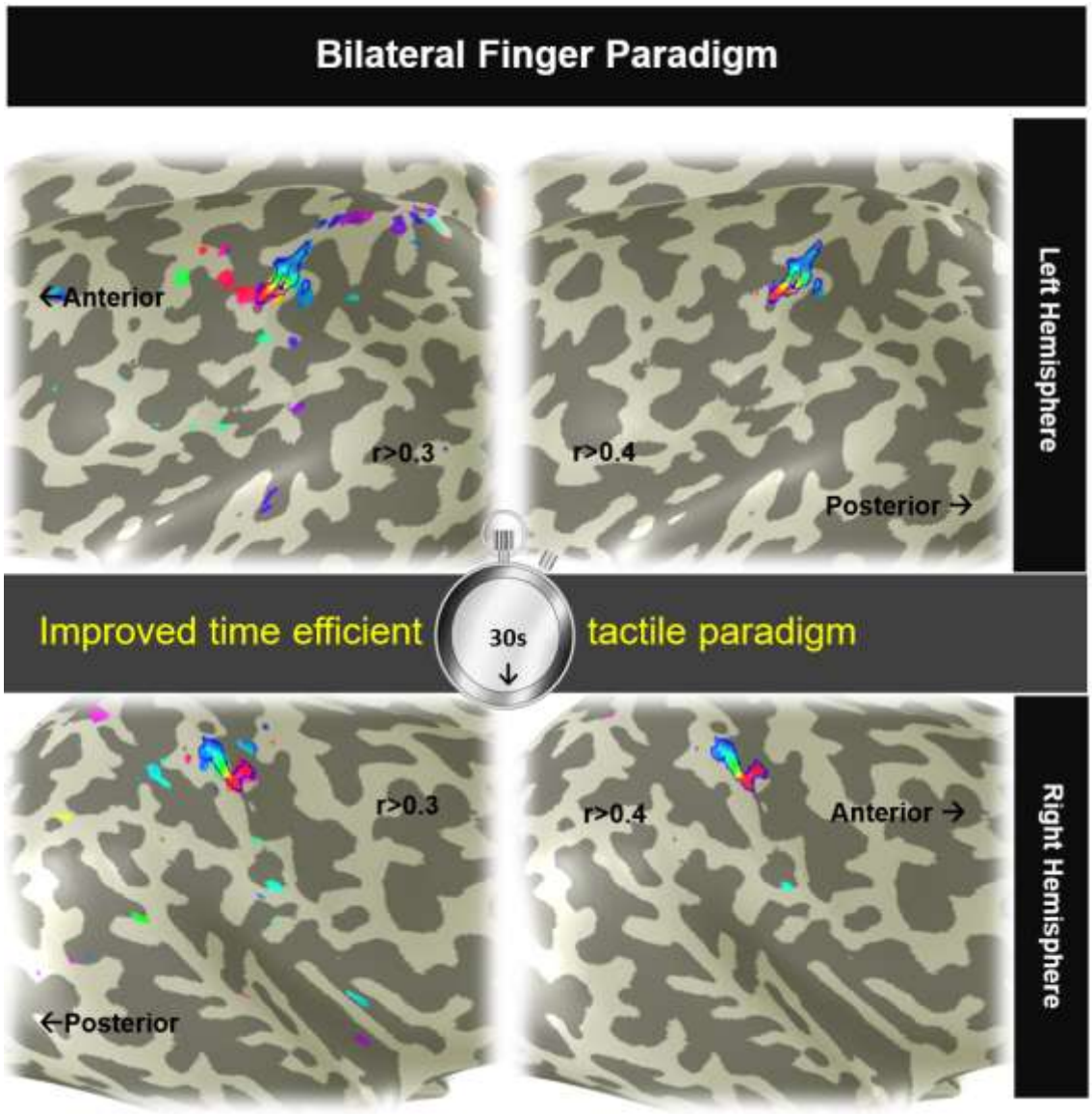


Figure 3-4: Highlighted brain section of fingertip mapping for four digits in native subject space on the corresponding contralateral hemisphere using the bilateral finger paradigm.

For images on the left of the figure, $n = 1260$, $r \geq 0.30$, $p < 10^{-5}$ and for images on the right $r \geq 0.40$, $p < 10^{-5}$. The regions for the BFP fingertip maps marked in blue outline from this figure are contrasted with the results in Figure 3-3.

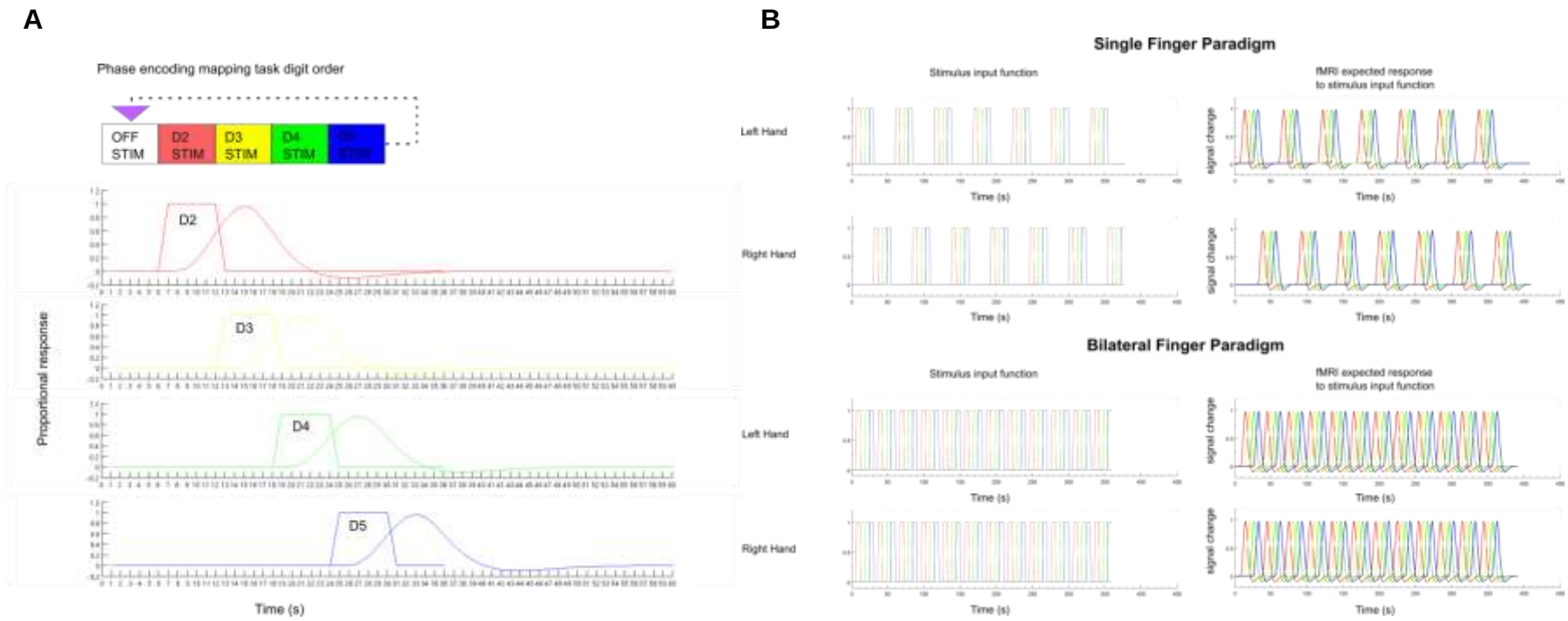


Figure 3-5: Phase encoding task digit order and experimental paradigms for the Single Finger Paradigm (SFP) and Bilateral Finger Paradigm (BFP).

A: Phase encoding task digit order for one hand is shown over time in seconds on the x-axis and the proportional response on the y-axis. The order of digit representation is from index finger, middle finger, ring finger to little finger (D2 - red, D3 - yellow, D4 - green and D5 - blue). The stimulus onset is shown for each digit and then the corresponding sinusoid of the haemodynamic response curve sequentially. The off stimulus period is a 6 second rest. **B:** Complete experimental paradigms for SFP and BFP are illustrated. The left panels show the stimulus input , right panels show the expected BOLD responses, the colour coding for digits are as in panel A. The figure illustrates the BFP paradigm as considerably denser than the SFP. In the SFP, individual stimulation of each of the four fingers in one hand is followed by a 24 seconds rest period for the same hand, while the contralateral hand is stimulated. This off stimulus period is significantly shorter (6 seconds) in the BFP. Considering that the cortical representation for each digit is spatially mostly separate from its neighbouring digits, this results in an extended rest period of 42 seconds after 6 seconds of stimulation for each digit. The rest period between repeated stimulation of the same digit is only 24s in the BFP.

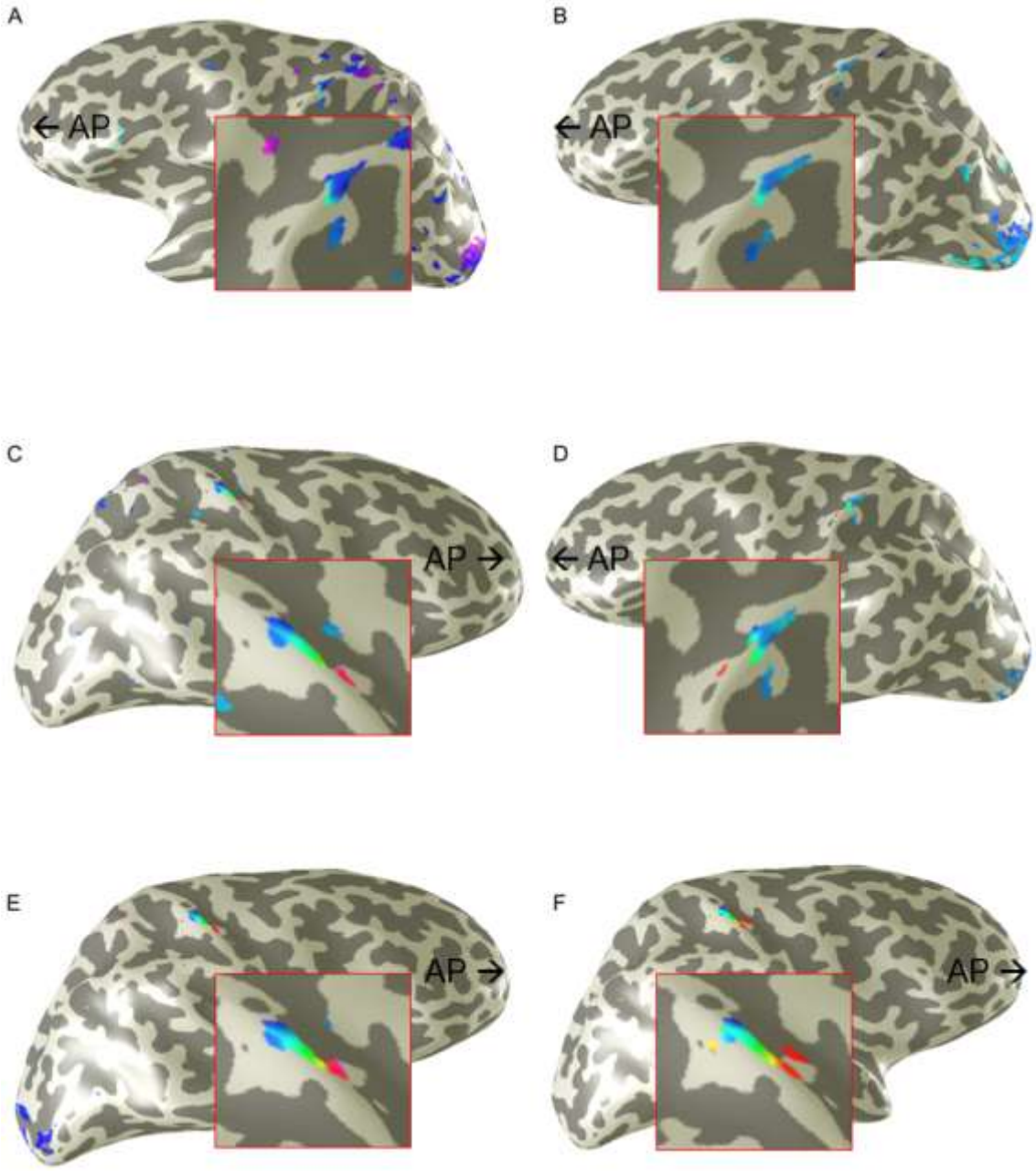


Figure 3-6: Exemplars of bilateral finger paradigm fingertip maps bootstrapped for reliability. These maps were rated poor (A and B), moderate (C and D) and good (E and F). All maps are thresholded at corr > 0.35. All four-digit fingertip maps are shown magnified in red lined square box position with anterior posterior directional arrow (AP). (A) scan average of runs 3, 6 and 7 of the left hemisphere (LH) and the (B) scan average of runs 1 and 7 of LH; moderate ratings to the (C) scan average of runs 2, 3, 7 and 5 of the right hemisphere (RH) and the (D) scan average of runs 1, 4 and 7 of LH; good ratings to the (E) scan average of runs 4, 6 and 7 of RH and the (F) scan average of runs 1, 2, 4 and 5 of RH.

Table 3-1: Boot strapping optimisation procedure results. Fingertip maps on each hemisphere with different scan run combinations were rated from visual evaluations.

Scan run combination	**Right hemisphere** Rating (comment)	**Left hemisphere** Rating (comment)
6-3	moderate	*poor*
4-7	moderate	moderate
2-3	*poor*	*poor*
1-7	*poor*	*poor*
4-6	good	moderate
5-3	*poor*	moderate
7-2	*poor*	*poor*
6-5	moderate	*poor*
1-4	good	*poor*
1-5	moderate	moderate
3-6-7	good (with noise ++)	*poor*
1-4-7	good (with little noise)	moderate
2-3-7	good	*poor*
4-6-7	good (with little noise)	good
3-5-7	*poor (with +++ noise)*	moderate
2-5-7	moderate	moderate
2-5-6	good	good
2-4-7	good	moderate
1-3-4	good	good
1-5-7	moderate	*poor (with noise +++)*
6-3-7-5	good (with noise ++)	moderate (with ++ noise)
4-7-1-6	good	good
2-3-7-5	moderate	*poor*
3-4-5-6	good	good
2-4-6-7	good	good
2-5-6-7	good	good
1-3-4-7	good	moderate to good
1-2-5-7	good	good
1-3-5-7	good	good
1-2-4-5	good	good

Note: Poor ratings are highlighted in *italics* and in grey.

3.5 Discussion of Results

The current study developed a simple, efficient and robust experimental design to map fine-grained fingertip representations in healthy controls that would be also suitable for CRPS patients. The first experiment resulted in consistent S1 activations from the tactile stimulus, similar to previous work (Taylor and Davis, 2009), which had repeatedly scanned participants and found reproducible intra-subject S1 activity. The overall mapping quality was good with observed delineations of individual finger somatotopy (Figure 3-1). The main conclusions from the first experiment were that activations were found confined to S1 and that stimulus by manual brushing was feasible for acquiring finger somatotopy.

It also became clear that some parameters required adjusting and optimising for the tactile stimulus. First, the brushing of adjacent fingertips simultaneously might be difficult on a dystonic hand posture, common in CRPS. The plastic brush calliper tool can also only be adjusted to wider or narrower in a two dimensional plane. This limitation would decrease feasibility for use as a tool for patients with CRPS. Second, the need for a single researcher to switch from one hand to the other within a single run was problematic for the researcher. This required the researcher to physically reposition themselves in a very limited time (6 seconds or less), from one side to the other of the scanning table. Third, it was concluded that more repetitions were required with the stimulus paradigm, either more cycles per run or more runs to achieve sufficiently reliable fingertip maps. This level of data collection would come at a cost of increased scan time, making it potentially intolerable and burdensome for patients with CRPS.

The second experiment optimised the protocol for somatosensory mapping and compared two designs based on the feasibility issues discovered in the first experiment. One design improvement was to include two researchers and a plastic brush to improve mapping quality by the reduction of scan time requirements. Both designs required each of the researchers to have a plastic brush and deliver passive manual tactile stimulus in turn for each hand using the SFP or in synchrony for both hands using the BFP. Both were found to deliver excellent mapping of individual finger somatotopy but the BFP provided improved time efficiency. The maps observed agreed with the expected digit representations starting with digit 2 represented mostly inferior and lateral, the following digits (D3, D4, D5) were represented in increasingly superior and medial locations (Overduin and Servos, 2004, Nelson and Chen, 2008, Sanchez-Panchuelo et al., 2010).

The representations for index fingers were observed to cover a larger surface area of the S1 map compared to the other fingertips. This finding was observed in both experiments. Previous research (Gelnar et al., 1998, Francis et al., 2000, Maeda et al., 2014) have speculated that the intensity of functional activations of the fingers in fMRI studies are related to the neuronal territory devoted to the peripheral density of receptors in each finger (Kandel et al., 2013). Previous research demonstrated that compared to other digits, the index finger and thumb have increased tactile acuity with lower two-point discrimination thresholds (Duncan and Boynton, 2007a) and this correlated to increased peripheral innervation density (Mancini et al., 2013). This is reflected in the increased representation of the thumb and index finger in the sensory homunculus (Martuzzi et al., 2014, Nakamura et al., 1998) compared to that found for other digits (Overduin and Servos, 2004, Sutherling et al., 1992).

The current study observed that the BFP was more consistent and effective at delineating individual fingertips than the SFP. Comparing two alternative stimulation protocols, Ruben et al (2006) reported that the BOLD response to simultaneous stimulation in their study (n = 12) was smaller than the sum of the responses to separate stimulation of the second and the third finger. This suggests less BOLD response for simultaneous stimulation in the BFP compared to single finger stimulation in the SFP. However, this is not in agreement with this study's findings. The current study suggests three notable differences between the work by Ruben et al. (2006) and also explain this. Firstly, Ruben et al. (2006) simultaneously stimulated two adjacent fingers of the same hand, while the study simultaneously stimulates the corresponding fingers of the two hands. Secondly, repetitive electric stimulation may not be easily compared to manual brushing. Repetitive electrical stimulation is known to have habituation effects that can reduce BOLD amplitude (Driemeyer et al., 2008, Tomasi et al., 2004, Qin et al., 2003). Thirdly, Ruben et al. (2006) examined BOLD amplitude, while this study investigated reliability (Table 3-1). However, the limited number of participants and the scope of this pilot study do not allow clear distinctions between BOLD amplitude and reliability across trials, and more data on healthy participants would be required to answer these questions.

It is unclear why the BFP paradigm was more efficient than the SFP. One speculative reason might be that a unilateral touch stimulus activates a small MRI (BOLD) representation in the contralateral S1 hemisphere. This would reduce the power for a test that expects no activity in the left hemisphere when stimulating the right hand i.e. the SFP. For the BFP it would instead increase the power. This rationale is based on known corresponding but transient effects on the ipsilateral S1 and bilateral M1 (Hlushchuk and Hari, 2006). These effects are thought to be due to transcallosal interhemispheric inhibition (Hlushchuk and Hari, 2006, Ragert et al., 2011)

bilaterally in the brain which might consequently be possible reason for improved BOLD contrast.

Overall, a protocol with a single researcher stimulating both hands had significant practical barriers compared to the protocol with two researchers simultaneously on both hands. There are also some suggested disadvantages associated with using two researchers. For example, each researcher required extensive training and practice (approximately a minimum of 15 hours) to deliver the brushing stimulus coordinated with the timing cues and in the correct brushing direction. As pointed out by Overduin and Servos (2004), consistent brushing is important to avoid inconsistent distribution of anatomical finger maps associated with phase reversal, and achieving this with two researchers adds complexity to the protocol.

However, a single researcher as found in the first experiment had many drawbacks that would have made the finalised protocol for CRPS patients unfeasible. As an example, the researcher would need to walk around the MR plinth on which the patient was lying when switching hands (hence every 20-30 seconds or so). Otherwise, the patient's hands would need to be positioned in such a way that both hands were accessible from the same side of the plinth. While such a posture may be, with some limitations, feasible for most healthy participants, it could cause distress and pain in a significant proportion of the CRPS cases. This protocol would then need to account for these factors in the methods, resulting in an overall increased duration of scanning time, further increasing the burden for CRPS patients.

The use of a plastic brush in both the first experiment and second experiment as a stimulus device for passive touch was considered to be a significant contribution to the overall success of S1 fingertip mapping. It may be that since plastic is a familiar texture in modern life; it increases the salience of the stimulus touch (van der Zwaag et al., 2015). The use of a manual tactile stimulus prevented known technical complications reported by Di Pietro et al. (2015) associated with automated devices, such as a vibrotactile device, and with intolerance of the delivered vibrotactile stimulus for patients with CRPS. Thus, a manual plastic stimulus with a texture that could be encountered regularly in life (Martuzzi et al., 2014, van der Zwaag et al., 2015) was considered more suitable for the intended future CRPS participants than any automated stimulus device, where simplicity and reliability were paramount.

Quality control procedures in the protocol were successfully trialled. This included how the stimulus was delivered by the researchers; the use of auditory metronome cues via Presentation and the use of consistent participant instructions to account for discomfort from prolonged lying in the scanner including minimising head movement during the scan. The rationale for the last

procedure was that most people with CRPS were more likely to change posture or position compared to healthy controls (Schasfoort et al., 2003, Schasfoort et al., 2006). Specifically the study allowed a participant to move the distal part of their bodies, such as toes, between run acquisitions, whilst keeping still during an on-going measurement. This would allow CRPS participants improved tolerance to the environmental discomfort of being in the scanner. Improved tolerance would avoid excessive head movements reducing the likelihood of severe distortions in the scan results due to movement artefacts.

Increased signal to noise ratio and reduced scan time are part of the goal for obtaining the necessary parameters suitable for imaging CRPS patients (Bennett and Miller, 2010, Deshmane et al., 2012). This study accounted for the natural delay in haemodynamic response function from its baseline post stimulus (Bandettini et al., 1993, Boynton et al., 1996, Handwerker et al., 2012) by adding extra stimulus time at the start of the EPI protocol (Table 9-1). The final planned parameters (shown in Table 9-2 in Appendix for Chapter 3) for experiments with CRPS participants (For details, please see Chapter 4) were a voxel size of 1.5 mm^3 with the retained short repetition time of two seconds through a smaller field of view, but an increased scan resolution within the field of view. Due to the reduced field of view at higher spatial resolution, the fMRI scan was confined over M1, S1 and its immediate surroundings. The brushing paradigm using two researchers reduced scanning times allowing for an increase in spatial resolution for scan acquisition.

The change in sampling from 2 x 2 x 2.5 mm to 1.5 x 1.5 x1.5 mm voxel size represents a volume reduction from 10 mm^3 to 3.372 mm^3. This volume reduction does not necessarily reflect a reduction in efficacy of an fMRI design, demonstrated and explained by the work from Triantafyllou et al. (2006). Essentially the relevant metric for fMRI is contrast to noise (CNR) not SNR. Triantafyllou et al (2006, 2011) suggested smaller voxels optimises CNR, without an excessive trade off in SNR, thereby improving the overall fMRI design (Triantafyllou et al., 2006, Triantafyllou et al., 2011).

There are a number of factors determining the efficiency of an fMRI measurement. Voxel volume is simply one component. Importantly, the increased image SNR offered by multi-channel arrays (e.g. 32- channel) produces the greatest benefit in the temporal SNR for medium to small voxel volumes and higher accelerations in parallel imaging (Triantafyllou et al., 2011). Voxel volume remains a minor factor in determining fMRI measurement efficiency as the use of 32 - channel phased array coils (Fellner et al., 2009, Kaza et al., 2011) greatly improves image SNR in fMRI (Triantafyllou et al., 2011). Instead the most relevant source of variance is the

subject, as subject noise is constant at any voxel size. Simplified, SNR only becomes relevant when it is large in relation to subject noise (Deshmane et al., 2012, Weiger et al., 2005).

The use of bilateral simultaneous brushing also appeared to prevent the confounding problem of selective attention to touch on one hand or to specific digits (Ruben et al., 2006), which can affect the BOLD response and contrast (Tomasi et al., 2004). The participants reported that they were aware of the tactile stimulus *per se*, but were not able to habituate to which side or digit was being brushed. Swapping of sides by the two researchers after each run again reduced the predictability of the stimulus. All these factors aimed to minimise habituation, adaptation and significant loss of BOLD responses (Driemeyer et al., 2008, Tomasi et al., 2004, Qin et al., 2003). The current study suggests efforts to provide a naturalistic stimulus while also minimising habituation, were key components that made the BFP paradigm so effective.

3.6 Conclusion

The BFP tactile paradigm was preferable to the SFP tactile paradigm for planned experiments with unilateral upper limb CRPS participants. The BFP requires shorter mapping times compared to the SFP without a compromise on the quality of the fingertip maps. This provides significant advantage for neuroimaging participants with CRPS, who are unable to tolerate long periods in the MR scanner. Therefore, the most efficient and effective paradigm was the BFP and was used to investigate fine-grained maps of the four fingertips in the S1 of participants with CRPS. The reasons for the observed effect of improved delineation from BFP are not fully clear and should be further evaluated in the future research with healthy participants.

Quality control procedures were determined to be useful for future experiments. Although this type of manual tactile stimulus requires rigorous pre-experimentation practice of the researchers applying the sensory stimulation, it becomes possible to deliver a consistent stimulus with sufficient practice. The participants reported minimal habituation and were unable to selectively focus their attention to the stimulus during the BFP. The protocol was successful in achieving minimal movement distortions which might have affected the quality of scans.

Somatosensory fingertip mapping was feasible with a manual stimulus using concepts adapted from visual field mapping techniques, such as cyclic phase mapping and a bilateral stimulation paradigm analogous to bow-tie type polar angle mapping in the visual cortex (Schira et al., 2009, Wandell et al., 2007). The fingertip maps produced were in good agreement with textbook knowledge for somatosensory anatomy. The maps revealed clear order and clear delineations, particularly those provided by the BFP. The bootstrapping analysis revealed that three repetitions of the tactile paradigm should provide acceptable finger delineations the majority of the time and four repetitions should provide good finger delineations almost all of the time. Hence the paradigm was deemed suitable for use in CRPS patients and that four runs should be attempted for the protocol.

4 Functional fingertip maps and underlying structural morphometry of touch in unilateral complex regional pain syndrome (CRPS)

4.1 Introduction

Much controversy remains in neuroimaging pain literature. For example, findings of structural brain changes of increased grey matter density associated with CRPS were not reproduced (van Velzen et al., 2016) and functional maladaptive brain changes believed to be isolated to a smaller affected-CRPS hand representation in S1 (Maihöfner et al., 2003) might present at the same time as an enlarged representation of the healthy hand (Di Pietro et al., 2015) in the same study. Several reviews (Woo and Wager, 2015, Poldrack, 2012, Lee and Tracey, 2013) and studies (Wager et al., 2013, Mutso et al., 2014, Schwedt et al., 2015) have argued for the use of advanced techniques in pain neuroimaging that would allow new and flexible concepts of brain-related changes, which differ from earlier brain morphometric studies that used voxel based morphometry (Apkarian et al., 2009).

Little attention has been paid to the potential role of structural neuroimaging measures, as a source of candidate biomarkers for the neuropathology of chronic pain (Olesen et al., 2010) including CRPS. Woo and Wager (2015) pointed out that despite much effort in the field of neuroimaging and chronic pain, no potential biomarkers have proven to be robust enough to be of clinical or diagnostic use. A re-assessment - with new techniques or at least unambiguous reporting - is required, allowing clear comparisons between studies.

Structural neuroimaging measures may provide potential clues about supraspinal contributions to pain (Woo and Wager, 2015) and highlight potential relationships to the widely explored features of pain risk in the literature. To date, pain-related neuroimaging research has focused on acute experimental pain (Wager et al., 2013) or on co-morbid conditions commonly found with chronic pain conditions rather than directly on the mechanistic properties of chronic pain. One reason is that the quantification of causal relationships from neuroimaging markers remains difficult and controversial in chronic pain. In contrast, risk factors found in co-morbid conditions and associated with chronic pain have been already explored. These have included depression (Schwartz et al., 2014), stress (Vachon-Presseau et al., 2013), post-traumatic stress disorder (Li et al., 2014), and early-life adversity (Luby et al., 2013).

Apkarian et al. (2004) published the first brain morphometry study in chronic pain, showing anatomical evidence for brain atrophy in chronic back pain. Their results demonstrated that back pain patients had brains with 5% to 11% smaller grey matter volume than the brains of healthy

controls. In addition, the grey matter density over the bilateral dorsolateral prefrontal cortex and right thalamus was reduced in patients compared to controls. The extent of grey matter loss was also positively related to the extent of neuropathic pain features (Apkarian et al., 2004). Subsequent studies replicated these results and similar conclusions were made regarding other chronic pain conditions and their association with neural degeneration (Schmidt-Wilcke et al., 2005, Kuchinad et al., 2007, Yang et al., 2017). The review by Bushnell et al. (2013) concluded that grey matter abnormalities were not only found in the prefrontal cortex (Apkarian et al., 2004), but were also present in the insula, and anterior and midcingulate cortices. The authors suggested the abnormalities found were in areas known to be associated with pain processing, pain regulation and affective regulation for cognition.

There is variability in the direction of grey matter volume changes reported in published pain research on brain morphometry (Smallwood et al., 2013). Variability in these volumetric changes is attributable to patient characteristics such as: the type of diagnostic parameters used, when diagnosis was made, and which body areas were primarily affected by chronic pain (Davis and Moayedi, 2013, Bushnell et al., 2013, Kregel et al., 2015). Alternatively, the variability in these findings might be related to the problems associated with fMRI analysis (Eklund et al., 2012, Eklund et al., 2016, Scarpazza et al., 2013, Scarpazza et al., 2015) in voxel based-morphometry to calculate volumetric changes (Good et al., 2001). Therefore, grey matter changes in VBM associated with chronic pain should not be considered in isolation from factors related to analysis, pain duration, demographics, pain resolution and medication.

One such study showed that grey matter density negatively correlated with the duration of pain in patients with CRPS and was independent of the side affected by CRPS. Geha and colleagues (2008) compared brain morphology of CRPS patients to healthy control subjects using voxel-based morphometry (VBM). Their results indicated that CRPS patients had decreased density within a single cluster in the right hemisphere, spanning the ventromedial prefrontal cortex (VMPFC), anterior insula (AI), and nucleus accumbens. The patient group included patients suffering from CRPS pain localised to right, or left or affecting bilateral body regions, which could have confounded the analysis. The effect of sidedness was then accounted for when performing the VBM analysis separately for the unilateral CRPS groupings and respective matched controls. The results showed that patients had lower grey matter density than controls in this same right AI and VMPFC region regardless of CRPS-sidedness (Geha et al., 2008).

Moayedi et al. (2012) found evidence that abnormal patterns of grey matter volume changes in patients with temporomandibular (TMD) pain may be related to both pain duration and age. Overall, there was accelerated total brain grey matter loss in the patients compared to controls. However, in the thalamus, TMD patients had age-related grey matter volume increases compared to the usual sustained thalamus volumes in controls. Furthermore, TMD patients did not have expected atrophy associated with aging in the dorsal striatum and pre-motor cortex.

Recent evidence also suggests grey matter volumes can be influenced by medication. For example, Upadhyay et al. (2010) conducted a small exploratory study of 10 patients with opioid dependence (had no pain diagnosis or medical co-morbidities) and compared their brain morphometry with matched controls. They assessed the effects of prescription opioid dependence on grey matter volumetric loss or gain, the duration of prescription opioid dependence and age of each patient. They also specifically excluded patients with a chronic pain condition and opioid dependence, so as not to confound the effects of pain with the effects of opioids. The opioid-dependent group had significantly smaller grey matter volumes in the amygdala in both hemispheres compared with the control group. There were no significant differences between the two groups in the grey matter volumes of other subcortical structures. In addition, no significant correlation was found between the amygdala volume and duration of prescription opioid dependence. This finding of isolated brain structural changes related to use of opioid-based medication must be considered when studying pain patients, given that chronic pain patients commonly take opioid medications.

In patients who have chronic pain, opioid use seems to be associated with grey matter volume changes. A study by Younger et al. (2011), found that one month of daily use of prescription opioids can cause long-lasting regional neuroplasticity changes in patients (n = 10) with chronic low back pain. Control patients given a daily placebo had no significant changes in grey matter volume over the month of the study. However, the daily opioid users had increased grey matter volume in the cingulate (middle, dorsal posterior, and ventral posterior regions) and a significant volume reduction in the right amygdala. The degree of volumetric change in several regions was also independently and significantly correlated with opioid dosage. Strikingly, the opioid-induced volumetric changes were persistent, even after 4.7 months cessation.

Effects of non-opioid based medication on the brain have also been investigated. Non-steroidal anti-inflammatory medications, for example, have been associated with neuroprotective effects against age-related atrophy. Walther et al. (2011) found a neuroprotective effect from this class of medications on both grey and white matter. The brain

regions protected included grey matter in the superior and medial frontal gyri, middle and inferior temporal gyri, fusiform and parahippocampal gyri, and occipital area. White matter in the temporal, parietal, and midbrain areas was also protected against age-related changes. Similarly, Bendlin et al. (2010) found that non-steroidal anti-inflammatory medication users had smaller age-related losses of volume in the medial temporal lobes compared with controls who did not use these medications. Age related volume decreases in the bilateral hippocampus were smaller in medication users compared with controls, and the neuroprotective effect of the medication was greatest in small portions of left bilateral parahippocampal grey matter.

4.1.1 Cortical morphometry measurements in chronic pain

Grey matter changes can also be measured by examining cortical thickness (Fischl and Dale, 2000) rather than volume. Neuroimaging studies have reported on measurements of cortical thickness in patients with chronic pain, but the results are inconclusive. Studies by Kim et al. (2014) and DaSilva et al. (2007) found increases in the primary somatosensory cortex (S1) cortical thickness of chronic migraine sufferers without aura (n=56 female only and right handed) and chronic migraine sufferers with and without aura (n=24). However, another study (n=48) in chronic migraine with and without migraine aura, found no such significant association (Datta et al., 2011). Kong et al. (2013) found increased cortical thickness associated with both S1 in patients with chronic low back pain. However, two studies (DaSilva et al., 2008, Gustin et al., 2011) found a mixture of increased and decreased in cortical thickness in S1 for patients with trigeminal neuralgia. Moayedi et al. (2012) found that TMD pain patients had age-related cortical thinning, whereas the controls had age-related cortical thickening, in the anterior mid-cingulate cortex and pregenual anterior cingulate cortex. The study by Blankstein et al. (2010) demonstrated a relationship between functional continuous nociceptive drive and structural abnormalities in irritable bowel syndrome pain (IBS), where there was an increase from less insula thickness, as the disease progressed from short term IBS pain to long term IBS pain. They concluded that a thicker anterior insula was associated with a longer exposure to IBS pain.

Studies found that opioids (Ranger and Grunau, 2014) and early pain experiences (Walker et al., 2009, Ranger and Grunau, 2014, Ranger et al., 2013) were also associated with cortical morphometry differences including cortical thickness. These neuroimaging studies have speculated that the morphological sequelae of centrally mediated alterations were associated with the modulation of C-fibre nociceptor pathways. This perhaps alters supraspinal structural development and confers a pre-morbid risk factor for the development of chronic pain (Brummelte et al., 2012, Attarian et al., 2014, Baliki and Apkarian, 2015). These suggested

effects have been investigated by altering the opioid analgesia system in animal studies (Grace et al., 2014, Fan et al., 2003, Ellis et al., 2016, Ammon-Treiber and Hollt, 2005) and were found to be associated with early life stress (Howard Kinsley et al., 1988, Insel et al., 1990) with consequential changes to normal animal behaviours. Future research could explore pre-morbid factors and the use of opioids or other medications in chronic pain neuroimaging research.

The investigation of altered cortical morphometry may lead to better understanding of chronic pain symptom presentations (Wand and O'Connell, 2008). Functional and structural MRI findings point to brain and peripheral nerve abnormalities in patients with chronic pain: some of these are pre-existing and others develop over time with prolonged pain and related neuroinflammation (Davis and Moayedi, 2013, May, 2008). These results do not necessarily establish causation between brain changes and chronic pain states (Davis and Moayedi, 2013), rather the changes could be the consequence of neuropathology from persistent pain experienced in chronic pain states such as back pain or migraine (Hubbard et al., 2014). Wand and O'Connell (2008) have also argued that, in patients with chronic pain (specifically non-specific low back pain), the physical peripheral symptoms changes such as altered biomechanics are features of epiphenomena of cortical dysfunction, rather than cortical changes being the underlying mechanism (Apkarian et al., 2009).

Studies using longitudinal designs have been infrequently reported, but can be used to determine if grey matter changes in chronic pain are due to altered pathophysiology rather than being a consequence of chronic pain. One example, provided by Rodriguez-Raecke et al. (2013), measured VBM-longitudinal changes in a subgroup of 20 osteoarthritic hip pain patients before and after total hip replacement. The patients were scanned prior to surgery, and, post-surgery at six to eight weeks, 10 to 14 weeks and 10 to 14 months. Partial increase in grey matter after surgery was observed that broadly overlapped over the same areas where the grey matter volumetric changes had been abnormally low prior to surgery (Rodriguez-Raecke et al., 2009). The longitudinal method of this study was able to reveal specific changes related to pain resolution.

4.1.2 The measurement of brain morphology: voxel based morphometry or surface-based morphometry?

Neuroimaging of structure, such as cortical morphometry have traditionally used voxel-based morphometry (VBM) measures rather than surface-based methods. Technical aspects and differences in how the method is applied can lead to different results on the same data. Other factors that appear to influence the outcome of these methods include individual variability in brain size and the brain structures that are being evaluated, for example, grey matter or

subcortical structures (Voets et al., 2008, Kong et al., 2015, Blankstein et al., 2009). Registration techniques, or taking measures in native versus a template space, can warp these measurements and affects cross-validation between studies and reproducibility (Bookstein, 2001, Ashburner, 2007). Furthermore, technical issues such as voxel size, intensity thresholds (Ridgway et al., 2009) and resampling voxel sizes through interpolation - especially upsampling from lower resolution scans (Puri, 2006).

Interpretation of voxel-based morphometric changes should take into account age and gender-related changes, due to the known effects of these factors on healthy brains. On average, males have a larger total brain volume than females. Ruigrok et al. (2014) used whole-brain voxel-wise meta-analyses of brain volume and density in subjects of six age-categories to examine sex differences. The authors found regional sex differences in volume and tissue density that included the amygdala, hippocampus and insula. These areas are known to be implicated in sex-biased neuropsychiatric conditions. However, the interpretation of Ruigrok et al. (2014) findings requires caution due to an acknowledged bias towards a heterogeneous sample of mature subjects of more than 42 years of age. Good et al. (2001) investigated total grey matter volume in a large sample of 456 healthy adult brains. They found that global grey matter volume decreased linearly with age, with a significantly steeper decline in males. Local areas of accelerated loss were observed bilaterally in the insula, superior parietal gyri, central sulci, and cingulate sulci in older adults. Conversely, areas exhibiting little or no age effect (relative preservation) were noted in the amygdala, hippocampi, and entorhinal cortex.

Another factor influencing morphometry analysis is the processing method used. For example, automated processing for VBM can yield different results from gold-standard region of interest (ROI) analysis on the same subjects. A study using automated VBM and ROI-analyses were performed on subjects with schizophrenia and both methods indicated a lower than usual volume of left inferior and right superior frontal cortical grey matter (GM) in these subjects (Giuliani et al., 2005). However, VBM indicated a significantly lower concentration of GM in the middle and superior temporal gyri, not detected using ROI, and ROI showed parietal changes not shown by VBM. The authors discussed methodological differences between voxel-averaged, landmark-based ROI analyses and the single, voxel-by-voxel whole brain VBM measurements. They concluded that although VBM was rapid and fully automated, it was not a replacement for manual ROI-based analyses. Therefore, both methods to measure brain morphology provide different types of information and should be used in tandem for validation studies.

A viable alternative to the traditional VBM approach to cortical morphometry is to use surface-based analysis methods. Surface-based methods provide a sensitive tool for investigating cortical atrophy by breaking down measures of local cortical volume into separate and almost orthogonal components of thickness and surface area (Worker et al., 2014). While thickness measures may provide some indication of underlying neuronal loss, reduced size of neuronal cell bodies or degradation, surface area measures may reflect underlying white matter fibres (Van Essen, 1997); with tension or shrinkage of these fibres leading to deeper sulci and extended area measures. In addition to providing increased pathological specificity, cortical thickness and area measures provide a direct index of cortical morphology that is less susceptible to variations in individual positioning, because the extraction of the cortex follows the grey matter surface regardless of positional variance (Kim et al., 2005). Furthermore, cortical thickness measures have an advantage over voxel-based measures in that they allow for sub-voxel precision, with thickness values being assigned to individual vertices rather than to voxels (Fischl and Dale, 2000). Studies that have used volume-based methods along with surface-based methods to measure cortical thickness and surface area, have shown that both techniques lead to largely similar findings. However, surface-based methods are able to provide greater sensitivity (Hutton et al., 2009) and accounts for inter-subject morphometry variability (Anticevic et al., 2008).

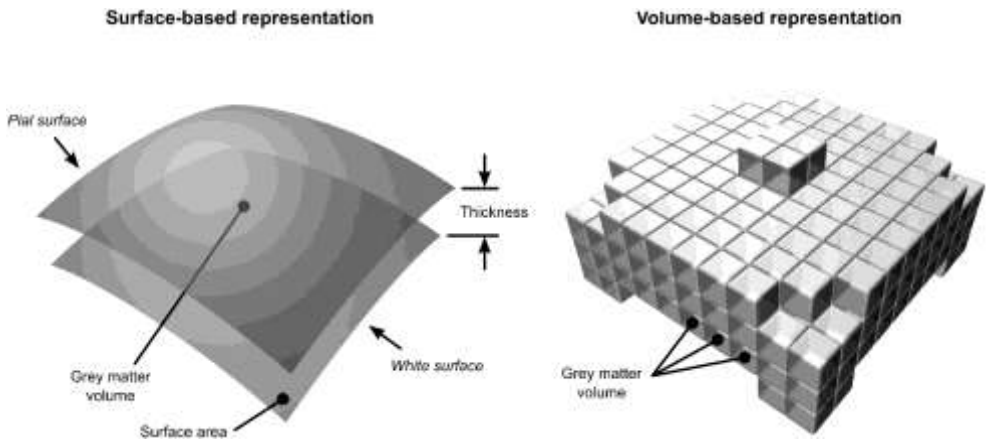


Figure 4-1: Geometrical relationship between cortical thickness, surface area and grey matter volume.

In the surface-based representation, the grey matter volume is a quadratic function of distances in the surfaces and a linear function of the thickness. In the volume-based representation, only the volumes can be measured directly and require partial volume-effects (not depicted) to be considered. Adapted from the study by Winkler et al. (2010).

Cortical thickness and surface area measurements were found to be genetically and phenotypically independent. Winkler et al. (2010) compared cortical surface area, cortical thickness and grey matter volume measurements using the volume-based software method of FMRIB Software Library or FSL (Oxford Centre for Functional MRI of the Brain, University of Oxford, UK) to the surface based software method of Freesurfer (Athinoula A. Martinos Center for Biomedical Imaging, Harvard University, Cambridge, MA, USA) on a large genetic study sample (n = 1,000). The differences and relationship between surface-based representation and the volume-based representation on the three measurements are illustrated, in Figure 4-1. The results of the study showed that, while both thickness and area influenced volume measurements of cortical grey matter, volume had a closer relationship to surface area than cortical thickness. The results of this comparison study suggest that surface area and cortical thickness measurements should be considered separately and preferred over grey matter volumes when a genetic component could be an important associative factor when imaging specific pathologies. Further comparisons between surface based and volume based methods are also detailed in Appendix for Chapter 4.

4.1.3 Cortical morphometry and chronic pain

The relationship between brain function and structure has long been studied at a gross anatomical level, and recently been supported by more precise neuroanatomy research. One method of advancing the understanding of the brain structure - function relationship is measuring area connections through high spatial resolution T1 scans in humans and examining laminar properties of histological data in primates. Wagstyl et al. (2015) explored cortical thickness gradients in a single macaque monkey study and 83 healthy subjects with these techniques, focusing on the somatosensory cortex, visual and auditory cortex. Cortical thickness was found to be correlated with specific cytoarchitectural characteristics and the structural hierarchal organisation of the cortex in both species. Human cortical thickness measurements in gyri were found to be thicker than sulci in healthy participants. This finding was in agreement with previous literature (van Essen and Maunsell, 1980, Fischl and Dale, 2000).

Evidence towards cortical structure and functional relationships has been obtained by using direct methods in primate research and indirect methods in human research. This includes measuring the structural hierarchal level of sensory processing directly in primates with direct neuronal recordings or histology and confirming findings through indirect MRI experiments in humans. The hierarchy of the somatosensory cortex follows a caudal progression across the post-central gyrus, from BA 3a, 3b, 1, 2 to 5 (Felleman and Van Essen, 1991, Iwamura, 1998). The receptive field neuronal properties in the brain are also thought to progress in complexity caudally. It has been reported in primate research, that the anterior bank of the intraparietal sulcus, the caudal most part of the postcentral gyrus, is responsible for the systematic integration of bilateral body parts such as the hands (Iwamura et al., 2002), as well as of somatic and visual information (Iwamura, 1998, Iwamura, 2000).

There is ongoing debate in the literature on the precise details of these structural- functional hierarchies in the primary cortices. Duncan and Boynton (2003) studied the relationship between function and structure in the visual and somatosensory cortices of healthy subjects and demonstrated that visual acuity was predicted by the size of the functionally defined primary visual cortex (Duncan and Boynton, 2003). Given the accuracy with which the borders of the primary visual cortex are localized by folding patterns alone, visual acuity could be inferred directly from brain structure measurements. In a later study on the somatosensory cortex, this same group concluded that tactile acuity was correlated with cortical representation in the primary somatosensory cortex of the fingers (Duncan and Boynton, 2007b). These findings in healthy subjects raise the question of what relationships might exist between the brain function and structural neuroanatomy of subjects with chronic pain.

The reviewed literature on surface-based cortical morphometry measures in chronic pain indicates wide variation in candidate areas for the involvement of chronic pain in brain morphometry including the insula, somatosensory, parietal, prefrontal and anterior cingulate cortices (Neuroimaging and CRPS page 19 and Appendix to Chapter 1, page 163 – Literature review section). It is clear that chronic pain is associated with changes in brain morphometry, with changes in overall global measures of volume and thickness. More difficult to elucidate are the causal mechanisms underlying the association of chronic pain with altered cortical morphometry measures. Therefore, future work on the development of cortical morphometry and pain might provide concepts for targeted investigations in the future.

The research in this area to date requires cautious interpretation, as it is unlike the prospective cohort studies where a condition can be tested prior to the development of chronic pain and the risk factors identified. Due to the limited nature of research on pain subjects, neuroimaging case-control studies need to be carefully planned and are easily subject to confounding factors. Although the effect of known confounding factors such as age, gender and personality traits on cortical morphometry measures can be controlled for, statistically or methodologically, unknown confounding continues to present a major problem. Consequently, the methods and results will need clear reporting to explain any potential deficits in the study.

Since research that have reported gross measures, such as total grey matter volume in chronic pain states is conflicting, could advancement in neuroimaging techniques assist in more specific questions? Perhaps newer techniques could provide fine-grained details. Higher spatial and accurate temporal resolution to a simple known block-type stimulus might answer the question of whether corresponding maps differ in pain states or controls. The literature review for the pilot study (Chapter 3) reported how fMRI research on healthy subjects indicates that tactile finger maps have a consistent order of the fingers from the index finger to the little finger. The orientation is from lateral and inferior, to medial and superior, in S1 but can be angled slightly differently in different individuals (Schweizer et al., 2008, Kurth et al., 1998, Schweisfurth et al., 2014, Francis et al., 2000, Sanchez-Panchuelo et al., 2010). Therefore, are the functional brain maps of people with CRPS affecting the hand and fingers, the same or different? Do unilateral pain states only affect the cortical morphometry of one hemisphere or both?

Most of the surface-based cortical morphometry studies use a combination of surface-based measures and voxel-based morphometry measurements. Surface-based measures provide technical advantages over VBM, for inter-subjective variability (Argall et al., 2006, Anticevic et al., 2008). In general, a decrease in grey matter could be due to a simple decrease in cell size,

neural or glial cell apoptosis, a decrease in density, changes in blood flow or interstitial fluid (Hasenbring et al., 2012). To date, surface-based measurements have been used in pain-related studies of hepatology, gastroenterology and migraine, but only in one study in CRPS (Lee et al., 2015). This study by Lee et al. (2015) suggested that their results found a decrease in cortical thickness in the right dorsolateral prefrontal cortex (DLPFC) and the left ventromedial prefrontal cortex. This was associated with a decline in neurocognitive function performance in a mixed multi-limb clinical CRPS study sample. Further details of this study by Lee et al. (2015) were presented in Chapter 1.4: Neuroimaging and CRPS.

S1 representation of the hand has been measured using the Euclidian distance between the thumb and little finger in fMRI and MEG. With improved techniques, it is now possible to obtain the finger representation of all the fingers. This would be useful, because clinical symptoms and reports of CRPS are not merely confined to the thumb and index finger. It is here proposed that the hand representation in CRPS could be improved upon from previous research by using increased spatial and temporal resolution from phase-encoded fMRI (using the techniques developed in Chapter 3). This would allow measurements of the fine-grained details of individual fingertip representation in response to a stimulus of light touch, which is considered innocuous to controls, but painful to patients with CRPS in the hand. The structure-functional representation of the four fingertips in the primary somatosensory cortex can be investigated quantitatively using cortical surface morphometry measurements of surface area, grey matter volume, average thickness and geodesic distances.

4.2 Aims and hypotheses of the study

There are two aims for this study, which relate to:

i) functional fMRI fingertip maps, and

ii) the underlying structural cortical morphometry analysis of these functional fingertip maps.

4.2.1 Functional fMRI fingertip maps

The main aim was to compare fingertip maps between healthy controls and patients with unilateral affected CRPS of the hand, exploring the order, orientation and size of the fingertip maps. The secondary aim was to describe fine-grained fingertip maps for all four fingertips of healthy controls, with the use of the higher spatial and temporal resolution of phase-encoded fMRI.

Compared to control subjects, it was hypothesised that patients with CRPS will have distorted functional somatotopic maps of the fingertips in the primary somatosensory cortex. A second hypothesis was that in healthy controls, the order and orientation of the representation of the fingertips will be from inferior laterally to superior medially over the primary somatosensory cortex, with the index finger in the most inferior position and the little finger in the most superior position.

4.2.2 Structural cortical morphometry

The main aim was to quantify the cortical morphometry measurements of surface area, grey matter volume, and average cortical thickness of the functional map of all four fingertips, as well as the geodesic distance from the centroid of the map of all four fingertips of each hand, to the central sulcus.

Based on the literature, the first hypothesis was that the cortical surface and volume area of fingertip maps will be larger in CPRS patients than in controls, due to continual nociceptive bombardment in CPRS, but cortical thinning will be present in the CRPS fingertip maps. A second hypothesis was that the centroid of fingertip maps of CPRS patients will be altered due to a shift of the position of the finger tips relative to the central sulcus (Areas 3b and 1).

As the literature review identified a lack of published information on the relationship between cortical thickness and medication use, a priori post–model comparison of cortical thickness and opioid medication use was planned. Exploratory associations of cortical morphometry measurements with the clinical variables of pain pressure point thresholds, pain intensity and duration of CRPS were performed as well.

4.3 Methods

4.3.1 Study sample

42 subjects were recruited (Chapter 2) and scanned. 40 subjects with unilateral upper limb CRPS and age-gender-handedness-matched healthy controls (HC) were included in this study.

4.3.2 Procedure

All experimental procedures were carried out in accordance with the Declaration of Helsinki and approved by the University of New South Wales Human Research Ethics Committee and South Eastern Local Health District Human Ethics Committee (HC13214 and HREC 10/051), respectively. Informed consent was given by each study participant. The experimental

procedures were explained to all subjects but they were unaware of the exact experimental hypotheses.

Pain intensity was assessed during and after the MRI scan with a self-report questionnaire. Ratings of pain intensity were on an 11-point Likert scale where zero was 'no pain' and ten was like 'worse pain imaginable' like 'a red hot poker through your eye'. As part of the clinical assessment of CRPS diagnosis, pressure pain threshold (PPT) using a digital pressure algometer, FDX® (Wagner instrument, Greenwich, USA) was assessed and recorded by a research assistant on two sites on each hand; the thenar eminence and the third proximal interphalangeal joint.

4.3.2.1 Blinding

The primary researcher had direct contact with each study participant and was aware if the participant had a diagnosis of CRPS. The second researcher delivering the brushing stimulus for the phase encoded functional magnetic resonance imaging (fMRI) scan was blinded to their CRPS diagnosis. Each run of the four runs of the fMRI was randomised as to who would be delivering the stimulus on each side of the patient. The reasons behind this was that this randomisation in the protocol would control for inadvertent unblinded behaviours e.g. if the unblinded researcher brushed harder or softer because of their knowledge of CRPS - affected side. However, in practice if a CRPS subject displayed obvious one-sided symptoms, behavioural guarding, avoidance or aids such as tubigrip or extra hand / wrist guards on the affected side, the blinded researcher may have been able to guess which hand was affected.

The assessor (FM) for analysis of phase encoded fMRI fingertip maps was also blinded to the condition of the subjects for the first level analysis and in determining the necessary region of interest for subsequent use by the primary researcher for cortical morphometry analysis.

4.3.3 MRI scanning session

Task specification: Each participant lay supine in the scanner and was well propped with cushioning material to minimise any movement. Their hands were placed with the palmar surface aspect visible outside the scanner bore and they wore earplugs and headphones. Each participant was asked to remain awake, eyes open, relaxed and aware during the tactile stimulus.

Design: A task-based, block design stimulus was used. The tactile stimulus was manual brushing of the skin with a plastic brush. The plastic brush made from polypropylene was similar to the design used by Gustin et al. (2012) and constructed in-house at NeuRA. Repeated

cycles of tactile stimulation were delivered successively to each volar tip of the fingers, in a pattern that was named the 'bilateral finger paradigm'. The finger stimulation pattern is described in Chapter 3. Twelve cycles were made per run.

4.3.4 Data acquisition

Anatomical scan collection and processing were based on previous work by Schira et al. (2009). The somatosensory cortex, posterior to the central sulcus, was the specific interest. Data acquisition parameters for whole brain anatomy scans were outlined in Table 4-1 and also in Appendix for Chapter 3.

Echoplanar images (EPI) were collected on a Phillips 3T MRI scanner with a 32-channel head coil with a resolution of 1.5 x 1.5 mm^2 in plane, 1.5 mm slice thickness, matrix 128 x 128, FOV = 192 mm, 43 oblique slices, and 180 volumes per run (four runs) were collected . Coverage of EPI data included the precentral sulcus and post central sulcus to ensure ample coverage over the primary somatosensory and motor areas. The scan slices were aligned over the central sulcus with approximately 7 slices captured posteriorly after the posterior horn. Full parameters used are given in Table 4-1 below. To achieve high resolution and speed and to minimise distortions, a SENSE (Weiger et al., 2005, Pruessmann et al., 1999) accelerated echoplanar imaging (EPI) sequence was used for functional data.

4.3.5 Image Processing

High resolution T1 images were pre-processed using the automated pipeline in the software program Freesurfer version 5.3.0 on a Linux machine. The automatic segmentation from Freesurfer was used with manual checks made by an independent researcher (FM based at UCL, London), who was not involved in the data collection. The researcher (FM) was also blinded to group type that was if the participant was classified as a control or had CRPS. First level analysis of the all phase–encoded functional fingertip maps were made whilst FM was blinded. To allow a blinded assessment, calculation of the geodesic distances were made off-site (in London) whilst FM was blinded to affected side in CRPS but not blinded to group type. All other measurements including cortical morphometry analyses were performed by the principal investigator using the functional scan labels provided by FM..

FreeSurfer version 5.3.0 (Fischl, 2012) was used to reconstruct the cortical surface from the anatomical scans. The high resolution T1 scan was down-sampled to a voxel size of 1 mm^3,

from the original 0.75 mm^3 voxel scan. This down sampling is a technical requirement in order to process the T1 structural images via Freesurfer pipeline (Lüsebrink et al., 2013). In four subjects (28, 29, 33, 34), structural T1 images were corrected for non-uniform intensity using the AFNI (Analysis of Functional NeuroImages) tool '*3dUnifize*' before surface reconstruction.

Table 4-1: Parameters used in performing the anatomical and echoplanar scans.

Scan parameters	T1 Anatomy	pfMRI (per run)
Image slices/ location	250	32
No of dynamics	1	183
repetition time (TR)	6.318 ms	2 s
Field of view (scan res *voxel size)	256 256 256	48 192 192
Scan resolution	340 340	128 128
Duration(s)	316	372
Slice thickness	0.75	1.5
Voxel size	0.727 x0.727	1.5 x1.5
Flip angle(°)	8	82

Functional series were aligned and motion-corrected using the AFNI program *3dvolreg*. To improve the signal-to-noise ratio, four functional runs for each subject were combined, time point by time point. Each functional run was registered to its first run in the native space. The functional MRI dataset was processed with customised AFNI and Freesurfer software. Functional images were first registered to the T1 images, and then were refined with a manual blink comparison for quality control(Mancini et al., 2012, Sereno and Huang, 2006).

After linear removal of baseline drift, functional MRI data were analysed using a Fourier transform, computed for the time series at each voxel fraction (vertex). Frequencies below three cycles per scan were ignored for calculating signal to noise, as very low frequencies are dominated by movement artefacts (Boynton et al., 1996, Boynton et al., 2012, Greve et al., 2013). No high frequency cut-off was applied. The phase angle was displayed using a

continuous colour scale. Cross-subject spherical averaging was performed with Freesurfer and used for the calculation of the geodesic distance (Fischl et al., 1999b).

Surface files containing surface sampled F- statistic statistics were put through a surface-based cluster exclusion filter using *surfclus* (Hagler et al., 2006). The output files consisted of: real and imagery components of the Fourier transform at the stimulus frequency; the real and imagery components where the complex amplitude has been replaced by a significance statistic, and the F-ratio and the surface-based cluster filtered F- ratio. The data were then visualised on *tksurfer* with vertex-number / value pairs. These values was visualised on the inflated hemisphere using the visualisation software *tksurfer* from the Freesurfer suite of programs (Fischl, 2012). The functional region of interest (ROI) area derived from the fMRI scan of the four fingertips of each hand was defined as a functional area label by the blinded researcher (FM) using *tksurfer*. The D2-D5 ROI of each hand in each individual was the area confined within the Brodmann areas from the 'Desikan-Killiany' cortical atlas that showed a significant periodic response at the spatial frequency of the tactile stimulation ($p < 0.01$). The Brodmann areas- 3a, 3b, 1 and 2- are located within the postcentral gyrus. "The rostral and caudal extents of the central sulcus were the rostral and caudal boundaries of the postcentral gyrus, respectively. The medial and lateral boundaries were the lateral bank of the precentral gyrus and the lateral fissure and/or the medial bank of the superior parietal gyrus, respectively"(Desikan et al., 2006).

4.3.5.1 Surface-based cortical morphometry measurements and geodesic distance

Each of these functional area labels were used to calculate surface-based anatomical measurements (performed by the principal investigator) including cortical surface area, cortical thickness and grey matter volume. The Freesurfer toolkit '*mris_anatomical_stats'* was used to derive these measurements.

The grey matter surface area and volume measurements were controlled for brain size by dividing them by the whole brain cortical surface area and whole brain grey matter volume respectively. The whole-brain cortical surface area was calculated by summing the surface areas of the left and right hemisphere. The whole-brain grey matter volume was derived only from surface-based calculations and not voxel counts based on the output from *aseg.stats* on *Cortex* (For further details, please see: https://surfer.nmr.mgh.harvard.edu/fswiki/MorphometryStats). The volume was calculated by taking the volume inside the pial surface, then subtracting the volume inside the white surface and subtracting the tissue inside the ribbon that is not part of cortex (e.g., hippocampus). The output variables for cortical morphometry were surface area

and grey matter volume of the fingertips region of interest maps as percentages and thickness average (Fischl, 2012).

The geodesic distance (Figure 4-2) was calculated after each ROI finger map was morphed onto the corresponding average spherical surface. The centre of the anatomical central sulcus and centroid of the ROI was located by the independent researcher (FM) and the geodesic distance extracted. The geodesic distance is the spherical distance between the centroid of the central sulcus to the centroid of the map of all four fingertips.

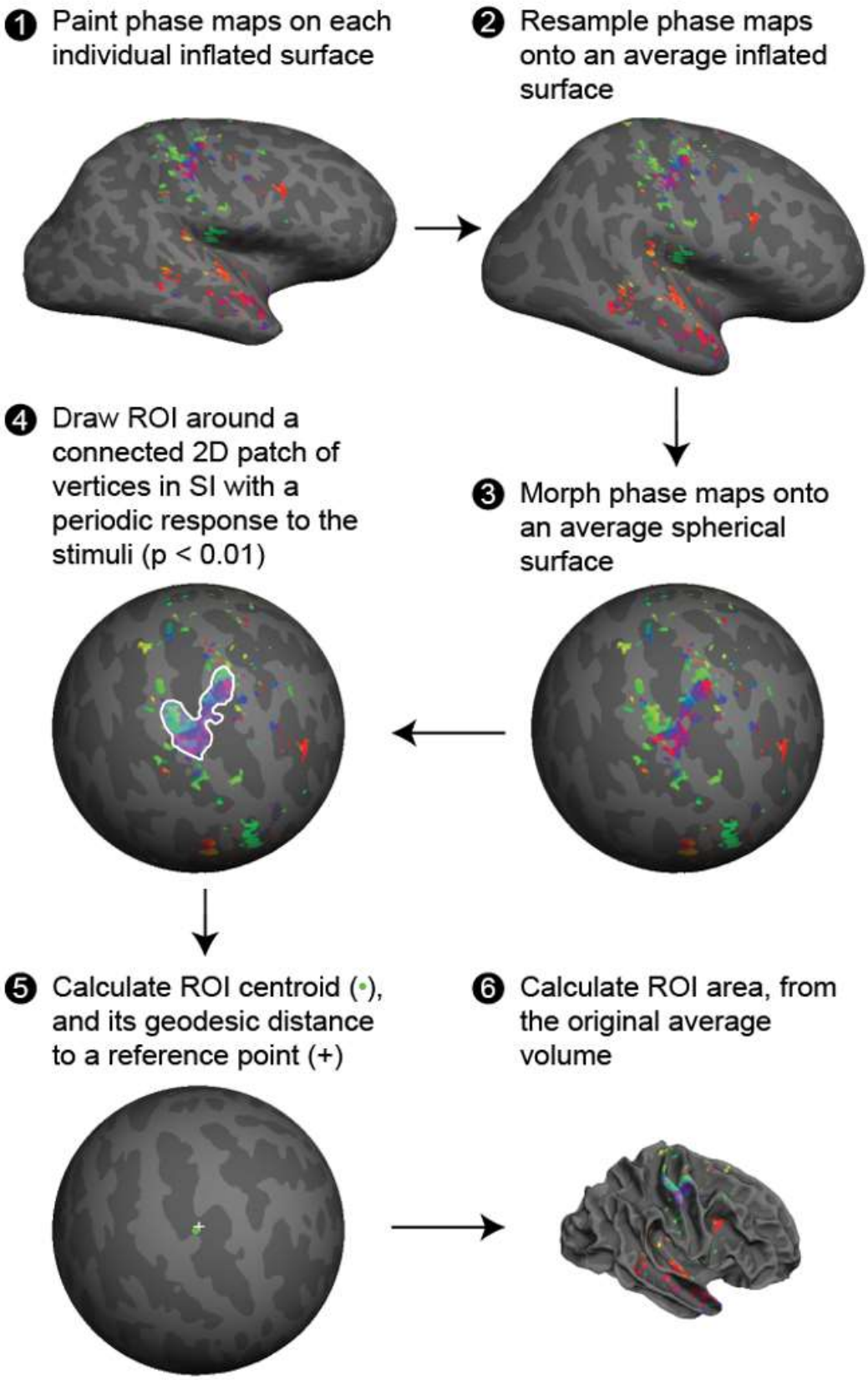


Figure 4-2: The process of determining the surface based geodesic distance[2].
The green dot represents the ROI centroid within S1 and the reference point (+) is determined to be the central sulcus.

[2] Image credit: F. Mancini.

4.3.6 Statistical analysis

Statistical analyses were performed on these anatomical measurements. SPSS version 22 was used for the analyses, using syntaxes for mixed models. The variables of age, gender and handedness were controlled for by matching unilaterally-affected upper limb CRPS subjects with healthy controls. Matching was based on assumed affected hemispheres and dominant hemispheres, as measured by the Edinburgh Handedness questionnaire (Oldfield, 1971).

Fingertip maps were displayed with colour wheels for temporal and spatial information of each finger. Each was cluster threshold corrected at $p < 0.01$ or denoted as $p < 0.05$ for illustration purposes (Please see Supplementary Information for Chapter 4 for individual participant fingertip maps). No smoothing was performed on the data. Manual blink comparisons of the fingertip maps for quality control were made to investigate the fingertip maps were within the boundaries of the Brodmann areas similar to previous work (Mancini et al., 2012, Pfannmöller et al., 2016, Kolasinski et al., 2016) .

Repeated measures mixed ANOVA was deemed unsuitable for testing surface area, grey matter volume and thickness means because there was an unbalanced design for 84 hemispheres ($n = 42$) with 19 hemisphere labels missing. The missing labels included both hemisphere labels of four controls, both hemisphere labels of three CRPS subjects, and one hemisphere label for each of another five CRPS subjects.

The underlying cortical morphometry measures were derived from the functional fingertip maps of four digits in each hand marked as the region of interest. SPSS MIXED was used to conduct a mixed linear effects model analysis for these continuous outcome measures of cortical thickness and cortical surface. Analyses assumed a random intercept and random slope, to allow for individual differences for each outcome measure. The procedure of SPSS MIXED that utilises a Satterthwaite approximation to calculate the degrees of freedom. This method is valid for both balanced and (this study) unbalanced designs. The within-subject errors were modelled using an unstructured (co)variance structure. The maximum likelihood estimation method was used; variance-covariance parameters (random effects) and fixed levels coefficients (fixed effects) were estimated by maximising their joint likelihood. The estimation was used in preference over the restricted maximum likelihood ratio test that is available only for testing the variance - covariance parameters (i.e. assuming the fixed effects are known). For further details, please see the SPSS MIXED manual (SPSS, 2015, Brown and Prescott, 2014).

The mixed linear effects model was used with step-wise modelling for: (1) random intercepts; (2) random slopes; and (3) both random intercepts and slopes because of the unbalanced design. To identify which outcome variable was to be included in the initial (data-driven) model, each variable of interest was modelled into a random intercept and slope model, combined and retained only if it predicted differences between CRPS and control. The current study modelled the variables of interest cortical surface, cortical grey matter volume, geodesic distance and cortical thickness (*a priori* hypothesised based on the literature) to determine which cortical morphometry variables could best model the predicted differences. Second, the relationship between cortical surface and cortical thickness was then modelled with group type, affected hemisphere, dominance and their various interactions as the fixed effects. To check for linearity, residuals were examined using Q-Q plots. The final mixed effects model used identified the influence of the independent variables (fixed effects) of group type, affected hemisphere, and hand dominance on the outcome measure of average cortical thickness. Pairwise comparisons were used to check the individual contributing factors from the final model. These checks also ensured that healthy control data had no significance differences that might explain our final results from mixed modelling.

Age and Gender are known co-variates that may influence brain imaging results from previous literature. The covariate of age and gender was added to the final mixed effects model to ensure that significant results were not biased (sensitivity analysis) by the effects of these covariates. A post–model analysis of the cortical thickness measurements and morphine-based medication from their medication history was used to evaluate the effect of opioid medication on cortical thickness, as an additional fixed effect in the mixed linear effects model.

Difference scores for the following variables were obtained by subtracting scores of the affected hand or hemisphere from the scores of the unaffected hand or hemisphere: ROI surface area (as a percentage of total brain area), ROI thickness, PPT, pain intensity during MRI scan and pain intensity after the MRI scan.

Exploratory correlations were made between clinical measurements and cortical morphometry measurements. The cortical morphometry measurements used were surface based grey matter volume, surface area, average cortical thickness and geodesic distances. The clinical measurements used were CRPS pain duration, pain intensity during scan, pain intensity after the scan, pressure point thresholds and age at onset of CRPS symptoms. Age at onset of CRPS symptoms for patients was the estimated age at the start of their symptoms, and for healthy controls it was recorded as their age at the time of the scan. The variables of pressure point threshold (PPT), pain intensity, surface area, grey matter volume and cortical thickness were

checked for parametric distribution using plots and Shapiro-Wilks statistics. Exploratory correlations were tested on difference scores of ROI Surface area over total brain and thickness compared to differences in: PPT; pain intensity scores during MRI and after the MRI scan; duration of CPRS and age at onset of CRPS. In all statistical testing, a minimum probability level of 0.05 was used to assess whether differences or effects were significant.

4.4 Results

4.4.1 Participants

Of the 42 subjects recruited, two subjects (one CRPS and one control) were not able to complete their scan due to a technical MRI fault and claustrophobia. The final study sample had equal numbers of completed T1 scan acquisitions for 20 healthy controls and 20 CRPS participants. Hand dominance and affected side information is given in Table 4-2: The proportion of right and left hand affected hands in participants with CRPS and healthy controls (n = 40).

Hand dominance was estimated using Edinburgh Handedness Questionnaire, answered based on their recall of hand usage prior to their CRPS diagnosis Table 4-2.

Table 4-2: The proportion of right and left hand affected hands in participants with CRPS and healthy controls (n = 40).

Hand dominance was estimated using Edinburgh Handedness Questionnaire, answered based on their recall of hand usage prior to their CRPS diagnosis.

Hand Type	CRPS	Control
Right hand dominant	17	17
Right hand affected	*9*	
Left hand affected	*8*	
Left hand dominant	2	2
Right hand affected	*1*	
Left hand affected	*1*	
Ambidexterous-(Right)	1	1
Left hand CRPS	*1*	
Total	20	20

Note: Handedness was defined by the Edinburgh Handedness Questionnaire, where left to right scores ranged from -100 to 100 (Oldfield, 1971). The Ambidextrous CRPS participant scored 4.35 and their matched control scored 12.50.

65 hemisphere labels of fingertip maps were available for analysis. Four controls and two CRPS subjects had no hemisphere labels for both hemispheres. One hemisphere label was missing from five CRPS subjects; missing labels were from the dominant (n = 4) and the non - dominant (n = 1) hemispheres. Complete ROI labels for both brain hemispheres were only present for 13 CRPS subjects and 17 controls. Cortical morphometry data of cortical thickness, surface area, and grey matter volume were not calculated for a total of 19 missing ROI hemisphere functional labels. Phase-encoded fingertip maps overlaid on high resolution T1 scans for all 65 hemisphere labels, deemed suitable for analysis by FM, are shown in the Supplementary Information for Chapter 4. Geodesic distance was only calculated if a clear centre of the ROI map from the central sulcus was subjectively assessed by the blinded assessor. Assessment of geodesic distance was missing from controls in both hemispheres (n = 4) and one dominant hemisphere (n = 1). Assessment of geodesic distance was missing from CRPS participants in both hemispheres (n = 3) and in one hemisphere (n = 5); three dominant

hemispheres and 4 non-dominant hemispheres). In total, 20 distances were missing from the analysis of geodesic distance.

4.4.2 Functional fMRI fingertip maps

Fingertip maps from healthy participants showed finger representations in the expected order from D2 to D5 i.e. located on the post central gyrus- inferolateral to superomedial in the primary somatosensory cortex. Specifically, fingertip maps were largely confined to Brodmann area 3b and 1 of the post central gyrus. This work found a common variation of rotated but still ordered fingertip maps in some healthy participants. In addition, one healthy participant (#22) had incomplete fingertip maps for the right hand. Limited visualisations of the fingertip maps were also found in a healthy control with thresholding at $p < 0.05$ (#40), loss of visualisation of the individual fingertips maps in a healthy control (#26) and complete exclusion of the data in three healthy controls (#32, #1, #42). Increased signal to noise was seen in data from some participants, for example the data from healthy participant #4 had a mirrored reflection for the four fingers with co-activation in M1 (see Figure 4-3).

Fingertips maps from CRPS participants showed wide variability in the order of the fingers. The maps showed disordered, poorly defined or merged representations of fingertips. Eight fingertip maps are shown in Figure 4-5, and all available ROI maps are shown in the Supplementary Information for Chapter 4. Limited visualisations of the fingertip maps were also found in CRPS participant #26.

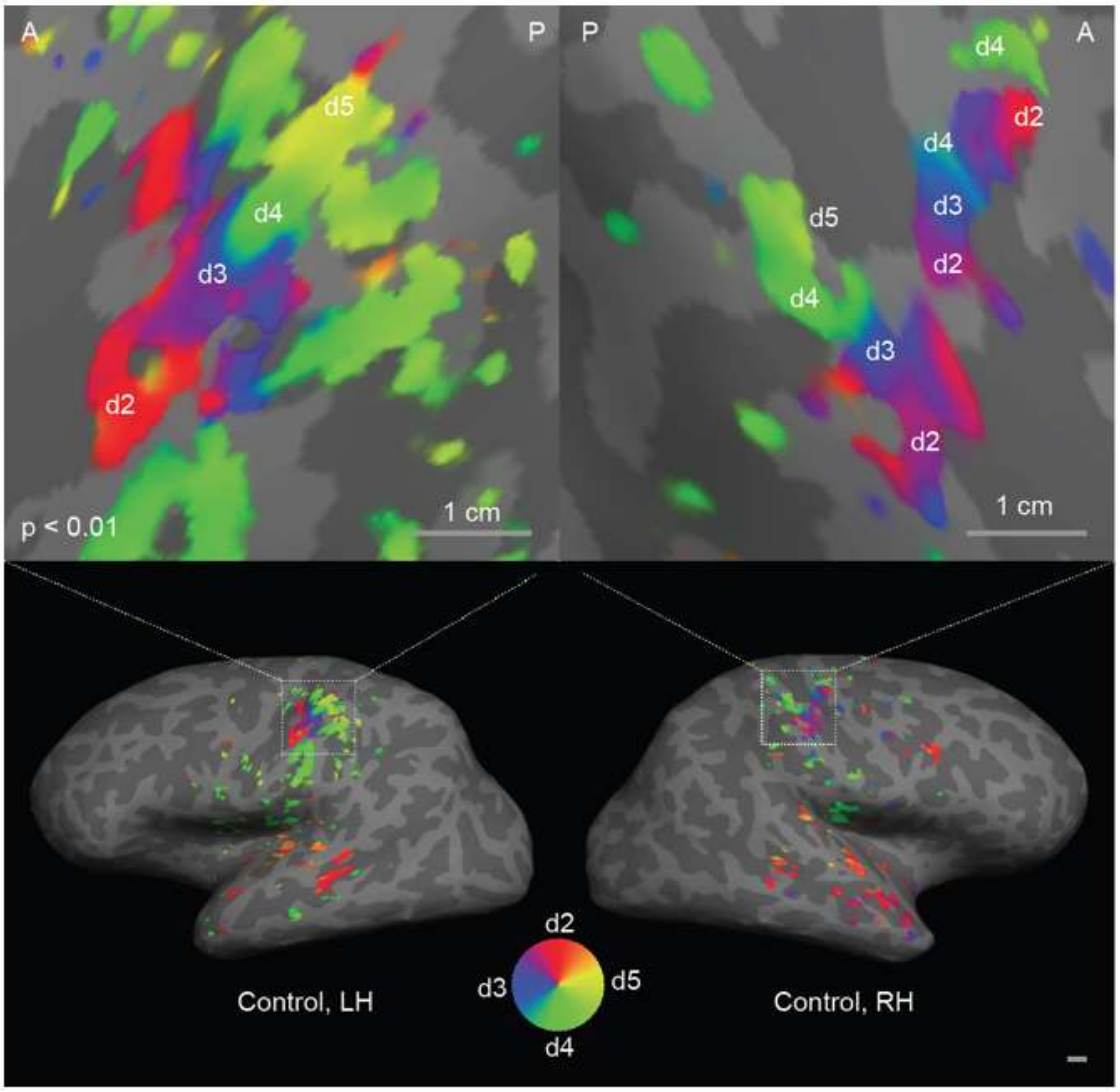


Figure 4-3: Exemplar fingertip maps of healthy participant (#4).

There is a clear order from D2 to D5 in the left hemisphere (LH) and right hemisphere (RH), with some co-activation in the primary motor cortex on the right hemisphere of the left hand. Colour wheel key: Index finger, D2, Red; Middle finger, D3, Blue; Ring finger, D4, Green; Little finger, D5, Yellow.

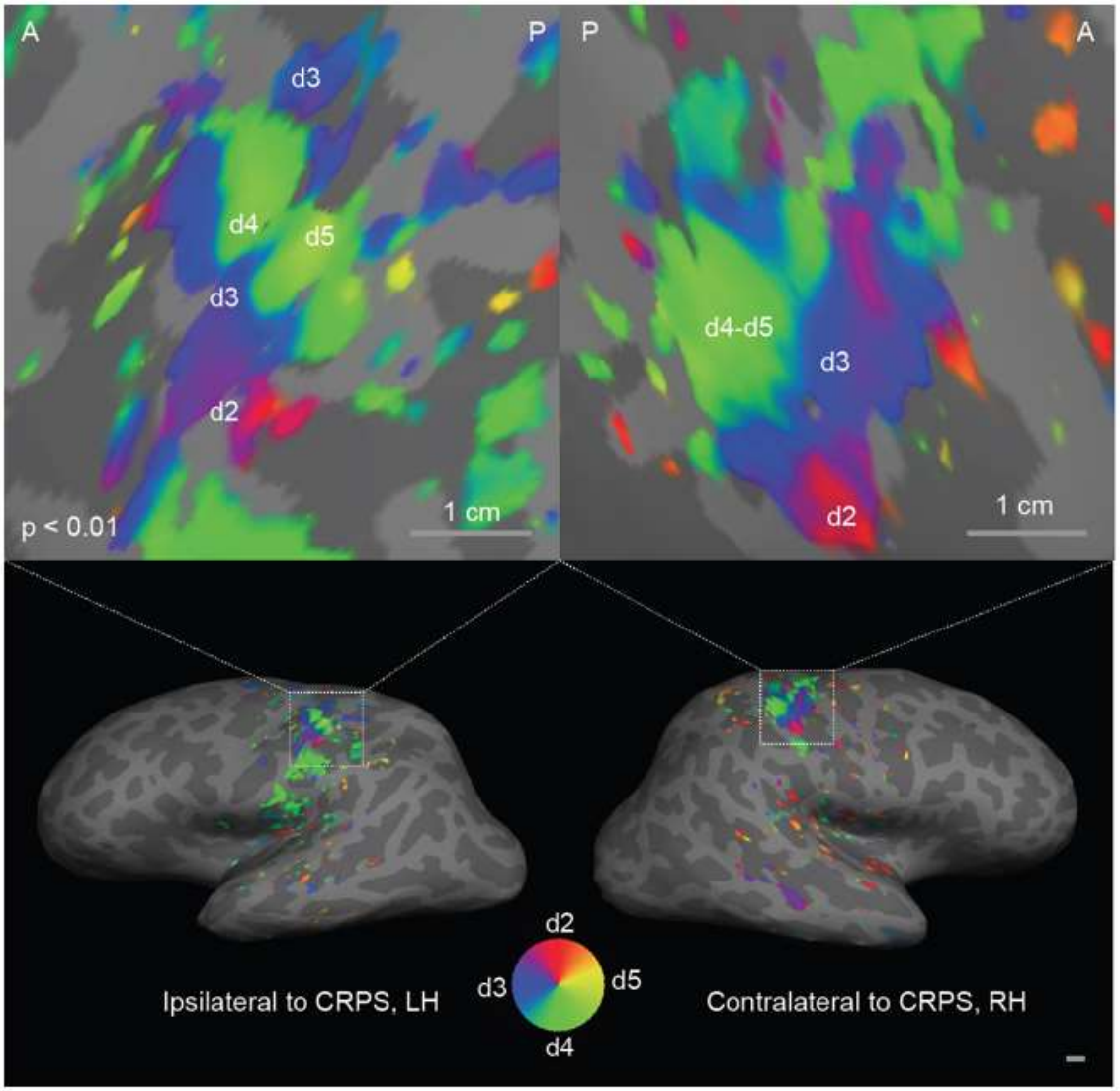


Figure 4-4: Exemplar fingertip maps of a participant with left affected CRPS hand (#6). There is a clear order from D2 to D5 in the ipsilateral to CRPS hemisphere and merged functional representation of D4 and D5 in the contralateral to CRPS hemisphere. Colour wheel key: Index finger, D2, Red; Middle finger, D3, Blue; Ring finger, D4, Green; Little finger, D5, Yellow.

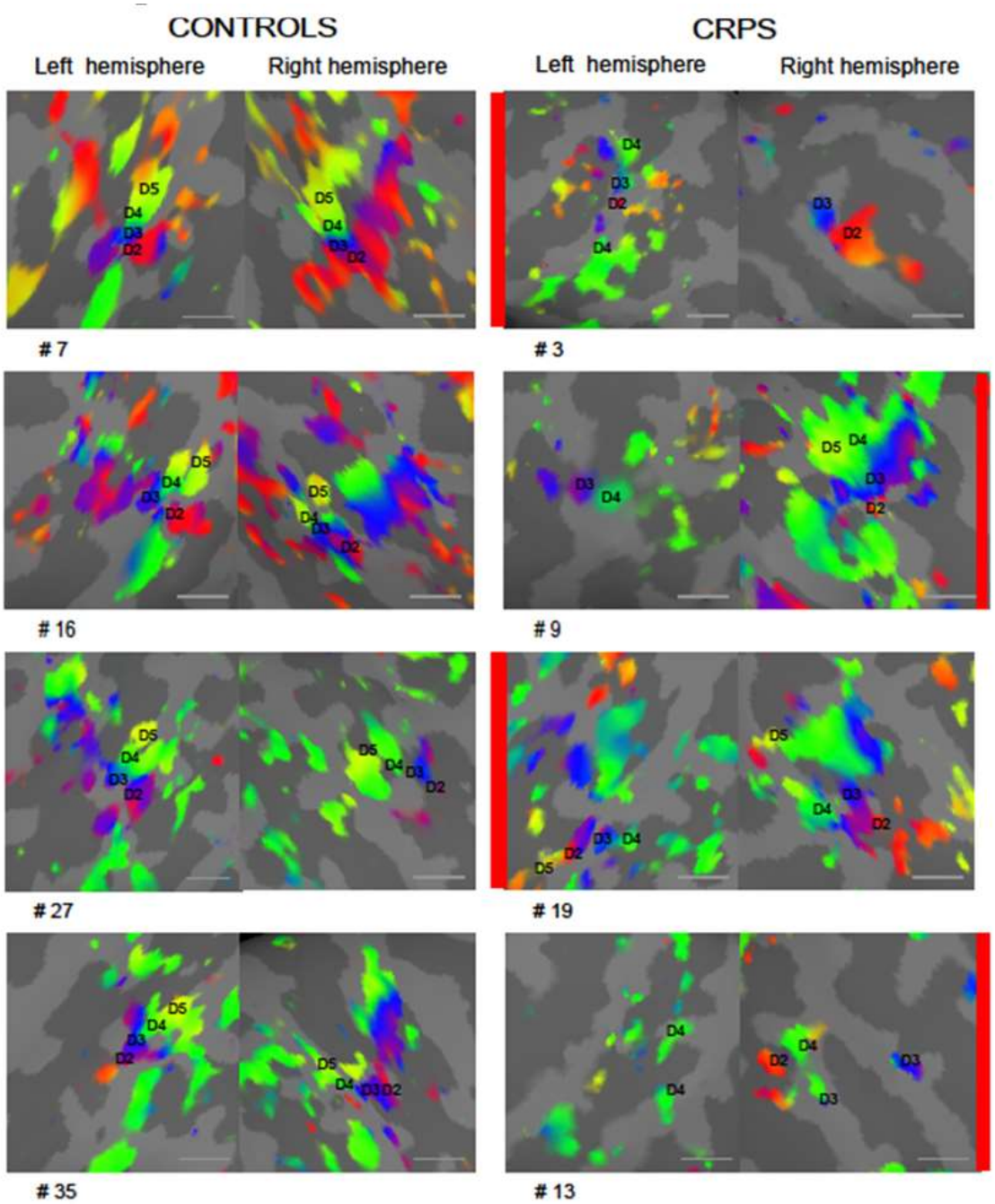


Figure 4-5: Comparisons of fingertip map activations overlaid on individual anatomical maps between controls and CRPS participants.

The single thick red vertical line on the border of the box indicates the hemisphere corresponding to the CRPS-affected hand. Fingertip activations are overlaid on high resolution inflated T1 maps (FreeSurfer) labelled with individual finger tips positions on the post central gyrus. Colour wheel key: Index finger, D2, Red; Middle finger, D3, Blue; Ring finger, D4, Green; Little finger, D5, Yellow.

4.4.3 Structural cortical morphometry

Whole-brain surface area, grey matter volume, geodesic distance and cortical thickness - were not significantly different - between the affected and unaffected hemispheres in CRPS (Please see Table 10-2 for details of pairwise comparisons in CRPS). Mean relative cortical surface area, relative grey matter volume and cortical thickness in the CRPS-affected hemisphere and the CRPS-unaffected hemisphere were reported in in Table 4-3. These included mean ROI surface area of 0.309% compared to 0.274% , the mean cortical thickness was 2.020 mm compared to 1.954 mm, and the mean grey matter volume was 0.316% compared to 0.237%.

Surface area or geodesic distance were tested in the mixed model analysis and found not to be a significant predictor of differences between CRPS and controls. Therefore, the hypothesis of a shift of the finger maps relative to the central sulcus to explain the differences between CRPS participants and controls, was not met. The pattern of CRPS fingertip map distortions was not uniform in this study sample of CRPS and unlikely to agree with previous results of surface area or grey matter volume changes or Euclidian distance differences in CRPS (Please see Chapter 1 - Neuroimaging and CRPS).

In healthy controls, the mean cortical surface area, grey matter volume and cortical thickness for the fingertip region of interest was smaller in the matched affected hemisphere than the matched unaffected hemisphere. There were no significant differences in any those measures between these matched hemispheres (Please see Table 10-1 for pairwise comparisons in controls). No significant differences were found between CRPS and controls in any of these measures (Table 4-4). There were also no significant differences found for pairwise comparisons for the factor of hand dominance in controls (Full details are available Table 10-1 in the Appendix for Chapter 4).

Table 4-3: The differences in cortical morphometry between the affected and unaffected sides in CRPS participants and controls.

Cortical morphometry data were derived from each fingertip region of interest map. Means and 95% confidence intervals for relative surface area (%), cortical thickness (mm), relative grey matter volume (%) and geodesic distance (mm) in each corresponding hemisphere are described with region of interest fingertip maps.

Group Type and Hemisphere Affected		Cortical surface area relative to total brain surface area (%)	Cortical thickness (mm)	Grey matter volume relative to whole brain grey matter volume (%)	Geodesic distance (mm)
CRPS Affected Hemisphere n = 16	Mean	0.309	2.020	0.316	9.851
	95% CI	(0.223, 0.395)	(1.797, 2.243)	(0.235, 0.397)	(5.518, 14.184)
CRPS Unaffected Hemisphere n = 15	Mean	0.274	1.954	0.237	9.216
	95% CI	(0.194, 0.354)	(1.853, 2.055)	(0.176, 0.298)	(5.014, 13.417)
Controls Matched Affected n = 17	Mean	0.303	1.862	0.258	9.204
	95% CI	(0.245, 0.361)	(1.792, 1.932)	(0.218, 0.298)	(5.725, 12.683)
Controls Matched Unaffected n = 17	Mean	0.332	2.003	0.310	8.837
	95% CI	(0.149, 0.514)	(1.864, 2.141)	(0.157, 0.463)	(6.809, 10.865)

Table 4-4: The differences in cortical morphometry between dominant and non-dominant sides in CRPS participants and controls.

Cortical morphometry data were derived from each fingertip region of interest map. Means and 95% confidence intervals for relative surface area (%), relative grey matter volume (%) and cortical thickness (mm) in each corresponding hemisphere are described with region of interest fingertip maps.

Group Type and Hemisphere Dominance		Cortical surface area relative to total brain surface area (%)	Cortical thickness(mm)	Grey matter volume relative to whole brain grey matter volume (%)	Geodesic distance (mm)
CRPS: Dominant n = 14	Mean	0.285	2.147	0.300	7.622
	95% CI	(0.194, 0.377)	(1.936, 2.358)	(0.208, 0.392)	(5.295,9.949)
CRPS: Non-dominant n = 17	Mean	0.297	1.858	0.260	11.246
	95% CI	(0.219, 0.375)	(1.746, 1.969)	(0.199, 0.320)	(6.146, 16.345)
Controls: Dominant n = 17	Mean	0.364	1.937	0.321	8.665
	95% CI	(0.184, 0.544)	(1.832, 2.043)	(0.172, 0.469)	(6.288, 11.042)
Controls: Non-dominant n = 17	Mean	0.271	1.927	0.247	9.344
	95% CI	(0.215, 0.327)	(1.802, 2.052)	(0.196, 0.298)	(6.229, 12.459)

The cortical thickness of CRPS participants was significantly different to controls; although the diagnosis of CRPS and hemisphere dominance had no significant effects on grey matter volume or surface area. Cortical thickness measurements are described in Table 4-4 and illustrated in Figure 4-10. There was a significant difference between the mean cortical thickness of the dominant hemisphere ($\bar{x}$ = 2.147 mm) and the mean thickness of the non-dominant hemisphere ($\bar{x}$ = 1.858 mm) in CRPS subjects. There was no significant difference in

cortical thickness between the dominant and non-dominant hemispheres ($\bar{x}$ = 1.937 mm and $\bar{x}$ = 1.927 mm respectively) in healthy controls.

4.4.3.1 Exploratory correlations with clinical signs

All CRPS participants in this study had reported allodynia in their respective affected hand. Pain intensity was rated using an 11-point Likert scale. During the MRI scan, the mean pain intensity rating by CRPS subjects (n = 21) was 5.84 ± 3.02, and the mean rating after the MRI scan (n = 19) was 5.58 ± 2.69. Mean pain scores for controls were minimal during the scan at mean score of 0.24 ± 0.89 during (n = 21) and after the MRI scan (n = 21) at a mean score of 0.10 ± 0.44, after the scan. Pain intensity in both controls and CRPS participants were not statistically significantly different during and after the scan with cortical morphometry measurements, $p > 0.05$.Evoked sensations of pain reported during the non- noxious tactile stimuli are shown in Table 10-3 for interest. Participants with CRPS reported increased sensitivity to pressure related pain compared to controls, as illustrated in Figure 4-6.

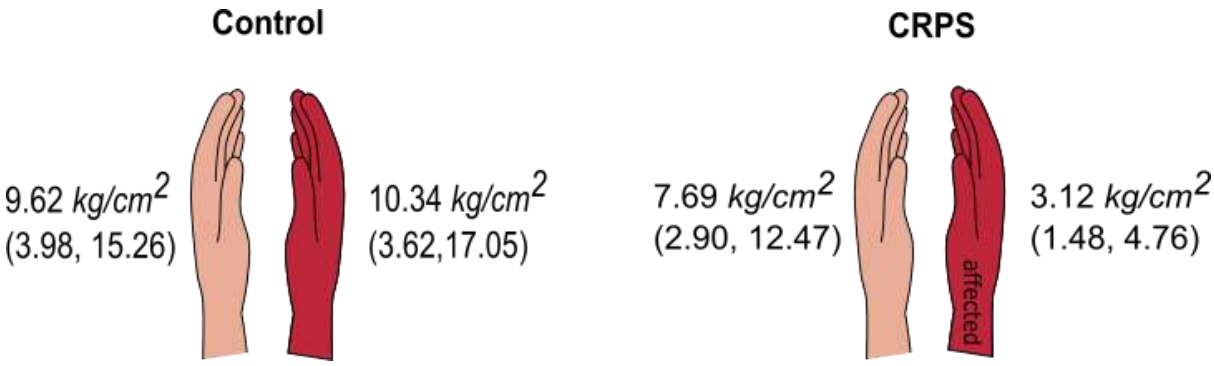


Figure 4-6: Pressure pain thresholds were compared between groups.

CRPS participants are more sensitive to pressure related pain, with lower average pressure pain thresholds (PPT) compared to controls. The lowest average PPT was found in the affected CRPS hand. PPT means and 95% confidence intervals are displayed by each affected and unaffected hands and the corresponding matched hands for controls.

Exploratory correlations between cortical thickness and the variables of age, and age at onset of CRPS were normally distributed according to the Shapiro-Wilks test. However, the cortical morphometry measurements were not normally distributed. Therefore, non-parametric Spearman's rho was calculated for these correlations. Data from healthy participant #4 were identified as an outlier due to a much larger area of the cortex devoted to the four fingertips

ROI. Sensitivity analysis without this outlier narrowed the confidence intervals (Please see exemplar between ROI surface area and cortical thickness in Figure 4-8), but did not change the significance of any results. Therefore, data for this subject were not removed from any of the analyses.

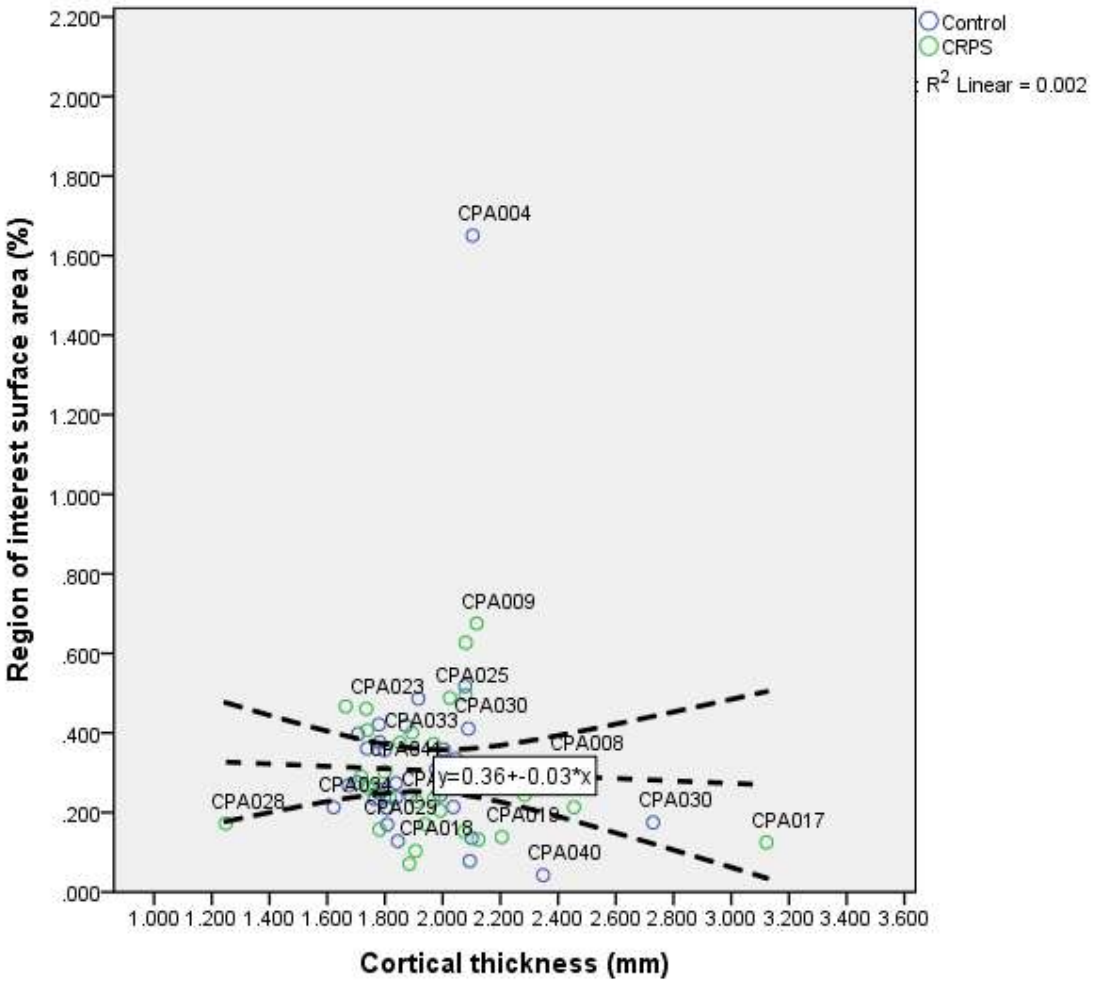


Figure 4-7: Scatterplot including outlier showing the surface area and cortical thickness. The relationship between percentages of surface area over the whole brain surface and cortical thickness within the same region of interest brain label for all participants. 95% confidence intervals for the regression line within the scatterplot are shown.

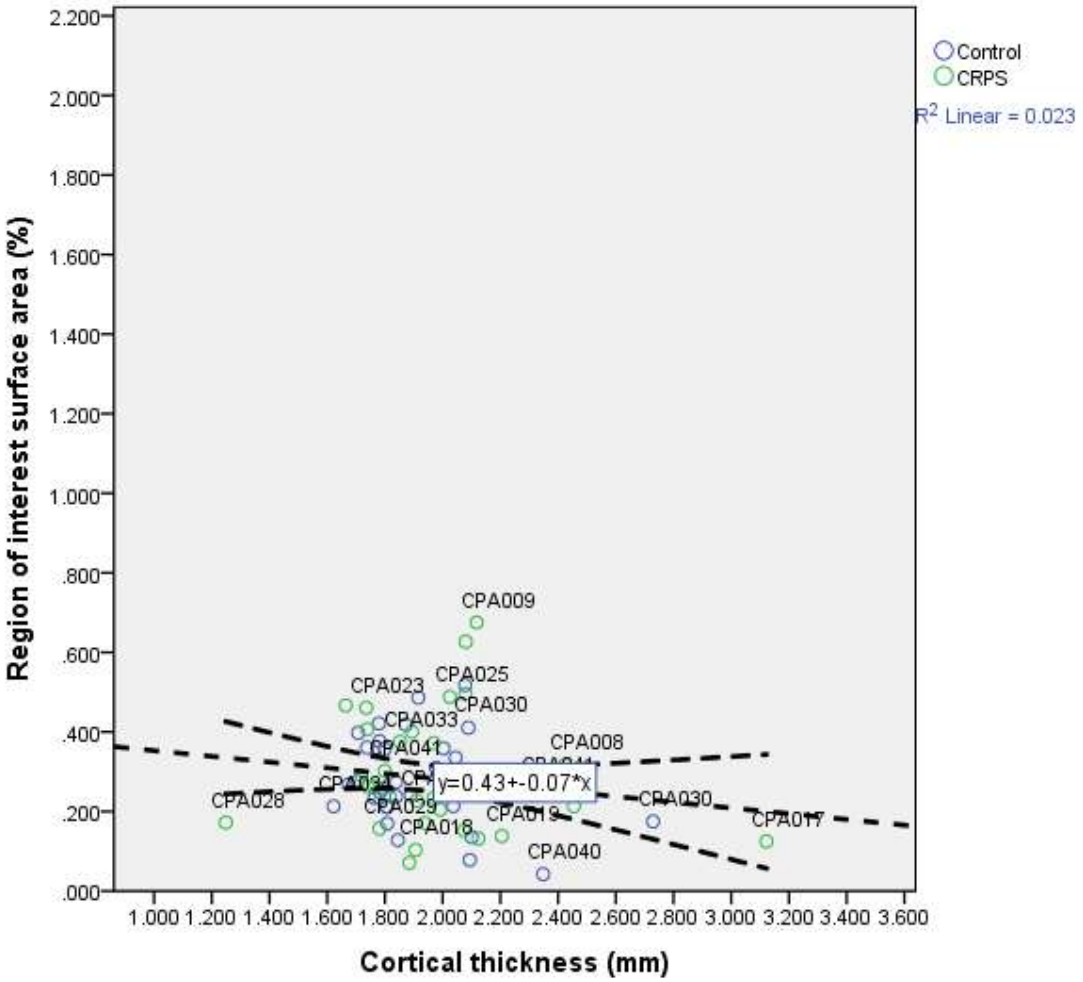


Figure 4-8: Scatterplot without outlier comparing surface area and cortical thickness. The relationship between percentages of surface area over the whole brain surface and cortical thickness within the same region of interest brain label for all participants except CPA004 are illustrated. Smaller 95% confidence intervals for the regression line within the scatterplot are shown compared to Figure 4-7.

Those CRPS participants with a longer history of pain symptoms were also more sensitive in their pressure pain thresholds. There was a significant negative correlation between duration of pain and pressure pain threshold (n = 21 per group, two hands per participant), $r_s = -0.461$, $p = 0.0001$ (two-tailed) and the age of onset of CRPS, $r_s = -0.291$, $p = 0.01$ (two-tailed). There was a strong and significant correlation between the percentage of grey matter volume in the ROI and the percentage of surface area in the ROI ($r_s = 0.823$, $p = 0.0001$). There were no significant correlations for clinical variables in CRPS participants except that pain intensity during the MRI scan correlated highly with pain intensity after the scan, and pressure pain thresholds of the affected hand were correlated with those from the unaffected hand, $p < 0.05$.

4.4.3.2 Mixed modelling analysis and post model analysis of the influence of opioids

Cortical thickness measurements and hand dominance were modelled as final predictors of group membership. Cortical ROI surface area measurements were found to be unsuitable as a predictor of group membership. The relationship between pain group and cortical thickness showed significant variance in intercepts across subjects when modelling for the following variables and their interactions: group (CRPS or control), affected hemisphere and hemisphere dominance. Stepwise model testing of random intercepts only (AIC = 17.001), slopes only (AIC = 19.419) or both (AIC= 25.419), showed that the random intercept model had the smaller-is-better form of information criteria. The random intercept model (with the smallest Akaike Information Criterion) provided the best model for goodness-of-fit of data compared to random slopes or the full model of both random intercepts and slopes. This random intercept model predicted that the interaction effect between hemisphere dominance and pain group (CRPS or controls) had significantly predicted the differences in cortical thickness between groups ($F(1, 31.592) = 5.030$, $p = 0.032$). The fixed effect of hemisphere dominance also predicted cortical thickness differences regardless of group membership ($F(1, 31.592) = 5.816$, $p = 0.022$).

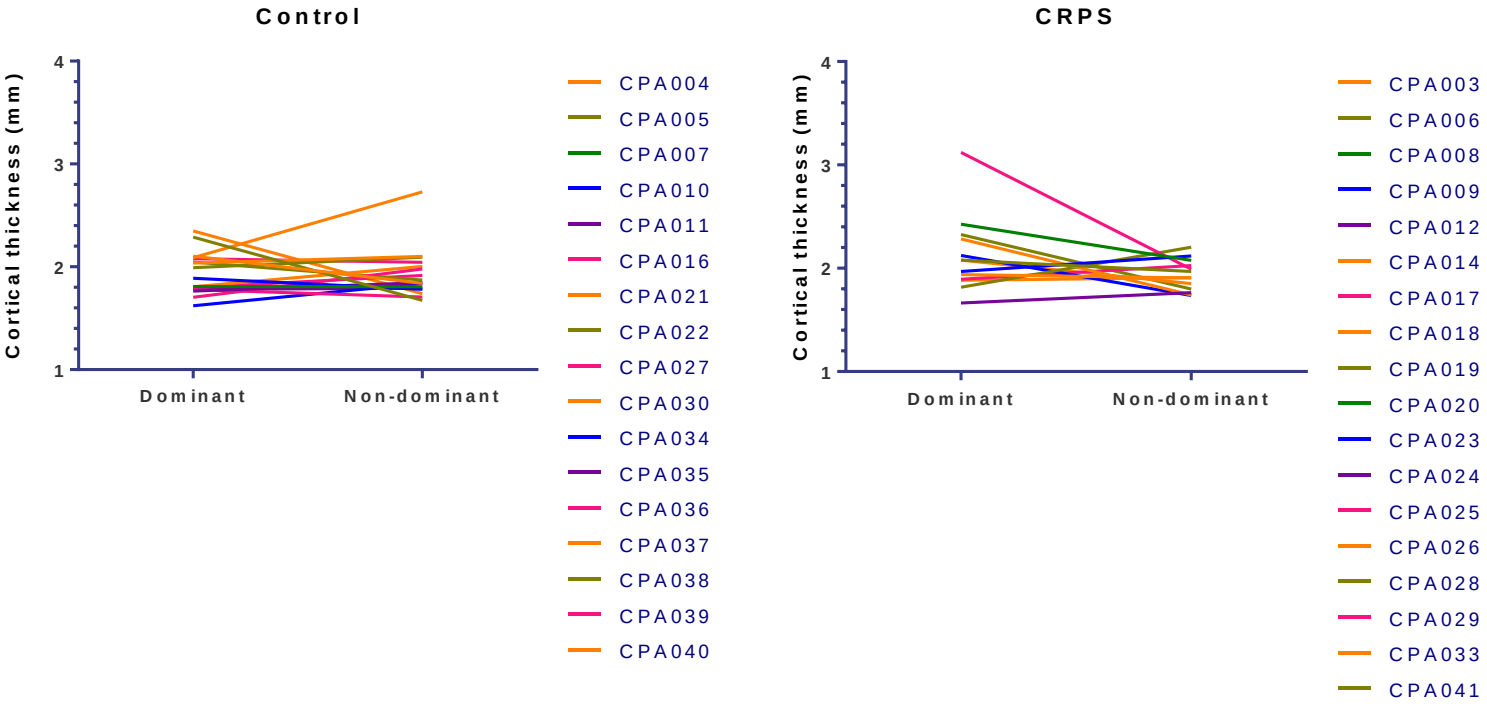


Figure 4-9: The individual data points on the line plots are shown for cortical thickness.

There is increased cortical thickness for the dominant hemisphere for CRPS compared to controls. Mixed modelling predicted the random intercepts model as the best model for the predicted differences in cortical thickness between groups, modelling the interaction effect between hemisphere dominance and pain grouping significantly; ($F(1, 31.592) = 5.030$, $p = 0.032$).

Differences in cortical thickness measurements between the groups were also influenced by hand dominance. The simple effect of group type on cortical thickness within hemisphere dominance was significant, ($F(1, 64.932) = 5.232$, $p = 0.025$). Analysis of the interaction effect showed that the effect of dominant hemisphere predicted the difference in cortical thickness between CRPS subjects and controls ($b = 0.277$, $t(31.592) = 2.243$, $p = 0.032$). Pairwise comparisons (Full details are presented in Appendix for Chapter 4) found that the mean difference in cortical thickness between the dominant and non-dominant hemispheres was significant in CRPS subjects was 0.287 mm (95% CI: 0.10, -0.469). The mean difference in cortical thickness between the dominant and non-dominant hemispheres in healthy controls was not significant at 0.010 mm (95% CI: -0.163, 0.184). Differences in intercepts for hemisphere dominance predicted cortical thickness in CRPS subjects compared to controls. The dominant hemisphere, but not the non-dominant hemisphere, predicted that cortical thickness was greater in CRPS subjects compared to controls, with a mean difference in thickness of 0.208 mm (95%CI: 0.026 - 0.389).

Recent exposure to pain medication influenced cortical thickness in CRPS participants. Eleven of the 20 CRPS subjects were currently taking opioid-based medication, four had no current or recent history of taking pain medication, and five subjects were taking other classes of pain-relieving medication including non-steroidal anti-inflammatories, amitriptyline, steroids, anti-epileptics and bisphosphonates. One participant with CRPS reported an excessive consumption of alcoholic drinks for pain relief. In the post hoc analysis of the best chosen model, this study added the fixed effect of the categorical variable of reported recent opioid use (n = 15 brain hemispheres) versus no opioid use (n = 16 brain hemispheres). None of the control group had exposure to opioids. Cortical thickness in CRPS participants, with and without opioid history is illustrated in Figure 4-11.

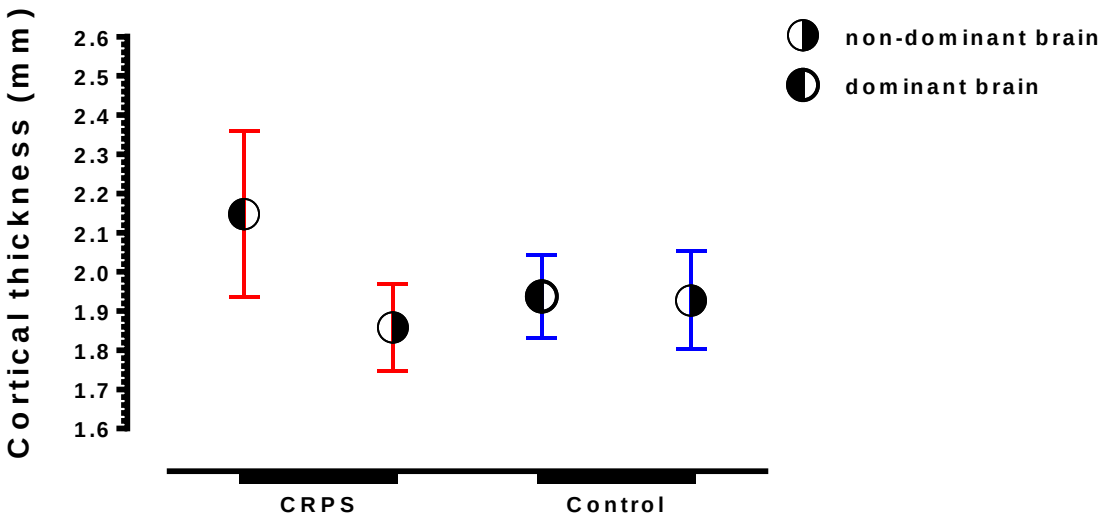


Figure 4-10: The effect of brain hemisphere dominance on cortical thickness. Original hand dominance assessed by the Edinburgh Handedness Questionnaire significantly predicted the difference in cortical thickness between CRPS subjects and controls. Symbols represent mean and error bars are 95% confidence intervals.

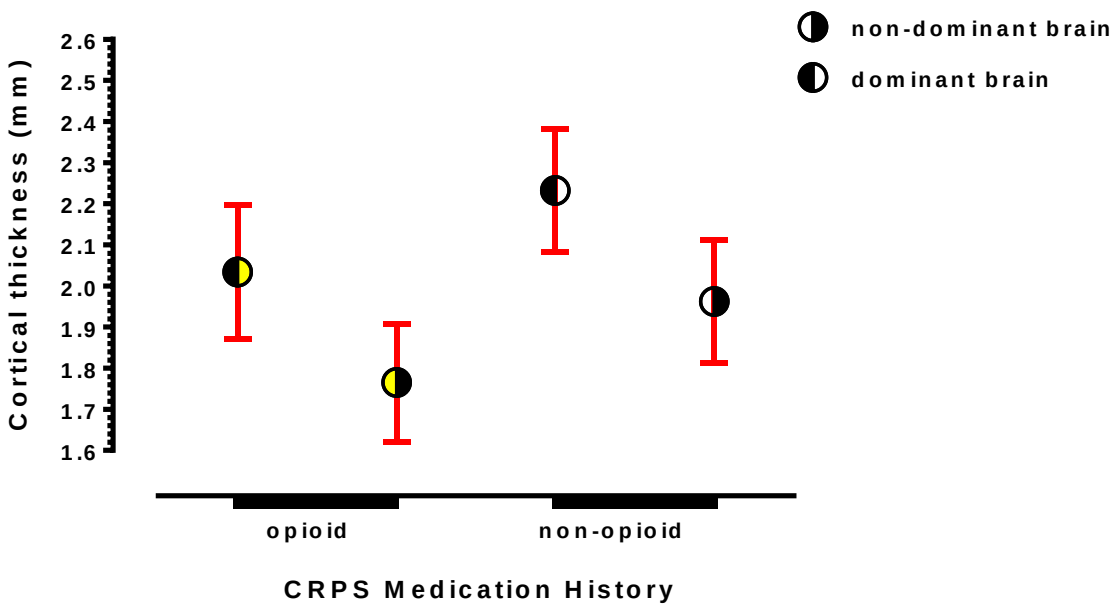


Figure 4-11: Reported history of opioid medication exposure in CRPS reduced cortical thickness, independent of hand dominance.

Error bars represent the 95% confidence intervals around each mean, with yellow semicircles representing opioid exposure and clear semi-circles representing no opioid exposure.

Cortical thickness was significantly thinner in CRPS subjects who had recent opioid exposure than in those who were unexposed (b = -0.1974, t (65) = -2.256, p = 0.027). In CRPS subjects who had recent exposure to opioid medication, cortical thickness in the dominant hemisphere (n = 6) and non-dominant hemisphere (n = 9) was 2.034 mm (95% CI: 1.871, 2.198 and 1.765 mm (95% CI: 1.621-1.908), respectively. In CRPS subjects who had no exposure to opioids, cortical thickness in the dominant hemisphere (n = 8) and non-dominant hemisphere (n = 8) was 2.232 mm (95% CI: 2.082-2.381) and 1.962 mm (95% CI: 1.813-2.111 mm) respectively. The fixed effect of opioid exposure significantly predicted cortical thickness differences regardless of hemisphere (F (1, 65) = 5.033, p = 0.028). However, updating the model for effects of medication on cortical thickness did not change the original significant effect of brain dominance and group type on cortical thickness.

4.5 Discussion

4.5.1 Functional somatotopic representation of the fingertips in the primary somatosensory cortex

Fingertip maps of healthy controls were successfully mapped and compared to the maps of those with CRPS using the new bilateral tactile stimulus paradigm developed in Chapter 3. The original study hypothesis of an orderly digit representation in S1 located from an inferior, anterior and lateral location for the index finger to a superior, posterior and medial location for the little finger (D5) was met. This was described earlier (n = 2) in Chapter 3 and was reproduced in healthy participants (n = 17) in this current study. In this study, the representation of the fingertip maps were confined to S1 region and was not subdivided into specific Brodmann regions. However, detailed inspections of the cytoarchitectural regions of the fingertip maps were made via manual blink comparisons of the fingertip maps. This quality control ensured that the fingertip maps were in these regions similar to previous work (Moore et al., 2000, Mancini et al., 2012, Schweisfurth et al., 2014, Pfannmöller et al., 2016, Kolasinski et al., 2016). These regions that constitute the S1 cannot be defined accurately on the basis of gross anatomy alone (Kolasinski et al., 2016, Moore et al., 2000) and extra functional activations beyond S1 might also reflect the increasing evidence that touch has some form of interplay between sub modalities in the cortical neurons (Saal and Bensmaia, 2014, Saal et al., 2017).

These orderly fingertip maps of four digits from both hands found in these experiments augments the body of evidence in previous finger somatotopy in S1 by: Francis et al. (2000) in two digits in the left hand (n = 8); Overduin and Servos (2004) in three digits in both hands (n = 6); Nelson and Chen (2008) in all five digits in the right hand; Sanchez-Panchuelo et al.(2010) in all five digits in the left hand (n = 5); Schweisfurth et al. (2014) in all five digits in the dominant hand (n = 14) and Sanchez-Panchuelo et al. (2014) in three digits in the left hand (n = 4). Finger somatotopy in controls derived with an efficient BFP share similar characteristics in anatomical order and orientation reported by the previously reviewed research studies on healthy controls. This paradigm was tolerated by participants with CRPS for the duration of the scan and had no consequential loss of data due to intolerance of the tactile stimulus which was reported by Di Pietro et al. (2015) with their vibrotactile stimulus.

The hypothesis that patients with CRPS have distorted functional somatotopic maps of the fingertips in S1 compared to controls was confirmed. These functional distortions were widely variable including: disordered maps; maps spreading across into the primary motor cortex or posterior parietal cortex; unclear maps with some missing fingertip representations; maps with rotated or maps with enmeshed functional representation of several finger tips (Figure 4-5). No

uniform pattern of map distortions emerged in the CRPS participants and using the common approach of deriving a group average map of each hemisphere would have been an inadequate description (For further details, please see 10.2.3: Supplementary Part C – Average group functional fingertip maps). A whole group hand type of analysis might be useful for controls but less so for CRPS as it is uncertain whether the hand area could have shifted in CRPS, found in previous work (Maihöfner et al., 2003, Pleger et al., 2006). Individual fingertip maps take advantage of the higher spatial resolution from the fMRI design used. Further, manual blink comparisons of the individual maps with their matched controls found no evidence of an overall smaller hand representation of the affected hand in CRPS (Maihöfner et al., 2003, Di Pietro et al., 2013b) or a healthy hand representation in CRPS that was larger (Di Pietro et al., 2015) than either the dominant or non- dominant hand in healthy controls.

Bilateral distortion patterns in the fingertip maps were apparent in some CRPS participants despite the study sample including only those with unilateral upper limb CRPS symptoms. These heterogeneous changes lends some support to the idea that maladaptive neuroplasticity changes might impact the unaffected-CRPS side, reported from clinical observations by van Rijn et al. (2011) or Shenker et al. (2015) and reported in fMRI by Di Pietro et al. (2015) in findings of a larger unaffected hand representation in S1 in CRPS. Observations of a reduced hand size representation in the CRPS- affected hemisphere have been explained as related to chronic noxious stimulation of the upper limb resulting in overlapping or “smeared” cortical finger representations (Juottonen et al., 2002, Maihöfner et al., 2003). Previous studies of S1 on CRPS functionally mapped the thumb, but this was not of interest in this study as the goal was the overall description of direction and distribution of fingertip maps and to be as efficient as possible within the time limits considering subject tolerability concerns (Barch et al., 2013). Although these findings did not yield the same conclusions as the study by Di Pietro et al. (2015) or by van Velzen et al. (2016), this study agrees in principle that the commonly accepted notion that there is a smaller CRPS – affected hand representation in S1 is now under dispute.

The use of fixed cluster thresholding and the participant variability in BOLD responses limited the visualisation of the study data, despite the use of the best available techniques for data acquisition. Limited visualisations of the fingertip maps were found in a healthy control (#40) and a CRPS participant (#26), loss of visualisation of the individual fingertips maps in a healthy control (#22) and complete exclusion of the data in another healthy control (#32). Increased noise was seen in data from some participants, for example the data from participant #4 where the data shows co-activations of the four fingers in M1 and S1 (see Figure 4-3). As previously mentioned, these extra fMRI activations might reflect some form of interplay between sub modalities in the touch cortical neurons (Saal and Bensmaia, 2014, Saal et al.,

2017). Future studies should be consider individualised thresholding rather than fixed cluster thresholding for spatial quantification of fingertips (Glasser et al., 2016, Dubois and Adolphs, 2016) and would better adapt to measurements in cortical morphometry.

The current study accepts that a limitation of these fingertips maps is that patterns of fingertip maps in S1 might actually implicate allodynia associated with innocuous touch in CRPS rather than just disordered tactile maps (Table 10-3). Therefore, the co-activation of nociceptive maps (Mancini et al., 2013, Disbrow et al., 1998) with tactile maps in S1 cannot be disentangled as the majority of participants with CRPS reported pain during the scan and healthy participants had no pain with the stimulus. The notion that this possible entanglement could be discounted is by functionally mapping nociceptive maps in CRPS without the confounding effect of tactile stimulation.

The current study also addressed two major concerns, unclear sampling methods bias and unblinded outcome analysis, about previous fMRI studies in CRPS identified in the S1 review by Di Pietro et al. (2013b).The sampling technique in Overview of Study Sample - Chapter 2 was clearly defined and the strict research Budapest criteria used unlike the older criteria used in the only other CRPS morphometry study Lee et al. (2015). The fMRI data were processed and reported by a researcher (FM) blinded to group membership.

4.5.2 Cortical morphometry

The anatomical area underlying the functional fine-grained fingertip maps provide an inferred measure of the CRPS neuronal cytoarchitecture (Wagstyl et al., 2015) in this study. Surface based measures in S1 in this study were chosen as they provide improved accuracy than traditional volumetric measures. This is because the surface co-ordinate system is more faithful to the actual variability of the folds of the cortex (Fischl et al., 2008, Hinds et al., 2008). These measures are supported by studies which compare actual anatomical slices of the brain to the predicted topology given by these tools (Hinds et al., 2009, Cardinale et al., 2014).

There were no significant inter hemispheric differences in any of the cortical morphometry measures in healthy controls based on hand dominance or matched CRPS-type hemispheres (Please see Table 10-1 in Appendix for Chapter 4 for further details). The ROI fingertip maps had greater mean relative cortical surface area, relative grey matter volume and cortical thickness in the CRPS-affected hemisphere than the CRPS-unaffected hemisphere. However, the CRPS affected or unaffected hemisphere was not a significant predictor of group differences

in CRPS. This contrasted with previous studies (Di Pietro et al., 2013b, Maihöfner et al., 2004, Pleger et al., 2006) that found that the affected hemisphere was smaller.

This work hypothesised that a larger cortical surface and volume area would be accompanied by cortical thinning in CRPS, but this was not supported by the analysis of the neuronal structure underlying CRPS fingertip maps. The only predictor was increased cortical thickness in S1, which along with hand dominance were the best predictors of significant differences between CRPS and controls. This was despite CRPS participants being equally affected in either their original dominant or non-dominant hand (see Table 4-2). The only other study in CRPS that had investigated cortical thickness by Lee et al. (2015) also identified cortical thickness was the only predictor for neurocognitive deficits in CRPS (Lee et al., 2015). The effect was a decrease in this measure rather than the current study's finding of increased cortical thickness in S1.

Firm interpretations from structural neuroimaging research are elusive at present. The findings of the current study argue that the variable direction of cortical thickness changes in the CRPS brain indicates dependency on the particular brain function being evaluated. Lee et al. (2015) had concluded that reduced cortical thickness in the right dorsolateral prefrontal cortex (DLPFC) and the left ventromedial prefrontal cortex were associated with a decline in neurocognitive function performance in a mixed multi-limb clinical CRPS study. This study has demonstrated similar results of an increase in cortical thickness investigated previously in chronic pain conditions such as chronic migraine (Maleki et al., 2012), chronic low back pain (Kong et al., 2013) and chronic trigeminal neuropathic pain (DaSilva et al., 2008).

Although the direction of cortical thickness changes were opposite to that which was hypothesised, thickness changes in the cortex may occur independently from surface area, grey matter volume and geodesic distance. Previous research suggests that due to distinct genetic and phenotypic independence (Winkler et al., 2010); surface area and cortical thickness measurements should be considered separately (Van Essen, 1997). Cortical thickness changes in this current study might indicate underlying neuronal loss, reduced size of neuronal cell bodies or degradation (Van Essen, 1997) or a consequential changes to structural hierarchical level of sensory processing (Wagstyl et al., 2015, Cardinale et al., 2014) in CRPS.

Increased ROI cortical thickness of S1 fingertip maps were predicted by original hand dominance in CRPS participants versus these differences were not found in controls. In the dominant hemisphere, the model predicted the mean cortical thickness of CRPS subjects to be 0.208mm (95% CI: 0.026, 0.389) greater than that of control subjects. This mean predictive

effect is at least 9% of the mean cortical thickness of the dominant CRPS brain hemisphere, larger than any possible differences that might occur due to marginal processing errors (95% CI: 1.1 – 7.7%) on different computer platforms (Gronenschild et al., 2012). Age and gender are known predictors of brain morphometry measures (Good et al., 2001, Moayedi et al., 2012, Ruigrok et al., 2014). These results remain robust when age and gender were modelled as co-variates. Age and gender were not retained in the final model. The final model from the mixed linear effects analysis was the random intercepts model with a significant interaction between group membership (CRPS or control group) and hemisphere dominance.

None of the correlations were significantly related to cortical morphometry measurements but some variables were related as found in previous literature investigating pain and sensory changes in CRPS (Rommel et al., 2001, Drummond, 2010, Birklein et al., 2000). For example, CRPS participants who had a longer history of pain symptoms were younger at the onset of CRPS; r_s = -0.291, p = 0.07 (two-tailed) and had increased hyperalgesia in their pressure pain thresholds; r_s = -0.461, p = 0001 (two-tailed).

Anatomical data correlations were as expected for both CRPS and controls. The percentage of grey matter volume in the ROI was highly correlated to the percentage of surface area in the ROI (r_s = 0.823, p = 0.0001). These changes in grey matter volume are often highly correlated as reported in the literature from healthy controls (Worker et al., 2014, Winkler et al., 2012, Winkler et al., 2010).

Several theories might explain the study's functional imaging and structural morphometry results in CRPS. This current study suggests that a redistribution of the lateralised pattern previously available with their original dominant hand might occur in CRPS. For example, all manual tasks require the use of either a preferred dominant hand in unimanual tasks or assistance by the non-dominant hand in bimanual tasks. CRPS symptoms might redistribute the laterality associated with hand dominance on manual tasks. Therefore, cortical changes of the underlying neuronal structure in S1 and hand dominance might explain this redistribution of the hand laterality found in CRPS more than affected versus unaffected hand in S1 changes (Di Pietro et al., 2015, Di Pietro et al., 2013b). The concept of being forced to use a non-dominant hand has been found in: previous education practices for left handers with resulting bilateral brain related changes (Siebner et al., 2002, Kloppel et al., 2007, Kloppel et al., 2010, Grabowska et al., 2012) and the concept of being forced to use an unaffected hand has been investigated before in constraint-induced therapy for stroke (Wittenberg et al., 2003, Corbetta et al., 2015). Therefore, future CRPS studies should at least account for hand dominance as a

factor in their analysis of structure and function in neuroimaging rather than merely collecting it for demographic purposes (Freund et al., 2010, Lee et al., 2015).

The effects of opioids on the results of neuroimaging studies in CRPS are lacking (Di Pietro et al., 2013a, Di Pietro et al., 2013b, Lee et al., 2015). Ranger et al. (2013) reported that opioids had an effect of increased cortical thickening in the anterior cingulate in pre-term infants, opposite to the effect found in this current study. The study data also contrast with the study by Lee et al. (2015) which found that there was no effect modification of opioids on their overall results of reduced cortical thickness in their simple factorial analysis of variance. However, this study results are supported by a similar effect of reduction but to grey matter volumes of the amygdala in a small pilot (n = 10) by Upadhyay et al. (2010) in opioid dependent but pain-free subjects. In contrast, long term increased grey matter volumes were associated with opioid usage in chronic back pain after just a month of taking opioids (Younger et al., 2011). These studies (Younger et al., 2011, Upadhyay et al., 2010, Gustin et al., 2010, Attarian et al., 2014), previously discussed animal studies and this current study support the concept of long term alteration of structural brain matter from any exposure to opioids. However, this current study urge caution in generalising these results to other populations of pain subjects since this study's best predictive model was the random intercept rather than the random slope model (The latter model allows generalisation beyond the individuals in the study). Although opioid medication had a global effect of thinning in the cortical cortex, this study did not measure medication usage directly and therefore this effect may be subject to recall bias.

The current study used surface based methods on high spatial resolution data, allowing for natural occurring cortical gyrification, that also reduces subject inter-variability (Wagstyl et al., 2015) for the measurement of geodesic distance. This differs from the measurement of Euclidian distance that is the shortest distance through 3-dimensional space (see Appendix for Chapter 4). There were no significant interhemispheric differences found in controls for all morphometry measures. In CRPS participants, geodesic distance mean scores (Table 4-4) were smallest in the CRPS-dominant hemisphere and largest in the CRPS non-dominant hemisphere. Geodesic distance mean scores were larger in the CRPS affected hemisphere compared to matched controls and the CRPS unaffected hemisphere. However, the geodesic distance results from the current study did not model differences between CRPS and controls. Therefore, the second hypothesis that the centroid of fingertip maps of CPRS patients would be altered due to a shift of the position of the finger tips relative to the central sulcus (Areas 3b and 1) was not supported. Thus, suggesting that interhemispheric differences previously found between CRPS and controls using the Euclidian distance, between the thumb and little finger in fMRI (Di Pietro et al., 2015) or from the lip to the mid-point of the hand using MEG (Maihöfner et al.,

2004, Maihöfner et al., 2003), might not be reproducible with surface based techniques or that this study sample differed due to the selection criteria.

Mixed models are statistically efficient due to data inclusion methods. All available data from this study sample was included even if data were missing from one hemisphere. The sample size had 18 participants with CRPS with ROI labels in both hemisphere (n = 13) and one hemisphere only (n = 3). Therefore, this CRPS sample size was comparable to relevant neuroimaging studies in CRPS by: Di Pietro et al. (2015), n = 12; van Velzen et al. (2016), n = 19; Lee et al. (2015), n = 25; Pleger et al. (2006), n = 17 and Maihöfner et al. (2003) , n = 12. However, the last two studies used MEG which has improved temporal or poor spatial resolution and the study by van Velzen et al. (2016) only evaluated structural but not functional differences. The CRPS study sample by Lee et al. (2015) had multi-limb involvement of CRPS and a less strict IASP criteria as their inclusion criteria which limits the comparisons to this current study.

Recommendations for future functional and structural neuroimaging studies include the use of the highest possible spatial resolution with an adequate stimulus for improved individualistic description of functional fingertip map changes and account for potential factors such as the role of hand dominance. The influence of confounding factors should also be considered including pain medication and pain history from childhood. Future research on structural cortical morphometry measurements and opioid use might include: controlling the dose and duration of medication use; comparing to people with opioid dependency that have no pain; investigating the effect post long-term withdrawal from pain medication and assessing handedness.

4.6 Conclusion

The current study provides the first comprehensive description of the functional fine-grained individual fingertip maps associated with painful allodynic touch in CRPS using phase encoded fMRI. There were no distinct functional fingertip map patterns for CRPS-affected hands, but a range of distorted patterns disputing the accepted notion of a smaller CRPS affected hand representation. This study also found that the patterns of distortions in fingertip maps are unlikely to be adequately quantified with two representative points and can be improved upon with newer spatial and temporal resolution from phase encoded fMRI techniques with surface based cortical analysis.

At the time of writing, cortical thickness changes in S1 associated with functional fingertip maps had not been reported before in CRPS. An increased cortical thickness in S1 with original

hand dominance history was the only measure to predict significant differences between CRPS and controls, rather than which side was affected by CRPS. Furthermore, a history of opioid use was associated with global reduction in cortical thickness underlying the ROI fingertip maps in CRPS. This current study suggests that the findings associated with cortical thickness and hand dominance appear robust within the study sample whilst urging a sense of caution for generalisability beyond the study sample.

The current study also suggests future CRPS neuroimaging studies that aim to discover the relationship between CRPS pain and brain changes should investigate cortical thickness and hand dominance. Surprisingly, hand dominance is often reported as demographic characteristics in CRPS studies but not investigated as a potential predictor of cortical changes in CRPS. The focus on which side is affected and painful in CRPS and how this has affected cortical function might have been misguided in the past. This is despite that the interaction of hand dominance would have fundamentally altered post CRPS for all patients.

5 Changes in a 'finger' illusion in complex regional pain syndrome (CRPS)

5.1 Introduction

Complex regional pain syndrome (CRPS) is characterised by excessive pain, usually in a peripheral limb such as the hand; affecting touch, movement and eventually function (Marinus et al., 2011). Deficits in the affected hand in CRPS include higher thresholds for two-point discrimination in the index finger (Pleger et al., 2006), impaired hand size estimation (Moseley, 2005a, Peltz et al., 2011), finger misidentification (Forderreuther et al., 2004, McCabe et al., 2005), errors in bilateral limb positioning (Lewis et al., 2010) and reduced fine motor skills (Kolb et al., 2012). These deficits implicate distortions in body representation (Tsay et al., 2015) and cortical re-organisation in CRPS (Forderreuther et al., 2004, Lewis et al., 2007, Lotze and Moseley, 2007, Lewis and Schweinhardt, 2012, Birklein and Schlereth, 2015), but the exact mechanisms are still debatable (Forderreuther et al., 2004, Legrain et al., 2012).

Several of the deficits in CRPS are also associated with both the affected limb and the side of space in which the affected limb usually resides. These problems include spatially-defined prioritisation of tactile stimuli (Moseley et al., 2009), midline-dependent changes in thermoregulation (Moseley et al., 2013), spatial judgement performance (Reid et al., 2016), motor imagery and motor control, spontaneous pain and the sense of ownership over the limb (Moseley et al., 2012a). These disruptions were conceptualised by Moseley et al. (2012b) in terms of the cortical body matrix - an integrative theory involving a dynamic neural representation of the body and the space around it. Their experimental work, and case reports on CRPS (Galer and Jensen, 1999, Frettloh et al., 2006, Bultitude and Rafal, 2010), suggest a causal link between disrupted body representation in CRPS and pain (Haggard et al., 2013). For a comprehensive review of the perception of bodily illusions in healthy subjects and perceptual dysfunction in CRPS, please see Chapter 1.

During a bimanual task, the reliability of a given sensory channel determines its influence on proprioception, such that the least reliable input is sometimes discarded completely (Buckingham et al., 2010, Kelso et al., 1979, Iandolo et al., 2015, Squeri et al., 2012, Wong et al., 2014). Task performance from each hand also depends on the relative influence of interhemispheric inhibition and coordination (Vercauteren et al., 2008). The weighting of proprioceptive information from each hand also depends on the relative reliability of each input (Wong et al., 2014). These various contributors to performance are all critical for optimal motor and sensory function (Ostry et al., 2010). However, people with unilateral upper limb CRPS

show poor motor and sensory function (Kolb et al., 2012, Wasner et al., 1998, Schilder et al., 2012) including: reported deficits in bilateral joint positioning (Lewis et al., 2010, Bank et al., 2013); greater variability in generating the necessary movement amplitude; and poor co-ordination for bimanual tasks (Maihöfner et al., 2007, Bank et al., 2015, Bank et al., 2013).

This study aimed to determine whether people with unilateral CRPS of the upper limb have reduced weighting of bimanual hand representations. The aim was also to determine whether proprioceptive input from their unaffected hand was weighted more than proprioceptive input from the affected hand. Finally, this study aimed to determine whether this imbalance also depends on which side of space their hands are located. To test these predictions, this study used a novel artificial finger illusion in which healthy people perceive their hands to be closer together than they really are (Heroux et al., 2013, Walsh et al., 2011); an illusion that reflects the weighting of bimanual representations. This work hypothesised that people with CRPS would report increased awareness of the perceived location of their hands; hence the illusion would be weaker in people with CRPS than in healthy controls. The secondary hypothesis was that people with CRPS would have a weaker sense of ownership when grasping the artificial finger, a sense also thought to be dependent on bimanual representations.

5.2 Methods

5.2.1 Recruitment and Ethics

A controlled experiment using matched pairs was used to investigate the finger illusion in CRPS. Recruitment of participants was by convenience sampling. Participants were recruited into the study through advertising from the Australian states of Victoria, Queensland, South Australia, New South Wales, and included a concurrent Sydney-based study investigating recovery following wrist and hand fractures (Parkitny et al., 2013b). Participant consent and all experimental procedures were carried out in accordance with the Declaration of Helsinki (2008). The University of New South Wales Human Research Ethics Committee and South Eastern Local Health District Ethics Committee approved the study. The approval numbers were HC13214 and HREC 10/051 respectively.

5.2.2 Participants

Telephone screening, consent and assessment procedures were separated. Responders to the advertisement, aged 18 to 89 years with sufficient command of the English language for the study, were included for preliminary telephone screening. Those screened to be suitable were invited for an assessment at the investigation site or at their home. The result from each

assessment was re-checked against the study criteria by a different researcher. These researchers were also blinded to any previous clinical diagnosis of CRPS in the participants. Only participants with unilateral upper limb CRPS using the Budapest research criteria (Harden et al., 2010) were included. As participants with CRPS had one affected hand or upper limb, their other hand or upper limb was assumed to be their "unaffected" hand or side. Healthy pain-free participants were included if they had no previous history of a chronic pain disorder, excessive medication or drug usage and were currently pain-free. Healthy pain-free participants were matched with CRPS participants for potential confounders: age, gender and hand dominance as evaluated by the Edinburgh Handedness Inventory Questionnaire (Oldfield, 1971). Exclusion criteria were: pregnancy; any other areas of significant pain (for participants with CRPS); and any significant medical disorders that the experimenters felt, *a priori*, would impact on their participation.

5.2.3 *Experimental procedure*

5.2.3.1 Equipment

A custom made box (length 50 cm, width 30 cm, height 15 cm), with an upper and lower platform, each covered with memory foam (1 cm thick) on which to place two forearms and hands, was placed on a table in front of a height adjustable chair but concealed with drapery. Inside the box was a rigid metal shaft with an artificial finger attached perpendicular to the shaft at its top. This artificial finger was made from silicone with a narrow rigid plastic cylinder (diameter 0.5 cm, length 3 cm) running down the inside of the finger like a bone. The distance from the artificial finger to the mid-point of the pipe was 12 cm. A small pipe (2.5 cm diameter, length 5 cm) was attached perpendicular to the shaft at its bottom. A chart holder was placed at eye-level, in front of the participant. Each chart had 21 randomly ordered distance markers ranging in height from 0 to 21 cm (Figure 5-1).

5.2.3.2 Measurement variables and conditions

There were two primary outcomes. First, a distance estimate made by the participant, of the vertical distance between their two index fingers. This estimate was made by matching what the distance *felt* like, with one of the distance markers shown on the chart holder. Second, participants rated their sense of finger ownership using a 7-point Likert scale chart (Figure 5-5).

5.2.3.2.1 Workspace

This current study defined three spatial 'workspaces': centre, unaffected side (or matched unaffected side for controls), and affected side (or matched affected side for controls). For example, for a participant with CRPS of their right hand, the space to the right of the body midline was defined as the affected workspace; for the matched control participant, the space to the right of body midline was defined as the matched affected workspace.

5.2.3.2.2 Hand

Conditions were labelled according to whether the affected or unaffected hand was placed on the top platform.

5.2.3.2.3 No Grasp and Grasp condition

The No Grasp condition involved the researcher's hand guiding the participant's fingers, on their top hand, to be adjacent to, but not grasping the artificial finger (Figure 5-1 B). The Grasp condition was similar except that the researcher was guiding the participant's fingers in a pincer grip to passively grasp the artificial finger (Figure 5-1 C).

5.2.3.3 Procedure

Each participant sat on the height adjustable chair in front of the table. The researcher sat directly opposite the participant, obscured from view by a dark partition (Figure 5-1 A), allowing the researcher to manipulate the participant's hand posture under the screen. Both hands of the participant were passively placed in a box, with one arm on the lower platform and the other 12 cm above on the upper platform. A screen and drapery over the box concealed their hands and the experimental apparatus.

All measurements were tested in the centre workspace first. After this workspace, testing was randomised to either the affected or unaffected workspace (Figure 5-1). Hand placement was randomised for each workspace.

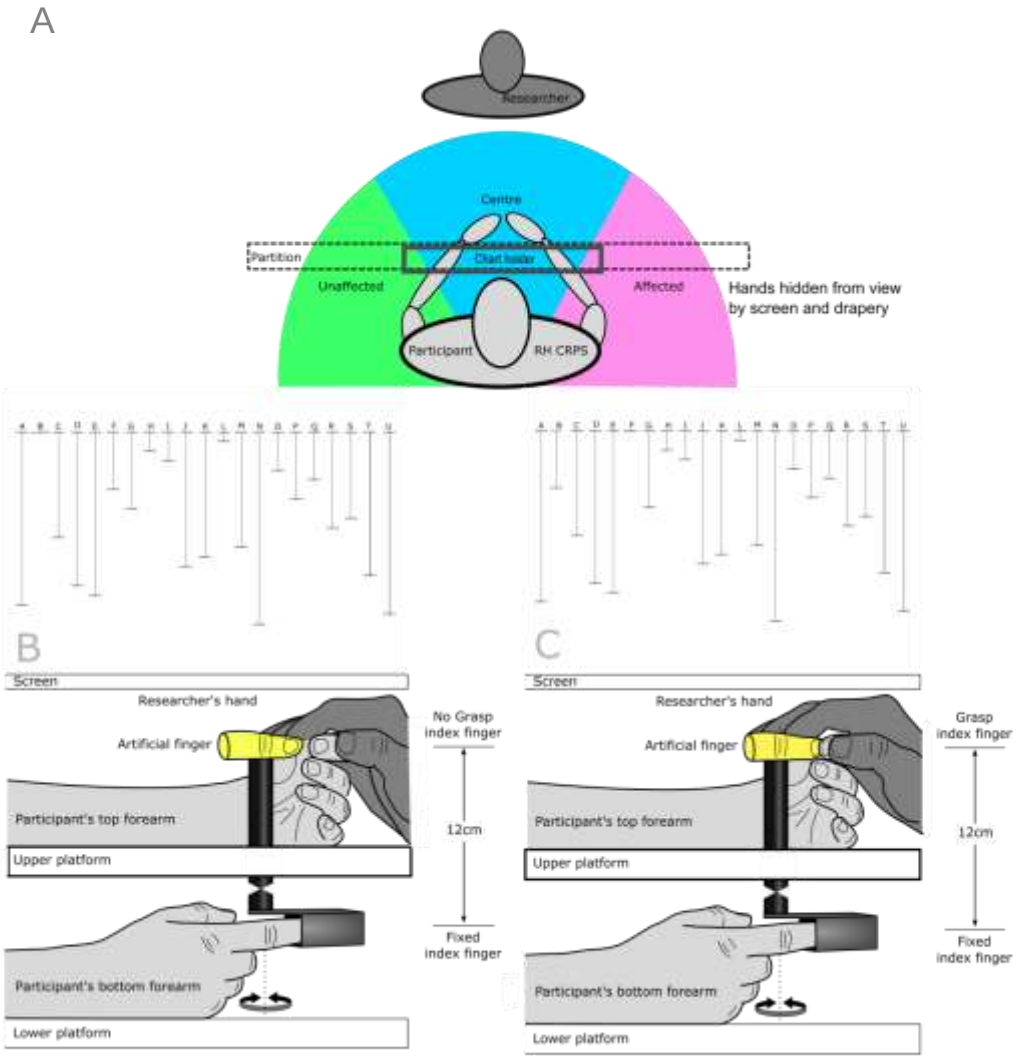


Figure 5-1: The finger illusion experimental set-up.

A. An aerial-view diagram of the experimental set-up, showing the unaffected, centre and affected workspace for a participant with CRPS of the right hand. The distance markers used for distance estimates are also shown. B. A view of the set-up for the No Grasp condition. The hands were out of view of the participant. Note the artificial finger and the pipe either end of the shaft. Here, the researcher's hand is shown guiding the participant's fingers, on their top hand, to be adjacent to, but not grasping the artificial finger. C. A view of the set-up for the Grasp condition. This was an identical set-up except that the researcher is guiding the participant's fingers to passively grasp the artificial finger.

An example of the procedure in the right hand of the participant within the centre workspace was - their right forearm and hand rested semi-pronated on the lower of two tables inside the box. The distal and middle segments of the right index finger (referred to as the fixed index finger) were then wrapped in a piece of neoprene and placed snugly in the pipe attached to the bottom of the rotatable shaft. The shaft was aligned with the approximate axis of the proximal interphalangeal joint of both the artificial finger and the participant's finger in the pipe. The shaft's coupling was locked and fixed. The researcher ensured that there was adequate padding below each hand and that there was no skin touching the steel shaft or the box at any time.

During testing, the researcher estimated the mid-point tip of the top index finger to ensure adequate positioning and ensured their own limbs (e.g. elbow) were supported to reduce the effect of intermittent vibrations or tremors for feedback. The distance from the artificial finger to the mid-point of the pipe in which the participant's index finger was placed was 12 cm. After each experiment, the researcher re-measured both distances to record any measurement bias or any height adjustment.

5.2.4 Finger illusion and Measurement Order

The *finger illusion* was measured in the following order: the No Grasp condition, Grasp condition and artificial finger ownership. The distance drift of the finger illusion was the sequential change from No grasp condition to Grasp condition. The rating of the artificial finger ownership during the Grasp condition, measured the subjective level of finger ownership, induced by the illusion.

5.2.4.1 No Grasp condition

First, the researcher placed the participants finger and thumb in the No Grasp position (Figure 5-1, bottom left). The researcher instructed the participant to look at the chart (Figure 5-1 B) and to estimate the perceived vertical distance as follows: *"Looking at this chart, which line represents the vertical distance between the tip of your left index finger and the tip of your right index finger?"* The participant was asked to estimate the vertical distance between their index fingers immediately by choosing a line on the chart.

5.2.4.2 Grasp condition

Second, the researcher tested the grasp condition by passively placing the participant's index finger and thumb in a pincer grip over the artificial finger (Figure 5-1 C). Again, the participant

was asked to estimate the vertical distance between their index fingers immediately by choosing a distance marker on the chart.

The distance drift during the finger illusion was the sequential distance change from the No grasp to Grasp finger position.

5.2.4.3 Rating of artificial finger ownership

Third, embodiment of the artificial finger during the Grasp condition was interrogated with finger ownership statements. The researcher read out either one of the two statements depending on which 'finger' was held: "*Looking at this chart how strongly do you agree or disagree with this statement*: I feel that I am holding my right index finger with my left hand" or "*Looking at this chart how strongly do you agree or disagree to this statement*: I feel that I am holding my left index finger with my right hand". Participants rated their level of agreement using a 7-point Likert scale, shown in Figure 5-5.

The participant's hands were removed from the box after the measurement order was completed. They were reminded to look at their hands during the 2 minute break. Measurements were repeated so that data were collected in each of six conditions, which involved the two hand positions (upper platform and lower platform) and the three workspaces (unaffected, centre and affected). The order of the remaining five conditions was randomised.

5.3 Data and Statistical Analysis

5.3.1 Data management

Pairs (participant and control) were matched for dominance, rather than matching the dominant hand of controls to the unaffected hand of CRPS participants. The independent variables were: Group (CRPS or healthy control), space (unaffected, centre or affected) and top hand (unaffected or affected). The dependent variables were: the perceived vertical distance between the fingertips, called 'Distance', and finger ownership rating.

5.3.2 Statistics

Each dependent variable was subjected to a repeated measures analysis of variance, the repeated measures being the scores of the two members of each matched pair in each experimental condition. This analysis yields a Between-Pairs component, not bearing on the effects of the test conditions, and a Within-Pairs component testing the effects of Group (2 levels - CRPS vs control), Workspace (3 levels - centre, affected and unaffected), Hand (2 levels

- affected and unaffected), and Finger (2 levels - No grasp and Grasp), and the interactions of these four factors. The effects of chief interest are the interactions with the effect of Group for the first hypothesis. For the second hypothesis, the effects of chief interest are the interactions with the effect of Group with finger ownership ratings.

The analysis used the SPSS computational procedure called multivariate analysis of variance (MANOVA), to test the differences across dependent variables simultaneously. If the Mauchley test is significant, the assumption of sphericity is not met (Field, 2007). Non-sphericity was corrected with a Greenhouse-Geisser correction to the degrees of freedom of the F-ratio in the repeated measures ANOVA.

The first hypothesis was tested in two parts. The study first tested (1); the accuracy of the perceived location was investigated in the No Grasp condition (Group x No Grasp). and (2) the Grasp condition (Group x Grasp), using the reported vertical distance between the index fingers in CRPS compared to controls. Then, the study tested (1) the weakness of the illusion (Group x Workspace x Hand x Finger) between CRPS and controls, by comparing the distance drift during the *finger illusion*; the sequential distance change from No grasp condition to Grasp condition (as in the original study by Heroux et al. (2013)). For the second hypothesis, the study hypothesised that people with CRPS would have a weaker sense of ownership over the artificial finger, than that reported by controls (Group x Workspace x Hand x Finger Ownership).

Any significant interactions found with the repeated measures factorial ANOVA were followed up with post-hoc simple contrasts. Statistical power and effects sizes, using partial ETA-squared (η^2_ρ), were calculated. Data are presented as means with 95% CI where appropriate. All tests were carried out using SPSS (version 22: SPSS Inc., Chicago, IL, USA) with $\alpha = .05$.

5.4 Results

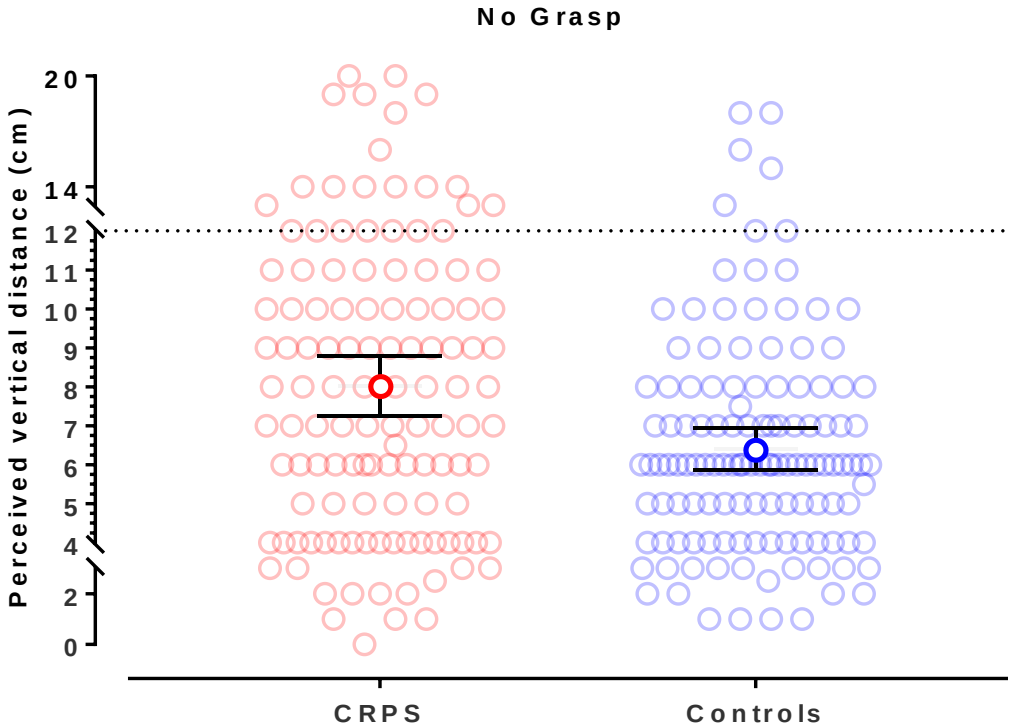
Twenty-one age, gender and dominance-matched pairs consented for the study (36 female, 6 male, mean age 44.4 ± 11.7 years). Data from the 20 of the original 21 matched pairs were included for the final analysis of all experimental conditions. One CRPS participant did not complete the side workspaces measurements. There were 10 left hand affected CRPS participants and 10 right hand affected CRPS participants. Among them, there were nine participants with non-dominant affected upper limb CRPS and 10 participants with dominant affected upper limb CRPS and one participant who reported they were ambidextrous and scored borderline right-handedness on the Edinburgh Handedness Questionnaire.

Analysis confirmed that the data were normally distributed. The results are presented in the order of the hypotheses tested.

5.4.1 First hypothesis – No Grasp condition

For No Grasp, all participants perceived the distance between their index fingers to be less than the true distance of 12 cm (Figure 5-2). CRPS participants perceived their index fingers to be further apart at a mean of 8.03 cm (95% CI: 7.26, 8.80), than the controls did at 6.40 cm (95% CI: 5.85, 6.95) regardless of the workspace used (main effect of Pain - $F(1,19) = 4.82$, $p = 0.041$, $\eta^2_\rho = 0.202$, power= 0.550)

The post-hoc contrast on CRPS data only, comparing affected and unaffected hands revealed the perceived vertical distance between index fingers at 'no grasp' in each side workspace was significant, ($F(1,19) = 6.13$, $p = 0.023$, $\eta^2_\rho = 0.244$, *power* = 0.651). This result was modulated by the orientation of the hands and the workspace in which the task was conducted – specifically, which hand was on the top platform in which workspace (Figure 5-3). The perceived vertical distance with the CRPS-affected hand on the top table in the affected work space was 8.10 cm (6.13, 10.07) and 6.68 cm (5.08, 8.27) in the unaffected workspace. In contrast, the CRPS-unaffected hand on the top table in the affected workspace had a mean perceived distance of 6.65 cm (4.67, 8.63) and 8.58 cm (6.54, 10.61) in unaffected space. Hence, the perceived vertical distance at 'no grasp' was dependent on both the hand placement at the top table and which type of side workspace (Figure 5-3). However, individual post hoc t-tests failed to detect which factor(s) were mediating the interaction.



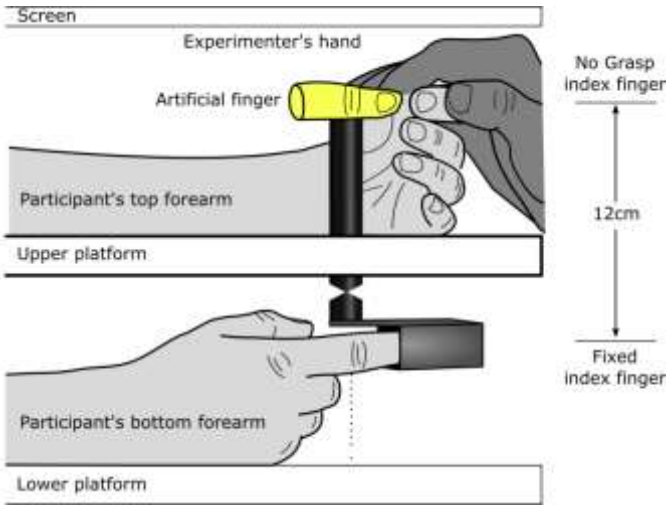


Figure 5-2: The No Grasp condition of the finger illusion.

CRPS participants perceived their index fingers to be further apart than controls did, F (1,19) = 4.82, p = 0.041, η^2_ρ = 0.202, power = 0.550). Circles (red circle, ○ = CRPS; blue circle, ○ = Controls) represent the means and error bars represent 95% CI around each mean: CRPS at 8.03 cm (95% CI: 7.26, 8.80) and controls at 6.40 cm (95% CI: 5.85, 6.95). Transparent circles (red = CRPS, blue = Controls) represent individual perceived vertical distances during No Grasp. The horizontal dotted line indicates the actual distance of 12 cm. The unseen posture of the

participant's top hand (left hand) at No Grasp relative to the artificial finger during the experiment is shown under the graph.

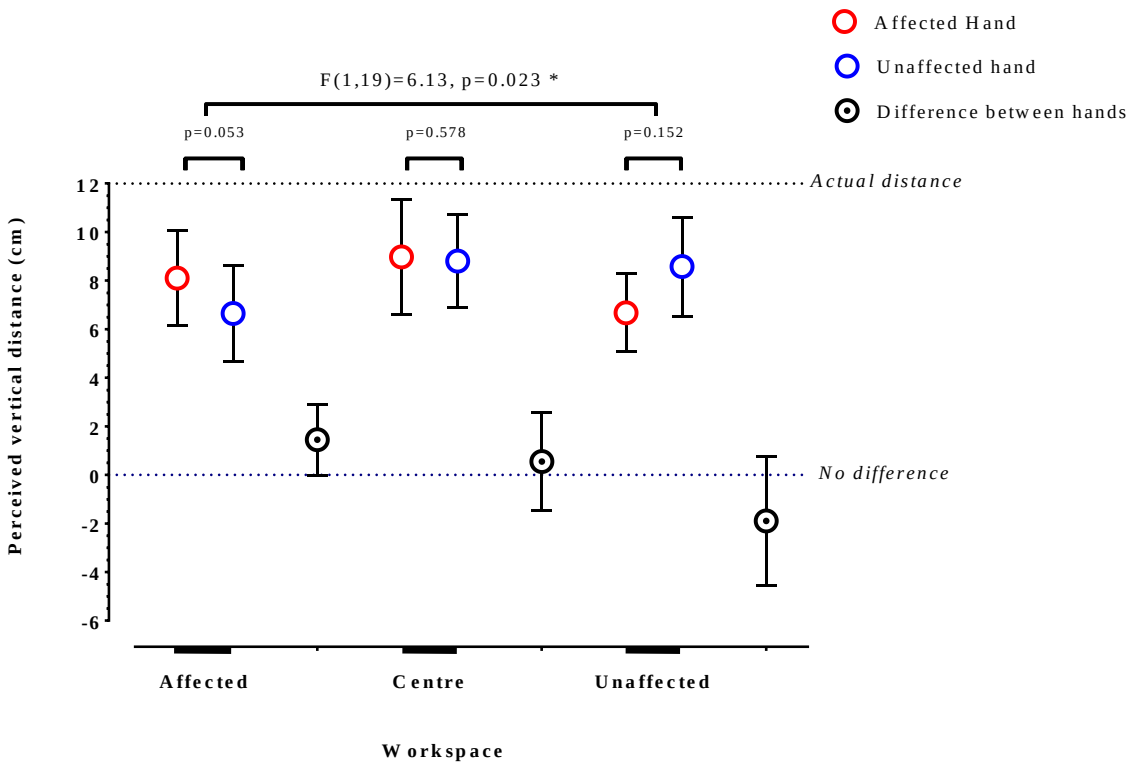


Figure 5-3: The effect of hand placement on the top platform by workspace on the perceived vertical distance between index fingers for CRPS patients in the 'No grasp' condition.

Circles represent the means and error bars represent 95% CI around each mean. The top dotted line indicates the true distance of 12 cm and the bottom dotted line indicates no difference between hands in each workspace.

5.4.2 First hypothesis- Grasp condition

Mean perceived vertical distance at No grasp finger position for CRPS participants was similar at 5.27 cm (*95% CI*: 4.58, 5.95) compared to 5.03 cm (*95% CI*: 4.58, 5.49) in healthy controls. There were no significant differences between CRPS and controls ($p > 0.05$, for all).

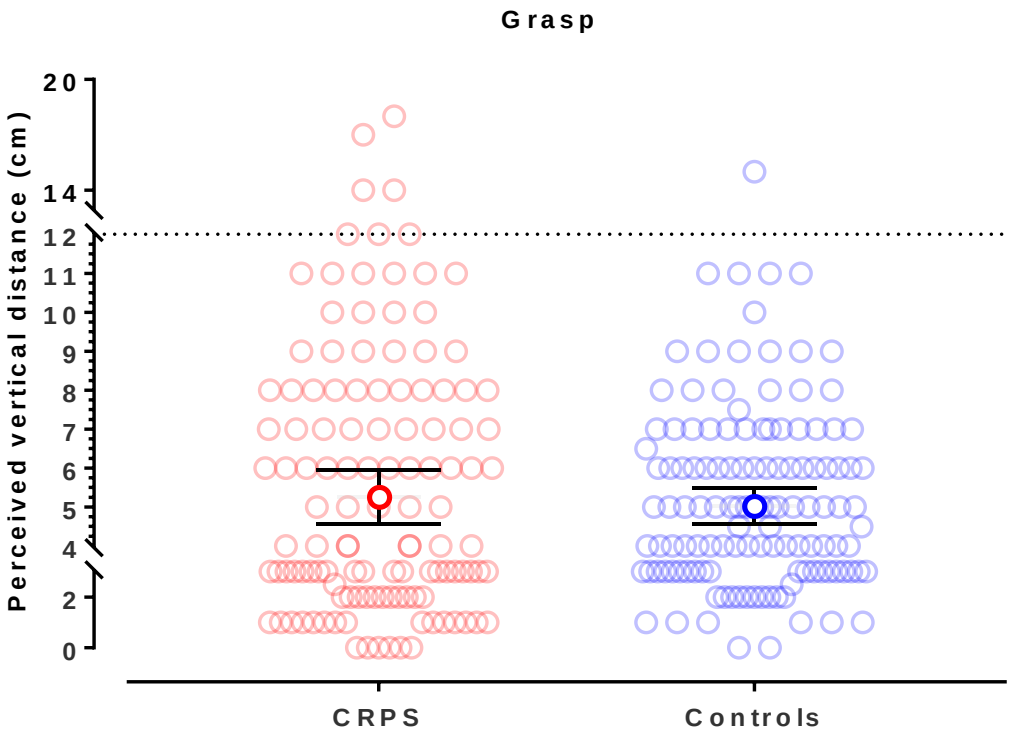


Figure 5-4: The Grasp condition of the finger illusion.

Circles (red circle, ○ = CRPS; blue circle, ○ = Controls) represent the means and error bars represent 95% CI around each mean: CRPS at 5.27 cm (*95% CI*: 4.58, 5.95) and controls at 5.03 cm (*95% CI*: 4.58, 5.49), p > 0.05, for all interactions. Transparent circles (red = CRPS, blue = Controls) represent individual perceived vertical distances during Grasp. The horizontal dotted line indicates the actual distance of 12 cm.

5.4.3 First hypothesis- distance drift during finger illusion

The main hypothesis was that this illusion is weaker in people with CRPS than in matched healthy controls. There were no significant differences in distance drift between CRPS and controls**Error! Reference source not found.**, using reported vertical distances between index fingers at No Grasp and Grasp ($p > 0.05$). There were no interactions for: Group x Workspace ($p > 0.05$); Group x Hand ($p > 0.05$); and Group x Finger; F (1,19) = 3.49, $p = 0.077$). Finally, there was no Group x Workspace x Hand x Finger interaction ($p > 0$ .05). Therefore the null hypothesis was accepted - that there was insufficient evidence that the effect of grasping the artificial finger, as marked by 'distance drift', was different between CRPS participants and controls.

The main effect of workspace was significant, $F(2,38) = 6.87$, $p = 0.003$. Further, this significant effect was due to the comparison between the centre workspace to the two side workspaces combined ($t = 3.11$, $p = 0.0057$). This effect of workspace was not significant when comparing, only between the two side workspaces ($t = -1.41$, $p > .005$). To investigate the individual differences between centre workspace and side workspaces, post-hoc contrasts were used as simple effects analysis. There was a significant interaction effect of workspace when comparing centre workspace to affected side, $F(1,19) = 12.99$, $p = 0.002$, *power* = 0.927 as well as comparing centre workspace to unaffected workspace, $F(1,19) = 4.73$, $p = 0.042$, *power* = 0.542, but no significant difference comparing the affected and unaffected workspaces.

Continuing with no distinction in data between CRPS and controls, there was a significant main effect of which hand type was placed on top (affected or unaffected), $F(1,19) = 4.85$, $p = 0.040$. A significant main effect of finger position, $F(1,19) = 36.13$, $p < 0.0001$, was also found. The mean distance drift of 2.11 cm (*95% CI*: 1.37, 2.85) between the 'No Grasp' and 'Grasp' finger position, was statistically significant, $p < 0.05$.

In summary, both CRPS and controls experienced a similar downward trend in distance drift, indicating a strong finger illusion effect. When no distinction was made between pain groupings, significant main effects for workspace, hand and finger position were found, with a significant interaction effect between workspace and hand on perceived distance for the distance drift of the 'finger' illusion. For emphasis, there were no differences between CRPS and controls for the interactions of Group X Workspace X Hand X Finger during the finger illusion.

5.4.4 Second hypothesis

Hypothesis two was "people with CRPS would have a weaker sense of ownership over the artificial finger when subjective ratings of finger ownership were compared". Mauchly's test assumption of sphericity was violated for the interaction effect of Group by Workspace ($X^2(2) = 7.97$ $p < 0.05$). Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.734$) was used to correct for the degrees of freedom. There was no difference between CRPS participants and controls on subjective ratings of finger ownership**Error! Reference source not found.**, and no significant interactions ($p > 0.05$, for all).

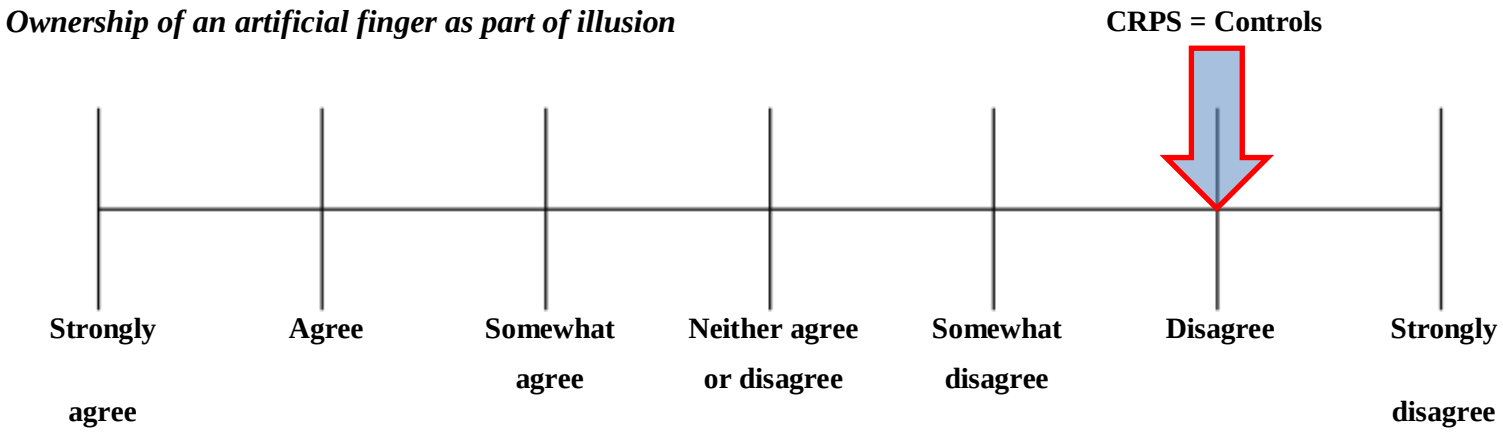


Figure 5-5: Ownership rating of an artificial finger as part of the illusion.

Both CRPS and healthy control participants had the same median rating of 'Disagree' when asked either "I feel that I am holding my left index finger with my right" or "I feel that I am holding my right index finger with my left hand", when presented with the 7-point Likert-scale artificial finger ownership chart.

5.5 Discussion

People with unilateral CRPS of the upper limb had reduced weighting of bimanual hand representation, as compared to matched controls. This result was shown in the No Grasp condition, where those with CRPS perceived the vertical distance between their index fingers to be closer to the actual distance of 12 cm than it was for the controls. The (post–hoc analysis) relative location of their CRPS hand in the affected and unaffected workspaces (but not in the centre workspace) influenced this reduced weighting of bimanual hand representation (Figure **5-3**). In contrast, these differences found in perceived vertical distance between CRPS and controls were lost in the Grasp condition (when grasping the artificial finger). In this condition, neither hand, nor workspace, nor any other factor influenced the weighting of bimanual hand representation in CRPS differently, compared to controls.

People with CRPS did not have a weaker finger illusion than the matched controls. All participants perceived the distance between their index fingers to be closer during the Grasp condition than during the No Grasp condition, and there was no difference in the judged distance between the two groups. Despite this significant behavioural effect of the illusion**Error! Reference source not found.**, perceptual reports did not reflect a similar effect (Figure 5-5), with the sense of ownership over the artificial finger (median rating of ownership was "Disagree") in both groups. This divergence found between the behavioural measure - distance drift - and the perceptual rating is consistent with the original 'finger' illusion experimental results (Heroux et al., 2013). In that study, a perceptual illusion emerged only when congruent movement was added or when the fingers were anaesthetised (accredited to the removal of tactile input to discredit that an artificial finger was being touched).

To best knowledge, this is the first finger illusion study to be reported in CRPS and the second study in CRPS to use illusions after Reinersmann et al. (2013), who used the RHI. This chapter suggests caution with the interpretation from their results, that there was an intact ability to integrate the RHI indicating an intact higher order multisensory integration in CRPS related to body representation. First, this chapter found there is a reduced weighting of bimanual hand representation in the No Grasp condition. Second, this chapter found that all participants perceived the illusion in a similar way (with a large distance drift), without the corresponding perceived ownership over the artificial finger- unlike- the study by Reinersmann et al. (2013) where similarity in skin conductance between CRPS and controls, was accompanied by corresponding perceptual reports that the rubber hand was like their own hand. However, their subgroup of patients with CRPS of the right hand who scored higher on neglect-like symptoms,

reported a significantly lower effect of the illusion of the affected hand than patients with CRPS of the left hand (Reinersmann et al., 2013); unlike their main conclusions. Therefore, factors that might affect the ability to integrate illusions - cannot be entirely ruled out in CRPS; with their subgroup and the study results from this work.

Methodological differences might explain these separate interpretations; making this current study only indirectly comparable to that by Reinersmann et al. (2013). This current study used a finger illusion that involves passive bimanual hand representation in workspaces, compared to the RHI; which involves only one hand at a time and requires congruent brushing. This concept of additional information, such as tactile stimuli, to induce a sense of ownership over a fake body part in healthy participants, was previously reported in other studies. This included the embodiment of the whole body (Petkova et al., 2011, Maselli and Slater, 2013), RHI (Suzuki et al., 2013, Guterstam et al., 2011) experiments, increased perceived ownership of a mannequin (Petkova et al., 2011) or even an artificial limb (Braun et al., 2014, Makin et al., 2008). While these experiments had additional information which increased congruency between different sensory modalities (such as visual feedback and tactile feedback), the 'finger' illusion did not include visual feedback or additional information other than a passive posture of grasping an artificial finger. Hence, this might explain the disagreement felt in perceived ownership in our study.

This work made several novel contributions to the study of body representation in controls and how it might be disrupted in CRPS. The static spatial posture that mimics biologically plausible grasping was sufficient to induce the distance drift of the 'finger' illusion in both CRPS participants and controls, even in side workspaces. The study result in the No Grasp condition, of reduced bimanual hand representation is novel . It is further evidence of a disruption to bimanual hand representation- that is likely to be cortically driven (Di Pietro et al., 2013b, Di Pietro et al., 2015). This study tested (during the experiment- please see supplementary information in Appendix for Chapter 5) and found this illusion was not dependent on hand dominance in healthy participants, eliminating this possible effect and increasing the robustness of our findings.

This ‘finger’ illusion is easily induced passively (within seconds), and was tolerable for CRPS participants despite allodynia. It provides a clear practical advantage over other ‘illusions’, such as the RHI that require brushing for a few minutes, which might induce ‘wind up’ and thus augment allodynia and hyperalgesia (Reinersmann et al., 2013) or become too painful to tolerate (Knudsen and Drummond, 2014). As it avoids repeated tactile stimulation, our artificial finger illusion offers a method to explore body ownership in CRPS without excessive exacerbation of symptoms.

How should we interpret the differences in the two conditions of the finger illusion and possible effects on the weighting of bimanual hand representations? One interpretation is that a different mechanism is driving proprioceptive input in the No Grasp condition in CRPS. It could be argued that this was not an increase in accuracy of location perception, but rather inefficient preparatory mechanisms in readiness for a bimanual functional task. This work proposes that, in CRPS, additional touch information is required to override this imbalance of information ‘weighting’, conveyed via ‘grasping’ an artificial finger (Grasp), before these preparatory mechanisms occur in the bimanual posture adopted in the ‘finger’ illusion experiment. An effect during the first part of a trial in a motor task test was also definitively found in in older adults at risk for Parkinsons’ disease. The study authors’ also found it difficult to reconcile to mechanisms for their interesting result citing supraspinal mechanisms in the motor cortex (Todd et al., 2014).

5.5.1.1 Measurement bias and limitations to study

Pre-emptive steps were taken in the design of the experiment to reduce possible measurement bias. This study tested if asking the measurement for a second time would affect the perceived vertical distance *felt*. For example, after each finger position, the researcher asked the subject to estimate the vertical distance with one chart and then again immediately afterwards with a second randomly chosen chart. The reason for the second measurement was to ensure that there was no latent effect of asking the question the second time, which might systematically affect ratings. Statistical analysis of data from the centre workspace confirmed that there was no effect of asking the measurement for a second time in this workspace (Please see Appendix for Chapter 5: Supplementary Information). Therefore, for the final analysis, only the first distance estimates of each finger position (of ‘no grasp’ and ‘grasp’) were used.

There were also some minor difficulties with matching and completion of all conditions. One CRPS subject only agreed to participate in the centre workspace experiments. Thus, this subject and their matched pair could not be included in the final repeated measures ANOVA for

matched pairs in the side workspaces. This study had a larger age difference for one matched pair, otherwise suitably matched. The CRPS subject was right-hand dominant, her left-hand was affected by CRPS, and she was 72 years old. The matched control subject was similarly right-hand dominant, female, but 46 years old.

Anecdotal evidence reported after the experiment by two participants showed that they judged the index fingers as closer together vertically but felt that their fingers had drifted apart horizontally. This study did not formally assess perceived horizontal distance drift during the experiment, so it was not possible to evaluate this at a group level. It is also acknowledged that the order of workspace in the experiments was not randomised-rather the experimental design tested the centre workspace first before the randomisation of either the affected or unaffected workspace. This decision was made *a priori* because of extensive evidence that working in one side of space could induce temporary but within-experiment neuroplasticity changes in healthy controls (Azañón and Soto-Faraco, 2008, Azañón et al., 2015), and that hands crossing over the midline are associated with changes in nociceptive processing (Gallace et al., 2011) in healthy controls and changes in tactile processing (Moseley et al., 2009), temperature regulation (Moseley et al., 2013, Moseley et al., 2012a), sense of ownership (Moseley et al., 2012a) , and motor performance in people with unilateral CRPS. A final limitation is that this study did not account for attentional modulation of participants on the outcome measures during the experiments, although no systematic effect of time was found on the results. For example, the timing of the artificial finger ownership rating immediately after asking the perceived vertical distance at Grasp condition, might explain the results due to attentional modulation for rapid task switching.

5.6 Conclusion

This chapter showed that people with unilateral CRPS had a reduced weighting of bimanual hand representation than healthy controls. However, they performed in a similar fashion to healthy controls when tactile input was enhanced, suggesting that the deficit could be compensated for in CRPS. This study postulates that the mechanisms involved are related to efficiencies of information filtering and weighting of bimanual hand representations, during the preparation phase for bimanual tasks. This study also extended the finding that the spatial disruption in unilateral CRPS occurs in the affected space even when both hands adopt a bimanual hand posture in that affected space.

This chapter suggests that bimanual hand representations are impaired in unilateral CRPS, but this impairment can be overcompensated for by enhanced sensory input, when contributing to contextual realism of the illusion. Future research in CRPS could investigate if bimanual

hand representation in the absence of this enhanced sensory input could be spatially normalised, with the prospect of possible clinical therapeutic benefit.

6 Conclusion

This work reported several forms of evidence that cortical integration of tactile sensation appears disrupted for patients with unilateral upper limb CRPS. Individual somatotopic fingertip maps in CRPS suggest a disruption and disordering with no unifying pattern compared to the orderly homogenous pattern found in the maps of healthy controls. Functional fine-grained somatotopic mapping in S1 in both hands was first made feasible in this study due to pilot methodological work in controls (Chapter 3). Subsequent functional imaging observations in CRPS and controls were strengthened by the key finding that increased cortical thickness underlying these maps together with original hand dominance predicted group (CRPS versus healthy controls) membership. Loss of cortical thickness was globally influenced by previous opioid use in CRPS. An abnormal finger illusion response in CRPS compared to controls also suggested a central disruption to the spatial context of touch in bimanual hand representation. With further tactile input, the response was not significantly different to that of controls. There was no relationship found between the disordered cortical finger representations or changed cortical thickness, and any measure of pain, including pain intensity or duration of CRPS. These changes in this study sample were fairly representative of the general population for hand dominance and similar to the CRPS-UK Registry (Chapter 2) for symptoms of CRPS.

6.1 Functional mapping of the fingertips is disrupted in CRPS compared to controls

Disordered functional fingertip maps found in CRPS implicates cortically mediated disordering in tactile representation, casting light on contrasting views in the literature on the size of hand representation. Perhaps the size of the S1 maps is not the critical issue in CRPS - rather how well organised the individual inter-digit differences are. Although past studies (Maihöfner et al., 2003, Pleger et al., 2006) have reported these affected hand S1 maps as smaller by using the first and fifth digit as the proxy measurement of hand size in the brain, a more recent study (Di Pietro et al., 2015) has suggested CRPS patients remain similar in their affected hand size. In fact, the results in this most spatially resolved study prior to this current study, seemed to indicate that an unaffected hand S1 map was larger than normally expected even in controls (Di Pietro et al., 2015). Further work from the authors found no association between hand use and S1 map size in CRPS (Di Pietro et al., 2016). Limitations acknowledged in their work may have led to a false negative finding and therefore further work would be required. The work from this thesis leaves open the possibility that disorganisation found in fine-grained S1 maps results from changes from the way both hands are used. This current work was cross-sectional in nature and had no direct quantitative hand usage measures that were

contemporaneous when patients entered the study. As disorganised S1 maps in this work in some cases were bilateral, clearly further research is required to understand the driving mechanisms behind the development of these disorganised maps including its spread bilaterally. This work suggests that individual fine-grained inter-digit differences in this study might explain the variable results of a larger or smaller CRPS proxy hand representation that previous studies found (Maihöfner et al., 2003, Di Pietro et al., 2015, Di Pietro et al., 2013b).

The work in this study progressed fine-grained mapping for individual fingertips at the highest spatial resolution (1.5 mm^3 voxel size fMRI; 0.75 mm^3 voxel size for T1 scan) through a highly efficient tactile stimulus for those with pathological pain such as CRPS. Finger mapping is not new in healthy controls (Nelson and Chen, 2008, van Westen et al., 2004, Schweisfurth et al., 2014, Sanchez-Panchuelo et al., 2010) but the novel aspect in this current study was that all four fingertips in both hands were mapped using bilateral stimulation. This level of mapping resolution allowed fine-grained individual inter-digit relationship between fingertips in CRPS showing individual patterns of disruption in some cases on both hands despite only having unilateral CRPS. This study was limited to describing sufficient CNR in the individual somatotopy in S1, not average grouped functional activation statistics. This has limited direct comparisons to proxy measures of Euclidian distance (of the thumb and little finger) in previous work (Di Pietro et al., 2015, Di Pietro et al., 2013b). However, no unifying pattern of alteration was found either for geodesic measures (surface based) from the centroid of fingertip maps location relative to the central sulcus (previously discussed in Chapter 4). These results provides further support again to the doubt cast by previous work that CPRS might not be associated with a smaller CRPS – affected functional hand representation in S1 (Di Pietro et al., 2015, Di Pietro et al., 2013b).

6.2 Structural morphometry in CRPS is disrupted and different to that in controls

Original hand dominance, not CRPS-sidedness and increased cortical thickness predicted those who had CRPS in this work That is, CRPS patients showed a difference between hemispheres in the cortical thickness of S1 hand areas, but the control participants did not. This difference was between the dominant and non-dominant hemispheres, with the dominant being thicker. It is worthwhile noting that this difference did not depend on which hand was affected with CRPS, and specifically, it was determined by the dominant hand prior to injury. This is a new finding and raises the possibility that a side-to-side difference in cortical thickness in S1 may reflect a vulnerability to the condition. An alternative interpretation might be that CRPS induces the side-to-side difference, but, considering that the differential depended on dominance

not the side of injury, it would be difficult to explain the effect by disuse, pain or the injury. Further investigation of this type of side-to-side issue seems warranted.

This study also performed a comprehensive surface-based analysis of the structural changes underlying function by using functional data from fine-grained fingertip maps to confine the analysis. This technique was different from recent chronic pain structural morphometry studies (Lee et al., 2015, van Velzen et al., 2016). Most neuroimaging work rely on standard structural analysis morphometry methods and standardised brain atlas parcellations sourced from healthy subjects (Glasser et al., 2016, Brett et al., 2002). This is not problematic in itself but is a possible confounder when applying these methods to those with a pathological condition with atypical areal patterns. This work has also attempted to increase transparency of the selective and recruitment process of this study sample and the screening used for CRPS diagnosis criteria overlooked in neuroimaging pain studies, as highlighted by systematic reviews (Di Pietro et al., 2013a, Di Pietro et al., 2013b). Current neuroimaging research in CRPS (Lee et al., 2015, van Velzen et al., 2016) often have gender matched controls but the hand dominance data collected, often remain unused as a covariate or predictor of structural changes seen. This again might be a missed opportunity for a more comprehensive analysis.

In this study, there was a global effect of thinning in both hemispheres in S1 associated for those with CRPS and opioid usage. This distinction between those with or without a history of opioid use was an unusual finding in CRPS that did not affect the robust findings of the differences in increased cortical thickness and original hand dominance when predicting group membership (in the model). Few studies have reported opioid related morphometry changes in grey matter volume (which has a relationship to cortical thickness). Volumetric increases were found in those with chronic low back pain (Younger et al., 2011) but had variable directional effects in those with early life experiences of pain (Ranger and Grunau, 2014, Ranger et al., 2013, Brummelte et al., 2012). The finding of cortical thinning in this thesis adds to a growing body of evidence (Hutchinson et al., 2011, Johnson et al., 2014, Corrigan et al., 2015) concerning the potential impact of long term opioid use on the central nervous system (CNS). The current work was not able to investigate functional or behavioural impacts of this difference, but the finding does suggest investigation would be worthwhile. Although opioids are well known for their analgesic effect in the sensory cortices (Gustin et al., 2010), its long term use might affect structural changes in the cortex (Attarian et al., 2014). The unwitting influence of opioids on the effects reported in neuroimaging in chronic pain also seems under investigated.

6.3 A disruption to the weighting of bimanual hand representation in CRPS

'Improved' performance on the finger illusion experiment might reasonably reflect 'worse' bimanual integration. Perhaps counterintuitively, normal performance (believing that your hands are closer than reality) on the finger illusion probably reflects the brain's predilection for bimanual activities, a suggestion reinforced by the added error on the task during the Grasp condition of the illusion. Participants with CRPS reported a vertical distance perception ('less error') between their fingers as closer to the actual distance compared to controls (in the No Grasp condition discussed in Chapter 5). The discrepancy between groups disappeared once additional input was given by grasping a fake finger during the finger illusion (Grasp condition). As this was a novel finger illusion tested for the first time in a clinical condition, there were no comparative studies in other clinical conditions available. One of the key advantages of this illusion experiment was the minimal tactile input required in CRPS, which made patient tolerability more acceptable with no drop-outs. This was in contrast to tolerability issues affecting similar work that interrogated the role of spatial perception and sensory integration in CRPS (Knudsen and Drummond, 2014, Reinersmann et al., 2013). Despite this advantage in this current study, the minimal input requirement might have also impacted the level of embodiment required for finger ownership compared to ownership being easily induced in other illusion studies in healthy controls (Suzuki et al., 2013, Guterstam et al., 2011, Heroux et al., 2013).

Much research has been done to investigate spatial effects on body representation in CRPS (Moseley et al., 2009, Moseley et al., 2012a, Moseley, 2004b, Lotze and Moseley, 2007) but there is a lack of studies on interrogating the bimanual representation of hands and limbs in space in CRPS such as in this study. The deficit in the weighting of bimanual hand information in the first condition (No Grasp) suggests a disruption to multisensory integration in CRPS, unlike the results found by Reinersmann et al. (2013) during the RHI in CRPS. The results of the second condition (Grasp) suggest that with extra tactile input this possible disruption to multisensory integration was compensated for. Hence, this current study speculates that some residual cortical reserve is available in CRPS that allows these bimanual hand weighting deficiencies to be adjusted.

It is likely that the grasping finger illusion in this thesis in theory would activate both the pre-motor and somatosensory cortex (Section on Chapter 1: Functional anatomy of illusory sensations). This is because the illusion consists of a finger that is grasping an artificial finger passively (a perception of an action) and another finger that is placed passively in position (perception of position) within a pipe (described in Chapter 5). As this thesis has focussed on

the role of the somatosensory cortex, the involvement of other cortical areas could be considered in future research the investigating mechanisms of the finger illusion.

6.4 Secondary findings from this body of work and other mechanisms of interest

In this thesis, a homogenous unilateral upper limb CRPS study sample (Chapter 2) yielded heterogeneous distortions to the individual fingertip maps, and in some cases to both S1 maps. Although no association with clinical characteristics of CRPS was found, the co-activation of nociceptive maps cannot be disentangled as the majority of participants with CRPS reported pain during the scan and healthy participants had no pain with the tactile stimulus (Chapter 4). Importantly, CNS adaptations associated with persistent pain mean that it is not possible to attribute pain on touch to peripheral, spinal or supraspinal mechanisms without recording from primary nociceptors. However, it is certainly possible that a non-noxious stimulus (touch) activated nociceptive processes anywhere along the sensory neuroaxis (Miraucourt et al., 2007, Keller et al., 2007). Fine-grained nociceptive and tactile fingertip maps using separate stimuli, have also been shown to overlap in healthy people (Mancini et al., 2012). This strongly suggests that nociceptors converge with non-nociceptive pathways. Indeed, contemporary understanding of spinal somatosensory processing advocates a neural network approach where there is much computational capacity (Rosa and Seymour, 2014, Moseley and Butler, 2015). Therefore, this work speculates that disordered patterns of fingertip maps found might represent both nociceptive and tactile maps in CRPS rather than just tactile maps. Thus, is allodynia in CRPS a dysregulation of cortical responses to normal touch and the normal analgesic effect of concomitant touch (Mancini et al., 2015) found in healthy people? The full disambiguation of these disordered maps can only be fully addressed in future studies by phase encoded fMRI mapping of non-tactile nociceptive maps in people with CRPS.

The bilateral finger paradigm (BFP) provides significant advantage for neuroimaging participants with CRPS, who are unable to tolerate long periods in the MR scanner. During the efforts for time efficiency for functional mapping suitable for pathological pain in the pilot (Chapter 3), the bilateral tactile stimulus appeared to provide a naturalistic stimulus while also minimising habituation. It is difficult to decipher the exact mechanisms behind why the BFP paradigm was more efficient than the single finger paradigm (SFP). The level of increased power that might be provided when testing the BFP compared to SFP could be investigated in a larger cohort of healthy controls. The mechanistic rationale is based on known corresponding but transient effects due to transcallosal interhemispheric inhibition (Hlushchuk and Hari, 2006,

Ragert et al., 2011) bilaterally in the brain, which might consequently be the reason for the improved BOLD contrast observed in BFP.

6.5 Rationale proposed for disruptions to cortical integration of tactile sensation in CRPS

Taken together, the results of each of the studies of this thesis raise an interesting speculation. Perhaps the brain alterations found might indicate some previous vulnerability or could be due to forced changes to the dynamics of bilateral hand usage in relation to original hand dominance. First, the emphasis on bilateral hand dynamics stems from the data showing original hand dominance cortical thickening changes in CRPS yet the patients were nearly equally affected in either their dominant or non-dominant hand. Second, there was no hand dominance differences in cortical thickness findings or in the finger illusion results found in healthy controls. Third, structural changes in cortical thickness found only in CRPS implicate measurable markers of the local cytoarchitecture (Wagstyl et al., 2015, Cardinale et al., 2014). Fourth, the psychophysical measure that interrogates bimanual performance, showed a clear deficit (an 'improved' performance) during the No Grasp finger illusion. It is only speculative but might indicate original structural hierarchical organisation of the somatosensory cortex as now being vulnerable, and affecting bilateral dynamic changes in hand dominance. These structural effects are likely to be bi-directional depending on the functional changes being investigated as found in the focus of tactile function in this current study and focus of neurocognitive function in the study by Lee et al. (2015).

Much confusion exists in the data on structural changes in CRPS due to replication issues (Pleger et al., 2014, van Velzen et al., 2016). The effects of cortical thinning in S1 of those who had opioid use in this study contributes to the lack of published data regarding how the brains of patients with pain respond to long-term opioid therapy use (Lee et al., 2014). The confounding effects of long term opioid use might contribute to the confusion about the directional changes found in chronic pain literature.

It remains unclear whether cortical reorganisation in S1 occurred prior to the advent of CRPS or is a consequence of ongoing interactive changes in bilateral hand use caused by the initial injury. This thesis might suggest that instead of functional disuse (Di Pietro et al., 2015, van Velzen et al., 2016, Di Pietro et al., 2016) that the very act of immobilisation in the acute stages of unilateral upper limb CRPS alone, might trigger rapid unilateral cortical changes (Meugnot et al., 2015) followed by eventual widespread bilateral changes (Meugnot and Toussaint, 2015). This idea has support from studies that demonstrated right hand cast immobilisation: i) for 72 hours in healthy people (n=11) showed abnormal activation of the

(ipsilateral) left hemisphere with left hand tactile stimulation (Weibull et al., 2011); ii) after 2 weeks in right hand dominant and injured patients (n=10) showed a reduced cortical thickness of the left S1 and M1 (Langer et al., 2012) and an increased cortical thickness in the right M1. These results in healthy people also lend support to the idea that changes to interhemispheric dominance might occur quickly post immobilisation without pain. However, this still does not explain the directional effect of increased cortical thickness in CRPS found in this work. Perhaps immobilising one hand and compensating with the other becomes highly problematic if there is a side-to-side difference in cortical thickness. This is highly speculative but the possibility cannot be elucidated in this current body of work. The investigations would need to investigate non-dominant hand immobilisation effects in healthy controls first, to see definitively whether this is not merely an immobilisation issue in acute or chronic CRPS. Longitudinal prospective neuroimaging studies could identify and track the progression of any cortically mediated tactile changes in patient groups that might be at risk of developing CRPS (Chapter 1) including limb fractures.

6.6 Summary and Future Research

This thesis suggests the disruption to normal efficiencies of bimanual hand representation found in the novel finger illusion (Chapter 5) and disordered fingertip cortical S1 representation (Chapter 4) might reflect shared mechanisms. The cortically mediated S1 structural changes result might suggest both forced changes to hand dominance and increased nociceptive and sensory input resulting from CRPS. Combinational coding input (Theories of pain in Chapter 1) suggests that the extra input might be first processed within S1 neurons, then within a complex interplay of hierarchal changes in S1 to higher sensory areas such as posterior parietal cortex and supra-marginal gyrus (Iwamura, 1998, Kim et al., 2015, Wagstyl et al., 2015) and finally, bilateral effects spread (Garraghty et al., 1990, Iwamura, 2000, Iwamura et al., 1994) through interhemispheric transcollosal input (Hlushchuk and Hari, 2006). The extra input might confuse the neuronal pruning processes (Schmidt-Wilcke et al., 2006, Kuchinad et al., 2007, Schmidt-Wilcke et al., 2007) and lead to increased cortical thickness changes. These changes have been previously investigated in both immobilisation studies (Wittenberg et al., 2003, Weibull et al., 2011, Langer et al., 2012) and to those forced to covert the use of their dominant hand (Siebner et al., 2002, Kloppel et al., 2010).

This work is cautiously confident that the resultant neuroimaging findings are robust within this sample of CRPS patients by accounting for known significant processing biases or errors previously reported in the neuroimaging literature (in Chapter 2, 3 and 4). However, this work cannot extrapolate the findings to anyone with CRPS without replication studies with these

model predictors (Bennett and Miller, 2010, Woo and Wager, 2015). These questions and generated hypotheses from this work can only be confirmed with future research in CRPS that includes white matter and structural connectivity seeded from S1 and fMRI studies that also include higher hierarchical cortical areas related to tactile sensation.

CRPS pain reflects distortions of the perception of touch and of the properties attached to the significance of touch - as innocuous touch generates pain in those suffering from CRPS. This thesis proposes that the disruption to the cortical integration of touch in CRPS might reflect an interactive change in cortical connections of hand dominance related to forced changes to both hands instead of CRPS side-to-side differences. However, whether this precedes the onset of CRPS pain is unknown or if remediation of hemispheric dominance changes would have an effect on fine-grained disordered S1 maps in CRPS. This idea that CRPS pain has dependently altered the original role of the dominant hand has not been proposed before. This work suggests that this idea should be explored in future studies to further illuminate the path to an objective diagnostic marker for CRPS.

7 Appendix to Chapter 1

7.1 Literature Search- surface-based cortical morphometry measures in chronic pain and complex regional pain syndrome.

A literature search and review on surface-based cortical morphometry measures in chronic pain and complex regional pain syndrome was using the following databases; MEDLINE, EMBASE and Pub Med (12/08/2015).

Studies were limited to those using human participants and those published in English. There were no limits on the dates of publication. Key words used were chronic pain, complex regional pain syndrome, cortical thickness and cortical surface.

The search on MEDLINE and EMBASE used the following key words: chronic pain, cortical thickness and cortical surface. Thesaurus mapping from the keywords resulted in: pain , sensorimotor cortex, neuroanatomy, somatosensory cortex, Image Processing, Computer-Assisted, brain region, neuroimaging, brain mapping, functional magnetic resonance imaging, Magnetic Resonance Imaging, patient, imaging, Humans, human. The MEDLINE and EMBASE searches together resulted in 55 relevant abstracts.

The search on the PubMed database used the same key words. MESH terms and subheadings were also selected for the main keywords: cortical thickness, cortical surface, complex regional pain syndrome and chronic pain. Only 15 abstracts were found with this search. Duplicate articles were checked and matched across all databases. In total, 70 abstract and full texts were considered appropriate and relevant for the current purpose, and these are reviewed below. Interestingly, there were only two specific articles on cortical morphometry measurements and CRPS (Geha et al., 2008, Mutso et al., 2012). Subsequently, another article on cortical thickness and neurocognitive function in CRPS was found (Lee et al., 2015).

7.1.1 Gut-related pain

Seminowicz et al. (2010) used magnetic resonance imaging–based techniques, including voxel-based morphometry, and cortical thickness analysis to examine brain anatomical differences in a relatively large (n=55), tightly screened sample of irritable bowel syndrome (IBS) patients. Compared to healthy controls, IBS was associated with decreased grey matter density (GMD) in widespread areas of the brain, including the medial prefrontal and ventrolateral prefrontal cortex, posterior parietal cortex, ventral striatum, and thalamus. Conversely, the patients with IBS had increased GMD, relative to controls, in the pre-genual

anterior cingulate cortex and the orbitofrontal cortex, as well as trends to increases in GMD in the posterior insula or secondary somatosensory cortex, (para) hippocampus, and left DLPFC. The results changed when differences between anxiety and depression in participants were controlled for. Several of the brain regions involved in affective processing no longer differed between patients with IBS and controls, whereas the differences in prefrontal and posterior parietal cortices remained. The areas of decreased GMD associated with IBS were largely consistent across clinical subgroups, based on predominant bowel habit and pain predominance of symptoms. No overall or regional differences were observed in cortical thickness between patients with IBS and controls (Seminowicz et al., 2010).

In another study of IBS, 11 patients and 16 age-matched healthy participants underwent structural magnetic resonance imaging (Blankstein et al., 2010). Voxel-based morphometry and cortical thickness analysis were used to identify abnormalities in subcortical and cortical regions, respectively. These brain measures were also correlated with the individuals' psychological characteristics and pain duration. The researchers found that relative to controls, IBS patients had increased grey matter density in the hypothalamus, a finding that fits with the previously neurobiological theories that functional pain which may be related to the association among IBS, stress, and the hypothalamic-pituitary-adrenal axis. Also relative to controls, the IBS patients had cortical thinning in the anterior midcingulate cortex. There was a negative correlation between pain catastrophising and dorsolateral prefrontal cortex (DLPFC) thickness, consistent with an important role for the DLPFC in the relationship between the catastrophising tendency of these patients and increased pain. Finally, there was a positive correlation between pain duration and anterior insular cortex thickness, which raised the possibility of innate predisposing factors in IBS as opposed to secondary changes (Blankstein et al., 2010)

Likewise, a mixture of increases and decreases in grey matter (GM) volume was found in a study of irritable bowel syndrome in females (Labus et al., 2014). There were also alterations in regional network properties. Increased sensitivity to somatic and visceral stimuli was associated with higher GM volumes in S1, increased emotional arousal was associated with lower GM in the hippocampus, and other chronic pain-related mechanisms were related to lower GM in the insula and cingulate cortices, and differences in the properties of the insula, cingulate, thalamus and brain stem. Consistent with extensive alterations in the somatosensory system are qualitative symptom reports and quantitative pain measurements showing widespread somatic hyperalgesia in IBS patients, including heat pain stimuli (Labus et al., 2014). These mixed results for grey matter changes in IBS patients might reflect different pathophysiological components of the disease processes underlying IBS symptoms.

Patients with chronic pancreatitis also experience gut pain. A study of such patients indicated that the overall whole brain cortical thickness was reduced compared to healthy controls, with means of 1.98 mm and 2.11 mm respectively (Frokjaer et al., 2012). Since the researchers found no differences between patients and controls in the thickness of the occipital middle sulcus, a control brain area used in the study. The main result of decreased thickness was found in the following brain areas: the DLPFC defined as the middle frontal gyrus, the laterofrontal cortex (FC) defined as the orbital parts of the superior and inferior frontal gyrus, the mid cingulate cortex, the secondary somatosensory cortex (S2) defined as the Rolandic operculum and the entire insula. The latter two brain areas of pancreatic patients had lesser cortical thickness in the left hemisphere compared to the right hemisphere. No differences were detected in the several other ROIs chosen including S1, the anterior and posterior cingulate cortices (Frokjaer et al., 2012).

7.1.2 Back pain

Research on patients with chronic low back pain (CLBP) have found show changes in grey matter. A longitudinal anatomical and functional MRI study found CLBP patients had gross widespread relative activation compared to controls (Seminowicz et al., 2011). In particular, the left DLPFC was thinner and associated with abnormal cognitive task-related activity in CLBP patients before spinal surgery or facet joint injection treatment. Following treatment that alleviated pain, this area became significantly thicker and cognitive activity returned to normal. The degree of recovery in cortical thickness depended on the extent of the patient's improvement after treatment. The authors of the study strongly suggested that effective pain relief could restore normal brain function (Seminowicz et al., 2011).

Research on the neuroanatomical and functional changes of the primary somatosensory cortex (S1) imply that this brain region in particular may play an important role in the pathophysiology underlying sensory aspects of chronic pain. Kong and colleagues examined this brain area, and compared the functional connectivity (FC) and structural differences in patients with CLBP and matched healthy controls (Kong et al., 2013). The findings were that FC differed between patients and healthy controls at S1 (in a masked area corresponding to the lower back), and also that the strength of FC increased with greater intensity of with endogenous lower back pain. The cortical thickness of the bilateral postcentral gyri or bilateral S1 was significantly greater in the patients than in the controls. In addition, patients had a larger cortical volume in the top third of the postcentral gyrus bilaterally compared to controls, even when age and gender were controlled as co-variates. Voxel-wise whole brain regression analysis

between the cortical thickness and the duration of LBP within patients found no statistically significant relationship (Kong et al., 2013).

7.1.3 Temporomandibular Disorder

Moayedi and colleagues investigated the relationships between chronic pain, neuroticism and forebrain grey matter (GM) in patients with temporomandibular disorder (Moayedi et al., 2011). Their findings indicated that several aspects of an individual's pain experience during temporomandibular disorder affected their brain GM. They found that: 1) GM volume in the sensory thalamus was positively correlated with temporomandibular disorder duration, 2) cortical thickness in the primary motor (M1) and the anterior mid-cingulate cortices (aMCC) were negatively correlated with pain intensity, and 3) pain unpleasantness was negatively correlated with cortical thickness in the orbitofrontal cortex (OFC). Lastly, they examined the possibility that neuroticism might confer a pre-existing vulnerability to grey matter changes. In the temporomandibular disorder patients, they found that there was a positive correlation between neuroticism and OFC thickness, in contrast to the negative correlation found in the healthy controls. They concluded that neuroticism may contribute to temporomandibular disorder pathophysiology and suggested that GM in the brains of patients with chronic temporomandibular disorder pain can be shaped by both personality and pain characteristics (Moayedi et al., 2011). In another study by this research group, Moayedi et al. (2012) reported that both pain duration and age-related changes also contributed to the abnormal grey matter aging in temporomandibular (TMD) pain patients compared to controls.

7.1.4 Trigeminal Neuralgia

Parise et al. (2014) investigated structural changes in grey and white matter and their relationship to sensory deficits, disease duration and medication use, in patients with trigeminal neuralgia (TN). TN patients were found to have significantly increased cortical thickness in the following areas: sensory, premotor, prefrontal, middle temporal cortex and cingulate gyrus. They had decreased cortical thickness in other areas, including the motor, insular, orbito-frontal, cuneusor precuneus and inferior temporal or fusiform cortex. However, after correction for multiple comparisons, only the inferior temporal or fusiform cortex and cuneus or precuneus areas remained significantly thinner. Cortical thickness at these areas correlated neither with disease duration nor with tactile and pain perception thresholds. However, a significant negative correlation was found between fusiform cortex thickness and carbamazepine medication dose (Parise et al., 2014).

The first published study to evaluate cortical thickness in relation to specific functional changes in evoked pain was by DaSilva et al. (2008), who studied patients with chronic trigeminal neuropathic pain (TNP). The authors investigated structural (grey matter thickness) and functional (blood oxygenation level dependent – BOLD) changes in cortical regions of precisely matched patients with chronic TNP affecting the right maxillary (V2) division of the trigeminal nerve. Functional and emotional characteristics of patients were mapped to anatomical changes in somatotopy. Cortical regions were chosen based on sensory cortices (S1 and S2), motor (M1) and posterior insula), or emotional (DLPFC, frontal, anterior insula, cingulate) processing of pain. Both structural and functional (reaction to brush-induced allodynia) scans were obtained and averaged from two different imaging sessions separated by 2–6 months in all patients. Age and gender-matched healthy controls were also scanned twice for cortical thickness measurement (DaSilva et al., 2008).

Compared with the controls, the patients with chronic TNP demonstrated significant cortical thinning in the most caudal bilateral sections of S1, representing the craniofacial region. This thinning extended from the primary to the secondary somatosensory cortex, and was localised with BOLD activation using a functional stimulus of allodynic brushing of the contralateral and affected areas of facial trigeminal neuropathic pain. Conversely, the TNP patients had bilateral thickening of the rostral neighbouring S1 area representing the hand and trunk. Thinning was also found in the emotional regions of the brains of TNP patients. The control cortical ROI in the occipital middle sulcus showed no differences between pain patients and healthy controls. The authors argued that the observed patterns of changes in cortical thickness suggest a dynamic functionally-driven plasticity of the brain. The structural changes in the brains of TNP patients correlated with the pain duration, age-at-onset, pain intensity and cortical activity. The authors concluded that these structural changes may be useful specific targets for evaluating therapeutic interventions (DaSilva et al., 2008).

7.1.5 Fibromyalgia

Another later study which examined the association between structural and functional brain changes was that of Jensen et al. (2013) who studied patients with fibromyalgia (FM). Compared to healthy matched controls, the FM patients had significantly thinner cortices and smaller brain volumes in the rostral anterior cingulate cortex, a key region for modulation of pain. Also, the regional functional connectivity in FM patients was less compared with healthy controls. Volumetric changes were more marked with prolonged exposure to FM pain. In the mesolimbic areas of the brain, structural and functional changes were related to the severity of co-morbid symptoms of depression.

7.1.6 Chronic Pain and Emotions

Salomons et al. (2012) wanted to quantify the construct of helplessness in chronic pain as a predictor of treatment outcomes, reasoning that a poorly controlled stressor would result in structural MRI changes in this population. They reported that the magnitude of self-reported helplessness was positively correlated with cortical thickness in the supplementary motor area (SMA) but negatively correlated with posterior cingulate cortex, regions implicated in cognitive aspects of motor behaviour. They examined the white matter connectivity of these regions and found that fractional anisotropy of connected white matter tracts along the corticospinal tract was also associated with helplessness, and mediated the relationship between supplementary motor area cortical thickness and helplessness (Salomons et al., 2012). Interestingly, they did not find any significant correlation between pain intensity, unpleasantness and duration and their cortical thickness findings.

Gustin et al. (2013) investigated the relationship between regional grey matter volume and, depressive traits or states. Using voxel-based morphometry of T1-weighted anatomical images, they compared 42 chronic pain patients with 35 controls. In chronic pain patients, state and trait depression scores were significantly correlated to subtle changes in the thalamus and the cingulate, dorsolateral prefrontal, and hippocampal cortices. Unexpectedly, grey matter volumes in these regions were not correlated with trait depressive scores in healthy controls, but were so in chronic pain patients. This difference between chronic pain patients and controls led the authors to suggest that subtle changes in brain anatomy could evoke changes in individuals' trait depression values (Gustin et al., 2013).

7.1.7 Meditation, pain regulation and morphometry measures

Grant et al. (2010) compared Zen meditators and controls in relation to the temperature required to produce moderate pain. Meditators had significantly lower pain sensitivity than controls. Structural MRI scans were also performed on their brains. Assessed across all participants, lower pain sensitivity was associated with a thicker cortex in affective, pain-related brain regions including the anterior cingulate cortex, bilateral parahippocampal gyrus and anterior insula. Comparing groups, meditators were found to have a thicker cortex in the dorsal anterior cingulate and bilaterally in the secondary somatosensory cortex. Greater years of meditation experience was associated with thicker grey matter in the anterior cingulate, and more hours of experience predicted more grey matter bilaterally in the lower leg area of the primary somatosensory cortex as well as the hand area in the right hemisphere. Results generally suggest that pain sensitivity is related to cortical thickness in pain-related brain

regions and that the lower sensitivity to pain observed in meditators may be the product of alterations to brain morphometry from long-term meditation practice (Grant et al., 2010).

Grant et al. (2011) extended the above research on brain structure, by examining effects of meditation and pain on brain function. Again they used a thermal pain paradigm, but their outcome measures were from functional magnetic resonance imaging. Compared to controls, Zen meditation practitioners had reduced activity in the executive, evaluative and emotion areas during thermally-induced pain (prefrontal cortex, amygdala, and hippocampus). Meditators with the most experience showed the largest reductions in activation. Simultaneously, meditators had more robustly activated primary pain processing regions (anterior cingulate cortex, thalamus and insula). Importantly, the lower pain sensitivity in meditators was strongly predicted by reductions in functional connectivity between the executive and pain-related cortices. The authors suggested a functional decoupling of the cognitive-evaluative and sensory-discriminative dimensions of pain, possibly allowing practitioners to view painful stimuli more neutrally. The activation pattern is remarkably consistent with the mindset described in Zen and the notion of mindfulness. Their findings challenged current concepts of pain, emotion regulation and cognitive control, which had been commonly thought to manifest through increased activation of frontal executive areas. The authors suggested that it is possible to self-regulate in a more 'passive' manner, by reducing higher-order evaluative processes, as indicated by the relative disengagement of anterior brain systems in meditators (Grant et al., 2011).

7.2 Studies that have investigated sensory cortex connections and mechanisms.

In order to understand how normal and aberrant tactile sensation such as allodynia in humans might be linked to the supraspinal mechanisms, detailed electrophysiological mapping, histology and anatomical tracing work in animal studies have been conducted. Animal studies mainly on primates have allowed detailed analysis of connections to the sensory cortex. Iwamura et al. (1994) discovered neurons with bilateral hand representation in the posterior bank of the postcentral gyrus in BA 2 and along the ambiguous border between BA 2 and BAs 5 or 7 (Iwamura et al., 1994). They proposed that a plausible explanation for their findings were the following: immediately after activation of the contralateral BA 3b by tactile input, BAs 1 and 2 on the same side are activated via anteroposterior corticocortical projections. The ipsilateral S1 area obtained input through transcallosal connections, likely from BA 2 and has the densest transcallosal connections among all S1 areas (Killackey et al., 1983). BA 2 also has reciprocal connections to BA 3b and dense connections to the motor cortex, investigated in Yumiy and Gehz's study on cat brains (Yumiya and Ghez, 1984). These connections could be responsible for the observed deactivations in the ipsilateral BA 3b and M1 cortex. The well-

established, although sparse, transcallosal connections between the M1 cortices (Rouiller et al., 1994)) is another potential route for the observed ipsilateral S1 activations. However, a transcallosal route originating from or affecting BA 3b directly is highly unlikely because hand representations in BAs 3b and 1 are practically free of transcallosal connections (Killackey et al., 1983, Hlushchuk and Hari, 2006). The precise pathway mediating the ipsilateral response is unclear. Three possibilities have been considered including: transcallosal input from contralateral S1 (Allison et al., 1989); direct uncrossed afferent projections to ipsilateral S1 and top-down input from higher-level processing areas such as S2 (Sutherland, 2006).

Somatosensory cortical changes are driven by the cortex in a top down process. The primary somatosensory cortex (S1) contains a complete body map that mirrors the subcortical maps developed by peripheral sensory input projecting to the sensory hindbrain, the thalamus and S1. Kim et al. (2015) provided evidence to support a hierarchal model of tactile processing, where pure touch is processed in S1 but adjacent cortical regions including the posterior parietal cortex and supramarginal gyrus are responsible for higher levels of processing and interpretation for the spatial location of finger stimulation. In an older primate study on the primary somatosensory cortex (Garraghty et al., 1990), the researchers investigated the significance of the interconnections of the 4 cytoarchitectonic fields, namely BA 3a, 3b, 1 and 2 on contralateral hand representation. Ablations of specific parts of the hand representations in BAs 3a and 3b immediately deactivated the corresponding part of the hand representation in BA 1. The conclusion from this primate study supported the idea that processing of somesthetic inputs across the S1 was predominantly hierarchical (Garraghty et al., 1990). However, these functional neuronal processes are malleable even after many years as shown by the recovery of hand representations in S1 after a hand transplant (Frey et al., 2008).

Peripheral changes during development alter these maps through ‘bottom-up’ plasticity. It is unknown how S1 size influences map organization and if an altered S1 map feeds back to affect sub-cortical maps. Again, mouse or rat models have investigated whether subcortical changes were driven by top down processes instead of bottom up processes (Pais-Vieira et al., 2013, Aronoff et al., 2010). Zembrzycki et al. (2013) provided evidence in developing mice that the size of S1 in mice was significantly reduced by cortex-specific deletion of Pax6 gene, resulting in a reduced body map and loss of body representations by an exclusion of later-differentiating sensory thalamocortical input. An initially normal sensory thalamus was re-patterned to match the aberrant S1 map by apoptotic deletion of thalamic neurons representing body parts with axons excluded from S1. Deleted representations were rescued by altering competition between thalamocortical axons using sensory deprivation or increasing the size of S1. Thus, S1 size determined the resolution and completeness of body maps and engaged ‘top-down’ plasticity

that re-patterned the sensory thalamus to match S1. A mouse in vivo recording study (Manita et al., 2015) has identified another long-range reciprocal projection between the secondary motor cortex (M2) and S1 that initiated dendritic spikes and persistent firing of S1 layer 5 (L5) neuron. Inhibition of M2 input to S1 decreased layer 5 firing and the accurate perception of tactile surfaces. Therefore, providing support for another top-down control circuit.

Table 7-1: Cutaneous mechanoreceptors involved in discriminative touch (Chapman et al., 1996)

Table has been removed due to copyright restrictions

Table 7-2: The contribution of different sensory modalities, the functional properties and the neural mechanisms for the peripersonal space and the body schema (Cardinali et al., 2009)

	Peripersonal space	**Body schema**
Sensory inputs	Vision	Proprioception
	Audition	Kinesthesis
	Touch	Touch
Functional properties	Defensive movements	Body knowledge
	Voluntary actions	for action
Neural mechanisms	Parietal–frontal	Pre-frontal and
	bimodal neurons	parietal cortex

7.3 Noxious perception of touch and impaired tactile acuity in CRPS

CRPS has an unusual presentation of non-noxious touch being associated with nociception. Tactile hypoestesia, hyperalgesia and allodynia are typical symptoms in patients who suffer from the condition (Juottonen et al., 2002). The patterns of distribution of symptoms are atypical, not confined to a nerve root or nerve distribution. Allodynia occurs when non-painful stimuli, such as light touch, are perceived as noxious stimuli resulting in pain. Hyperalgesia occurs when a painful stimuli, such as a pin-prick, evokes a greater intensity of pain than is expected or usual.

Knudsen and Drummond (2014) explored the relationship between hyperalgesia and when motion sickness was induced in CRPS, through an increase in sensory conflict using 10 minutes of optokinetic stimulation. Their findings suggested that sensory conflicts activated mechanisms of general pain facilitation in the condition, reduced the baseline threshold to pressure pain and, in the most nauseated participants, also activated a pain facilitatory mechanism with persisting hyperalgesia over their ipsilateral-affected side forehead. Due to adverse side-effects from the experiment, seven out of their 21 participants could not complete the study and had a longer recovery time to baseline once hyperalgesia was induced.

Pain intensity, illness duration and the extent of sensory deficit are related to feelings of foreignness and inability to identify fingers in CRPS. In a study of 114 CRPS patients (Forderreuther et al., 2004) with one upper limb affected, 54.4% of the patients reportedly found their hand 'foreign' or 'strange'. Interestingly, the feeling of foreignness was not associated with the ability to identify the fingers, allodynia or hyperalgesia. The ability to identify individual fingers of the affected hand in contrast to their contralateral hand was impaired in 48% of the patients. In contrast, the ability to identify fingers on the unaffected hand compared with the contralateral hand was impaired in only 6.5% of the patients. Response latencies to answering were longer for touch on the affected hand compared to the unaffected hand. However, sensory extinction to simultaneous stimulation was intact and they were able to differentiate between bilateral or unilateral light touch (Forderreuther et al., 2004).

CRPS participants frequently have higher thresholds or poorer acuity, compared to healthy controls when tactile acuity is measured using two-point discrimination threshold devices. Pleger and colleagues (2006) reported the following results for two-point discrimination thresholds of CRPS participants. The mean for the affected index finger was 3.23mm, significantly higher than that of the contralateral non-affected index finger (2.2 mm) and the index fingers of healthy controls (right index finger: 1.97 mm; left index finger: 1.98 mm). There were no significant differences between the non-affected index finger of CRPS participants and the corresponding index finger of healthy controls (Pleger et al., 2006). Reiswich and colleagues (2012) demonstrated impaired tactile spatial acuity in the index finger of CRPS participants when compared to healthy participants. Using one particular device to stimulate the index finger, eight of 16 CRPS participants were not able to discriminate the stimuli, whereas all of the healthy participants could do so. CRPS participants could only discriminate stimuli when the researchers used a device with larger distances between the stimuli compared to controls, ranging from 1.5 mm to 7.0 mm (Reiswich et al., 2012).

8 Appendix for Chapter 2

The following forms were used in the study:

8.1 Edinburgh Handedness Inventory (EHI)

Medical Research Council Speech & Communication Unit

EDINBURGH HANDEDNESS INVENTORY

Surname..... Given Names.....

Date of Birth..... Sex.....

Please indicate your preferences in the use of hands in the following activities *by putting + in the appropriate column.* Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, *put ++.* If in any case you are really indifferent *put + in both columns.*

Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

		LEFT	RIGHT
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife (without fork)		
7	Spoon		
8	Broom (upper hand)		
9	Striking Match (match)		
10	Opening box (lid)		
i	Which foot do you prefer to kick with?		
ii	Which eye do you use when using only one?		

L.Q.		Leave these spaces blank	DECILE	

MARCH 1970

8.2 MRI safety checklist

diagnosticMRIservices

RESEARCH PARTICIPANTS

MRI SAFETY SCREENING QUESTIONNAIRE

For your own SAFETY all questions must be answered before entering MRI

Full Name	Date of Birth	Weight Kg
	Project:	Male ☐ Female ☐

Please circle either YES or NO. Do you have any of the following?

1. Do you have a cardiac pacemaker?	**YES**	**NO**
2. Do you have an artificial heart valve?	**YES**	**NO**
3. Do you have blood vessel/cardiac stents?	**YES**	**NO**
4. Do you have aneurysm clips?	**YES**	**NO**
5. Have you EVER had metal fragments in your eye/s	**YES**	**NO**
6. Do you have a cochlear or stapes Implant?	**YES**	**NO**
7. Do you have a neurostimulator or implanted wires?	**YES**	**NO**
8. Do you have any bone screws, nails or pins?	**YES**	**NO**
9. Do you have shrapnel, bullets or foreign bodies?	**YES**	**NO**
10. Do you have dentures or prosthetic devices?	**YES**	**NO**
11. Do you have any metal body piercings or tattoos?	**YES**	**NO**
12. Do you have an intrauterine contraceptive device (IUD)?	**YES**	**NO**
13. Magnetically Activated Implant or Device?	**YES**	**NO**
14. Are you or could you be pregnant?	**YES**	**NO**
15. Have you had a MRI before:	**YES**	**NO**

If any previous surgery please list:

_____

_____

Please tick the following to indicate that you agree:

- I will remove all metal from myself including keys, coins, piercings, jewellery, hearing aids, bobby pins etc before entering the room. (locker available in your change room) ☐
- I acknowledge that this form is accurate to the best of my knowledge, I have read and understood the questionnaire and I have had the opportunity to ask questions about this questionnaire. ☐
- I acknowledge that Neuroscience Research Australia and Diagnostic MRI Services have taken reasonable precautions and is not liable for any event that might result from incorrect answers on this form. ☐

Signature _____ Date _____

8.3 quickDASH

THE QuickDASH OUTCOME MEASURE

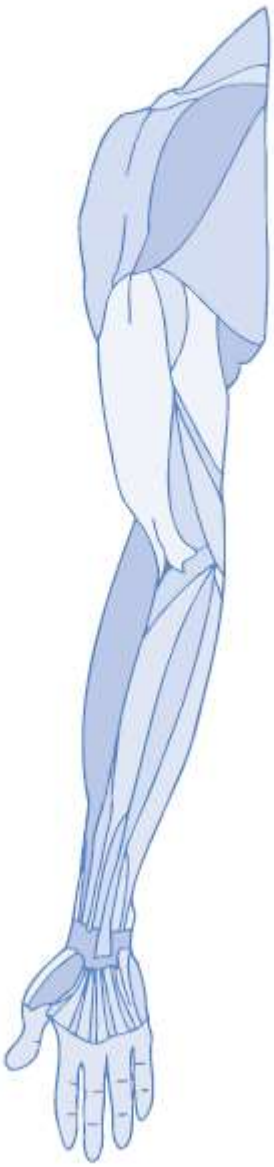
INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to perform certain activities.

Please answer *every question*, based on your condition in the last week, by circling the appropriate number.

If you did not have the opportunity to perform an activity in the past week, please make your *best estimate* of which response would be the most accurate.

It doesn't matter which hand or arm you use to perform the activity; please answer based on your ability regardless of how you perform the task.



*Quick*DASH

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Do heavy household chores (e.g., wash walls, floors).	1	2	3	4	5
3. Carry a shopping bag or briefcase.	1	2	3	4	5
4. Wash your back.	1	2	3	4	5
5. Use a knife to cut food.	1	2	3	4	5
6. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
7. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
8. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*	NONE	MILD	MODERATE	SEVERE	EXTREME
9. Arm, shoulder or hand pain.	1	2	3	4	5
10. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

*Quick*DASH DISABILITY/SYMPTOM SCORE = $\left(\left[\frac{\text{sum of n responses}}{n}\right] - 1\right) \times 25$, where n is equal to the number of completed responses.

A *Quick*DASH score may <u>not</u> be calculated if there is greater than 1 missing item.

WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including homemaking if that is your main work role).

Please indicate what your job/work is:_____

p I do not work. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week.

Did you have any difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for your work?	1	2	3	4	5
2. doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. doing your work as well as you would like?	1	2	3	4	5
4. spending your usual amount of time doing your work?	1	2	3	4	5

SPORTS/PERFORMING ARTS MODULE (OPTIONAL)

The following questions relate to the impact of your arm, shoulder or hand problem on playing *your musical instrument or sport or both*. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you:_____

o I do not play a sport or an instrument. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week.

Did you have any difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for playing your instrument or sport?	1	2	3	4	5
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. playing your musical instrument or sport as well as you would like?	1	2	3	4	5
4. spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

SCORING THE OPTIONAL MODULES: Add up assigned values for each response; divide by 4 (number of items); subtract 1; multiply by 25.
An optional module score may not be calculated if there are any missing items.

8.4 PRWE

Neuroscience Research Australia
Discover. Conquer. Cure.

Name: _____

Participant ID: _____

Date: _____

PATIENT RATED WRIST/HAND EVALUATION

The questions below will help us understand how much difficulty you have had with your wrist/hand in the past week. You will be describing your ***average*** *wrist/hand symptoms* ***over the past week*** *on a scale of 0-10.* Please provide an answer for **ALL** questions. If you did not perform an activity, please **ESTIMATE** the pain or difficulty you would expect. If you have **never** performed the activity, you may leave it blank.

1. PAIN

Rate the average amount of pain in your wrist/hand over the past week by circling the number that best describes your pain on a scale from 0-10. A zero (0) means that you did not have any pain and a ten (10) means that the pain is the worst possible (i.e worst you have ever experienced or that you could not do the activity because of pain).

RATE YOUR PAIN:	None										Worst
At rest	0	1	2	3	4	5	6	7	8	9	10
When doing a task with a repeated wrist/hand movement	0	1	2	3	4	5	6	7	8	9	10
When lifting a heavy object	0	1	2	3	4	5	6	7	8	9	10
When it is at its worst	0	1	2	3	4	5	6	7	8	9	10

How often do you have pain?	0	1	2	3	4	5	6	7	8	9	10
	Never										Always

Please turn the page...

Moseley group PRWE 28/04/2011

2. FUNCTION

A. SPECIFIC ACTIVITIES

*Rate the **amount of difficulty** you experiences performing each of the items listed below over the past week, by circling the number that describes your difficulty on a scale of 0-10. A **zero** (0) means you did not experience any difficulty and a **ten** (10) means it was so difficult you were unable to do it at all. Tick the box if you have not tried the task at all.*

	No difficulty										Unable to do	*Not tried*
Turn a door knob using my affected hand	0	1	2	3	4	5	6	7	8	9	10	☐
Cut food with my affected hand	0	1	2	3	4	5	6	7	8	9	10	☐
Fasten buttons on my shirt	0	1	2	3	4	5	6	7	8	9	10	☐
Use my affected hand to push up from a chair	0	1	2	3	4	5	6	7	8	9	10	☐
Carry a 5kg object with my affected hand	0	1	2	3	4	5	6	7	8	9	10	☐
Use toilet paper with my affected hand	0	1	2	3	4	5	6	7	8	9	10	☐

B. USUAL ACTIVITIES

*Rate the **amount of difficulty** you experienced performing **usual** activities in each of the areas listed below, over the past week, by circling the number that best describes your difficulty on a scale of 0-10. By "usual activities" we mean the activities you performed **before** you started having a problem with your wrist/hand. A **zero** (0) means that you did not experience any difficulty and a **ten** (10) means it was so difficult you were unable to do any of your usual activities. Tick the box if you have not tried the task at all.*

	No difficulty										Unable to do	*Not tried*
Personal care activities (dressing, washing)	0	1	2	3	4	5	6	7	8	9	10	☐
Household work (cleaning, maintenance)	0	1	2	3	4	5	6	7	8	9	10	☐
Work (your job or usual everyday work)	0	1	2	3	4	5	6	7	8	9	10	☐
Recreational activities	0	1	2	3	4	5	6	7	8	9	10	☐

Please turn the page...

Moseley group PRWE 28/04/2011

APPEARANCE (optional)

How important is the appearance of your hand?

☐ Very much ☐ Somewhat ☐ Not at all

Rate how dissatisfied you were with the appearance of your wrist/hand during the past week.

0 1 2 3 4 5 6 7 8 9 10

No dissatisfaction — Complete dissatisfaction

Any other comments?

End of questionnaire

Moseley group PRWE 28/04/2011

8.5 DASS-21

DASS21

Name: *Date:*

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

The rating scale is as follows:

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

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

8.6 Self-efficacy (PSEQ)

PAIN SELF EFFICACY QUESTIONNAIRE (PSEQ)
M.K.Nicholas (1989)

NAME: _____ DATE: _____

Please rate how **confident** you are that you can do the following things at present, **despite the pain**. To indicate your answer circle **one** of the numbers on the scale under each item, where 0 = not at all confident and 6 = completely confident.

For example:

0	1	2	3	4	5	6
Not at all Confident						**Completely confident**

Remember, this questionnaire is **not** asking whether of not you have been doing these things, but rather **how confident you are that you can do them at present, despite the pain.**

---

1. I can enjoy things, despite the pain.

0	1	2	3	4	5	6
Not at all Confident						**Completely confident**

2. I can do most of the household chores (e.g. tidying-up, washing dishes, etc.), despite the pain.

0	1	2	3	4	5	6
Not at all Confident						**Completely confident**

3. I can socialise with my friends or family members as often as I used to do, despite the pain.

0	1	2	3	4	5	6
Not at all Confident						**Completely confident**

4. I can cope with my pain in most situations.

0	1	2	3	4	5	6
Not at all Confident						**Completely confident**

Turn over

5. **I can do some form of work, despite the pain. ("work" includes housework, paid and unpaid work).**

0	1	2	3	4	5	6
Not at all Confident						Completely confident

6. **I can still do many of the things I enjoy doing, such as hobbies or leisure activity, despite pain.**

0	1	2	3	4	5	6
Not at all Confident						Completely confident

7. **I can cope with my pain without medication.**

0	1	2	3	4	5	6
Not at all Confident						Completely confident

8. **I can still accomplish most of my goals in life, despite the pain.**

0	1	2	3	4	5	6
Not at all Confident						Completely confident

9. **I can live a normal lifestyle, despite the pain.**

0	1	2	3	4	5	6
Not at all Confident						Completely confident

10. **I can gradually become more active, despite the pain.**

0	1	2	3	4	5	6
Not at all Confident						Completely confident

Source: Nicholas M.K. Self-efficacy and chronic pain. Paper presented at the annual conference of the British Psychological Society. St. Andrews, 1989.
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8.7 Pain catastrophising (PCS)

Ψ

PCS-EN

Client No.: _____ Age: _____ Sex: M(__) F(__) Date: _____

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I'm in pain …

1. ☐ I worry all the time about whether the pain will end.
2. ☐ I feel I can't go on.
3. ☐ It's terrible and I think it's never going to get any better.
4. ☐ It's awful and I feel that it overwhelms me.
5. ☐ I feel I can't stand it anymore.
6. ☐ I become afraid that the pain will get worse.
7. ☐ I keep thinking of other painful events.
8. ☐ I anxiously want the pain to go away.
9. ☐ I can't seem to keep it out of my mind.
10. ☐ I keep thinking about how much it hurts.
11. ☐ I keep thinking about how badly I want the pain to stop.
12. ☐ There's nothing I can do to reduce the intensity of the pain.
13. ☐ I wonder whether something serious may happen.

…Total

Updated 11/11

8.8 Pain Questionnaire

Participant ID: _____ CPAIN Project HREC13214

Score Date: _____ / _____ / _____ Time:

FIRST PAIN QUESTIONAIRE

Instructions:
Please circle one number only to each question. 0 would mean **'I have had no pain'** and **10** would mean **'I have had the worst possible pain'.**

On a scale of 0 to 10, how would you rate your average pain level over the last 7 days?

PLEASE CIRCLE ONE NUMBER ONLY

0 1 2 3 4 5 6 7 8 9 10

NO PAIN **WORST POSSIBLE PAIN**

On a scale of 0 to 10, how would you rate your average pain level over the last 2 days/ 48 hours?

PLEASE CIRCLE ONE NUMBER ONLY

0 1 2 3 4 5 6 7 8 9 10

NO PAIN **WORST POSSIBLE PAIN**

On a scale of 0 to 10, how would you rate your average pain level today?

PLEASE CIRCLE ONE NUMBER ONLY

0 1 2 3 4 5 6 7 8 9 10

NO PAIN **WORST POSSIBLE PAIN**

8.9 Pre-Post Pain Questionnaire

Participant ID: _____
Score Date: _____ / _____ / _____ Time:

PRE/ POST TEST/ SCAN

Instructions:
Please circle one number only to each question. 0 would mean **'I have had no pain'** and **10** would mean **'I have had the worst possible pain'.**

During the test/ scan

On a scale of 0 to 10, how would you rate your average pain level during the test/ scan?

PLEASE CIRCLE ONE NUMBER ONLY

0 1 2 3 4 5 6 7 8 9 10

NO PAIN **WORST POSSIBLE PAIN**

Post the test/scan

On a scale of 0 to 10, how would you rate your average pain level after the test/scan?

PLEASE CIRCLE ONE NUMBER ONLY

0 1 2 3 4 5 6 7 8 9 10

NO PAIN **WORST POSSIBLE PAIN**

Any other details or sensation during the test or after the test/scan

DURING

POST TEST/ SCAN

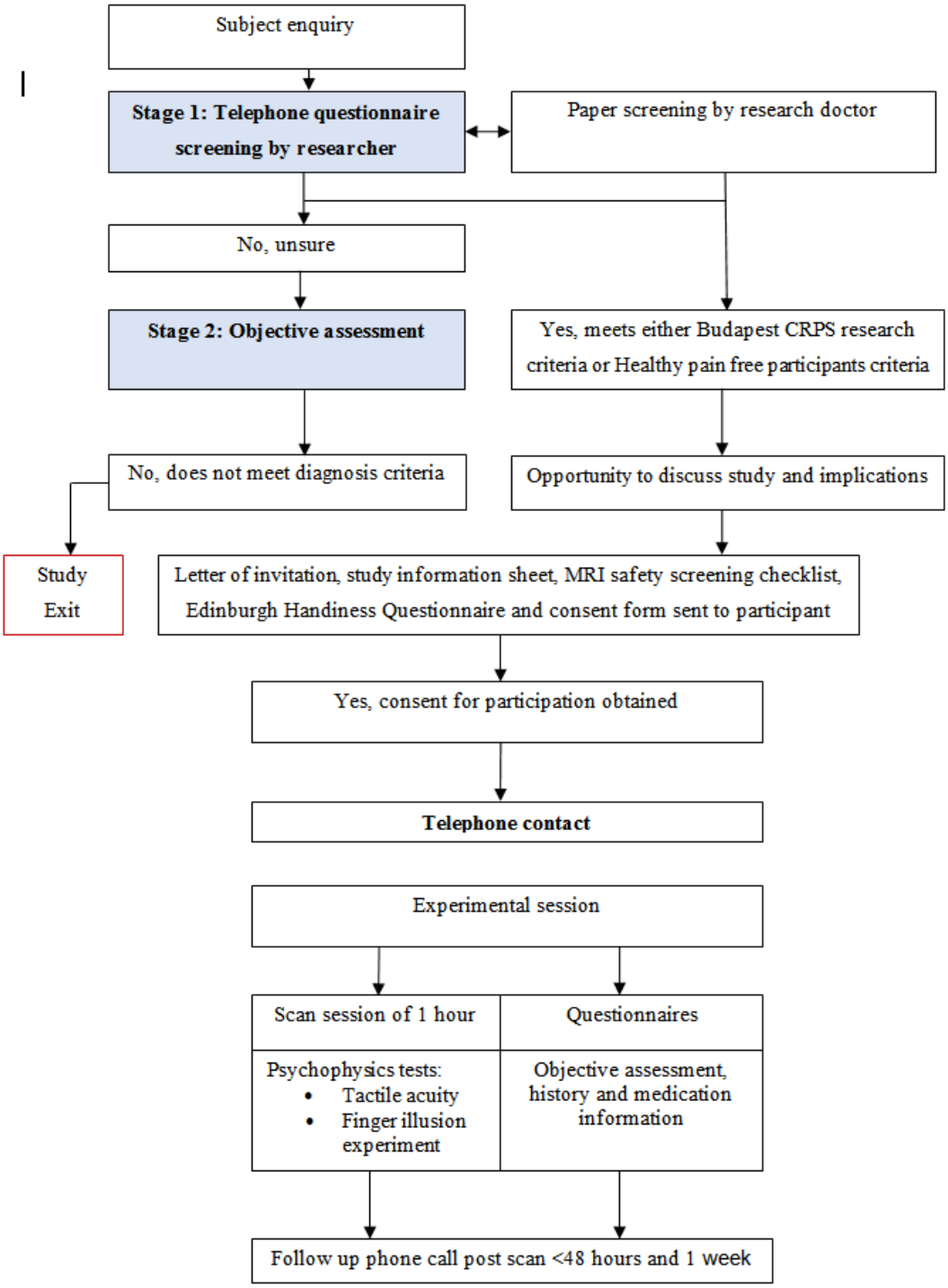


Figure 8-1: Decision tree of recruitment and summary of experimental day

8.10 Clinimetrics of Questionnaires

8.10.1 QuickDASH

Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire is related to function and ability to perform daily activities. The shortened version of this questionnaire- QuickDASH (Beaton et al., 2005) uses 11 items to measure physical function and symptoms in people with any or multiple musculoskeletal disorders of the upper limb. It is. The items relate to their ability to carry out common daily tasks, irrespective of which upper limb. Each item was calculated as per the guidelines, a higher score indicated poorer upper limb function and disability. A scoring tool is available on http://dash.iwh.on.ca/scoring. A recent study on this measure had concluded that upper limb disability was significantly greater if the dominant limb is involved (Kachooei et al., 2015).

The DASH has been subject to extensive psychometric analyses; it has shown good reliability (Raven et al., 2008, Solway et al., 2002), validity (Navsarikar et al., 1999, Gummesson et al., 2003), and responsiveness (Kotsis and Chung, 2005, Jester et al., 2005, Greenslade et al., 2004, Gay et al., 2003, Macdermid and Tottenham, 2004). DASH has been shown to have excellent test-retest reliability with an intraclass correlation coefficient ≥ 0.96 (Beaton et al., 2001, Raven et al., 2008), and strong internal consistency with Cronbach's α of 0.97 (Raven et al., 2008, Beaton et al., 2001). Good convergent construct validity of the DASH with correlations exceeding 0.70 (Pearson). This was demonstrated by finding correlations in the expected direction and of the expected magnitude with other measures of upper limb function and symptoms (Beaton et al., 2001).

8.10.2 Patient-Rated Wrist and Hand Evaluation (PRWHE)

The Patient-Rated Wrist and Hand Evaluation (PRWHE) consists of 5 items on pain and 10 items on function (MacDermid et al., 1998). A total score out of 100 can be computed by equally weighting the pain score (sum of five items) and the disability score (sum of ten items, divided by 2). A higher score would indicate poorer wrist and hand function and a lower score indicating no problems with wrist or hand function. Test-retest reliability was excellent in acute fractures and treated fractures with a range of intraclass correlation coefficient from 0.90 to 0.98 for each sub-scale (MacDermid et al., 1998). Validity assessment demonstrated that the instrument detected significant differences over time ($p < 0.01$) following therapy (Macdermid and Tottenham, 2004) and was appropriately correlated with alternate forms of assessing parameters of pain and disability (MacDermid et al., 1998).

8.10.3 Depression Anxiety and Stress Scale

The DASS-21 has 21 items on a 4 point Likert scale with three specific subscales on depression, anxiety and stress (Lovibond and Lovibond, 1995). It is the short form of the Depression Anxiety and Stress Scale, which has 42 items. The depression subscale of the questionnaire focusses on self-reported low mood, hopelessness and lack of interest, the anxiety subscale on physiological autonomic arousal, perceived fear and panic, and the stress subscale on nervousness, irritability and tension. A higher score indicates a higher likelihood of depressive symptoms associated with their condition. Internal consistency has been found to be high for each of the subscales of the 42-item and 21-item versions of the questionnaire. This is reflected in Cronbach's α = 0.84-0.92 for DASS-depression,α = 0.84-0.92 for DASS-anxiety, and α = 0.90-0.95 for DASS- Stress (Antony et al., 1998, Clara et al., 2001, Page et al., 2007, Lovibond and Lovibond, 1995, Brown et al., 1997). Confirmatory factor analysis favours a three-factor solution as the three scales has been found consistently across samples and factor-analytic techniques with only minor variations (Sinclair et al., 2012, Clara et al., 2001).

A recent RASH analysis of the DASS-21 concluded that it was suitable for research use involving groups, consisting of individuals with pain or pain related disability (Parkitny et al., 2012). DASS-21 scores can be calculated to obtain DASS scores and compared to normative data. The totalled subscale scores from DASS-21 are doubled to obtain the full DASS scores for each sub-scale. A composite score of negative emotional symptoms of by DASS can be calculated averaging all three sub-scales or adding all three sub-scales. If required, individual patients' scores on the DASS subscales can be interpreted by converting them to z-scores to allow comparison with normative values within the DASS manual (Lovibond and Lovibond, 1995).

8.10.4 Pain Self-Efficacy Questionnaire (PSEQ)

The Pain Self-Efficacy Questionnaire (PSEQ), an established 10-item measure of pain self-efficacy (Nicholas, 1989), asks participants to rate on a 7 point Likert scale how confident they are with doing things despite the pain. The higher they scored on the summation of the scale, the more confident they were. PSEQ scores were correlated with depression, anxiety, unhelpful coping strategies, pain ratings, somatic focusing, and perceived capacity work-related tasks (Miles et al., 2011).

Reliability was assessed by examination of internal consistency and stability over time (test–retest analysis with Pearson correlations and analysis of change) in a study by Nicholas (2007). Internal consistency was high with (Cronbach's α coefficient = 0.92). The test–retest correlation

(r) from baseline to 3-months was 0.73; ($p < 0.001$). Their results suggested that the PSEQ has a high degree of reliability, both internally and across a period of at least three months under conditions of no change in either pain or disability. The same study assessed validity through analysis of the PSEQ's factor structure (principal components factor analysis) and by examination of the PSEQ's relationships with validated measures of constructs that would be expected to have different types of relationship with self-efficacy (Nicholas, 2007). Validity was high with correlations of 0.67 to 0.84. Significant correlations of $r > 0.40$ ($p < 0.001$) were found between the PSEQ and active coping strategies measured. These active strategies included ignoring pain, coping self-statements, increase behaviour and control pain subscales of the Coping Strategies Questionnaire (Rosenstiel and Keefe, 1983).

8.10.5 Pain Catastrophising Scale (PCS)

Catastrophising is currently defined as: "an exaggerated negative mental set brought to bear during actual or anticipated painful experience" (Sullivan et al., 2001). The pain catastrophising scale (Sullivan et al., 1995) ask participants to reflect on past painful experiences, and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on 5-point Likert scales with end points (0) not at all and (4) all the time. PCS total scores range from 0 – 52. The higher the summed score of the PCS, the more they had experienced distressing catastrophising thoughts and feelings whilst in pain. The PCS subscales are computed by summing the item of responses of rumination, magnification and helplessness.

Test-retest reliability has been demonstrated in PCS. Reliability assessed by internal consistency, has been shown to be high with Cronbach's α for the total PCS was 0.87. Individual internal consistency for the rumination, magnification, and helplessness subscales Cronbach's α were 0.87, 0.60, and 0.79, respectively (Sullivan et al., 1995).

9 Appendix for Chapter 3

Table 9-1: The timings of the bilateral finger paradigm are compared with the single finger paradigms in the second experiment are shown for 4 cycles of the BFP and 2 cycles of the SFP. A full run has 12 cycles for BFP and 7 cycles for SFP.

Stimulation BFP	Duration of brushing at 2Hz	Stimulation SFP	Duration of brushing at 2Hz
Lead in (dummy scans)	6 seconds	Lead in (dummy scans)	6 seconds
LHD2+RHD2	6 seconds	LHD2	6 seconds
LHD3+RHD3	6 seconds	LHD3	6 seconds
LHD4+RHD4	6seconds	LHD4	6seconds
LHD5+RHD5	6seconds	LHD5	6seconds
BREAK	6 seconds	BREAK	6 seconds
LHD2+RHD2	6 seconds	RHD2	6 seconds
LHD3+RHD3	6 seconds	RHD3	6 seconds
LHD4+RHD4	6seconds	RHD4	6seconds
LHD5+RHD5	6seconds	RHD5	6seconds
BREAK	6 seconds	BREAK	6 seconds
LHD2+RHD2	6 seconds	LHD2	6 seconds
LHD3+RHD3	6 seconds	LHD3	6 seconds
LHD4+RHD4	6seconds	LHD4	6seconds
LHD5+RHD5	6seconds	LHD5	6seconds
BREAK	6 seconds	BREAK	6 seconds
LHD2+RHD2	6 seconds	RHD2	6 seconds
LHD3+RHD3	6 seconds	RH D3	6 seconds
LHD4+RHD4	6seconds	RH D4	6seconds
LHD5+RHD5	6seconds	RHD5	6seconds

Key: LH= Left hand; RH= Right Hand; D2=Index finger; D3= Middle finger; D4= Ring finger; D5= Little finger

9.1 Phase encoded fMRI techniques and S1 mapping.

Phase encoded fMRI techniques, an advancement from traditional fMRI in the early 1990s (Kwong, 2012), offers increased temporal and spatial resolution when using appropriate stimulus paradigms. As summarised by in the review by Engel (2012), page 1195, "Phase-encoded designs are used for two related, but complementary purposes: 1) to measure aggregate response properties of neurons in a voxel, for example the average visual field location of receptive fields, and 2) to segregate the set of voxels that corresponds to an organized cortical region".

These techniques have been applied to improving functional localisations in primary cortices (Wandell et al., 2007, Schira et al., 2009, Pitzalis et al., 2015, Engel, 2012) and are highly related to the corresponding anatomical and cytoarchitectonic labels (Brett et al., 2002). An orderly map of individual fingers exists as a topographical map on the primary somatosensory cortex from fMRI (Kurth et al., 1998, Francis et al., 2000, McGlone et al., 2002) and phase encoded fMRI experiments in healthy participants (Overduin and Servos, 2004). This order of fingers is from lateral and inferior, to medial and superior, in S1, but can present with variations of angles in individuals receiving tactile sensation (Kurth et al., 1998, Francis et al., 2000, Schweizer et al., 2008, Schweisfurth et al., 2014, Sanchez-Panchuelo et al., 2010).

In a phase-encoded stimulus design, each finger is stimulated consecutively, typically separated by around 6 seconds to allow sufficient time for the slow BOLD response. Once the last finger is stimulated the cycle starts again with the first finger and so forth. Hence each finger is activated and deactivated roughly in sync with the stimulation cycle. The term phase encoded is related to the pattern that each finger is activated with a unique phase delay in the cycle. Phase values represent the temporal shift required to achieve maximal correlation between the reference time course and the measured haemodynamic activity in a voxel. Fingers that are represented by a range of phase values, are visualised with an ordered colour map.

9.2 Basics of BOLD response in fMRI

Prior to further discussing more effective stimulus paradigms for the sensory cortex, a brief recapitulation of the basics of the blood oxygen level dependent (BOLD) response on which fMRI experiments rely upon is useful. The BOLD response is a hemodynamic response; specifically it reflects small local changes in blood oxygenation and flow in response to changes in neuronal activity (Ogawa et al., 1990). When neuronal activity increases in response to

stimulation, there is an increase in metabolism accompanied by a change in cerebral microvasculature, which is assumed to be due the local tissue requiring more energy and hence oxygen (Kim and Ogawa, 2012).

The BOLD response primarily corresponds to the concentration of deoxyhaemoglobin within the haemodynamic changes and accompanying paramagnetic effects (Ogawa et al., 1993). Importantly, the BOLD response is rather slow and delayed with a peak approximately 6 seconds after the initial stimulus (Bandettini et al., 1993, Boynton et al., 1996, Handwerker et al., 2012). This delay is the time it takes for dilation in local vasculature with the increased volume, leading to an oversupply of rich oxygenated blood for the energy hungry neurons. This large increase in cerebral blood flow changes the ratio of oxygenated to deoxygenated blood, allowing a measureable fMRI signal of the change in iron levels and relative paramagnetism. Accordingly, the BOLD response entails a low pass filter, dampening fast and transient responses, requiring appropriately timed experiments (Ogawa et al., 1993). These biological constraints require careful planning of an appropriate stimulus to ensure that the targeted cortical area will provide an observable and consistent response that is measurable in a successful mapping experiment.

Table 9-2: The final parameters used for scanning CRPS participants (Chapter 4) are compared with the experimental parameters used for bilateral fingertip stimulation from experiment 2 (Chapter 3).

	Bilateral Finger Paradigm			
	FINAL PARAMETERS OPTIMISED FOR CRPS		EXPERIMENTAL PARAMETERS	
Scan parameters	T1 Anatomy	pfMRI (per run)	T1 Anatomy	pfMRI (per run)
Image slices/ location	250	32	250	43
No of acquired dynamics (volumes)	1	183	1	183
repetition time (TR)	6.318 ms	2 s	6.318 ms	2s
Field of view (ap,fh,lr)	256 256 187.5	48 192 192	256 256 187.5	192 107.5 192
Scan resolution	340 340	128 (pixel) 128	340 340	96 96
Duration (s)	316	372	316	366
Slice thickness (mm)	0.75	1.5	0.75	2.5
Voxel size (mm)	0.75 x 0.75	1.5 x1.5	0.727 x 0.727	2.0 x 2.0
Flip (°)	8	82	8	82

10 Appendix for Chapter 4

10.1 Background to the volume and surface-based methods

10.1.1 Voxel-based morphometry (VBM)

Voxel-based morphometry (VBM) is a volume based method involving a voxel-wise comparison of the local concentration of grey matter between two groups of subjects (Mechelli et al., 2005, Ashburner and Friston, 2001). The procedure involves spatially normalising high-resolution MR images, from all subjects, into the same stereotaxic space. This is followed with segmenting the grey and white matter volumes from the spatially normalised images, and smoothing those segments. Then the smoothed grey and white matter images from the groups are compared using voxel-wise parametric tests. Corrections for multiple dependent comparisons are made using the theory of Gaussian random fields (Mechelli et al., 2005). In VBM methods, the definition of regions of interest in measurements relies heavily on the accuracy and precision of registration methods (Klein et al., 2009). More detail is given in a comprehensive summary of VBM by Ashburner and Friston (2000).

10.1.2 Surface-based Analysis (SBA)

Surface based analysis (SBA) derives morphometric measures from geometric models of the cortical surface. The main software discussed and used in this study is from the Freesurfer stream (Dale et al., 1999), though other software implementations of SBA are available. Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Reuter et al., 2012, Han et al., 2006). Like VBM, the input to SBA is a high-resolution T1-weighted MRI.

The first step of SBA is the extraction of the cortical surface. The cortex, being the outer layer of the brain, has an inherent two-dimensional structure. In Figure 10-1, the dotted blue line indicates the surface boundary between cortical white matter and cortical grey matter known as the white surface; this represents the inner boundary of cortex. The dark grey line in Figure 10-1 represents the boundary between the grey matter and dura and/or cerebrospinal fluid; which is referred to as the pial surface. The cortex is modelled as a mesh of triangles. Each triangle is known as a face. The place where the corners of the triangles meet is called a vertex. The parameters of the model are the coordinates (i.e., the X, Y, and Z) at each vertex. These coordinates are determined from the MRI during the extraction process. Once the coordinates of each vertex are known, the surface can be rendered in three-dimensions as seen in the exemplar in Figure 10-2.

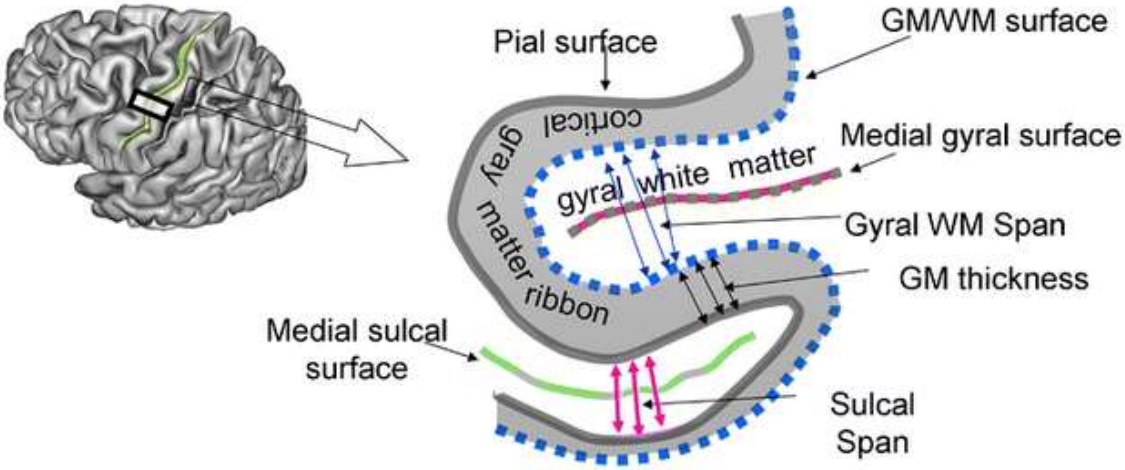


Figure 10-1: An illustration of how cortical thickness is measured as a difference between the white matter border to the pial surface, over the central sulcus area. Adapted from Kochunov et al. (2012) with permission.

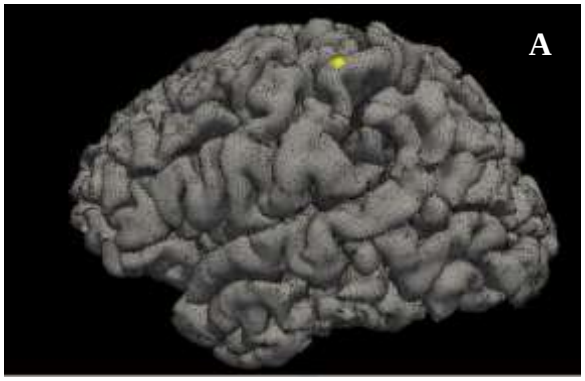


Figure 10-2: Exemplar functional representation of all four fingertips (Participant #7) confined to on the pial surface. The representation is coloured yellow (A) with the surface mesh of triangle vertices overlaid, shown enlarged in B.

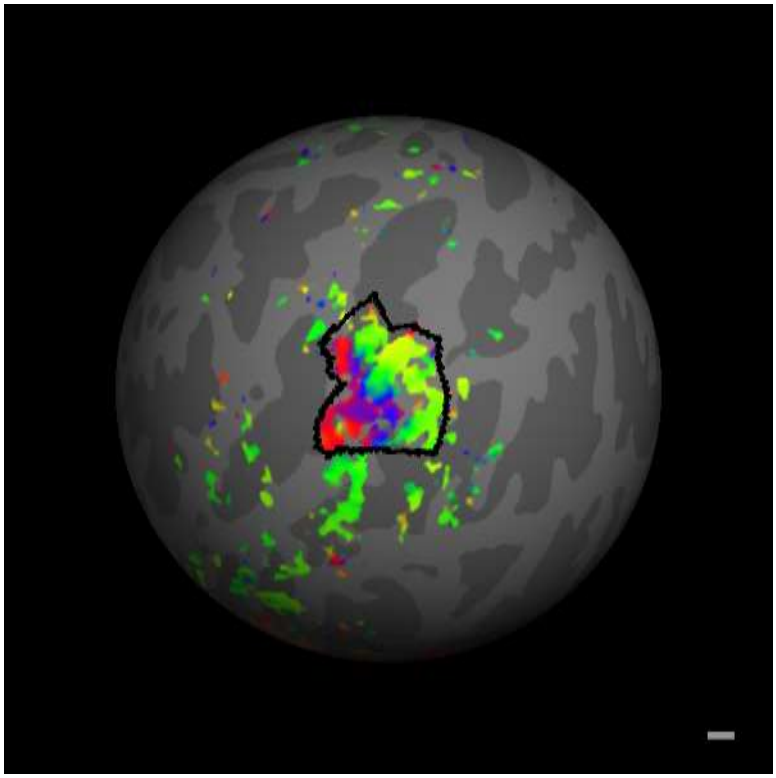


Figure 10-3: Exemplar fingertip maps (Participant #4) on fsaverage inflated surface shows the outline of the region of interest label.

Various manipulations could be applied to the surface. For example, the surface can be inflated as shown Figure 10-3. Inflation is a process of unfolding the surface so that there is no area hidden behind a fold; it is similar to unfolding a paper bag that was previously wadded into a ball. Knowledge of the coordinates enables the computation of many morphometric measures. For example, the surface area of cortex can be computed by summing up the areas of the triangles (Figure 10-2).

Thickness is a direct measure of the amount of grey matter present at each point on the surface. The distance between the white and pial surfaces gives a measure of the cortical thickness, labelled as GM thickness, in Figure 10-1. Procedures for the measurement of cortical thickness in Freesurfer have been validated against histological analysis (Rosas et al., 2002, Hinds et al., 2009, Cardinale et al., 2014) and manual measurements (Salat et al., 2004, Kuperberg et al., 2003). Like VBM's measure of grey matter concentration, thickness can be used in a group analysis to track changes associated with age and disease process. Another measure derived from SBA is curvature, which is a measure of how sharply the cortex is folded at each point. Curvature is a direct measure of the folding pattern of cortex. The whole brain surface can be morphed into a sphere as shown in Figure 10-3. This type of display clearly

shows the two-dimensional nature of the surface as each vertex can be localized with only two spherical coordinates (longitude and latitude). The curvature in the sphere is important for surface-based spatial normalization (Greve, 2011).

A further SBA measure, cortical thickness, is systematically related to cytoarchitecture and to the structural hierarchical organisation of the cortex. Patterns of cortical thickness mirror a key motif of the cortex, specifically its structural hierarchical organisation in the visual, auditory and somatosensory cortex. Cortical thickness gradients are significantly correlated with structural hierarchical level of sensory processing hierarchies in macaque and human subjects (Wagstyl et al., 2015). These results provides support for the hypothesis that a gradient of cortical thickness, from thinner primary sensory areas to thicker higher-order areas, may be a useful biomarker of changes in cortical cytoarchitecture, structure and potentially functions of the hierarchy. Cardinale et al. (2014) demonstrated good agreement between Freesurfer cortical thickness measurements and histological resections from epilepsy patients. The study authors concluded that cortical thickness is a potential biomarker for neurological conditions. In summary, the measurement of cortical thickness may become an important way to develop the understanding of brain structure–function relationships.

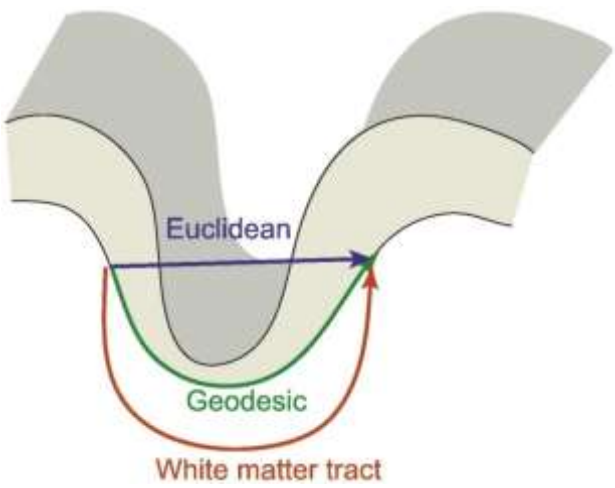


Figure 10-4: Various cortical distance measures are illustrated. Geodesic distance measures the shortest path between two points across the white matter (or pial) surface of the cortex. Euclidean distance is the shortest distance through 3-dimensional space. White matter tract distance approximates the length of an axon connecting two regions (Wagstyl et al., 2015)

Geodesic distance is a measure of the shortest distance between two points following the curvature of the pial surface of the cortex. This is another type of SBA based measurement that takes into account that inter-subject variability and cortical gyrification (Wagstyl et al., 2015). The mechanics of cortical gyrification, causes gyri to be on average 20% thicker than sulci (van Essen and Maunsell, 1980, Fischl and Dale, 2000). This gyrification will influence the measurement of geodesic distance; please see Figure 10-4. However, these effects, although relatively under-explored, have been easily accounted for by using MR-based surface

reconstruction approaches.

There are other factors that do influence both SBA and VBM measurements. For example, cortical thickness and volume measures need to be treated with caution when researchers do not report the software or computer versions used. Gronenschild et al. (2012) demonstrated that older software versions from Freesurfer (older than version 5.00) and type of computer workstation used, can affect cortical thickness and volume measures. These differences were on average 8.8 ± 6.6% (range 1.3 – 64.0%) for volume and 2.8 ± 1.3% (1.1 – 7.7%) for cortical thickness. About a factor of two smaller differences were detected between Macintosh and Hewlett-Packard workstations and between OSX 10.5 and OSX 10.6. The observed differences are similar in magnitude to effect sizes reported in accuracy evaluations and neurodegenerative studies. Therefore, clear reporting of the software version and computer platform used is required (Carp, 2012) for analyses using either VBM or SBA.

10.2 Supplementary Information for Chapter 4

Individual region of interest functional fingertip maps for every participant confined to the view over S1 and its surrounds are illustrated as averaged maps in Supplementary Part C. Some participants do not have available ROI interest maps confined within S1 or sub-threshold activations for the chosen threshold (blank maps). Therefore, phase-encoded fingertip maps overlaid on high resolution T1 scans for all 65 hemisphere labels, deemed suitable for analysis by FM are illustrated in Supplementary Part A and Part B.

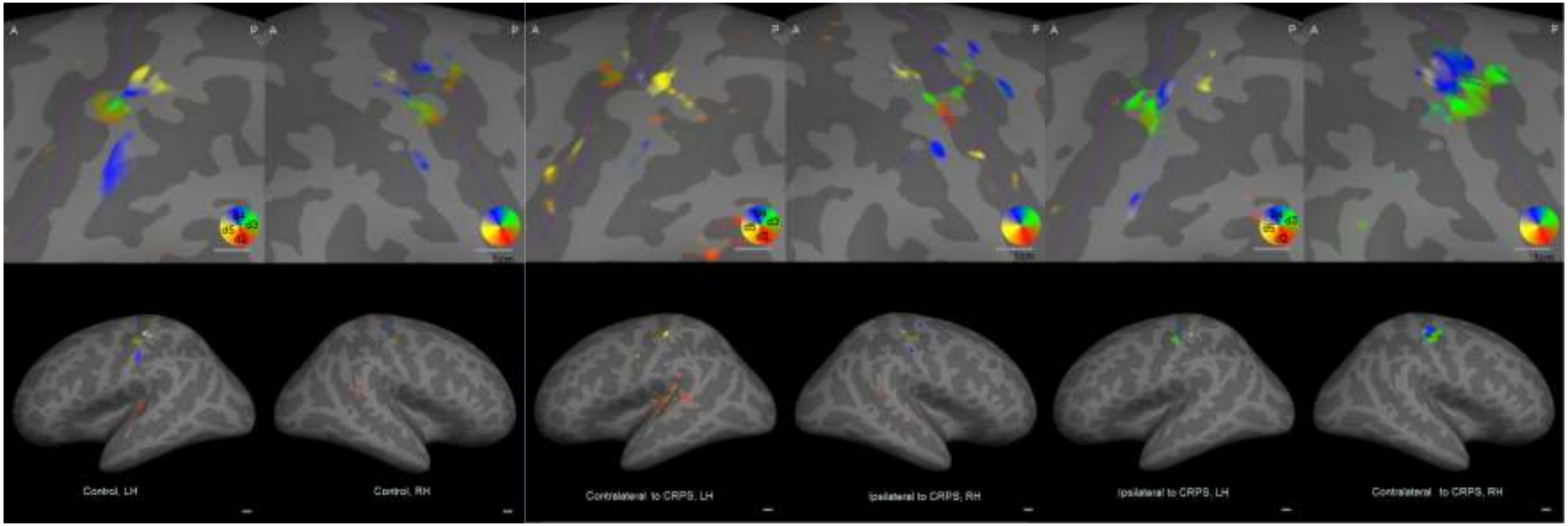
10.2.1 Supplementary Part A - Functional fingertips maps

(file name: 3408008 _Thesis_SupAmaps.pdf)

10.2.2 Supplementary Part B- Functional fingertips maps

(file name: 3408008_Thesis_SupBmapsU.pdf) Updated

10.2.3 Supplementary Part C – Average group functional fingertip maps



Functional activations maps were averaged across all subjects of each group (controls, n=17; right hand CRPS, n=10; left hand CRPS, n = 8), and overlaid on an average inflated surface. The data were smoothed using a 4 mm kernel and thresholded at $p < 0.05$ (uncorrected for multiple comparisons). The scale and orientation at which the maps are displayed are indicated by a grey bar at the bottom of each figure: the bar corresponds to 1 cm, A= anterior and P= posterior. Fingertip representations are mapped using different colours, as indicated by the colour wheel: Index finger, D2, Red; Middle finger, D3, Green; Ring finger, D4, Blue; Little finger, D5, Yellow.

Table 10-1: Pairwise comparisons of cortical morphometry measures in Controls.

Control	Brain Type (I)	Brain Type (J)	Mean diff (I-J)	95% CI	df	Sig*
Surface Area (%)	Dominant brain	Non-dominant brain	0.093	-0.048, 0.233	32.938	0.189
	Affected hemisphere	Unaffected hemisphere	-.029	-0.172, 0.115	32.692	0.686
Gray Volume (%)	Dominant brain	Non-dominant brain	.074	-0.047, 0.194	32.829	0.221
	Affected hemisphere	Unaffected hemisphere	-.052	-0.170, 0.066	31.944	0.379
Geodesic Distance (mm)	Dominant brain	Non-dominant brain	-.692	-4.849, 3.465	32.824	0.737
	Affected hemisphere	Unaffected hemisphere	.361	-3.971, 4.693	33.415	0.866
Cortical Thickness (mm)	Dominant brain	Non-dominant brain	.010	-0.163, 0.184	28.729	0.903
	Affected hemisphere	Unaffected hemisphere	-.141	-0.323, 0.041	25.509	0.123

**Unadjusted for multiple comparisons.*

The underlying cortical morphometry measures were derived from the functional fingertip maps of four digits in each hand marked as the region of interest. Surface area and grey matter volume were surface based measurements expressed as a percentage of the whole brain matter measurement.

Table 10-2: Pairwise comparisons of cortical morphometry measures in CRPS.

CRPS	Brain Type (I)	Brain Type (J)	Mean diff (I-J)	95% CI	df	Sig*
Surface Area (%)	Dominant brain	Non-dominant brain	-.012	-0.160, 0.136	38.540	.868
	Affected hemisphere	Unaffected hemisphere	.037	-0.113, 0.187	38.351	.619
Gray Volume (%)	Dominant brain	Non-dominant brain	.039	-0.087, 0.166	38.451	.532
	Affected hemisphere	Unaffected hemisphere	.081	-.042, 0.205	37.612	.191
Geodesic Distance (mm)	Dominant brain	Non-dominant brain	-3.311	-7.550, 0.929	36.093	.122
	Affected hemisphere	Unaffected hemisphere	.691	-3.717, 5.099	36.711	.752
Cortical Thickness (mm)	Dominant brain	Non-dominant brain	.287	0.105, 0.469	34.413	.003**
	Affected hemisphere	Unaffected hemisphere	.066	-0.123, 0.256	31.122	.480

**Unadjusted for multiple comparisons. ** sig >0.05*

The underlying cortical morphometry measures were derived from the functional fingertip maps of four digits in each hand marked as the region of interest. Surface area and grey matter volume were surface based measurements expressed as a percentage of the whole brain matter measurement.

Table 10-3 : Evoked sensations of the non-noxious tactile stimuli reported by participants during the MRI scan.

CRPS participants	Controls
• Blacked out x2, lost awareness during stimulation, painful. Burning increased on left side and right forearm. Increased pain. Felt decreased awareness. Felt increase tingling and pain • Seems very painful • Brushing like sharp object on left hand • Horrible. Pain up to neck (most pain in shoulder). Itchy everywhere due to brushing .Stopped itching after brushing. • Sensation like scrapping and irritating on left hand. Normal feeling like popsicle stick on right. Both eyes burning and running • Numbness. Left hand more pressure, felt like makeup brush. Right felt like plastic brush. Tingling. Left hand to armpit needle like shock sensations • Electric shooting pain, stopped after test end • Feeling numb and tingly • Didn't feel brushing after a while. Each finger felt different. Very painful solid object. Squeezing. Middle finger: flame. Ring: blade cutting. Little finger: felt like it was being squeezed • Ears burning. When brushing started, could feel more in Right than Left. Intensified in right ring and pinkie. Felt like brushing with something blunt, more blunt on right. Dreaded brushing on right • Right: sharp pain, tingling up arm, did not hurt on pinky. Less pressure sensation but pain index, middle and ring finger. Left: felt like light touch, stronger pressure • Lighter brushing, "like a thread", very light on left finger tips. Feel more brushing on right hand fingers. Pain up the arm and hard to feel left shoulder. Weird sensations- electrical shocks going up and down. Then shoulder was numb. • Right hand-tingling up arm- goose bumps, cold. Also, felt burning up arm Left hand- Felt softer	• Brushing felt the same both sides. Felt like plastic brush • Felt like brushing with something solid. Similar both sides. • Nice feeling for brushing, same both sides. Felt awake during scan

11 Appendix for Chapter 5

11.1 Supplementary 1

We hypothesised that healthy controls will perceive a difference in the 'finger' illusion experiment with their dominant hand compared to their non-dominant hand.

Perceived distances between index fingers estimated by healthy controls are shown in the following two tables. Means are given for dominant and non-dominant hands in each workspace in Table 11-1, and each grasp position in Table 11-2.

Table 11-1: The effect of hand dominance and workspace on the perceived distance between index fingers estimated by healthy control subjects during the 'finger' illusion experiment. Mean distances and 95% CI are in cm.

			95% Confidence Interval	
Hand	**Space**	**Mean (cm)**	***Lower Bound***	***Upper Bound***
Non-dominant	Centre	6.33	5.09	7.57
	Dominant	5.00	3.89	6.11
	Non-dominant	5.63	4.60	6.66
Dominant	Centre	6.44	5.02	7.86
	Dominant	5.81	4.50	7.12
	Non-dominant	5.04	4.24	5.83

Table 11-2: The effect of hand dominance and 'grasp' position on perceived distance between index fingers estimated by healthy control subjects during the 'finger' illusion experiment. All means and 95% CI are in cm.

			95% Confidence Interval	
Hand	**Grasp**	**Mean (cm)**	***Lower Bound***	***Upper Bound***
Non- dominant	No Grasp	6.33	5.27	7.39
	Grasp	4.98	4.03	5.93
Dominant	No Grasp	6.36	5.31	7.41
	Grasp	5.17	4.24	6.09

In healthy participants data, Mauchly's test indicated that the assumption of sphericity was violated for the main effect of workspace ($X^2(2)= 12.33$, $p< 0.05$); therefore the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon= 0.68$). However, the assumption of sphericity was met for the interaction effect of workspace by hand dominance ($X^2(2)= 1.47$, $p>.05$).

Planned a priori hypothesis contrasts of the effect of hand dominance on variables of work space and grasp type of healthy controls were not significant; between dominant and non-dominant workspace, $F(1, 20)= 0.085$, $p=0.773$, $\eta^2_\rho= 0.085$, *power*= 0.059, and the effect of hand dominance on perceived distances during 'no grasp' and 'grasp'; $F(1,20)= 0.064$, $p=0.803$, $\eta^2_\rho= 0.003$, *power*= 0.057.

11.2 Supplementary 2

Healthy controls in the centre workspace did not have significant differences between their first and second ratings.

There was a significant effect of grasping on the perceived vertical distance in the centre workspace in controls, F (2, 42) = 28.43, $p<0.0001$. However, the first time the perceived vertical distance at No Grasp was reported, was not significantly different compared to the second time this was reported , $t(42) =0.452$, $p >0.05$ (two-tailed). Neither were the results were not significant at Grasp condition, $t(42)= 1.688$, $p >0.05$ (two-tailed). The mean differences at No Grasp in the midline for controls were; $\bar{x}$ = -0.083, 95 % CI: -0.512 to 0.3454 and at Grasp were; $\bar{x}$ = 0.321, 95% CI: -0.122 to 0.764. These differences are plotted in Figure 11-1.

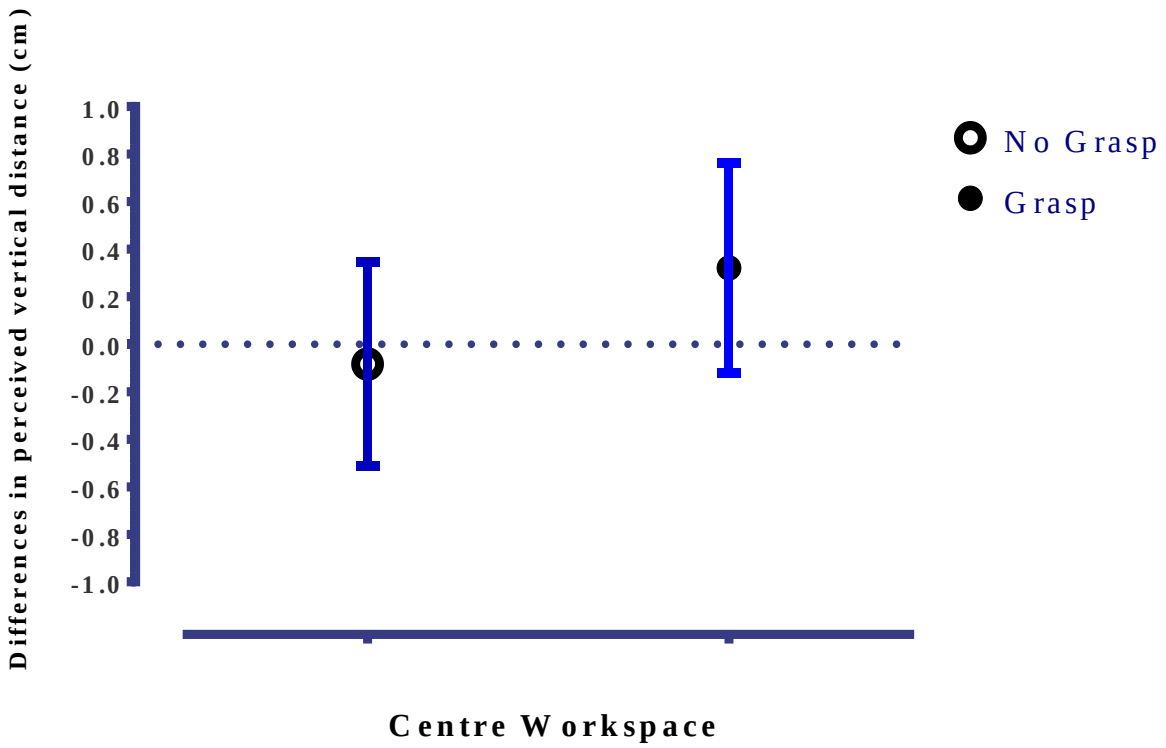


Figure 11-1 : The first rating was not significantly different from the second rating during No grasp and Grasp condition in healthy controls.

Mean and 95 % confidences intervals error bars of the differences are shown on the graph.

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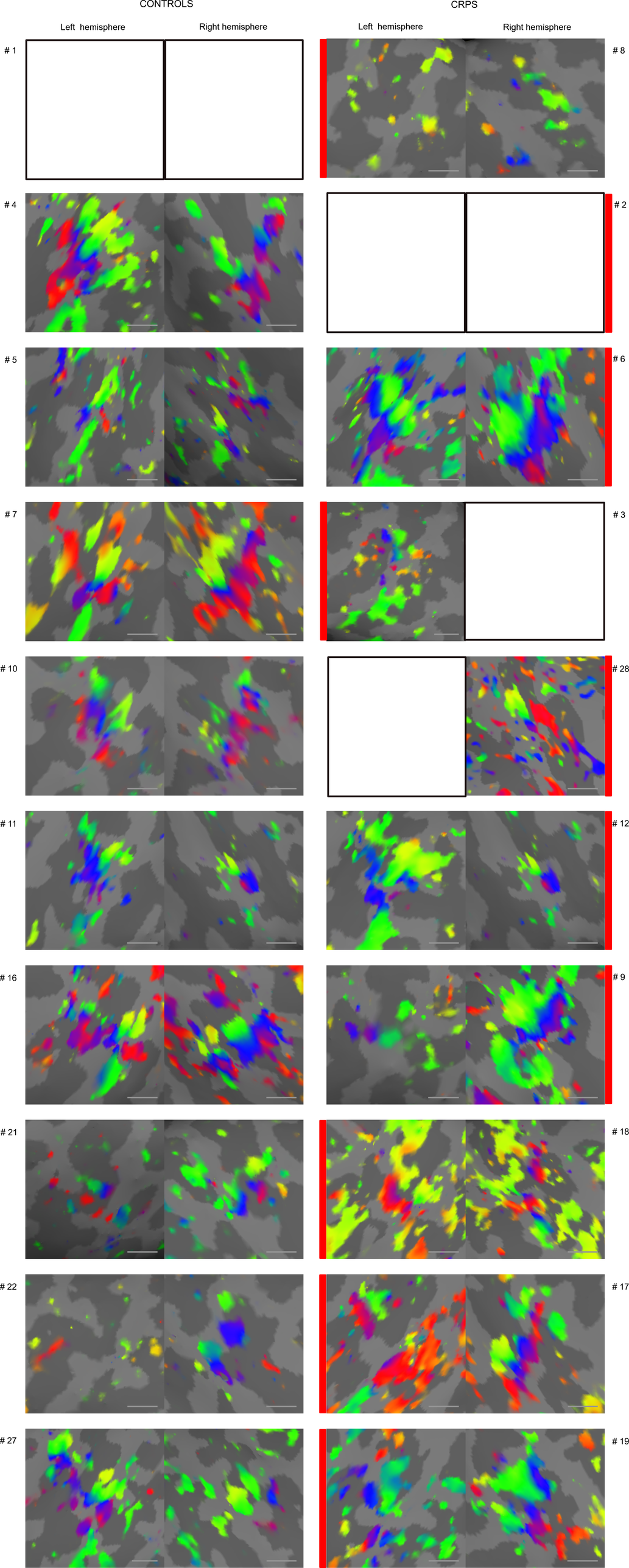
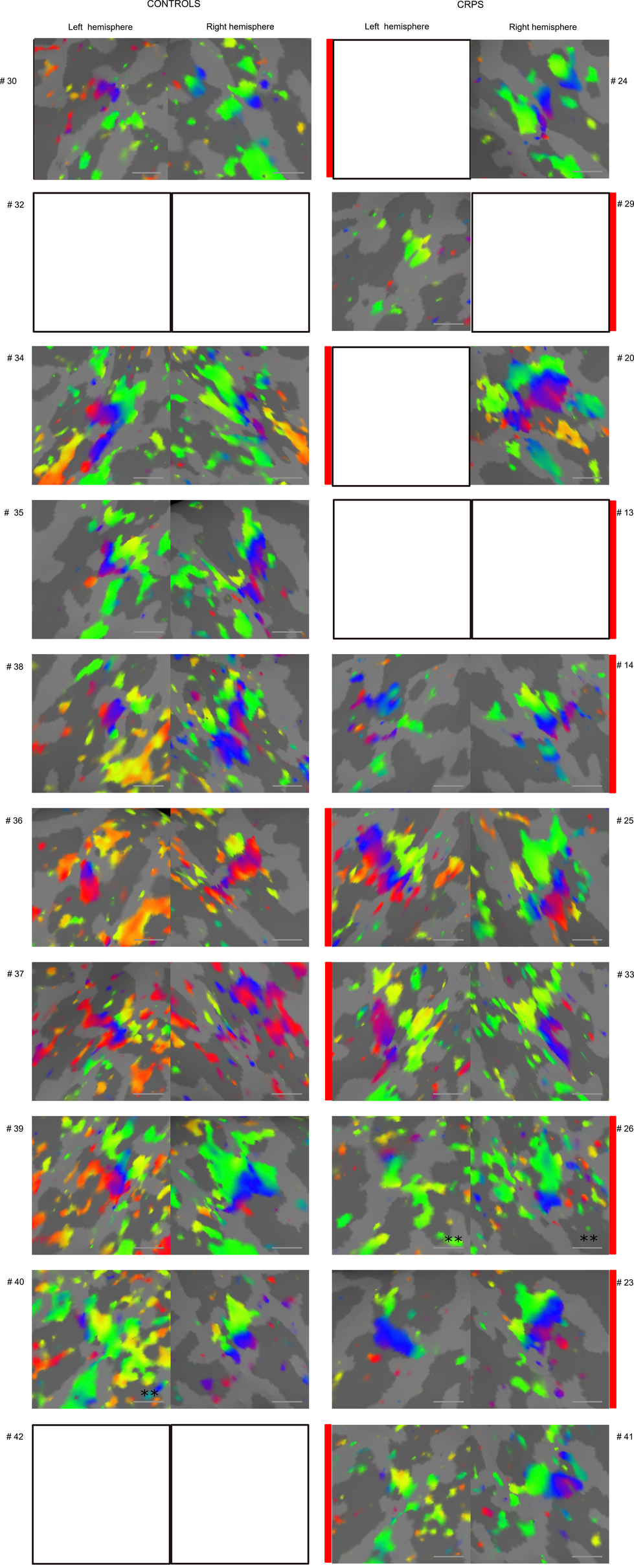

CONTROLS
CRPS
Left hemisphere
Right hemisphere
Left hemisphere
Right hemisphere
1
8
4
2
5
6
7
3
10
28
11
12
16
9
21
18
22
17
27
19



Notes:

* *#26 Right hemisphere (RH) and Left hemisphere (LH) p >0.05 threshold

#40 LH p >0.05 threshold RH p >0.01 threshold

#42 had multiple maps and had acute arm pain and numbness injury

#32 had inadequate data acqusition lacking adequate coverage of S1

#1 and #2 had inadequate fMRI runs to process