

# **Cortical Reorganisation in Complex Regional Pain Syndrome (CRPS)**

(Establishing the diagnostic utility of novel clinical signs and exploring high density electroencephalogram markers of cognitive dysfunction in CRPS)

## **MD Thesis**

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## Summary

Complex Regional Pain Syndrome (CRPS) is a debilitating pain condition of unknown aetiology, usually occurring post-traumatically. Early diagnosis of CRPS remains a challenge with adverse implications on rehabilitation and recovery. The main goals of my research were to help develop clinically useful bedside tests as well as objective biomarkers to improve the early diagnosis of CRPS.

The first research project in this thesis, 'Novel signs in CRPS and their diagnostic clinical utility' was a prospective observational cohort study which defined the four novel signs (finger misperception, abnormal hand laterality, astereognosis and abnormal body scheme report) in CRPS, examined their prevalence in CRPS and other chronic pain conditions and assessed their diagnostic utility (Sensitivity, Specificity, Predictive values and Likelihood ratios) for identifying patients at risk of CRPS within a Fracture cohort. This study demonstrates that novel signs are present in the majority of CRPS patients and can be reliably detected following simple training. They are practical and have significant clinical utility in diagnosing persistent pain in a fracture group. They can be used to identify patients at high risk of developing chronic pain post-fracture thereby allowing targeted early intervention.

Cortical reorganisation, defined as structural and functional changes within the cerebral cortex, is implicated in many chronic pain conditions including CRPS. The second research project in this thesis 'Cortical reorganisation and finger misperception in CRPS- a high density electroencephalogram study' was a prospective case control design study which investigated the EEG parameters suggestive of cortical reorganisation in CRPS patients by studying the somatosensory ERPs (Event Related Potentials) elicited on painless finger stimulation. There was no significant difference in the GFP (Global Field Power) latency in the patient group compared to healthy subjects or between affected and unaffected sides of the patient group suggesting there was no impairment of somatosensory conduction from the periphery to the somatosensory cortex. However, GFP amplitude corresponding to P300 was

significantly higher in the patient affected side compared to the healthy subjects suggesting cognitive dysfunction possibly related to increased allocation of attentional resources.

## Preface

**Declaration:** This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University of similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit of 60,000 words.

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Finally, I would like to dedicate this thesis to my parents, my wife Carine and my daughter Annabelle. I am forever grateful for their tremendous love and support.

*Anoop Kuttikat*



# **Chapter 1: Complex Regional Pain Syndrome (CRPS)**

## **– an overview**

### **1.1 Definition**

Complex Regional Pain syndrome (CRPS) is a debilitating pain condition that usually arises after trauma to a limb. It is characterised by dis-proportionate pain, swelling, vasomotor, sudomotor, trophic and motor changes. CRPS is classified as Type 1 if a definite nerve lesion cannot be identified and Type 2 if there is a definite nerve lesion (Harden et al. 2007).

Symptoms and signs of CRPS can vary in severity and duration. Pain is the predominant symptom of CRPS and is seemingly disproportionate in degree or time to the usual course of any known inciting event. It is usually triggered by a fracture, soft tissue injury or surgery, although spontaneous onset has also been described in a small minority of patients. The pain is regional i.e.; not in a specific dermatome or nerve territory (Marinus et al. 2011; Birklein, Neill, et al. 2015).

Initially there is swelling of the affected part although with time this may subside. Oedema can result from inflammation and/or autonomic changes. Vasomotor changes can cause colour changes of the skin (redness or purplish/bluish discolouration) and changes in skin temperature. In most cases skin is warm to touch initially although in some it can be cold at presentation or change from warm to cold (Marinus et al. 2011; Birklein, Neill, et al. 2015).

Sudomotor changes (abnormal sweating) of the affected limb can also occur. Trophic changes recognised in CRPS include increased or decreased growth of hair and nail as well as skin atrophy. Movement difficulties are reported by almost all patients usually due to pain but can also be due to contractures in late stages. Some patients also develop central motor features such as tremors, myoclonus and dystonia (Marinus et al. 2011; Birklein, Neill, et al. 2015).

Traditionally, experts considered that there are 3 sequential stages of CRPS as described below (Bonica 1953).

Stage 1 is characterised by burning, throbbing pain; sensitivity to touch or cold; and localized oedema. The distribution of the pain is not compatible with a single peripheral nerve, trunk, or root lesion. Vasomotor disturbances occur with variable intensity, producing altered colour and temperature. The radiograph is usually normal but may show patchy demineralization.

Stage 2 is marked by progression of the soft tissue edema, thickening of the skin and articular soft tissues, muscle wasting, and the development of brawny skin. This may last for three to six months.

Stage 3 is most severe and is characterized by limitation of movement, contractures of the digits, waxy trophic skin changes, and brittle, ridged nails. Bone radiography reveals severe demineralization.

Evidence for the sequential development of these 3 stages, however is lacking and hence this concept is not currently accepted by many CRPS experts(Harden et al. 2013; Bruehl et al. 2002).

It is clinically useful to think of CRPS in terms of early, late & recovery phases. Vasomotor and sudomotor features of CRPS (discolouration, temperature disturbance, altered sweating, and oedema) tend to be most common in early CRPS and have the greatest likelihood of resolving(Beau et al. 2014). Early CRPS has much better prognosis than the late stage and most cases improve or stabilize early after disease onset, while later improvement is less common(Goebel 2011). Motor symptoms such as weakness, stiffness, and limited range of motion are the symptoms most likely to persist in the late phase. Body perception disturbances are also reported more commonly in the late phase (Bailey et al. 2013). A formally accepted definition of recovery phase is still lacking. However, a recent study found that from patients' perspective, recovery means, in order of priority, as relief from: their CRPS-related pain, generalised pain, movement restriction, reliance on medication, and stiffness(Llewellyn et al. 2018).

## 1.2 Historical perspective

The earliest documented clinical description of CRPS is probably by the 16<sup>th</sup> century French surgeon, Ambroise Pare (Figure 1.1). He reported that King Charles IX developed persistent arm pain and muscle contractures following blood-letting procedures undertaken for treatment of small pox (Dommerholt 2004).



Figure 1.1: Ambroise Pare (1510-1590)

Silas Weir Mitchell (Figure 1.2), an American physician, in his book "Gunshot wounds and other Injuries of nerves", described American civil war (1861-65) veterans suffering from a burning pain which persisted long after the removal of the bullets. He attributed this to the consequences of nerve injury and named it "causalgia" coined from the Greek terms 'kausis' (fire) and 'algos' (pain). Mitchell observed: *"In our early experience of nerve wounds, we met with a small number of men who were suffering from a pain which they described as 'burning', or as 'mustard red hot', or as a 'red hot file rasping the skin'. In all of these patients and many later cases, this pain was an associate of the glossy skin.....The part itself is not alone subject to an intense burning sensation, but becomes exquisitely hyperaesthetic so that a touch or tap of the finger increases the pain (Mitchell et al. 1864)."*

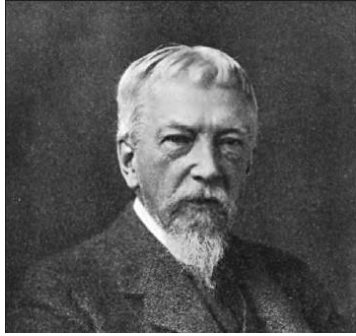


Figure 1.2: Silas Weir Mitchell (1829-1914)

Paul Sudeck (Figure 1.3), a German surgeon described the radiographic changes of patchy osteopenia (spotty decalcification) in some patients with this condition in 1900 and ascribed them to an exaggerated process of inflammation and healing (Plewes 1956). The terms 'Sudeck's atrophy (Morbus Sudeck)' and 'post-traumatic osteodystrophy' became popular especially in Europe to describe this condition.

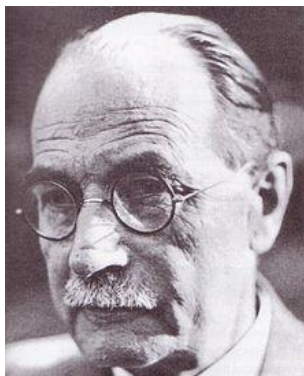


Figure 1.3: Paul Sudeck (1866-1945)

Rene Leriche (Figure 1.4), a French surgeon, was the first to recognise the importance of sympathetic nervous system in maintenance of chronic pain and reported pain relief in a patient after extensive periarterial sympathectomy (Leriche 1928).



Figure 1.4: Rene Leriche (1877-1955)

James Evans, an American physician, coined the term ‘reflex sympathetic dystrophy’(Evans 1946). He suggested that afferent activity triggered by trauma set up a spinal cord reflex that, in turn, stimulated sympathetic efferent activity. This vicious circle induced arterial vasospasm and tissue ischemia that increased capillary filtration pressure with resultant oedema and swelling. This concept was adopted and popularised by John Bonica in his classic textbook ‘The management of pain’ (Bonica 1953) and dominated medical thinking throughout the latter half of the 20<sup>th</sup> century.

The recognition that only some and not all patients respond to sympathectomy has led some to question the relevance of sympathetic nervous system as a therapeutic target and an underlying pathology (Stanton-Hicks 2000). The multitude of names (Table 1a) with imprecise classifications had led to confusion and misunderstanding in both research and clinical management of this complex condition.

**Table 1a: Previous names for CRPS in the literature**

Algodystrophy	Morbus Sudeck	Shoulder-hand syndrome
Reflex Sympathetic Dystrophy	Post-traumatic osteodystrophy	Sudeck’s algodystrophy
Causalgia	Algoneurodystrophy	Sudeck’s atrophy

### 1.3 Diagnostic Criteria

In 1993, a task force was set up by International Association for Study of Pain (IASP) to review nomenclature and devise diagnostic criteria. The consensus conference in Florida in 1994 adopted CRPS as the preferred terminology (Stanton-Hicks et al. 1995) and proposed the IASP diagnostic criteria ( Table 1b). CRPS was further subdivided into Type 1 (without a definite peripheral nerve injury) and Type 2 (with a definite peripheral nerve injury).

**Table 1b: IASP diagnostic criteria for CRPS\* (1994)**

1. The presence of an initial noxious event, or a cause for 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 a sign or symptom)
4. This diagnosis is excluded by the presence of other conditions that would otherwise account for the degree of pain and dysfunction

*\* if seen without major nerve damage, diagnose CRPS type 1, otherwise type 2*

*# not required for diagnosis; 5-10% will not have this. Must meet criteria 2, 3&4 for diagnosis*

The internal validity of IASP criteria was assessed by Harden and colleagues in a study of 123 patients fulfilling the IASP diagnostic criteria for CRPS. Data on CRPS-related signs and symptoms was obtained using a standardized sign/symptom checklist. Principal Components factor Analysis was used to detect statistical groupings of signs/symptoms (factors). Although a separate pain/sensation criterion was supported, vasomotor symptoms formed a factor distinct from a sudomotor/oedema factor. Changes in range of motion, motor dysfunction, and trophic changes, which are not included in the IASP criteria, formed a distinct fourth factor. Scores on the pain/sensation factor correlated

positively with pain duration ( $P < 0.001$ ), but there was a negative correlation between the sudomotor/edema factor scores and pain duration ( $P < 0.05$ ). The motor/trophic factor predicted positive responses to sympathetic block ( $P < 0.05$ ). These results suggested that the internal validity of the IASP/CRPS criteria could be improved by separating vasomotor signs/symptoms from sudomotor dysfunction and oedema. Results also indicated that motor and trophic changes may be incorporated in the IASP criteria as a distinct component (Harden et al. 1999).

External validity of diagnostic criteria refers to their usefulness for distinguishing between patients on the basis of some external reference or 'gold standard'. External validity of the IASP criteria were examined by Bruehl and colleagues in a study of series of 117 CRPS patients and 43 patients diagnosed with non-CRPS (diabetic neuropathy, polyneuropathy, post herpetic neuralgia and radiculopathy) neuropathic pain (Bruehl et al. 1999).

Multiple discriminant function analyses were used to test the ability of the IASP diagnostic criteria to discriminate between CRPS patients and those experiencing non-CRPS neuropathic pain. IASP criteria and decision rules discriminated significantly between groups ( $P < 0.001$ ). However, although sensitivity was quite high (0.98), specificity was poor (0.36), and a positive diagnosis of CRPS was likely to be correct in as few as 40% of cases. A decision rule, requiring at least two sign categories and four symptom categories to be positive optimized diagnostic efficiency, with a diagnosis of CRPS likely to be accurate in up to 84% of cases, and a diagnosis of non-CRPS neuropathic pain likely to be accurate in up to 88% of cases.

The poor specificity of IASP diagnostic criteria can potentially lead to over diagnosis. One reason for poor specificity was the assumption that signs and symptoms of vasomotor, sudomotor, and oedema-related changes provide redundant diagnostic information; that is, the presence of any one of these is sufficient to meet criterion 3. Diagnosis based solely on patient-reported historical symptoms was permitted as per the IASP criteria and this also likely contributed to overdiagnosis. Failure to include motor/trophic signs and

symptoms in the IASP criteria also lead to important diagnostically discriminatory information being ignored (Harden et al. 2007).

An IASP consensus workshop was held in Budapest in 2003 to address the lack of specificity in the original IASP diagnostic criteria. Their recommendations were informed by the results of the validation studies (Harden et al. 1999; Bruehl et al. 1999) of IASP criteria described above. They approved and codified empirically validated, statistically derived revisions of the IASP criteria for CRPS and this is referred to as the 'Budapest criteria' (Tables 1c & 1d). The Budapest clinical diagnostic criteria retain the sensitivity of the IASP criteria, but improve the specificity (0.68) (Harden et al. 2007).

### Tables 1c & 1d (Budapest diagnostic criteria for CRPS)

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in  $\geq 3$  symptom categories.

**Table 1C - Symptom categories in CRPS**

<b>Sensory</b>	Reports of hyperesthesia and/or allodynia
<b>Vasomotor</b>	Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
<b>Sudomotor/ Oedema</b>	Reports of oedema and/or sweating changes and/or sweating asymmetry
<b>Motor/Trophic</b>	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 1 sign at time of evaluation in  $\geq 2$  signs categories

**Table 1D - Signs categories in CRPS**

<b>Sensory</b>	Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
<b>Vasomotor</b>	Evidence of temperature asymmetry ( $>1^{\circ}\text{C}$ ) and/or skin colour changes and/or asymmetry
<b>Sudomotor/ Oedema</b>	Evidence of oedema and/or sweating changes and/or sweating asymmetry
<b>Motor/Trophic</b>	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

\*For research criteria there must be at least 1 symptom in all 4 symptom categories, and at least 1 sign in 2 or more sign categories.



## 1.4 Pathophysiology

Although the precise aetiology of CRPS remains unknown, there is evidence for pathophysiology being multifactorial in nature. In particular, aberrant inflammation (including neurogenic inflammation), vasomotor dysfunction and maladaptive neuroplasticity are the key mechanisms implicated and clinical heterogeneity stems from the inter-individual variation in the degree of activation of these pathways after tissue injury (Marinus et al. 2011).

Initial step in the pathophysiology usually involves post-traumatic inflammation. Inflammatory cytokines are released from the keratinocytes in the skin, endothelium and other damaged tissues by activation of innate immunity (Birklein & Dimova 2017). A skin biopsy study of 55 CRPS patients (Birklein, Drummond, et al. 2015) found that keratinocytes were activated in the affected skin, resulting in proliferation, epidermal thickening, and upregulated TNF- $\alpha$  and IL-6 expression in early CRPS. On the other hand, in chronic CRPS there was reduced keratinocyte proliferation with epidermal thinning. This study also found that acute CRPS (but not chronic CRPS) patients also had increased mast cell accumulation in the affected skin.

The inflammatory cytokines in turn excite the nociceptors leading to long term peripheral sensitization. Action potentials resulting from stimulation of nociceptive C-fibres travel centrally but also invade peripheral nerve terminals via axonal reflex or dorsal root reflex. This results in the release of neuropeptides (mainly Calcitonin gene-related peptide and substance P) from the cytokine-sensitized nociceptors (neurogenic inflammation) and cause vasodilation and protein extravasation resulting in redness, warmth, and oedema (Borchers & Gershwin 2014).

CRPS patients are also found to have elevated levels of the pro-inflammatory cytokines IL-1 $\beta$  & IL-6 in their cerebrospinal fluid, as well as reduced levels of the anti-inflammatory cytokines IL-4 and IL-10 suggesting an important role for central neuroimmune activation (Alexander et al. 2005).

Neuroinflammation can also spread either anterograde or retrograde, via axonal projections and establish neuroinflammatory tracks within the neural axis. Neuroinflammation spreading to second-order synapses in supraspinal centres can then potentially destabilize feedback circuits involved in proprioception, nociception, and autonomic functions, in CRPS (Cooper & Clark 2013).

Further evidence for the role of adaptive immunity comes from the detection of agonistic serum auto-antibodies against adrenergic and cholinergic receptors in some CRPS patients (Kohr et al. 2011; Dubuis et al. 2014). Two small studies (Goebel et al. 2010; Goebel et al. 2002) also suggested that treatment with low dose intravenous immunoglobulin (IVIg) may improve pain symptoms in CRPS implicating a role for auto-immunity; however a recent larger study failed to confirm the efficacy of IVIg in moderate to severe CRPS of 1-5 years duration (Goebel et al. 2017).

Vasomotor dysfunction is commonly noted in CRPS. The affected limb is usually warmer than the unaffected limb in early stages and then switches to being colder in later stages. However, in 20% of cases the affected limb is cold from the start. This temperature changes suggests a temporal shift in vasoconstrictor neuron activity. CRPS is associated with a unilateral inhibition of cutaneous sympathetic vasoconstrictor neurons, which leads to a warmer limb in the acute stage in majority of cases (Marinus et al. 2011).

In addition to affecting peripheral circulation, the sympathetic nervous system is also thought to play a role in pain (sympathetically maintained pain). Peripheral nociceptors develop catecholamine sensitivity as a result of decreased activity of cutaneous sympathetic vasoconstrictor neurons (Baron et al. 1999). However, meta-analyses of trials (O'Connell et al. 2016) have failed to show that local anaesthetic sympathetic blocks are effective in reducing pain in CRPS leading some experts to question the importance of sympathetic nervous system dysfunction in CRPS (Birklein & Dimova 2017).

Maladaptive neuroplasticity is another key mechanism implicated in CRPS (Marinus et al. 2011). Structural and functional changes within the central nervous system cause central sensitization. Disinhibition of spinal and trigeminal nociceptive neurons and facilitation of nociceptive activity by excitatory neurons that project from the rostroventral medulla are thought to be the main mechanisms of central sensitization (Vera-Portocarrero et al. 2006). Activation and upregulation of glutamate receptors causes spinal nociceptive neurons to become hyper-responsive to peripheral input (Kuner 2010) and inhibition of glutamergic NMDA receptors by intravenous infusion of ketamine has been shown to be effective in treating pain in some CRPS patients (Azari et al. 2012). Cortical reorganisation has been reported in somatosensory and motor cortices in CRPS (Di Pietro et al. 2013b; Di Pietro et al. 2013a) and these are discussed in detail in chapter 4 of this thesis.

Body perception disturbances (for example, finger misperception, astereognosis, 'not feeling as if affected limb belongs to them', distorted mental image of affected part) are also reported in CRPS and can contribute to pain (Lewis et al. 2007; Förderreuther et al. 2004; Cohen et al. 2013; Galer & Jensen 1999). The underlying mechanisms including the role for executive functions of fronto-parietal networks as well as the "salience network" including anterior insula and midcingulate cortex with reference to the "Hierarchical Predictive Coding" accounts of perception are discussed in detail in chapter 2 of this thesis (Kuttikat et al. 2016).

## 1.5 Epidemiology

CRPS is almost as common as rheumatoid arthritis and six times as common as multiple sclerosis. A Dutch community-based retrospective cohort study (de Mos et al. 2007) estimated the incidence as 26/100,000 life-years. The peak incidence was found to be between the ages of 61 and 70 years. The incidence rate in this study is four times that reported in a previous population based study done in Olmsted county, USA (Sandroni et al. 2003).

This difference in reported incidence between the two studies is likely to be due to differences in case definition and validation. For example, Sandroni and colleagues applied strict IASP CRPS criteria on electronic medical records data whereas the Dutch study did not require that all cases should fulfil diagnostic criteria; they retained all cases on the basis of a reconfirmed diagnosis of CRPS by general practitioner or specialist. The differences in population characteristics such as ethnicity, socio-economic factors and incidence of fractures may also partly explain the observed difference.

Both studies found that females were around four times more likely than males to be affected and that upper limbs were more commonly affected than lower limbs with no side preference. Fracture was the most common precipitating event accounting for around 40% of cases.

70-80% report significant recovery within 1 year of disease onset (Sandroni et al. 2003). However, if the disease persists for more than 1 year, the prognosis is considerably worse. In a study by de Mos and colleagues, 102 CRPS patients were assessed at an average of six years (range 2 – 11 years) after disease onset (de Mos et al. 2009). In this group, 15% reported the CRPS as still progressive with no improvement in symptoms and overall, 30 % of patients who worked before CRPS onset remained unable to work.

## 1.6 Diagnostic issues in CRPS

UK CRPS guidelines recommend prompt diagnosis and early treatment to avoid secondary physical problems associated with disuse of the affected limb and the psychological consequences of living with undiagnosed chronic pain (Turner-Stokes & Goebel 2011). However, diagnosing CRPS early is a challenge. It is estimated that CRPS patients have an average delay in diagnosis of 6 months after symptom onset (Shenker et al. 2014).

Currently, the diagnosis of CRPS is a clinical one based upon the presence of dis-proportionate pain associated with vasomotor, sudomotor, trophic and motor changes. However, the signs vary with time and many patients may not fulfil the strict diagnostic criteria. The current diagnostic criteria define established and more severe CRPS but may not capture earlier or lesser presentations (Dutton & Littlejohn 2015). Delayed diagnosis also results from lack of awareness of diagnostic criteria for CRPS among healthcare providers. In particular, failure to notice subtle signs of autonomic dysfunction may be an important contributing factor for the missing CRPS diagnosis (Lunden et al. 2016).

Current imaging modalities of thermography (TG), triple phase bone scan (TPBS) and contrast-magnetic resonance imaging (MRI) have poor sensitivity (TG-29%, TPBS-14% and MRI-13%) and low positive predictive value (TG-17%, TPBS-53%, MRI-31%) and are unable to reliably differentiate normal post-traumatic changes from CRPS (Schürmann et al. 2007).

In summary, the pathophysiology of CRPS suggests central neurological mechanisms dominate for patients with chronic symptoms and these may well be associated with novel clinical signs. The early detection of these signs may predict poor outcome in patients susceptible to CRPS and warrants further assessment.

## **Chapter 2: Novel clinical signs in CRPS**

### **2.1 Introduction**

Clinical signs such as finger misperception, impaired hand laterality recognition, astereognosis and abnormal body scheme have been reported in patients with CRPS (Förderreuther et al. 2004; Moseley 2004). The CRPS patients may also report unusual symptoms such as 'feeling of foreignness' and wish to amputate the affected limb (autotomy wish)(Galer & Jensen 1999; Lewis et al. 2007).

Although these signs and symptoms have been known to be present in CRPS for some years, they have not been included in the current diagnostic or classification criteria(Harden 2010). Hence we have labelled them novel clinical signs and the current understanding of the factors underlying these neurocognitive dysfunctions are discussed in detail below.

### **2.2 Finger misperception**

Finger misperception is defined as an impaired ability to identify fingers correctly with eyes closed when tactile stimuli is applied to the fingers.

This has been previously reported in some patients with CRPS.

For example, in a study by Förderruether and colleagues (Förderreuther et al. 2004), 73 CRPS patients were tested for the ability to name the fingers touched with a cotton swab on the dorsal side of the first segment. They ensured prior to the test that the touch stimuli were clearly and readily felt on both hands. The unaffected hand was examined first. The fingers were fully extended and slightly spread, if possible. Each finger was stimulated twice in random order. All patients were instructed not to move the fingers during the investigation in order to exclude additional sensory input. The results for the affected and the unaffected hand were compared by a Chi-square test. The

ability to identify the fingers of the affected hand compared with those of the contralateral hand was impaired in 37 (48%) patients. In contrast, the ability to identify fingers on the unaffected hand compared with the contralateral hand was impaired in only five (6.5%) patients. This difference was highly significant ( $\chi^2 = 33.5$ ,  $df = 1$ ,  $p = 0.0001$ ). Impaired identification of the fingers was not related to the affected side of CRPS (right hand affected,  $n = 19$ ; left hand affected,  $n = 18$ ). This study authors also reported that all patients stressed that their difficulties naming the fingers could not be explained by reduced perception of the cotton swab.

### **2.3 Impaired hand laterality recognition**

Hand laterality recognition task tests the ability of a subject to judge the handedness of visually presented stimuli (images of hands shown in a variety of postures and orientations) and indicate whether they perceive a right or left hand. The task engages kinaesthetic and sensorimotor processes and is considered a standard example of motor imagery (Coslett et al. 2010; Moseley 2004; Boonstra et al. 2012).

Motor imagery is the mental rehearsal of an action without movement (Jeannerod 1995). Functional neuroimaging studies have demonstrated that same brain structures are involved in action as well imagining the same action (Grèzes & Decety 2001). A motor imagery task such as recognising the laterality of pictured image of a hand as either left or right requires the mental rotation of the image of one's own hand to match that of the picture (Parsons 1987). This neurocognitive ability is reported to be impaired in chronic pain conditions including CRPS. For example, in a study of 18 CRPS patients and age matched controls (Moseley 2004), CRPS patients had delayed hand laterality recognition on the affected side which was related to symptom duration and to the pain that would be evoked by executing the movement.

Reinersmann and colleagues (Reinersmann et al. 2010) reported significantly delayed reaction times in both CRPS and phantom limb pain patients in a

study of 12 CRPS patients, 12 phantom limb pain patients and 38 healthy subjects. They found that the impairment was present in both affected and unaffected sides and that this was independent of attentional performance.

Coslett and colleagues (Coslett et al. 2010) reported a study in which 19 patients with chronic musculoskeletal or radiculopathic arm or shoulder pain, 24 subjects with chronic pain not involving the arm or shoulder and 41 normal controls were asked to indicate if a line drawing was a right or left hand. Relative to normal and pain control subjects, arm or shoulder pain subjects were significantly slower for stimuli that required greater amplitude rotations. This interaction between group and rotation suggests that the differences between controls and arm or shoulder pain subjects are not simply a non-specific effect of pain or its treatment. For the arm or shoulder pain subjects only there was a correlation between degree of slowing and the rating of severity of pain with movement but not the non-specific pain rating. This study did not find any differences in accuracy between groups.

## **2.4 Astereognosis**

Astereognosis is defined as the inability to identify an object by touch only without visual input despite having intact cutaneous sensation; and this usually results from damage to the cortical regions important for haptic input integration (Amick 2011). Classically, this is reported in patients who have had stroke mainly affecting the parietal lobe (Connell et al. 2008; Knecht et al. 1996). Roland in a study of 93 patients showed that damage to anterior part of the middle third of postcentral gyrus caused impairment of astereognosis contralateral to the lesion (Roland 1976).

Astereognosis has also been reported in some patients with CRPS. For example, Cohen and colleagues (Cohen et al. 2013) reported that in a study of 22 CRPS patients, 14 (64%) had astereognosis.



## 2.5 Abnormal body scheme report

Body scheme is the dynamic real time representation of one's own body in space; and it represents centrally the body's spatial properties including limb segment lengths, their hierarchical arrangement, the configuration of the segments in space and the shape of the body surface (Haggard & Wolpert 2005).

Body scheme is generated by the proprioceptive, somatosensory, vestibular and other sensory inputs. This representation is also integrated with motor systems for control of action and normally this integration is automatic and seamless. Sensory deprivation can result in impairment of even routine movements such as reaching towards an object or balancing on a chair as noted in patients with sensory neuropathy underlying the importance of body scheme in guiding movement (Schwoebel et al. 2001). Neuropsychological evidence also suggests that parietal cortex is the neural substrate for the body scheme as it appears to be involved in monitoring the sensory and motor information required for accurate real and imagined movements (Sirigu et al. 1996).

Body scheme is sensitive to central insults that affect motor performance such as motor cortex lesions and basal ganglia dysfunctions (Dominey et al. 1995). It is also affected by peripheral factors such as pain as demonstrated by a study of patients with chronic unilateral arm pain (Schwoebel et al. 2001).

Abnormal body scheme has also been reported in CRPS patients and has been proposed as a contributor to pain in this condition (Lewis et al. 2007; Lewis & McCabe 2010; Lewis & Schweinhardt 2012; Galer et al. 1995; Galer & Jensen 1999).

Galer and colleagues used the term 'neglect-like' to describe some of the body perception disturbances in CRPS as they were thought to be similar to the post-stroke neurological neglect (Galer et al. 1995). For example, some

CRPS patients perceive their own affected limb to be 'foreign' and not belonging to them and this was dubbed 'cognitive neglect'. Similarly, some CRPS patients may need to focus mental and visual attention in order to move their affected limb and this was referred to as 'motor neglect'.

Galen and Jensen (Galer & Jensen 1999) did a questionnaire survey of CRPS patients to determine the frequency of 'neglect-like' symptoms. 242 patients (10%) returned the questionnaire and 224 patients were included in the analysis. 84% (188/224) endorsed at least one of the four neglect-like symptom statement and 47% (105/224) endorsed both motor and cognitive neglect statements. The main limitation of this study was that the subjects were members of a national patient support group who claimed to have CRPS and direct confirmation of their diagnosis by physical examination was not made. The other limitation was the extremely low response rate and inherent selection bias as subjects who had symptoms were more likely to respond. Nevertheless, this study suggests that these symptoms are important in a subset of CRPS patients.

Lewis and colleagues (Lewis et al. 2007) undertook a qualitative study using semi-structured interviews of 27 patients with CRPS and reported that patients revealed bizarre perceptions of affected body parts and that some patients expressed a desire to amputate the affected part despite the prospect of further pain and functional loss. There was a mismatch experienced between the sensation of the limb and how it looked. Anatomical parts of the CRPS limb were erased in mental representations of the affected area. Pain generated a raised consciousness of the limb yet there was a lack of awareness as to its position. These feelings were about the CRPS limb only as the remaining unaffected body was felt to be normal. These findings from this study suggest that there is a complex interaction between pain, disturbances in body perception and central remapping.

In a study of 22 CRPS patients (Lewis & Schweinhardt 2012), body perception disturbance was found to positively correlate with pain (those in greater pain had more extensive body perception disturbance) and two-point

discrimination thresholds (those with greater body perception disturbance had worse tactile acuity). This study also showed that those with longer disease duration had significantly greater body perception disturbance.

The Bath CRPS Body Perception Disturbance Scale has been developed by Lewis & colleagues and this tool provides a comprehensive assessment of the extent of body perception disturbance and helps to monitor changes in body perception over time (Lewis & McCabe 2010). The original English version of this scale has also been translated and validated in German speaking CRPS patients (Tschopp et al. 2018).

## **2.6 Neurocognitive and neuroplastic mechanisms of novel clinical signs**

The constellation of novel clinical signs in CRPS is reminiscent of neurocognitive dysfunctions seen in patients with parietal lobe lesions in Gerstmann syndrome (Gerstmann 1940). Austrian neurologist, Josef Gerstmann reported patients with the tetrad of finger agnosia, agraphia (difficulty in writing), acalculia (difficulty in performing calculations) and left to right confusion. Finger agnosia was considered a disturbance of orientation and consisted of failure of the patient to recognise, show and name the fingers of either hand in the presence of normal vision and tactile sensation. Gerstmann suggested that these symptoms constitute a syndromal entity and are because of a defect in a common functional denominator and localized it to the dominant parietal lobe.

Neuropsychological studies during open brain surgery have confirmed a relation between the Gerstmann tetrad and left parietal cortex and have, demonstrated a certain degree of proximity and overlap of those cortical sites where electrical stimulation can elicit these symptoms (Morris et al. 1984).

Rusconi and colleagues (Rusconi et al. 2009) used *f*-MRI and diffusion tensor imaging in healthy subjects to seek out the common cortical substrate accounting for the tetrad. They construed a functional activation paradigm that mirrored each of the four clinical deficits in Gerstmann syndrome and determined cortical activation patterns. They then applied fibre tracking to diffusion tensor images and used cortical activation foci in the four functional domains as seed regions. None of the subjects showed parietal overlap of cortical activation patterns from the four cognitive domains. However, in every subject, the parietal activation patterns across all four domains consistently connected to a small region of subcortical parietal white matter at a location that is congruent with the lesion in a well-documented case of pure Gerstmann syndrome. This study suggests that pure form of Gerstmann

syndrome might arise from disconnection, via a lesion, to separate but co-localized fibre tracts in the subcortical parietal white matter. Indeed, it has been suggested that these findings arise from cortical changes within the parietal lobe in CRPS patients as well (Cohen et al. 2013).

Plasticity in cortical representations of the affected limb, manifesting as a reversible shrinkage of the somatosensory cortex has been reported in CRPS (Maihöfner et al. 2003; Maihöfner et al. 2004; Pleger et al. 2006; Di Pietro et al. 2013b; Vartiainen et al. 2008; Juottonen et al. 2002). A shrinkage in the Penfield's homunculus (Penfield & Boldrey 1937) provide a plausible explanation for many of the perceptual disturbances seen in CRPS. Cortical reorganization may disrupt the internal body map and impair performance on the tasks requiring the identification of somatosensory information and coding of body posture. However, the evidence supporting this hypothesis has some limitations as discussed below.

Firstly, there is a high risk of bias (due to unclear sampling methods and unblinded analysis of outcomes) in many of the studies as reported in a meta-analysis by Di Pietro and colleagues (Di Pietro et al. 2013b). In order to address this, data from a more recent fMRI study (Di Pietro et al. 2015) was analyzed blind to the group (CRPS patients or healthy controls) and hand (affected or unaffected). Contrary to previous findings, CRPS was associated with an enlarged representation of the healthy hand, not a smaller representation of the affected hand.

A methodological limitation of EEG/MEG, is that the reported spatial changes in somatosensory responses in comparing thumb and little finger (in the region of 5 mm on average) are comparable to or smaller than the estimated spatial resolution and accuracy of the best available source modelling methods with MEG and EEG based on simulated data (Darvas et al. 2005; Yao & Dewald 2005), which must therefore be considered optimistic when applied to clinical data (Kuttikat et al. 2016). With clinical data, the accuracy of the source model may be affected by unknown/unmodelled concurrent neural responses such as those involved with top-down modulation from higher-

order cortical regions. Subject motion during recording/scanning, which is more likely in patients with more severe symptoms, can reduce data quality and introduce artefactual effects that may underestimate the observational parameters. The introduction of “noise” from the above sources risks biasing results, especially in studies with small samples sizes (Kuttikat et al. 2016).

Intact somatosensory awareness depends also on the late cognitive stages of neuronal processing (Aukstulewicz et al. 2012; Adhikari et al. 2014) and neurological disturbances of the body scheme can be caused by the frontal lobe abnormalities (Weijers et al. 2013). Perceptual disturbances in some patients with CRPS may in fact point to disturbed cognitive-executive functioning. Somatosensory perception dependency on the executive functions of fronto-parietal networks as well as the “salience network” including anterior insula and mid-cingulate cortex has been investigated based on “Hierarchical Predictive Coding (HPC)” accounts of perception (Rao & Ballard 1999; Friston 2005; Friston 2008).

Hierarchical predictive coding accounts of perception originate from the work of Hermann von Helmholtz (Helmholtz 1962) who proposed that the brain does not represent sensations per se, but rather models the causes of those sensations. Because these causes cannot be perceived directly, they must be inferred from sensory data.

However, the problem is that sensations can potentially have multiple causes that interact and the brain must deal with this inherent uncertainty in the causes of sensory impressions to generate perceptions and guide actions (Friston 2003). One solution to this problem is for the brain’s model of the environment to contain prior expectations about how causes interact.

HPC models (Clark 2013) depict that top-down expectancy-related information is used to predict and “explain away” the sensory inputs, leaving residual “prediction errors.” These prediction errors then propagate information forward within the system – they report the “surprise” induced by a mismatch between sensory signals and predictions of those signals and serve to update the brain’s virtual model of the causes of those sensations so as to

improve the reliability of predictions. Such errors can occur at multiple levels of a processing hierarchy, such that higher-level systems generate predictions about the inputs to lower-level systems based on modelling the causal structure of the world. This scheme is attractive due to being computationally efficient (i.e., it reflects computations that neurons could feasibly produce) and providing a structure reminiscent of cortical circuits (Kuttikat et al. 2016).

Optimal perception and behaviour depends on minimizing prediction error. This can either be achieved by changing the brain's predictions to explain sensory input by perception and learning or by actively changing sensory input to fulfil the brain's predictions. In the latter case, the agent can selectively sample the sensory inputs that it expects. This is known as active inference (Friston 2003). Selective sampling of sensory data in order to confirm expectations may help to explain why expectations, as formed by prior experiences, have been known to modify sensory perception, including the perception of pain. Pain expectancies can trigger anticipatory neural responses that result in changes in perception, emotion, and behaviour (Ploghaus et al. 1999; Brown et al. 2008; Clark et al. 2008; Kong et al. 2013; Seidel et al. 2015). Such changes are adaptive for avoiding acute injury but are potentially maladaptive in chronic pain conditions.

There is also evidence that key nodes of the frontoparietal and salience networks, the dorsolateral prefrontal cortex and anterior insula cortex show aberrant responses during anticipation of pain that are common across chronic pain populations suffering both nociceptive and non-nociceptive (unexplained) pain (Brown et al. 2014).

Interestingly, greater spectral power in the EEG in the low-frequency delta (<4 Hz) and theta (4–9 Hz) ranges, localized to both somatosensory and ventral PFC, have been found in CRPS patients compared to control subjects (Walton et al. 2010) in a similar region to that showing grey matter atrophy in patients with CRPS (Geha et al. 2008) and that appears to be important for the top-down self-regulation of pain (Woo et al. 2015). This suggests that the somatosensory processing abnormalities in CRPS are mediated by the long-

range and low-frequency entrainment across frontal and somatosensory cortices, representing the influence of high-level predictions on somatosensory perception. This view is also supported by *f*-MRI evidence of greater functional connectivity patterns between the post-central gyrus and prefrontal, cingulate and thalamic regions to cold allodynia in paediatric patients with CRPS (Linnman et al. 2013) compared to healthy controls.

Modelling techniques such as Dynamic Causal Modelling (DCM) can be used to investigate somatosensory forward (bottom-up) and backward (top-down) connections in body misperceptions. DCM allows the study of neuronal architecture underlying observed electromagnetic signals (from EEG and MEG) and the effective connectivity between its sources (David et al. 2006).

DCM has been applied to EEG data to assess evidence for feedforward, feedback, and recurrent processing between S1 and S2 in a somatosensory detection task (Auzztulewicz et al. 2012) – also see Figure 2.1. Recurrent processing within the somatosensory system, dominated by an enhanced S1–S2 connection, underlies somatosensory detection and awareness. This is consistent with dominant neural models of consciousness suggesting that reportable perceptual experiences depend on (1) sufficient early sensory processing, (2) wide distribution of sensory representations within the executive functions, and (3) recurrent interactions between sensory and frontal brain regions (Lamme 2006; Dehaene & Changeux 2011). If so, any reported perceptual abnormality may be caused not only by disturbed sensory processing but also by disturbed executive functions, or abnormal interaction between the sensory and executive regions of the brain. Abnormalities in such recurrent connections may underlie body misperceptions in CRPS (Kuttikat et al. 2016).

Anterior insula cortex plays an important role in the anticipation of pain (Porro et al. 2002; Wager et al. 2004; Brown & Jones 2008; Palermo et al. 2014) and mediating the effect of expectations on pain (Koyama et al. 2005; Atlas et al. 2010). The insula is a centre of salience processing across multiple sensory, emotional, and cognitive domains (Uddin 2014). The anterior insula is thought

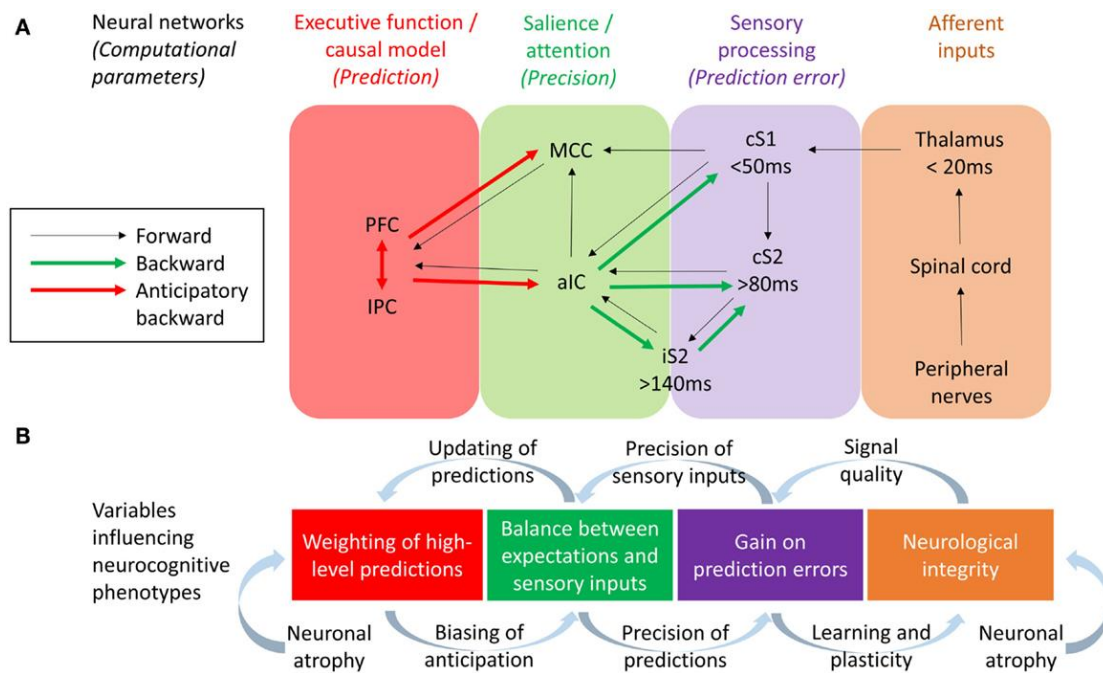


to be crucial for the hierarchical processing of bodily information, integrating afferent thalamic and sensory inputs with top-down control signals arising in the prefrontal and cingulate cortex (Seth et al. 2011; Seth 2013). The right anterior insula is highly interconnected with primary somatosensory areas such as posterior insula and somatosensory cortex (Cerliani et al. 2012; Chang et al. 2013) and anticipates the sensory and affective consequences of pain and touch (Lovero et al. 2009). The anterior insula also projects to the amygdala, forming a network contributing to emotional salience (Seeley et al. 2007). Functional connectivity between the insula and amygdala is thought to be related to levels of pain-related fear and is dampened by effective psychological treatment in paediatric patients with CRPS (Simons et al. 2014).

Observations of the centrality of the insula in salience processing have led researchers to investigate the role of recurrent connections between the insula and somatosensory cortex in somatosensory perception. DCM has revealed that unexpected somatosensory stimuli increase the strength of forward connections along a caudal to rostral hierarchy – projecting from thalamic and somatosensory regions toward insula, cingulate and prefrontal cortices – reflecting the role of forward connection in conveying prediction error (Allen et al. 2016). The anterior insula, however, was the only region to show increased backwards connectivity to the somatosensory cortex, augmenting a reciprocal exchange of neuronal signals. These results suggest that the anterior insula acts as a hub for regulating somatosensory responses in a top-down manner (Figure 2.1).

It has been proposed that the anterior insula and midcingulate cortex form a “salience network” (Seeley et al. 2007). Salience and attention has been linked to the “precision” (reliability/degree of certainty) of sensory inputs (Feldman & Friston 2010). Within the HPC framework, attention serves the function of balancing top-down and bottom-up influences on perception according to their respective precision weights (Figure 2.1). In HPC, precision enhances the influence of ascending prediction errors via the regulation of post-synaptic cortical gain (Moran et al. 2013). By this means, attention (via the salience network) can drive learning and appropriate plasticity. By

extension of this logic, a lack of precision/attention to a particular limb, i.e., cognitive neglect, may result in a relative loss of cortical function akin to disuse, a hypothetical explanation for cortical changes in patients with CRPS in cases in which no other neuropathology can be observed. A useful illustration of how this might work in relation to CRPS neglect-like symptoms is the rubber hand illusion (RHI). The RHI refers to the illusory sense of ownership of a plastic hand, which is induced by synchronous tactile stimulation of the fake and the participant's real (but hidden) hand. In order for the brain to assign the experience of ownership to the artificial hand, certain sensory evidence must be suppressed, namely proprioceptive evidence that the two hands are in different positions (Zeller et al. 2015). In HPC, this corresponds to a reduction in the precision/attention afforded to sensory prediction errors (Feldman & Friston 2010). As evidence in favour of this account, an ERP study (Zeller et al. 2015) identified an attenuation of somatosensory-evoked responses in frontal electrodes that corresponded to cortical sources in the (contralateral) perirolandic area and the parietal lobe. In the absence of an illusion but in the presence of a (perceived) artificial hand, responses were larger in primary somatosensory cortex and inferior parietal lobule. This is consistent with a hypothetical reduction in gain mediated by superficial pyramidal cells in order to resolve the multisensory conflicts arising under the illusion. Should similar multisensory conflicts arise in a patient with CRPS, as implied by the success of mirror therapy in some patients (McCabe et al. 2003), the brain may naturally attempt to resolve these conflicts by attenuating somatosensory prediction errors, with the consequence of driving hemispatial neglect and body misperceptions.



**Figure 2.1 (A) Neural networks and their effective connections underlying somatosensory perception**-Figure adapted from (Kuttikat et al. 2016).

Frontoparietal executive networks are likely to mediate perceptual predictions while the salience network (aIC and MCC) mediate the effect of predictions on the perception of tactile and pain stimuli, with the aIC acting as a “hub” controlling the balance between bottom-up and top-down information.

PFC, prefrontal cortex; IPC, Inferior parietal cortex; MCC, Midcingulate cortex; aIC, Anterior insular cortex; iS2, Ipsilateral secondary somatosensory cortex; cS2, Contralateral secondary somatosensory cortex; cS1, Contralateral primary somatosensory cortex.

**(B) Variables hypothesized to influence the neurocognitive phenotype of CRPS,** based on a hierarchical predictive coding (HPC) account of parameters describing the computational function of each neural network. The integrity of somatosensory neurons could be potentially influenced both by neurological factors (e.g., neuroinflammation leading to neuronal atrophy) and neurocognitive factors (i.e., changes in neural plasticity related to attention and learning). Resulting changes in signal quality from early cortical processing could change the precision weights attributed to sensory inputs and thereby the gain on prediction errors, a process balanced by the relative precision weights on top-down predictions. According to HPC models, this balance affects the extent to which predictions are updated according to sensory inputs (thereby determining the acuity of tactile perceptions) and also affects the content and influence of top-down predictions as mediated by anticipatory neural activity prior to expected tactile or nociceptive stimuli. Finally, evidence for neuronal atrophy in the executive and salience networks in CRPS lends to the hypothesis of long-term changes in neuroplasticity related to the weighting of top-down predictions, possible leading to aberrant perceptual decision-making.

## **Chapter 3: Clinical utility of novel clinical signs in CRPS**

### **3.1 Introduction**

Diagnosis of CRPS remains sub-optimal and this has an adverse effect on the effective management of this chronic debilitating pain condition. Several novel clinical signs have been reported anecdotally in CRPS, although their clinical diagnostic utility is not well defined. We undertook this prospective observational cohort study to provide diagnostic clinical utility (sensitivity, specificity, predictive values and likelihood ratios) of these novel signs in CRPS.

### **3.2 Central hypothesis and objectives**

We investigated the following central hypothesis in our study:

“The prevalence of novel clinical signs will be significantly higher in patients with CRPS compared to patients with other chronic pain conditions”.

The main objectives were to define and validate these novel signs, assess their prevalence in chronic pain conditions, and finally to assess their diagnostic clinical utility (sensitivity, specificity, predictive values and likelihood ratios) in identifying CRPS in a Fracture cohort.

### **3.3 Methods**

**3.3.1 Study design:** This was a clinically based prospective cohort study.

**3.3.2 Study setting:** The study was done in the following clinical areas of Addenbrooke’s Hospital, Cambridge: Clinics 1 (Fracture) and 5 (Rheumatology).

### 3.3.3 Inclusion criteria:

1. Patients with **chronic unilateral upper and/or lower limb CRPS** will have had the condition for at least 6 months and meet the IASP (International Association for the Study of Pain) research criteria for CRPS (Harden et al. 2007) below.

- Continuing pain which is disproportionate to any inciting event.
- Report at least one symptom in each of the four following categories
- Display at least one sign in two or more of the following categories
  - Sensory: hyperaesthesia
  - Vasomotor: temperature asymmetry, and/or skin colour changes and/or skin colour asymmetry
  - Sudomotor: oedema and/or sweating changes and/or sweating asymmetry.
  - Motor/trophic: Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

2. Patients with **rheumatoid arthritis** will meet the American Rheumatology Association's classification criteria (4 from 7 criteria) (Arnett et al. 1988):

- Morning stiffness around joints for at least 1 hour (more than 6 weeks)
- 3 or more swollen joints (doctor-observed, reported to be more than 6 weeks)
- Proximal interphalangeal, metacarpal or wrist joints (more than 6 weeks)
- Symmetrical swelling (more than 6 weeks)
- Rheumatoid nodules
- Rheumatoid factor (blood test)
- Radiographic evidence of erosions and/or periarticular osteopaenia

3. Patients with **fibromyalgia** will meet the American College of Rheumatology 1990 classification criteria (Wolfe et al. 1990) as unexplained pain that is:

- Chronic
- Widespread (bilateral, axial, above and below waist)
- Associated with at least 11 of 18 pre-specified tender points

4. Patients with **chronic low back pain** will meet the European Commission Research Directorate Guidelines (Airaksinen et al. 2006)

- Pain and discomfort localised below the costal margin and above the inferior gluteal folds
- With or without referred leg pain
- Which has persisted for at least 12 weeks

5. Patients with upper or lower limb **fracture** requiring plaster-of-Paris casting

6. **Healthy controls** were recruited from the members of staff of Cambridge University Hospitals NHS Foundation Trust and the students of University of Cambridge, Clinical School of Medicine.

### **3.3.4 Exclusion criteria:**

Patients with a neurological condition that is likely to confound the tests such as peripheral neuropathy, carpal tunnel syndrome, multiple sclerosis, stroke and Parkinson's disease were excluded from the study.

Patients unable to give full informed consent, such as those under 16 years and those unable to make competent decisions were also excluded.

### **3.3.5 Study procedures:**

At the initial visit, the following baseline data were collected in all patients: date of diagnosis, age, sex, past medical history, medication, body part affected (if CRPS or fracture), hand dominance and history of dyslexia. For

fracture patients, additional data regarding date of fracture and date of casting were collected. All patients completed the following five questionnaires assessing pain severity, physical function, body perception disturbance and emotional state. (Appendix 5).

1. **Brief Pain Inventory – BPI** (Cleeland & Ryan 1994)

This is a widely used well-validated questionnaire (Cleeland & Ryan 1994; Tan et al. 2004) for all chronic pain conditions with numerical value scores from 0 (no pain) to 10 (pain as bad as you can imagine) in several domains (maximal pain, minimal pain, average pain) commenting from the last 24 hours and also current pain. Using similar scales of 0 (does not interfere) to 10 (interferes completely), patients are also asked to rate the extent to which their pain interferes with 7 quality-of-life domains that include general activity, walking, mood, sleep, work, relations with other persons, and enjoyment of life. Interference domains provide depth to the pain scores.

The BPI has been used in more than 400 published studies in a variety of pain conditions including musculoskeletal and neuromuscular conditions. Tan and colleagues (Tan et al. 2004) validated the psychometric properties of BPI in chronic non-malignant pain population and found that the BPI scales show acceptable internal consistency for both intensity and interference items. They also found that BPI scales showed statistically significant improvement with treatment confirming the responsiveness of BPI in detecting and reflecting improvement in pain over time.

2. **Upper Extremity Functional Index - UEFI** (Stratford et al. 2001)

This is a validated questionnaire (Stratford et al. 2001; Chesworth et al. 2014) for functional assessment of the upper limb. 20 domains are scored and each item uses a 5-point adjectival response scale to rate difficulty in performing Upper Extremity activities: 0 = extreme difficulty or unable to perform activity, 1 = quite a bit of difficulty, 2 = moderate difficulty, 3 = a little bit of difficulty and 4 = no difficulty. Summing the items yields a total score from 0 (worst) to 80

(best) points. This score has an error +/- 5, with both Minimally Detectable Change and Minimal Clinically Important Difference scores of 9 (90% confidence).

### 3. **Lower Extremity Functional Index - LEFI** (Binkley et al. 1999)

This is a validated questionnaire (Binkley et al. 1999) for functional assessment of the lower limb. 20 domains are scored from 0 (extreme difficulty or unable) to 4 (no difficulty) giving a total possible score 80. This score has an error +/- 5, with both Minimally Detectable Change and Minimal Clinically Important Difference scores of 9 (90% confidence). The LEFI is efficient to administer and score and is applicable for research purposes and clinical decision making for individual patients.

### 4. **Neglect-like Symptom Questionnaire - NLSQ** (Galer & Jensen 1999)

This questionnaire reports on 5 domains scored 1-6 describing 'body perception disturbance' in patients with chronic pain (Galer & Jensen 1999; Frettlöh et al. 2006). It has been validated in a chronic pain cohort. Frettlöh and colleagues (Frettlöh et al. 2006) in a study of CRPS patients (n=123) and chronic limb pain of other causes (n=117) found that the number of patients confirming such symptoms was significantly higher in the CRPS group, and moreover, these patients reported more severe symptoms.

Body perception disturbance is more commonly used in the CRPS field in preference to 'depersonalisation'(Lewis & McCabe 2010; Lewis et al. 2007) and this is discussed in detail in chapter 2 of this thesis. Depersonalisation is defined as an alteration in the perception or experience of the self so that one feels detached from and as if one is an outside observer of one's mental processes or body (Medford et al. 2005) and is described in neuropsychiatric conditions (e.g. major depressive disorder, schizophrenia, temporal lobe epilepsy).



5. **Hospital Anxiety and Depression Scale - HADS** (Zigmond & Snaith 1983; Snaith 2003)

This widely used and well-validated questionnaire (Bjelland et al. 2002; Snaith 2003) assesses anxiety and depression using 7 domains on each aspect. Each domain is scored 0-3 giving a total score of 21. Cut-off scores are available for quantification, for example, a score of 8 or more for anxiety has a specificity of 0.78 and sensitivity of 0.9, and for depression a specificity of 0.79 and a sensitivity of 0.83.

A score of 0 to 7 for either subscale is regarded as being in the normal range, a score of 11 or higher indicating probable presence ('caseness') of the mood disorder and a score of 8 to 10 being just suggestive of the presence of the respective state. Mild (8-10), moderate (11-14) and severe (15-21) cut-offs are defined for each aspect of anxiety and depression (Stern 2014). HADS has been shown to perform well in assessing the symptom severity and caseness of anxiety disorders and depression in both somatic, psychiatric and primary care patients and in the general population (Bjelland et al. 2002).

The following clinical tests were performed

1. Finger perception
2. Hand laterality task
3. Astereognosis
4. Body scheme report

### **3.3.6 Finger perception**

Finger perception was assessed bilaterally to allow intra-individual comparison between affected and unaffected sides. Ten touches were applied in a predefined order to the fingers of each hand. This allowed clear standardisation between observers. No contiguous finger was consecutively touched. Time was measured (using a stop watch) as the total time from when the first finger was touched to when the last answer was given after the 10<sup>th</sup> touch. Regardless of the answer being correct or wrong for each touch, the next touch is applied as soon as the patient gives an answer. This continues till the 10 touches in total are applied per hand. If no answer was given, the test was finished after 60 seconds with the number of correct and incorrect answers recorded to give a percentage. Two outcome measures were generated: accuracy (%) and time (seconds). The test was administered in a stereotyped fashion and all the participants were given the following instruction:

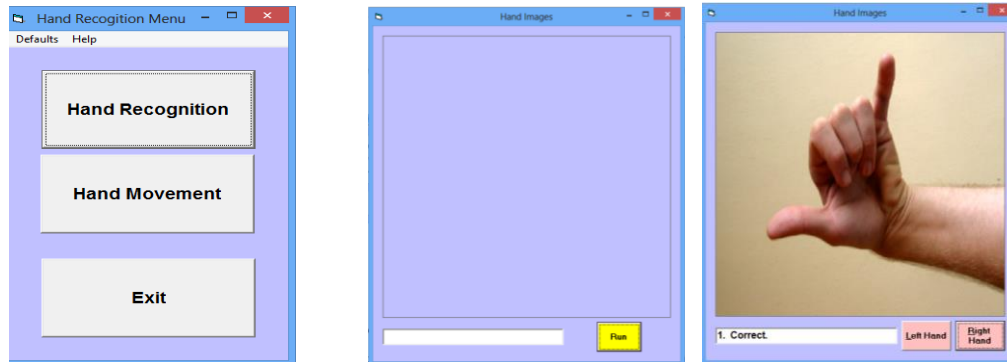
*“I’d like to test the sensation in your fingers with your eyes shut. I’d like to call your thumb number 1, index finger number 2 and so on to the little finger and similarly on your other hand. Please place your hands on your lap. Do not move your fingers when I touch them, but simply tell me the number corresponding to the finger that I touch. I will first touch your [left / right] hand and then move on to the other. Do you have any questions to me? Thank you. Please close your eyes and we will start.”*

The administration of this test takes 2 minutes maximum and does not require any resources other than a stop watch.

### **3.3.7 Hand laterality task**

A computer program was created in-house in the department of Medical Physics, University of Cambridge which presented 56 pre-loaded images in a random order. The patients and healthy controls were required to identify the presented image as a left or right hand by clicking the mouse and this would generate the next image. The process continues till all 56 images have been

presented. The program calculates the accuracy out of a total possible score of 56. The 'time' taken was measured (using a stop watch) as the total time in seconds from the first image shown to the last response clicked.



**Fig 3.1-3.3** (Hand laterality programme menu, hand recognition & an image of a hand)

Stereotyped instruction was given as follows: *“I would like to understand how quickly and reliably you can identify left and right hands presented to you using the computer programme. Please do not move your hand into the position shown but try to use mental imagery to decide whether the picture is of a left or right hand. Please select left or right using the mouse. We will time you and score how many you get right. Do you have any questions to me? Thank you.”*

The time taken to complete this task depends upon the patient but usually is around 3-5 minutes. The administration of this task requires a computer device with the program installed and a stop watch.

### **3.3.8 Astereognosis**

Patients were asked to feel an object with their eyes closed and identify it by touch using only one hand. Three common objects were used for each hand. A penny, paperclip and key were used for right hand. A ten pence coin, bull dog clip and micropore tape were used for left hand. Two outcomes were measured for each hand: accuracy (%) and time (s).

Stereotyped instruction was given as follows: *“I would like to test whether you are able to identify different objects by touch only. I would like you to close your eyes and hold out your hand. I will put an object into the palm of your hand and I would like you to tell me what it is. You may move it around in your hand, but please don’t transfer it to the other hand. I will first test your left/right hand and then test the other side. Do you have any questions? Thank you.”*

The time taken to complete this task depends upon the patient but usually is around 1-2 minutes. The administration of this task requires the common objects used in the test and a stopwatch.

### **3.3.9 Body scheme report**

Patients and healthy controls compared the sensations from left and right sides of their body while deprived of visual (eyes closed) and motor feedback (instructed not to move).

21 areas were included: forehead; cheeks; chin; shoulders; upper arms; elbows; forearms; wrists; each digit; lower back; hips; thighs; knees; shins; ankles; big toes; other toes. If an asymmetry was perceived, subjects quantified the differences in size, length and heaviness, expressed as a percentage compared to the normal side.

Stereotyped instruction was given as follows: *“I would like to understand how you perceive your body with your eyes closed. I am going to ask you to close your eyes, keep your arms and legs still and describe how different parts of your body feel. I would like you to compare both sides in terms of size, weight and length as well as any other feelings you may be getting from those areas. I do not want you to move anything. We will start from your face and move down to your arms and legs. Do you have any questions to me? Thank you. Please close your eyes and we will start.”*

An example is described below to explain in detail how the scoring was done for the body scheme report. Subject A is given the stereotyped instruction as above and is instructed to compare the left side to the right side starting at the forehead. They are then asked specifically 1) are the two sides same size? 2) same length? and 3) same weight? If the answer is 'same on both sides' then they are asked to compare the next body area just below and the process repeated for all 21 body areas. If for example; they say their right wrist feels bigger or smaller than the left, they are asked to quantify the difference – 'how much bigger/smaller than the left wrist in percentage'. If they say it feels 10 % bigger on the right wrist compared to left wrist, then this is documented in the excel spreadsheet as +10% for the right wrist and if they say it is 20% smaller, it is documented as -20% and so on. Please see appendix 5.6 for a sample data collection chart. The administration of the 'body scheme report' test takes around 10 minutes.

All the investigators involved in data collection were given face to face training and were checked to make sure that they were administering the above tests in the correct and standardised fashion.

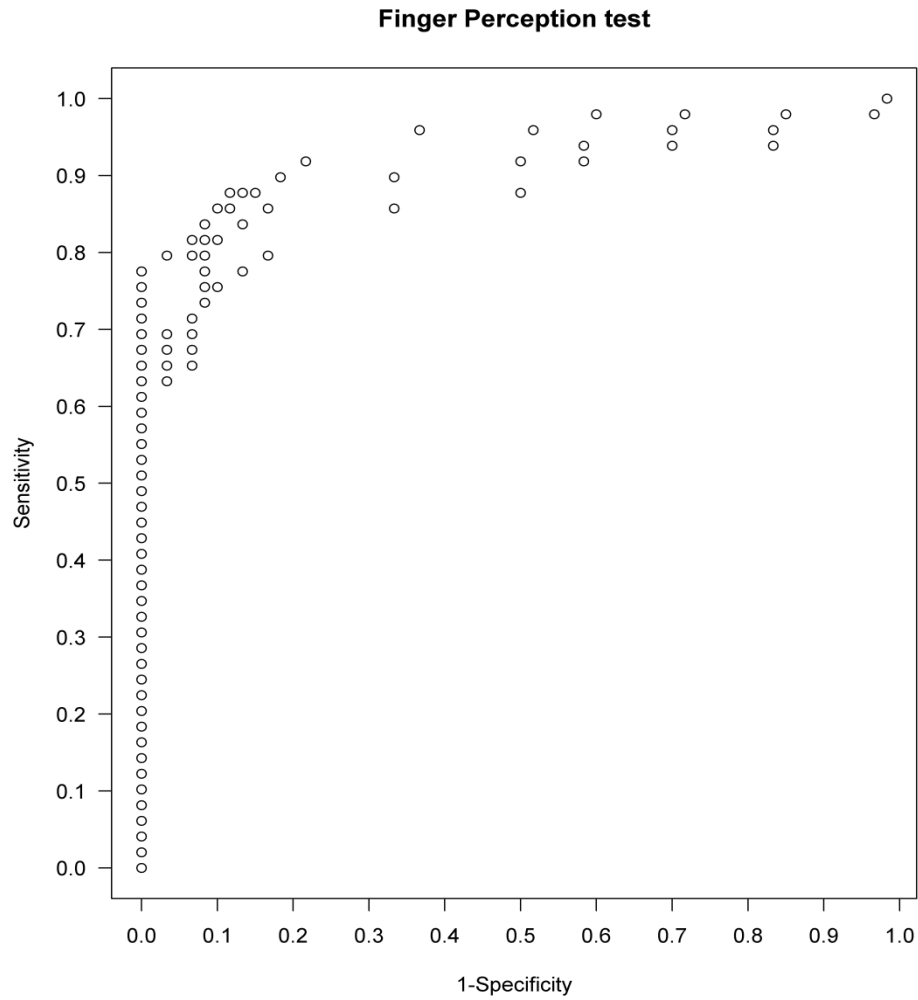
'Body Scheme Report' is a novel test. We developed the test by piloting on healthy individuals and CRPS patients. We chose several dimensions of the test (size, length & weight) to be assessed. These were developed from clinical experience that when patients were describing, these were the areas of their body that did not feel the same, the descriptors that they used were those of size / length / weight. Size does include length but is a common characteristic described by patients in terms of the body part described as being 'bigger' or 'smaller'. We decided to use percentages as a way of quantifying the changes after discussions within the research group. Previous public displays of distorted body scheme in patients with chronic pain (Wellcome portrait displays for example) support this approach to dividing subjective descriptions into these broad areas. We validated this in the healthy individuals and CRPS patients for intra-and inter-observer assessments over time.

### 3.3.10 Defining a positive test

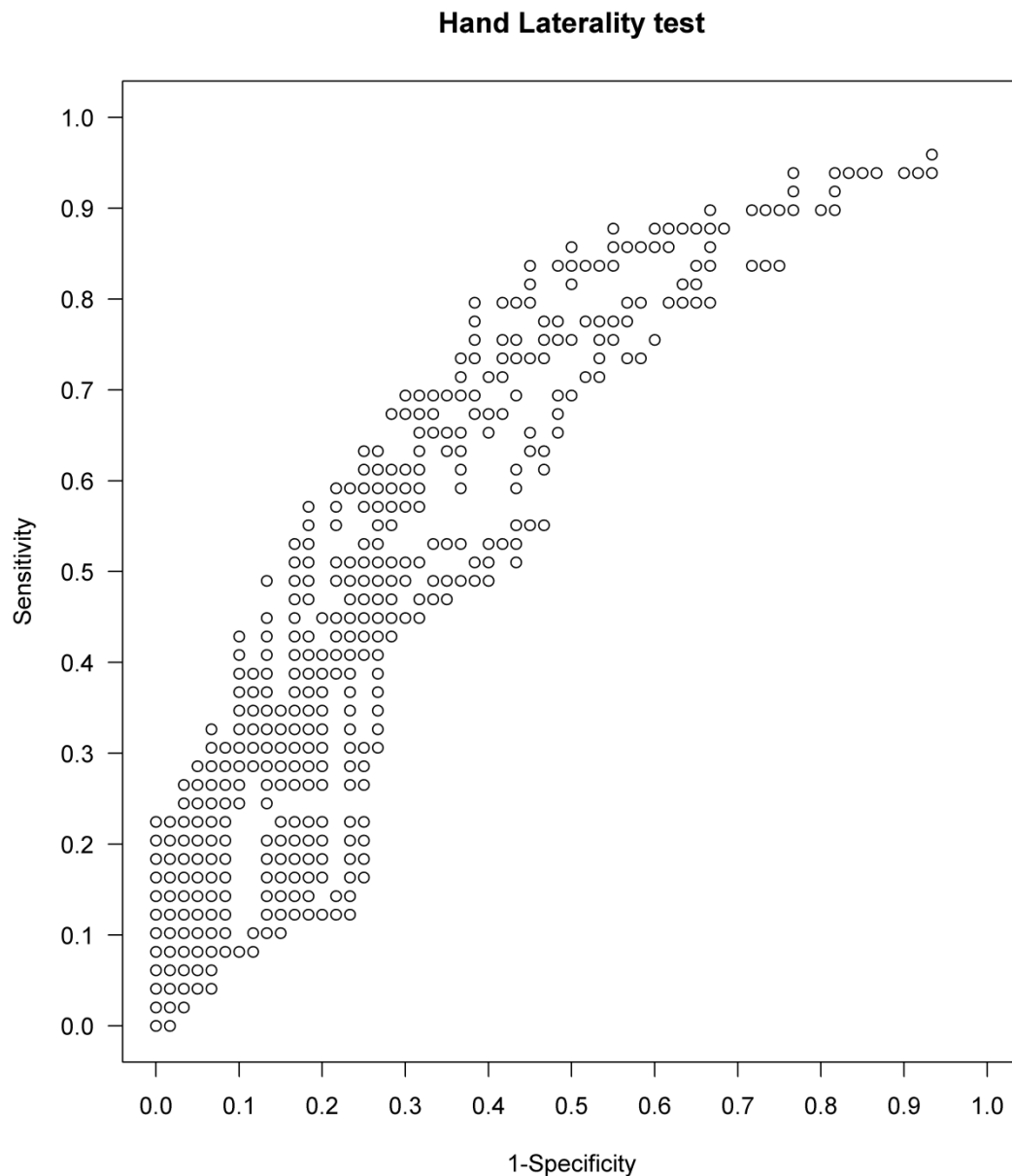
Data in 60 healthy controls and 49 CRPS patients was taken to determine the optimum 'cut off' for all tests. The sensitivity was plotted against the 1-specificity using every possible cut-off point of accuracy and time for Finger Perception (FP) and Hand Laterality (HL) and Receiver Operating Characteristic (ROC) curve analysis was performed (Figures 3.4 & 3.5).

The optimum sensitivity and specificity for FP was determined to correspond to an accuracy of <10/10 OR a time of >20 seconds. For HL the cut off was determined to be an accuracy of <50/56 AND a time of >100 seconds. Astereognosis (AS) was considered positive if the accuracy was <3/3 OR the time was >30 seconds. Body Scheme (BS) was summarized as a composite score, where an abnormal perception of two contiguous areas  $\geq 5\%$  (e.g. shoulder and upper arm or ankle and lower leg) was regarded as a positive test result. For the 'Body Scheme Report', the expert statistical advice was that it was not appropriate to do a ROC analysis because the data was multi-dimensional and not on a continuous scale (i.e. often categorical). Therefore it made sense to reduce the dimensionality of the data by deriving a composite score. The changes refer to any of the three measurements of size, length and weight. We reflected following discussions within the research group and data analysis from preliminary data. We developed the cut off of 2 contiguous areas based on the data and putative underlying mechanism of this altered perception (i.e. cortical reorganisation) to maximise sensitivity/specificity. We decided on  $\geq 5\%$  change so that we were only considering non-negligible differences.

**Figure 3.4:** Receiver Operating Characteristic (ROC) plot with data points representing the sensitivity and 1-specificity corresponding to every possible cut-off point combination of thresholds of time and accuracy for the finger perception test. This was constructed based on using the affected arm of CRPS patients and the non-dominant hand of healthy controls. The optimum cut-off point combination is when Accuracy <10 or Time > 20 seconds indicates a positive test, corresponding to a



**Figure 3.5:** Receiver Operating Characteristic (ROC) plot with data points representing the sensitivity and 1-specificity corresponding to every possible cut-off point combination of thresholds of time and accuracy when using the Hand laterality test to diagnose CRPS. The optimum cut-off point combination is when Accuracy < 50 and time > 100 seconds indicates a positive test for CRPS, corresponding to a sensitivity of 69% and specificity of 70%.





### **3.3.11 Inter-rater variability testing**

We established that there was no significant inter-rater variability in testing as follows. Five subjects were tested for novel clinical signs by four investigators separately during one session. Each investigator attended two 30-minute training sessions and was assessed that they were performing the clinical tests to the same standard. The results showed that there was a high inter-rater agreement (Fleiss' Kappa=0.84, SE=0.11, 95% CI= 0.6-1.0).

### **3.3.12 Intra-rater variability testing**

We established that there was no significant intra-rater variability as follows: Nine subjects were tested on the novel signs on two separate occasions by the same investigator less than 4 weeks apart. There was a good strength of agreement between the results from 2 sessions (Cohen's Kappa=0.65, SE=0.34, 95% CI= 0.02-1.0).

### **3.3.13 Study outcomes**

The primary outcome measures were the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio for the novel signs in the CRPS group compared to the Fracture group. The secondary outcome measures of the study were the prevalence of novel signs in different groups.

### **3.3.14 Statistical analyses**

Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were calculated using MedCalc for Windows, version 12.7 (MedCalc Software, Ostend, Belgium). ROC curve analysis, ANOVA and Kappa testing were done using IBM SPSS Statistics for Windows, Version 20.0.

The statistical tests used in this study are described in detail below (Bland 2000; Lalkhen & McCluskey 2008; Altman 1991).

The sensitivity of a clinical test refers to the ability of the test to correctly identify those patients with the disease. It is derived by the formula: true positives divided by the sum of true positives and false negatives.

The specificity of a clinical test refers to the ability of the test to correctly identify those patients without the disease. It is derived by the formula: true negatives divided by the sum of true negatives and false positives.

The Positive Predictive Value of a test is a proportion that answers the question: 'How likely is it that this patient has the disease given that the test result is positive?' It is derived by the formula: true positives divided by the sum of true positives and false positives.

The Negative Predictive Value of a test answers the question: 'How likely is it that this patient does not have the disease given that the test result is negative?' It is derived by the formula: true negatives divided by the sum of true negatives and false negatives.

Positive likelihood ratio is the probability of a person who has the disease testing positive divided by the probability of a person who does not have the disease testing positive. It is derived by the formula: Sensitivity divided by (1-Specificity).

Negative likelihood ratio is the probability of a person who has the disease testing negative divided by the probability of a person who does not have the disease testing negative. It is derived by the formula: (1-sensitivity) divided by specificity.

In a Receiver Operating Characteristic (ROC) curve, the true positive rate (Sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points. Each point on the ROC curve represents a

sensitivity/specificity pair corresponding to a particular decision threshold. The area under this curve (AUC) represents the overall accuracy of a test, with a value approaching 1.0 indicating a high sensitivity and specificity. A test with perfect discrimination (no overlap in the two distributions) has a ROC curve that passes through the upper left corner (100% sensitivity, 100% specificity). Therefore the closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test (Zweig & Campbell 1993).

ANOVA (Analysis of Variance) is a statistical technique for testing whether different groups have different means on some metric variable. One-way (one independent variable) or two-way (2 independent variables) refers to the number of independent variables in the ANOVA test. Repeated measures analysis of variances (ANOVA) is used when the same parameter has been measured under different conditions on the same subjects. If the ANOVA test is positive (P less than the selected significance level) then a post hoc test (Tukey's) is used for pairwise comparison of subgroups (Altman 1991).

Cohen's kappa is a measure of the agreement between two raters who determine which category a finite number of subjects belong to whereby agreement due to chance is factored out. Cohen's kappa takes into account disagreement between the two raters, but not the degree of disagreement. A weighted version of Cohen's kappa can be used to take the degree of disagreement into account (Cohen 1968). Another modified version of Cohen's kappa, called Fleiss' kappa, is used where there are more than two raters (Fleiss et al. 2003).

## 3.4 Results

### 3.4.1 Study population

A total of 313 subjects (60 healthy controls and 253 patients) were recruited into the study from a single centre (Addenbrooke's Hospital) between August 2009 and August 2013. The patients were recruited from the five different groups of CRPS (n=49), FMS (n=50), RA (n=60), LBP (n=47) and fracture (n=47). In the CRPS group, 31 (63%) had an upper limb affected and 18 (37%) had a lower limb affected. In the fracture group, 39 (83%) had upper limb fracture and eight (17%) had lower limb fracture.

The baseline characteristics of the subjects are documented in Table 3a.

Single factor ANOVA revealed a significant difference between the mean ages of different groups,  $F(5, 307) = 15.88, p = <0.001$ . A Tukey post-hoc test revealed that there were no statistically significant differences between the ages of CRPS ( $43.6 \pm 13.2$  years) and healthy controls ( $36.1 \pm 13.9$  years,  $p=0.078$ ), however the ages of healthy controls were lower than RA ( $56.0 \pm 14.4$  years,  $p = <0.001$ ), FMS ( $46.7 \pm 13.5$  years,  $p = 0.002$ ), LBP ( $54.0 \pm 13.8$  years,  $p = <0.001$ ) and Fracture ( $53.5 \pm 17.2$  years,  $p = <0.001$ ) subjects. The proportion of females in the study ranged from 55.3% in the fracture group to 92% in the FMS group, reflecting the expected female preponderance. Majority of subjects in each group (ranging from 78.7% in the LBP group to 89.3% in the fracture group) were right handed. A small minority of subjects in each group had self-reported diagnosis of dyslexia (ranging from 6.1% in CRPS to 14.8% in LBP). All patient groups had multiple co-morbidities and were on various medications.

**Table 3a:** Baseline characteristics of subjects

<b>Characteristics</b>	<b>HC</b> (n=60)	<b>CRPS</b> (n=49)	<b>FMS</b> (n=50)	<b>RA</b> (n=60)	<b>LBP</b> (n=47)	<b>Fracture</b> (n=47, 39 upper limb, 8 lower)
<b>Age in years</b> <b>Mean (range)</b>	36.1 (20-64)	43.6 (18-64)	46.7 (22-80)	55.4 (22-78)	54.0 (20-85)	53.6 (19-88)
<b>Female sex (%)</b>	47 (78.3)	39 (79.6)	46 (92)	47 (78.3)	33 (70.2)	26 (55.3)
<b>Right handed (%)</b>	52 (86.6)	42 (85.7)	41 (82)	50 (83.3)	37 (78.7)	42 (89.3)
<b>Dyslexia (%)</b>	0	3 (6.1)	4 (8.0)	5 (8.3)	7 (14.8)	3 (6.4)
<b>Disease duration in years Mean (range)</b>	N/A	3.5 (0.5-10)	4.0 (0.5-22)	11.6 (1-50)	10 (1-40)	*
<b>Past medical history</b>						
<b>Depression/Anxiety</b>	<b>none</b>	<b>2 (4.0)</b>	<b>4 (8.0)</b>	<b>2 (3.3)</b>	<b>3 (6.4)</b>	<b>0</b>
Other psychiatric		0	2 (4.0)	1(1.7)	0	0
<b>IBS</b>		<b>2 (4.0)</b>	<b>1 (2.0)</b>	<b>0</b>	<b>2 (4.2)</b>	<b>0</b>
Asthma/COPD		8 (16.3)	10 (20.0)	7 (11.7)	2 (4.2)	2 (4.2)
<b>Migraines</b>		<b>1 (2.0)</b>	<b>2 (4.0)</b>	<b>0</b>	<b>0</b>	<b>0</b>
Other medical		24 (48.9)	23 (46.0)	25 (41.7)	21 (44.7)	15 (31.9)
<b>Medications at the time of study (%)</b>						
<b>Paracetamol</b>	<b>none</b>	<b>16 (32.6)</b>	<b>12 (24.0)</b>	<b>14 (23.3)</b>	<b>18 (38.3)</b>	<b>8 (17.0)</b>
NSAIDs		6 (12.2)	5 (10.0)	12 (20.0)	8(17.0)	1 (2.1)
<b>Weak opioids</b>		<b>22 (45)</b>	<b>11(22.0)</b>	<b>7(11.6)</b>	<b>11(23.4)</b>	<b>4(8.5)</b>
Strong opioids		10(20.4)	5 (10.0)	2(3.3)	2(4.2)	1(2.1)
<b>Anti-depressants</b>		<b>22 (45)</b>	<b>13 (26.0)</b>	<b>3(5.0)</b>	<b>7(14.9)</b>	<b>0</b>
Anti-convulsants		28(57.1)	14(28.0)	0	7(14.9)	0
<b>Other medications</b>		<b>8(16.3)</b>	<b>10(20.0)</b>	<b>59(98.3)</b>	<b>11(23.4)</b>	<b>8(17.0)</b>

\*All fracture subjects had acute fractures of less than 2 weeks duration and were in plaster casts at the time of testing

### 3.4.2 Clinical Outcomes

Table 3b demonstrates the prevalence of each of the signs across all of the groups. Abnormal BS had a very high prevalence in the CRPS group (93.9%) that was significant when compared to all of the other groups (23-50%). Abnormal FP was also significantly higher in the CRPS group (85.6%) when compared to the other groups (23-62%). Abnormal HL was very prevalent in all chronic pain groups – CRPS (69.4%), FMS (72%), RA (76.7%) and LBP (63.8%). AS had the lowest prevalence within each group (12-36%) and there were no significant differences between the groups.

Individually, the tests did not appear to reliably distinguish patients with CRPS from other chronic pain conditions, although most patients with CRPS had abnormal finger perception and body scheme reports. However, when we combined the two best performing tests in CRPS (finger perception and body scheme report) as a composite test and this still has a prevalence of 75.5% in the CRPS group while significantly decreasing the prevalence in all other groups compared to all four signs individually. There was no statistically significant difference in the number of positive signs between the upper and lower limb affected groups in either the CRPS group ( $p=0.15$ ) or the fracture group ( $p=0.38$ ).

**Table 3b:** Prevalence of novel clinical signs in all groups

Category	Finger Perception +	Hand Laterality +	Astereognosis +	Body scheme +	FP+ AND BS+
<b>HC</b> (n=60)	14 (23.3%) p <0.0001	18 (30.0%) p <0.0001	7 (11.6%) p <0.03	14 (23.3%) p <0.0001	6 (10.0%) p <0.0001
<b>CRPS</b> (n=49 )	42 (85.6%)	34 (69.4%)	14 (28.6%)	46 (93.9%)	37 (75.5%)
<b>FMS</b> (n=50)	28 (56.0%) p<0.0018	36 (72.0%) p <0.8275	18 (36.0%) p <0.52	25 (50.0%) p <0.0001	11 (22.0%) p <0.0001
<b>RA</b> (n=60)	33 (55.0%) p <0.0080	46 (76.7%) p <0.5138	14 (23.3%) p <0.66	17 (28.3%) p <0.0001	6 (10.0%) p <0.0001
<b>LBP</b> (n=47)	24 (51.1%) p <0.0004	30 (63.8%) p <0.6661	13 (27.6%) p <1.0	20 (42.6%) p <0.0001	11 (23.4%) p <0.0001
<b>Fracture</b> (n=47, 39 UL, 8 LL)	29 (61.7%) p <0.01	26 (55.3%) p <0.2062	14 (29.8%) p <1.0	13 (27.7%) p <0.0001	7 (14.9%) p <0.0001
<b>Fracture</b> (6 months) (n=20, 15 UL, 5 LL)	13 (65.0%) p <0.09	12 (60.0%) p <0.5748	2 (10.0%) p <0.12	4 (20.0%) p <0.0001	1 (5.0%) p <0.0001

2-tailed p-values were calculated by Fisher's exact test and represents the significance of difference when compared to CRPS group

The prevalence of the four novel signs is shown in Table 3c.

35% of the healthy control did not have a single positive sign compared to at least one positive test in all 49 patients with chronic CRPS. Furthermore 9/16 patients with four positive tests had a diagnosis of CRPS. 67.3% of the CRPS group had 3 or more signs, compared with 3.3% of the healthy control group and 13.3%; 21.3%; 27.7%; 32% in the RA; LBP; Fracture and FMS groups respectively. Of interest is that there was no significant difference in the prevalence of positive clinical signs in the CRPS group when comparing upper and lower limb involvement in either the CRPS group ( $p=0.15$ ) or the fracture group ( $p=0.38$ ).

**Table 3c:** Prevalence of novel clinical signs

Category	0 sign	1 sign	2 signs	3 signs	4 signs	≥1 sign	≥2 signs	≥3 signs
HC (n=60)	21 (35%)	26 (43.3%)	11 (18.3%)	1 (1.6%)	1 (1.6%)	39 (65%)	14 (23.3%)	2 (3.3%)
CRPS (n=49)	0	3 (6.1%)	13 (26.5%)	24 (48.9%)	9 (18.4%)	49 (100%)	46 (93.8%)	33 (67.3%)
FMS (n=50)	0 (0%)	12 (24%)	22 (44%)	13 (26%)	3 (6%)	50 (100%)	38 (76%)	16 (32%)
RA (n=60)	3 (5%)	20 (33.3%)	29 (48.3%)	7 (11.7%)	1 (1.7%)	57 (95%)	37 (61.7%)	8 (13.3%)
LBP (n=47)	6 (12.7%)	14 (29.7%)	17 (36.2%)	9 (19.1%)	1 (2.1%)	41 (87.2%)	27 (57.4%)	10 (21.3%)
Fracture (n=47, 39 UL, 8 LL)	6 (12.8%)	15 (31.9%)	13 (27.6%)	12 (25.5%)	1 (2.1%)	41 (87.2%)	26 (55.3%)	13 (27.7%)
Fracture 6 months (n=20, 15 UL, 5 LL)	2 (10%)	6 (30%)	10 (50%)	2 (10%)	0	18 (90%)	12 (60%)	2 (10%)



The clinical utility (sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio) of four clinical signs were calculated compared to the fracture group as this is the most relevant group in terms of being a risk factor for development of CRPS (Table 3d).

BS had the highest sensitivity (93.9%) and specificity (72.3%). The absence of BS was clinically useful in being able to rule out CRPS (91.9% negative predictive value with a negative LR of 0.1). Combining the two best performing tests of FP & BS improves the specificity (85.1%) with a high positive predictive value (84.1%).

**Table 3d:** Clinical utility of novel clinical signs (compared to fracture group)

	<b>Sn</b>	<b>Sp</b>	<b>PPV</b>	<b>NPV</b>	<b>PLR</b>	<b>NLR</b>
<b>Finger Perception+</b>	85.7% (72.7-94.0)	38.3% (24.5-53.6)	59.1% (46.8-70.6)	72.0% (50.6-87.9)	1.4 (1.1-1.8)	0.4 (0.2-0.8)
<b>Hand Laterality +</b>	69.3% (54.5-81.7)	44.6% (30.1-59.8)	56.6% (43.2-69.4)	58.3% (40.7-74.4)	1.2 (0.9-1.7)	0.7 (0.4-1.2)
<b>Astereognosis +</b>	28.5% (16.6-43.2)	70.2% (55.1-82.6)	50.0% (30.7-69.3)	48.5% (36.2-61.0)	1.0 (0.5-1.8)	1.0 (0.8-1.3)
<b>Body Scheme +</b>	93.9% (83.1-98.6)	72.3% (57.4-84.4)	78.0% (65.3-87.7)	91.9% (78.1-98.2)	3.4 (2.1-5.4)	0.1 (0.0-0.3)
<b>FP+ AND BS+</b>	75.5% (61.1-86.6)	85.1% (71.7-93.8)	84.1% (69.9-93.3)	76.9% (63.2-87.4)	5.1 (2.5-10.2)	0.3 (0.2-0.5)
<b>≥1 sign +</b>	100% (92.7-100)	12.7% (4.8-25.7)	54.4% (43.6-64.9)	100% (54.1-100)	1.2 (1.0-1.3)	0
<b>All 4 signs +</b>	18.3% (8.7-32.0)	97.8% (88.7-99.9)	90.0% (55.5-99.7)	53.5% (42.4-64.3)	8.6 (1.1- 65.5)	0.8 (0.7-1.0)

(Sn=Sensitivity, Sp=Specificity, PPV=Positive Predictive Value, NPV=Negative Predictive Value, PLR=Positive Likelihood Ratio, NLR=Negative Likelihood Ratio)

\*95% confidence intervals in brackets

### 3.4.3 Questionnaires results

The data on pain severity, physical function, emotional state and depersonalisation were collected using five questionnaires – (Brief Pain Inventory (Cleeland & Ryan 1994), Upper Extremity Functional Index (Stratford et al. 2001), Lower Extremity Functional Index (Binkley et al. 1999), Hospital Anxiety Depression score (Snaith 2003) and Neglect-like Symptom Questionnaire (Galer & Jensen 1999). (Table 3e)

The subjects in the CRPS group had the highest pain, anxiety and depression scores and the lowest functional scores although these differences were not statistically significant. ANOVA revealed a significant difference between the mean NLSQ scores of different groups,  $F(4, 248) = 24.2, p = <0.001$ . A Tukey post-hoc test revealed that the average NLSQ scores were significantly higher in the CRPS group ( $4.21 \pm 0.95, p = <0.001$ ) compared to all other groups suggesting a significant degree of depersonalisation in CRPS. The scores on the questionnaire data did not correlate significantly (Spearman's rho) with any of the novel clinical signs in any group.

**Table 3e:** Summary of questionnaires data

Category	CRPS (n=49 )	FMS (n=50)	RA (n=60)	LBP (n=47)	Fracture (n=47)
<b>Maximum Pain</b>	8 (1.68)	7.34 (1.25)	4.81 (2.6)	6.53 (2.02)	3.31 (2.61)
<b>Least Pain</b>	5.74 (2.29)	4.5 (2.62)	2.41 (1.91)	3.63 (2.42)	1.44 (2.03)
<b>Average Pain</b>	6.59 (1.86)	5.8 (1.78)	3.85 (1.92)	5.29 (1.66)	2.41 (2.18)
<b>Current Pain</b>	7.38 (1.45)	7.2 (1.30)	4.53 (2.30)	6.42 (1.93)	2.31 (1.98)
<b>Pain Interference (Average )</b>	7.06 (2.14)	6.43 (1.88)	3.97 (2.47)	5.23 (2.42)	2.54 (2.24)
<b>UEFI</b>	34.85 (25.58)	35.6 (16.48)	50.46 (19.82)	48.17 (21.28)	36.72 (22.51)
<b>LEFI</b>	29.20 (21.39)	34.36 (18.34)	43.78 (22.52)	33.25 (21.64)	63.65 (25.37)
<b>HAD-Anxiety</b>	11.10 (4.31)	11 (4.64)	6.7 (4.02)	7.68 (4.71)	3.89 (2.69)
<b>HAD-Depression</b>	10.71 (3.91)	9.44 (4.66)	5.15 (3.55)	7.51 (5.11)	3.93 (3.17)
<b>NLSQ-Average</b>	4.21 (0.95)	2.88 (1.29)	2.36 (1.26)	2.32 (1.24)	2.17 (1.19)

Mean scores for each group with standard deviations in brackets.

### 3.4.4 Fracture follow-up

20 subjects with fracture (n=14 upper limb & 6 lower limb) were re-tested for the novel clinical signs after six months of the plaster cast removal (Tables 3f & 3g).

There was a statistically significant decrease in the average number of positive signs per subject from 1.55 to 1.0 in six months (paired t test,  $p=0.02$ ). 50% (n=10) had finger misperception when in plaster cast, but this had resolved in 30% (n=3) of them at 6 months. 50% (n=10) had abnormal hand laterality at the onset but only 35% (n=7) at 6 months. The proportion of

subjects with astereognosis had also improved from 35% (n=7) to 10% (n=2). 15% (n=3) were positive for the composite test of finger misperception and abnormal body scheme report initially but none were positive for this at 6 months.

The mean of the average pain score of the 20 subjects improved from 2.45 to 1.4 (paired t test, p=0.01). There was also a statistically significant improvement in the Neglect like Symptom Questionnaire (NLSQ) score from 2.35 to 1.58 (paired t test, p=0.01).

We reviewed the electronic hospital records of all 47 fracture patients in the study to assess the clinical progress for a mean duration of 3.2 years (range 1.5-5). 4/47 (8.5%) patients had persistent pain as documented by the clinical record. Out of 7 patients who were positive for both FP and BS report at initial testing, 3 had persistent pain with one having a formal diagnosis of CRPS. Another patient (who was negative for both finger perception and body scheme report) also had persistent pain but this was attributed to the severity of injury (i.e. not disproportionate pain) and there were no clinical signs of CRPS. There was no significant correlation between baseline pain report and the development of chronic pain.

**Table 3f:** Prevalence of novel clinical signs: Fracture follow-up

Category	Finger Perception +	Hand Laterality +	Astereognosis +	Body Scheme +	FP and BS +
<b>Fracture (0 months) (n=20)</b>	10 (50%)	10 (50%)	7 (35%)	4 (20%)	3 (15%)
<b>Fracture (6 months) (n=20)</b>	7 (35%)	7 (35%)	2 (10%)	4 (20%)	0

**Table 3g:** Prevalence of novel clinical signs: Fracture follow-up

Category	0 Sign+	1 Sign+	2 Signs+	3 Signs+	4 Signs+	≥1 Signs+	≥2 Signs+	≥3 Signs+
<b>Fracture (0 months) (n=20)</b>	3 (15%)	8 (40%)	4 (20%)	5 (25%)	0	17 (85%)	9 (45%)	5 (25%)
<b>Fracture (6 months) (n=20)</b>	7 (35%)	6 (30%)	7 (35%)	0	0	13 (65%)	7 (35%)	0

### 3.5 Discussion

Previous studies have reported the presence of novel signs in CRPS (Galer et al. 1995);(Förderreuther et al. 2004);(Reinersmann et al. 2012).

However, the clinical diagnostic utility of these signs in CRPS have not been established previously in a systematic fashion.

We recruited a large cohort of patients (253 patients in five different groups of CRPS, FMS, RA, LBP and Fracture) and healthy controls (60 healthy) and objectively defined bedside tests for FP, HL, AS & BS.

CRPS & Fracture patients were recruited with unilateral involvement only as comparisons could then be made between affected and unaffected sides in the same subject. Patients with other chronically painful conditions (for eg; RA, FMS & LBP) were also recruited to the study to assess the prevalence of novel signs in these groups. These groups are obviously clinically distinguishable and different to CRPS but were recruited as it would be scientifically insightful to see if novel signs are unique to CRPS.

Carpal Tunnel Syndrome (or other painful mononeuropathy) would also have been a useful control group. This group was used in the original research studies to develop and validate the diagnostic criteria for CRPS (Harden et al. 2007; Harden et al. 1999). However, we focused on control groups mainly seen at the Rheumatology clinics. In future studies, Carpal Tunnel Syndrome (or other painful mononeuropathy) is definitely worth considering as a control group as they provide a non-CRPS neuropathic pain group with objective diagnosis made by nerve conduction studies.

We chose the 4 signs based on their relationship to body scheme and parietal function. We considered others such as Synchronia and Two-Point Discrimination. Synchronia is a phenomenon in which, although there is no apparent loss of sensation, stimulus applied to one side of the body is referred by the patient to both sides(Krämer et al. 2008). Dysynchronia is a term derived from synchronia and describes the phenomenon whereby stimulation of the intact limb elicits pain (brush-evoked allodynia) or paraesthesia at the

corresponding site on the affected limb, if the patient watches the stimulation in a mirror (Krämer et al. 2008). This has been reported in CRPS patients (Moseley et al. 2014; Acerra & Moseley 2005).

Impaired tactile acuity is reported in chronic pain patients including CRPS (Catley et al. 2014). Two-Point Discrimination (TPD) threshold is a quantitative measure of tactile acuity and is measured using calipers. Large variability in TPD measurements has been reported between subjects and across multiple body sites, suggesting random error. Therefore, although TPD may be reliable within a person, it may lack precision (Cashin & McAuley 2017). We wanted to pick those signs that would be applicable with little specialist equipment and practical in a busy clinic or fracture room. Hence, we discarded synchiria and TPD as we thought they would be too complex.

We wanted to develop a series of tests that can be applied in busy outpatient clinics. The Bath CRPS Body Perception Disturbance Scale may not be suited to this in our view. Further work can be established to assess the relationship between the CRPS BPDS and the body scheme test but these are not directly comparable as one is a paper-based questionnaire and the other phenomenological report. Although this would be an interesting comparison, it was not a relevant line of enquiry to our research in developing clinically useful bedside tests.

We validated tests for FP, HL, AS & BS with a small number of assessors following a short training programme and the results showed that there was good intra- and inter-rater agreement. An ROC curve analysis was carried out to determine the cut-offs for optimum sensitivity and specificity. These were then used to calculate the prevalence of the novel signs in different groups.

Förderreuther et al had reported that 48 % had impaired accuracy to identify fingers in the affected hand compared to contra-lateral hand in their study of 73 CRPS patients (Förderreuther et al. 2004). However, this study did not take into account the time delay (latency) in responding to the touch. We used

both accuracy and time (latency) to define the cut-offs and we found that a higher proportion (85.6% of 49 patients) had finger misperception.

Reinersmann et al reported delayed reaction time and reduced accuracy in limb laterality recognition in CRPS and Phantom limb pain patients compared to healthy controls (Reinersmann et al. 2010). However, this was a small study (n=12) and also did not assess the presence of this sign in other chronic pain conditions unlike our study.

Our study found that the prevalence of abnormal body scheme report and finger misperception were significantly higher in the CRPS group compared to other chronically painful conditions. However, the prevalence of other two signs (abnormal hand laterality and astereognosis) was not significantly higher in the CRPS group. Hence, this study partially confirmed the central hypothesis – “the prevalence of novel clinical signs will be significantly higher in patients with CRPS compared to patients with other chronic pain conditions”. The higher prevalence of abnormal body scheme report and finger misperception in CRPS group suggests that body perception disturbance plays a significant role in CRPS and this is in keeping with findings from previous studies in CRPS (Lewis et al. 2007; Cohen et al. 2013).

Our findings also demonstrate that the novel signs are not unique to patients with CRPS, but appear in all chronic pain groups. This suggests that some of the underlying mechanisms responsible for the novel signs are shared across the various chronically painful conditions. Further research is needed to establish the relevance of these findings in these groups and also to test whether these may be useful in stratifying a sub-group of patients (for eg; within RA patients) that may respond better to chronic pain management strategies rather than those focusing on inflammation control.

There was no relationship between the presence of a positive test and self-reported pain scores; anxiety and depression scores; nor functional scores. The absence of correlation between clinical tests and pain scores may also be a reflection of multiple factors underlying chronic pain and their complex



interactions. The study was also not powered to detect such differences however and further work is needed to explore any possible relationships.

We calculated the diagnostic clinical utility (sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio) of novel signs in patients with CRPS. BS had the highest positive predictive value (78%) and the highest negative predictive value (91.9%). The diagnostic clinical utility was further increased by combining the two best performing tests of FP and BS as a composite test.

There are many predictors of chronic pain following trauma. These include leaving education early; low self-efficacy scores; high baseline pain scores; high levels of sleep disturbance; and high levels of depression and anxiety (Castillo et al. 2006). None of these predictors perform well enough to predict persistent pain in the acute phase.

Moseley et al report that a pain score of less than 5 rules out a diagnosis of CRPS (Moseley et al. 2014). 10/47 patients recorded a baseline pain VAS of 5+ in our cohort and yet only 4 developed persistent pain of which 2/4 patients had a baseline average pain score of <5/10. We were therefore unable to replicate Moseley's findings in our smaller cohort and it seems unlikely that using pain scores *per se* will be a sufficient marker to predict persistent post-fracture pain. It's possible that this difference reflects the timing of when the question was asked with Moseley's cohort being asked within the first week, whereas patients in this cohort were captured within 4 weeks of the injury.

Tests of altered body scheme are much more predictive. The absence of either abnormal finger perception or body scheme report was highly predictive of the absence of persistent pain. Their presence was associated with a significant increase in the presence of persistent pain. These findings support Moseley et al's findings that dysynchiria (bilateral sensations when one limb is touched) is a strong predictor of CRPS when present. Assessing for dysynchiria takes 25 minutes and would not be practical in a clinical setting. Finger perception and abnormal body scheme assessments take less than 5 minutes to perform. Using these tests will stratify patients rapidly into those 'at

risk' of developing persistent pain including CRPS; and those who are not. The prevalence of both signs together is 14.9% thus stratifying a manageable cohort in the Fracture clinic for targeted intervention, such as education, physiotherapy and analgesics.

This is a single centre study and the numbers included are small. In this study the optimum cut-offs for each test were derived and then the prevalences of positive signs estimated using the same dataset. Validation of the optimum cut-offs is required in future studies using independent data. The healthy control group were importantly balanced in terms of age to the CRPS group, but were younger than the patient groups of LBP, FMS, RA and Fracture. This significant age difference is likely to under-estimate the predictive values. Patients with CRPS were more likely to be taking anti-neuropathic agents or anti-depressants. Both of these groups of drugs have cognitive side effects. It's doubtful that these medications contribute significantly to the presence of signs as the RA and Fracture demonstrated a high prevalence of signs but very few patients took these medications.

These bedside tests assess higher cognitive functions, known to be disrupted in some patients with CRPS and correlating to the size of mechanical allodynia (Cohen et al. 2013). FP did not correlate with the site of chronic pain suggesting that abnormal central processing is the dominant mechanism. Serial functional neuroimaging studies in these patient groups may provide further evidence and possible therapeutic targets in this regard. The pain phenotype may be better understood if future studies take into account changes in the body scheme.

### **3.6 Conclusions**

Novel signs of FP, HL, BS, AS are present in CRPS patients and have significant clinical diagnostic utility. They are also present in other chronically painful conditions such as rheumatoid arthritis, fibromyalgia syndrome and low back pain. Combining FP and BS is helpful in stratifying a cohort of at risk patients post-fracture. It is a quick, simple and reliable test that can easily be taught. The pain phenotype may be better understood by assessing for changes in body scheme.

## **Chapter 4: Cortical reorganisation**

### **4.1 Definition and mechanisms**

The adult brain is plastic and maintains the ability to reorganise throughout life. Cortical reorganisation refers to structural and functional changes in the cerebral cortical properties. This has been reported in somatosensory (Merzenich et al. 1984; Pascual-Leone & Torres 1993; Maeda et al. 2014), motor (Giraux et al. 2001), auditory (Pape et al. 2014; Pantev et al. 1998) and visual (Darian-Smith & Gilbert 1994; Gilbert & Li 2012) cortices. It is of major interest to both neuroscientists and clinicians as it is increasingly recognised to play an important role in learning and functional recovery after injury to the nervous system.

Cortical reorganisation is caused by a combination of 'unmasking' of latent synaptic connectivity and formation of new functional connections through axonal sprouting. Activation of NMDA receptors, reduction of GABAergic inhibition, increased Brain-derived Neurotrophic Factor (BDNF) and downregulation of Nogo (Neurite outgrowth inhibitor) have been shown to be important underlying mechanisms (Endo et al. 2009).

### **4.2 Measuring cortical reorganisation**

Researchers have used various modalities including microelectrodes, haemodynamic (PET, f-MRI) and electromagnetic (EEG, MEG) techniques to measure cortical reorganisation. The relative merits of these techniques with a special focus on EEG are discussed below.

EEG (Electroencephalogram) measures the voltage fluctuations along the scalp through multiple surface electrodes placed on the scalp. There are mainly two types of electrical activity associated with neurons inside the brain,

namely action potential and post-synaptic potentials (Olejniczak 2006). Action potentials are discrete voltage spikes lasting about a millisecond, and travel from axon cell body to terminals resulting in release of neurotransmitters. The surface electrodes cannot usually detect them as they tend to cancel each other out in different axons. Post-synaptic potentials are generated when neurotransmitters bind to receptors causing opening or closing of ion channels resulting in a transmembrane potential. These are confined to the cell body and dendrites rather than travelling down the axon at a fixed rate. They last tens to hundreds of milliseconds and under certain conditions summate allowing us to record them at the scalp using EEG (Luck 2005).

Hans Berger, a German neuro-psychiatrist is credited with the first recording of human EEG in 1924. He used silver foil electrodes attached to the head by rubber band and recorded the electric voltages by a galvanometer (Berger 1969).



Fig 4.1: Hans Berger

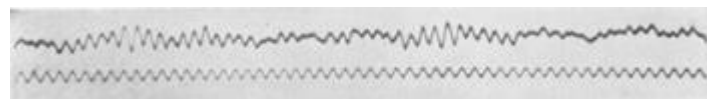


Fig 4.2: One of the first EEG recordings by Berger  
Top trace is the EEG and the bottom trace is a 10 Hz  
frequency reference.

In clinical contexts, EEG usually refers to measuring spontaneous electrical activity of brain and is used in the diagnosis of various clinical conditions including epilepsy, encephalopathies and sleep disorders (Noachtar & Remi 2009; Kaplan & Rosetti 2011; Arriaga & Paiva 1990). EEG is a coarse measure of brain activity and represents a myriad collection of numerous different sources of neural activity. However, averaging techniques can be used to extract specific neural responses to sensory, cognitive and motor events which are embedded within the whole EEG. These specific responses

are called Event Related Potentials (ERP) as they are electric potentials that display stable time relationships to specific definable events. ERP measures averaged EEG signals time-locked to complex processing of stimuli. Analysis of ERP waveforms can yield information on cortical structure and function, and they are used in various fields of neuroscience research(Luck 2005).

ERP provides a continuous measure of processing between a stimulus and a response and this helps to study the effect of experimental manipulations on different stages of processing. They also provide information on processing of stimuli even in the absence of a behavioural response(Blackwood & Muir 1990; Luck 2005). The functional significance of an ERP component may be difficult to interpret compared to a behavioural measure. The other disadvantage of ERP technique is that large numbers of trials are necessary per subject in each condition to measure the ERPs accurately as they are small amplitude signals (Beres 2017; Luck 2005).

Grand average ERP waveforms are created by averaging together the averaged waveforms of individual subjects in a study. This masks the individual variability across subjects which is useful in studying similarities but has the disadvantage that the grand average may not be a true reflection of individual patterns (Luck 2005). One of the factors responsible for the between-subject variation is the idiosyncratic folding pattern of cortex which influences the ERP waveforms. Medications, age and psychopathology are other factors that affect the shape of waveforms (Blume 2006; Polich 1997; Nuwer 2012).

ERP waveforms will have positive and negative deflections called peaks or components which are labelled P1, N1, P2, N2, P3 etc. P refers to positive and N refers to negative, and the numbers refer to the peak's position within the waveform (Luck 2005). It is also common to give a precise latency in milliseconds (ms) such as P300 as the P3 wave had a peak latency of around 300 ms in the original experiment. However, this can be misleading as the latency can vary widely. For example, P300 usually peaks anywhere between 250 to 500 ms and not at 300 ms (Polich 2009).

The somatosensory ERP begins with a rare ERP component that reflects action potential from peripheral nerves followed by a set of sub-cortical components (10-20 ms) and short and medium latency cortical components (20-100 ms). Classically, an N1 wave is observed at approximately 150 ms followed by a P2 wave at approximately 200 ms (Luck 2005).

P3 or P300 refers to the positive peak seen between 250 and 500 ms after stimulus onset. This is an endogenous potential as it does not depend upon the physical attributes of the external stimulus but on the person's reaction to the stimulus. This has two components, P3a (also called novelty P3, between 250 & 280 ms) and P3b (also called classic P3). P3a originates from stimulus driven frontal attention mechanisms during task processing, whereas P3b originates from temporo-parietal activity associated with attention and appears related to subsequent memory processing (Polich 2009). The hallmark of P3 is its sensitivity to target probability. Discriminating the target from the standard stimulus produces a robust P300 that increases in amplitude as the target's global and local sequence probability decreases (Duncan-Johnson & Dunchin 1977).

In addition to analysing the amplitude and latency of ERP voltage waveforms, Global Field Power (GFP), which is a single, reference independent measure of response strength, is often used in neuroimaging studies. The concept of GFP was first introduced by Lehman & Skrandies (Lehmann & Skrandies 1980). GFP is defined as the root mean square (RMS) across the average-referenced electrode values at a given instant in time. In the case of ERPs, the resultant GFP waveform is a measure of potential as a function of time. However, as GFP is a non-linear transformation, the GFP of the group-average ERP is not equivalent to the mean GFP of the single-subject ERPs (Murray et al. 2008).

**Table 4a:** Comparison of different neurophysiology measurement techniques; adapted from- (Luck 2005)

	Microelectrode Measures	Haemodynamic Measures (PET, f-MRI)	Electromagnetic Measures (EEG,MEG)
Invasiveness	Poor	Good (PET) Excellent (f-MRI)	Excellent
Spatial Resolution	Excellent	Good	Poor (EEG) Average (MEG)
Temporal Resolution	Excellent	Poor	Excellent
Cost	Expensive	Expensive	Inexpensive (EEG) Expensive (MEG)

EEG, MEG and f-MRI are non-invasive and involve no radiation exposure making it possible to collect large amount of data from each subject. Microelectrode measures are extremely invasive and PET scan involves radiation exposure making both of these techniques less suitable in human subjects.

EEG and MEG have excellent temporal resolution of around 1 millisecond whereas the haemodynamic measures of PET and f-MRI have a limited resolution of several seconds. However, the haemodynamic measures have an excellent spatial resolution in the millimetre range which EEG cannot match. Measuring ERPs using EEG is also less expensive compared to other techniques.



### 4.3 Somatosensory cortical reorganisation

The somatosensory system detects peripheral sensations and conveys them via pathways through the spinal cord, brainstem, and thalamus to the sensory cortex in the parietal lobe (Brodal 1969).

A $\delta$  and C fibres carry noxious sensory information and A $\beta$  fibres carry non-noxious stimuli from the periphery. A $\beta$  fibres are highly myelinated and of large diameter, therefore allowing rapid signal conduction (Conduction velocity >40 m/s). They have a low activation threshold and usually respond to light touch and transmit non-noxious stimuli. A $\delta$  fibres are lightly myelinated and smaller diameter, and hence conduct more slowly than A $\beta$  fibres (Conduction velocity 5-15 m/s). They respond to mechanical and thermal stimuli. They carry rapid, sharp pain and are responsible for the initial reflex response to acute pain. C fibres are unmyelinated and are also the smallest type of primary afferent fibre. Hence they demonstrate the slowest conduction (Conduction velocity <2 m/s). C fibres are polymodal, responding to chemical, mechanical and thermal stimuli and their activation leads to slow, burning pain (Waxman 1980; Krarup & Buchthal 1985; Rivner et al. 2001).

The sensations are transmitted via the peripheral nerves to the dorsal root ganglion, which houses the first-order neuron for the somatosensory system. The fibres split into 2 functional groups: a lateral group (or anterolateral system) that carries pain and temperature sensations; and a medial group (or dorsal column-medial lemniscal system) that carries proprioceptive impulses. The sensation of touch is mediated by both systems (Parent 1996; Brodal 1969).

The lateral group of fibres enters the spinal cord, then ascend or descend approximately 2 spinal cord segments to terminate on the substantia gelatinosa and the nucleus proprius, where the second-order neurons are housed. These neurons have projections that cross over to the contralateral

side via a tract called the anterior white commissure. Fibres then ascend via the brainstem to the thalamus in the spinothalamic tracts. Two primary spinothalamic tracts exist: the lateral spinothalamic tract, which conveys pain and temperature information, and the anterior spinothalamic tract, which conveys pain and poorly localizable touch sensation (Brodal 1969; Parent 1996).

The medial group also sends its fibres into the posterior spinal cord; however, upon reaching it, most fibres ascend to the dorsal column nuclei in the medulla and synapse there. These tracts synapse on a second-order neuron in the nucleus gracilis and cuneatus, which are located in the medulla. Their axons then decussate (via internal arcuate fibres) and form a bundle known as the medial lemniscus. Fibres of the posterior columns and medial lemniscus are concerned primarily with position sense and fine discriminative touch (Parent 1996; Brodal 1969).

The third-order neurons then project, via the posterior limb of the internal capsule, to the primary somatosensory cortex (S1), which is located in the postcentral gyrus of the parietal lobe (Parent 1996). Primary somatosensory cortex serves to integrate sensory information. It also receives connections from the motor cortex, somatosensory association cortex, and the contralateral primary somatosensory cortex. S1 representation refers to the pattern of neuronal activity that is evoked when a body part is stimulated. This is generally in keeping with the topographic 'homunculus' model proposed by Wilder Penfield (Penfield & Boldrey 1937). Genital and leg fibres are located medially, whereas arm, hand, face, and tongue fibres are on the lateral surface of the somatosensory area. Body areas particularly important to the sensory system (for example the face, lips, and hand) are given larger representation than other areas (Parent 1996).

Cortical reorganisation within the somatosensory cortex is discussed in detail below.

#### **4.3.1 Animal studies**

Merzenich *et al* used microelectrode mapping techniques to show that digit amputation in adult monkeys resulted in increased cortical representation of the 4 adjacent digits. They found that within two months the area of cortex corresponding to amputated digit started to respond to touch stimuli delivered to adjacent digits, i.e.; this area was 'taken over' by sensory input from adjacent digits (Merzenich *et al.* 1984).

Jenkins *et al* in a related experiment using normal adult monkeys showed that behaviourally controlled tactile stimulation produced an expansion of cortical representation zone in trained fingers (Jenkins *et al.* 1990).

#### **4.3.2 Human studies (other than CRPS)**

Elbert *et al* in a magnetic source imaging study showed that cortical representation of the digits of the left hand of string players (violinist, cellists, guitarists) was larger compared to controls. No such differences were observed for the right hand digits. Moreover, the amount of cortical reorganization in the representation of the fingering digits was correlated with the age at which the person had begun to play (Elbert *et al.* 1995).

Pascual-Leone *et al* reported increased cortical representation for the index finger used in reading by blind Braille readers. They studied organisation of somatosensory cortex in 15 proficient Braille readers (10 using Somatosensory evoked potential elicited by electrical stimuli to the index finger and 5 using transcranial magnetic stimulation) and compared them to the control group of 15 non-blind non-Braille readers. The scalp areas from which they recorded N20 and P22 components of somatosensory evoked potential were significantly larger in the reading fingers compared to the non-

reading fingers of the braille readers as well as both left and right hand fingers of the control subjects (Pascual-Leone & Torres 1993).

Reversible cortical reorganisation has been reported in phantom limb pain. MEG (magnetic encephalogram) source imaging showed that the mouth area of S1 shifted into that of the former hand and the extent of this shift highly correlated with the intensity of pain (Flor et al. 1995). Behaviourally relevant sensory discrimination training in the stump area reduced the cortical reorganisation (Flor et al. 2001).

## **4.4 CRPS neuroimaging studies**

Investigators have used several functional neuroimaging techniques such as electroencephalography (EEG), magneto-encephalography (MEG), functional magnetic resonance imaging (f-MRI), and positron emission tomography (PET) to study changes within the somatosensory and motor cortices in patients with CRPS.

### **4.4.1 Somatosensory Cortex**

The main studies investigating the somatosensory cortex function in CRPS are discussed below in detail and summarised in Table 4b.

#### **EEG Studies**

Pleger and colleagues (Pleger et al. 2004), using 32 channel EEG, performed somatosensory evoked potential (SSEP) mapping with non-painful electrical stimulation of median and ulnar nerve in seven CRPS patients and compared them to healthy controls. They performed source reconstruction for the N20

SSEP component based on a single rotating dipole model in a spherical volume conductor. The polar angle difference between the N20 dipoles after median and ulnar nerve stimulation was used as a parameter to describe the dimension of the cortical hand representation. The dipole co-ordinates were therefore projected onto an adjusted 3D co-ordinate system (y-axis: joined acoustic meati of both ears; x-axis: joined centre point of y-axis and origin of nasion; z-axis: joined centre point and vertex). The polar angle of each nerve representation was calculated by referring the connection between dipole position and y-axis to z-axis. The results of somatosensory potential measurement in all seven patients showed latencies and amplitudes of the N20 component without any side-to-side differences.

However, the differences between the polar angles of the N20-dipole locations of both nerve representations were significantly smaller on the CRPS-associated hemisphere.

[median nerve N20-dipole:  $27^{\circ} \pm 4^{\circ}$  (“CRPS hemisphere”) vs  $28^{\circ} \pm 5^{\circ}$  (“healthy hemisphere”); ulnar nerve N20-dipole:  $27^{\circ} \pm 2^{\circ}$  (“CRPS hemisphere”) vs  $26^{\circ} \pm 2^{\circ}$  (“healthy hemisphere”); difference between the median and ulnar nerve polar angle:  $1.1^{\circ} \pm 1^{\circ}$  (“CRPS hemisphere”) vs  $3.2^{\circ} \pm 1^{\circ}$  (“healthy hemisphere”);  $Z = -2.36$ ,  $p = 0.018$ ; Wilcoxon signed rank test]

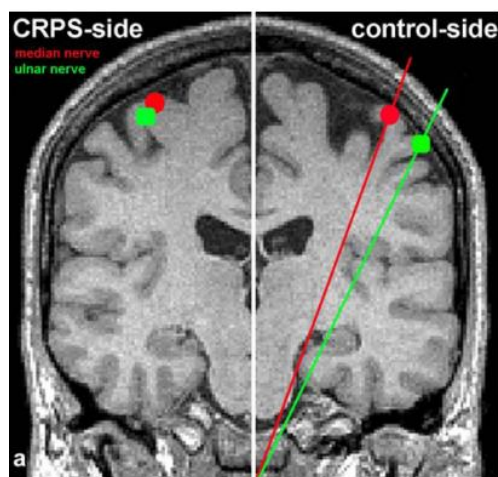


Fig 4.3: The cortical representations of the median (red) and ulnar nerve (green) were projected onto a coronal magnetic resonance imaging slice. The average positions of the N20-dipoles are given by the polar angles showing a larger hand representation on the control hemisphere than on the CRPS-associated hemisphere (Pleger et al. 2004).

In the control group, they found no significant differences between dominant left and non-dominant right hemisphere (difference between the median and the ulnar nerve polar angle: dominant hemisphere:  $2.7^{\circ} \pm 1.3^{\circ}$ ; non-dominant hemisphere:  $2.9^{\circ} \pm 1.4^{\circ}$ ; Wilcoxon signed rank test:  $Z = -0.69$ ,  $p=0.5$ ). Non-parametric analysis (Kendall's tau-b and Spearman's rho) further revealed that the observed reduction in the CRPS-associated hemisphere significantly correlated with the degree of the CRPS-induced pain experienced continuously for the 4-week period before SSEP measurement. Accordingly, low pain levels were associated with small changes in SI, whereas subjects with higher pain intensity levels exhibited a marked asymmetry of SI, indicating a higher degree of cortical reorganization.

van Rijn and colleagues (van Rijn et al. 2009) investigated spatiotemporal integration of sensory stimuli in an EEG study of 33 CRPS patients with dystonia and 19 healthy controls. N9, N14, N20 and N35 amplitudes were recorded after paired electrical stimulation of median and ulnar nerves ("spatial") and after stimulation of both nerves with single stimuli and with interstimulus intervals of 20 and 40 ms ("temporal" stimulation). Finally, both methods were integrated resulting in spatiotemporal stimulation. Somatosensory evoked potentials were recorded using a four electrode system: Erb's point, cervical lead aimed at N14 and other two recording ipsilateral & contralateral cortical activity. Statistical testing was performed using linear mixed model analysis of variance. SSEP amplitudes were significantly suppressed after spatial and temporal stimulation. No difference was observed between patients and healthy controls. Spatio-temporal stimulation did not show an additional suppressive effect in any group. This study concluded that central sensory integration of proprioceptive afferent input is normal in patients with CRPS-related dystonia.

Lenz and colleagues (Lenz et al. 2011) measured paired pulse suppression of somatosensory evoked potential in 21 CRPS patients with unilateral involvement of hand. The control groups were 11 patients with non-neuropathic pain and 21 healthy controls. Innocuous electrical stimulations were administered to median nerve at the affected and unaffected hands in the patient groups. Somatosensory evoked potentials were measured using a

three electrode array: two electrodes C3' and C4' over left and right primary somatosensory cortex and a reference electrode over the midfront position (FZ). They analyzed peak-to-peak amplitudes of the cortical N20–P25 response component for the first and second paired-pulse stimulus.

ANOVA revealed no significant difference between the patients' affected (mean amplitude ratio  $\pm$ SE; CRPS group =  $0.96 \pm 0.09$ , control group =  $0.74 \pm 0.06$ ) and clinically unaffected side (mean amplitude ratio  $\pm$  SE; CRPS group =  $0.95 \pm 0.07$ , control group =  $0.71 \pm 0.06$ ;  $F=0.311$ ,  $p=0.581$ ). In contrast, ANOVA revealed increased amplitude ratios in patients with CRPS compared with patients with non-neuropathic pain (CRPS group vs control group;  $F=5.622$ ,  $p=0.024$ ). The ANOVA result was confirmed by post hoc t-tests (affected hand CRPS vs control group,  $p=0.045$ ; unaffected hand CRPS vs control group,  $p=0.006$ ). This finding of significant reduction of paired pulse suppression of both sides in the CRPS group compared to both the control groups, supports the hypothesis that complex impairment of central sensory integration or cortical disinhibition plays a role in CRPS. This is in contrast to the study by van Rijn and colleagues (van Rijn et al. 2009) described before where they found no evidence for that assertion.

## **MEG studies**

Juottonen and colleagues (Juottonen et al. 2002) investigated central tactile processing in CRPS by recording somatosensory evoked fields in six patients with CRPS and six matched controls, using a 306-channel whole-head neuromagnetometer. Non-painful tactile stimuli were delivered to the fingertips of thumb, index, and little fingers (D1, D2, and D5) of the left and right hand with balloon diaphragms driven by compressed air. Stimulus-related reactivity of the 10-Hz (originating predominantly from somatosensory cortex) and 20-Hz (originating predominantly from primary motor cortex) sensorimotor rhythms was quantified and statistically analysed using Student's paired two-tailed t-test. They found that in the whole patient group the SI responses were

25–55% stronger for stimulation of the affected than the healthy side; this difference was observed regardless of the side of pain ( $P = 0.03$ ).

The contralateral SII response was also stronger to stimulation of the painful side but this difference did not reach statistical significance. The amplitude of the SI response showed a statistically non-significant trend for positive correlation with the intensity of pain evaluated by VAS scale, at the level of  $r=0.60$ , but it did not correlate with duration of pain or tactile sensitivity.

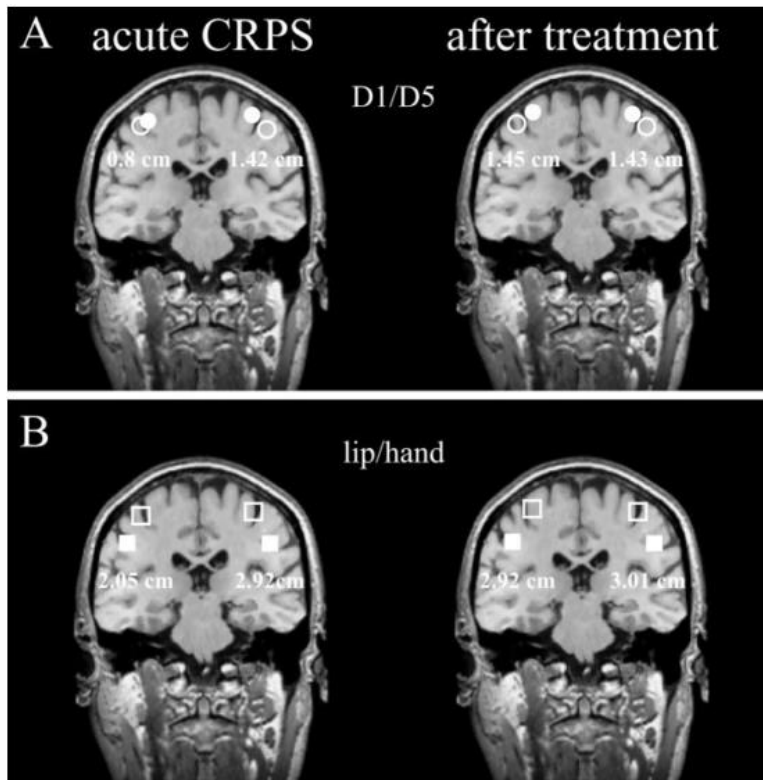
The SI responses peaked at the same time regardless of the side of stimulation. The mean source strengths to the healthy side stimulation of the patients did not differ from the source strengths of the control subjects. In the control group, the amplitudes and latencies of SI and contralateral SII responses did not differ between right and left-sided stimulation. The SI responses to thumb vs. little finger were 40% closer to each other in the SI cortex corresponding to the painful hand than the other hand so that in patients with severe pain, the distance between finger representations was shorter. There was no significant correlation between the distance and the level of pain (measured with VAS) or the duration of pain.

Maihöfner and colleagues (Maihöfner et al. 2003) recorded somatosensory evoked magnetic fields of 12 patients with CRPS after non-painful stimulation of their thumb (D1), little finger (D5) and lower lip with air-puff derived tactile stimulator. Cortical responses were recorded by using a 37-channel neuromagnetometer in a magnetically shielded room. To visualize results with respect to brain anatomy, the dipole locations were superimposed on MR images. No significant difference was found in the peak latencies of affected and unaffected sides. However, the mean strengths of the magnetic fields for D1/D5 were significantly increased on the CRPS side compared to the unaffected side and this increase on the painful side was independent of the side of pain (left or right) or patient handedness. They also found that this increase in dipole moment was significantly correlated with the intensity of spontaneous pain at the moment of the MEG recordings but had no correlation with other clinical signs and symptoms. They found a significant shrinkage of the extent of the cortical hand representation for the CRPS affected side. The centre of the hand was shifted toward the cortical



representation of the lip. The cortical reorganization correlated with the amount of CRPS pain ( $r = 0.792$ ), as measured by the McGill questionnaire, and the extent of mechanical hyperalgesia ( $r = 0.860$ ). Using multiple regression analysis, the best predictor for the plastic changes was found to be mechanical hyperalgesia.

Maihöfner and colleagues (Maihöfner et al. 2004) did a follow up study of 10 out of the 12 patients from the previous study a year after treatment to assess potential changes in cortical representation. The patients all had significant improvement in their symptoms with treatment. There were no statistically significant differences in the peak latencies or magnetic field strengths between sides this time. However, the cortical reorganisation had reversed in parallel to the clinical improvement (see fig 4.4 A&B).



**Fig 4.4 (A):** Projection of the equivalent current dipole (ECD) localizations for D1 (filled circle) and D5 (open circle) onto individual MRI slices. There was a reduction of the hand extension from 1.42 cm (unaffected side) to 0.8 cm (CRPS-affected side) during acute CRPS. After the follow-up time of 62 months, the distance between D1 and D5 increased to 1.45 cm on the affected side, whereas the corresponding distance on the unaffected side remained unchanged (1.43 cm).

**(B):** Projection of the ECDs for the center of the hand (open squares) and the lower lip (filled squares) onto individual MRI slices. The distance between the center of the hand and the lower lip increased from 2.05 cm to 2.92 cm following therapy on the CRPS-affected side, whereas the respective ECD localizations for the unaffected side remained unchanged (distance hand–lip 2.92 vs 3.01 cm, before and after treatment).

Sinis and colleagues (Sinis et al. 2007) studied the effect of N-methyl-D-aspartate receptor antagonist memantine in six patients with CRPS of one upper extremity. In one of these six patients, somatosensory evoked fields were recorded after pneumatic stimulation of thumb and little finger using a whole head MEG with 151 first-order gradiometers. The functional organization of S1 was determined by dipole analysis of the first prominent peak of the magnetic brain response. The localization was represented in a 3 dimensional grid and was expressed as the angle “ $\theta$ ” between Cz and a

direct line from the middle of the sphere to the dipole localization. Cortical reorganization was expressed as the difference between the “ $\theta$ ” angle of the cortical distance D1/D5 of the affected side mirrored in the unaffected side in S1. This difference was seen in the S1 cortex of the affected limb unlike the contralateral unaffected limb (difference “ $\theta$ ” angle = 11 degrees). These changes returned to a cortical pattern comparable to the unaffected side after treatment with memantine for eight weeks.

Vartiainen and colleagues (Vartiainen et al. 2008) recorded somatosensory evoked fields in 8 CRPS patients and 9 healthy controls using MEG after delivering non-painful tactile stimuli to thumb (D1), index finger (D2) and little finger (D5) using diaphragms driven by compressed air. The size of the hand representation area in the SI cortex was estimated by calculating the distance (in xyz-space) between D1 and D5 sources. The peak amplitude of the equivalent current dipole waveform was considered to reflect the strength of the source. The strengths and peak latencies of the sources were compared between the groups and between the painful and healthy hands with a two-tailed t-test. Pearson’s correlation coefficients were calculated to correlate the source strengths with the stimulation energy and intensity of perceived pain.

In all subjects, the earliest cortical responses to tactile stimuli peaked at about 54–58 ms at the contralateral parietal cortex. The source of the response was identified in all subjects in the posterior wall of the central fissure, in the SI cortex. Longer-latency responses peaked bilaterally at 99–105 ms in the temporo-parietal regions. These responses were generated in the upper lip of the Sylvian fissure in the secondary somatosensory (SII) cortex. A later response peaked at the contralateral parietal cortex at 95–152 ms, and it was generated in the bottom of the post-central fissure in the posterior parietal cortex (PPC). At group level, the SI sources were 33% stronger ( $P = 0.05$ ) to the stimulation of the painful than that of the healthy hand in the patients, whereas no such side difference was observed in the control group.

The strengths and latencies of the SII sources did not differ between the groups or between the sides in either group. PPC was activated in all control subjects but only in three CRPS patients. The mean ( $\pm$ SEM) PPC source strength was weaker in the CRPS patients than in the control subjects.

The PPC source strength did not correlate with the tactile sensitivity or discrimination in the patients. At group level, the D1–D5 distance was statistically significantly shorter for the painful than the healthy hand (mean  $\pm$  SEM;  $6 \pm 2$  mm vs.  $10 \pm 2$  mm,  $P = 0.02$ ). In the control subjects, the distance was similar in both hemispheres ( $10 \pm 2$  mm vs.  $12 \pm 1$  mm, n.s.).

### **Functional MRI studies**

Forster and colleagues (Forster et al. 2000) used f-MRI to identify the activated brain regions in 7 CRPS patients and 7 healthy controls. The different stimuli conditions were finger tapping, impact pain, tonic pain (using a mechanical pneumatic device) and light touch. They found that in both healthy and CRPS group there were activations in primary and secondary somatosensory cortices, insula and anterior cingulate cortex (ACC). In addition, there was activation in motor (primary and supplementary) and frontal areas. There was no significant difference in activation between the two groups. However, in one CRPS patient with strong mechanical hyperalgesia, even light touch stimuli caused activation of ACC which was not seen in any of the healthy subjects with non-painful stimuli.

Maihöfner and colleagues (Maihöfner et al. 2005) studied brain processing in mechanical hyperalgesia in 12 CRPS patients (control=unaffected side) using f-MRI. They found mechanical stimuli using von-Frey filaments in the unaffected side (non-painful) led to activations in contralateral primary somatosensory cortex, insula and bilateral secondary somatosensory cortices. Stimuli in the affected hand (perceived as painful due to hyperalgesia) revealed activations in additional areas of anterior cingulate cortex and frontal cortex. Maihöfner and colleagues (Maihöfner et al. 2006) in a related study ( $n=12$  CRPS patients, control=unaffected side) also showed that a complex cortical network is involved in allodynia similar to that in mechanical hyperalgesia.

Pleger and colleagues (Pleger et al. 2005) subjected 6 CRPS patients to f-MRI imaging during non-painful electrical stimulation to index finger before

and after 1-6 months of graded sensorimotor training. They showed that shrinkage of cortical maps of primary (S1) and secondary (S2) somatosensory cortex contralateral to the affected side was reversible and associated with a decrease in pain intensity and improvement in two-point discrimination. In a subsequent larger study (Pleger et al. 2006) of 17 patients (which included the six from previous study) they confirmed the findings that patterns of cortical reorganization in SI and SII seem to parallel impaired tactile discrimination.

Freund and colleagues (Freund et al. 2010) reported that there was increased activation of posterior cingulate cortex and decreased opercular activation compared to healthy controls in a f-MRI study where they delivered graded electrical painful stimulation to index fingers of both hands of 10 CRPS patients. These changes were not limited to the affected side and may be a reflection of generalised motor inhibition and decreased sensory discrimination in these patients. In a follow up study of the same patient group (Freund et al. 2011), they reported that there was less activation of periaqueductal gray and cingulate cortex during a pain suppression task suggesting impairment of descending opioid pain suppression pathway.

Di Pietro and colleagues (Di Pietro et al. 2015) compared the S1 spatial representation of the hand in 16 patients with upper-limb CRPS to 16 healthy controls, using functional MRI. Innocuous vibration was delivered to digits one (D1) and five (D5) in a block design. Distance between D1 and D5 activation maxima, calculated for both hands, was used as a measure of S1 representation. Analyses were blinded to group and hand. In patients, S1 representation was smaller for the affected hand than it was for the healthy hand. However, S1 representation of the affected hand was no different to that of either hand in controls. S1 representation of the healthy hand of patients was larger than that of controls' hands. This study suggests that CRPS seems to be associated with an enlarged representation of the healthy hand, not a smaller representation of the affected hand unlike previous studies. This study addressed various methodological limitations of previous studies such as unblinded data analysis and failure to report on healthy controls. Further exploration (Di Pietro et al. 2016) using the f-MRI data from

the same study, did not show any relationship between the size of the healthy hand representation in S1 and the severity of functional impairment of the CRPS-affected hand or pain duration. This suggests that the enlarged S1 healthy hand representation may be pre-existing and not related to compensatory use.

## **PET Studies**

Shiraishi and colleagues (Shiraishi et al. 2006) used 18 F-fluorodeoxyglucose PET scanning in 18 CRPS patients and 13 age-matched healthy controls and found that the cerebral glucose metabolism was elevated bilaterally in the areas concerned with somatosensory perception such as anterior cingulate cortex, posterior parietal cortex, secondary somatosensory cortex, insula and cerebellum. In contrast, the glucose metabolism was reduced in the contralateral pre-frontal cortex and primary motor cortex. The changes in the anterior cingulate cortex, posterior cingulate cortex and posterior parietal cortex correlated with pain duration.

## **Meta-analysis**

A systematic review and meta-analysis by Di Pietro and colleagues (Di Pietro et al. 2013b) came to the following conclusions regarding primary somatosensory cortex changes in CRPS :

1. S1 spatial representation was found to be reduced on the affected hand compared to the unaffected hand in CRPS in the meta-analysis of pooled data from four MEG studies (Juottonen et al. 2002; Maihöfner et al. 2003; Sinis et al. 2007; Vartiainen et al. 2008) and one EEG study (Pleger et al. 2004). Data available from two studies (Pleger et al. 2004; Vartiainen et al. 2008) reporting on healthy controls indicated that the representation size of the affected hand in CRPS patients was smaller than that of healthy controls.

2. There was no difference in the activation strength in S1 comparing hemispheres in CRPS patients or comparing CRPS patients with non-CRPS controls.
3. There were no significant differences in S1 peak latency after stimulation of CRPS-affected and unaffected hands or comparing CRPS patients with non-CRPS controls.
4. Contrasting data on cortical disinhibition: One study (Lenz et al. 2011) found bilateral S1 cortical disinhibition in CRPS patients compared to non-CRPS controls; whereas another study (van Rijn et al. 2009) found no evidence of cortical disinhibition.
5. There was an overall high risk of bias in the included studies introduced by non-consecutive sampling, unblinded assessment of outcomes and unclear or selective reporting of outcomes.

**Table 4b:** Neuroimaging studies investigating somatosensory cortex function in CRPS

Study/ Modality	Stimulation/ Paradigm	Outcomes Assessed	Condition & Comparison [Study size (M/F) Age in years]	Main Results
(Pleger et al. 2004) <b>EEG</b>	Electrical stimulation to median and ulnar nerves—affected and unaffected sides	Cortical SSEPs to determine- Hand representation size; S1 activation strength& latency	<b>CRPS</b> : n=7 (4/3); age=40 (19–64); <b>Healthy Controls</b> : n=7 (1/6); age=28 (20–45) <b>Unaffected side</b>	Differences between the polar angles of the N20-dipole locations of both nerve representations were significantly smaller on the CRPS-associated hemisphere. No difference between hemispheres in N20 latency or amplitude
(van Rijn et al. 2009) <b>EEG</b>	Electrical stimuli to median and ulnar nerves of both wrists; right arm in control group	Cortical (N20 and N35) amplitudes and latencies to determine: S1 activation strength& latency	<b>CRPS</b> : n=33 (1/32) ; age=39.7 ±10.9 (SD); <b>Healthy Controls</b> : n=19 (0/19); age=40.2 (23–55)	No difference between patient and control groups in suppression of SSEP after spatio-temporal stimulation
(Lenz et al. 2011) <b>EEG</b>	Paired-pulse stimulation to median nerve	Paired-pulse suppression to determine strength of S1 activation	<b>CRPS</b> : n=21 (9/12) ; 51± 10.8 (SD); <b>Healthy Controls</b> : n=21 (9/12) ; 51.3 ± 10.9 (SD)	Significant reduction of paired pulse suppression of both sides in the CRPS group compared to the control group. No difference between affected and unaffected side in the CRPS group
(Juottonen et al. 2002) <b>MEG</b>	Compressed-air tactile stimulation to D1, D2 and D5 of both hands	Cortical SEFs to determine: Hand representation size; S1 activation strength& latency	<b>CRPS</b> : n= 6 (0/6); age=45.4 (33-54); <b>Healthy controls</b> : n= 6 (0/6); age=45.1 (34-55) <b>Unaffected side</b>	Significantly stronger response in the contralateral S1 in affected hand compared to unaffected. Distance between the S1 representations of the D1 and D5 of the affected hand significantly shorter compared with the unaffected hand
(Maihöfner et al. 2003) <b>MEG</b>	Air-puff stimulation to D1,D5 and lower lip on both sides	Cortical ECDs to determine: Hand representation size; S1 activation strength& latency	<b>CRPS</b> : n=12 (3/9); 57.4±18.7 (SEM) <b>Unaffected side</b>	Increased strength of magnetic fields and a reduced distance between D1 and D5 representation in S1 contralateral to the affected hand. S1 representation of the affected hand shifted toward the lip representation. Amount of cortical reorganization correlates with the intensity of CRPS pain and the extent of mechanical hyperalgesia



(Maihöfner et al. 2004) <b>MEG</b> (Follow-up study)	Air-puff stimulation to D1,D5 and lower lip on both sides	Cortical ECDs to determine: Hand representation size; S1 activation strength& latency	<b>CRPS</b> : n=10 out of the 12 patients from the previous study in 2003	Cortical reorganisation noted in the initial study in 2003 had reversed in parallel to clinical improvement
(Sinis et al. 2007) <b>MEG</b>	Pneumatic stimulation to D1 and D5 both hands	Cortical SSEPs to determine hand representation size	<b>CRPS</b> : n=1 male, age=59 <b>Unaffected side</b>	Cortical representation decreased in affected hand compared to unaffected hand
(Vartiainen et al. 2008) <b>MEG</b>	Compressed- air tactile stimulation of D1, D2 and D5 of both hands	Cortical ECDs to determine: Hand representation size; S1 activation strength& latency	<b>CRPS</b> : n= 8 (0/8) ; age=45.5 (26–57); <b>Healthy controls</b> n= 9 (0/9) ; age=46 (28–57) <b>Unaffected side</b>	SI sources significantly stronger to the stimulation of affected compared to unaffected hand. Significantly shorter D1-D5 distance in affected compared to unaffected hand
(Forster et al. 2000) <b>f-MRI</b>	Finger tapping, Impact pain, Tonic pain, Light Touch. Stimulated D2 and D3.	S1 signal change	<b>CRPS</b> : n= 7 (1/6) ; age =27–68; <b>Healthy Controls</b> n= 7 (7/0) ; age =22–55	Bilateral activation of S1, S2, insula and ACC in both groups by painful stimuli. No significant difference in activation between the two groups
(Maihöfner et al. 2005) <b>f-MRI</b>	Painful pin-prick stimulation to affected limb; pin-prick to corresponding site on unaffected limb	S1 signal change : To explore central processing during hyperalgesia	<b>CRPS</b> : n=12 (4/8) ; 45.3± 3.5 (SEM); <b>Unaffected side</b>	Pinprick stimulation to unaffected side caused activation in contralateral S1, bilateral S2 and insula. Pinprick stimulation of affected side (perceived as painful due to hyperalgesia) caused significantly increased activation in S1, bilateral insula, S2 and additional activation in ACC and frontal cortex
(Pleger et al. 2005) <b>f-MRI</b>	Electrical stimulation to D2 on both hands	S1 activation level : To assess possible alterations in cortical maps before & after sensori-motor training program	<b>CRPS</b> : 6 (gender & age not reported) <b>Unaffected side</b>	Shrinkage of cortical maps of S1 and S2 contralateral to the affected side was reversible and associated with a decrease in pain intensity and improvement in two-point discrimination

(Maihöfner et al. 2006) <b>f-MRI</b>	Brush-evoked allodynia to affected side; brushing of the corresponding site on unaffected limb	S1 signal change: To explore allodynia related brain areas activations and deactivations	<b>CRPS:</b> n= 12 (5/7); 47.5 ± 3.1 (SEM); <b>Unaffected side</b>	A complex cortical network is involved in allodynia similar to that in mechanical hyperalgesia
(Pleger et al. 2006) <b>f-MRI</b>	Electrical stimulation to D2 on both hands.	S1 signal change	<b>CRPS :</b> n=17 (7/10); age=40.1 ± 9.5 (SD); <b>Healthy Controls:</b> n=17 (7/10); age=40.2 ± 10 (SD) <b>Unaffected Side</b>	Patterns of cortical reorganization in S1 and SII seem to parallel impaired tactile discrimination
(Freund et al. 2010) <b>f-MRI</b>	Graded electrical non-painful and painful stimulation to D2 both hands	S1 signal change- To investigate for a generalized change in pain processing	<b>CRPS:</b> n=10 (5/5); age=45 (28–61) <b>Healthy Controls:</b> n=15 (10/5); age= 35.5 (25-64)	Increased activation of posterior cingulate cortex and decreased opercular activation in CRPS compared to healthy controls
(Freund et al. 2011) <b>f-MRI</b>	Tonic painful electrical stimulation to D2 of both hands	S1 signal change- To investigate for dysfunction in the descending opioid pain system	<b>CRPS :</b> n=10 (5/5); age=45 (28-61); <b>Healthy Controls :</b> n=15 (10/5) ;age= 35.5 (25-64)	Less activation of Periaqueductal gray and cingulate cortex during a pain suppression task
(Di Pietro et al. 2015) <b>f-MRI</b>	Vibration stimuli to D1 & D5 of both hands	S1 signal change	<b>CRPS :</b> n=16 (5/11) ; age=48.9 ± 13.9); <b>Healthy Controls :</b> n=16 (5/11) ; age=43.9 ± 11.7)	In patients, S1 smaller in affected side compared to unaffected side. S1 representation of healthy hand in patients larger compared to controls.
(Shiraishi et al. 2006) <b>PET</b>	18F-fluorodeoxyglucose PET	Identification of active brain areas, via glucose metabolism	<b>CRPS :</b> n= 8 (10/8) ;age=40.7 (21–59) ; <b>Healthy Controls</b> n=13(11/2) ; age=38.7 (27–58)	Elevated glucose metabolism bilaterally in ACC, posterior parietal cortex, S2, insula and cerebellum

Abbreviations: T, Tesla; SEM, standard error of the mean; SEFs, somatosensory-evoked fields; SD, standard deviation; ECDs, equivalent current dipoles. NOTE. All stimulation paradigms were non-painful unless otherwise stated.  
Table adapted from (Di Pietro et al. 2013b)

#### **4.4.2 Motor cortex**

The main studies investigating the motor cortex function in CRPS are discussed in detail below and summarised in Table 4c.

##### **Functional MRI Studies**

Maihofner and colleagues (Maihöfner et al. 2007) studied cortical activations during finger tapping (n=12 CRPS Right arm affected, 12 age & sex matched controls) using f-MRI. They found increased activation in the primary motor cortex in both hemispheres on finger tapping of the CRPS affected side compared to the unaffected side (difference in cluster size in contralateral M1: 3142,  $P < .0001$ ; ipsilateral M1: 554,  $P=.0001$ ) and the right hand in controls (difference in contralateral M1: 1769,  $P = .0002$ ; ipsilateral M1: 3250,  $P = .0003$ ).

Gieteling and colleagues (Gieteling et al. 2008) studied cerebral activations during imagined and actual hand movements in CRPS patients with dystonia (n=8 CRPS, 17 age-matched healthy controls). Compared with controls, imaginary movement of the affected hand in patients showed reduced activation ipsilaterally in the premotor and adjacent prefrontal cortex ( $P$  corrected-cluster-level 0.030, cluster size 186 voxels), and in the anterior part of the insular cortex and the superior temporal gyrus ( $P$  corrected-cluster-level 0.010, cluster size 242 voxels). Contralaterally, reduced activation was seen in the inferior parietal and adjacent primary sensory cortex ( $P$  corrected-cluster-level 0.030, cluster size 186 voxels). There were no differences between patients and controls when they executed movements, nor when they imagined moving their unaffected hand (See figure 4.5).

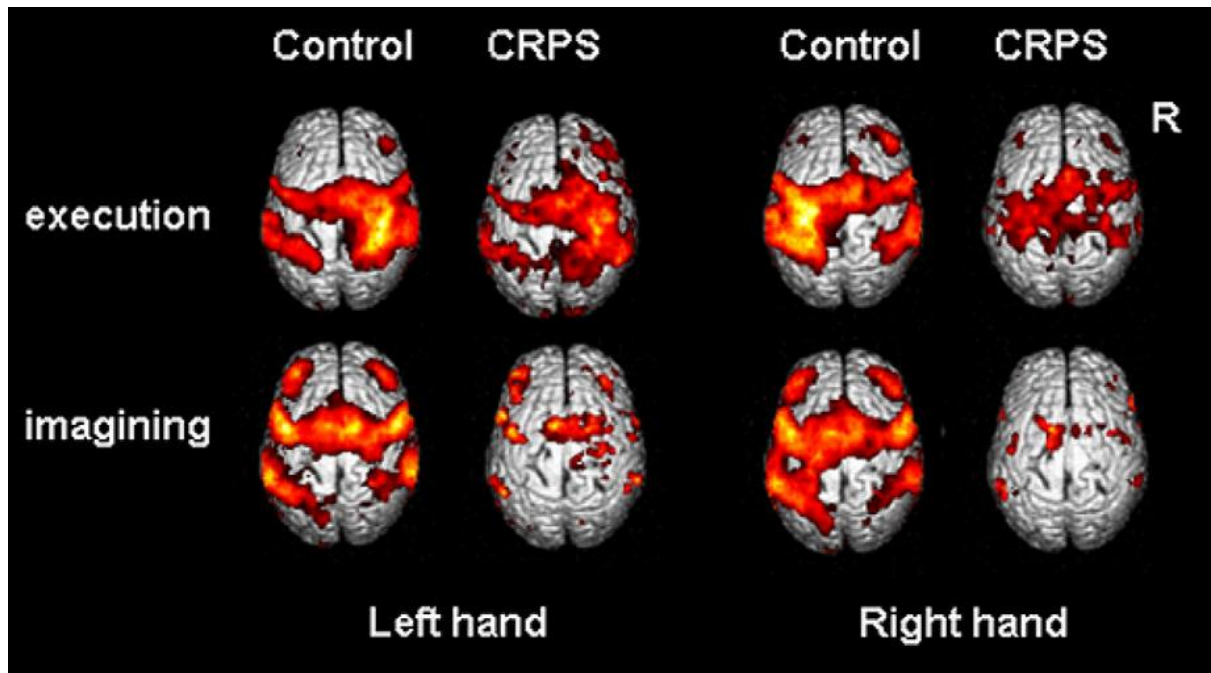


Fig 4.5: Areas of activation in controls (n = 17) and patients (n = 8). Four different tasks compared with rest condition, projected on a template rendered brain image. P, uncorrected <math><0.01</math>; extent threshold P5 voxels.(Gieteling et al. 2008)

### Transcranial Magnetic Stimulation Studies

Schwenkreis and colleagues (Schwenkreis et al. 2003) studied 25 CRPS patients (all unilateral upper limb affected) and 20 healthy controls using paired pulse paradigm and found significant reduction in intracortical inhibition on both sides of patients but no significant change in intracortical facilitation or motor threshold compared to the healthy. There was no significant difference between the affected and unaffected side in the patient group.

Eisenberg and colleagues (Eisenberg et al. 2005) delivered TMS (Magstim 200, figure of eight coil) to the motor cortex of subjects (6 upper limb CRPS and 6 Lower Limb CRPS, 14 age & sex matched healthy control) and measured the motor evoked potential using surface EMG from APB muscles of both wrists. A significant reduction in the short intracortical inhibition associated with a significant increase of the I-wave facilitation was found in the hemisphere contralateral to the affected side in the upper-limb CRPS group (paired t-test,  $p<0.05$ ). No significant inter-hemispheric asymmetry

between the affected and the non-affected sides was revealed in the lower-limb CRPS group.

Krause and colleagues (Krause et al. 2005) recorded the cortical and spinal motor evoked potentials (c-MEP and s-MEP), and the contralateral and ipsilateral cortical silent period (c-CSP and i-CSP) in subjects (12 patients with CRPS type I and 10 healthy controls) before and after conditioning repetitive magnetic stimulation, applied at cervical nerve roots innervating affected muscles. The silent period, the time between the stimulus delivery and the return of voluntary activity, is a reflection of inhibitory mechanisms at the motor cortex. They reported no difference in c-CSP and i-CSP between CRPS and healthy controls. The c-MEP but not s-MEP was significantly smaller in both hemispheres in CRPS group.

In a subsequent TMS experiment, Krause and colleagues (Krause et al. 2006) found a significant interhemispheric asymmetry between the motor cortical representation of affected and unaffected hand muscles in a group of CRPS I patients (n=14 CRPS, 10 Healthy). The cortical representation (size, Motor Evoked Potential, and calculated volumes) was significantly larger for the unaffected hand than for the affected hand. This asymmetry was not found in the control group of healthy subjects.

Turton and colleagues (Turton et al. 2007) coupled TMS with peripheral median nerve stimulation to evaluate sensorimotor interaction in CRPS (n=8 CRPS Type 1, 8 age and sex-matched healthy controls). They reported no difference in MEP suppression (patients,  $52.2 \pm 20.1\%$  vs controls,  $53.7 \pm 16.5\%$ ), thus demonstrating no evidence of abnormal interaction of sensory pathways with motor cortex in CRPS compared with healthy controls.

Van Velzen and colleagues (Van Velzen et al. 2015) used TMS to measure corticospinal excitability at rest and during motor imagery (explicit motor task) and motor observation (implicit motor task) in a study of 12 CRPS patients, 12 healthy controls & 6 patients with hand immobilisation due to scaphoid bone

fracture (SBF). Weightlifting of 2 distinct weights (heavy/1 kg and light weight/50 gram) was used for both motor imagery and motor observation tasks. Motor corticospinal excitation measured at rest and during implicit and explicit motor tasks was similar for CRPS patients and healthy controls. Patients with an immobilized hand showed an absence of motor cortical excitation of the corresponding hemisphere during motor imagery of tasks involving the immobilized hand, but not during motor observation. This study suggests that the nature of motor dysfunction in CRPS patients differs from that encountered in patients with functional paresis or under circumstances of limb immobilization.

### **MEG Studies**

Juottonen and colleagues (Juottonen et al. 2002) in the study previously discussed in the somatosensory section of this review also reported on the 20 Hz motor cortex rhythm and its reactivity to tactile stimuli. There was no difference between hemispheres or groups in the resting peak amplitude of the 20-Hz rhythm before stimulation or for the average rebound amplitude after stimulation. The 20-Hz rebound duration was significantly shorter in patients than healthy controls ( $P < .03$ ), although there was no difference between hemispheres.

Kirveskari and colleagues (Kirveskari et al. 2010) recorded whole scalp MEG during noxious laser stimulation of dorsum of hands (n=8 CRPS Type 1 patients and 8 age & sex-matched healthy controls) to study the reactivity of 20 Hz motor cortex rhythm. They defined reactivity as the sum of stimulus induced suppression of 20 Hz rhythm and subsequent rebound. The reactivity of the 20-Hz rhythm in the hemisphere contralateral to the painful hand in the patient group was significantly weaker than in control subjects. The reactivity correlated with the mean level of the spontaneous pain ( $r=0.64$ ,  $P= 0.04$ ). Suppression of the 20-Hz rhythm correlated with the grip strength in the painful hand ( $r= 0.66$ ,  $P= 0.04$ ). There were no differences between hemispheres either in the patient or healthy control groups.

## **PET Study**

Shiraishi and colleagues (Shiraishi et al. 2006) in the previously discussed study in this review reported decreased glucose metabolism in the contralateral primary cortex in CRPS patients compared to healthy controls.

## **Meta-analysis**

A systematic review and meta-analysis of studies investigating primary motor cortex function in adult CRPS by di Pietro and colleagues (Di Pietro et al. 2013a) found that the risk of bias across studies was high, mainly due to missing data and unblinded assessment of outcomes. Apart from a limited evidence for bilateral M1 disinhibition in CRPS of the upper limb, they could not draw any definitive conclusions regarding M1 spatial representation, reactivity, or glucose metabolism in CRPS.

**Table 4c:** Neuroimaging studies investigating motor cortex function in CRPS

Study/Modality	Stimulation/Paradigm	Outcomes	Condition & Comparison	Main Results
(Maihöfner et al. 2007) f-MRI	Finger-tapping task at 1-Hz frequency	Detection of activation within the motor system during motor performance	<b>CRPS</b> : n=12 (2/10); age= 41.2 ± 8.7; <b>Health Controls</b> : n=12 (2/10); age= 43.2 ± 8.7 ; <b>Unaffected Side</b>	Increased activation in M1 in both hemispheres affected side compared to the unaffected side
(Gieteling et al. 2008) f-MRI	Execution (painful) & imagined movement of wrist flexion/extension, both hands	Detection of activation in regions supporting primary motor function and higher-order motor control	<b>CRPS</b> : n=8 (1/7); age= 46.4 ±6.0; <b>Healthy Controls</b> : n=17 (2/15); age= 42.9 ± 9.2	Compared with controls, imaginary movement of the affected hand in patients showed reduced activation ipsilaterally in the premotor and adjacent prefrontal cortex & in the anterior part of the insula & the superior temporal gyrus
(Schwenkreis et al. 2003) TMS	TMS applied over the vertex. MEPs recorded with surface EMG from FDI; Use of a single- and paired pulse paradigm	MT, MEP, ICI, ICF	<b>CRPS</b> : n=25 (9/16); age= 29-80 (range); <b>Healthy Controls</b> : n=20 (10/10); age=20-79 (range) <b>Unaffected Side</b>	Significant reduction in intra-cortical inhibition on both sides of patients compared to healthy. No significant difference between the affected and unaffected side in the patient group
(Eisenberg et al. 2005) TMS	TMS applied to optimal scalp position M1. MEPs recorded with surface EMG from APB muscles of both wrists. Use of a single- and paired pulse paradigm	rMT; aMT; MEP/M-wave amplitude ratio; CMCT; ICF; SICI;LICl; I-wave facilitation	<b>CRPS</b> : n= 12 (3/9); age= 32±9; <b>Healthy Controls</b> : n= 14 (10/4); age= 30.9 ±12.7; <b>Unaffected Side</b>	Significant reduction in short intra-cortical inhibition & a significant increase of the I-wave facilitation in the hemisphere contralateral to the affected side in the upper-limb CRPS group. No significant difference in lower-limb CRPS.
(Krause et al. 2005) TMS	TMS applied to optimal scalp position M1. MEPs recorded with surface EMG from long extensor muscles of forearms	MEP; iCSP; cCSP (before and after a conditioning repetitive magnetic stimulation)	<b>CRPS</b> : n=12 (2/10); age= 48.2 ±15.6 <b>Healthy Controls</b> : n=10 (gender not reported); age=42.4 (only mean given) ; <b>Unaffected Side</b>	No difference in c-CSP and i-CSP between CRPS & healthy controls. c-MEP but not s-MEP smaller in both hemispheres in CRPS



<b>(Krause et al. 2006)</b>  <b>TMS</b>	TMS applied to hot spot on the motor cortex. MEPs recorded with EMG from long extensor muscles of both forearms	Spatial representation in M1 (i.e., size, volume); MEP; MT	<b>CRPS</b> : n=13 (4/9); age= 37 (18–72); <b>Healthy Controls</b> : n=10 (4/6); age= 38 (24–63); <b>Unaffected Side</b>	Significant interhemispheric asymmetry between the motor cortical representation of affected and unaffected sides. Cortical representation (size, Motor Evoked Potential, and calculated volumes) significantly larger for the unaffected hand than the affected hand
<b>(Turton et al. 2007)</b>  <b>TMS</b>	TMS applied to optimal scalp position M1. MEPs recorded with surface EMG from APB muscle on affected side in patients; matching side in controls. Recording EMG response to median nerve stimuli paired with subsequent TMS. Compared paired stimulation with TMS alone	Modulation of EMG responses to TMS induced by concomitant median nerve stimulation	<b>CRPS</b> : n=8 (1/7); age= 45 ± 13; <b>Healthy Controls</b> : n=8 (1/7); age= 45 ± 13	No difference in MEP suppression (no evidence of abnormal interaction of sensory pathways with motor cortex) in CRPS compared with healthy controls
<b>(Van Velzen et al. 2015)</b>  <b>TMS</b>	TMS applied to hot spot on the motor cortex. MEPs recorded from 1 <sup>st</sup> dorsal interosseous muscle of both hands. Motor threshold, Motor imagery & motor observation (weightlifting of heavy & light weights) measurements done.	MEP amplitudes	<b>CRPS</b> : n=12 (2/10); age=51± 9.5; <b>Healthy Controls</b> : n=12 (1/11); age: 52±13.0 <b>Scaphoid Bone Fracture patients</b> : n=6 (5/1); age: 24 (20.5–33.5)	Normal motor cortex activation at rest and similar motor cortex excitation in Motor Imagery and Motor Observation in compared to healthy controls. Patients with an immobilized hand due to scaphoid bone fracture showed an absence of motor cortical excitation of the corresponding hemisphere during motor imagery of tasks involving the immobilized hand, but not during motor observation.
<b>(Juottonen et al. 2002)</b>  <b>MEG</b>	Compressed-air-driven tactile stimulation to index finger of both hands.	Reactivity of the 20-Hz motor cortex rhythm (amplitude and duration of rebound) at rest and to tactile stimulation	<b>CRPS</b> :n=6 (0/6); age= 45.4 ± 8.4 ; <b>Healthy Controls</b> : n= 6 (0/6); age= 45.1,(34–55)(range); <b>Unaffected Side</b>	No difference between hemispheres or groups in the resting peak amplitude of the 20-Hz rhythm before stimulation or for the average rebound amplitude after stimulation. 20-Hz rebound duration was significantly shorter in patients than healthy controls, although there was no difference between hemispheres

<b>(Kirveskari et al. 2010)</b> <b>MEG</b>	Single-pulse painful laser stimulation to the dorsum of both hands	Reactivity of the 20-Hz motor cortex rhythm (amplitude and duration of rebound and suppression) at rest and to painful stimulation	<b>CRPS:</b> n=8 (0/8); age= 45.5 ± 10.5 ; <b>Healthy Controls :</b> n= 8 (0/8); age= 46.3 (28–52)(range) ; <b>Unaffected Side</b>	Reactivity of the 20-Hz rhythm in the hemisphere contralateral to the painful hand in the patient group was significantly weaker than in control subjects. No differences between hemispheres either in the patient or healthy control groups
<b>(Shiraishi et al. 2006)</b> <b>PET</b>	18F-fluorodeoxyglucose PET	Identification of active brain areas via glucose metabolism	<b>CRPS :</b> n=18(10/8); age=40.7 (21–59) <b>Healthy Controls:</b> n=13(11/2) ; age=38.7 (27–58)	Decreased glucose metabolism in the contralateral primary cortex in CRPS patients compared to healthy controls

**Abbreviations:** **EMG**, electromyography; **APB**, abductor pollicis brevis muscle; **rMT**, resting motor threshold; **aMT**, active motor threshold; **CMCT**, central motor conduction time; **ICI**, intracortical inhibition; **ICF**, intracortical facilitation; **SICI**, short-interval intracortical inhibition; **LICI**, long-interval intracortical inhibition; **f-MRI**, functional MRI; **FDI**, first dorsal interosseous muscle; **SAI**:short-latency afferent inhibition; **iCSP**, ipsilateral cortical silent period; **cCSP**, contralateral cortical silent period; **COG**, center of gravity; **MEP**, motor evoked potential.

NOTE. All data reported as mean and standard deviation unless otherwise stated. All stimulation paradigms were non-painful unless otherwise stated. Table adapted from (Di Pietro et al. 2013a).

### 4.4.3 Functional Connectivity

Default Mode Network (DMN) is a resting state brain network characterized by balanced positive and negative correlations between activities in the dorsal and ventral medial prefrontal cortex, the medial parietal cortex and the inferior parietal cortex. Bolwerk and colleagues (Bolwerk et al. 2013) found that functional DMN connectivity was significantly reduced in patients compared to controls in an f-MRI study (n=12 CRPS patients and 12 age & sex-matched healthy controls). They also reported that functional connectivity maps of sensorimotor cortex (S1/M1) and intra-parietal sulcus (IPS) in patients revealed greater and more diffuse connectivity with other brain regions, mainly with the cingulate cortex, precuneus, thalamus, and prefrontal cortex. In contrast, controls showed greater intraregional connectivity in S1/M1 and IPS. These spatial alterations in functional connectivity in CRPS also showed a trend towards correlation to the intensity of pain.

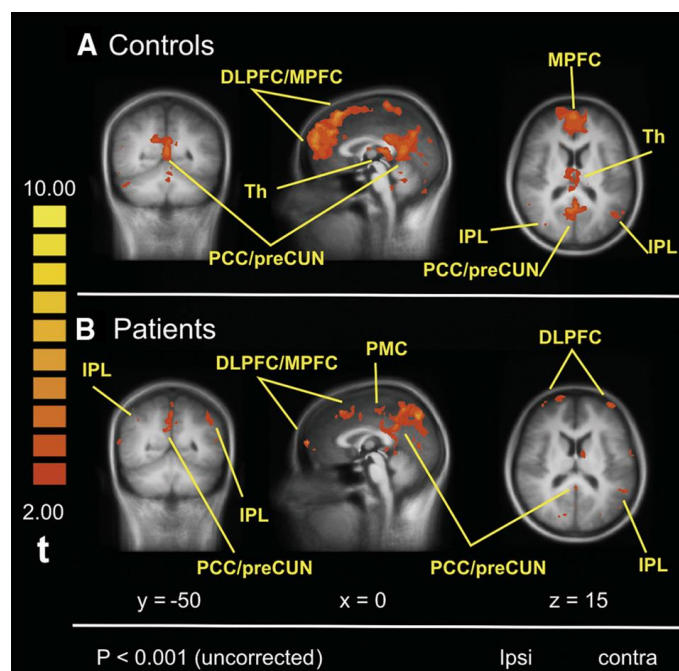


Fig 4.6: Functional connectivity map of DMN. (A) DMN Controls (B) DMN Patients

Abbreviations: DLPFC, Dorsolateral Prefrontal Cortex; MPFC, Medial Prefrontal Cortex; Th, Thalamus; IPL, Inferior Parietal Lobule; PCC/preCUN, Posterior Cingulate Cortex/pre Cuneate.

Kim and colleagues (Kim et al. 2017) in a f-MRI study of 25 patients with CRPS and 25 matched healthy controls, found that the functional connectivity of the anterior and posterior insular cortices with the postcentral and inferior frontal gyri, cingulate and dorsomedial prefrontal cortices was reduced in patients with CRPS. They also found that a reduced functional connectivity between the anterior insula and right postcentral gyrus was associated with increased perception of severe pain in patients with CRPS. This suggests that a disconnection between the somatosensory cortical function of perception and insular function of awareness or regulation may play a significant role in persistent pain in CRPS.

Kim and colleagues (Kim et al. 2018) investigated the role of the attention network and its dynamic interactions with other pain-related networks of the brain in a f-MRI study of 21 CRPS patients and 49 healthy controls. CRPS-related reduction in intra-network functional connectivity was found in the attention network. CRPS patients had greater inter-network connectivities between the attention and salience networks as compared with healthy controls. They also found that individuals within the CRPS group with high levels of pain catastrophizing showed greater inter-network connectivities between the attention and salience networks. These findings suggest that altered connectivities may be potentially associated with the maladaptive pain coping in CRPS patients.

#### **4.4.4 Summary of appraised literature and justification for undertaking high density EEG study**

Cortical reorganisation in both somatosensory and motor cortices in CRPS has been investigated using various neuroimaging techniques including functional MRI, MEG, PET and high density EEG. Most compelling evidence is for reduction of S1 spatial representation on the affected hand compared to the unaffected hand in CRPS as shown by the findings of a meta-analysis (Di Pietro et al. 2013b) of pooled data from four MEG studies (Juottonen et al. 2002; Maihöfner et al. 2003; Sinis et al. 2007; Vartiainen et al. 2008) and one EEG study (Pleger et al. 2004); Two studies (Pleger et al. 2004; Vartiainen et

al. 2008) reporting on healthy controls indicated that the representation size of the affected hand in CRPS patients was smaller than that of healthy controls. However, a more recent study (Di Pietro et al. 2015) which addressed some of the methodological limitations of previous studies such as unblinded data analysis and failure to report on healthy controls reported that CRPS seems to be associated with an enlarged representation of the healthy hand, not a smaller representation of the affected hand unlike previous studies.

Studies also suggest that there was no difference in the activation strength in S1 comparing hemispheres in CRPS patients or comparing CRPS patients with non-CRPS controls. There were also no significant differences in S1 peak latency after stimulation of CRPS-affected and unaffected hands or comparing CRPS patients with non-CRPS controls. There is some evidence for bilateral M1 disinhibition in CRPS of the upper limb but no other definitive conclusions can be drawn regarding the motor cortex changes.

Many studies have overall high risk of bias introduced by non-consecutive sampling, unblinded assessment of outcomes and unclear or selective reporting of outcomes (Di Pietro et al. 2013b; Di Pietro et al. 2013a). There is clearly a need for further well designed studies of cortical reorganisation in CRPS. Previously there are no published studies of CRPS specifically investigating neuro-imaging markers of cognitive dysfunction in CRPS. Hence, we decided to undertake this study (described in detail in chapter 5 of this thesis) to investigate the cortical changes in CRPS and also to explore whether these changes correlate with behavioural variables such as finger misperception.

# **Chapter 5: Cortical reorganisation in CRPS and digit misperception- a high density EEG Study**

## **5.1 Introduction**

We used high density EEG to investigate the cortical changes in CRPS patients by studying the somatosensory ERPs (Event Related Potentials) elicited on painless finger stimulation. We also examined whether the EEG parameters correlated with the behavioural variables such as finger misperception and pain severity in CRPS.

High-density EEG provides excellent temporal resolution of the order of a few milliseconds and hence provides an excellent tool for studying the functional changes within the somatosensory cortex (Luck 2005). Cortical reorganization can manifest both spatially and temporally. While f-MRI would be a preferred tool to assess spatial reorganization of S1 given the better spatial resolution, we were interested in temporal aspects of somatosensory processing (latency and/or amplitude of early responses). It is also non-invasive, well-tolerated by patients and relatively inexpensive (Luck 2005). Hence we decided to use this rather than other modalities such as f-MRI (expensive and poor temporal resolution) or PET scan (risk of radiation exposure) in our exploratory study.

## **5.2 Central hypothesis and objectives**

The central hypothesis of the study was that the “cortical reorganisation” as defined by EEG parameters will correlate significantly with finger misperception in CRPS. The primary objective was to determine whether cortical reorganisation in CRPS correlates with finger misperception. The secondary objective was to determine whether cortical reorganisation in CRPS correlates with pain severity.

The central hypothesis was developed based on the results from previous research studies which suggest that cognitive dysfunctions including finger misperception in CRPS may arise from cortical reorganisation. It would then be reasonable to hypothesise that the EEG parameters of cortical reorganisation would correlate with finger misperception. We were also interested in exploring the complex link of pain severity with markers of cortical re-organisation.

## **5.3 Methods**

### **5.3.1 Study design**

This was an experimental case-control study.

### **5.3.2 Study setting**

The study was done in the EEG lab in Herschel Smith Building for Brain and Mind Sciences, University of Cambridge, UK between March 2013 and July 2013.

### **5.3.3 Inclusion criteria**

Participant is willing and able to give informed consent for participation in the study; Male or Female, aged 18-80 years; Right handed; Able to communicate fluently in English; Healthy controls or Patients diagnosed with unilateral upper or lower limb Complex Regional Pain Syndrome according to modified Budapest Research Criteria (Harden et al. 2007) given below:

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in **all four** categories in Table 5A.

**Table 5A: Symptom categories in CRPS**

<b>Sensory</b>	Reports of hyperesthesia and/or allodynia
<b>Vasomotor</b>	Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
<b>Sudomotor/ Oedema</b>	Reports of oedema and/or sweating changes and/or sweating asymmetry
<b>Motor/Trophic</b>	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 1 sign at time of evaluation in  $\geq 2$  categories in Table 5B

**Table 5B: Signs categories in CRPS**

<b>Sensory</b>	Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
<b>Vasomotor</b>	Evidence of temperature asymmetry ( $>1^{\circ}\text{C}$ ) and/or skin colour changes and/or asymmetry
<b>Sudomotor/ Oedema</b>	Evidence of oedema and/or sweating changes and/or sweating asymmetry
<b>Motor/Trophic</b>	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

#### **5.3.4 Exclusion Criteria**

The participant may NOT enter the study if ANY of the following apply:  
Previous or current diagnosis of peripheral neuropathy, stroke, Transient Ischemic Attack, multiple sclerosis, malignancy or seizure disorder; Unable to communicate fluently in English; Unable to or unwilling to give informed consent.



### **5.3.5 Sample Size**

At the stage of study design and conduct, tools were not available for powering EEG studies for group contrasts using contemporary statistical methods for EEG as used in this report. Reporting of sample size calculations in the EEG/ERP literature is estimated to be extremely uncommon for this and a number of other likely reasons (Larson & Carbine 2017).

The aim was therefore to recruit as many as possible/practical with the available resources bearing in mind that many published EEG studies of CRPS report on around 10 subjects. Our aim was to recruit 20 patients, half of whom we expected (based on past literature (Förderreuther et al. 2004)) to show signs of digit misperception, and an equal number of healthy control participants.

### **5.3.6 Study Procedure**

Potential participants were identified from the CRPS UK registry and were approached for taking part in the study. The total number of potentially eligible CRPS patients contacted (who lived locally) was 30; 25 of these were confirmed eligible, of which 16 patients were able to be recruited before the recruitment period of the study ended. Data from 3 patients were excluded from the study analysis: one did not complete the study, and in the other two patients, data quality was extremely poor due to extreme movement artefact that could not be corrected or removed.

Also recruited were 13 age-and-sex frequency-matched healthy (pain-free) controls, recruited by advertising the study using posters in Addenbrooke's hospital.

Detailed written information leaflets for participants were provided in advance. Informed consent was taken and all the participants signed a consent form prior to taking part. It was stressed in the information sheet and at the time of taking consent that should a patient wish to withdraw their informed consent at any stage this can be done without being detrimental to their clinical care in anyway.

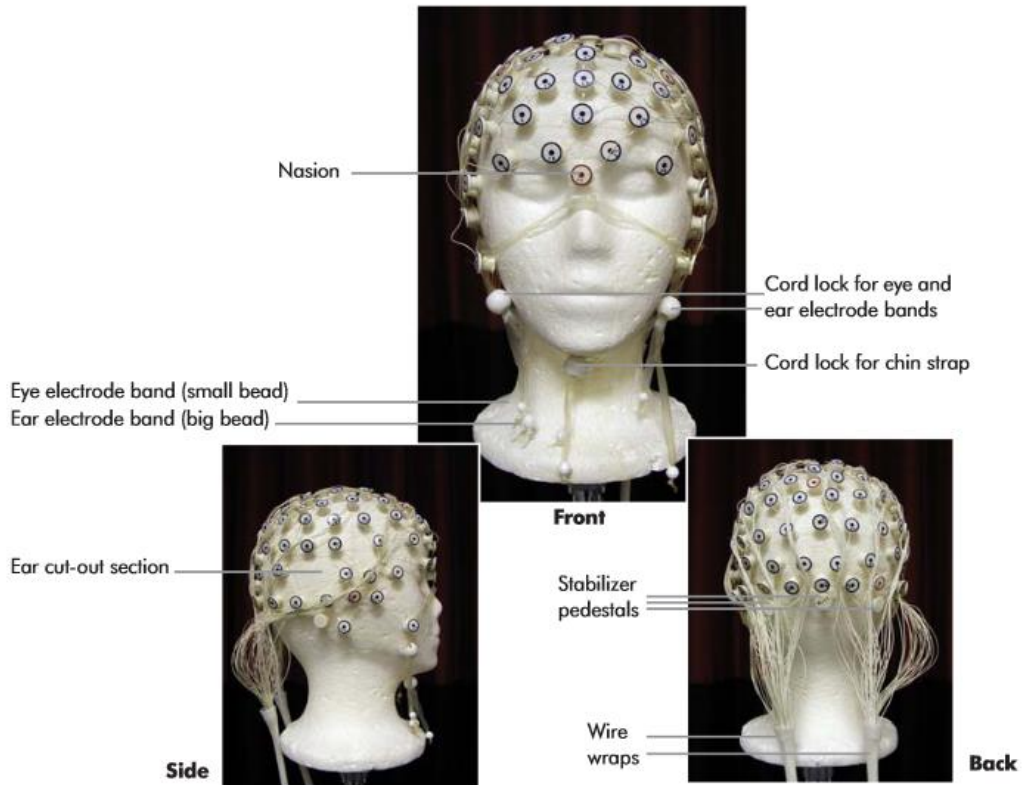
The participants were required to refrain from consuming alcohol or smoking tobacco for 24 hours and caffeine for 12 hours prior to the study. During the study visit, CRPS subjects (but not healthy controls) completed five questionnaires assessing pain severity, physical function, depersonalisation and emotional state: Brief Pain Inventory (Cleeland & Ryan 1994), Upper Extremity Functional Index (Stratford et al. 2001), Lower Extremity Functional Index (Binkley et al. 1999), Neglect-like Symptom Questionnaire (Galer & Jensen 1999), Hospital Anxiety and Depression Score (Snaith 2003).

Standardised clinical tests for finger perception, astereognosis, hand laterality and body scheme were then administered on the same day as the EEG testing. These were the same tests as described in detail for the study 'Novel clinical signs and their clinical utility in CRPS- an observational cohort study' (Kuttikat et al. 2017). They then underwent EEG testing according to the standardised protocol given below.

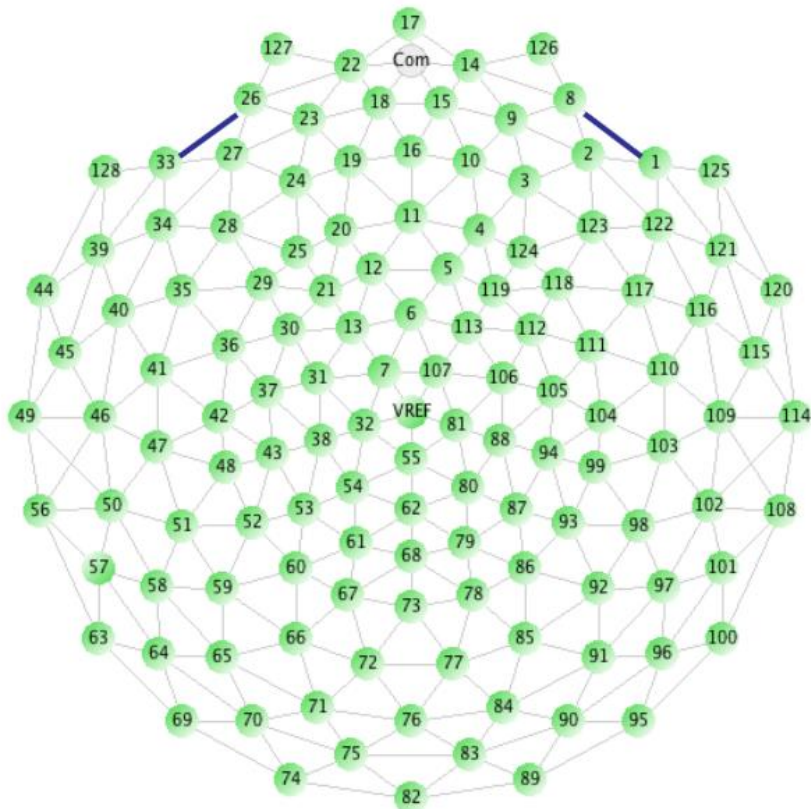
### **5.3.7 EEG Protocol**

Participants were sat in a comfortable chair in an acoustically and electrically shielded room. The room was air conditioned and temperature of the room kept constant within the limits of 18 - 22°C. Adjacent to the testing room was a connected investigator room, where we observed and listened to the participants using a headphone and video monitoring system.

Participants were fitted with the EGI electrolyte cap with 128 channels (see figures 5.1 & 5.2). The correct size of the cap for the individual participant was determined by measuring the head circumference. The cap was soaked in a solution of water and potassium hydrochloride for 10 minutes before fitting on the participant. The salt-water solution was pipetted into sponges of electrodes necessary to achieve good impedances (below 100 kΩ).



**Figure 5.1:** EGI 128 channel hydrocel sensor net



**Figure 5.2:** Sensor lay out for 128 channels

We instructed the participants to keep their eyes closed and head still as much as possible during the testing to minimise eye blink and muscle movement artifacts. We also provided the participants with soft ear plugs to block out any extraneous auditory input so that they can focus on the tactile stimuli.

Soft touch stimuli were delivered to the fingertips by using custom made handboxes (one for each hand) which were calibrated to deliver non-painful stimuli with the same force (See Figures 5.3 & 5.4 below). The participants were advised to report immediately if the sensation was uncomfortable or painful. The fingertips were also checked after each session to check for any redness of the skin.



**Figure 5.3:** Handbox used to deliver soft touch stimuli



**Figure 5.4:** A healthy control in the experimental room set-up

We carried out two experiments as described below.

### **5.3.8 Experiment 1**

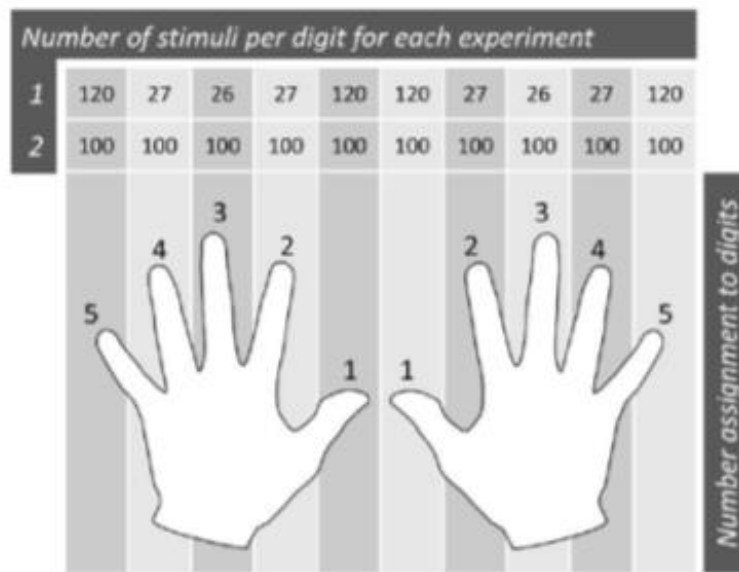
The main aim of Experiment 1 was to record (i) behavioural accuracy and response time for identification of each digit stimulated, (ii) SEPs related to task-relevant and spatially probabilistic tactile processing.

We instructed the participant to place one hand on the handbox. The fingers were numbered consecutively from one to five starting with thumb (i.e.; thumb=1, index finger=2, middle finger =3, ring finger=4 and little finger=5).

The participants had to respond to a stimulus by saying out loud the number corresponding to the finger which received the stimulus.

Each trial consisted of the following: The subject receives a stimulus in one finger and responds which finger is touched by saying out loud the number corresponding to that finger. We record the answer manually by typing the number on the computer. This triggered the next stimulus. We used a microphone attached to the EMG leads on the polygraph input box to capture the participant's response. The reaction time was measured from the delivery of the stimulus to the start of the voice deflection on the EMG lead recording. We did 80 trials per block and four blocks per hand. We tested only one hand in a block and alternated the hands after each block. We set a maximum time lock of three seconds per trial. The 80 trials were split into 30 each for thumb (Digit 1) and little finger (Digit 5) and the remaining 20 split between the remaining three fingers (Figure 5.5). The randomisation was done using MATLAB code which mixed up the order of the trials before presentation without changing the proportion stimulating each finger. The trials were weighted towards D1 & D5 and the 3 middle digits on each hand were stimulated rarely compared with the outer digits to assess the effects of spatial probability. This resulted in a significantly higher probability of digits 1 and 5 (37.5% of the time for each, or 75% in total) being stimulated compared to digits 2, 3 and 4 (8.3% each, or 25% in total). Over the 4 blocks, 80 trials were presented for the total of the middle three digits (D2-D4) and 120 for each of the little finger and thumb; this provided more than enough data for

robust measurement of the P300 potential, thought to require a minimum of 36 clean trials (Duncan et al. 2009).



**Figure 5.5** Number of stimuli delivered to each digit (randomised) and the number assignment to each digit that the subject used to respond as to which digit was stimulated.

The clinical finger misperception test as used in the first study - 'Novel signs in CRPS' - was designed specifically as an easy and practical test to do in the clinic setting. The second study utilised a more sophisticated method and a handbox to deliver exact same stimuli each time at a pre-defined frequency. Both tests are painless and can be used to elicit the finger misperception. The second method using handbox delivers precise calibrated stimuli and this is essential in generating robust somatosensory Event Related Potentials. The main limitation of this method is that this requires additional equipment and may not be practical in a clinic setting.

### 5.3.9 Experiment 2

The main aim of the Experiment 2 was to study group differences in sensory Event Related Potential (ERP) in the absence of cognitive task demands. We instructed the participants to sit relaxed with their eyes closed and head still. We delivered random stimuli to all fingers, one finger at a time, at a predefined frequency of 1 stimulus per second. The stimulus duration was 0.05 seconds; interstimulus interval was 0.95 seconds with a 10 seconds

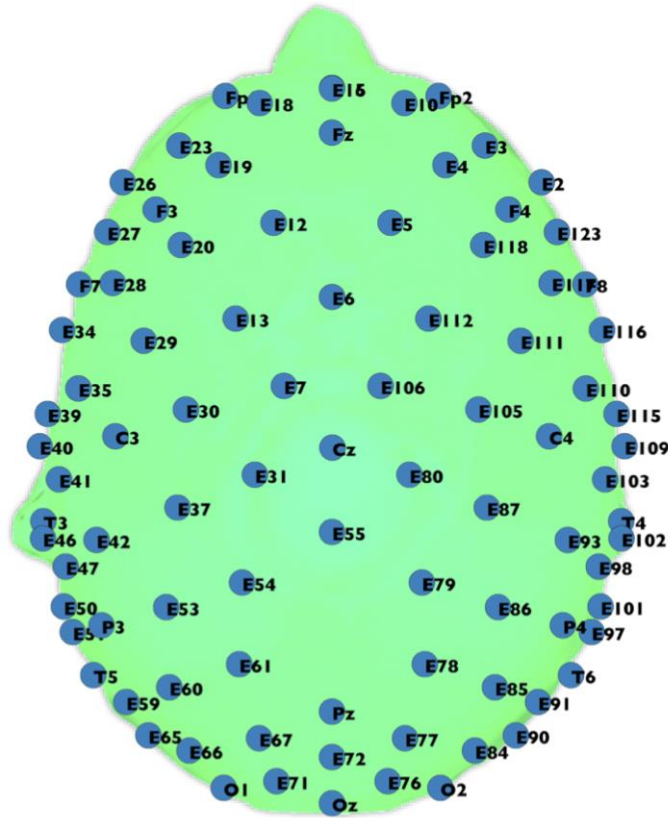
break after every 50 stimuli. In total 100 stimuli were delivered per finger of each hand generating 1000 trials in total in 20 minutes. We tested one hand at a time for five minutes and alternated the hand after every five minutes so that each hand would get a break improving participant comfort. Unlike in Experiment 1; they did not have to respond to the stimuli.

### **5.3.10 EEG data acquisition and pre-processing**

During the experiment, 128-channel high-density EEG data in microvolts ( $\mu\text{V}$ ), sampled at 250 Hz and referenced to the vertex, were collected using the Net Amps 300 amplifier (Electrical Geodesics Inc., Oregon, USA).

Due to the use of naturalistic touch stimuli with relatively long stimulus durations (compared to electrical stimuli, for example), early components (e.g.  $<100\text{ms}$ ) were expected to be difficult to detect, and as our main interest was long-latency components, the sampling rate was set at 250 Hz.

Data from 92 channels over the scalp surface (at locations shown in figure 5.6 below) were retained for further analysis. Channels on the neck, cheeks and forehead, which mostly contributed more movement related noise than signal in patients, were excluded. Files were then exported to MATLAB for pre-processing.



**Figure 5.6:** *Locations of 92 channels selected for analysis*

EEG data for the experiments were high pass filtered at 0.5 Hz, low pass filtered at 30Hz and segmented into epochs with the criteria of taking the 200 ms preceding the stimulus and 800 ms after the stimulus. Data containing excessive eye movement or muscular artefact were rejected by a quasi-automated procedure: noisy channels and epochs were identified by calculating their normalised variance and then manually rejected or retained by visual confirmation. Independent component analysis (ICA) based on the Infomax ICA algorithm (Bell & Sejnowski 1995) was run on the clean data excluding bad channels using ‘runica’ programme on MATLAB. ICA components were visually inspected and bad components rejected to further prune the dataset. Bad channels previously identified by visual inspection were then rejected and replaced by channels interpolated using spherical spline interpolation of the voltages from the neighbouring electrodes. Data was then re-referenced to the average of 92 channels. These processing steps were implemented using custom MATLAB scripts based on EEGLAB (Delorme & Makeig 2004).



### 5.3.11 Statistical Methods

We analysed behavioural data using IBM SPSS (Statistical Package for Social Sciences) software version 21 (IBM 2012). Paired and independent samples t-tests were used for comparisons of reaction times in healthy and patient groups. Data for accuracy and response times were not normally distributed, especially in the CRPS group. Hence, non-parametric tests were performed to investigate overall group differences averaged over all conditions (Mann-Whitney U test), and to investigate within-subject condition effects in each group separately (Wilcoxon signed rank tests). Spearman's rho (non-parametric) was used for correlation analyses.

We used FieldTrip, an open-source software developed at the Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, The Netherlands (Oostenveld et al. 2011) for analysis of EEG data.

FieldTrip is implemented as a MATLAB toolbox and has algorithms to perform time-frequency analysis, source reconstruction, connectivity analysis, and non-parametric statistical permutation tests at the channel and source level.

Two major approaches to study cortical reorganisation in CRPS are (a) source reconstruction, and (b) event-related potential analysis. Regarding (a), EEG is inferior compared to other methods (MEG, TMS, fMRI), plus we did not have MRI images of patients that would facilitate source reconstruction. Hence, we decided to focus on (b), which could be divided into temporal-spatial ERP (classical ERP studies) and temporal ERP, which is GFP. We initially aimed to use temporal-spatial ERP, but due to heterogeneity of patients, spatial distributions of individual ERP were rather different among patients, making the dataset set very noisy. Hence, we opted for GFP, which reduces space-time dimensions to a time vector. The strength of this approach is that it is relatively easy to elicit in an experimental setting, and hence provides a robust marker. Weakness is that exact identification of the generating sources in the brain is difficult, due to the limitations of source reconstruction.

Brain electric field data (EEG and ERP) recorded simultaneously from multiple channels can be viewed as a series of maps of the momentary spatial distributions of electric potential. Global Field Power is a measure of map strength computed as standard deviation of the momentary potential values (Lehmann & Skrandies 1980).

Epochs from an experimental condition and its own baseline period, or pairs of conditions of interest, were compared using a non-parametric t-test based on that employed in the FieldTrip toolbox. This test identified temporal clusters of statistically significant differences between the Global Field Power (GFP) of the ERPs in the two conditions using a Monte Carlo procedure for estimating p-values.

To elaborate, we first calculated ERPs by separately averaging epochs (for single-subject analysis) or subject-wise averages (for group analysis) included in each condition. The difference between the GFP time courses of the two ERPs was then tested for statistical significance using a randomisation testing procedure. To do this, the original epochs/subject-wise averages were mixed together and separated into two new sets that contained random samples from the original conditions. These sets were again separately averaged to calculate new ERPs and GFP difference time course. This randomised resampling step was repeated 1000 times, to generate as many GFP difference time courses. The original GFP difference at each time point within a time window of interest was then compared to the maximum GFP differences obtained within that time window over the randomisation iterations, to calculate a time point-wise t-value and p-value. Significant time points with p-values  $<0.05$  were clustered together based on temporal contiguity, and the cluster with the largest sum of constituent t-values, the cluster-level t-value, was retained. This procedure was then repeated for the GFP differences generated in every randomisation iteration, to identify the largest such cluster generated in each iteration. Finally, the cluster-level t-value generated with the original GFP difference was compared to the distribution of cluster-level t-values generated by the randomisation iterations, to calculate a non-parametric p-value. This represented the Monte Carlo

estimate of the level of statistical significance of the cluster identified in the original GFP.

As shown by (Maris & Oostenveld 2007), this comparison of the original GFP difference at each time point to the maximal GFP difference obtained in each iteration, followed by temporal clustering of time points, effectively and sensitively controls for family wise error (Type 1 error) and multiple comparisons.

## **5.4 Results**

### **5.4.1 Results-Demographics**

There were 13 patients with unilateral upper or lower limb CRPS of which 11 were females and two males. 9 had left sided CRPS and 4 had right sided CRPS. 4 had left arm affected, 2 had right arm affected, 5 had left leg affected and 2 had right leg affected. There were 13 age and sex matched healthy controls. All subjects (patients & healthy) were right handed. The baseline details of the subjects are documented below in tables 5C and 5D.

**Table 5C:** Summary of baseline characteristics of study subjects

Characteristics	CRPS (n=13)	Healthy (n=13)
<b>Age in years Mean (range)</b>	46.8 (30-63)	45.0 (28-63)
<b>Female sex (%)</b>	11 (84.6)	11 (84.6)
<b>Right handed (%)</b>	13 (100)	13 (100)
<b>Dyslexia (%)</b>	0	0
<b>Disease duration in years Mean (range)</b>	5.3 (1-14)	Not applicable
<b>Past Medical History</b>	Depression/Anxiety 7 (53.8) <b>Other psychiatric</b> 0 IBS 0 <b>Asthma/COPD</b> 6 (46.2) Migraines 2 (15.8) <b>Other medical</b> 8 (61.5)	None
<b>Medications at the time of study (%)</b>	Paracetamol 10 (76.9) <b>NSAIDs</b> 4 (30.8) Weak opioids 5 (38.5) <b>Strong opioids</b> 2 (15.4) Anti-depressants 7 (53.8) <b>Anti-convulsants</b> 6 (46.2) Other medications 6 (46.2)	None

**Table 5D: Details of patient characteristics**

Patient Identifier	Age	Gender	Area affected	Disease duration (years)	Past Medical History	Medications
P1	34	F	Right leg	1	Raynaud's phenomenon	Amitriptyline, Pregabalin, Paracetamol, Tramadol
P2	59	F	Left leg	8	Osteoarthritis Migraine, Cervical spondylosis Uterine fibroids	Chondroitin, Glucosamine
P3	63	F	Left arm	8	none	Pregabalin, Paracetamol Tramadol, Lidocaine patch
P4	42	F	Right arm	5	Rotator cuff Tendinopathy	Ibuprofen, Paracetamol , Tramadol
P5	53	F	Left leg	14	Asthma, Hypertension, Vitamin D deficiency, Depression/Anxiety	Tiotropium, Amitriptyline Duloxetine, Ramipril, Bendroflumethiazide, Paracetamol, Simvastatin Tramadol, Adcal D3, QVAR GTN spray, Omeprazole
P6	20	F	Left leg	5	Depression	Amitriptyline, Oxynorm, Paracetamol, Fluoxetine, Carbamazepine, Oxycontin
P7	57	F	Right arm	3	Migraine, Spondylosis cervical Depression, Asthma, Anxiety Hypertension	Amitriptyline, Pregabalin MST continus, Ramipril, Lactulose, Mebeverine Diazepam, Fluoxetine Furosemide, Naratriptan Symbicort
P8	52	F	Right leg	4	Adhesive capsulitis, Asthma, Anxiety	Naproxen , Paracetamol
P9	50	F	Left arm	5	Asthma, Anxiety/Depression	Beclomethasone Salbutamol, Nortriptyline Paracetamol, Tramadol Fluoxetine
P10	59	M	Left leg	5	Anxiety	Amitriptyline
P11	29	M	Left arm	3	Adhesive capsulitis	Amitriptyline, Ibuprofen, Gabapentin, Adcal D3
P12	34	F	Left leg	3	Joint Hypermobility Raynaud's, Asthma, Anxiety, Depression	Symbicort, Naproxen Pregabalin, Paracetamol Adcal D3, Sertraline, Zopiclone
P13	43	F	Left hand	5	Asthma	Beclomethasone, Buprenorphine patch Gabapentin, Paracetamol, Imipramine, Omeprazole

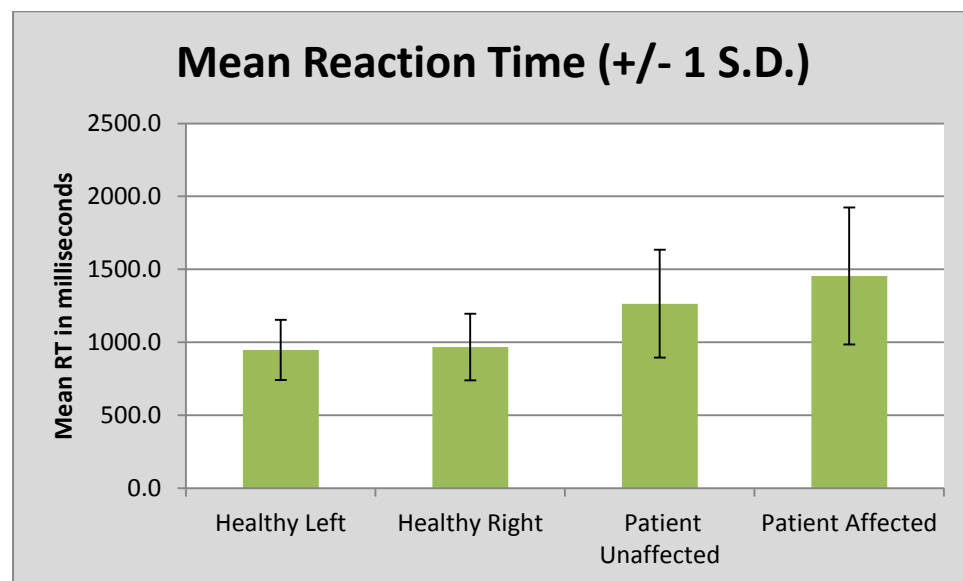
## 5.4.2 Results-Behavioural data

### Reaction Times

The average reaction times (in milliseconds) of the healthy controls (left and right hands) and patients (affected and unaffected hands) are tabulated below in table 5E.

**Table 5E:** Average reaction times (milliseconds) of individual study subjects (all fingers combined)

	Healthy Left Hand	Healthy Right Hand	Patient Unaffected Hand	Patient Affected Hand
1	746.6	716.2	1871.7	2014.3
2	963.6	1013.7	955.5	973.4
3	1401.6	1432.3	995.6	1097.6
4	875.9	862.0	1285.5	2193.3
5	953.4	1024.3	993.5	931.2
6	893.4	912.1	1236.7	1631.2
7	1096.9	1216.1	1473.6	1627.8
8	927.5	895.8	1157.4	1271.0
9	963.1	1056.7	1110.3	1331.5
10	520.2	520.4	1519.7	1866.1
11	941.5	957.1	1086.8	1262.0
12	867.5	827.9	732.8	717.0
13	1160.6	1146.8	2016.3	1992.0



**Figure 5.7:** Graphical representation of mean reaction time (RT) of different study groups with standard deviation error bars.

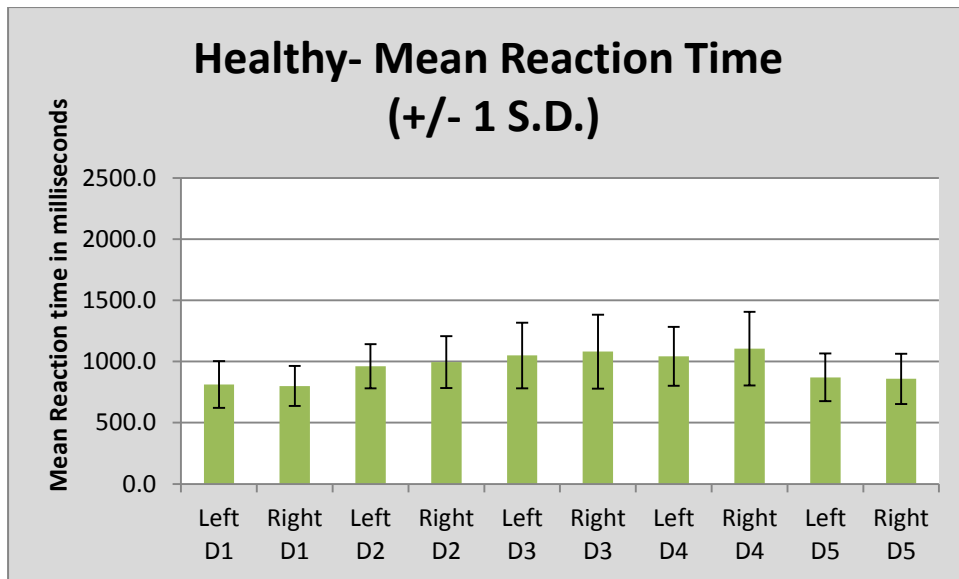
**Table 5F:** Average reaction time (milliseconds) of individual fingers in healthy subjects

	Left D1	Right D1	Left D2	Right D2	Left D3	Right D3	Left D4	Right D4	Left D5	Right D5
H1	637.8	612.9	795.5	749.1	782.7	728.2	783.8	786.9	732.9	703.8
H2	815.2	798.0	984.2	1054.8	1066.3	1104.7	1065.9	1201.2	886.4	909.9
H3	1209.1	1058.2	1227.6	1370.0	1728.3	1758.1	1562.3	1745.7	1280.5	1229.7
H4	774.6	806.8	871.1	954.2	995.3	907.2	904.3	845.2	834.1	796.5
H5	846.7	839.9	948.7	1053.3	1056.2	1133.1	1054.4	1194.3	860.9	900.7
H6	724.9	728.8	902.1	969.3	986.7	946.8	1061.1	1112.4	792.1	803.1
H7	1078.8	1067.8	1054.9	1131.7	1069.1	1343.7	1163.7	1358.4	1118.3	1178.7
H8	737.2	713.8	1012.6	976.3	1028.7	983.3	1037.7	1032.3	821.4	773.6
H9	787.9	779.0	1032.2	1122.9	1083.2	1306.3	1033.1	1214.5	879.2	861.1
H10	515.3	547.3	525.0	526.4	514.3	512.0	524.0	504.0	522.5	512.2
H11	795.5	788.9	975.5	994.1	1073.4	1086.9	1052.7	1098.4	810.3	817.3
H12	622.4	645.3	942.1	835.6	1038.4	1056.0	1032.2	987.9	702.3	614.9
H13	1010.0	1010.8	1231.5	1207.8	1215.1	1180.8	1270.4	1278.5	1075.8	1056.0

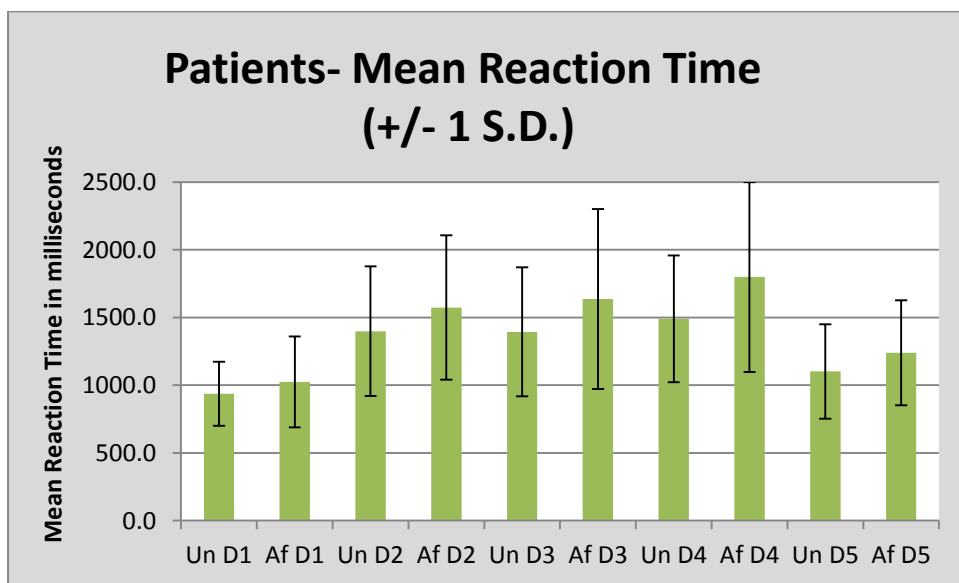
**Table 5G:** Average reaction time (milliseconds) of individual fingers in patients

	Un D1	Af D1	Un D2	Af D2	Un D3	Af D3	Un D4	Af D4	Un D5	Af D5
P1	1200.2	1180.2	1931.4	2262.0	2611.2	2733.1	2218.0	2551.1	1397.9	1345.3
P2	638.4	718.8	1232.7	1138.1	966.2	955.1	1178.3	1216.3	761.9	838.8
P3	896.9	863.6	963.5	1378.5	1082.3	1048.4	1113.2	1089.3	921.9	1108.1
P4	1002.6	1407.4	1415.7	2450.4	1362.1	2913.6	1459.4	2698.2	1187.9	1496.8
P5	810.0	773.6	976.3	850.0	1236.5	1138.8	1074.6	991.5	870.2	901.9
P6	776.2	934.7	1159.0	1878.5	1481.0	1942.3	1630.9	2060.3	1136.4	1340.1
P7	961.5	899.2	2118.3	1761.2	1457.2	1643.6	1743.3	2752.0	1087.9	1082.9
P8	954.5	931.1	1298.4	1527.5	1165.4	1251.4	1310.9	1486.3	1057.9	1158.7
P9	1004.5	1086.0	1258.0	1503.8	1166.8	1432.9	1167.3	1431.7	955.1	1203.3
P10	1002.9	1101.5	1622.3	1656.3	1614.0	1859.8	2240.0	2493.0	1119.2	2220.1
P11	835.3	930.3	1097.6	1183.9	1132.9	1238.4	1229.7	1532.3	1138.6	1425.2
P12	590.7	591.0	755.0	694.0	829.2	886.5	860.4	789.8	628.8	623.8
P13	1509.2	1894.0	2357.1	2170.9	2014.1	2233.6	2144.0	2294.0	2057.3	1367.3

D1-D5 = Thumb to little finger consecutively; Un =unaffected, Af =affected



**Figure 5.8:** Graphical representation of mean reaction time (RT) of individual fingers (D1 to D5, Thumb to Little finger) in healthy subjects with standard deviation error bars.



**Figure 5.9:** Graphical representation of mean reaction time (RT) of individual fingers (D1 to D5, Thumb to Little finger) in patients with standard deviation error bars. Un=unaffected, Af=affected



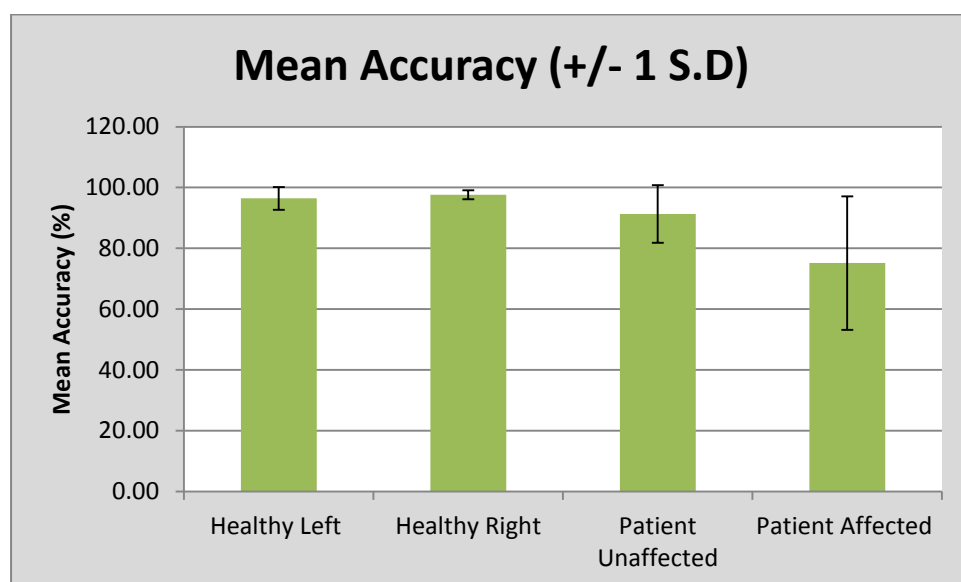
1. On average, healthy controls had similar reaction times in the left hand ( $M = 947.1$  ms,  $SE = 57.31$ ) and in the right hand ( $M = 967.8$  ms,  $SE = 63.31$ ,  $t(12) = -1.49$ , two-tailed  $p = 0.18$ ).
2. Within the same hand in healthy controls, on average, the reaction times were significantly longer in the little finger compared to the thumb in both left and right sides.  
 Left little finger ( $M=870.5$  ms,  $SE=53.94$ ) and left thumb ( $M=811.9$  ms,  $SE=53.05$ ,  $t(12) = 7.02$ , two-tailed  $p = 0.00001$ ).  
 Right little finger ( $M= 858.3$  ms,  $SE= 56.77$ ) and right thumb ( $M= 799.8$ ms,  $SE= 45.32$ ,  $t(12) = 3.53$ , two-tailed  $p = 0.004$ ).
3. On average, patients had significantly longer reaction times in the affected hand ( $M = 1454.5$  ms,  $SE = 130.12$ ), than in the unaffected hand ( $M = 1264.3$  ms,  $SE = 102.37$ ,  $t(12) = 2.68$ , two-tailed  $p = 0.02$ ).
4. There was a statistically significant difference (longer) in the average reaction times of patients' affected hand ( $M = 1454.5$  ms,  $SE = 130.12$ ) than to the healthy left hand ( $M = 947.1$  ms,  $SE = 57.31$ ,  $t = 3.12$ , two-tailed  $p = 0.009$ ).
5. There was a statistically significant difference (longer) in the average reaction times of patients' affected hand ( $M = 1454.5$  ms,  $SE = 130.12$ ) than to the healthy right hand ( $M = 967.8$  ms,  $SE = 63.31$ ,  $t = 2.97$ , two-tailed  $p = 0.012$ ).
6. There was a statistically significant difference (longer) in the average reaction times of patients' unaffected hand ( $M = 1264.3$  ms,  $SE = 102.37$ ) than to the healthy left hand ( $M = 947.1$  ms,  $SE = 57.31$ ,  $t = 2.32$ , two-tailed  $p = 0.038$ ).
7. There was a statistically significant difference (longer) in the average reaction times of patients' unaffected hand ( $M = 1264.3$  ms,  $SE = 102.37$ ) than to the healthy right hand ( $M = 967.8$  ms,  $SE = 63.31$ ,  $t = 2.16$ , two-tailed  $p = 0.049$ ).

## Accuracy

The average accuracy (in percentage) of patients (affected and unaffected hands) and the healthy controls (left and right hands) are tabulated below in Table 5H.

**Table 5H:** Average accuracy (%) of individual study subjects (all fingers combined)

	Healthy Left Hand	Healthy Right hand	Patient Unaffected hand	Patient Affected Hand
1	99.83	98.79	95.74	88.86
2	96.33	98.95	91.21	73.69
3	97.31	97.58	99.33	95.79
4	96.24	98.06	96.41	83.93
5	95.55	94.98	66.64	47.11
6	98.90	95.66	99.00	91.66
7	97.40	97.26	81.48	60.86
8	97.47	96.99	97.17	73.61
9	97.20	98.08	96.50	68.37
10	98.88	99.83	94.41	91.04
11	85.11	97.98	83.77	51.20
12	94.43	96.00	98.62	97.83
13	99.33	99.50	86.15	32.90



**Figure 5.10:** Graphical representation of mean accuracy (%) of different study groups with standard deviation error bars.

**Table 5I:** Average accuracy (%) of individual fingers in healthy controls

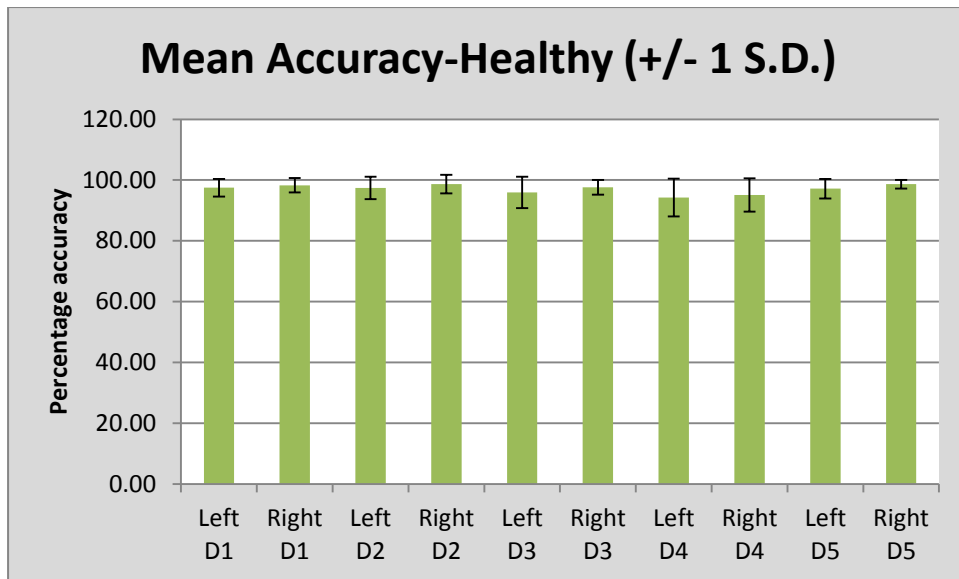
	Left D1	Right D1	Left D2	Right D2	Left D3	Right D3	Left D4	Right D4	Left D5	Right D5
H1	100.00	100.00	100.00	100.00	100.00	100.00	100.00	96.43	99.17	97.50
H2	98.33	98.33	100.00	100.00	91.67	100.00	95.83	96.43	95.83	100.00
H3	96.67	100.00	100.00	100.00	96.43	96.43	96.77	92.31	96.67	99.17
H4	95.00	97.50	96.55	96.67	96.15	100.00	96.00	96.15	97.50	100.00
H5	96.67	97.50	93.94	89.29	100.00	96.43	88.00	91.67	99.17	100.00
H6	98.33	91.67	100.00	100.00	100.00	96.15	96.15	95.45	100.00	95.00
H7	98.33	95.83	100.00	100.00	94.74	96.67	96.43	95.45	97.50	98.33
H8	99.17	99.17	96.88	100.00	91.30	94.29	100.00	92.31	100.00	99.17
H9	97.50	98.33	95.83	100.00	100.00	93.75	96.00	100.00	96.67	98.33
H10	100.00	100.00	100.00	100.00	100.00	100.00	95.24	100.00	99.17	99.17
H11	89.17	99.17	87.50	96.97	82.61	95.45	78.79	100.00	87.50	98.33
H12	99.17	100.00	96.00	100.00	93.94	100.00	86.36	80.00	96.67	100.00
H13	99.17	100.00	100.00	100.00	100.00	100.00	100.00	100.00	97.50	97.50

D1 to D5= Thumb to Little finger consecutively

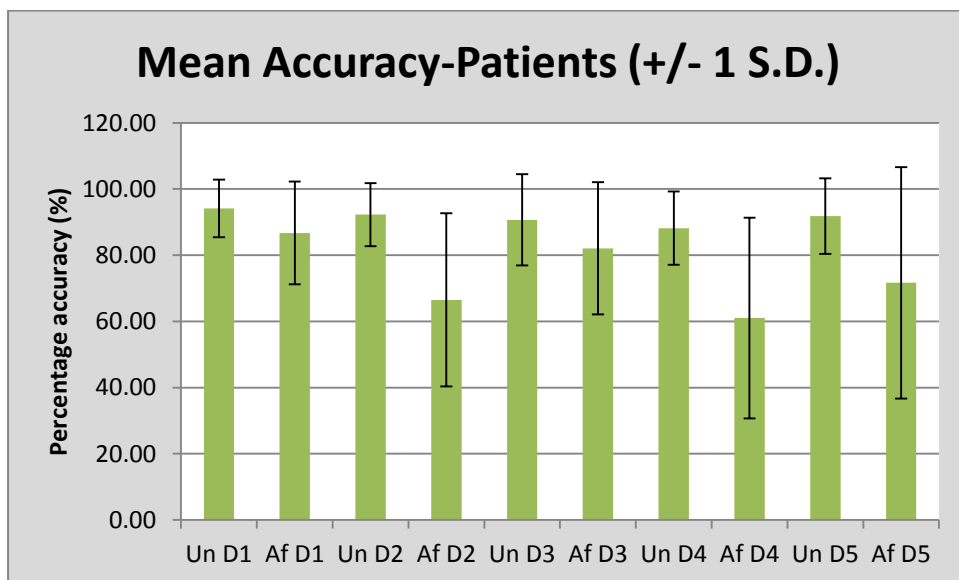
**Table 5J:** Average accuracy (%) of individual fingers in patients

	Un D1	Af D1	Un D2	Af D2	Un D3	Af D3	Un D4	Af D4	Un D5	Af D5
P1	94.17	92.50	100.00	96.15	100.00	93.75	92.86	72.73	91.67	89.17
P2	86.67	71.67	100.00	62.96	85.00	95.45	93.55	74.19	90.83	64.17
P3	96.67	98.33	100.00	89.47	100.00	100.00	100.00	92.00	100.00	99.17
P4	100.00	99.17	95.83	76.67	100.00	80.00	96.77	68.00	99.17	95.83
P5	67.50	50.00	78.26	52.94	56.00	39.13	65.63	43.48	65.83	50.00
P6	100.00	99.17	95.83	67.65	100.00	100.00	100.00	95.65	99.17	95.83
P7	95.83	96.67	73.45	27.27	71.43	77.42	70.00	6.25	96.67	96.67
P8	97.50	74.17	97.06	70.37	95.45	75.00	95.83	76.00	100.00	72.50
P9	95.83	77.33	100.00	64.10	100.00	85.00	86.67	38.10	100.00	77.33
P10	95.00	94.17	90.91	96.43	100.00	96.00	89.47	77.78	96.67	90.83
P11	97.50	98.33	78.95	43.33	86.67	92.59	77.42	21.74	78.33	0.00
P12	99.17	100.00	100.00	100.00	100.00	90.00	93.94	100.00	100.00	99.17
P13	98.33	75.83	89.05	17.39	84.54	42.86	83.85	27.59	75.00	0.83

Un= unaffected, Af= affected, D1 to D5= Thumb to Little finger consecutively



**Figure 5.11:** Graphical representation of mean accuracy (%) of individual fingers (D1-D5) in healthy subjects with standard deviation error bars.



**Figure 5.12:** Graphical representation of mean accuracy (%) of individual fingers (D1-D5) in patients with standard deviation error bars. (Un =unaffected, Af=affected)

1. Healthy controls, on average, had similar accuracy in the left hand (M = 96.46 %, SE = 1.03) compared to the right hand (M = 97.67%, SE = 0.41, Wilcoxon Signed Rank test,  $z = -1.08$ ,  $p = 0.28$ ).
2. Healthy controls, on average, had similar accuracy in the left little finger (M = 97.18 %, SE = 0.89) compared to the left thumb (M = 97.5%, SE = 0.80, Wilcoxon Signed Rank test,  $z = -0.26$ ,  $p = 0.53$ ).
3. Healthy controls, on average, had similar accuracy in the right little finger (M = 98.65 %, SE = 0.39) compared to the right thumb (M = 98.27%, SE = 0.66, Wilcoxon Signed Rank test,  $z = -0.76$ ,  $p = 0.45$ ).
4. Patients, on average, had statistically significant lower accuracy in the affected hand (M = 75.17 %, SE = 6.09) than in the unaffected hand (M = 91.26 %, SE = 2.63, Wilcoxon Signed Rank test,  $z = -2.97$ ,  $p = 0.003$ ).
5. Patients had statistically significant lower accuracy in the affected hand (M = 75.17 %, SE = 6.09) compared to the left hand in healthy (M = 96.46 %, SE = 1.03, Mann-Whitney-U test, Z score= -3.03, U= 25,  $p = 0.002$ ).
6. Patients had statistically significant lower accuracy in the affected hand (M = 75.17 %, SE = 6.09) compared to the right hand in healthy (M = 97.67%, SE = 0.41, Mann-Whitney-U test, Z score= -3.44, U= 17,  $p = 0.0006$ ).
7. Patients had lower accuracy (but not reaching statistical significance) in the unaffected hand (M = 91.26 %, SE = 2.63) compared to the left hand in healthy (M = 96.46 %, SE = 1.03, Mann-Whitney-U test, Z score= -1.62, U= 52.5,  $p = 0.11$ ).
8. Patients had statistically significant lower accuracy in the unaffected hand (M = 91.26 %, SE = 2.63) compared to the right hand in healthy (M = 97.67%, SE = 0.41, Mann-Whitney-U test, Z score= -2.10, U= 43,  $p = 0.036$ ).

## **Was there a difference in reaction times and accuracy between right side affected and left side affected CRPS patients?**

There were four patients who had CRPS clinically affecting their right side and nine patients with left side affected. We were interested to see if the affected side (left or right) had a bearing on the reaction times or the accuracy rates.

There was a statistically significant difference in the average reaction times of patients' affected hand in right sided (n=4) CRPS (M = 1869.52 ms, SE = 145.50) compared to the left sided (n=9) CRPS (M = 1311.33 ms, SE = 145.96,  $t = 2.71$ , two-tailed  $p = 0.02$ ). However, there was no statistically significant difference in the average reaction times of patients' unaffected hand in right sided (n=4) CRPS (M = 1447.08 ms, SE = 155.73) compared to the left sided (n=9) CRPS (M = 1183.04 ms, SE = 126.42,  $t = 1.32$ , two-tailed  $p = 0.23$ ).

There was no statistically significant difference in the average accuracy of patients' affected hand in right sided (n=4) CRPS (M = 76.81%, SE = 6.20) compared to the left sided (n=9) CRPS (M = 72.18%, SE = 7.98,  $t = 0.46$ , two-tailed  $p = 0.66$ ). Similarly, there was no statistically significant difference in the average accuracy of patients' unaffected hand in right sided (n=4) CRPS (M = 93.18%, SE = 3.94) compared to the left sided (n=9) CRPS (M = 90.63%, SE = 3.54,  $t = 0.48$ , two-tailed  $p = 0.64$ ).

The numbers in the groups used in subgroup testing are small and hence the results have to be interpreted with caution. Results are not always generalizable to larger samples. Small sample sizes may not be sufficient to pick up significant differences even if they exist and that is a limitation of this particular analysis.

NB: t-tests with independent samples and assuming unequal variances were used for both reaction times and accuracy as Mann-Whitney U-test statistic will be highly unreliable given the small numbers (n=4 and 9 in the two groups).

## **Was there a difference in reaction times and accuracy between upper and lower limb affected patients?**

There were six patients with upper limb clinically affected with CRPS and seven with lower limb affected. We were interested to see if the affected limb (upper or lower) had a bearing on the reaction times or accuracy scores.

There was no statistically significant difference in the average reaction times of patients' hand on the affected side in upper limb (n=6) CRPS (M = 1584.03 ms, SE = 177.35) compared to the lower limb (n=7) CRPS (M = 1343.47 ms, SE = 189.66, t = 0.93, two-tailed p = 0.37).

There was no statistically significant difference in the average reaction times of patients' hand on the unaffected side in upper limb (n=6) CRPS (M = 1328.04 ms, SE = 154.15) compared to the lower limb (n=7) CRPS (M = 1209.63 ms, SE = 144.47, t = 0.56, two-tailed p = 0.59).

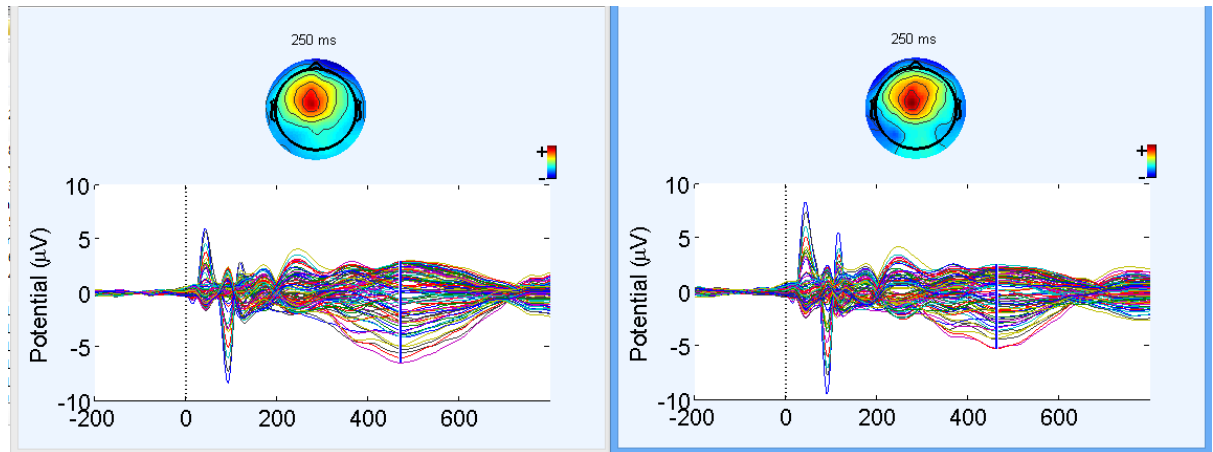
There was no statistically significant difference in the average accuracy of patients' hand on the affected side in upper limb (n=6) CRPS (M = 65.51%, SE = 9.23) compared to the lower limb (n=7) CRPS (M = 80.54%, SE = 6.57, t = -1.33, two-tailed p = 0.22).

There was no statistically significant difference in the average accuracy of patients' hand on the unaffected side in upper limb (n=6) CRPS (M = 90.61%, SE = 3.13) compared to the lower limb (n=7) CRPS (M = 91.83%, SE = 4.32, t = -0.23, two-tailed p = 0.82).

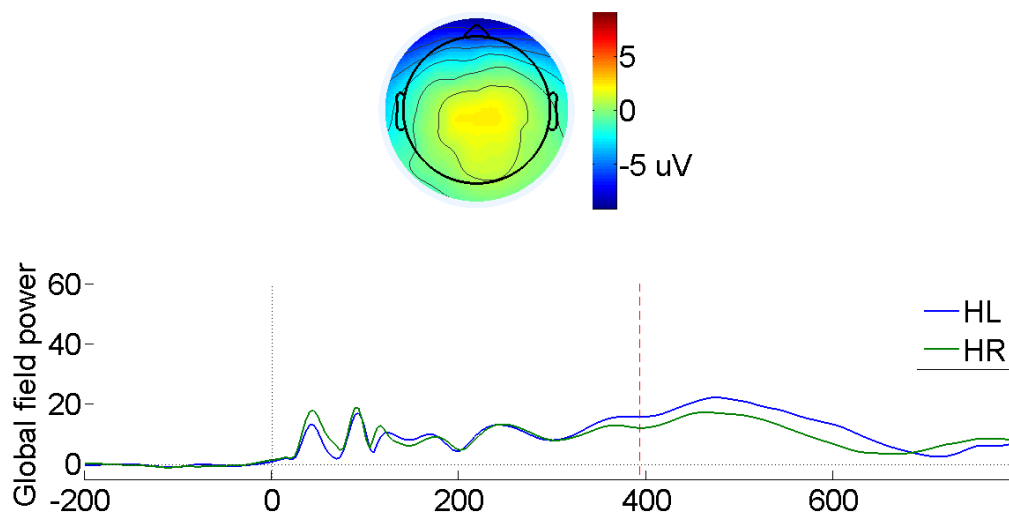
### 5.4.3 Results-Experiment 1 Global Field Power (GFP) analysis

#### Group level

1. No statistically significant difference between Left & Right hand stimulations in healthy controls (Figures 5.13 & 5.14).



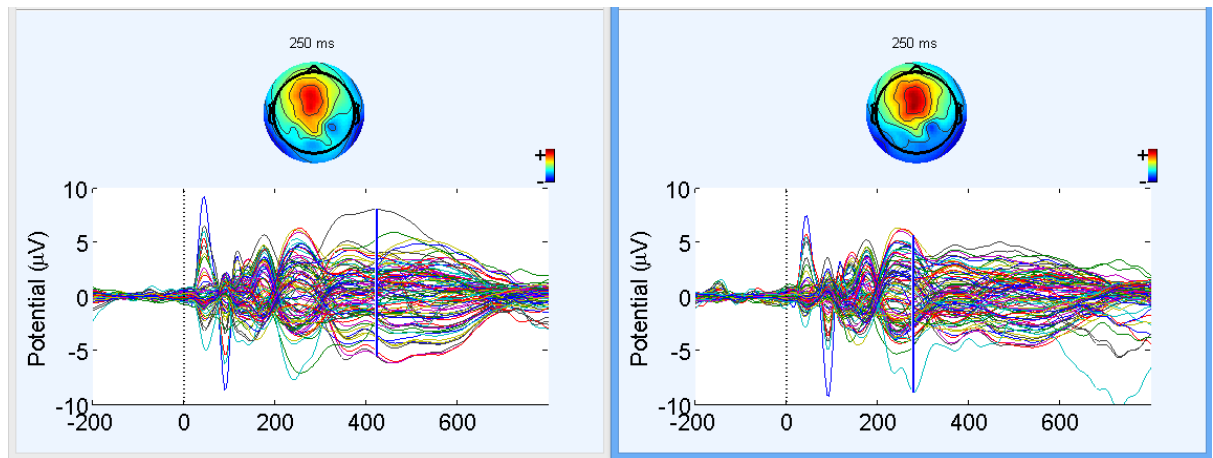
**Figure 5.13:** Left and Right hand stimulations-grand average of ERPs of all healthy controls



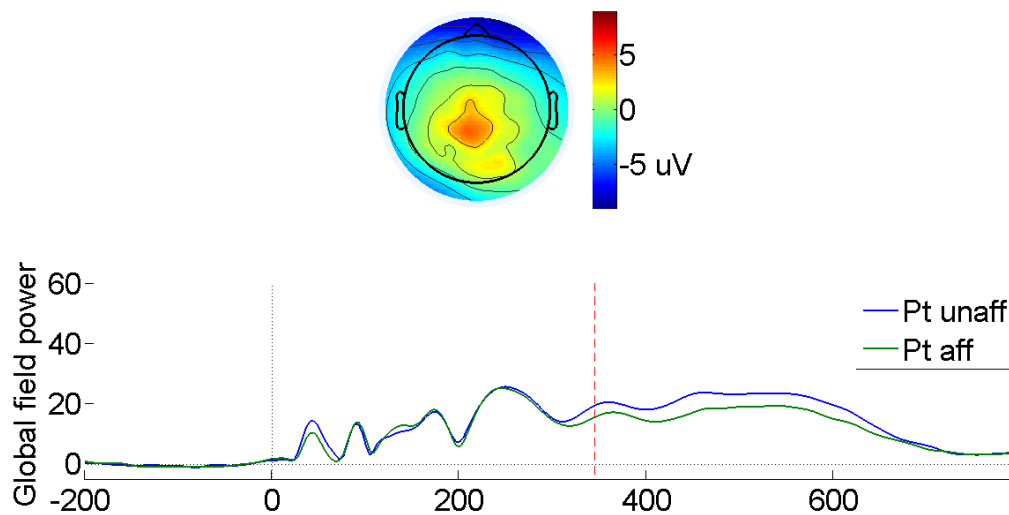
**Figure 5.14:** Time course of GFP of ERP grand average of healthy left (blue line) and right (green line). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point.



2. No significant difference between affected & unaffected hand stimulations in patients (Figures 5.15 & 5.16).

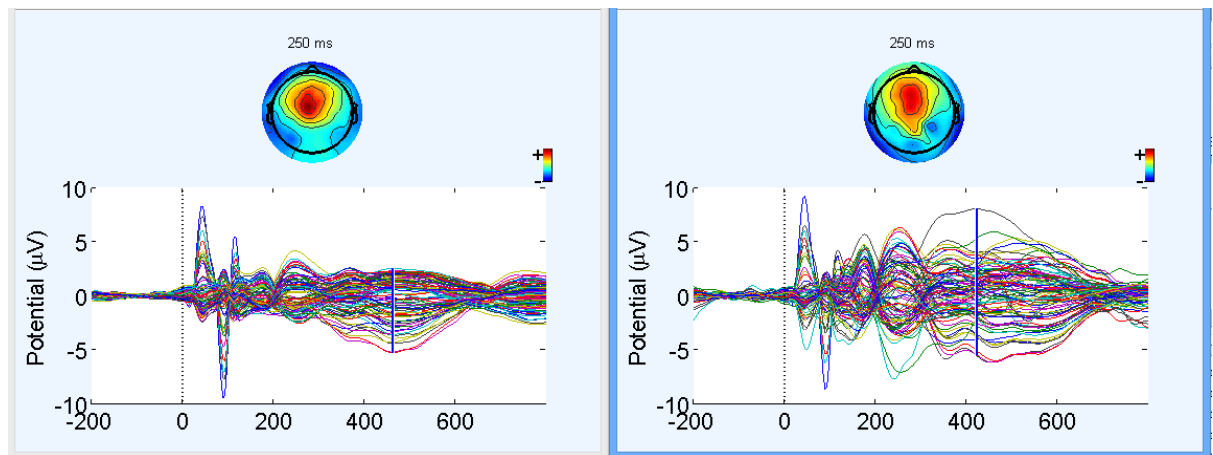


**Figure 5.15:** Affected and unaffected side hand stimulations - grand average of ERPs of all patients

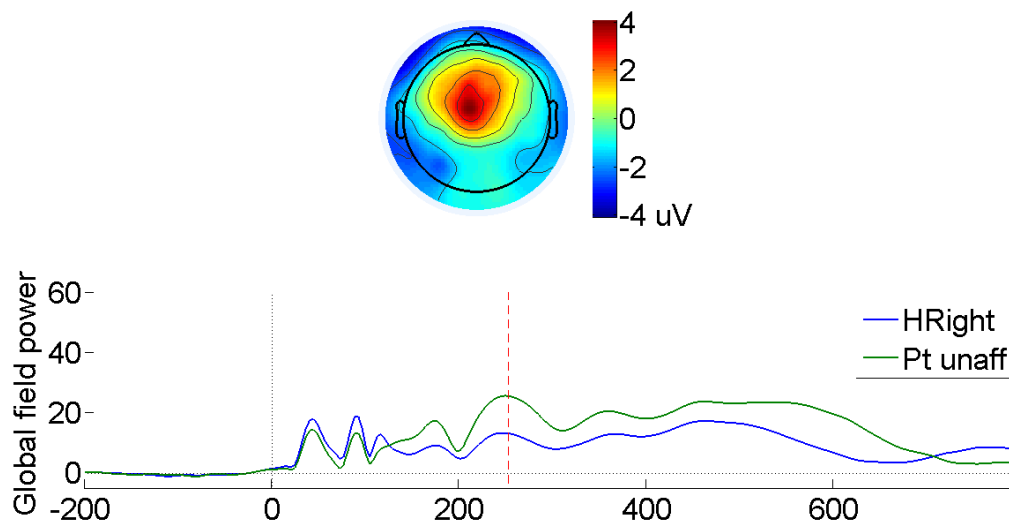


**Figure 5.16:** Time course of GFP of ERP grand average of patient unaffected (blue line) and affected (green line). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point.

3. No significant difference between Right hand stimulations in healthy controls compared to unaffected hand stimulation in patients (Figures 5.17 & 5.18).

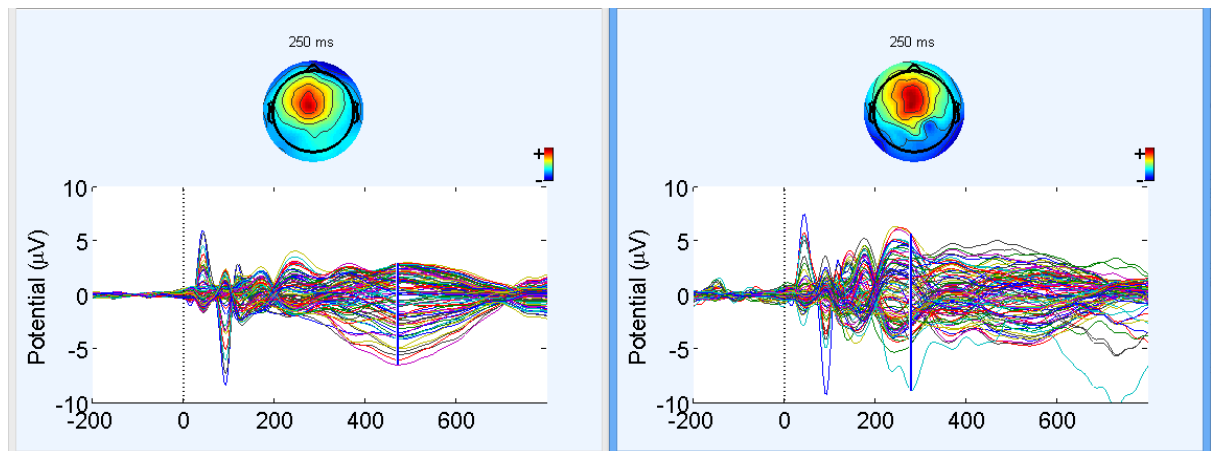


**Figure 5.17:** Healthy right hand and patient unaffected side hand stimulations - grand average of ERPs of all subjects.

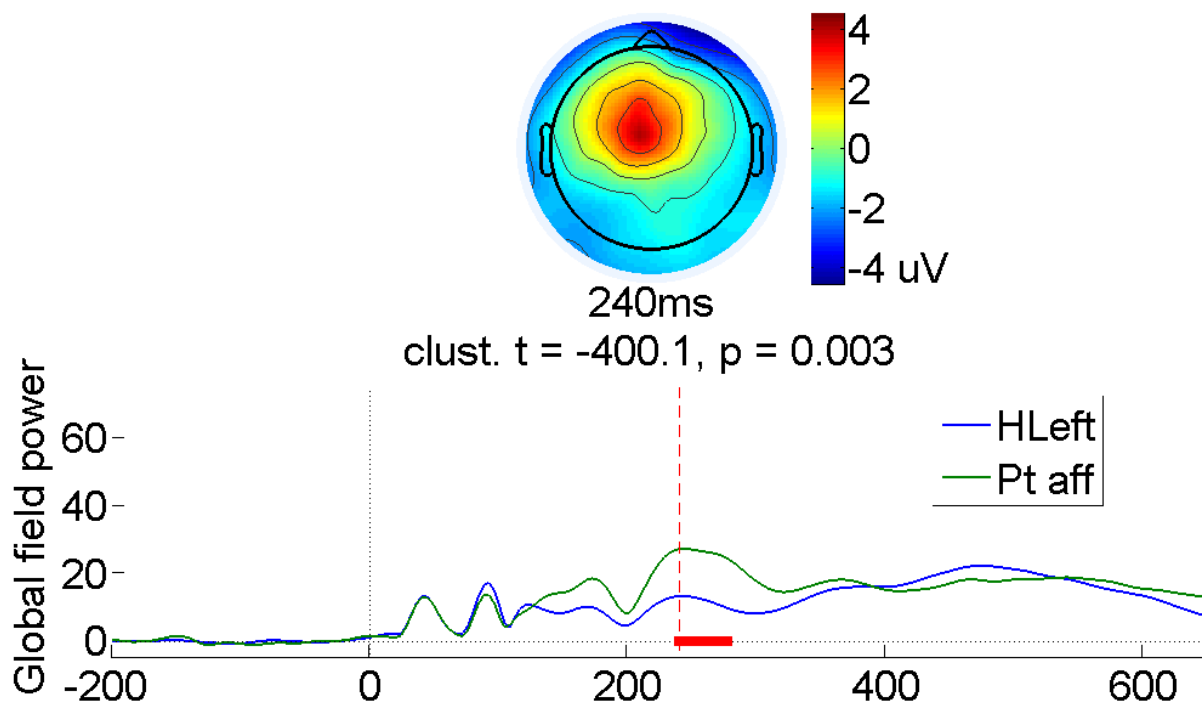


**Figure 5.18:** Time course of GFP of ERP grand average of healthy right (blue line) and patient unaffected (green line). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point.

4. Statistically significant difference ( $p=0.003$ ) between healthy left compared to affected hand in patients in the time segment 200 -400 ms but not between 0-200 ms (Figures 5.19 & 5.20).

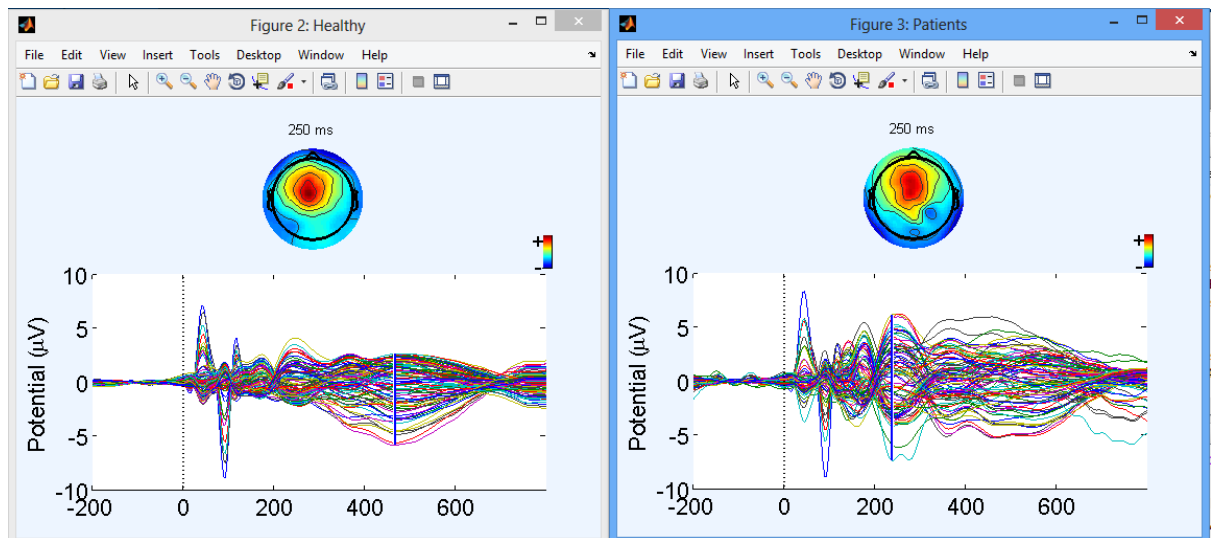


**Figure 5.19:** Healthy left hand and patient affected side hand stimulations - grand average of ERPs of all subjects.

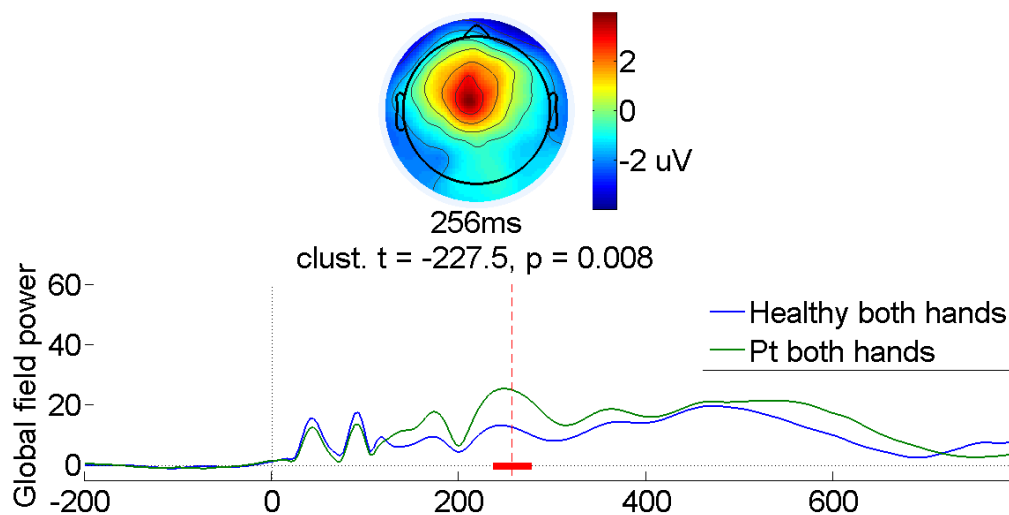


**Figure 5.20:** Time course of GFP of ERP grand average of healthy left (blue line) and patient affected (green line). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of ERP (condition 1) at this time point. The horizontal thick red line indicates the temporal extent of a statistically significant cluster of contiguous time points where GFP was greater in patients affected side than healthy left.

5. Statistically significant difference ( $p=0.008$ ) between healthy (Left and right combined) compared to patients (affected and unaffected combined) in the time segment 200 -400 ms but not between 0-200 ms (Figures 5.21 & 5.22).



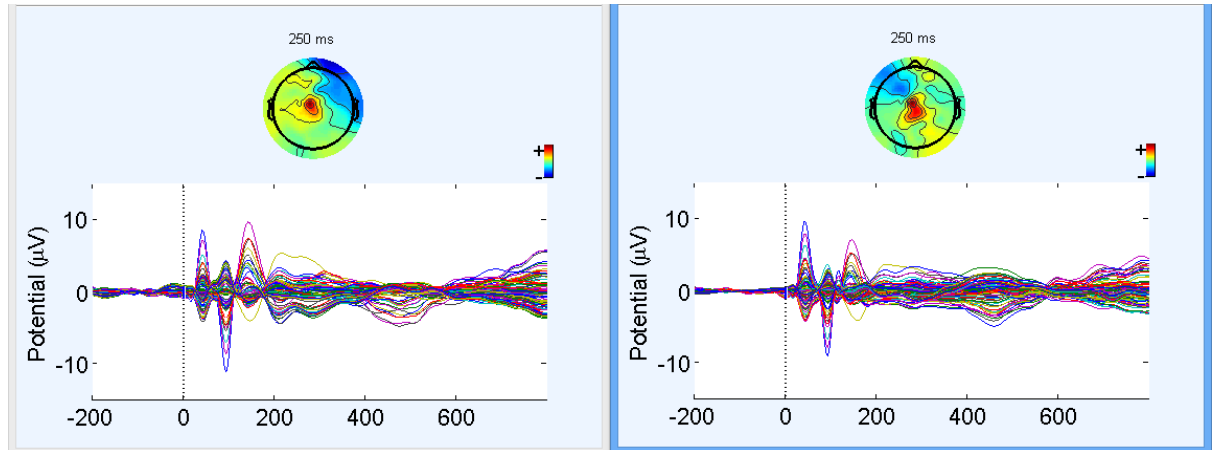
**Figure 5.21:** Healthy and patients both hand stimulations combined - grand average of ERPs of all subjects.



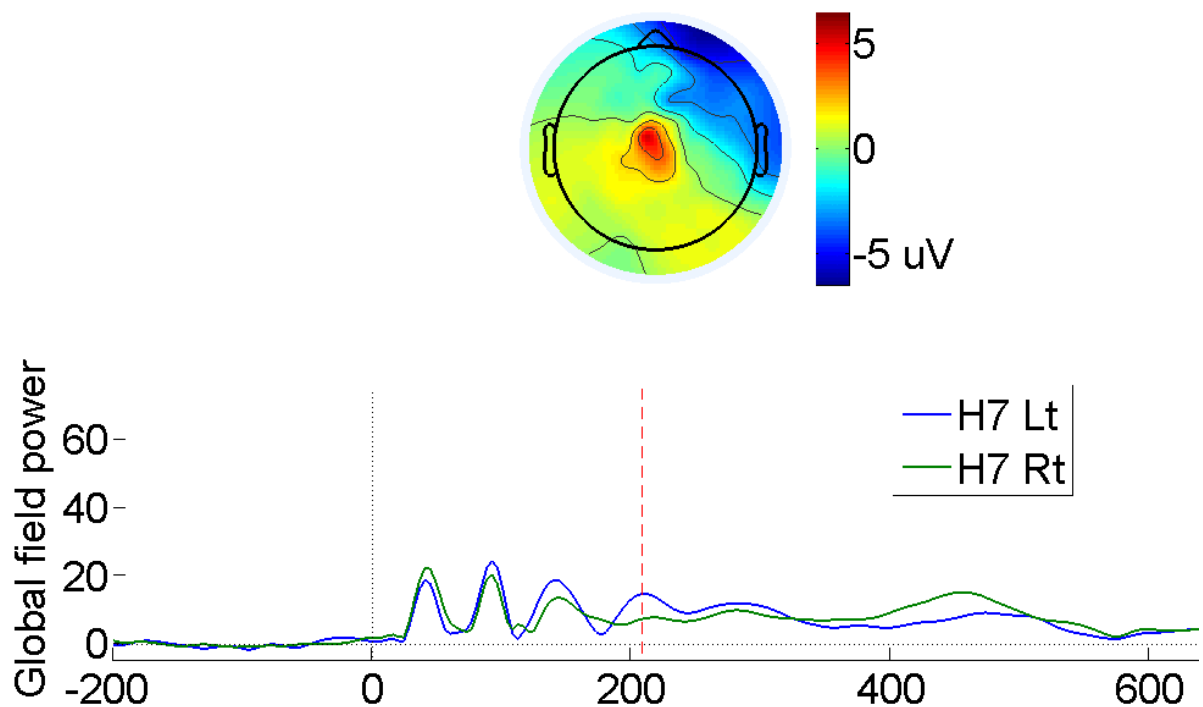
**Figure 5.22:** Time course of GFP of ERP grand average of hands combined, healthy (blue line) and patients (green line). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point. The horizontal thick red line indicates the temporal extent of a statistically significant cluster of contiguous time points where GFP was greater in patients (both hands) than healthy (both hands).

Individual level (focus on the time segment 200-400 ms to capture P300 effects)

1. No statistically significant difference between left or right hand in any of the healthy controls (Figures 5.23 & 5.24).



**Figure 5.23:** ERP plot of a single healthy subject (H7), left and right hand stimulations

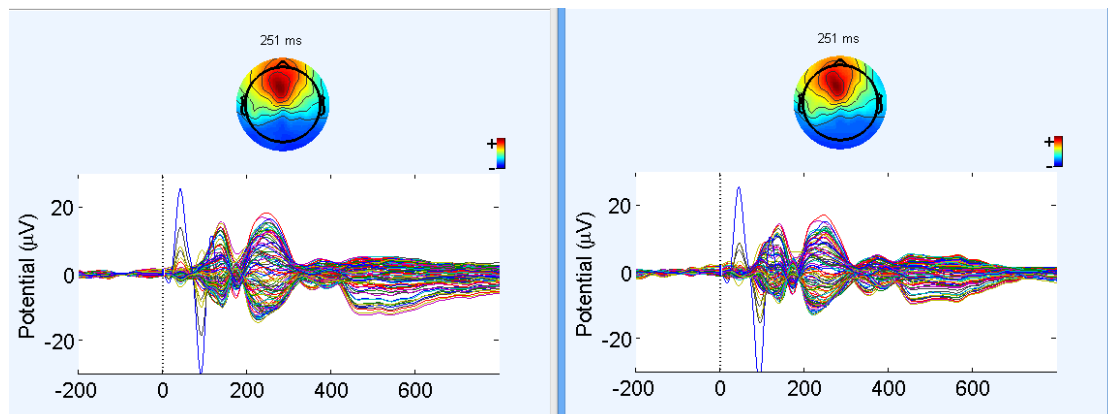


**Figure 5.24:** Time course of GFP of ERP average of a single healthy subject, left hand (blue) and right hand (green). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP at this time point.

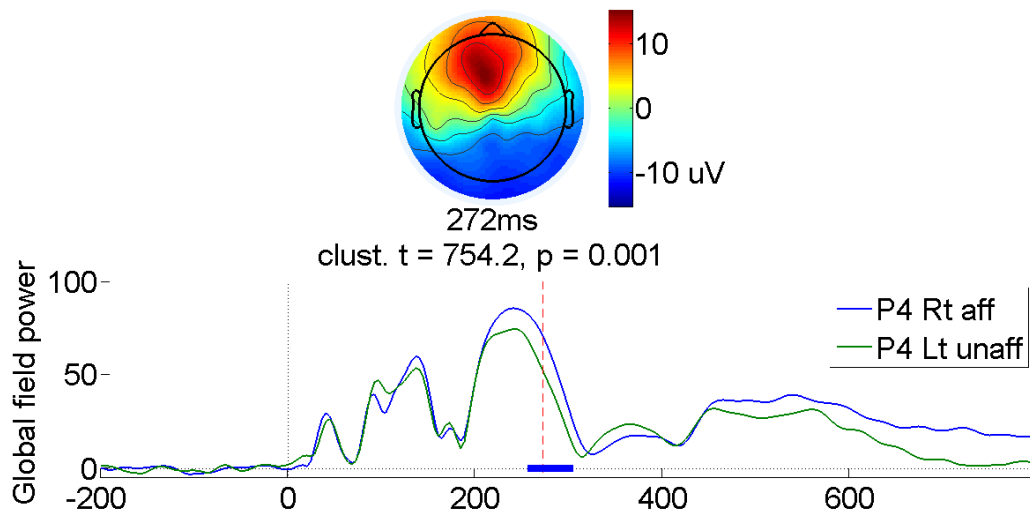
2. Statistically significant difference between affected and unaffected hands in four of the 13 patients. In three of those four, GFP on the affected side was higher than the unaffected side (shaded yellow) whereas in one, the reverse was true (shaded green in the Table 5K). The individual ERP plots and GFP time course of these 4 patients are detailed in figures 5.25-5.32

**Table 5K:**

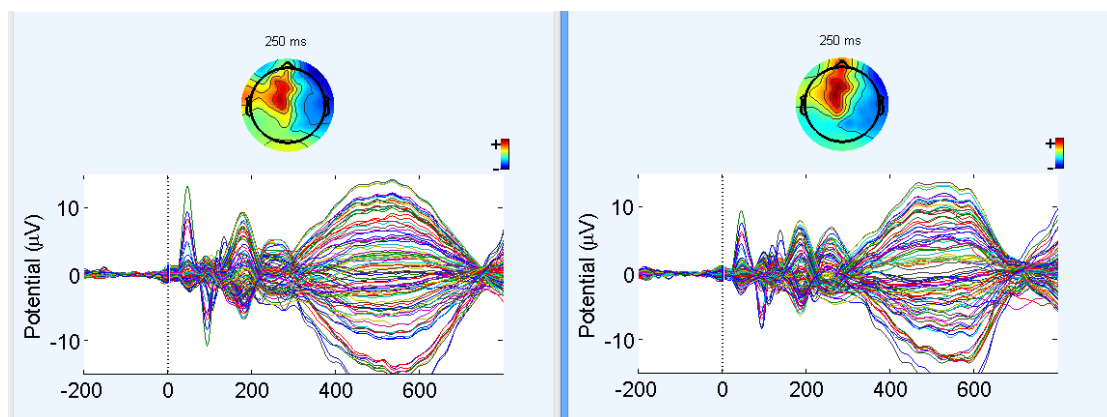
Patient identifier	Age, sex, affected limb	Time of peak difference	Cluster value	t	p value
P4	42,F,Right arm	272 ms	754.2		0.001
P5	53,F,Left leg	376 ms	268.1		0.006
P8	52,F,Right leg	320 ms	400.9		0.002
P3	63,F,Left arm	364 ms	-480.9		0.002



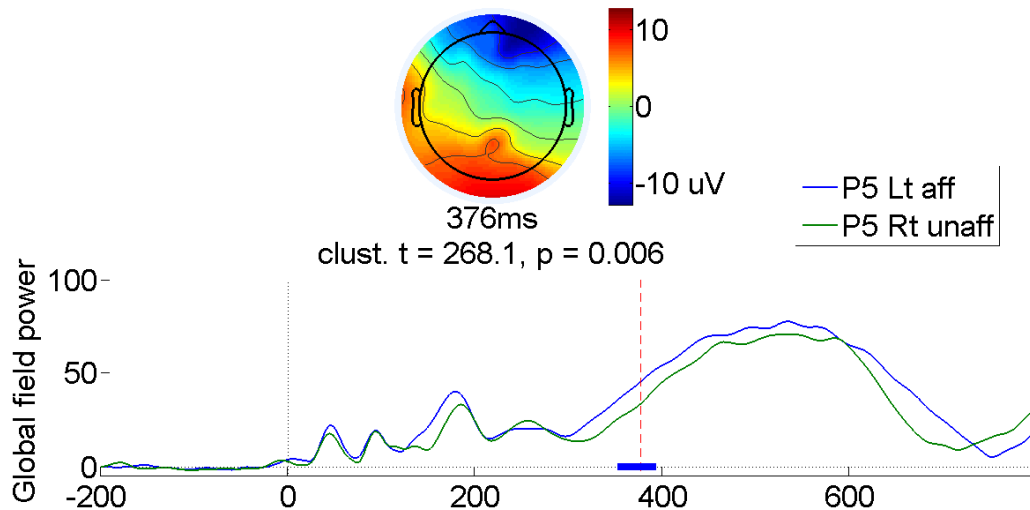
**Figure 5.25:** ERP plot of a single patient (P4), affected and unaffected hand stimulations



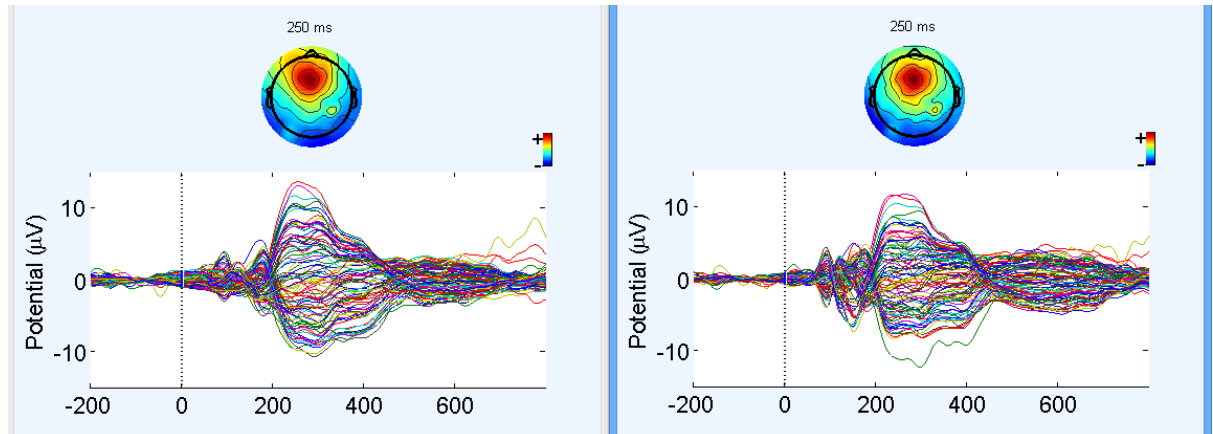
**Figure 5.26:** Time course of GFP of ERP average of a single patient (P4), affected hand (blue) and unaffected hand (green). The vertical red dashed line indicates the time point within the cluster at which GFP (condition 1) was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point. The horizontal thick blue line indicates the temporal extent of a statistically significant cluster of contiguous time points where GFP was greater in patient's affected hand than unaffected hand.



**Figure 5.27:** ERP plot of a single patient (P5), affected and unaffected hand stimulations

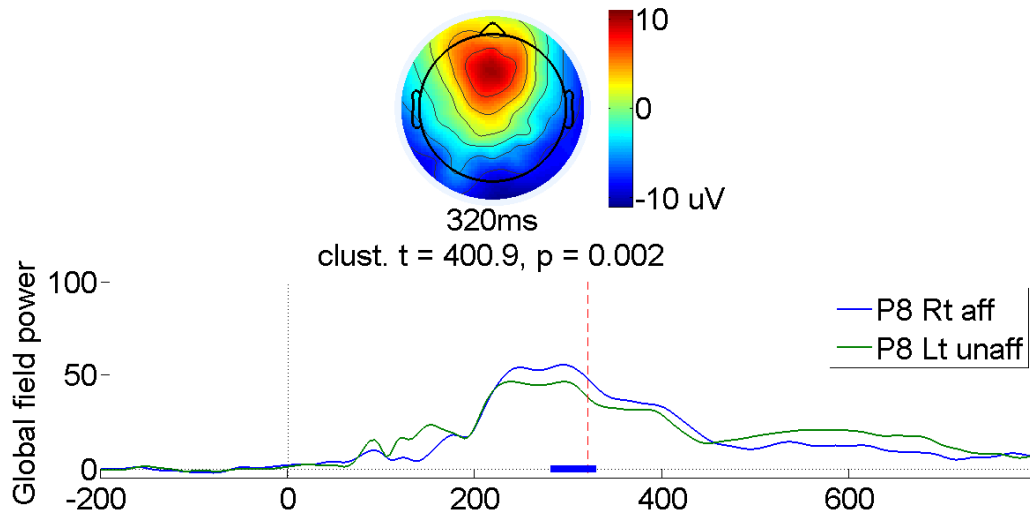


**Figure 5.28:** Time course of GFP of ERP average of a single patient (P5), affected hand (blue) and unaffected hand (green). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point. The horizontal thick blue line indicates the temporal extent of a statistically significant cluster of contiguous time points where GFP was greater in patient's affected hand than unaffected hand.

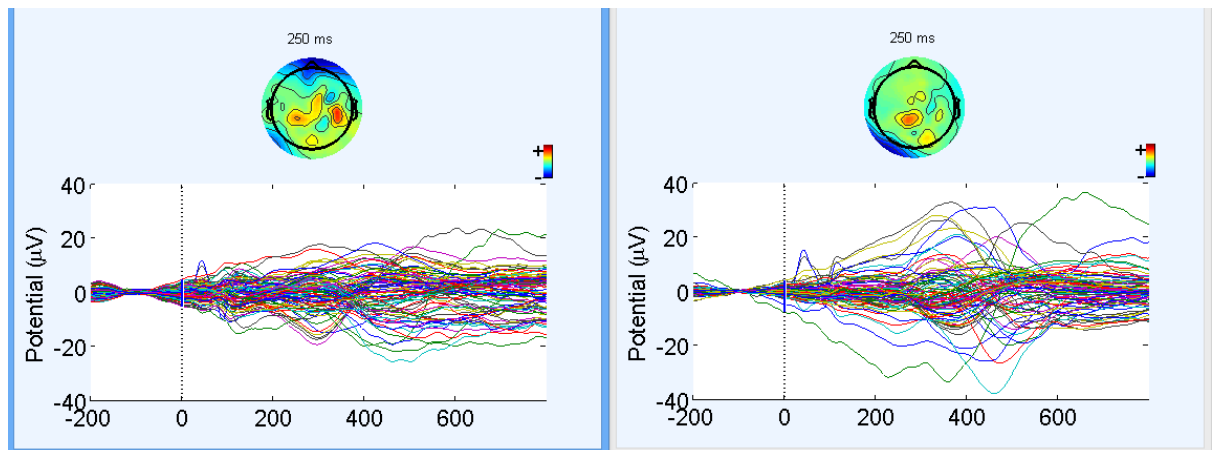


**Figure 5.29:** ERP plot of a single patient (P8), affected and unaffected hand stimulations

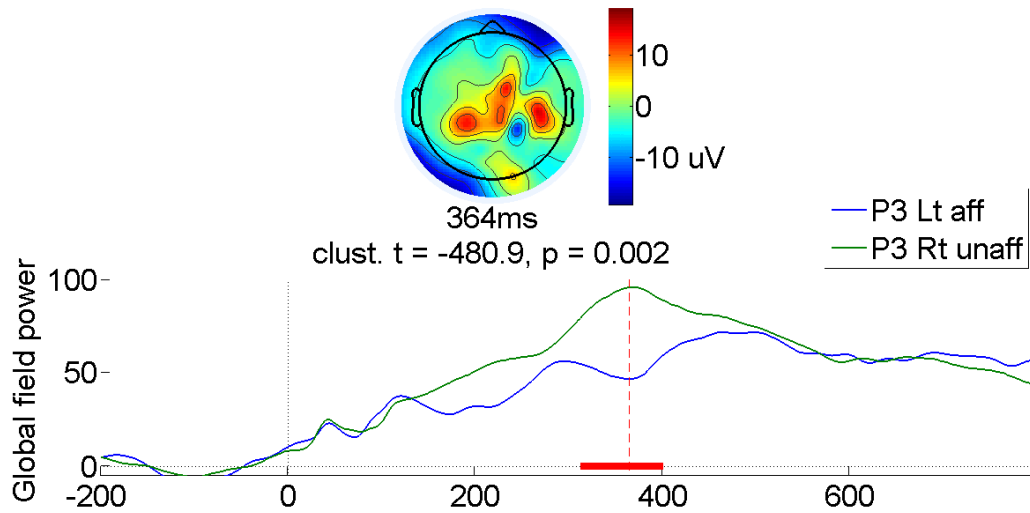




**Figure 5.30:** Time course of GFP of ERP average of a single patient (P8), affected hand (blue) and unaffected hand (green). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point. The horizontal thick blue line indicates the temporal extent of a statistically significant cluster of contiguous time points where GFP was greater in patient's affected hand than unaffected hand.



**Figure 5.31:** ERP plot of a single patient (P3), affected and unaffected hand stimulations

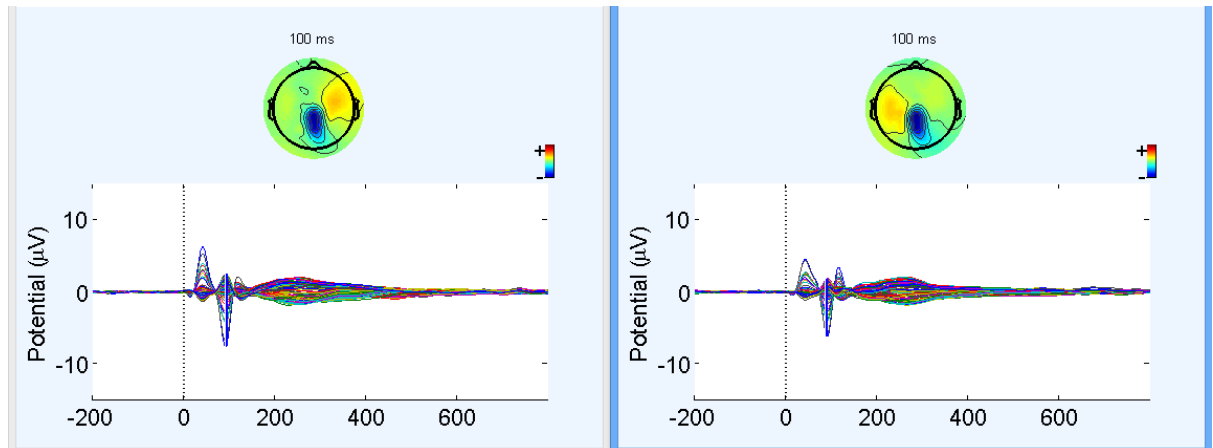


**Figure 5.32:** Time course of GFP of ERP average of a single patient (P3), affected hand (blue) and unaffected hand (green). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point. The horizontal thick red line indicates the temporal extent of a statistically significant cluster of contiguous time points where GFP was greater in patient's affected hand than unaffected hand.

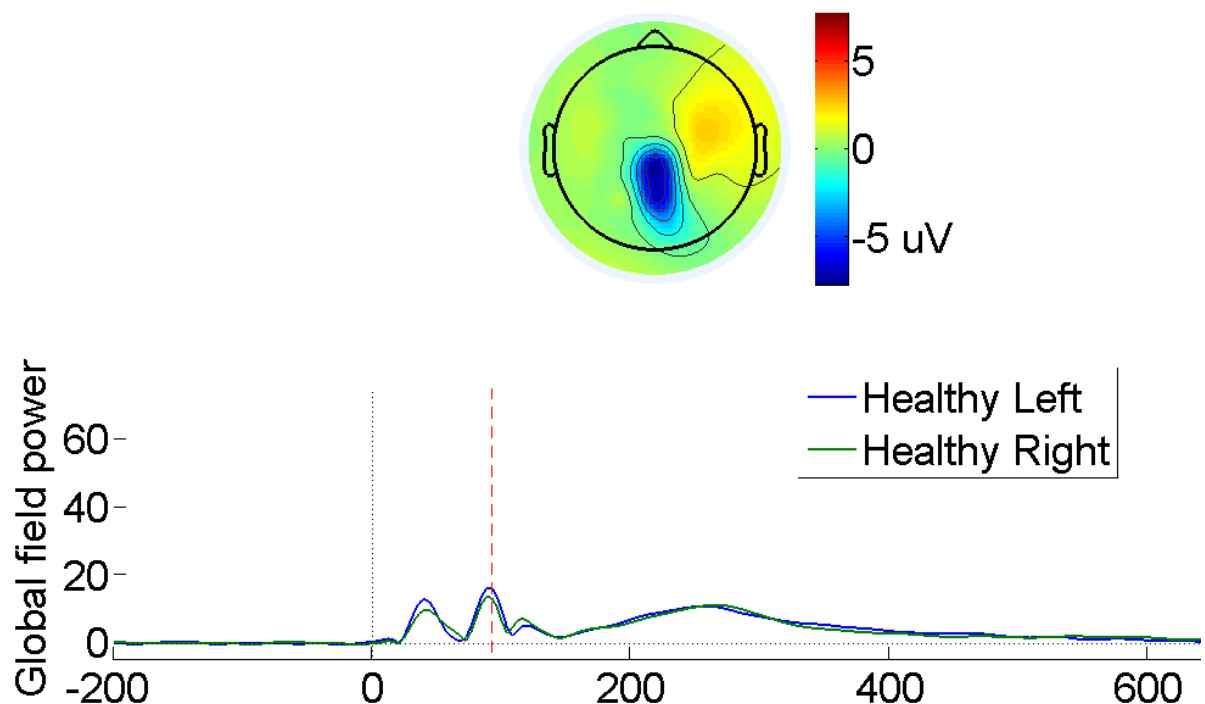
#### 5.4.4 Results-Experiment 2 Global Field Power (GFP) analysis

##### Group level

1. No significant difference between Healthy Left & Right stimulations (Figures 5.33 & 5.34).

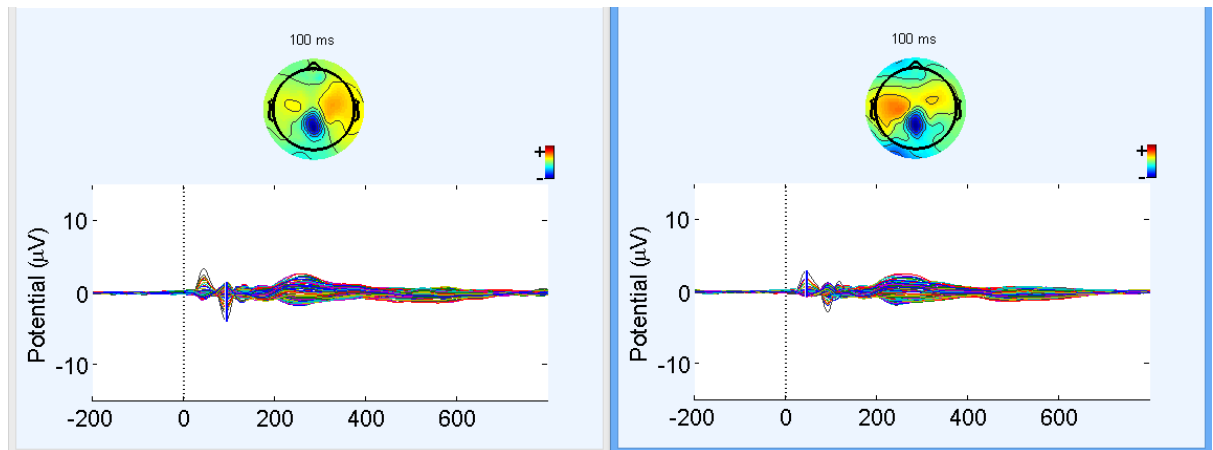


**Figure 5.33:** Left and Right hand stimulations-grand average of ERPs of all healthy.

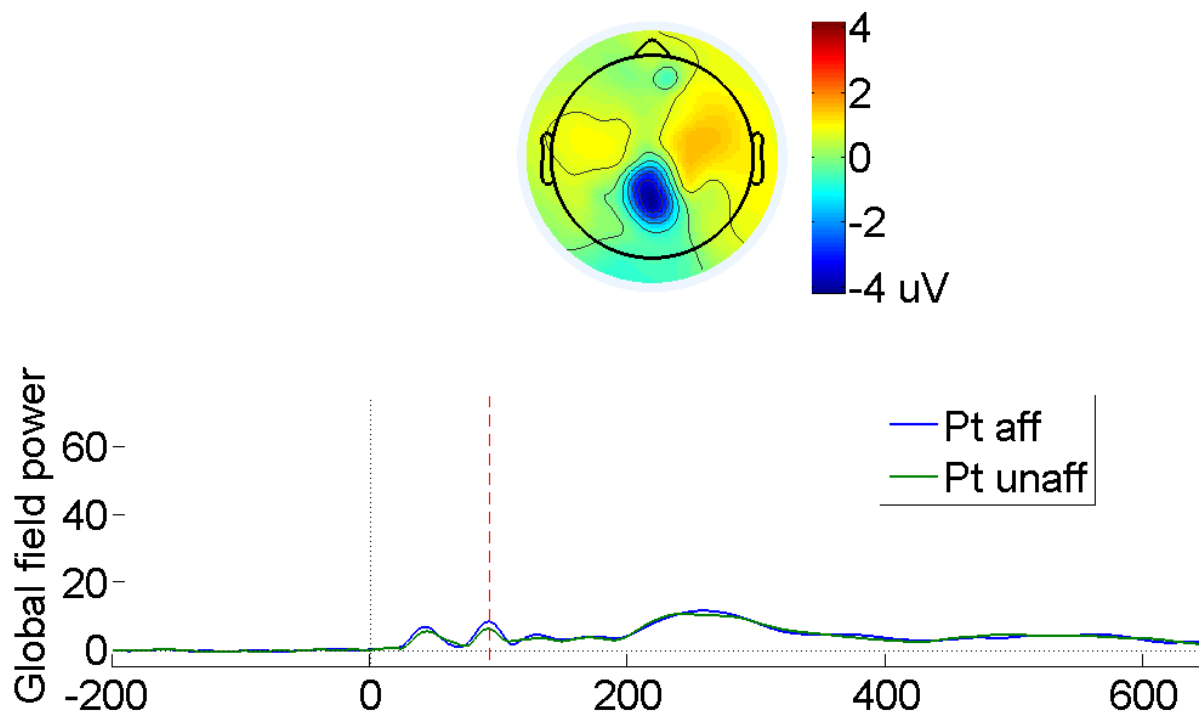


**Figure 5.34:** Time course of GFP of ERP grand average of healthy left (blue line) and right (green line). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point.

2. No significant difference between Patient affected and unaffected (Figures 5.35 & 5.36).

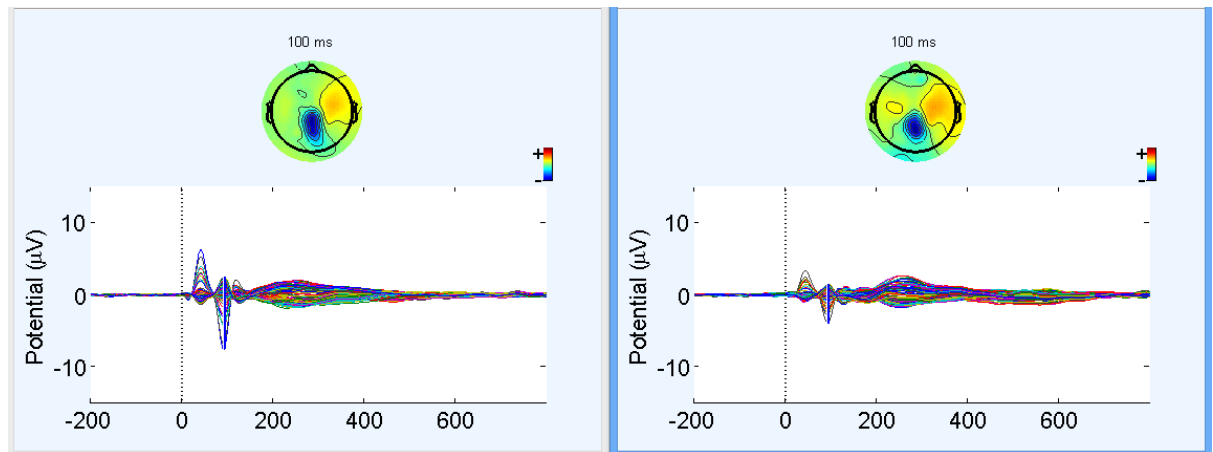


**Figure 5.35:** Affected and unaffected hand stimulations-grand average of ERPs of all patients

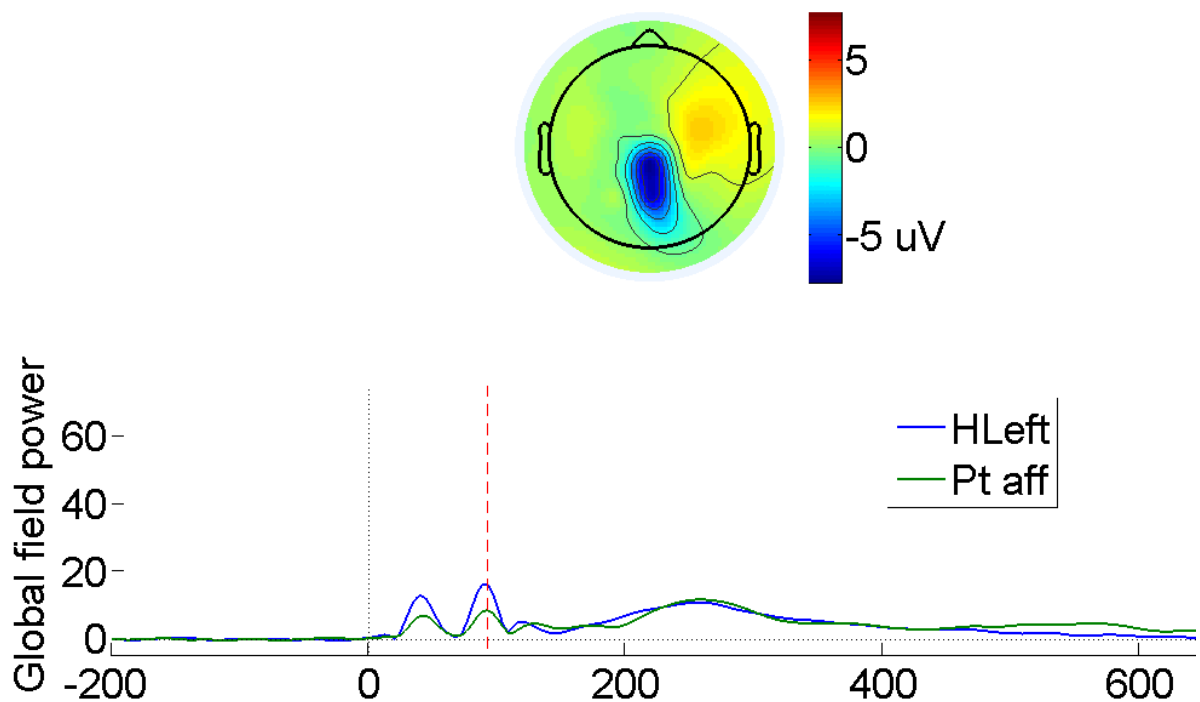


**Figure 5.36:** Time course of GFP of ERP grand average of patients affected (blue line) and unaffected (green line). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point.

3. No significant difference between healthy Left and Patient affected (Figures 5.37 & 5.38).

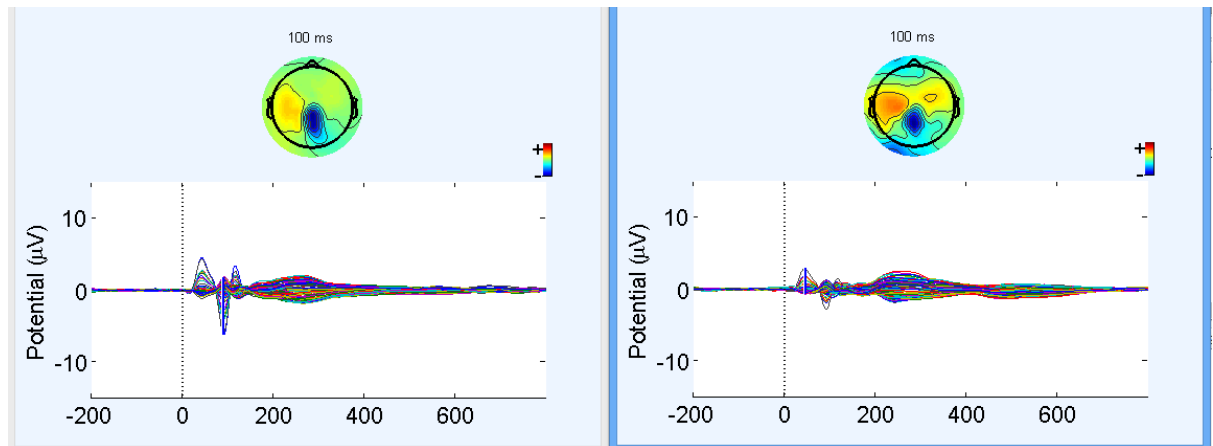


**Figure 5.37:** Healthy Left and patient affected hand stimulations-grand average of ERPs of all subjects

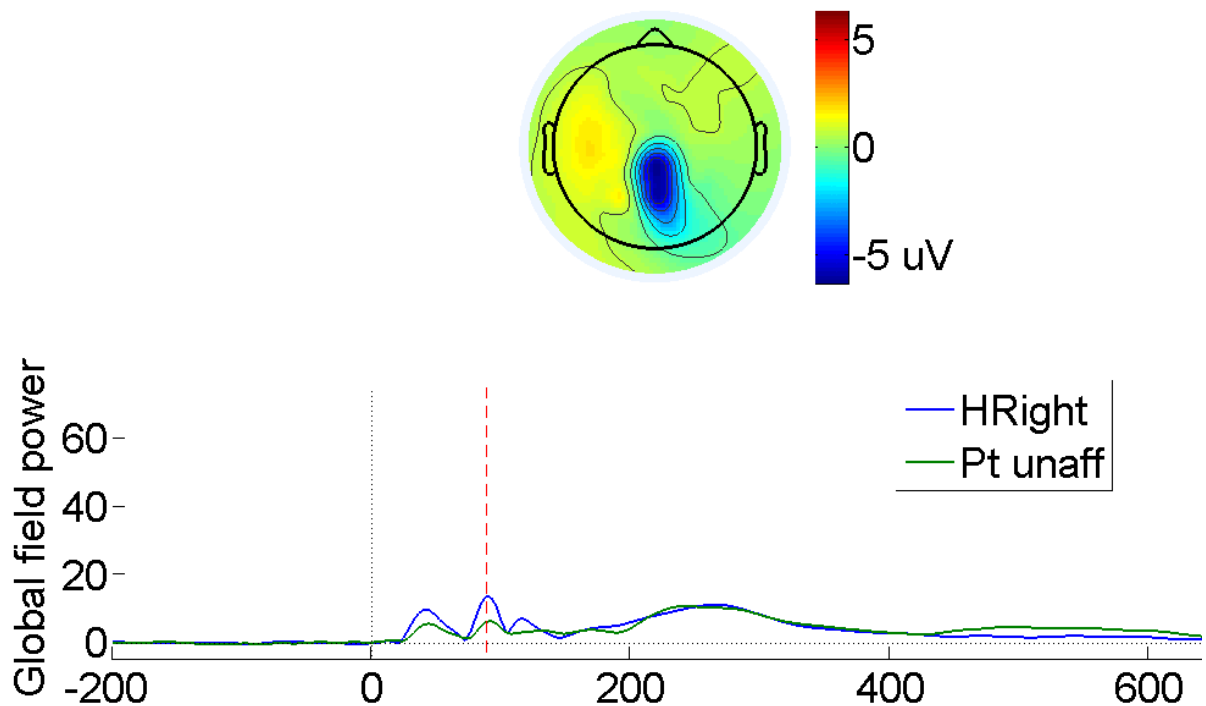


**Figure 5.38:** Time course of GFP of ERP grand average of healthy left (blue line) and patients affected (green line). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point.

4. No significant difference between healthy Right and Patient unaffected (Figures 5.39 & 5.40)

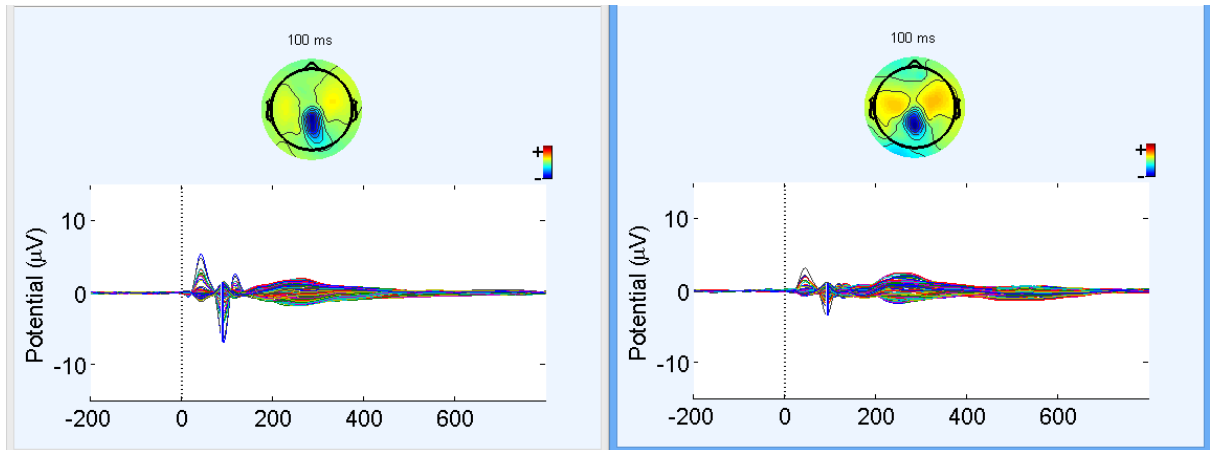


**Figure 5.39:** Healthy right and patient unaffected hand stimulations-grand average of ERPs of all subjects

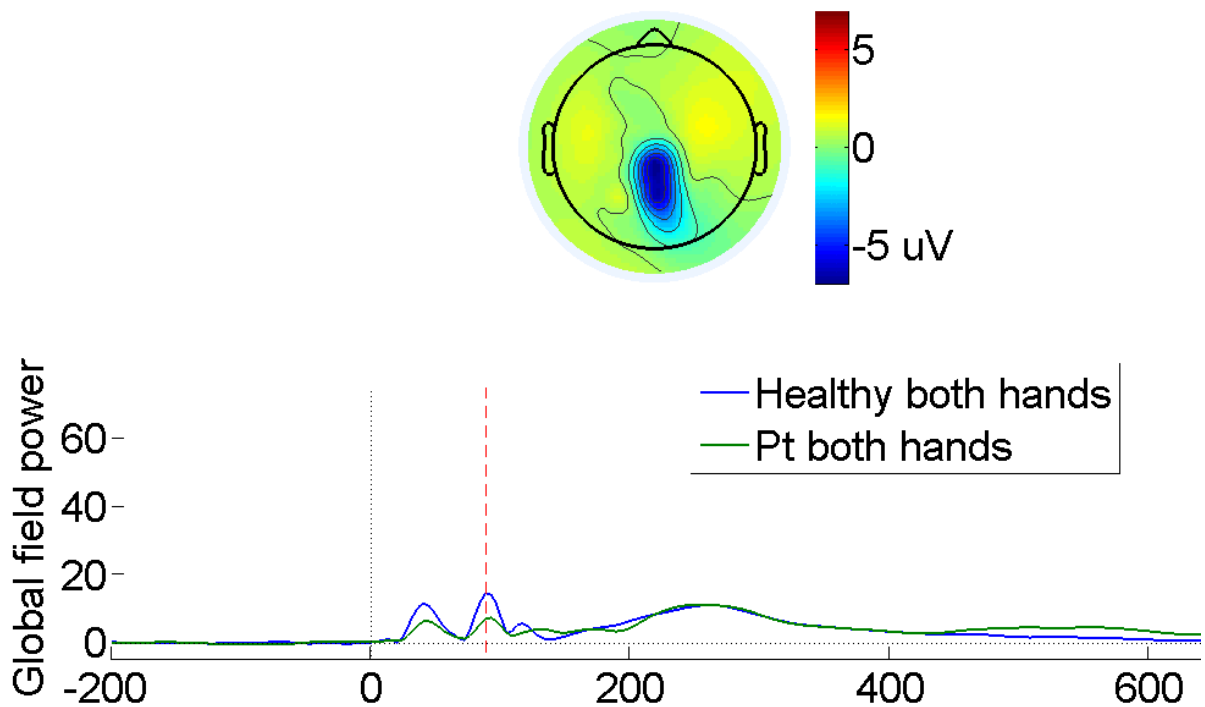


**Figure 5.40:** Time course of GFP of ERP grand average of healthy right (blue line) and patient unaffected (green line). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point.

5. No significant difference between healthy and patients, both hands combined (Figures 5.41 & 5.42).



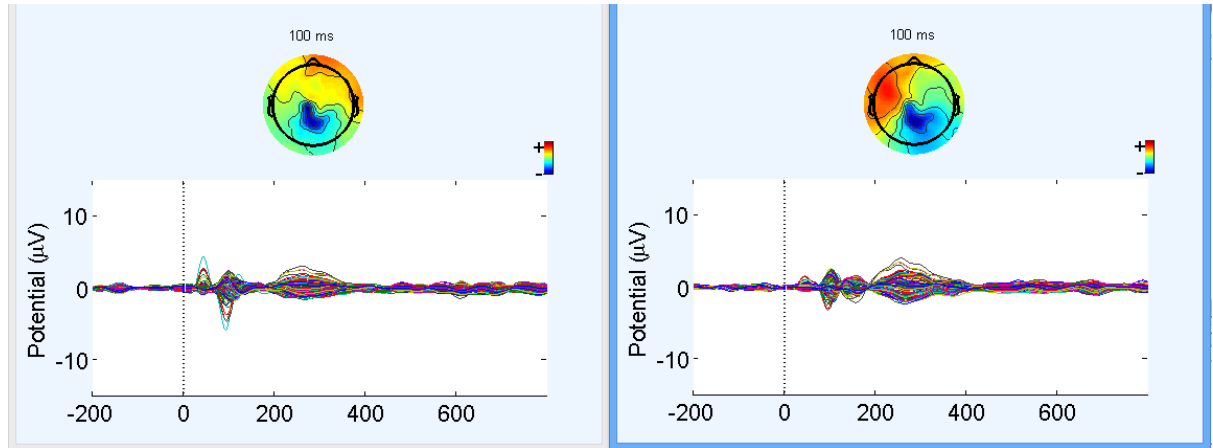
**Figure 5.41:** Healthy and patient both hands combined -grand average of ERPs of all subjects.



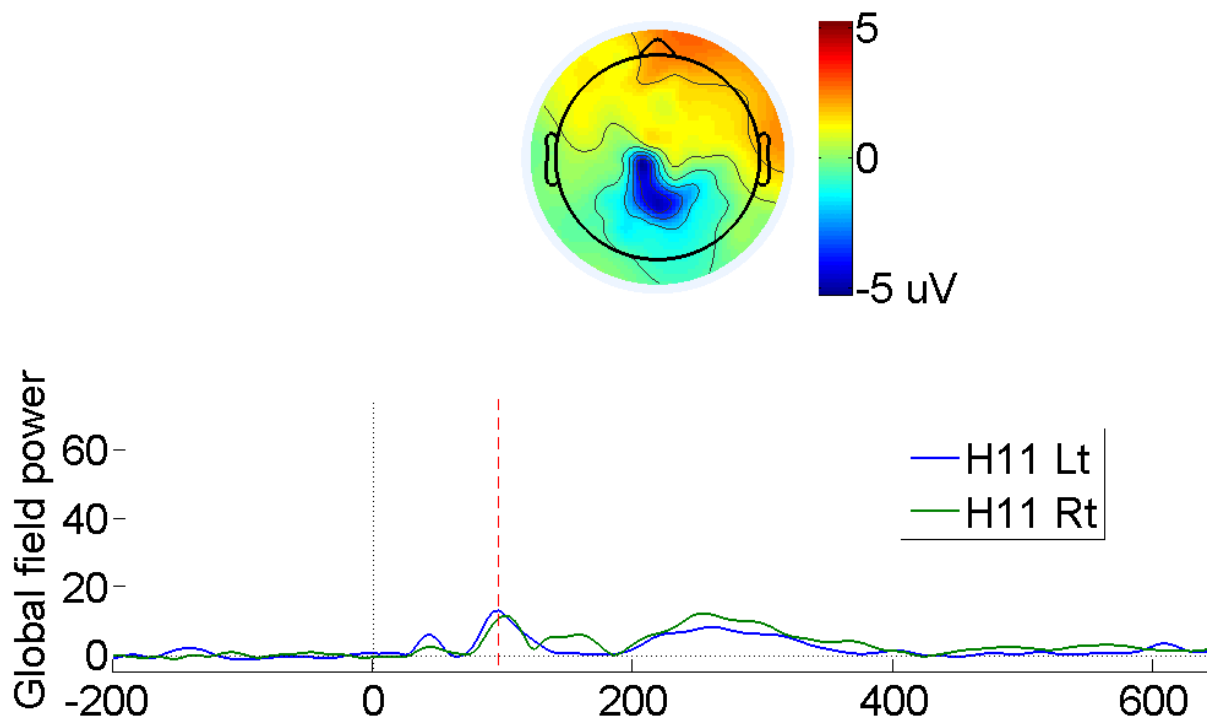
**Figure 5.42:** Time course of GFP of ERP grand average of both hands combined, healthy (blue line) and patient (green line). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point.

Individual level

1. No statistically significant difference between left or right hand in any of the healthy controls (Figures 5.43 & 5.44)



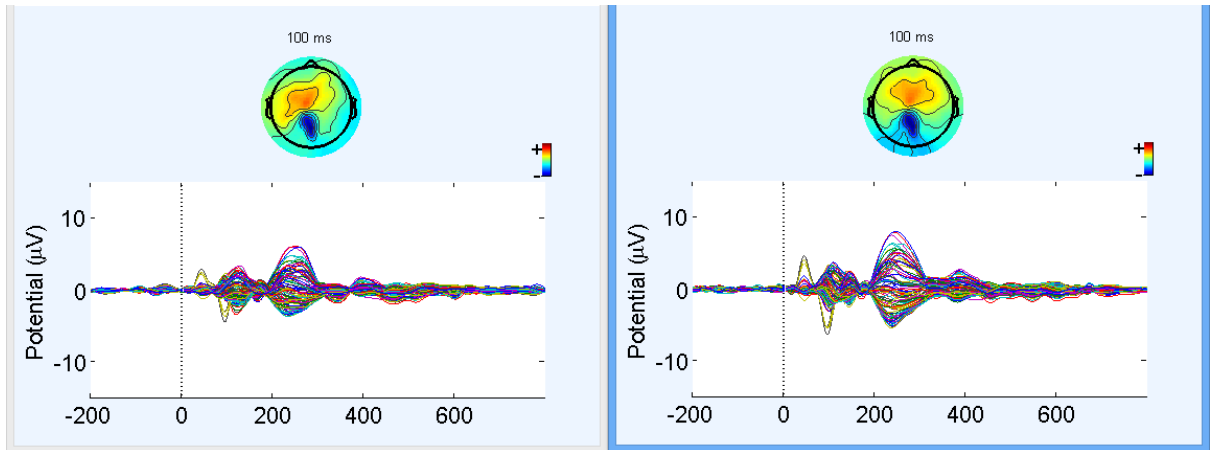
**Figure 5.43:** A single healthy control, left and right hand stimulations



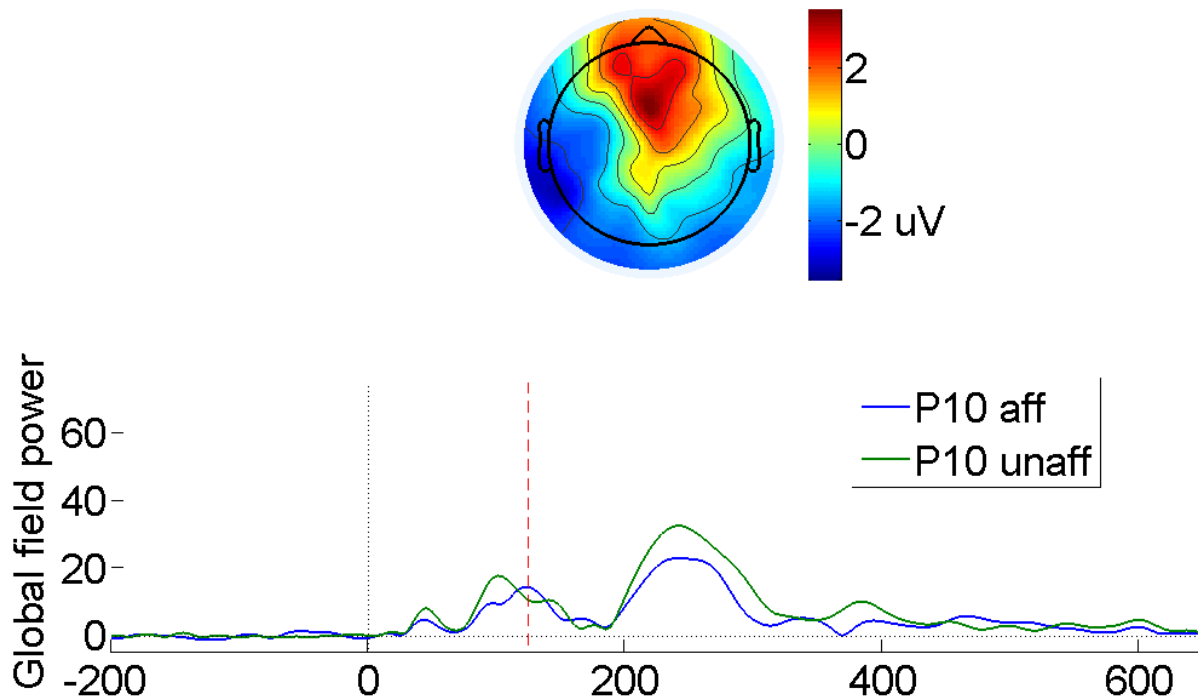
**Figure 5.44:** Time course of GFP of ERP average of a single healthy control, left hand (blue) and right hand (green). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point.



2. No statistically significant difference between affected or unaffected hand in any of the patients (Figures 5.45 & 5.46).



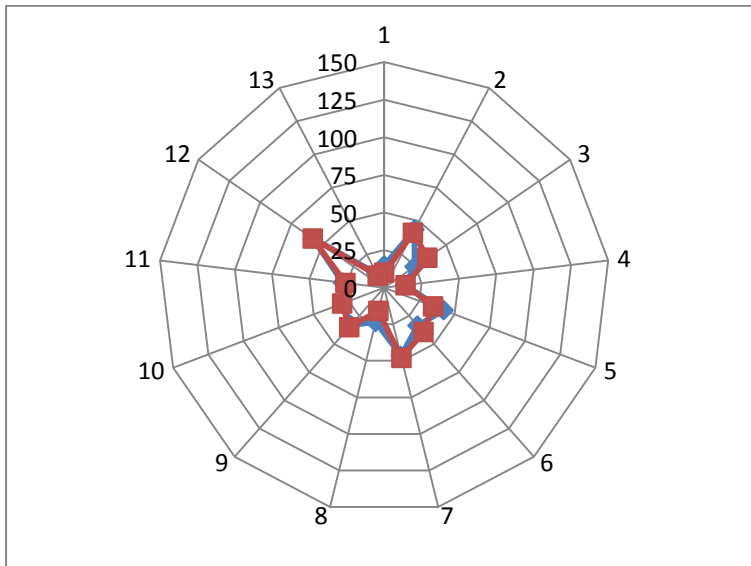
**Figure 5.45:** A single patient, affected and unaffected hand stimulations



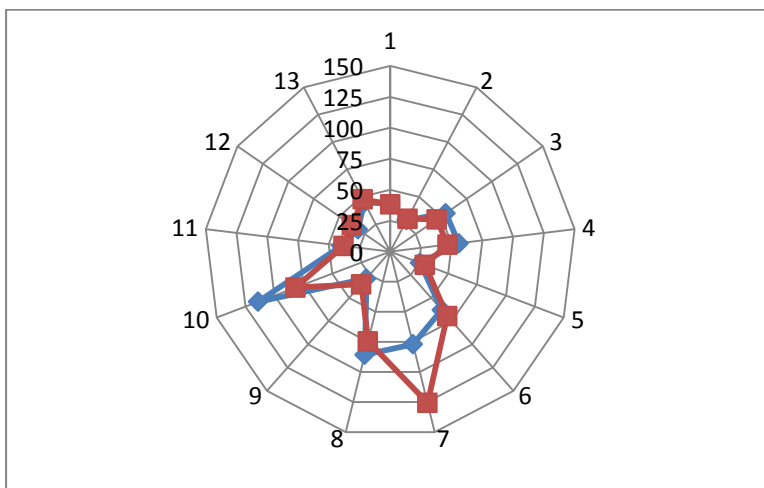
**Figure 5.46:** Time course of GFP of ERP average of a single patient, affected hand (blue) and unaffected hand (green). The vertical red dashed line indicates the time point within the cluster at which GFP difference was maximal, and the upper half of the panel plots the scalp topography of the ERP (condition 1) at this time point.

### 5.4.5 Results- Variability analysis

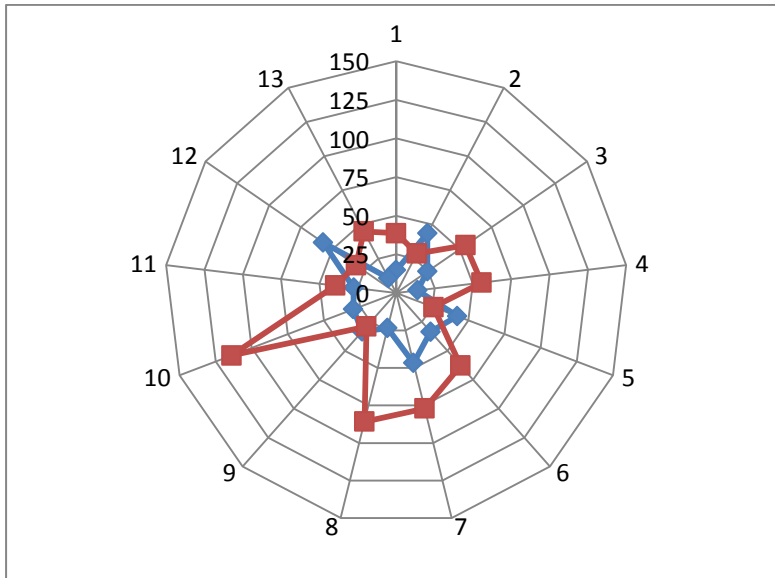
We graphically represented the variability of GFP and latency in both healthy and patient groups using spider plots as below (Figures 5.46-5.54) and also formally tested the homogeneity of variances in the patient and healthy groups using Levene's test. The GFP score and the latency are from 200-400 ms segment in experiment 2.



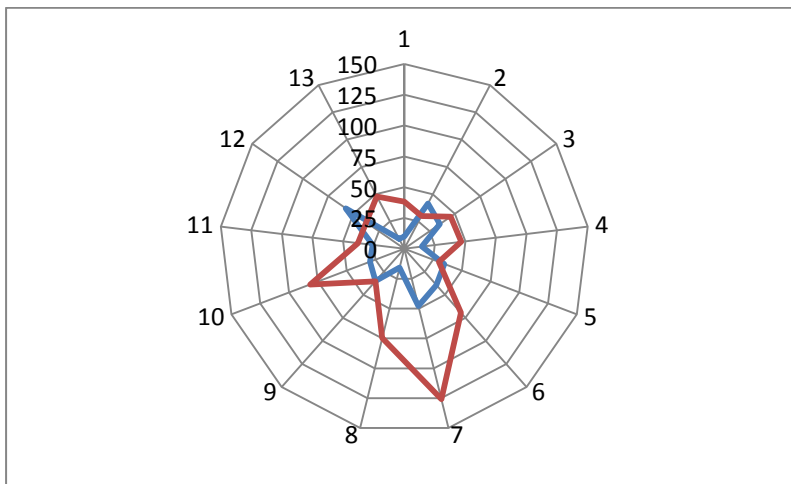
**Figure 5.47:** GFP variability in Healthy Left (blue) Vs Healthy Right (red). The spokes 1 to 13 represent the 13 individual subjects. The GFP score (0 to 150 in multiples of 25) is in microvolts.



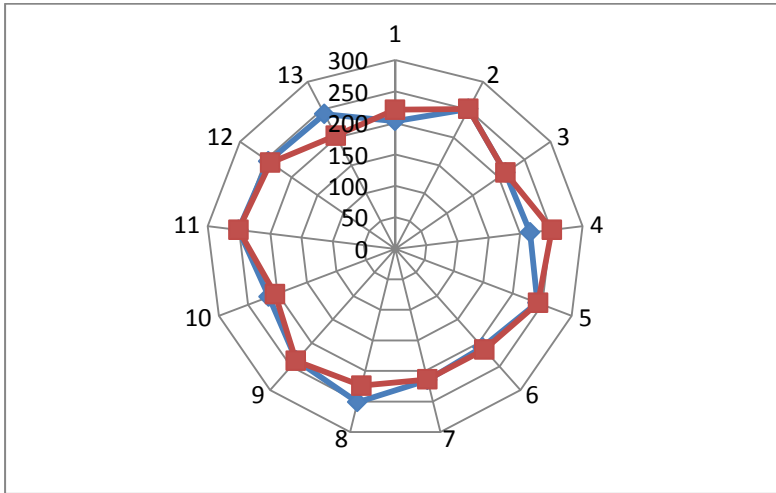
**Figure 5.48:** GFP variability in Patients affected (blue) Vs unaffected (red). The spokes 1 to 13 represent the 13 individual subjects. The GFP score (0 to 150 in multiples of 25) is in microvolts.



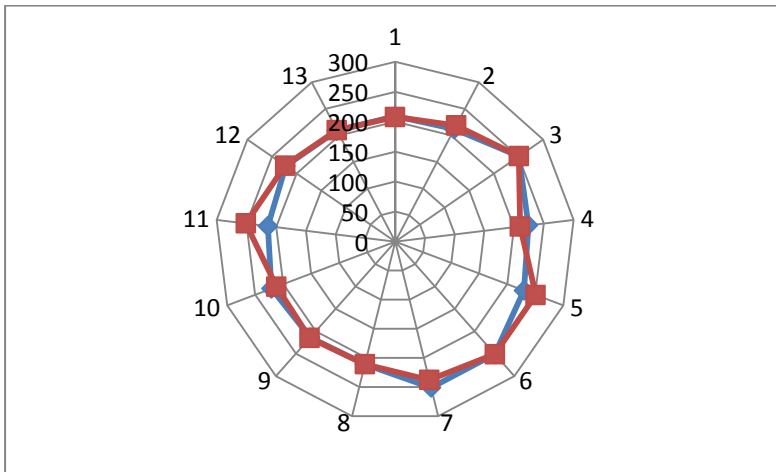
**Figure 5.49:** GFP variability in Healthy Left (blue) Vs Patient affected (red). The spokes 1 to 13 represent the 13 individual subjects. The GFP score (0 to 150 in multiples of 25) is in microvolts.



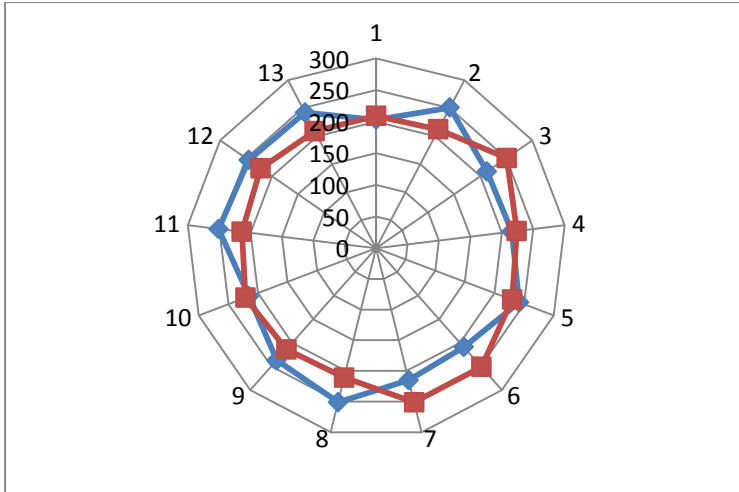
**Figure 5.50:** GFP variability in Healthy Right (blue) Vs Patient unaffected (red). The spokes 1 to 13 represent the 13 individual subjects. The GFP score (0 to 150 in multiples of 25) is in microvolts.



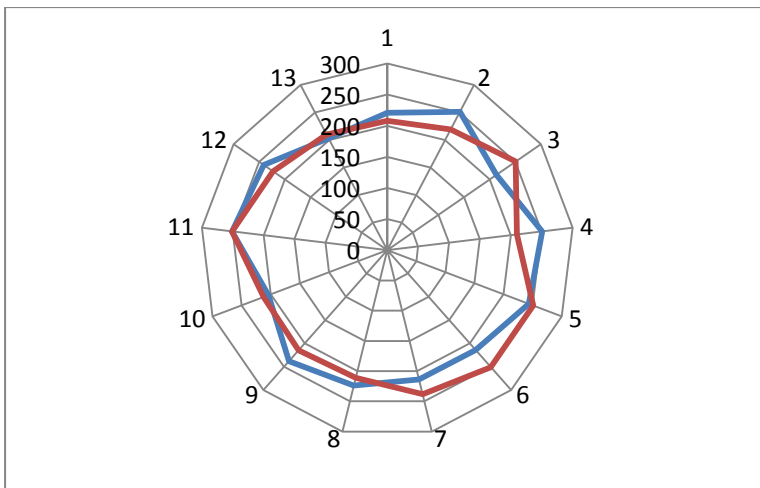
**Figure 5.51:** Latency variability in Healthy Left (blue) Vs Right (red). The spokes 1 to 13 represent the 13 individual subjects. The latency (0 to 300 in multiples of 50) is in milliseconds.



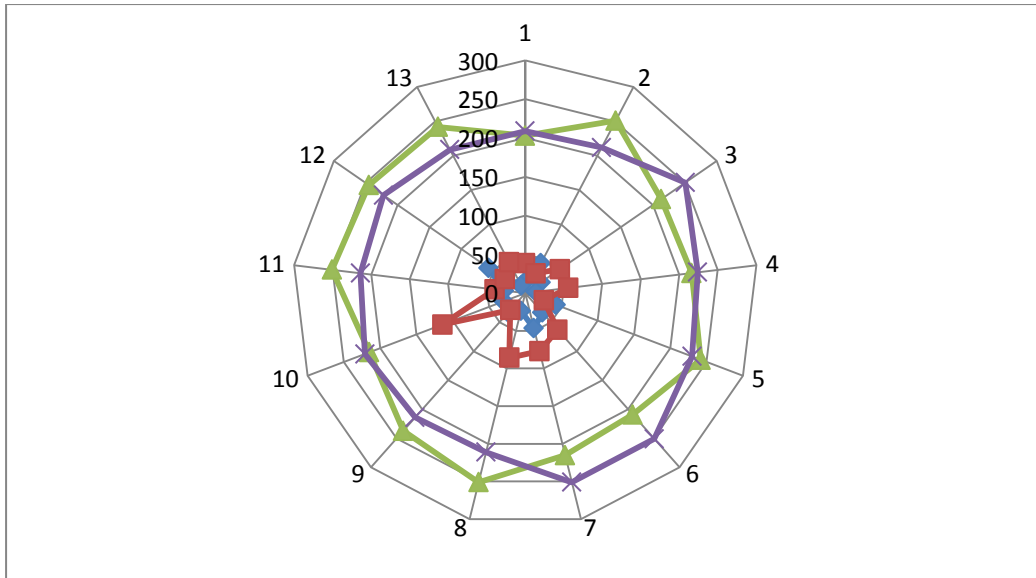
**Figure 5.52:** Latency variability in Patients affected (blue) Vs unaffected (red). The spokes 1 to 13 represent the 13 individual subjects. The latency (0 to 300 in multiples of 50) is in milliseconds.



**Figure 5.53:** Latency variability in Healthy Left (blue) Vs Patient affected (red). The spokes 1 to 13 represent the 13 individual subjects. The latency (0 to 300 in multiples of 50) is in milliseconds.



**Figure 5.54:** Latency variability in Healthy Right (blue) Vs Patient unaffected (red). The spokes 1 to 13 represent the 13 individual subjects. The latency (0 to 300 in multiples of 50) is in milliseconds.



**Figure 5.55:** Composite spider plot of GFP and Latency variability in Healthy and Patients. The spokes 1 to 13 represent the 13 individual subjects. The GFP score (Blue = Healthy left, Red=Patient affected) is in microvolts. The latency (Green = Healthy left, Purple=Patient affected) is in milliseconds.

The above spider plots illustrate two main points:

1. Significant variability in the patient group compared to the healthy group in terms of GFP score for both affected (Levene's test, one-tailed  $p=0.03$ ) and unaffected (Levene's test, one-tailed  $p=0.045$ ) sides.
2. No significant variability in the patient group compared to the healthy group in terms of peak latency.

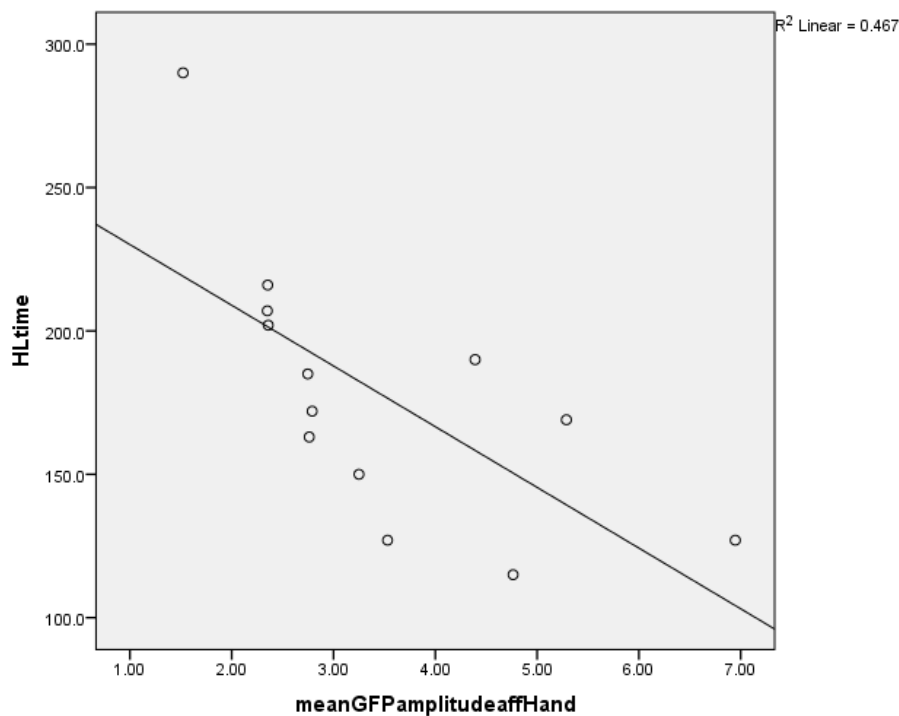
### 5.4.6 Results - Correlations

Correlation analyses were done using GFP & Behavioural variables described below:

GFP variables (calculated over the time period of 200-400 ms): Peak latency, peak amplitude and mean amplitude

Behavioural variables: Average Reaction Time, average accuracy, BPI pain scores, HAD Anxiety & Depression Scores, NLSQ (Neglect-Like Symptom Questionnaire) and Hand Laterality (accuracy & time). Pain severity was derived from the Brief Pain Inventory and included the 'worst' pain and 'average' pain in the last 24 hours as well as the 'current' pain. Pain interference was scored as the mean of the seven interference items.

Hand laterality time showed significant correlation (after Bonferroni correction for multiple comparisons) with mean GFP amplitude of affected hand. (Figure 5.55). None of the other behavioural variables including pain severity correlated with any of the GFP variables.



**Figure 5.56:** HL Time & mean GFP amplitude (affected hand), Spearman's rho, correlation coefficient= -0.809, significance=0.02

## 5.5 Discussion

We recruited 13 CRPS patients (11 females, mean age=46.8 years) and 13 age-and- sex matched healthy controls. In the CRPS group, 4 had left arm, 2 had right arm, 5 had left leg and 2 had right leg affected respectively. The mean disease duration was 5.3 years (range 1-14).

On average, healthy controls had similar reaction times in the left and right hands, while the patients had significantly longer reaction times in the affected hand compared to the unaffected hand. The average reaction times of patients affected as well as unaffected hands were significantly longer than both the left and right hands of healthy controls.

Healthy controls, on average, had similar accuracy in the left and right hands. In contrast the patients, on average, had statistically significant lower accuracy in the affected hand than in the unaffected hand. Patients had statistically significant lower accuracy in the affected hand compared to either the left or right hand in healthy controls. In the unaffected hand, patients had a lower accuracy (but not reaching statistical significance) compared to the left hand in the healthy controls and statistically significant lower accuracy compared to the right hand in the healthy controls.

The average reaction times of patients' affected hand in right sided (n=4) CRPS was significantly longer compared to the left sided (n=9) CRPS. However, there was no statistically significant difference in the average reaction times of patients' unaffected hand in right sided CRPS compared to the left sided CRPS. There was no statistically significant difference in the average accuracy of patients' affected or unaffected hands in right sided CRPS compared to the left sided CRPS.

There was no statistically significant difference in the average reaction times of patients' hand on the affected or unaffected side in upper limb (n=6) CRPS compared to the lower limb (n=7) CRPS. Similarly, there was no statistically



significant difference in the average accuracy of patients' hand on the affected or unaffected side in upper limb CRPS compared to the lower limb (n=7) CRPS.

All patients and healthy volunteers were right handed and there were no statistically significant differences between healthy left and healthy right hands on GFP analysis. Hence we could have used either healthy left or healthy right as comparator group to the patient group. We compared healthy left to patient affected and healthy right to unaffected group. We also compared combined left and right hands in healthy to combined affected and unaffected hand in patients.

In the Experiment 1 designed to elicit P300 responses (where the patients had to behaviourally respond to the stimuli), we noted interesting differences in the GFP in 200-400 ms segment.

At the group level, there was a statistically significant difference ( $p=0.003$ ) with the GFP score in the affected hand in patients being higher compared to healthy left in the time segment 200-400 ms but not between 0-200 ms. There was also a statistically significant difference ( $p=0.008$ ) between healthy (left and right combined) compared to patients (affected and unaffected combined) in the time segment 200 -400 ms but not between 0-200 ms.

There was no significant difference between right hand stimulations in healthy controls compared to unaffected hand stimulation in patients. There were no statistically significant differences either between left and right hand stimulations in healthy subjects or between affected & unaffected hand stimulations in patients. We also ran an ANOVA to test the interaction between left & right hands in healthy and affected & unaffected hands in patients and found that there were no statistically significant interactions ( $F=0.24$ ,  $p=0.62$ ).

At the individual level, there were no statistically significant differences between left or right hand in any of the healthy controls. In contrast, statistically significant differences between affected and unaffected hands were noted in four of the 13 patients. In three of these 4, GFP on the affected side was higher than the unaffected side whereas in one, the reverse was true.

There was significant variability within the patient group compared to the healthy group in terms of GFP score for both affected (Levene's test, one-tailed  $p=0.03$ ) and unaffected (Levene's test, one-tailed  $p=0.045$ ) sides. There was no significant variability in the patient group compared to the healthy group in terms of peak latency.

In the Experiment 2 designed to study the somatosensory ERPs, GFP analysis revealed no statistically significant differences between left and right hand stimulations in the healthy controls either at the group or the individual level. There were also no statistically significant differences between the affected and unaffected sides in the patients either at the group or the individual level. Comparisons between the healthy and the patient groups also failed to reveal any statistically significant differences in the somatosensory ERPs.

Our finding of no significant differences in the GFP analysis in both the time segment of 0-200 ms in the Experiment 1 as well as the Experiment 2 suggest that there was no impairment of somatosensory conduction from the periphery to the somatosensory cortex in the CRPS patients in this study. This is in keeping with the finding of a systematic review and meta-analysis of somatosensory cortex function in CRPS (Di Pietro et al. 2013b).

Despite the somatosensory signals apparently reaching the cortex normally, the patients took significantly longer to respond to stimuli and also had lower accuracy rate compared to healthy controls. This suggests a higher cognitive dysfunction in the way signals are processed in the cerebral cortex which may be a result of structural or functional cortical reorganisation. This altered

cognitive processing during tactile perceptual decision-making is likely downstream of early-latency somatotopic mapping.

P300 (positive peak seen usually between 200 and 400 ms after stimulus onset) has been studied as a marker of cognitive dysfunction in a variety of clinical contexts including chronic headache (DeMirci & Savas 2002), chronic lower back pain (Tandon et al. 1997; D. S. Veldhuijzen et al. 2006), phantom limb pain (Karl et al. 2004), schizophrenia (Ford 1999) and dementia (Parra et al. 2012).

P300 is an endogenous potential which does not depend upon the physical attributes of the external stimulus but on the person's reaction to the stimulus. Some experts have further classified P300 into two components, P3a (also called novelty P3) and P3b (also called classic P3). P3a originates from stimulus driven frontal attention mechanisms during task processing, whereas P3b originates from temporo-parietal activity associated with attention and appears related to subsequent memory processing (Polich 2009; Linden 2005).

Previous studies have provided inconsistent results on the P300 latency and amplitude in chronic pain conditions as discussed below.

Increase in P300 latency was reported in chronic back pain patients compared to healthy adults in a study using visual odd-ball paradigm (Tandon & Kumar 1993). Another visual ERP study (n=12) reported that improvement in pain scores in chronic back pain patients with treatment (epidural steroid injection) was associated with parallel decrease in the baseline P300 latency (Tandon et al. 1997).

An auditory ERP study (n=23 chronic back pain, 23 episodic tension-type headache & 23 age-and-sex matched healthy controls) did not find any baseline differences in P300 latency or amplitude between groups (DeMirci & Savas 2002).

A visual ERP study on chronic non-malignant pain patients (n=14 patients, 30 healthy) also found no differences in P300 latency or amplitude between patient and healthy groups in the primary task. However with increasing task difficulty, in contrast to the healthy, the patients did not show a decrease in P300 amplitude (D. S. Veldhuijzen et al. 2006).

A visual ERP study on phantom pain patients (n= 5 upper limb amputees without pain, 5 upper limb amputees with phantom pain & 10 age-and-sex matched healthy controls) found that P300 amplitude was higher and latency was longer in the phantom pain group compared to the other groups. They also reported that the pain severity correlated with the P300 amplitude (Karl et al. 2004).

We did not find any significant differences in the latency between patient and healthy groups in our study in line with some previous studies (DeMirci & Savas 2002; D. S. Veldhuijzen et al. 2006) and in contrast to others (Karl et al. 2004; Tandon et al. 1997; Tandon & Kumar 1993).

We found that at the group level the P300 amplitude was increased in the affected side of the patient group compared to the healthy group. However there were no statistically significant differences between affected and unaffected sides in the patient group. This was broadly in line with other studies (Karl et al. 2004) and may reflect increased allocation of resources in terms of attention and perceptual sensitivity.

Additional analyses (collaborative work with Dr Chris Brown; (Kuttikat et al. 2018) ) were carried out considering 3 factors: digit type, side affected (by CRPS), and group (CRPS, Healthy Control). These analyses focused on EEG source analysis and were done using SPM12 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)) and showed augmented P300-like responses in supplementary motor area (SMA), positively correlating with longer response times in CRPS patients. The response was also observed in Experiment 2, but was substantially diminished (indicating sensitivity to task demands) and there was no group difference. This suggests that the augmented response was due to the need

for greater attentional resources to perform the task in this group. Interestingly, the magnitude of the P300 activity in CRPS patients predicted better limb functioning, suggesting it compensates to the disease rather than directly marking disease pathology.

Our study findings did not support our central hypothesis that EEG markers of cortical reorganisation will correlate significantly with finger misperception. We also did not find any correlation between cortical reorganisation in CRPS and pain severity.

Patients were on medications that may affect neural responses as described below. A study of intravenous Tramadol in the anaesthetic setting has been reported to show activation of EEG variables including power frequency, spectral edge, Delta Power and Alpha/Delta ratio but no significant change in amplitudes or latencies (Vaughan et al. 2000).

A study of fluoxetine and amitriptyline in depressed patients showed a significant decrease in the amount of beta activity but no EEG evidence of drowsiness or epileptiform activity (Tarn et al. 1993). Another study found that amitriptyline increased reaction times after acute but not after sub-chronic administration. ERP analyses showed that P300 amplitudes to the task stimuli were not affected by amitriptyline (Veldhuijzen et al. 2006). Sertraline can cause augmentation and acceleration of alpha activity and attenuation and acceleration of delta activity (Saletu et al. 1986).

Gabapentin and Carbamazepine can slow the alpha rhythm and median EEG frequency, and increased the percentage of theta and delta power (Salinsky et al. 2002). Pregabalin has been shown to decrease alpha and beta band power during NREM sleep and increase the delta band power (Wilson et al. 2011).

Morphine is known to increase alpha and theta power, and decrease delta power (Phillips et al. 1994). Diazepam can decrease theta and alpha activity and increases beta activity (Montagu 1972).

Patients in our study have been on stable medications and it is difficult to be certain what effects these had on the EEG findings. Medication use raises a complex confound in that certain medications (such as opioids) may reduce

cognitive performance, but also more severely affected patients are more likely to be prescribed such medication; establishing cause and effect is impossible from cross-sectional data.

There was variability within the patient group in terms of clinical characteristics. The disease duration ranged from 1 year to 14 years and some had upper limb affected while others had lower limb affected. In addition to this clinical heterogeneity, another limitation of the study was the small sample size which can impact on the robustness and generalisability of the findings. General limitations of EEG technique such as low spatial resolution also make it difficult to draw any strong conclusions about the structural reorganisation within the cerebral cortex.

Future studies with larger sample sizes can allow clustering into mechanistically homogeneous patient sub-groups and these are necessary to further characterise the cortical changes in CRPS. Follow up studies will help us delineate the neural cortical changes in the patient group that may fluctuate with the clinical course of the disease. Spatial localisation studies using f-MRI and functional connectivity studies to assess the spectral signatures of cognition may provide objective biomarkers that are clinically useful in this condition.

## **5.6 Conclusion**

In our case control design study, CRPS patients had significantly reduced accuracy and prolonged reaction time in the affected side compared to the unaffected side in the behavioural task of identifying the finger stimulated by a handbox. They also had significantly reduced accuracy and prolonged reaction time in both hands when compared to the age-and-sex matched healthy subjects. There was also high variability in the tactile discrimination performance across CRPS patients.

There was no significant difference in the GFP latency in the patient group compared to healthy subjects. There was also no difference between affected and unaffected sides of the patient group suggesting there was no impairment of somatosensory conduction from the periphery to the somatosensory cortex. However, GFP amplitude corresponding to P300 was significantly higher in the patient affected side compared to the healthy controls suggesting cognitive dysfunction possibly related to increased allocation of attentional resources.

Our study did not find any correlation between cortical reorganisation in CRPS and either finger misperception or pain severity.

Additional collaborative work (EEG source analysis) revealed augmented P300-like response in SMA in CRPS patients that was positively correlating with longer response times in CRPS patients.

## **Chapter 6: Overall Conclusions**

### **6.1 Background and hypotheses explored**

Delays in diagnosis occur in CRPS adversely affecting patient outcomes.

The first research project in this thesis, 'Novel Signs in CRPS and their Diagnostic Clinical Utility' was a prospective observational cohort study which defined the four novel signs of finger misperception, abnormal hand laterality, astereognosis and abnormal body scheme report in CRPS, examined their prevalence in CRPS and other chronic pain conditions and assessed their diagnostic utility (Sensitivity, Specificity, Predictive values and Likelihood ratios) for identifying patients at risk of CRPS within a Fracture cohort. The main hypotheses explored in this study were that the prevalence of novel signs in CRPS will be higher compared to other chronic pain conditions and also that these signs will have significant diagnostic clinical utility in diagnosing CRPS compared to a group of fracture patients.

Cortical reorganisation, defined as structural and functional changes within the cerebral cortex, is implicated in many chronic pain conditions including CRPS. The second research project in this thesis 'Cortical Reorganisation and Finger Misperception in CRPS- a High Density Electroencephalogram Study' was a prospective case control design study which investigated the EEG parameters suggestive of cortical reorganisation in CRPS patients by studying the somatosensory ERPs (Event Related Potentials) elicited on painless finger stimulation. The central hypothesis of this study was that the "cortical reorganisation" as defined by EEG parameters will correlate significantly with finger misperception in CRPS.

### **6.2 Diagnostic utility of novel clinical signs**

We demonstrate that novel signs are present in the majority of CRPS patients and can be reliably detected following simple training. They are practical and have significant clinical utility in diagnosing persistent pain in a fracture group



thereby allowing targeted intervention. They are also present in other chronically painful conditions such as RA, FMS, and LBP.

Finger misperception (FP) and abnormal body scheme report (BS) were the best performing tests and by combining them the diagnostic utility can be further improved. Prospective monitoring of fracture patients showed that out of 7 fracture patients (total n=47) who had both finger misperception and abnormal BS report at initial testing, 3 developed persistent pain with 1 having a formal diagnosis of CRPS.

### **6.3 P300 as a high density EEG marker of cognitive dysfunction**

Our study confirmed that CRPS patients had altered cognitive processing of tactile stimuli. During a task to discriminate the digit simulated, patients (compared to controls) had significantly lower accuracy and slowed response times but with high between-subject variability.

In our study, there was no significant difference in the GFP (Global Field Power) latency in the patient group compared to healthy subjects or between affected and unaffected sides of the patient group suggesting there was no impairment of somatosensory conduction from the periphery to the somatosensory cortex. However, GFP amplitude corresponding to P300 was significantly higher in the patient affected side compared to the healthy subjects suggesting cognitive dysfunction possibly related to increased allocation of attentional resources. Additional source analysis showed augmented P300-like response under task demands that localised to supplementary motor area (SMA). Source activity in SMA correlated with slowed response times, while its scalp representation correlated with better functioning of the affected limb, suggesting a compensatory mechanism. Our study did not find evidence to support our hypothesis that cortical reorganisation in CRPS will correlate with finger misperception and pain severity.

## 6.4 Clinical Relevance

The two research studies described in this thesis are complementary to each other. The first study sets out the diagnostic utility of clinical signs in diagnosing CRPS and the second study explored the high density EEG markers of cortical reorganisation in CRPS.

Clinical tests in the first study were designed to be used in a practical clinic setting with minimal equipment and hence are simple and time efficient. Behavioural test for finger misperception in the second study was robust and elaborate but requires additional equipment (eg; handbox) and hence may not be practical in a busy clinic setting. However, this study also established the presence of finger misperception in a significant proportion of CRPS patients and thus provides further validation for this study.

The tests for finger misperception and abnormal body scheme performed well in the study but the tests for astereognosis and abnormal hand laterality did not. Some modifications in these tests such as increasing the number and complexity of objects used in astereognosis test and the images in hand laterality test may improve their diagnostic utility and this possibility merits further exploration in future studies.

The clinical tests presented in this thesis potentially add value over the modified Budapest criteria as they test for facets of body perception disturbance not included in the formal criteria. Patients may not also fulfil the strict 'modified Budapest criteria' due to variability of their clinical features.

Therapeutic strategies targeting cortical reorganisation such as graded motor imagery training, tactile discrimination training, electrical sensory discrimination therapy and neurofeedback have been used in CRPS patients (Bowering et al. 2013; Moseley & Wiech 2009; Bailey et al. 2013). Comprehensive Graded Motor Imagery training incorporates 3 components namely - 1) Left/Right laterality judgements, 2) Motor Imagery and 3) Mirror Visual Feedback (Bowering et al. 2013). Mirror Visual Feedback is often used

as a stand-alone therapy without the previous two stages. It provides a visual illusion whereby the reflection of the unaffected limb is superimposed on the affected limb. This can reduce pain levels by providing corrective sensory feedback which reduces sensorimotor conflict (Bailey et al. 2013).

Tactile discrimination training can increase tactile acuity and decrease pain in CRPS patients (Moseley & Wiech 2009). Electrical Sensory Discrimination Training involves application of electrodes around the painful area and participants then choose which electrodes to be stimulated. Feedback is given after each electrode is stimulated and the participants progress through a hierarchy of training levels. Early pilot work suggests that this is safely tolerated and in CRPS patients and improves two-point discrimination (McCabe et al. 2011).

Our study provides evidence for altered neurocognitive processing of tactile stimuli in CRPS and thus offers mechanistic reasons why these treatment strategies that target cortical reorganisation may be useful. The tests that we describe in our study may also allow us to stratify a sub-group of patients who respond better to these treatments although this needs to be tested formally in future studies.

## **6.5 Future directions**

The work presented in this thesis has the potential to alter clinical practice in terms of using the novel clinical signs to identify high risk patients from a fracture cohort. However, longer term prospective follow up of a larger cohort of fracture patients are necessary to confirm the diagnostic utility in some of these patients who may eventually develop CRPS. Importantly, our study also reveals that novel signs are present in other pain conditions including inflammatory conditions such as rheumatoid arthritis. This raises the intriguing possibility that some of these patients may have common underlying mechanistic reasons for developing chronic pain. This is an area for further explorative research which has significant implications in optimising management of these patients.

We have shown that somatosensory ERPs recorded using high density EEG can be useful to study the cortical changes in CRPS. In particular, mid-to-late latency responses (corresponding to P300) could potentially provide convenient and robust biomarkers of abnormal perceptual decision-making mechanisms in CRPS to aid in clinical detection and treatment. Future research should investigate the clinical utility of these putative markers of tactile decision-making mechanisms in CRPS.

Novel therapeutic strategies targeting cortical reorganisation are being trialled and developed in CRPS. It will be of great clinical utility to develop objective functional and structural neuro-imaging biomarkers that help identify sub-groups of patients that are more likely to respond to these interventions.

Larger studies will allow clustering of patients into more homogeneous sub-groups and these are necessary to overcome the challenge of significant clinical and mechanistic heterogeneity in CRPS. Follow up studies are required to delineate the neural cortical changes in the patient group that may fluctuate with the clinical course of the disease. Spatial localisation studies using f-MRI and functional connectivity studies to assess the spectral signatures of cognition may provide objective biomarkers that are clinically useful in this condition.

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# Appendices

## Appendix 1: Funding details and ethics approval

**Study 1:** Clinical utility of novel clinical signs in patients with CRPS

Funding source: BMA Doris Hillier Award & Cambridge Arthritis Research Endeavour (CARE)

NIHR CRN (National Institute of Health Research, Clinical Research Network) portfolio adopted study (Ref No: 11545)

Ethics: Approved by the Research Ethics Committee, East of England-Essex (REC Ref No: 09/H0302/83)

**Study 2:** Cortical reorganisation in CRPS and digit misperception-

A high density Electroencephalogram Study

Funding source: Cambridge Arthritis Research Endeavour (CARE)

Ethics: Approved by the Research Ethics Committee, East of England-South Cambridge (REC Ref No: 12/EE/0305)

## Appendix 2: Location of Research

All research was carried out in Addenbrooke's hospital, Cambridge University Hospital NHS Foundation Trust and Herchel Smith building for brain and mind sciences, Cambridge.

## Appendix 3: Personal contribution to research

I recruited the subjects, administered the tests for novel clinical signs, collected and analysed the data for the study 'Novel clinical signs and their diagnostic clinical utility in CRPS'. I successfully applied for the inclusion of this study into the NIHR portfolio.

I prepared the study protocol and successfully applied for ethics approval for the study, 'Cortical reorganisation in CRPS and digit misperception-A high density EEG study'. I helped design the handbox used in the study to deliver somatosensory stimuli. I recruited subjects, administered the tests and collected high density EEG data from the subjects. I pre-processed the EEG

data using custom MATLAB scripts based on EEGLAB. I analysed the EEG data using FieldTrip, open source software implemented as a MATLAB toolbox. I also analysed the behavioural data using IBM SPSS.

The following contributions have been made by others:

Dr. Nicholas Shenker and Dr. Maliha Shaikh prepared the study protocol and obtained funding and ethics approval for the study, 'Novel signs and their clinical diagnostic utility in CRPS'. Research nurses, Ms. Yin Fan and Ms. Alison Mitchell helped with patient recruitment and data collection for this study. Mr. Richard Parker and Prof Toby Prevost provided guidance on the statistical analyses.

Dr. Tristan Bekinschtein and Dr. Valdas Noreika helped with the conceptualisation and preparation of study protocol for the study, 'Cortical reorganisation in CRPS and digit misperception-A high density EEG study' and also trained me in acquisition, pre-processing and analysis of the EEG data. Dr. Srivas Chennu provided the scripts used in running the experiments and data analysis and also trained me in EEG data analysis. Dr Christopher Brown did additional analyses (including source analysis) on the EEG data.

#### **Appendix 4: Supervision**

Prof Hill Gaston, Professor of Rheumatology, University of Cambridge and Dr Nicholas Shenker, Consultant Rheumatologist, Addenbrooke's hospital provided overall supervision for my MD.

Dr. Nicholas Shenker supervised the study 'Novel clinical signs and their diagnostic clinical utility in CRPS'. Dr. Nicholas Shenker and Dr. Tristan Bekinschtein supervised the study 'Cortical reorganisation in CRPS and digit misperception-A high density EEG study'.

## Appendix 5: Questionnaires used

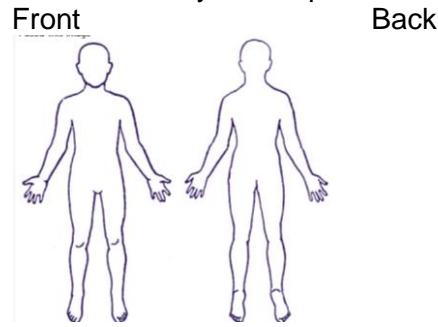
### 5.1 Brief pain inventory

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes

No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10  
No Pain as bad as you can imagine  
Pain

4. Please rate your pain by circling the number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10  
No Pain as bad as you can imagine  
Pain

5. Please rate your pain by circling the number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10  
No Pain as bad as you can imagine  
Pain

6. Please rate your pain by circling the number that tells how much pain you have right now.





## 5.2 Upper extremity functional index (UEFI)

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your arm problem. Please circle a number for **each** activity. Today, do you or would you have any difficulty at all with:

Activities	Extreme difficulty / Unable	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty
Any of your usual work, housework, or school activities	0	1	2	3	4
Your usual hobbies, recreational or sporting activities	0	1	2	3	4
Lifting a bag of groceries to waist level	0	1	2	3	4
Lifting a bag of groceries above your head	0	1	2	3	4
Grooming your hair	0	1	2	3	4
Pushing up on your hands (e.g. from bathtub or chair)	0	1	2	3	4
Preparing food (e.g. peeling, cutting)	0	1	2	3	4
Driving	0	1	2	3	4
Vacuuming, sweeping or raking	0	1	2	3	4
Dressing	0	1	2	3	4
Doing up buttons	0	1	2	3	4
Using tools or appliances	0	1	2	3	4
Opening doors	0	1	2	3	4
Cleaning	0	1	2	3	4
Tying or lacing shoes	0	1	2	3	4
Sleeping	0	1	2	3	4
Laundering clothes(e.g. washing, ironing, folding)	0	1	2	3	4
Opening a jar	0	1	2	3	4
Throwing a ball	0	1	2	3	4
Carrying a small suitcase with your affected limb	0	1	2	3	4
Column Totals:					

### 5.3 Lower extremity functional index (LEFI)

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your leg problem. Please circle a number for **each** activity. Today, do you or would you have any difficulty at all with:

Activities	Extreme Difficulty/ unable	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty
Any of your usual work, housework, or school activities	0	1	2	3	4
Your usual hobbies, recreational or sporting activities	0	1	2	3	4
Getting into or out of the bath	0	1	2	3	4
Walking between rooms	0	1	2	3	4
Putting on your shoes or socks	0	1	2	3	4
Squatting	0	1	2	3	4
Lifting an object, like a bag of groceries from the floor	0	1	2	3	4
Performing light activities around home	0	1	2	3	4
Performing heavy activities around home	0	1	2	3	4
Getting into or out of a car	0	1	2	3	4
Walking 2 blocks	0	1	2	3	4
Walking a mile	0	1	2	3	4
Going up or down 10 stairs (about 1 flight of stairs)	0	1	2	3	4
Standing for 1 hour	0	1	2	3	4
Sitting for 1 hour	0	1	2	3	4
Running on even ground	0	1	2	3	4
Running on uneven ground	0	1	2	3	4
Making sharp turns while running fast	0	1	2	3	4
Hopping	0	1	2	3	4
Rolling over in bed	0	1	2	3	4
Column Totals:					



#### **5.4 Neglect-like Symptom Questionnaire**

Painful limbs can sometimes feel alien due to nervous system changes. For each of the five items, please circle the statement with which you most strongly agree.

1. If I don't focus my attention on my painful limb it would lie still, like a dead weight.

Never - Very rarely - Rarely - Occasionally - Very frequently - Always

2. My painful limb feels as though it is not part of the rest of my body.

Never - Very rarely - Rarely - Occasionally - Very frequently - Always

3. I need to focus all of my attention on my painful limb to make it move

Never - Very rarely - Rarely - Occasionally - Very frequently - Always

4. My painful limb sometimes moves involuntarily, without my control.

Never - Very rarely - Rarely - Occasionally - Very frequently - Always

5. My painful limb feels dead to me.

Never - Very rarely - Rarely - Occasionally - Very frequently – Always

### **5.5 Hospital anxiety and depression score**

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more. This questionnaire is designed to help your doctor to know how you feel. Please read each item and circle the reply which comes closest to how you have been feeling in the last week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a thought out response.

1. I feel wound up

Most of  
the time

A lot of  
the time

From time  
to time

Not at  
all

2. I still enjoy the things I used to enjoy

Definitely  
as much

Not quite  
so much

Only a  
little

Hardly at  
all

3. I get a sort of frightened feeling as if something awful is about to happen

Very definitely  
and quite badly

Yes, but not  
so badly

A little but it  
doesn't worry me

Not at  
all

4. I can laugh and see the funny side of things

As much as I  
always could

Not quite as  
much now

Definitely not  
so much now

Not at  
all

5. Worrying thoughts go through my mind

A great deal  
of the time

A lot of  
the time

From time to time  
but not often

Only  
occasionally

6. I feel cheerful

Not at  
all

Not often

Sometimes

Most of the time

7. I can sit at ease and relax

Definitely

Usually

Not often

Not at  
all

8. I feel as if I am slowed down

Nearly all of  
the time

Very often

Sometimes

Not at  
all

9. I get a sort of frightened feeling like butterflies in the stomach

Not at  
all

Occasionally

Quite  
often

Very  
often

10. I have lost interest in my appearance

Definitely

I don't have as  
much care as I  
should

I may not take  
quite as much  
care

I take as much  
care as ever

11. I feel restless as if I have to be on the move

Very much  
indeed

Quite  
a lot

Not very  
much

Not at  
all

12. I look forward with enjoyment to things

As much as  
I ever did

Rather less  
than I used to

Definitely less  
than I used to

Hardly  
at all

13. I get sudden feelings of panic

Very often  
indeed

Quite  
often

Not very  
often

Not at  
all

14. I can enjoy a good book or radio/TV programme

Often

Sometimes

Not  
often

Seldom

**Appendix 5.6 – Sample of data collection chart for Body Scheme Report**

Body Part	Size			Length			Weight	
	Left	Right		Left	Right		Left	Right
Forehead								
Cheeks								
Chin								
Shoulders								
Upper arms								
Elbows								
Forearms								
Wrists								
Thumb								
Index finger								
Middle finger								
Ring finger								
Little finger								
Lower Back								
Hips								
Thighs								
Knees								
Shins								
Ankle								
Big Toes								
Other Toes								

Example of scoring : If a subject reports that right thumb feels 20 % bigger than left, then it is documented as +20% in the column under size for right thumb

## **Appendix 6: Relevant publications of Dr Kuttikat related to the MD thesis**

- 1. Kuttikat A**, Noreika V, Chennu S, Shenker N, Bekinschtein T, Brown CA. Altered cognitive processing of tactile stimuli in patients with Complex Regional Pain Syndrome (CRPS). *J Pain*. 2018 Apr; 19(4):395-409.
- 2. Kuttikat A**, Shaikh M, Oomatia A, Parker R, Shenker N. Novel signs and their clinical utility in diagnosing Complex Regional Pain Syndrome (CRPS): A prospective observational cohort study. *Clin J Pain*. 2017 Jun; 33(6):496-502.
- 3. Kuttikat A**, Noreika V, Shenker N, Chennu S, Bekinschtein T, Brown CA. Neurocognitive and neuroplastic mechanisms of novel clinical signs in CRPS. *Front Hum Neurosci*. 2016 Jan 27; 10:16.
- 4. Dubuis E**, Thompson V, Leite MI, Blaes F, Maihöfner C, Greensmith D, Vincent A, Shenker N, **Kuttikat A**, Leuwer M, Goebel A. Longstanding Complex Regional Pain Syndrome is associated with activating autoantibodies against alpha-1a adrenoceptors. *Pain*. 2014 Nov; 155(11):2408-17.
- 5. Kuttikat A**, Shenker N. 'Fibromyalgia & diffuse pain syndromes: Adult onset.' *Oxford Textbook of Rheumatology*. 4<sup>th</sup> Ed. 2013.
- 6. Kuttikat A**, Shenker N. 'Chronic Pain in RA-Is it mediated by cortical reorganisation?' *Rheumatology* 2013;52(1):i122.
- 7. Kuttikat A**, Shenker N. 'Pharmacological modulation of central nociception in the management of chronic musculoskeletal pain.' *Pain Management* 2011; 1 (6): 549-556.