Title: Imaging and clinical evidence of sensorimotor problems in CRPS: utilizing novel treatment approaches

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Abstract 150-250 words

Inflammation and altered autonomic function are diagnostic signs and symptoms of Complex Regional Pain Syndrome. In the acute stages these are commonly at their most florid accompanied by severe pain and reduced function. Understandably this has directed research towards potential peripheral drivers for the causal mechanisms of this condition. In particular this is now focused on the inflammatory process and the potential role of autoantibodies. More subtle changes also occur in terms of altered tactile processing within the affected limb, disturbances in body perception and motor planning problems that become more evident as the condition progresses. Through careful clinical observation and neuro-imaging techniques, these changes are now thought to be associated with altered cortical processing that includes reorganisation of both the motor and sensory maps. Furthermore, there appears to be a close relationship between the intensity of pain experienced and the extent of cortical re-organisation.

This increased knowledge around the peripheral and central mechanisms that may be operating in CRPS has been used to inform novel therapeutic approaches.

We discuss here the presenting signs and symptoms of CRPS, with particular focus on sensory and motor changes and consider which mechanisms may drive these changes. Finally, we consider the emerging therapeutic options designed to correct these aberrant mechanisms.

Key words: 4-6

Complex Regional Pain Syndrome; cortical reorganisation; sensory system; motor system; pain; body perception disturbances

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Introduction

The painful, commonly hot, red and swollen limb of early Complex Regional Pain Syndrome (CRPS) meets the classic definition of inflammation: ‘dolor’, ‘calor’, ‘rubor’, ‘tumor’ and ‘loss of function’ as originally defined by Celsus in the 1st century A.D and later added to by Galen of Pergamon (Rather 1971). These signs and symptoms would appear to indicate a protective response to harmful stimuli and suggests CRPS is most likely to be an autoimmune condition but the causative pathogen has yet to be established. Recent research in this area has identified autoantibodies in approximately 90% of those with CRPS (Kohr et al. 2011) but this still leaves a proportion of patients unaccounted for and does not adequately explain how acute CRPS may evolve into the chronic form (see Marinus et al. 2011 for review). In addition, no correlation has been observed between autoantibodies titres, age of patient, or years since onset of CRPS.

Routine serology markers for inflammation are not raised in CRPS, though recent analysis of blister fluid from CRPS affected limbs has shown elevated inflammatory markers (Huygen et al. 2002; Groeneweg et al. 2006). These changes in cytokine activity are not associated with disease duration or other clinical signs (Marinus et al 2011) but appear to be related specifically to the degree of mechanical hyperalagesia, rather than pain per se, as they remain high even when the pain disappears (Wesseldijk et al. 2008). Autoantibodies in some patients with CRPS have been reported by a number of groups (Blaes et al. 2004; Goebel et al. 2010; Kohr et al. 2011) but it is not yet clear whether the autoantibodies are pathogenic or potentially protective against future reinfection.

CRPS it is not cured by immunosuppressants; these commonly only provide moderate benefit in acute cases with no response seen in chronic disease (Christensen et al.1982). Furthermore, other signs and symptoms quite quickly develop in the affected limb that would not commonly occur with an inflammatory response, such as dramatic changes in hair and nail growth (Harden et al. 2010), significant problems with motor control (Van Hilten et al. 2005), neglect and perceived lack of ownership of that limb (Galer et al. 1995, 1999; Lewis et al. 2007; Lewis & McCabe 2010). In addition, recent imaging studies have demonstrated that the motor and sensory cortical maps representing the painful limb become altered (Maihöfner et al. 2003; 2004) and the magnitude of those changes appears to closely correlate to the intensity of perceived pain and a reduction in tactile acuity.

Over time, the impact of this dysfunctional limb on a person's life may lead to problems with mood, disrupted sleep, loss of earnings and social isolation (Bruehl et al. 2006). The symptoms may spread to other limbs (Van Rijn 2011) and the level of disability increase. What started as a seemingly relatively straight forward, classic inflammatory response has now become a complex, multi-system syndrome with little clear indication of what was cause or effect. Treating, or indeed curing, such a condition remains a challenge for clinicians and researchers.

In order to illuminate some of these clinical and scientific puzzlements, research into CRPS has historically polarised into either peripheral or central 'mechanisms camps' with both 'sides' robustly defending their own ideology (see Baron et al 2002 for review). However, in recent years there has begun to be recognition that these two worlds are not mutually exclusive and CRPS undoubtedly is a multi-system syndrome that probably starts via a peripheral trigger but rapidly involves central changes which continue to drive the condition in its chronic form (Marinus et al. 2011). It is therefore

important to understand how peripheral and central systems are affected and may interact in CRPS in order to see the complete picture.

This article will provide a picture of the clinical presentation of CRPS and its impact on the sufferer. It will, in particular, discuss the changes in the sensory and motor systems as well as the more subtle signs and symptoms that a clinician may not normally be aware of in routine clinical practice. We will consider which mechanisms, peripheral and/or central may drive these sensorimotor changes and how imaging techniques have helped advance our understanding of this complex condition. Finally, we will discuss the emerging new therapeutic options, pharmacological and non-pharmacological, which have been designed to correct these aberrant mechanisms and ultimately relieve the pain and suffering associated with CRPS (Fig 1).

Clinical presentation of Complex Regional Pain Syndrome

Complex Regional Pain Syndrome is divided into two diagnostic categories, Type 1 and Type 2, which are defined by the presence (CRPS-2) or absence (CRPS-1) of an identifiable nerve lesion. The clinical presentation for these two types is the same but CRPS-2 would meet the formal classification of a neuropathic pain syndrome whereas CRPS-1 is excluded (Jensen 2011).

CRPS is characterised by persistent pain that is disproportionate to the initiating event and is accompanied by signs and symptoms of sensory, motor, autonomic and trophic abnormalities (Harden et al. 2010). We focus here on the changes in sensory and motor function.

Altered sensory perceptions

The most common sensory perception in the affected body part is that of pain and this may be described as burning, shooting, stinging, throbbing, pressing and aching which is often associated with allodynia, mechanical and thermal hyperalgesia, hypoaesthesia, dysaesthesia and hyperpathia (see Birklein 2005 for review). Over time, symptoms may change so the patient reports reduced sensory perception such as hypoesthesia, hypoalgesia and hypothermesthesia (Maier et al. 2010; Drummond 2010) and the symptoms can spread. The pattern of spread is initially on a single limb from distal to proximal but in some people CRPS can progress to involve the contralateral or ipsilateral limb/s. A younger age at onset and more severe CRPS are both risk factors for an increased chance of spread, with a contralateral pattern of spread the most common form (Van Rijn et al. 2011).

Changes in sensory perception not only occur within the limbs. Hemisensory impairment has been demonstrated in the upper quadrant of the body ipsilateral to the limb affected by CRPS (Rommel at el. 1999). Those patients who had the most extensive deficits also had the longest disease duration, the highest levels of pain, the highest incidence of mechanical allodynia and a greater tendency to develop changes in the somatomotor system, than those with more limited sensory deficits (Rommel at el. 1999). Of relevance here is an fMRI study by Diers and colleagues (2010) that has demonstrated high levels of pain in upper limb amputees is associated with reduced activity in the sensorimotor cortex. Thereby demonstrating that pain directly impacts on sensorimotor processing and the greater the pain, the larger the disruption to sensorimotor processing.

In addition to the sensory changes described above, referred sensations in CRPS have been documented. Referred or ‘double’ sensations are when touch of an anatomical

area distant from the painful site, but importantly adjacent to it on the somatosensory cortex, evokes the same sensation of touch in the painful limb. Similarly, touch of the affected limb may evoke the exact same sensation in that anatomically distant area (McCabe et al. 2003). This finding is considered to be indicative of the neuroplastic changes known to occur in the somatosensory cortical maps (Maihöfner et al. 2003; 2004). Referred sensations in CRPS and other chronic pain conditions with known cortical reorganisation are commonly lost, or reduced in intensity, if the patient watches the clinician touch their limb (McCabe et al. 2003; Hunter et al. 2003). Vision and pain perception are known to be closely linked in CRPS. Recent published work from our group has demonstrated that the intensity of CRPS derived pain may be significantly increased when patients view a Necker cube. A Necker cube is a flat drawing of a cube that appears to tilt in two different directions, depending on the viewer's mental vantage point. The fact that viewing this bi-stable reversible object incurred a painful response in some CRPS patients provides evidence of abnormal sensory integration in these patients (Hall et al. 2011). Of the 30 CRPS patients who underwent the intervention, 13 (43%) reported an increase in pain whilst viewing the reversible figure, 16 (53%) reported no change and 1 reported a reduction in pain. This response was significantly different ($p < 0.01$) to the comparison Rheumatology pain group where only 2 (6%) subjects reported an increase in pain and the majority had no change (n=18, 54.5%) or a reduction in pain (n=13, 39.4%). In addition to pain, patients with CRPS described changes in other sensations within their CRPS limb (increased sensations n=15, 50%) no change n=12(40%), reduction in sensations n=3(10%) whilst viewing the Necker cube. These sensory changes included perceived temperature change, weight change and "tingling" sensations. There were also more generalised effects reported such as dizziness, nausea and a "trance like state" (Hall et

al. 2011). Work by Schoth and colleagues (2007), using fMRI and EEG, demonstrated the dorsal rather than ventral stream of the visual pathway is activated while a subject views the Necker cube. This evolutionary older pathway involves processing within the parietal lobe and visual areas and is thought to be concerned with orienting oneself to an object and its location in extrapersonal space. We will see below how parietal function and extrapersonal space are altered in CRPS and how these may affect sensory perceptions.

Motor problems

A person with CRPS may take time to 'connect' with their affected limb when asked to initiate a movement and report increased levels of pain before any actual movement is observed. Motor disorders in CRPS include weakness and tremor in the affected limb, slowness of repetitive movements (bradykinesia), dystonias and myoclonus (see Van Hilten et al. 2005 for review).

The usually flexed postures of a CRPS dystonia occur in approximately 25% of all patients (Munts et al. 2011). The frequency of these disorders increases with the duration of the condition (Veldman et al. 1993) and research suggests that central neural networks involved with the inhibition of movement may be dysfunctional at the spinal and cortical levels (Van Hilten et al. 2005). Cooper (2011) has suggested that a retrograde spread of neuroinflammation from the spinal level to the motor cortex via corticospinal neurons may cause functional changes in the motor cortex thus giving rise to CRPS dystonia. Oaklander and colleagues (2009) hypothesised that these dystonias could be caused by small and large fibre neuropathies. However, sensory integration of proprioceptive afferent input has been found to be normal (Van Rijn et al. 2009) thus ruling out large nerve fibre involvement. More recent work by

Munts and colleagues (2011) suggests that dystonias in CRPS arise from problems in peripheral control of muscle force. Specifically, an imbalance in reflex sensitivity to muscle force is thought to create an over contraction in either the agonist or antagonist of a paired muscle group, which is not counterbalanced by its paired partner (Munts et al. 2011) thereby leading to fixed flexion (most commonly) or extension of a joint.

Magnetoencephalography (MEG) studies have identified increased activity in the primary motor cortex contralateral to the CRPS affected limb in patients with upper limb CRPS (Maihöfner et al 2007). This has been shown to correlate with poor function in motor planning tasks, particularly those that require integration with visual and proprioceptive cues such as gripping an object. Kirveskari and colleagues (2010) employed MEG to demonstrate a reduced reactivity in the ~20Hz rhythm in the motor cortex hemisphere contralateral to the CRPS affected limb when an external painful stimulus was applied. Those with CRPS demonstrated a significantly weaker response than control participants and the degree of response correlated with mean levels of pain. This abnormal motor cortex reactivity maybe linked with motor dysfunction of the affected limb in CRPS.

Evidence for motor inhibition in CRPS has also been proposed by Freund and colleagues (2010). Using Functional Magnetic Resonance imaging (fMRI) they reported activation of the anterior insula, the posterior cingulate cortex (PCC) and the caudate nucleus during painful stimulation of the symptomatic hand in those with CRPS but not in healthy control participants. They proposed that this stronger PCC activation may be interpreted as a correlate of motor inhibition.

Disturbances in body perception

An increasingly recognised feature of CRPS is the altered manner in which an individual perceives their painful limb. These perceptual changes present in various ways.

Those with CRPS express a sense that the limb no longer belongs to them, referring to the limb in the third person and as foreign or alien (Forderreuther et al. 2004; Galer et al. 1995; Lewis et al. 2007). Some describe hostile thoughts and feelings about the limb and report a strong desire for amputation despite receiving medical advice to the contrary (Lewis et al. 2007). Commonly, patients can easily identify the location at which they would like to remove the affected limb which is referred to clinically as the hypothetical amputation line.

The limb is subjectively perceived as distorted in shape and size compared to reality (see Fig. 2), described commonly as being enlarged or smaller and thinner in some cases (Lewis et al. 2007; Moseley 2005; Peltz et al. 2011). Studies show that patients have impaired judgments about their affected hand size, typically overestimating it by at least eight percent (Moseley 2005; Peltz et al. 2011). Furthermore, patients perceive the affected limb as heavier, pressurised or different in temperature from objective assessment whilst perceiving the contralateral unaffected limb as normal (Lewis et al. 2007; Lewis & McCabe 2010).

When asked to close their eyes and mentally visualise both limbs, individuals describe distortions in shape and size (see Figs. 3a & b) and indeed some are unable to picture anatomical affected limb parts in contrast to the visualised normally proportioned unaffected limb (Lewis et al. 2007).. Patients speak of being averse to looking at the affected limb and commonly hide it under clothing or positioned outside of their field of view.

Although such disturbances in body perception are not unique to CRPS, the majority of those with the condition (between 54.4% to 84%, Forderreuther et al. 2004; Galer & Jensen 1999 respectively) describe one or more features. Moreover, those with a longer disease duration and/or with greater pain present with more extensive disturbances in body perception (Lewis & Schweinhardt 2012; Peltz et al. 2011). Body perception disturbance is also associated with impairments in tactile acuity of the affected region (Lewis & Schweinhardt 2012; Peltz et al.2011)

A plausible explanation for these disturbances in body perception may be neural alterations in central representation of the affected limb. For example shrinkage in cortical representation of the affected limb is known to occur within the primary somatosensory cortex (SI) (Juottonen et al. 2002; Maihofner et al. 2003; Maihofner et al. 2004; Pleger et al. 2005; Pleger et al. 2006). SI is responsible for processing tactile inputs and provides a central somatosensory representation of the body surface. This information integrates with that from proprioceptive, vestibular and visual inputs interrelating with motor systems to form an on-line neural representational map of the body (termed body schema). This map is stored in the cortices, including SI and at a higher order such as the parietal cortex (Haggard et al. 2003; Haggard & Wolpert 2005).

Body schema is essential for our sense of body ownership and contributes to body perception, the typically conscious process of how we perceive our bodies enabling us to create a mental representation of our physical body (Haggard & Wolpert 2005). This sense of the bodily self persists even when sensory input stops.

Pain occurs during the processing and integration of neural activity including that of SI (Tracey & Mantyh 2007). Pathologic cortical reorganization in SI (a region

associated with tactile and body representation) is known to occur in chronic pain states (Flor et al. 2006; Maihofner et al. 2003). The extent of cortical alterations relate to the degree of pain (Maihofner et al. 2004). Importantly, aberrant mapping reverses as pain diminishes (Maihofner et al. 2004; Pleger et al. 2005). In light of this, it is unsurprising that pain seems to have a detrimental influence on thoughts, feelings and how individuals perceive their affected body part (Lewis et al. 2007; Lewis et al. 2010). Fear of someone knocking the painful limb, the unpredictability of symptoms and the patients disordered body perception may lead to social isolation and broken personal relationships which can reduce the patients' capacity to cope with their condition (Bruehl & Chung 2006).

The impact of body perception disturbances and altered sensorimotor processing in CRPS

Clinical observations suggest that patients with body perception disturbances have difficulty relating normally to their painful limb and that this affects rehabilitation outcomes. This is in part because they do not wish to engage with their painful limb but also because a disrupted body schema will negatively impact on motor planning. Prior to the execution of a movement, the body has to make a 'guestimate' of the sensory consequences of that movement in order to prepare the body for further activity, ensure the smooth execution of that movement and maintain the safety of the individual. Once the movement is actually performed then this 'guestimate', or efference copy, is matched against actual sensory feedback and the motor planning system is updated (Haggard & Wolpert 2005). The efference copy will in part be informed by the cortical maps. In the presence of altered body perception and cortical

reorganisation, where the motor and sensory maps may no longer accurately portray the actual location of body parts, then it is easy to see how a disruption in sensorimotor function may occur (see McCabe et al. 2009 for review).

Studies involving participants with and without chronic pain have demonstrated that when a discrepancy between sensory input and motor output is artificially generated, via the use of a mirror to provide incongruent visual feedback on limb movement (Fig. 4 a, b and c), then new sensations are evoked and movement may become clumsy in the limb hidden behind the mirror (McCabe et al. 2007). These new symptoms may include the onset of pain, or an exacerbation of pre-existing pain, changes in temperature, weight and loss of ownership of a limb. These symptoms will be lost when normal visual feedback is restored to a limb or congruent movements performed; that is, when sensory input and motor output now match.

A recent MEG study by Wasaka and Kakig (2012) involving healthy volunteers conducting thumb movements with and without modulating mirror feedback identified significantly increased activity in the secondary somatosensory area (S11) and the posterior parietal cortex when motor output conflicted with sensory input. Although they did not specifically ask participants about altered sensory or motor function, some spontaneously volunteered that during mirror movements, when sensorimotor conflict was present, they felt less control and ownership of their moving body part. This highlights again the important role of the parietal cortex in limb position sense and body ownership. We will see below how abnormalities in parietal function have been observed in CRPS and how this may impact on perceived levels of pain.

Associated parietal dysfunction

Symptoms of limb neglect, as well as finger agnosia (Forderreuther et al. 2004) and a recorded delay in the performance of imagined movements would suggest that there is disturbance within parietal lobe function in patients with CRPS (Schwoebel 2003). Clinical evidence supports this theory with patients demonstrating asterognosis (problems with object recognition via touch), confusion with number and word sequencing, errors in copying drawings and left/right disorientation (Cohen et al. 2009; Robinson et al 2010).

Imaging evidence in this area demonstrates altered parietal lobe activity in those with CRPS. Shiraishi and colleagues (2006) used Positron Emission Tomography (PET) to study cerebral glucose metabolism in CRPS and demonstrated bilateral increases in several brain areas including the parietal cortex. Wu et al (2006) also used PET to demonstrate the impact of treatment (a lumbar block and epidural morphine and ketamine) in CRPS on cerebral blood flow. Prior to treatment they recorded increased activity in the right parietal and left frontal lobes, which decreased after treatment (Wu et al 2006). Vartiainen et al (2008) used MEG to assess tactile processing in CRPS patients with allodynia and identified defective posterior parietal cortex activity that they suggested may contribute to the neglect-like symptoms seen in CRPS. This is an interesting finding in light of the study by Wasaka and Kakig (2012) described above, where sensorimotor incongruence increased activity in the posterior parietal cortex and appeared to produce altered body perception. Furthermore, it fits well with the evidence that shows a relationship between pain, tactile perception and body perception disturbances.

As the parietal cortex is important in the activation and maintenance of an internal representation of a desired movement one can see how problems with motor planning

may arise in CRPS. Furthermore, the parietal cortex is important for the assimilation of sensory and motor information to determine the level of perceived threat to the body. We have seen from the information above that sensory input and processing is grossly distorted in CRPS both with altered body perception, visual perceptions and pain related sensations. When this is combined with disrupted motor planning it is not surprising that those with CRPS present with high levels of anxiety and an over riding fear of touch to their affected limb. Patients often associate any increase in pain with injury, a misconception that may be detrimental to successful rehabilitation (Bruehl & Chung 2006; Rodham 2009). Similarly as progress in rehabilitation can often seem slow, patients frequently perceive they are regressing rather than progressing (Bruehl & Chung, 2006). Such disordered illness beliefs result in negative emotional states and decreased capacity to cope with the condition. The lack of any easy 'fix' and difficulty understanding physiological symptoms can also increase uncertainty and may serve to increase anxiety (Rodham 2009). This fear related response will be reflected by changes in autonomic regulation and therefore autonomic pathway activity (Jänig & Baron 2006).

Autonomic disturbances

The patient with CRPS commonly describes considerable temperature fluctuations in their affected limb. Levels of pain, stress and the surrounding environment will influence these thermal changes. In the early stages the limb is likely to be perceived hotter than normal and gradually progresses to considerably cooler as time passes. Impaired autonomic responses in both the affected and unaffected limbs have been found in CRPS (Schürmann et al. 1999; Schürmann et al.2000), with recovery of vasomotor function on resolution of the CRPS (Gradl & Schürmann, 2005; Wasner et

al.1999). However, the pattern of autonomic dysfunction in CRPS varies over time (Ide et al. 1997; Wasner et al. 1999) and its contribution to pain is unclear (Baron et al. 2002). Intriguingly, what has been observed recently using laser Doppler flowmetry is an asymmetrical pattern of response in those with CRPS when the Necker cube (see figure 1) is viewed such that there is significant variation in autonomic response between the affected and contralateral limbs (Cohen et al. in press). Of the total cohort of patients (n=30), 33.5% had asymmetric vasomotor responses only when viewing the Necker cube and all of the participants experienced increased pain as they looked at the image. All age and gender matched healthy controls in this study demonstrated a normal homologous symmetrical pattern of response and no reports of pain. This study provides direct evidence of the close relationship between pain, sensory processing and autonomic function.

Psychological impact on the patient of sensory and motor changes

The psychological impact of these motor and sensory changes on the patient should not be underestimated. The loss of previous social and work roles (as mother, father, partner, employee etc.) the inability to participate in hobbies and a loss of independence can result in low self-esteem, a decrease in the quality of life and a loss of self-identity. The emotional drain of coping with pain can impact on self-esteem, memory and the ability to concentrate. Frustration may arise from a lack of understanding by others (Rodham 2009). Ultimately, for some, the burden of coping with the condition can lead to suicidal ideation. Of note, it has been recently proposed that discordance in sensory and motor integration may in itself be a marker of a 'vulnerable brain' for future psychological problems (Levitt-Binun & Golland 2012). Once again we see the problems of untangling what is cause and effect in CRPS.

Pharmacological and non-pharmacological advances

There is no cure for CRPS or single therapeutic intervention that addresses the complex melange of symptoms. Recently published UK national guidelines for the care of those with CRPS recommend four pillars of intervention: pharmacological, psychological, functional rehabilitation and self-management/education strategies (Turner-Stokes et al. 2011). We briefly discuss below the more recent developments on pharmacological treatments, and those non-pharmacological treatments which target aberrant cortical processing.

Pharmacological

Current practice encourages clinicians to follow pharmacological interventions commonly used for neuropathic pain when caring for those with CRPS. However, it should be noted that in clinical practice it is common to observe atypical responses to pharmacological interventions in those with CRPS; for example, an increased sensitivity to a drug such that only low doses are tolerated. Recently, increasing evidence of raised cytokine activity (Huygen et al. 2002; Groeneweg et al. 2006) and autoantibodies in CRPS (Blaes et al. 2004; Goebel et al. 2005; Kohr et al. 2009, 2011) have encouraged consideration of different treatment approaches. Case study data suggests anti-TNF therapy may have a role in CRPS (Ozgül et al. 2011) but controlled trial data is still awaited. Goebel et al (2010) have demonstrated a significant reduction in pain for 5 out of 12 people with CRPS treated with low-dose intravenous immunoglobulin in a randomised controlled trial. This pain relief lasted for five weeks on average. Further trials in larger cohorts of participants are now required to see if this type of intervention gives substantial benefits over and above standard immune-suppressants such as cortisone.

Non-pharmacological interventions

As previously discussed, the chronic pain associated with CRPS has been linked to changes in the central nervous system, in particular alteration of the topography of the affected limb within S1. Therefore, in addition to treatments that act to address the peripheral instigators of pain (bottom up approach), therapies have now been developed that seek to ameliorate the cortical disorganisation (top down approach or 'training the brain'; Moseley 2004, 2005) thereby restoring the individual's disrupted body schema as well as reducing pain and disability.

Graded motor imagery

The Graded Motor Imagery Programme (GMIP) incorporates three distinct treatment steps: limb laterality recognition; imagined movements (IM) and mirror visual feedback (MVF). In robust randomised controlled trials it has been shown to reduce pain and improve function in patients with early and chronic CRPS (Moseley 2004). However, clinical application of GMIP has yet to demonstrate a replication of these findings as it is highly labour intensive and, in some cases, exacerbates symptoms (Johnson et al. 2011).

The first stage of GMIP requires the patient to imagine positioning their affected limb in a series of different postures. Once the patient is able to do this without eliciting any pain, they move to the imagination of simple pain-free movements in their affected limb. Such a task is thought to be beneficial, as it is known that imagining the execution of a movement activates the primary motor cortex in the same way as an actual movement thereby training the brain to believe that these movements can occur

without pain (Moseley 2004, 2005). On successful completion of the first two stages the patient moves to the final stage of Mirror Visual Feedback (MVF).

Mirror visual feedback

MVF was originally designed as a stand-alone therapy, and is still commonly used in this manner without the previous two stages of GMIP (McCabe et al. 2003b; McCabe 2011). MVF is a form of visuomotor training and essentially provides a visual illusion whereby the reflection of the unaffected limb is superimposed on the affected limb. Although, a number of theories have been proposed to explain the mechanisms underlying MVF (see Ramachandran & Altschuler 2009 for a more comprehensive review) one popular theory is that MVF provides corrective sensory feedback thereby resolving any underlying sensorimotor conflict (McCabe et al. 2003b; McCabe 2011). During MVF, action performance and observation increase activity in the primary motor cortex both ipsi- and contralaterally to the observed limb. Recent imaging studies suggest that modulation of the primary motor cortex excitability may mediate restoration of the sensorimotor mismatch via cortical re-organisation. This increased activity with MVF is postulated to modulate beneficial cortical re-organisation and hence reduce pain (Giraux & Jensen 2003).

Electrical sensory discrimination therapy

The aim of sensory discrimination therapy in CRPS is to normalize sensation over the allodynic territory thereby reducing the regional spread and intensity of pain. This technique has been shown to have a direct affect upon cortical reorganisation with enlargement of the previously shrunken representation of the affected limb on the primary and secondary somatosensory cortices (Pleger et al.2004). Traditionally

sensory discrimination has been achieved using graded textures applied manually to the margins of the allodynic area but this is labour intensive and requires good patient concordance with therapy. Flor and colleagues (2002) used intensive electrical sensory discrimination training (ESDT) over a period of two weeks to achieve a 60% reduction in phantom limb pain and showed a reversal of cortical reorganisation. ESDT involves the application of a small number of electrodes to the painful or adjacent site, and participants must choose which electrode is being stimulated. Feedback on performance is given after each stimulus and participants progress through a hierarchy of training levels. Levels of difficulty are determined by how many electrodes are stimulated and/or the spacing between electrodes; the closer the electrodes are together the higher the level of difficulty. Early pilot work using this technique in patients with CRPS has demonstrated that ESDT is tolerable for those with CRPS and two point discrimination is significantly improved (McCabe et al. 2011). Further work is needed in this area to determine the efficacy of this treatment on reducing CRPS pain.

Transcranial Stimulation

There are two types of therapeutic transcranial stimulation that have been applied to the treatment of CRPS so far, namely repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS has been found by Picarelli and colleagues (2010) to be efficacious as an add-on to pharmacological therapy in CRPS. Twenty-three patients with upper limb CRPS underwent best medical treatment (medication and physical therapy) followed by ten daily sessions of either real rTMS or sham rTMS of 10Hz to the motor cortex (M1). During treatment there was a significant reduction in pain visual analogue scores (VAS) with a mean

reduction of 465mm in the real rTMS group against 218mm in the sham group. The highest reduction occurred at the tenth session and correlated with improvement in the affective and emotional subscores of the McGill Pain Questionnaire and SF-36 (Health survey 36). This positive effect of rTMS on different aspects of pain opens the door for possible clinical uses of this technique.

Boggio and colleagues (2009) performed a randomised, sham, controlled cross-over study where eight patients with localised neurogenc pain were randomised to receive active tDCS with active TENS (transcutaneous electrical nerve stimulation) OR active tDCS and sham TENS OR sham both. The tDCS was applied over the contralateral MI. Post-hoc tests showed significant pain reduction, compared with baseline, after both active conditions, but not with the sham condition. There are no published randomised controlled trials of tDCS in CRPS, but a number of case studies suggest it has potential for improvement in pain and quality of life in this population (Schmid et al 2011; Sibirceva et al 2009).

Neurofeedback Training

Neurofeedback Training (NFT) has been found to be generally helpful in calming over excitable and over aroused nervous systems in other populations with chronic pain (Caro & Winter 2001; Sime 2004). For these reasons it is thought to be of potential use in those with CRPS but only one small, uncontrolled study has been published to date and NFT was not the only intervention (Jensen et al. 2007). In this study 18 CRPS patients participated in NFT in addition to receiving medication, physical therapy and psychotherapy. The NFT consisted of using EEG and feedback provided through visual, auditory and tactile modalities, with the training sites on the scalp including the parietal, temporal, central and frontal regions. Reinforcement

usually began at 12-15Hz and was then moved up or down until the patient reached a state of arousal where they felt optimally calm, alert and in a positive mood. Pain measures using the VAS were taken before and after a single 30 minute session of NFT and the ratings decreased on average by 230mm, with 50 % of patients reporting changes in pain intensity that were clinically meaningful. There were additional improvements in perceived muscle tension and well-being but the results need to be interpreted in the light of the study design limitations. However, this type of real-time, feedback on cortical activity may prove to be useful in the future.

Visual illusions

The use of visual illusions as a non-pharmacological approach to treat pain has been shown in patients with Osteoarthritis (OA). Preston and Newport (2011) demonstrated that by manipulating the size and shape of the painful OA hand using the 'MIRAGE' system, for example by stretching or shrinking the fingers via visual illusions participants reported immediate temporary pain relief and improved hand movement. The MIRAGE system digitally manipulated real-time video of the OA hands and displayed them so they appeared in the same physical and spatial location as the patients actual hands. Such promising results suggest that this approach may have exciting treatment potential for CRPS patients who present with alterations in body perception.

Summary and Conclusions

CRPS is a clinical and research challenge as the relationship between primary and secondary signs and symptoms is far from clear. In recent years modern imaging technology has considerably advanced our understanding of the impact of CRPS on

cortical structures and neural processing but there is still much work required to 'unpick' the network of interactions that has emerged. The parietal cortex appears to play a pivotal role in terms of sensorimotor integration and how this impacts on body perception and autonomic function. In the future, identifying those patients with parietal dysfunction may help to inform therapeutic strategies in a more tailored way than at present.

The increased knowledge around body perception disturbances in CRPS and other chronic pain conditions is starting to help us understand how pain, tactile processing and body representation are interlinked. Early evidence from studies that have employed novel therapies to target cortical reorganisation and enhance sensory feedback look promising which suggests this would be a fruitful area for future development. Applying such high tech approaches in clinical practice will require some thought.

The mechanistic complexity of CRPS, as described above, makes it highly apparent that in order for us to truly understand and treat this condition it will require clinical and research expertise from a wide range of specialties. These multi-disciplinary, international clinical research networks are just starting to emerge. For example, a European and North American research consortia supported by the American patient support group Reflex Sympathetic Dystrophy Syndrome Association. However, there is much work still to be done.

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Figure 1 Summary of CRPS clinical features and novel treatments for sensorimotor problems

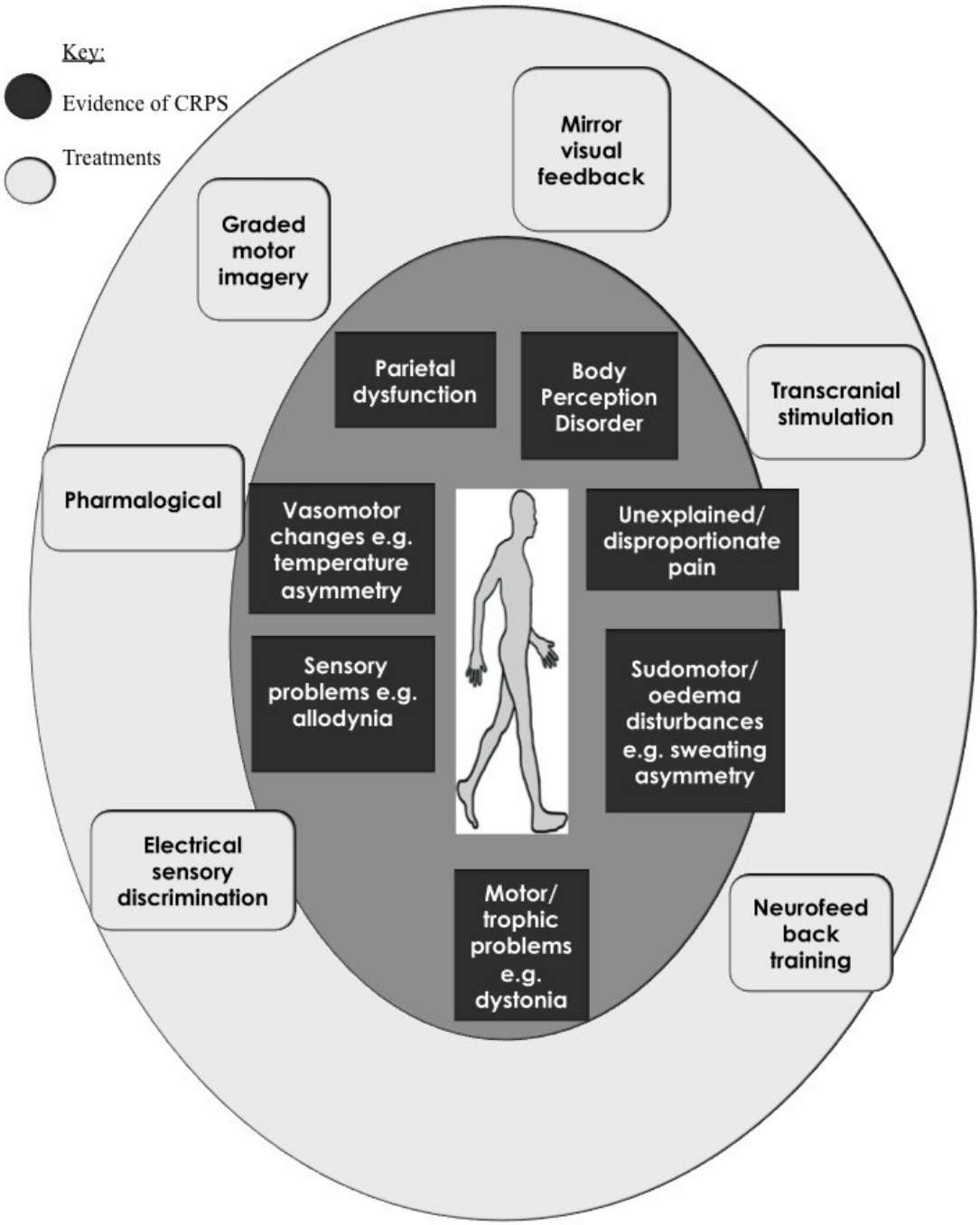
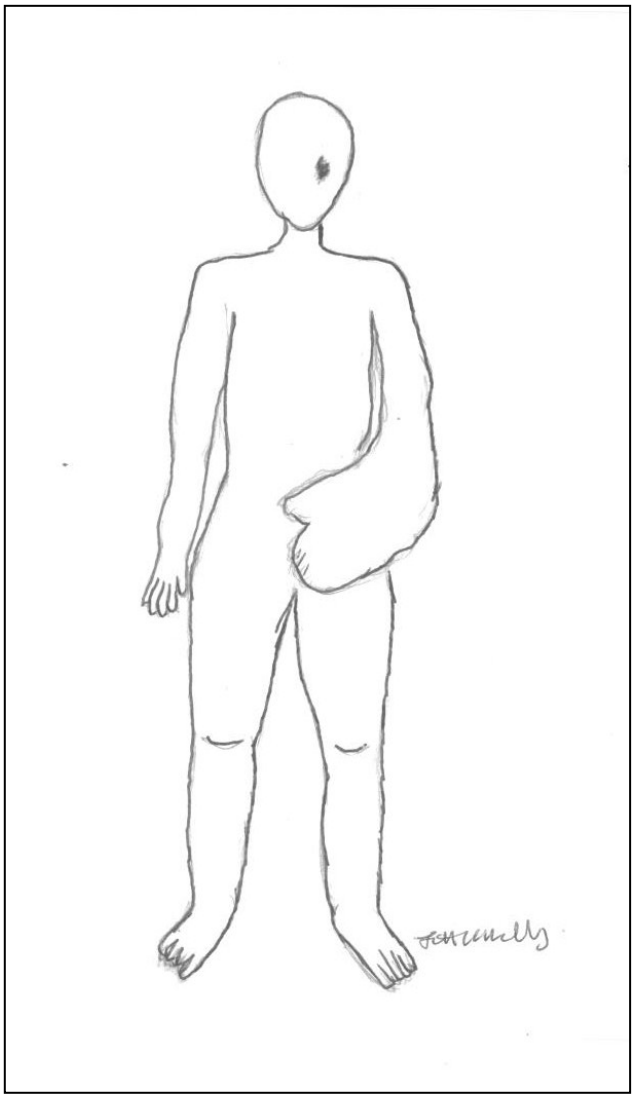


Figure 2: A patient's illustration of how they perceive their CRPS affected left hand and a perception of swelling on the left side of their cheek. This type of self-sketch diagram provides a practitioner with evidence that the patient is experiencing a form of body schema distortion. The diagram also provides a record for longitudinal study during rehabilitation therapy.



Figures 3 a & b: The CRPS patient here is living with a body perception disorder and perceives her left, CRPS affected hand as grossly distorted. With her eyes closed, she is using her right hand to demonstrate her perceived depth (a) and breadth (b) of her left hand.

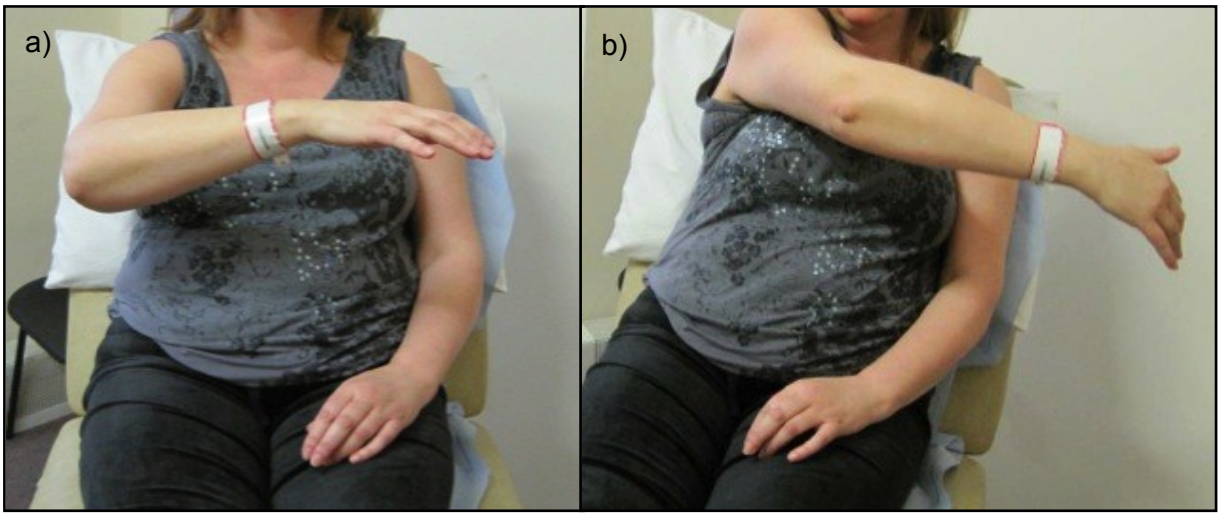


Figure 4 (a,b): A diagram (a,b) depicting congruent and incongruent movements whilst viewing a mirror to generate sensorimotor incongruence. The head (large oval) is tilted to the side, so that one arm cannot be seen. Instead the person views a reflection of their other arm/hand (small upper oval). Congruent movement occurs when the two arms are moved in the same direction at the same time (**a**) and incongruent movement when they are moving in opposite directions (**b,c**). Healthy volunteers and those with limb pain have reported new sensory problems, including pain and poor motor control, in the arm hidden from view during incongruent movement.