The role of sensorimotor incongruence in pathological pain

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The role of sensorimotor incongruence in pathological pain

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Declaration of any previous submission of the work

The material presented here for examination for the award of a higher degree by research has not ‘been incorporated into a submission for another degree.

Declaration of authorship

I am the author of this thesis, and the work described therein was carried out by myself personally. Individual chapters are accompanied by an authorship statement indicating my contribution to the work in terms of formulation of ideas, design of methodology, experimental work and presentation of the data in journal format.

Abstract

Pain normally provides our nervous system with useful information (e.g. by alerting us to potential harm). Yet sometimes pain persists long after an injury has healed, at which point it can be considered pathological. Many people with pathological pain conditions can present with neuropsychological changes that might impair sensorimotor processing, such as distorted body representations. According to the sensorimotor theory of pain (Harris, 1999), pathological pain could have a cortical origin. According to the sensorimotor theory of pain (Harris, 1999), pathological pain could have a cortical origin. He postulated that sensorimotor incongruence could be driving several pathological pain conditions. Such an incongruence was proposed to arise from a discrepancy between the predicted outcome of a movement (e.g. sensory, motor, proprioceptive), and the “true” sensory outcome (i.e. the sensory feedback). I will address this idea in my thesis, and aim to further our understanding of the role of sensorimotor incongruence in pathological pain. First, I present a comprehensive review of the existing literature to evaluate how sensorimotor processing might be altered in a broad range of pathological pain conditions, and if such changes are related to pain. I conclude that there is support for many of the hypotheses that can be derived from the theory. Next, I address some of these hypotheses experimentally in a clinical population, and a non-clinical population where pain was induced experimentally. Specifically, I look at sensorimotor processing in people with Complex Regional Pain Syndrome (CRPS), and in an experimental acute pain model. I find evidence of altered updating of bodily and spatial representations for people with CRPS, relative to controls, which is not seen in an acute pain model. Such changes could interfere with predicting the sensory outcome of a movement. In contrast, I find no evidence to suggest that sensorimotor adaptation is impaired. This finding opposes theoretical predictions, as it suggests that people with CRPS should be able to adapt to incongruent sensorimotor information. Taken together, the main contribution of my thesis is 1) to highlight areas in which sensorimotor processing might be altered in people with CRPS, which cannot be explained by the presence of acute pain, and 2) to challenge one of the assumptions underpinning the sensorimotor theory of pain. The broader findings from my thesis have implications for the sensorimotor theory of pain, and treatments that target sensorimotor processing for pain relief. For instance, they suggest that therapies focused on improving bodily and motor representations might be more appropriate for people with CRPS than those targeting sensorimotor adaptation. I conclude that the sensorimotor theory of pain does not provide a complete explanation of the changes seen in people with pathological pain conditions, and suggest ways of refining the theory. Nonetheless, the theory is a useful framework within which to generate testable hypotheses that focus on specific aspects of sensorimotor processing that appears to be altered in pathological pain conditions.

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Introduction

Pain can provide our nervous system with useful information. It can protect us from harm, and it can facilitate recovery when we are injured. For instance, we will quickly retract our hand if we touch something that is painfully hot, thereby avoiding harm. In the cases where we have not been so fortunate and injury has occurred, pain tells us to avoid moving or touching an injured area to aid its recovery. Despite its importance, pain is commonly (mis)conceived of as something to eliminate. However, in some cases pain persists after an injury has healed, and is no longer providing our nervous system with useful information. In such cases pain can be considered pathological. Certain pathological pain conditions are theorized to be maintained by conflicting sensory and motor information. Therefore, this thesis concerns how we use information from our senses and about movement, and how this process might be altered in people with pathological pain conditions. An incongruence might arise between the predicted outcome of a movement, and its "true" sensory outcome (e.g. if, during a pointing movement, the anticipated position of the hand differs from its perceived location). Therefore, the aim of the thesis is to further our understanding about the role of sensorimotor incongruence in pathological pain.

In this general introduction I will first describe the concept of pain, its functional value to the nervous system, and how it can become a disease state (i.e. pathological). Next, I will briefly outline the central changes that have been observed in pathological pain conditions. I will then introduce the sensorimotor theory of pain, which was developed as a result of the observations of cortical changes in pathological pain, and which provides the basis for the hypotheses that are addressed in this thesis. I will then introduce Complex Regional Pain Syndrome (CRPS), which is one example of a condition that is thought to be partly driven by central changes, and is the clinical population that I have studied in order to test the sensorimotor theory of pain. Finally, I will introduce the studies that are included in this thesis, and describe them in the context of the sensorimotor theory of pain.

1. Pain

The most common definition of pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey & Bogduk, 1994). Pain is not always useful, as this definition alludes to. In many cases, pain will persist after the need to protect us from harm has passed and the injury has recovered. At this stage it can be considered a disease of the central nervous system, and therefore pathological. When pain persists for more than 3 months it is typically described as "chronic". It is estimated that one in five people will experience persistent pain at any given time (Goldberg & McGee, 2011).

To the individual experiencing it, chronic pain can have devastating consequences. Pain impacts on all aspects of life, from social to financial. Chronic pain kills. Suicide rates are disproportionately high for people with chronic pain (Calati, Bakhiyi, Artero, Ilgen, & Courtet, 2015). It is therefore abundantly clear that we need to improve the quality of life for the many people living with chronic pain, which is where research into pain can play a role.

Chronic pain is more than a continuation of an acute state. As far as the nervous system is concerned, the 3-month cut-off for chronic pain is arbitrary. Instead, we can think about the different states that pain can have. Acute pain protects us from harm, and inflammatory pain facilitates healing. Pain enters a third state when it is no longer useful to the nervous system. As highlighted above, pain can exist when there is no potential harm, and no existing damage to make us aware of. In this case, pain is described as pathological, and can be considered a disease of the nervous system (Woolf, 2010).

2. Central changes in pathological pain

Pathological pain can involve central changes (Kuner & Flor, 2017), in addition to peripheral ones. These changes can occur at various levels of the nervous system. For instance, at the level of the nociceptors, the sensory receptor that relays nociceptive information to the brain, changes can be seen in their structure and signalling. Changes in the function and architecture of the spinal chord, and the brain are also known to occur in pathological pain conditions. In such conditions, central changes have been considered examples of maladaptive plasticity, which refers to the idea that changes to the central nervous system may cause spontaneous and exaggerated pain (Woolf, 1989).

Early findings provided evidence for reorganisation of the primary somatosensory cortex (S1) in amputees with phantom limb pain (Flor et al., 1995; Flor et al., 1998; Knecht et al., 1998). S1 reorganisation was not seen for people who were born without a hand, or who had an amputation and did not experience phantom pain. These findings inspired a wealth of research (Kuner & Flor, 2017) as they suggested that cortical changes might be related to the experience of pain. However, they do not offer any explanation as to why this reorganisation may be causing pain.

3. The sensorimotor theory of pain

The question of why reorganisation might cause pain was addressed by Harris (1999), who theorised that an asymmetry between the primary motor cortex (M1) and S1 would result in a sensorimotor conflict. The theory suggested that the representations corresponding to the affected area would show reduced M1 inhibition, and disorganised S1 representations. He based these assumptions on research that had found reduced M1 inhibition in people with focal hand dystonia, and overlapping S1 hand representations for people with repetitive strain injury, focal hand dystonia, and amputees. Harris proposed that this asymmetry would disrupt sensorimotor processing, as the predicted outcome of a movement would no longer match the “true” sensory outcome. The theory has since been named the sensorimotor theory of pain (McCabe & Blake, 2007), and has been proposed as an explanation for Complex Regional Pain Syndrome (CRPS), focal hand dystonia, phantom limb pain, and repetitive strain injury.

The sensorimotor theory of pain can be a useful framework for generating testable hypotheses about how sensorimotor processing might be altered for people with pathological pain conditions. For instance, the theory makes a number of assumptions that can be subjected to scientific scrutiny. Perhaps the most striking assumption is that incongruent sensorimotor information can trigger pain. This idea was described as analogous to motion sickness, which is caused by incongruent visual and vestibular

information. Motion sickness causes people to feel unwell and initiates a cascade of biological responses (Golding, 2006). For people with CRPS, experimentally induced motion sickness caused an increase in pain (Knudsen & Drummond, 2015). It is therefore plausible that sensorimotor incongruences can result in perceptual, and biological changes, as theorised by the sensorimotor theory of pain.

The idea that incongruent sensorimotor information can cause pain has been tested experimentally using incongruent mirror visual feedback. In a typical paradigm, participants place each arm on either side of a mirror that is aligned with the body midline. They perform bimanual movements while viewing one arm as well as its reflected image in the mirror, and vision of the other arm is occluded. When participants perform asynchronous arm movements (i.e. anti-phase), this procedure is described as incongruent mirror visual feedback. Incongruent mirror visual feedback provides participants with a mismatch between the predicted outcome of a movement and the visual feedback of said movement. People with pathological pain conditions, such as CRPS, and fibromyalgia (a widespread pathological pain condition), will more frequently experience pain during incongruent mirror visual feedback than controls (Don, Voogt, Meeus, De Kooning, & Nijs, 2017). In contrast, congruent mirror visual feedback has been trialled as a therapy, known as mirror therapy (Ramachandran & Rogers-Ramachandran, 1996). The assumption of mirror therapy is that it allows for sensorimotor incongruences to be overridden by capitalising on the intact sensorimotor processing for the non-affected limb, which can thus compensate for any mismatch between afference and efference that may exist for the painful limb. Although the evidence for the efficacy of mirror therapy is mixed, it has shown some promise for conditions such as CRPS (Thieme, Morkisch, Rietz, Dohle, & Borgetto, 2016; Wittkopf, Lloyd, & Johnson, 2018). These findings suggest that it is possible for the congruence of sensorimotor information to influence pain for people with pathological pain conditions.

The sensorimotor theory of pain provides a potential explanation for how and why pain arises in several pain conditions for which there are no clear causes. In this thesis I seek to investigate the extent to which the theory is supported by existing research, and to test as yet unsupported components of the theory. Testable hypotheses that can be formed from this theory about how sensorimotor processing might be disrupted in pathological pain processes relevant to predicting the consequences of a movement, performing a movement, and integrating the prediction with the outcome. These can be tested in people with pathological pain conditions as well as healthy controls.

The sensorimotor theory of pain therefore provides a framework within which testable hypotheses can be formulated. It suggests that when the predicted outcome of a movement does not align with the “true” sensory outcome people with certain conditions will experience pain and other symptoms. This theory can be used to generate testable hypotheses about a cortical origin of pathological pain. In this thesis, I will address some of these hypotheses.

4. Testing theoretical predictions

Sensorimotor processing, however, is more complex than mere correspondence between M1 and S1. The sensorimotor system has been studied in great detail (e.g. Shadmehr, Smith, & Krakauer, 2010), and so its basic properties are well understood. For instance, a lot is known about the processes that influence predictions of the consequences of a

movement, the execution a movement, and the sensorimotor integration that compares the prediction and the outcome. There are therefore many ways in which sensorimotor processing can be disrupted beyond a cortical asymmetry between M1 and S1. We can apply these insights to test the idea that sensorimotor processing might be disrupted in pathological pain, and that any disruption should cause pain and other symptoms. For instance, we would expect sensorimotor processing to be altered in people with pathological pain, relative to pain-free individuals, which could predispose people to developing painful conditions and/or be related to the disease itself. These changes would make it more likely for a sensorimotor incongruence to occur. Altered sensorimotor processing could relate to predicting the sensory consequence of a movement, the "true" sensory outcome of a movement, and/or integrating the prediction and the outcome, as I will discuss in more detail in Chapter 1.

To make an accurate prediction of a sensory outcome sensorimotor system needs to have up-to-date representations of our body and its position in space. Representations of the body and space, however, are not static, rather they constantly update as we interact with our environment (Martel, Cardinali, Roy, & Farnè, 2016; Medina & Coslett, 2010; Serino, 2019). Tool-use is a paradigm that has been used to test the malleability of these representations, as our nervous system will update to facilitate the tools (Maravita & Iriki, 2004).

The sensorimotor system needs to be able to compare the position of our body to external space. One simple way to assess these representations, and any distortion, is by having people point to what feels like straight ahead, known as manual straight ahead pointing. Therefore, we might expect such representations to be distorted for people with pathological pain conditions.

Sensorimotor integration is performed to compare the predicted outcome of a movement with its "true" sensory outcome. If the information is incongruent, the sensorimotor system will typically adapt (Bastian, 2008; Wolpert, Diedrichsen, & Flanagan, 2011). Therefore, the sensorimotor system assumes that such adaptation would be impaired in pathological pain conditions. One way to study sensorimotor adaptation is to have people perform movements whilst wearing goggles that create an optical displacement (i.e. prism goggles). After repeated movements the sensorimotor system will adapt. Prism adaptation therefore enables sensorimotor integration to be tested.

In this thesis, I will use these paradigms to test theoretical predictions made by the sensorimotor theory of pain in experimental and clinical models. People with CRPS are the clinical population that I have studied in order to test the sensorimotor theory of pain.

5. Complex Regional Pain Syndrome

CRPS is a pathological pain conditions that primarily affects wrists and ankles. It is characterised by pain and sensory, trophic, autonomic, and motor changes (Table 1; Harden et al., 2010; Harden, Bruehl, Stanton-Hicks, & Wilson, 2007). Crucially, these signs and symptoms are disproportionate to any inciting injury, cannot be explained by any underlying conditions, and are associated with continuous pain.

Table 1. Budapest criteria for CRPS.

Budapest criteria for CRPS (Harden et al., 2010; Harden et al., 2007)
1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three* of the *four* following categories: *Sensory*: reports of hyperesthesia and/or allodynia *Vasomotor*: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry *Sudomotor/edema*: reports of edema and/or sweating changes and/or sweating asymmetry *Motor/trophic*: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in *two or more* of the following categories: *Sensory*: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement) *Vasomotor*: evidence of temperature asymmetry and/or skin color changes and/or asymmetry *Sudomotor/edema*: evidence of edema and/or sweating changes and/or sweating asymmetry *Motor/trophic*: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

CRPS is typically preceded by a fracture (e.g. distal radial fracture) or soft-tissue damage (de Mos et al., 2007). However, this is not sufficient to explain CRPS, as most soft-tissue injuries do not result in CRPS. Early stages of the disease are typically dominated by peripheral changes, whereas central changes appear to play a more important role in later stages of CRPS (Birklein & Schlereth, 2015), at which point sensorimotor processes are thought to be disrupted. In this context, the difference between early and late stages of CRPS relate to the manifestation of CRPS, rather than a specific duration (e.g. 3 months), as the disease progression is highly variable (Birklein, O'neill, & Schlereth, 2015; Birklein & Schlereth, 2015).

People with CRPS commonly experience their affected area as distorted in shape and size (e.g. Fig. 1). This experience appears to be present from very early on in the disease (Lewis, Kersten, McCabe, McPherson, & Blake, 2007), sometimes within days of the initial injury. Self-reported body representation distortions are predictive of worse pain outcomes six months later for people with chronic CRPS (Wittayer, Dimova, Birklein, & Schlereth, 2018). Distorted representations of the body are therefore common in CRPS, and are related to the pain outcomes.

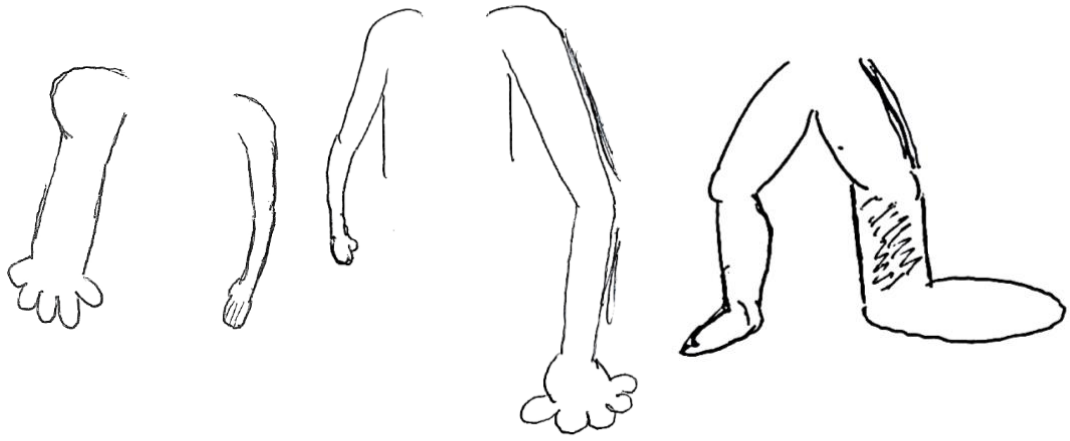

Figure 1. Distorted body representations.
Depictions of distorted body representations. People with CRPS described the shape and size of their body to the experimenter, who created these illustration. The people with CRPS agreed that the illustrations appropriately reflected of how they experienced the shape and size of their body. The abnormally shaped area corresponds to the CRPS affected limb.

CRPS is an appropriate condition for testing the sensorimotor theory of pain. The theory has been proposed as an explanation for the conditions (McCabe & Blake, 2007). Furthermore, there is evidence that sensorimotor processing can be disrupted in this population. In addition to the signs and symptoms that are characteristic of the condition (Table 1), people with CRPS will commonly report that their affected area feels distorted in size and shape (Fig. 1). In response to incongruent mirror visual feedback, people with CRPS have also been found to report pain more frequently than controls (Brun et al., 2019).

In this thesis, I will therefore focus on CRPS for my empirical work that involves a clinical population. However, not all of the predictions made by the theory can be assessed in clinical populations. For example, the theory assumes that pain is a consequence of sensorimotor incongruence, but such a causal relationship cannot be tested in patients in which pain is already established. Instead, this assumption can be tested using experimental pain in otherwise pain-free individuals

6. Thesis content

Pathological pain conditions are often accompanied by central changes, with early observations suggesting that cortical reorganisation might be related to pain. According to the sensorimotor theory of pain (Harris, 1999) these changes might be a cause of, rather than consequence of pain. The theory proposed that a mismatch between the predicted consequences of a movement and the actual sensory feedback might results in sensorimotor incongruencies. In my thesis, I include experimental work with a clinical population (i.e. people with CRPS), and a non-clinical population where pain was experimentally induced. These studies address the broader aim of my thesis, which is to further our understanding of the role of sensorimotor incongruence in pathological pain.

Chapter 1 is a comprehensive review of sensorimotor processing in pathological pain conditions. The narrative review aims to capture a broad range of sensorimotor processes that may be altered across a range of pathological pain conditions. It is structured to outline the existing evidence for specific hypotheses that can be derived from the sensorimotor theory of pain. In this chapter I conclude that altered sensorimotor processing can be present in a broad range of pathological pain conditions, and that there is some evidence to suggest that it is related to pain. There is also some evidence that incongruent sensorimotor information can trigger pain, although this evidence is less consistent than for other areas reviewed.

Chapter 2 is an empirical study that examines the influence of experimentally induced pain on the updating of bodily and spatial representations following tool-use. Bodily and spatial representations are used to inform the predicted outcome of a movement. As the sensorimotor theory of pain proposes that disrupted sensorimotor processing causes pain, this chapter tests the assumed directionality of this relationship. For the updating of bodily and spatial representations it could be that 1) impaired updating causes pain (i.e. as theorised), 2) pain disrupts updating, or 3) association between pain and updating is bidirectional. The research described in this chapter tests the possibility that pain disrupts sensorimotor processing. To do so, I examine the effect of inducing pain on how healthy participants updated representations of their body and peripersonal space during, and after a tool-use task.

Chapter 3 describes an experimental study looking at how people with CRPS update their bodily and spatial representations following tool-use, compared to healthy control participants. The research described in this chapter considers whether problems with updating can explain why bodily and spatial representations remain distorted, rather than be corrected to a “normal” state, for people with CRPS. Both types of representations are important for sensorimotor processing, as they are used to inform our predictions of the sensory consequences of a movement. The research described in this chapter also attempts to link the tested representations to the physical manifestation of CRPS.

Chapter 4 describes a study that examines manual straight ahead pointing in CRPS, relative to healthy control participants. This task has been used in neuropsychological research to assess the representations of left and right space for action (Jeannerod & Biguer, 1987). As manual straight ahead pointing depends on comparing the location of the body relative to external space, this study further addresses the idea that people with CRPS have difficulties using bodily and spatial information.

Chapter 5 describes a study that characterises the process of prism adaptation in people with CRPS, and compares it to that of healthy control participants. Adjusting to the optical shift introduced by wearing prismatic goggles requires strategic recalibration and sensorimotor realignment. The latter reflects the sensorimotor system’s ability to adapt to, and thus compensate for, incongruent sensorimotor information. This study addresses the idea that sensorimotor integration might be disrupted for people with pathological pain. I examine the changes in endpoint errors during the course of prism adaptation and de-adaptation; the rate that endpoint errors decay; and kinematic markers of feedforward motor control and sensorimotor realignment.

In the general discussion I summarise the main findings from my thesis, in the context of the sensorimotor theory of pain. I consider how my findings contribute to our understanding of sensorimotor processing in pathological pain.

By testing components of the sensorimotor theory of pain, I aim to further our understanding of the role of sensorimotor incongruence in pathological pain, which could have implications for the way we think about, and treat pain.

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Chapter 1: Sensorimotor incongruence in pathological pain

Chapter 1 – Introduction

In this chapter I present a comprehensive review of sensorimotor processing in pathological pain conditions. Altered sensorimotor processing has been reported in many different types of pathological pain conditions, and for many different types of sensorimotor processing. Therefore, I include a broad range of studies that I review in the context of the sensorimotor theory of pain, which has yet to be covered by any existing review.

The review starts by outlining the sensorimotor theory of pain, and its components, which are used to formulate testable hypotheses. The following part of the chapter reviews the literature that is relevant to sensorimotor processing. I group this information by the different processes that can influence sensorimotor processing that the review covers (i.e. cortical reorganisation, motor deficits, sensory changes, body representation, spatial perception, sensorimotor integration), before addressing sensorimotor treatments for pain. Within each of these sections, the information is organised by testable hypotheses that are derived from the sensorimotor theory of pain.

This review will provide an overview of the current state of knowledge about sensorimotor processing in pathological pain.

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Sensorimotor incongruence in pathological pain

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Abstract

The sensorimotor theory of pain proposed a new way of thinking about pathological pain, and potential avenues for treatment. It theorised sensorimotor incongruences to be a cortical origin of pathological pain. Twenty years after its formulation, the theory has yet to be reviewed. As sensorimotor processing is known to involve cortical representations (e.g. motor cortex, and somatosensory cortex), motor processes, sensory feedback, cognitive representations (e.g. bodily and spatial), and sensorimotor integration, their theorised relationship with pain can be subjected to scientific investigation. We therefore reviewed the evidence that the theory can explain certain painful conditions, and that it can provide a basis for treatments. Most frequent evidence in support of the prediction that altered sensorimotor processing should relate to pain was found in Complex Regional Pain Syndrome (CRPS), carpal tunnel syndrome, fibromyalgia, and phantom limb pain. The efficacy of sensorimotor therapies was most consistently found for CPRS. We conclude that the sensorimotor theory of pain provides a useful framework for research into sensorimotor processing in pathological pain conditions.

Highlights

- Sensorimotor processing is altered in several pathological pain conditions
- In some conditions altered sensorimotor processing is related to pain
- Targeting sensorimotor processes can provide pain-relief in conditions such as CRPS

1. Introduction

Harris (1999) theorised that incongruencies between motor predictions and sensory feedback could underlie several pathological pain conditions that cannot be fully accounted for by tissue pathology. This theory, which has since been titled the sensorimotor theory of pain (McCabe & Blake, 2007), has been proposed to explain phantom limb pain, focal hand dystonia, repetitive strain injury (Harris, 1999), and Complex Regional Pain Syndrome (McCabe & Blake, 2007), and has shaped the development of several therapies for pathological pain. Twenty years after the theory was first proposed, evidence for the sensorimotor theory of pain and whether it can indeed account for unexplained pain has yet to be reviewed. Furthering the understanding of how sensorimotor incongruence relates to the manifestation of pathological pain could aid the improvement of existing therapies and the development of new ones. Here we aim to bring together research on cortical reorganisation (3.1.), motor deficits (3.2.), sensory changes (3.3.), body representation (3.4.), spatial perception (3.5.), and sensorimotor integration (3.6.) to evaluate the extent that sensorimotor processing is altered in pathological pain conditions. We will also consider evidence that a sensorimotor incongruence might specifically *drive* pathological pain conditions, and therefore treatments targeting sensorimotor processing (3.7.) should be efficacious. We conclude that there is evidence of a relationship between altered sensorimotor processing and pain in certain painful conditions: Complex Regional pain Syndrome (CRPS), carpal tunnel syndrome, fibromyalgia, and phantom limb pain. The efficacy of sensorimotor therapies was most consistently found for CPRS. The sensorimotor theory of pain therefore provides a useful framework for investigating altered sensorimotor processing in pathological pain conditions.

2. The sensorimotor theory of pain

Harris's (1999) theory on the cortical origins of pathological pain was formulated based on evidence of abnormal representations of the affected limbs in the primary motor (M1) and primary somatosensory (S1) cortices in pathological pain. The sensorimotor theory of pain built on the idea of maladaptive plasticity (Woolf, 1989); that is, the idea that changes to the central and peripheral nervous system can cause spontaneous and exaggerated pain, without serving any protective, or reparative role (for reviews, see Kuner & Flor, 2017; Scholz & Woolf, 2002). Once pain ceases to provide any functional information to the nervous system, it can be considered a disease of the nervous system, and thus pathological (Woolf, 2010). The sensorimotor theory of pain was grounded in findings of people with phantom limb pain showing positive correlations between reorganisation of S1 and pain (Flor et al., 1995; Flor et al., 1998). Harris' proposal could be considered an extension of the maladaptive plasticity hypothesis by suggesting a mechanism to explain *how* changes in M1 and S1 could lead to pain, by causing errors in sensorimotor processing. These errors arise due to an incongruence between motor intentions and sensory feedback (Fig. 1), and were theorised contribute to the maintenance of pathological pain. The notion of pathological pain arising from sensorimotor incongruence is akin to motion sickness, in which nausea arises from incongruent visual and vestibular information (Golding, 2006).

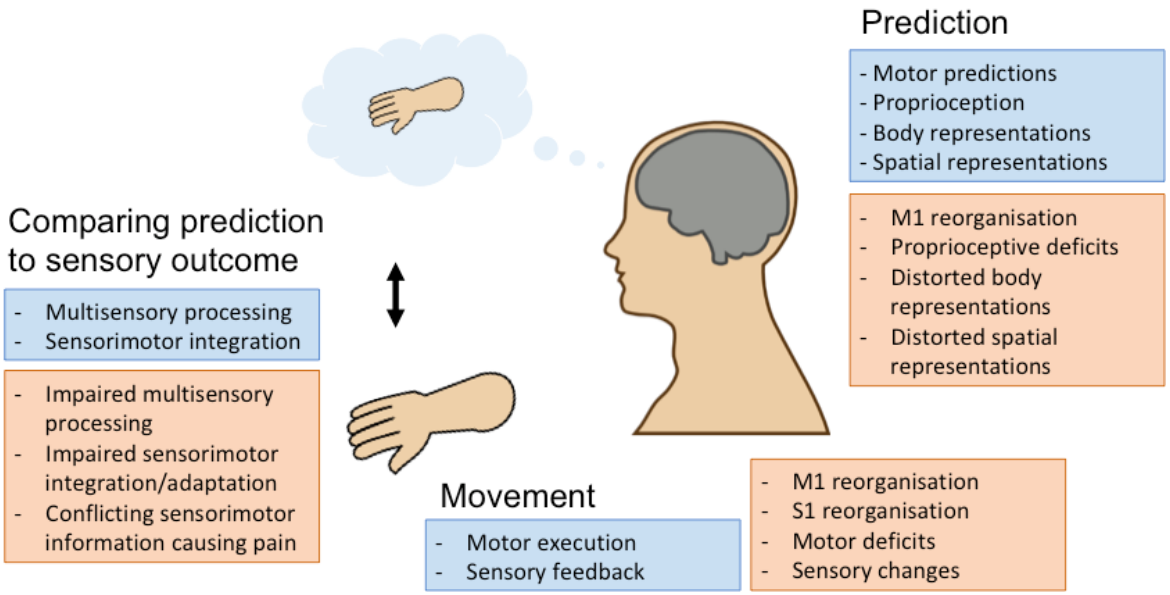

Figure 1. The sensorimotor theory of pain.
Simplified model of sensorimotor processing (blue; Blakemore et al., 2000; McCabe & Blake, 2007; McCabe et al., 2005), and factors that may interfere with it (orange). The sensorimotor theory of pain predicts that disrupted processing will result in sensorimotor incongruences, which serve to maintain pain and other symptoms (Harris, 1999). We would therefore expect people with pathological pain conditions to show the changes described in the orange boxes. M1 = primary motor cortex; S1 = primary somatosensory cortex.

The sensorimotor theory of pain therefore provides a framework for formulating testable hypotheses about the cortical origins of pathological pain (see 2.2.). The components that make up normal movement have been subjected to scientific investigation in pathological pain populations, which we will review (3.).

2.1. Components of the theory

Broadly speaking, the sensorimotor processes involved in typical movements can be broken into three components: generating a motor command, predicting the sensory outcome of the movement, and comparing the prediction with the true sensory outcome (see Fig. 1; Blakemore, Wolpert, & Frith, 2000). The sensorimotor theory of pain suggests that an error in any of these components could give rise to pain, associated anomalous sensations, and physical symptoms such as dystonia. Below we briefly outline what normal sensorimotor processing entails (2.1.1.), which we then use to formulate testable hypotheses (2.1.2.) derived from the sensorimotor theory of pain (for earlier discussion, see McCabe & Blake, 2007; McCabe, Haigh, Halligan, & Blake, 2005).

2.1.1. Normal sensorimotor processing

To perform a goal-directed movement, a motor command is generated in the motor cortex and transmitted to the relevant muscles. That is, a motor commands will activate neurons that innervate muscles (i.e. motor neurons), whose discharge results in muscle contractions (for review, see Stifani, 2014). In turn, the muscle contractions can control joints, and

thereby the kinematics of limb movements (Wolpert, 1997). Even movements that are not executed, just imagined, will create a similar cortical activation. For instance, the execution of bimanual finger tapping results in activity of the motor cortex, supplementary motor area, and cerebellum. Such activation can also be observed when the same movement is imagined, although to a lesser extent than when it is executed (Macuga & Frey, 2012). With the exception of saccades, when a movement is executed, joint angles and kinematics are monitored through sensory feedback (Shadmehr, Smith, & Krakauer, 2010). During the execution of a movement, sensory feedback (e.g. visual, proprioceptive) is used to correct for movement errors (Shadmehr et al., 2010). Spinal and cortical reflexes (Kurtzer, Pruszynski, & Scott, 2008; Soechting & Lacquaniti, 1988), and the predicted sensory consequences of a movement are also used to correct for movement errors. Hence, there are several processes involved in the successful execution of a movement. If either of these processes is compromised they may present conflicting or inconsistent information to the nervous system, which could be considered a sensorimotor incongruence. These processes that are relevant to cortically controlled movements are the main focus in this review, although we will also include evidence from certain spinal reflexes, such as the hand blink reflex (3.5.1.).

The sensory consequences of self-generated movements are predicted by an internal forward model (Blakemore & Sirigu, 2003; Blakemore et al., 2000). These predictions are thought to compensate for the noise and delay in sensory feedback (Shadmehr et al., 2010). The accuracy of these predictions depend on proprioception (Sober & Sabes, 2005; Tuthill & Azim, 2018), spatial representations (Soechting & Flanders, 1989), and knowing the state of the body (for review, see Franklin & Wolpert, 2011). For instance, proprioceptive information is combined with a representation of the body's size and shape (i.e. body representation) to create a sense of position in external space (Longo & Haggard, 2010; Proske & Gandevia, 2012). Bodily and spatial information are then used to make predictions about the expected sensory outcome of a movement (Shadmehr et al., 2010). These internal models of sensorimotor integration are thought to minimise prediction error (Clark, 2013). Representations of the body are related to cortical representations, although they also incorporate perceptual features of a somatic input (Longo, Azañón, & Haggard, 2010). Bodily and spatial representations are therefore key to making accurate sensory predictions, which, if degraded, would make a sensorimotor incongruence more likely to occur.

Motor information and sensory predictions are integrated to produce an appropriate motor response (Shadmehr et al., 2010). These different streams of information are integrated and weighted by their reliability (Kording & Wolpert, 2004). When they provide conflicting information, sensorimotor adaptation can occur to compensate, which allows the sensorimotor system to learn and improve (Wolpert, Diedrichsen, & Flanagan, 2011). Sensorimotor integration is therefore an important part of movement.

2.1.2. Testable hypotheses

The sensorimotor theory of pain can be used to generate testable hypotheses about pain and the manifestation of symptoms (e.g. Table 1). Problems with predicting the outcome of movements, performing movements, and/or comparing this prediction to the sensory

outcome of a movement should be present in pathological pain conditions. As reviewed above (2.1.1.), each of these stages of sensorimotor processing is influenced by a number of specific components (see Fig. 1 for a simplified model), which we will review grouped by cortical reorganisation (3.1.), motor deficits (3.2.), sensory changes (3.3.), body representation (3.4.), spatial perception (3.5.), and sensorimotor integration (3.6.). The sensorimotor theory of pain would therefore predict that these components could be compromised in pathological pain, thereby leading to a discrepancy between the expected and the actual sensory outcome of a movement, which in turn leads to pain and other sensory changes (Harris, 1999). If this is the case, then treatments that target sensorimotor processing should also provide pain relief (3.7.).

Table 1. Testable hypotheses.

Examples of testable hypotheses that can be formulated on the basis of the sensorimotor theory of pain.

Section	Hypothesis
Cortical reorganisation	
2.1.1.	M1 should be reorganised in people with pathological pain
2.1.2.	S1 should be reorganised in people with pathological pain
2.1.3.	Cortical reorganisation should relate to pain
2.1.4.	Pain can result from brain damage
Motor deficits	
2.2.1.	People with pathological pain should have motor deficits
2.2.2.	People with pathological pain should have difficulties imagining movements
2.2.3.	Motor deficits should relate to altered cortical processing
2.2.4.	Motor deficits should relate to pain
Sensory changes	
2.3.1.	People with pathological pain should have sensory deficits
2.3.2.	Sensory deficits should relate to altered cortical processing
2.3.3.	Sensory deficits should relate to pain
Body representation	
2.4.1.	People with pathological pain should have distorted representations of the body
2.4.2.	People with pathological pain should have difficulties updating the representations of their body
2.4.3.	Distorted body representations should lead to errors in predicting the consequences of a movement
2.4.4.	Distorted body representations should relate to altered cortical processing
2.4.5.	Distorted body representations should relate to pain
Spatial perception	
2.5.1.	People with pathological pain should have distorted representations of the space that surrounds their body
2.5.2.	People with pathological pain should have difficulties updating the space that surrounds their body
2.5.3.	Distorted spatial representations should lead to errors in predicting the consequences of a movement
2.5.4.	Distorted spatial representations should relate to altered cortical processing
2.5.5.	Distorted spatial representations should relate to pain
Sensorimotor integration	
2.6.1.	People with pathological pain should have deficits in multisensory processing
2.6.2.	People with pathological pain should have deficits in sensorimotor integration
2.6.3.	Deficits in sensorimotor integration should relate to altered cortical processing
2.6.4.	Deficits in sensorimotor integration should relate to pain
2.6.5.	Incongruent sensory and motor information should cause pain
Sensorimotor treatments for pain	
2.7.1.	Targeting sensation sensorimotor processing should reduce pain

3. Review of evidence for the sensorimotor theory of pain

3.1. Cortical reorganisation

Harris (1999) proposed that an asymmetry between M1 and S1 could be a cortical origin of pathological pain. This asymmetry was hypothesised to be facilitated by disorganised S1 representations and reduced in M1 inhibition, thereby contributing to a mismatch between sensory and motor information. This idea was based on early findings that showed reduced M1 inhibition (i.e. a reduced ability to inhibit a motor output; Duque, Greenhouse, Labruna, & Ivory, 2017) in people with focal hand dystonia, and overlapping S1 hand representations for people with repetitive strain injury, focal hand dystonia, and amputees. Harris (1999) suggested that such changes to M1 and/or S1 might result in the false detection of a sensorimotor incongruence, as these cortical areas would be disproportionately, and thus asymmetrically, activated by a movement. The theory was founded on the notion that there should be reorganisation of the motor and/or somatosensory cortices, and therefore suggests that cortical reorganisation is maladaptive. If this is the case, then cortical reorganisation should not only be present in pathological pain conditions (3.1.1., 3.1.2.), but also relate to pain and disability (3.1.3). Furthermore, if pathological pain has a cortical origin, brain damage should cause pain (3.1.4). There is mixed evidence for these claims.

The evidence for cortical changes in people with chronic pain has been extensively reviewed elsewhere (Chang et al., 2018; Dahlberg, Becerra, Borsook, & Linnman, 2018; Di Pietro et al., 2013a, 2013b; Furuya & Hanakawa, 2016; Goossens, Rummens, Janssens, Caeyenberghs, & Brumagne, 2018; Kuner & Flor, 2017; Parker, Lewis, Rice, & McNair, 2016; Tanasescu, Cottam, Condon, Tench, & Auer, 2016; Upadhyay, Geber, Hargreaves, Birklein, & Borsook, 2018). Below, we briefly outline some of the evidence looking at functional reorganisation of M1 (3.1.1) and S1 (3.1.2).

3.1.1. M1 should be reorganised in people with chronic pain

In short, there is evidence from functional magnetic resonance imaging (fMRI) suggesting reorganisation of M1 in lower back pain (Tsao, Galea, & Hodges, 2008), osteoarthritis (Shanahan, Hodges, Wrigley, Bennell, & Farrell, 2015), phantom limb pain (Karl, Birbaumer, Lutzenberger, Cohen, & Flor, 2001; Raffin, Richard, Giraux, & Reilly, 2016), dystonia (for review, see Furuya & Hanakawa, 2016), and spinal cord injury (for review, and meta-analysis see Dahlberg et al., 2018). Some fMRI studies have suggested a reorganisation of M1 contralateral to the affected-side in CRPS (e.g. Maihöfner et al., 2007), although this was not supported by a meta-analysis of the available data (Di Pietro et al., 2013a). The evidence for functional M1 reorganisation is inconclusive when chronic pain conditions are grouped, as identified by a recent meta-analysis of 67 studies (Chang et al., 2018). This suggests that any changes may be condition-specific rather than general to chronic pain. This evidence therefore suggests that there is only M1 reorganisation in certain pathological pain conditions.

3.1.2. S1 should be reorganised in people with chronic pain

There is also fMRI evidence suggesting S1 reorganisation in several pathological pain conditions such as carpal tunnel syndrome (Napadow et al., 2006), dystonia (for review, see Furuya & Hanakawa, 2016), low back pain (Goossens et al., 2018), and unilateral widespread pain from herpes simplex virus infections (Vartiainen, Kirveskari, Kallio-Laine, Kalso, & Forss, 2009). The evidence is mixed for other conditions, such as phantom limb pain (for a review, see Andoh, Milde, Tsao, & Flor, 2018), neuropathic pain (Gustin et al., 2012), orofacial pain (Lin, 2014), and spinal cord injury (for review, and meta-analysis see Dahlberg et al., 2018). There is evidence of cortical reorganisation of S1 in CRPS (Di Pietro et al., 2013b; Juottonen et al., 2002; Maihöfner, Handwerker, Neundörfer, & Birklein, 2003; Pfannmöller, Strauss, Langner, Usichenko, & Lotze, 2019; Pleger et al., 2004; Vartiainen, Kirveskari, & Forss, 2008) (for a review and meta-analysis, see Di Pietro et al., 2013b). Other studies, however, have found no difference in the S1 representations of the affected hand relative to the unaffected hand, or relative to pain-free individuals (Di Pietro, Stanton, Moseley, Lotze, & McAuley, 2016; Mancini et al., 2019). Therefore, there is evidence of S1 reorganisation in some, but not all pathological pain conditions.

3.1.3. Cortical reorganisation should relate to pain

Cortical reorganisation has been found to relate to pain for people with spinal cord injury, carpal tunnel syndrome, and neuropathic pain. For instance, there is some evidence to suggest that cortical reorganisation is associated with pain for people with spinal cord injury (for review and meta-analysis see Dahlberg et al., 2018). Similarly, the distance between digit representations in S1 was found to relate to motor deficits for people with carpal tunnel syndrome (Maeda et al., 2014). That is, a reduced distance between the representations of the second and third digits in S1, contralateral to the affected hand, was related to more severe symptoms and poorer motor performance. People with a diagnosis of neuropathic pain, but not those with non-neuropathic pain, showed a reorganisation of S1 (Gustin et al., 2012). This finding suggests that the pain alone is not sufficient to reorganise the somatosensory cortex.

The evidence is mixed for people with CRPS. One study found that successful treatment of CRPS coincided with normalisation of the cortical representation of S1 (Maihöfner, Handwerker, Neundörfer, & Birklein, 2004). However, more recent studies have not found S1 reorganisation to relate to pain (Di Pietro et al., 2016; Mancini et al., 2019).

It is also important to note that the direction of the association between cortical representations of the affected area and pain is unclear, and that the changes observed could be adaptive. In people with phantom limb pain, cortical reorganisation has been shown to inversely correlate with pain (Makin et al., 2013), or to not correlate with pain (Makin, Scholz, Slater, Johansen-Berg, & Tracey, 2015). These results contrast with earlier findings (e.g. Flor et al., 1995), and evidence that pain reduction from phantom pain was associated with a normalisation of S1 representations following mirror therapy (Foell, Bekrater‐Bodmann, Diers, & Flor, 2014). The evidence from phantom limb pain therefore provides mixed evidence for a relationship between cortical reorganisation and pain, and the direction of this association (for a review, see Andoh et al., 2018).

Taken together, the evidence suggesting that cortical reorganisation relates to pain is mixed.

3.1.4. Pain can result from brain damage

Direct evidence that cortical reorganisation can trigger pathological pain comes from people who have had brain injuries. Several painful conditions commonly occur after stroke (Paolucci et al., 2016), such as central post-stroke pain, CRPS, musculoskeletal pain, and post-stroke headache (for reviews, see Delpont et al., 2018; Harrison & Field, 2015). One study reported a 48% incidence of CRPS in the first 28 weeks in hemiplegic patients (Kocabas, Levendoglu, Ozerbil, & Yuruten, 2007), although the incidence of post-stroke CRPS is substantially lower if more stringent criteria are used (Oh, Choi, Park, & Shin, 2019). Furthermore, distorted representations of the body and its surrounding space are key features of asomatognosia (Baier & Karnath, 2008) and hemispatial neglect (Husain & Rorden, 2003; Vallar, 1997, 1998), respectively. These distorted representations are similar to those described for people with pathological pain in subsequent sections of this review (i.e. 3.4., and 3.5.). Similarities between people with pathological pain conditions and people with who have suffered brain injury demonstrate the possibility of a cortical origin of pathological pain.

3.1.5. Interim summary

There is partial evidence of cortical changes in pathological pain conditions, and evidence for the relationship with pain is inconsistent (Table 2). This mixed evidence base provides partial support for the notion that a distorted cortical representation of the body may be implicated in pathological pain, although the evidence for a relationship with pain is less consistent than would have been predicted by the theory. There is also some evidence to suggest that cortical reorganisation can be adaptive, which contradicts the sensorimotor theory of pain. In contrast, direct evidence of a cortical origin of pathological pain comes from neurological populations that experience pain after brain damage. Taken together, the mixed evidence suggests that cortical changes are not sufficient to explain pathological pain. Therefore, if sensorimotor incongruences are serving to maintain pain, they might be related to the functioning of sensorimotor processing rather than simply their cortical organisation.

Table 2. Cortical reorganisation.

Summary of the evidence relevant to hypotheses related to cortical reorganisation in pathological pain.

	Evidence for predictions	Mixed evidence for predictions	Evidence against predictions
M1 should be reorganised in people with pathological pain	Dystonia, low back pain, osteoarthritis, phantom limb pain, spinal cord injury	CRPS	
S1 should be reorganised in people with pathological pain	Carpal tunnel syndrome, dystonia, low back pain, unilateral widespread pain from herpes simplex virus infections	CRPS, neuropathic pain, orofacial pain, phantom limb pain, spinal cord injury,	
Cortical reorganisation should relate to pain	Carpal tunnel syndrome, neuropathic pain, spinal cord injury	CRPS, phantom limb	
Pain can result from brain damage	Central post-stroke pain, CRPS, musculoskeletal pain, post-stroke headache		

CRPS = Complex Regional Pain Syndrome.

3.2. Motor deficits

There are several processes that could interfere with the control of a movement, as would be predicted by the sensorimotor theory of pain. For instance, people with pathological pain could have difficulties with executing a movement (3.2.1.). They might imagine movements differently to those without pain (3.2.2.), which would add to the evidence that motor representations are compromised. Any motor deficits could relate to cortical changes (3.2.3.), and/or pain (3.2.4.). We will address all of these possibilities in the following section. We conclude that motor deficits are present in many pathological pain conditions, and that many people experience altered motor imagery compared to pain-free individuals. Motor deficits are also related to pain in several pathological conditions.

3.2.1. People with pathological pain should have motor deficits

People with pathological pain conditions often have movement impairments, although their exact nature can vary. It is important to consider that motor changes could be due to muscle atrophy (De Pauw et al., 2016; Lee et al., 1999), although this does not contradict the sensorimotor theory of pain. For instance, muscle atrophy could increase the rate of muscle fatigue, requiring adaptation of the sensorimotor system (Wolpert et al., 2011). As the latter is theorised to be disrupted in pathological pain (Harris, 1999), findings showing altered movement in these conditions can therefore be considered indirect support for the sensorimotor theory of pain.

Motor deficits have been reported for people with conditions such as low back pain, neck pain, and carpal tunnel syndrome. For instance, people with low back pain make slower lumbar movements compared to control participants (for review and meta-analysis see Laird, Gilbert, Kent, & Keating, 2014). When people with low back pain were clustered based on their movement kinematics, the group with the greatest motor impairments were found to have greater pain than other subgroups (Laird, Keating, & Kent, 2018). For reviews see (Meier, Vrana, & Schweinhardt, 2019; van Dieën, Flor, & Hodges, 2017). Similar changes have been seen in other painful conditions. People with neck pain have reduced range of movement, movement speed, and head positioning accuracy, compared to controls (for review see Hesby, Hartvigsen, Rasmussen, & Kjaer, 2019). Furthermore, people with carpal tunnel syndrome were found to have greater variability in precision pinch and reach-to-pinch movements than control participants (Gehrmann et al., 2008).

Both gross and fine motor control can be disrupted in fibromyalgia. Such deficits are not always detectable at a group level (Rasouli, Fors, Borchgrevink, Öhberg, & Stensdotter, 2017), although some studies do find such evidence (Pérez-de-Heredia-Torres, Martínez-Piédrola, Cigarán-Méndez, Ortega-Santiago, & Fernández-de-las-Peñas, 2013). For instance, impaired manual dexterity has been reported in fibromyalgia (Canny, Thompson, & Wheeler, 2009; Pérez-de-Heredia-Torres et al., 2013). However, as not all people with this condition experience movement difficulties, these findings only offer partial support for the sensorimotor theory of pain, or suggests that it is only applicable to specific aspects of painful conditions.

Movement difficulties are characteristic of dystonia, often involving sustained or intermittent muscle contractions (Albanese et al., 2013). For instance, focal dystonia in pianists was associated with altered dexterous joint coordination, due to decreased control of individual digits (Furuya, Tominaga, Miyazaki, & Altenmüller, 2015). Many of the motor deficits in dystonia relate to sensorimotor processing (for reviews see Avanzino, Tinazzi, Ionta, & Fiorio, 2015; Conte, Defazio, Hallett, Fabbrini, & Berardelli, 2019; Desrochers, Brunfeldt, Sidiropoulos, & Kagerer, 2019), which is consistent with the predictions made by the sensorimotor theory of pain.

In CRPS, motor deficits are part of the diagnostic criteria (Harden, Bruehl, Stanton-Hicks, & Wilson, 2007), although not required to receive a diagnosis. Approximately 25% of patients with CRPS experience movement disorders (Van Hilten, 2010), such as dystonia (for reviews of dystonia in CRPS see Avanzino et al., 2015; Patel, Jankovic, & Hallett, 2014). The pathophysiology of dystonia in CRPS is unclear (van Rijn, Marinus, Putter, & van Hilten, 2007), and is different to typical dystonia. For instance, it does not require sustained muscle activation (Bank, Peper, Marinus, Beek, & van Hilten, 2013a). In addition to dystonia, motor deficits in CRPS have been evidenced by poorer performance on tasks such as reach-to grasp movement (Maihöfner et al., 2007; Osumi, Sumitani, Kumagaya, & Morioka, 2017), finger tapping (Schilder et al., 2012), circle drawing (Reid et al., 2017), although such differences are not always found (Christophe et al., 2016a). These findings highlight the heterogeneity of motor deficits in CRPS, which therefore only offers partial support for this assumption of the sensorimotor theory of pain.

There is therefore evidence to suggest that people with some painful conditions, such as low back pain, neck pain, carpal tunnel syndrome, fibromyalgia, dystonia, and CRPS can have motor deficits, although their prevalence and severity may vary within conditions. The evidence for the sensorimotor theory of pain comes from sub groups of people with different conditions, rather than from specific patient populations, which therefore provides mixed support for the theory.

3.2.2. People with pathological pain should have difficulties imagining movements

The sensorimotor theory of pain would predict that people with pathological pain should have difficulties imagining movement. Difficulties with motor imagery would indicate that motor representations (Jeannerod & Decety, 1995) might be altered, which are important for successful sensorimotor processing.

Altered motor imagery has been reported in several painful conditions. For instance, people with chronic low back pain were slower, and reported more difficulty in generating visual and kinaesthetic images than control participants (La Touche et al., 2019). Motor imagery has also been found to cause pain. That is, imagining movement of the affected limb increased swelling and pain in CRPS (Moseley et al., 2008). Similarly, pain increased for people with complete thoracic spinal cord injury following imagined movement of the foot (Gustin et al., 2008). However, this was only the case for those with neuropathic pain, those without neuropathic pain reported only an increase in non-painful sensation during imagined movement. This is an important distinction, as it suggests a difference between those with

and without pathological pain. Specifically, this may indicate that motor imagery is only altered for specific pathological pain conditions.

More recently, people with spinal cord injury reported less vivid motor imagery than controls (Scandola, Aglioti, Pozeg, Avesani, & Moro, 2017). A greater impairment in motor imagery was associated with chronic pain, and a higher lesion. Similarly, motor imagery was slower for people with phantom limb than controls (Kikkert et al., 2017). These findings suggest a role of deefferentation (i.e. disruption of motor efferents) and deafferentation (i.e. disruption of sensory afferents) in motor imagery.

Taken together, these findings suggest that motor imagery can be altered in pathological pain conditions, and that altered sensory input may be contributing to the changes seen (e.g. deefferentation and deafferentation).

3.2.3. Motor deficits should relate to altered cortical processing

As the sensorimotor theory of pain proposes a cortical origin of pathological pain, motor deficits should relate to altered cortical processing.

Several neuroimaging studies of motor imagery have found different patterns of activation between people with pathological pain conditions, and pain-free controls. Altered cortical activity during motor imagery has been observed for people with CRPS and dystonia (Gieteling et al., 2008), focal writers' cramp (Delnooz, Helmich, Medendorp, Van de Warrenburg, & Toni, 2013), and for people with chronic low back pain (Vrana et al., 2015). In amputees, motor imagery has been found to cause different patterns of activation between those with and without phantom limb pain. Both groups showed higher activity of the supplementary motor area, however only the pain-free group had activation in the contralateral primary sensorimotor cortex (Diers, Christmann, Koeppe, Ruf, & Flor, 2010), for review see (Andoh et al., 2018). Taken together, these findings demonstrate that cortical activity in response to motor imagery can be altered in pathological pain conditions, which is compatible with the idea of altered motor representations.

Altered cortical activation during motor tasks has been found for people with fibromyalgia, CRPS, phantom limb pain, and knee osteoarthritis. A recent functional near-infrared spectroscopy study found lower activation of the superior parietal gyrus associated with fine motor loss in fibromyalgia (Eken et al., 2018). For people with CRPS, the degree of motor impairment was associated with the strength of activation in the posterior parietal cortices, supplementary motor cortices and M1 (Maihöfner et al., 2007). The reorganisation of S1 representations, however, was not found to relate to motor performance for the CRPS-effected limb (Pfannmöller et al., 2019). For people with phantom limb pain, slower finger tapping of the phantom was associated with greater pain, and greater activation of S1 (Kikkert et al., 2017). Furthermore, people with knee osteoarthritis were found to have an anterior shift in the cortical representation of the knee, compared to controls (Shanahan et al., 2015). This shift was associated with poorer performance on a motor task that involved the knee, which suggests a link between motor deficits and cortical reorganisation.

These findings demonstrate that motor impairments in pathological pain conditions are associated with altered cortical activity, which is consistent with the assumptions made by the sensorimotor theory of pain.

3.2.4. Motor deficits should relate to pain

According to the sensorimotor theory of pain, motor deficits should relate to pain, as impaired motor control could lead to errors in sensorimotor processing. There is some evidence for this hypothesis from people with carpal tunnel syndrome, and phantom limb pain. As the theory predicts that pain is a consequence of sensorimotor incongruence, impaired motor control should cause pain, or their relationship should be bidirectional. The available evidence, however, does not necessarily support this idea.

Pain can be associated with movement difficulties in pathological pain conditions. For instance, pain severity is associated with motor performance for people with carpal tunnel syndrome (Fernández-Muñoz et al., 2016). In amputees, slower phantom finger tapping has been found to relate to phantom limb pain (Kikkert et al., 2017), although motor imagery was not related to pain. Furthermore, altered motor performance is associated with an increased risk of developing low back pain (for review and meta-analysis see Sadler, Spink, Ho, De Jonge, & Chuter, 2017). Similarly, fixed dystonia in CRPS is associated with a poorer prognosis (Ibrahim et al., 2009; Schrag, Trimble, Quinn, & Bhatia, 2004), which demonstrates the role of importance of movement in these conditions in line with theoretical prediction.

However, experimental studies of motor deficits in CRPS contradict theoretical predictions. That is, pain was not related to motor performance on a finger tapping task (Schilder et al., 2012). Rather, pain relief caused improvements in motor performance in CRPS, following a ketamine infusion (Schilder et al., 2013), or a nerve blockade (Osumi et al., 2017). These findings contradict the sensorimotor theory of pain, as they suggest that motor deficits are a consequence of pain, although we cannot rule out that their relationship is bidirectional.

3.2.5. Interim summary

Taken together, these findings suggest that motor imagery can be altered in pathological pain conditions, which is also reflected in different cortical activation patterns. Altered sensory input may be contributing to the changes seen (e.g. deefferentation and deafferentation). These findings are in line with the predictions made by the sensorimotor theory of pain, as they demonstrate ways in which motor representations (Jeannerod & Decety, 1995) might be altered in pathological pain conditions, which are important for successful sensorimotor processing.

The presence of motor deficits in several pathological pain conditions is also consistent with the sensorimotor theory of pain (Table 3). These deficits are associated with cortical reorganisation (Duncan & Boynton, 2007) and cortical processing (Patel et al., 2014). This evidence, however, is not causal, and in some cases pain relief improves motor performance, contrary to what would be predicted by the sensorimotor theory of pain.

Nonetheless, evidence of altered motor imagery suggests that motor representations may be altered for people with pathological pain conditions, such as CRPS, dystonia, low back pain, neuropathic pain, and shoulder pain. In certain cases, such changes appear to be specific to the affected limb/area. The latter is consistent with the predictions made by the sensorimotor theory of pain. Therefore, the evidence of motor deficits, and motor imagery provides partial support for the theoretical predictions.

Table 3. Motor deficits.

Summary of the evidence relevant to hypotheses related to motor deficits in pathological pain.

	Evidence for predictions	Mixed evidence for predictions	Evidence against predictions
People with pathological pain should have motor deficits	Carpal tunnel syndrome, dystonia, low back pain, neck pain	CRPS, fibromyalgia	
People with pathological pain should have difficulties imagining movements	CRPS, complete thoracic spinal cord injury with neuropathic pain, low back pain, phantom limb pain, spinal chord injury		Complete thoracic spinal cord injury without neuropathic pain
Motor deficits should relate to altered cortical processing	CRPS, fibromyalgia, focal writers' cramp, low back pain, phantom limb pain, knee OA		
Motor deficits should relate to pain	Carpal tunnel syndrome, low back pain, phantom limb pain		CRPS

CRPS = Complex Regional Pain Syndrome; OA = osteoarthritis.

3.3. Sensory changes

According to the sensorimotor theory of pain the quality, precision, accuracy, and/or reliability of sensory input should be altered in people with pathological pain (3.3.1.). In the context of movement, we focus our review on tactile (3.3.1.1.), and proprioceptive (3.3.1.2.) sensation. That is, tactile information used to inform sensorimotor processing (Dijkerman & De Haan, 2007), and is used to form representations of the body and its surrounding space. Proprioception is needed for accurate motor predictions (Sober & Sabes, 2005; Tuthill & Azim, 2018), body representations, and muscle force (Proske & Gandevia, 2012). Furthermore, any sensory deficits should relate to altered cortical processing (3.3.2.), and pain (3.3.3.). We conclude that, there is evidence for sensory changes in many pathological pain conditions.

3.3.1. People with pathological pain should have sensory deficits

3.3.1.1. Tactile

Impaired tactile processing has been found in many pathological pain conditions, as evidence by altered tactile acuity, spatial discrimination threshold, tactile localisation, and somatosensory temporal discrimination threshold.

Tactile acuity, as assessed by two-point discrimination threshold typically near to, or on the affected body part, is impaired in several chronic pain conditions, including achilles tendinopathy (Debenham, Butler, Mallows, & Wand, 2016), people with cerebral palsy and lower back pain (Yamashita et al., 2019), CRPS (Pleger et al., 2006; Reiswich et al., 2012), fibromyalgia (Martínez, Guillen, Buesa, & Azkue, 2019), knee osteoarthritis (Stanton et al., 2013), neuropathic pain (Taylor, Anastakis, & Davis, 2010), arthritis, chronic low back pain, migraine (Luedtke et al., 2018), chronic neck pain (Harvie, Edmond-Hank, & Smith, 2018), and temporomandibular disorders (for review and meta-analysis see Catley, O'Connell, Berryman, Ayhan, & Moseley, 2014; La Touche et al., 2020). In contrast, tactile acuity appears to be normal for people with hand osteoarthritis (Magni, McNair, & Rice, 2018), and for people with burning mouth syndrome (for a reviews and meta-analyses see Adamczyk, Luedtke, & Saulicz, 2018; Catley et al., 2014). For people with CRPS, tactile acuity correlated with subjective reports of body perception disturbance (Lewis & Schweinhardt, 2012), and was found to improve when they view the mirror image of their non-affected limb, in the location of their affected limb (Moseley & Wiech, 2009). Two-point discrimination threshold is larger for the affected, compared to corresponding sites on the unaffected limb in unilateral pain conditions (for review and meta-analysis see Catley et al., 2014), suggesting that it is not a generalised impairment but instead reflects altered sensory processing that is specific to the affected area. The evidence therefore suggests that reduced tactile acuity can occur in many painful conditions, such as arthritis, CRPS, fibromyalgia, neuropathic pain, low back pain, migraine, neck pain, temporomandibular disorders, tendinopathy, and osteoarthritis.

Spatial discrimination thresholds, indexed by participants ability to distinguish between smooth and grooved surfaces presented at different orientations (i.e. the Grating Orientation Task Johnson & Phillips, 1981), were higher for people with focal hand dystonia,

benign essential blepharospasm, and cervical dystonia than for age matched controls. The study did not find any difference between people with primary generalized DYT1 dystonia and controls (Molloy, Carr, Zeuner, Dambrosia, & Hallett, 2003). There is therefore evidence to suggest that tactile spatial acuity on the finger pad is only altered in certain types of dystonia.

The ability to locate tactile sensations can be altered for people with CRPS, fibromyalgia, low back pain, and neuropathic pain. People with CRPS were worse at locating touch on their affected hand than pain-free control participants (Trojan et al., 2019). Similar findings have been reported for people with chronic low back pain (Wand et al., 2013). Furthermore, some people with pathological pain can experience referred sensations, as has been found for conditions such as CRPS (Maihöfner, Neundörfer, Birklein, & Handwerker, 2006; McCabe, Haigh, Halligan, & Blake, 2003), neuropathic pain following complete spinal cord injury (Soler et al., 2010), and in fibromyalgia (Martínez et al., 2019), but not for low back pain (Wand et al., 2013). Tactile mislocalisation and referred sensations are examples of how accuracy, and precision of sensory information can be degraded, and thus make tactile information less reliable. This idea is further supported by a recent study showing that people with CRPS do not use tactile information optimally when making predictions of the spatial location of stimuli during a tactile spatial oddball task (Brown, Scholtes, Shenker, & Lee, 2020) compared to pain-free controls. These findings could suggest that accuracy and precision of sensory information is degraded for people with pathological pain, and that they use this information differently to pain-free individuals.

Somatosensory temporal discrimination threshold, the shortest interval needed for two tactile stimuli to be perceived as separate (Lacruz, Artieda, Pastor, & Obeso, 1991), can be altered in painful conditions. This threshold relies on sensory processing that enables irrelevant information to be filtered out (Conte et al., 2012; Rocchi, Casula, Tocco, Berardelli, & Rothwell, 2016). Therefore, the sensorimotor theory of pain would predict that somatosensory temporal discrimination thresholds are altered in pathological pain, as this would result in more noise in the sensorimotor system. Altered somatosensory temporal discrimination thresholds have been reported for people with chronic back pain (Zamorano et al., 2015), dystonia (Conte et al., 2018b), fibromyalgia (Gunendi, Polat, Vuralli, & Cengiz, 2019), migraine (Vuralli, Evren Boran, Cengiz, Coskun, & Bolay, 2016), but is intact in tension-type headache (Vuralli, Boran, Cengiz, Coskun, & Bolay, 2017), and cervical dystonia with, or without tremor (Avanzino et al., 2020). Movement-dependent changes in thresholds were greater for people with cervical dystonia or focal hand dystonia compared to those with blepharospasm, and pain-free controls (Conte et al., 2018a). For reviews see (Avanzino, Fiorio, & Conte, 2018a; Avanzino et al., 2015; Conte et al., 2019; Desrochers et al., 2019). These findings therefore suggest that the filtering irrelevant sensory information may be altered in several painful conditions, such as dystonia, fibromyalgia, and migraine, but not for people with tension type headache. This is consistent with altered sensorimotor processing, as it is likely to result in more noise in the sensorimotor system.

3.3.1.2. Proprioceptive

Several painful conditions are accompanied by proprioceptive deficits (for a review see Tsay, Allen, Proske, & Giummarra, 2015). Proprioceptive deficits have been reported in conditions such as knee osteoarthritis (for review and meta-analysis see Van Tunen et al.,

2018), fibromyalgia (Bardal, Roeleveld, Johansen, & Mork, 2012; Celenay, Mete, Coban, Oskay, & Erten, 2019), and CRPS with dystonia (Schouten, Van de Beek, Van Hilten, & Van der Helm, 2003; van de Beek, Vein, Hilgevoord, van Dijk, & van Hilten, 2002). For people with unilateral CRPS, proprioceptive deficits can be bilateral (Lewis et al., 2010), and do not seem related to distorted representations of the body (Brun et al., 2019).

People with dystonia can also have proprioceptive deficits. Most of the evidence of altered proprioception in people with dystonia has looked at the illusory movement elicited by the tonic vibration reflex (i.e. 50-210 Hz stimulation of the muscle belly or tendon to active γ-motor neurons and muscle spindles; Eklund & Hagbarth, 1966). Studies of the tonic vibration reflex have found evidence suggesting an increased reflex and/or a reduced perception of the illusory movement, as identified by recent reviews (Avanzino et al., 2018a; Conte et al., 2019). People with cervical dystonia with tremors had impaired position sense for the head and wrist compared to those without tremors and pain-free controls (Avanzino et al., 2020). This suggests that proprioceptive deficits may be specific to certain types of dystonia, and therefore that the sensorimotor theory of pain may of greater relevance to these forms of dystonia.

There is mixed evidence of proprioceptive deficits in Ehlers-Danlos Syndrome, shoulder pain, neck pain, and low back pain. People with Ehlers-Danlos Syndrome had less precise proprioceptive estimates of hand position (Clayton, Cressman, & Henriques, 2013), and knee position (Rombaut, De Paepe, Malfait, Cools, & Calders, 2010; Sahin et al., 2008) compared to controls participants, but there was no difference for shoulder position (Rombaut et al., 2010). For people with shoulder pain, the evidence for proprioceptive deficits is also mixed (for review see Ager et al., 2019). The evidence is also mixed for people with chronic idiopathic neck pain. That is, they were found to make greater errors on head-to-neutral repositioning tests than pain-free controls (for review and meta-analysis see Stanton, Leake, Chalmers, & Moseley, 2016), but the evidence is conflicting for repositioning tasks with little vestibular input, and for complex, or postural repositioning tests. The cause of the neck pain (i.e. traumatic, or non-traumatic) did not influence proprioceptive deficits (for review see de Vries et al., 2015). Furthermore, people with low back pain were found to have impaired lumbar proprioception when measured actively in a sitting position (i.e. joint repositioning errors), and greater threshold to direction of passive motion compared to pain-free controls, as highlighted by recent reviews (Meier et al., 2019) and meta-analyses (Laird et al., 2014; Tong et al., 2017). Yet, a meta-analysis (Tong et al., 2017) did not find any difference between people with low back pain and controls for lumbar proprioception whilst standing, nor for passive joint repositioning errors whilst seated, which suggests that the deficits are not generalised.

In a non-specific sample of people with unilateral chronic pain, however, proprioception was found to be intact (Tsay & Giummarra, 2016). Therefore, these findings suggest that proprioceptive deficits are not general to all forms of pathological pain, and thus that the sensorimotor theory of pain may be less relevant to understanding their pathology.

3.3.2. Sensory deficits should relate to altered cortical processing

If sensory deficits contribute to a cortical origin of pathological pain as theorised, sensory deficits should be related to altered cortical processing. This hypothesis is evidenced by findings that relate tactile acuity, and proprioception to altered cortical activity.

Tactile acuity, which can be impaired in pathological pain conditions (see 2.3.1.1.; Adamczyk et al., 2018; Catley et al., 2014), is inversely correlated with the size of the cortical representation of the stimulated body part on the somatosensory cortex in pain-free individuals (Duncan & Boynton, 2007). Both the size of cortical representations and tactile acuity change following immobilisation of a limb (Lissek et al., 2009). Therefore, many studies looking at two-point discrimination make the assumption that any deficits relate to altered cortical representations, although they do not include any neurophysiological measures. One study of people with CRPS, found that two-point discrimination threshold is correlated with the degree of shrinking of the S1 representation of the CRPS-affected limb (Pleger et al., 2006), although such changes are not always found (Pfannmöller et al., 2019). The evidence from people with CRPS is therefore mixed.

There is also evidence that cortical processing of proprioceptive information is altered in lower back pain, and dystonia. A recent study found a lateral shift of activation peaks in right S2 in response to proprioceptive stimulation (i.e. local muscle vibration) of the lower back in people with low back pain, compared to controls (Goossens, Janssens, & Brumagne, 2019), which correlated with self-reported distortions of body perception. Furthermore, proprioceptive deficits in dystonia have been linked to altered cortical processing (Avanzino & Fiorio, 2014).

3.3.3. Sensory deficits should relate to pain

Sensory deficits should be related to pain, and pain pathology, as theorised by the sensorimotor theory of pain. This hypothesis is evidenced by quantitative sensory testing (QST), tactile acuity, and proprioception.

Sensory changes have been well documented in the QST literature, which has enabled sensory profiles for different patient groups to be identified (Magerl et al., 2010; Rolke et al., 2006). Differences in QST relative to pain-free controls have been described for people with CRPS (Gierthmühlen et al., 2012), dystonia (Conte et al., 2019), fibromyalgia (Kosek, Ekholm, & Hansson, 1996), knee pain (De Oliveira Silva, Rathleff, Petersen, Azevedo, & Barton, 2019), musculoskeletal pain (Georgopoulos et al., 2019), neuropathic pain (Krumova, Geber, Westermann, & Maier, 2012; Maier et al., 2010), osteoarthritis (Fingleton, Smart, Moloney, Fullen, & Doody, 2015; Lluch, Torres, Nijs, & Van Oosterwijck, 2014), shoulder pain (Sanchis, Lluch, Nijs, Struyf, & Kangasperko, 2015), temporomandibular disorders (La Touche et al., 2018), and whiplash (Van Oosterwijck, Nijs, Meeus, & Paul, 2013). As sensory profiles can have diagnostic value (Attal et al., 2013), the QST literature provides another example of altered sensory experiences in pathological pain conditions, and demonstrates how changes may vary between conditions.

Changes in tactile perception have been found to correlate with pain for people with neck pain, and CRPS. Two-point discrimination threshold was associated with pain intensity for neck pain (Harvie et al., 2018). For people with CRPS, mislocalisation of tactile stimulation

delivered to the affected hand was found to correlate with mechanical hyperalgesia (Maihöfner et al., 2006). Furthermore, the experience of referred sensations was found to evoke pain. That is, “dysynchiria”, where people experience pain in response to seeing the mirror image of their non-affected hand being stimulated, caused pain and paraesthesia with CRPS (Acerra & Moseley, 2005), but not for people with neuropathic pain (Krämer, Seddigh, Moseley, & Birklein, 2008). This suggests that some of the alterations in tactile sensation might be specific to CRPS, and may be experienced without direct stimulation.

Proprioceptive abilities have been found to relate to disability, although its relationship with pain is not clear. Impaired proprioception has been found relate to motor deficits in this CRPS (Bank, Peper, Marinus, Beek, & van Hilten, 2013b). Similarly, impaired lumbar proprioception has been found to be associated with disability in chronic low back pain, although its relationship with pain is not clear (for reviews see Ghamkhar & Kahlaee, 2019; Lin, Halaki, Rajan, & Leaver, 2019). In Ehlers-Danlos Syndrome, proprioceptive precision was not related to pain (Clayton, Jones, & Henriques, 2015).

Changes in how proprioceptive information is used may be related to the development of low back pain. These changes reflect a reweighting of proprioceptive information for people with low back pain, whereby proprioceptive sensitivity is refocused to the ankles and away from the trunk (Brumagne, Cordo, & Verschueren, 2004). A prospective study found such ankle-focused proprioceptive control whilst standing to be predictive of low back pain two years later (Claeys et al., 2015), which suggests that the way that proprioceptive information is processed may be important for progression of this condition.

3.3.4. Interim summary

In summary, there is evidence of several different sensory changes in many pathological pain conditions, which could contribute to a sensorimotor incongruence (Table 4). Impaired tactile acuity, greater somatosensory temporal discrimination threshold, tactile mislocalisation, and referred sensations could compromising quality of the sensory information available to the nervous system (e.g. by increasing noise), which would interfere with sensorimotor processing (Azañón et al., 2016; Wolpert & Flanagan, 2001). There is also evidence of impaired proprioception in many pathological pain conditions. Proprioception is needed for accurate motor predictions (Sober & Sabes, 2005; Tuthill & Azim, 2018), and informs the representation of the body (Longo & Haggard, 2010; Proske & Gandevia, 2012). Therefore, sensory changes in several pathological pain conditions offer at least partial support for the predictions made by the sensorimotor theory of pain, as they may be altering sensory feedback, and compromising motor predictions.

Table 4. Sensory changes.

Summary of the evidence relevant to hypotheses related to sensory changes in pathological pain.

	Evidence for predictions	Mixed evidence for predictions	Evidence against predictions
People with pathological pain should have sensory deficits			
Tactile	Achilles tendinopathy, CP with lower back pain, CRPS, dystonia, fibromyalgia, knee OA, neuropathic pain, low back pain, migraine, neck pain, temporomandibular disorders		Hand OA, burning mouth syndrome
Proprioceptive	CRPS, dystonia, fibromyalgia, knee OA	Ehlers-Danlos Syndrome, idiopathic neck pain, low back pain, shoulder pain	Non-specific unilateral chronic pain
Sensory deficits should relate to altered cortical processing	Dystonia, low back pain	CRPS	
Sensory deficits should relate to pain	CRPS, neck pain	Low back pain	Ehlers-Danlos Syndrome

CRPS = Complex Regional Pain Syndrome.

3.4. Body representation

Representations of the body are used to generate predictions about the sensory outcome of a movement (Shadmehr et al., 2010), and the accuracy of these representations serve to keep the prediction error to a minimum (Clark, 2013). The sensorimotor theory of pain would therefore suggest bodily representations are less accurate, and/or are more difficult to access (3.4.1.). Furthermore, it could be that some of the processes that are involved in maintain bodily representations are altered, such as their updating (3.4.2.). Any changes that occur should be related to altered cortical processing (3.4.4.), and/or the severity of pain (3.4.5.). We will address these hypotheses in the following section. We conclude that distorted representations of the body commonly occur in many different types of pathological pain conditions, such as CRPS, fibromyalgia, orofacial pain, painful post-traumatic trigeminal neuropath, and phantom limb pain.

3.4.1. People with pathological pain should have distorted representations of the body

Many people with pathological pain experience their body to be different in its shape, and/or size to its physical size, as evidenced by interviews, drawings, and hand matching tasks (Table 5). Evidence from people with CRPS, fibromyalgia, shoulder pain, osteoarthritis, and low back pain studies suggest that abnormal body representations of the affected area could be common in many chronic pain conditions (for reviews see Fuchs, Flor, & Bekrater-Bodmann, 2018; Giummarra & Moseley, 2011; Haggard, Iannetti, & Longo, 2013; Senkowski & Heinz, 2016; Tsay et al., 2015; Viceconti et al., 2020).

Table 5. Body representation.

Summary of studies examining body representations in people with pathological pain.

Task/method	Population	Finding	Citations
Interviews			
	CRPS	Altered shape/size	(Lewis, Kersten, McCabe, McPherson, & Blake, 2007; Tajadura-Jiménez, Cohen, & Bianchi-Berthouze, 2017)
	Phantom limbs	Altered length (i.e. shrinking, or telescoping), shape, and posture of phantoms	(Carlen, Wall, Nadvorna, & Steinbach, 1978; Giummarra et al., 2010; Jensen, Krebs, Nielsen, & Rasmussen, 1983)
	Fibromyalgia	Altered shape/size	(Valenzuela-Moguillansky, 2013)
	Orofacial pain	Painful area “swollen”	(Dagsdóttir et al., 2016)
	Shoulder pain	Arm length “normal”	(Alaiti et al., 2019)
Patient drawings			
	Low back pain	Altered shape/size	(Moseley, 2008)
Hand matching task			
	CRPS	Affected hand bigger	(Moseley, 2005; Peltz, Seifert, Lanz, Müller, & Maihöfner, 2011)
	Osteoarthritis	Affected hand smaller	(Gilpin, Moseley, Stanton, & Newport, 2015)

CRPS = Complex Regional Pain Syndrome.

3.4.1.1. Mental limb rotation

Performance on mental rotation tasks of body parts seems to be impaired in some types of pathological pain. The mental limb rotation task involves mentally rotating a drawing, or an image, of a body part to establish its laterality. This task requires motor imagery, and draws on the representation of the body (for a review and meta-analysis see Zacks, 2008).

Altered performance (i.e. reduced speed and/or accuracy) compared to pain-free participants has been reported for individuals with arm or shoulder pain (Coslett, Medina, Kliot, & Burkey, 2010b), back pain (Bowering, Butler, Fulton, & Moseley, 2014; Bray & Moseley, 2011), carpal tunnel syndrome (Schmid & Coppieters, 2012), CRPS (Moseley, 2004b; Reinersmann et al., 2010; Schwoebel, Friedman, Duda, & Coslett, 2001), dystonia (Fiorio, Tinazzi, & Aglioti, 2006), fibromyalgia (Martínez et al., 2019), hand osteoarthritis (Magni et al., 2018), knee osteoarthritis (Stanton et al., 2012), leg or foot pain (Coslett, Medina, Kliot, & Burkey, 2010a), neck pain (Elsig et al., 2014; Wallwork, Leake, Peek, Moseley, & Stanton, 2020), and phantom limb pain (Nico, Daprati, Rigal, Parsons, & Sirigu, 2004; Reinersmann et al., 2010) when rotating images of body parts, typically corresponding to the affected area (e.g. hand, foot, or trunk). No differences are typically observed for mentally rotating inanimate objects, suggest that the differences in rotating limbs are not due to a general impairment in mental rotation, as they are specific to bodily information. For recent reviews and meta-analyses of laterality judgements in chronic pain, see (Breckenridge et al., 2019; Ravat et al., 2019). These findings suggest that altered performance when mentally rotating a body part is common in painful conditions (Table 6).

Table 6. Mental limb rotation.

Summary of studies examining mental limb rotation in people with pathological pain.

	Population	Rotated body part	Results	Body part specific
Coslett, Medina, Kliot, and Burkey (2010b)	Arm/shoulder pain; other pain; controls	Hands	Longer RTs for arm/shoulder pain group than controls. Correlated with pain severity for arm and shoulder pain group	Yes
Bray and Moseley (2011)	Back pain; controls	Hands, trunks	RT similar. Accuracy lower for trunks in back pain group than controls	Yes
Wallwork, Leake, Peek, Moseley, and Stanton (2020)	Chronic neck pain; acute neck pain; controls	Hands, necks	Accuracy lower for chronic neck pain than controls when judging neck rotation	Yes
Bultitude, Walker, and Spence (2017)	CRPS; controls	Hands	Longer RTs for CRPS than controls	No
Kohler et al. (2019)	CRPS; controls		Longer RTs for CRPS than controls	No
Moseley (2004)	CRPS; controls	Hands	Longer RTs for CRPS than controls	Yes
Schwoebel, Friedman, Duda, and Coslett (2001)	CRPS; controls	Hands	Longer RTs for affected hand than non-affected hand	Yes
Reinersmann et al. (2010)	CRPS; PLP; controls	Hands	Longer RTs for CRPS, and PLP than controls	No
Reinersmann et al. (2012)	CRPS; UL pain; controls	Hands	No sig. differences in RTs	No
Schmid and Coppieters (2012)	CTS; controls	Hands, feet, necks, SM	RT similar. Accuracy lower for CTS hands and necks, not for feet or SM	Yes
Martínez, Guillen, Buesa, and Azkue (2019)	FMS; controls	Hands	Longer RTs and lower accuracy for FMS than controls	na
Magni, McNair, and Rice (2018)	Hand OA; controls	Hands	Longer RTs and lower accuracy for hand OA than controls	Yes
Stanton et al. (2012)	Knee OA; arm pain; controls	Hands, feet	Lower accuracy for knee OA than controls	Yes

(Coslett, Medina, Kliot, & Burkey, 2010a)	Leg or foot pain; other pain; controls	Feet, legs	Longer RTs and lower accuracy for leg or foot pain group than other pain, and controls.	Yes
	Population	Rotated body part	Results	Body part specific
(Bowering, Butler, Fulton, & Moseley, 2014)	Low back pain; controls	Trunks	Lower accuracy for people with low back pain than controls	Yes
(Richter, Röijezon, Björklund, & Djupsjöbacka, 2010)	WAD; neck pain; controls	Hands	Shorter RTs for WAD than controls	na
(Pelletier et al., 2018)	Wrist/hand pain	Hands, feet	Accuracy predicted by self-reported motor imagery ability	na

CRPS = Complex Regional Pain Syndrome; CTS = Carpal tunnel syndrome; FMS = fibromyalgia syndrome; na = not applicable; OA = osteoarthritis; RT = reaction time; sig = significant; SM = Shepard Metzler figures; UL = upper limb; WAD = whiplash-associated disorder.

There is some evidence to suggest that the altered performance of mental rotation of limbs is specific to the body part depicted. For instance, slower and/or less accurate mental rotation of hands corresponding to the painful limb compared to the non-painful limb, has been found for people with carpal tunnel syndrome (Schmid & Coppieters, 2012), CRPS (Reid et al., 2016; Schwoebel et al., 2001), and knee osteoarthritis (Stanton et al., 2012). However, other studies have found no difference between mentally rotating limbs corresponding to the painful area in CRPS (Bultitude, Walker, & Spence, 2017; Kohler et al., 2019; Reinersmann et al., 2012), dystonia (Fiorio et al., 2006), and phantom limb pain (Reinersmann et al., 2010). In contrast, people with neck pain of traumatic origin (i.e. whiplash associated disorder) were faster than pain-free controls at rotating images of hands (Richter, Röijezon, Björklund, & Djupsjöbacka, 2010), and their pain chronicity was associated with faster reaction times.

The role of bodily representations in mental limb rotation is emphasised by findings in amputees. People who had an amputation of their dominant hand performed worse relative to those with an amputation of a non-dominant hand (Nico et al., 2004), and approximately half of the amputees reported phantom sensations in response to the task. These findings suggest that the representation of the body, rather than its physical dimensions, are important for mental limb rotation, and that can result in phantom sensations.

Some studies have found the bias to be greater for images of hands and feet presented in the visual field corresponding to the affected side, compared to the non-affected side (e.g. in CRPS; Reid et al., 2016). The effect did not generalise to letters, suggesting that the bias is specific to bodily information and the affected side of space. However, not all studies find evidence for a bias (e.g. in CRPS; Breimhorst et al., 2018). These mixed findings make it difficult to determine if the difficulties in mental limb rotation are specific to the painful limb, or relate to bodily information more broadly, and suggest that difficulties may only be relevant to certain types of pathological pain.

The evidence from mental rotation of body parts suggests difficulties in many, but not all, painful conditions. As this task involved motor imagery, and relies on the body representation, evidence of altered performance in painful conditions, such as arm/shoulder pain, back pain, carpal tunnel syndrome, CRPS, dystonia, fibromyalgia, osteoarthritis, neck pain, and phantom limb pain, is consistent with the predictions made by the sensorimotor theory of pain. That is, motor imagery relies on motor representations that are needed for movement, and the body representation is needed to make accurate motor predictions (Haggard & Wolpert, 2005). Therefore, changes to either of these processes could impair sensorimotor processing.

3.4.2. People with pathological pain should have difficulties updating the representations of their body

Maintaining an accurate and up to date representation of the body is important for sensorimotor processes (Haggard & Wolpert, 2005), such as motor predictions. Therefore, the sensorimotor theory of pain would predict that updating such representations is altered in pathological pain conditions, which has been studied in amputees, and in people with CRPS.

Upper limb amputees scaled their body representation depending on whether they were wearing a prosthesis or not. That is, tactile distance perception suggested a larger representation of the upper limb when the prosthesis was worn, compared to when it was not worn (Canzoneri, Marzolla, Amoresano, Verni, & Serino, 2013), for review see (Niedernhuber, Barone, & Lenggenhager, 2018), although it should be noted that not all amputees in those studies experienced pain.

For people with CRPS, a recent study showed that they would modify their gait consistent with changes in perceived body weight in response to the manipulations of the auditory feedback they received whilst walking (Tajadura-Jiménez, Cohen, & Bianchi-Berthouze, 2017). This suggests that people with CRPS are able to update their overall body representation. However, this process might differ for the CRPS-affected, and the non-affected body side. We found that people with CRPS update their body representation differently for their CRPS-affected and their non-affected arm following tool-use (Vittersø, Buckingham, Halicka, Proulx, & Bultitude, 2020). We also observed a similar pattern when the arms of people with lower limb CRPS were tested. This suggests that people with CRPS update their body representations differently to people without pain.

Taken together, these studies suggest that amputees, and people with CRPS can update bodily representations, although this process may differ between the affected and the non-affected side of the body for people with CRPS.

3.4.3. Distorted body representations should lead to errors in predicting the consequences of a movement

For the predictions made by the sensorimotor theory of pain to be accurate, distorted repetitions of the body should impair motor predictions. However, as far as the authors are aware, this assumption has yet to be investigated in people with pathological pain. For a discussion on how to study the neural signature of motor predictions in the context of a distorted body representation see (Kuttikat et al., 2016).

3.4.4. Distorted body representations should relate to altered cortical processing

If distorted bodily representations are related to a cortical origin of pathological pain, as theorised, they should also relate to altered cortical processing. This idea has been investigated in people with CRPS, phantom limb pain, and low back pain.

People with CRPS showed longer reaction times on a mental hand rotation task than controls (Kohler et al., 2019). Performance on this task was predicted by putamen and nucleus accumbens activation for the CRPS group.

The painful phantom sensations (e.g. stretching telescoping) of a phantom limb has been found to relate to S1 reorganisation in amputees (Flor et al., 1995; Grüsser et al., 2001), although this does not appear to relate to non-painful phantom sensations. More recent studies suggesting an adaptive role of cortical reorganisation in amputees also support the

idea that painful and non-painful phantom sensations are unrelated (Kikkert, Johansen-Berg, Tracey, & Makin, 2018). These findings suggest that there are separate mechanisms involved in painful, and non-painful phantom sensations, and therefore only offers partial support for the predictions made by the sensorimotor theory of pain.

A recent study found a lateral shift of activation peaks in right S2 in response to proprioceptive stimulation (i.e. local muscle vibration) of the lower back in people with low back pain, compared to controls (Goossens et al., 2019), which correlated with self-reported distortions of body perception.

These findings therefore provide mixed evidence that distorted representations of the body are related to altered cortical processing, as would be predicted by the sensorimotor theory of pain.

3.4.5. Distorted body representations should relate to pain

According to the sensorimotor theory of pain, inaccurate motor predictions could cause pain and other symptoms. Therefore, distorted body representations should relate to pain, although the evidence reviewed provides mixed support for these predictions.

For people with orofacial pain, the magnitude of the distortion of their self-reported facial representations was predicted by pain intensity (Dagsdóttir et al., 2016). In contrast, pain was not associated with perceived arm length for people with shoulder pain (Alaiti et al., 2019). These findings suggest that the association between pain and distorted representations of the body may vary between pathological pain conditions.

The evidence that distorted body representations is related to pain is mixed for people with CRPS. The degree of self-reported body representation distortion is associated with disease duration (Moseley, 2005a), and two-point discrimination threshold in CRPS (Lewis & Schweinhardt, 2012; Peltz, Seifert, Lanz, Müller, & Maihöfner, 2011), although this association is not always found (Lewis et al., 2019). Pain reduction following multidisciplinary therapy delivered by physiotherapists, occupational therapists, and clinical psychologists, nurses, and pain physicians, was associated with a reduction in self-reported body perception distortions for people with CRPS (Lewis et al., 2019). Not all studies, however, find an association between body representation distortion and pain severity in CRPS. For instance, the perceived size of the affected area, measured with a hand-mapping task, was not fund to correlate with pain intensity, although it was correlated with disease duration (Moseley, 2005a).

3.4.6. Interim summary

Distorted representations of the body appear to be common in many different types of pathological pain conditions (Table 7), such CRPS, fibromyalgia, shoulder pain, osteoarthritis, low back pain, phantom limb pain, and orofacial pain. A distorted representation of the body could impair motor predictions (Shadmehr et al., 2010), and thereby results in a sensorimotor incongruence. Furthermore, evidence from mental

rotation of limbs further suggests changes in motor imagery and/or bodily representation, where altered performance is common in pathological pain conditions. In some cases, worse performance on mental limb rotation is specific to images corresponding to the painful limb of the participant. These findings suggest that motor representations might be distorted. Both motor representations (Jeannerod & Decety, 1995), and bodily representations (Haggard & Wolpert, 2005) are involved in motor predictions. Therefore, any distortion to these representations likely hinders sensorimotor processing, which is consistent with the predictions made by the sensorimotor theory of pain.

Table 7. Body representation.

Summary of the evidence relevant to hypotheses related to bodily representations in pathological pain.

	Evidence for predictions	Mixed evidence for predictions	Evidence against predictions
People with pathological pain should have distorted representations of the body	CRPS, fibromyalgia, shoulder pain, osteoarthritis, orofacial pain, low back pain, phantom limb pain		
Mental limb rotation	Arm/shoulder pain, back pain, carpal tunnel syndrome, CRPS, dystonia, fibromyalgia, hand osteoarthritis, knee osteoarthritis, leg/foot pain, neck pain, phantom limb pain		
People with pathological pain should have difficulties updating the representations of their body		CRPS	Amputees
Distorted body representations should lead to errors in predicting the consequences of a movement			
Distorted body representations should relate to altered cortical processing	CRPS, low back pain	Phantom limb pain	
Distorted body representations should relate to pain	Orofacial pain	CRPS	Shoulder pain

CRPS = Complex Regional Pain Syndrome.

3.5. Spatial perception

Spatial information is combined with bodily representations to make predictions about the sensory outcome of a movement (Shadmehr et al., 2010). Therefore the sensorimotor theory of pain would predict that spatial representations are distorted (3.5.1.), and that they function differently (e.g. altered updating; 3.5.2.). Such changes should relate to cortical processing (3.5.4.) and, crucially, to pain (3.5.5.). In this section we will review the evidence for altered spatial perception in pathological pain, and conclude that there is some evidence of such changes for certain conditions, such as CRPS, and trigeminal neuralgia.

3.5.1. People with pathological pain should have distorted representations of the space that surrounds their body

Changes in spatial perception can occur in certain pathological pain conditions (Haggard et al., 2013), and can involve altered representations of the space that surrounds their body (i.e. peripersonal). Such representations are relevant for defence and action (for discussion on the functional role of peripersonal space see De Vignemont & Iannetti, 2015). Evidence suggesting that spatial representations are altered in pathological pain comes from motor tasks, reachability judgements, and studies measuring the hand blink reflex.

Distorted representations of space have been inferred from spatially defined bias in motor deficits for people with CRPS. A recent study showed that CRPS patients' motor performance of the affected limb improved on a circle drawing task, and a button pressing task when the task was performed in the non-affected side of space (Reid et al., 2017). However, no spatially-defined motor biases were found in another study similar (Christophe et al., 2016b). These findings therefore provide mixed evidence for distorted spatial representations in CRPS (for review see Halicka, Vittersø, Proulx, & Bultitude, 2020b).

Reachability judgements have been used to infer spatial representations in people with shoulder pain. That is, people with shoulder pain showed no difference in reachability judgements compared to controls for targets at 45cm, or 100 cm (Alaiti et al., 2019), which suggests that their spatial representations are not distorted.

More direct evidence comes from studies where the dimensions of peripersonal space have been mapped out for people with trigeminal neuralgia, episodic migraine, and cervical dystonia. Bufacchi and colleges (2017) showed a greater spatial modulation of the hand blink response, measured as muscle activation of the orbicularis oculi in response to stimulating the median nerve (Sambo, Liang, Cruccu, & Iannetti, 2011), for their affected side. This finding suggests that the dimensions of peripersonal space representations were enlarged for the affected side in trigeminal neuralgia. Such a spatial modulation of the hand blink reflex was not found in people with migraine, only in pain-free controls (Ayas, E Kızıltan, Karaali-Savrun, & Gündüz, 2020), although this might have been due to a ceiling effects, as people with migraines had a significantly greater reflex than controls. People with cervical dystonia also show a greater hand blink response than controls, as measured by amplitude, and area under the curve (Öztürk, Gündüz, & Kızıltan, 2018). The spatial modulation of this reflex was found for controls, but the opposite pattern (i.e. a decrease in

strength when the hand was near the face) was found for people with cervical dystonia. Taken together, these findings suggest that the spatial modulation of the hand blink reflex, therefore the dimensions of defensive peripersonal space, is only altered in certain painful conditions.

A number of additional studies have examined peripersonal space representations in populations that commonly experience pain, such as amputees (Canzoneri et al., 2013; Gouzien et al., 2017), and people with spinal cord injury (Scandola et al., 2020; Scandola et al., 2019). However, as the focus of these studies was related to deafferentation/defferentation, rather than pain, we did not include them in this review.

3.5.2. People with pathological pain should have difficulties updating the space that surrounds their body

Spatial representations are malleable, and will update as we interaction with the external world (e.g. Serino, 2019). The sensorimotor theory of pain would therefore predict that the way spatial representations are updated could be altered in pathological pain condition.

To date, only one study has looked at how spatial representations are updated in pathological pain conditions. We showed that peripersonal space representations are more flexible, and perhaps be less stable for people with CRPS, than for control participants (Vittersø et al., 2020). That is, we found a more pronounced updating of peripersonal space for people with upper limb, and lower limb CRPS than controls following tool-use, measured using a visual-tactile crossmodal congruency task. This finding offers some support for the predictions made by the sensorimotor theory of pain.

3.5.3. Distorted spatial representations should lead to errors in predicting the consequences of a movement

For distorted spatial representations to lead sensorimotor incongruence, they should be the predicted outcome of a movement. To the authors' knowledge, this question has yet to be addressed in the pain literature. This question could be addressed using a visuomotor rotation task, where participants estimate the rotation that is applied to a virtual image of their arm following a pointing movement. This paradigm can also be used to measure adaptation (i.e. directional errors that are in the opposite direction to the visual rotation applied). For instance, people with schizophrenia showed a greater dependence on visual feedback than motor predictions, relative to control participants (Synofzik, Thier, Leube, Schlotterbeck, & Lindner, 2010). If combined with measures of spatial representations, this approach would enable the association between distorted representations of space and motor predictions to be examined in people with pathological pain.

3.5.4. Distorted spatial representations should relate to altered cortical processing

Peripersonal space representations depend on a network of cortical processes that involve frontal and parietal regions (e.g. di Pellegrino & Làdavas, 2015; Serino, 2019). Therefore,

distorted peripersonal space representation in pathological pain conditions might reflect altered processes in these networks, although this has yet to be studied in the context of pathological pain.

3.5.5. Distorted spatial representations should relate to pain

There is limited evidence that shows a relationship between distorted spatial representations and pain. Reachability judgements for people with shoulder pain were found to be associated with movement-related pain (Alaiti et al., 2019). In people with trigeminal neuralgia, greater spatial modulation of the hand blink response was found for the affected side, compared to the non-affected side (Bufacchi et al., 2017). This finding suggests that the dimensions of peripersonal space relate to pain, although a direct association with pain was not reported. Therefore, more research is needed to address the hypothesis that spatial representations should relate to pain.

3.5.6. Interim summary

The evidence suggests that peripersonal space can have altered stability, and/or dimensions for people with certain pathological pain conditions (Table 8), such as CRPS, and trigeminal neuralgia. As spatial representations are needed for sensorimotor processing (De Vignemont, 2010; De Vignemont & Iannetti, 2015; Di Vita, Boccia, Palermo, & Guariglia, 2016; Serino, 2019; Soechting & Flanders, 1989), their uncertainty should increase the likelihood of a sensorimotor incongruence. Therefore, the evidence demonstrating changes in spatial perception in certain pathological pain conditions are consistent with the sensorimotor theory of pain.

Table 8. Spatial perception.

Summary of the evidence relevant to hypotheses related to spatial perception in pathological pain.

	Evidence for predictions	Mixed evidence for predictions	Evidence against predictions
People with pathological pain should have distorted representations of the space that surrounds their body	Dystonia, trigeminal neuralgia	CRPS	Migraine, shoulder pain
People with pathological pain should have difficulties updating the space that surrounds their body	CRPS		
Distorted spatial representations should lead to errors in predicting the consequences of a movement			
Distorted spatial representations should relate to altered cortical processing			
Distorted spatial representations should relate to pain	Shoulder pain, trigeminal neuralgia		

CRPS = Complex Regional Pain Syndrome.

3.6. Sensorimotor integration

There are several stages of sensorimotor integration that can be studied in pathological pain, such as the sensitivity to incongruent sensorimotor information, sensorimotor adaptation, and reweighting of information. Predictions based on the sensorimotor theory of pain would suggest that either of these processes could be impaired in pathological pain conditions (3.6.2.). Furthermore, inducing a mismatch between sensory and motor information should cause pain (3.6.5.). We will review the evidence for altered multisensory processing (3.6.1.) and sensorimotor integration (3.6.2.) in the following section. We conclude that there is evidence suggesting altered and/or suboptimal sensorimotor integration in conditions such as CRPS, dystonia, fibromyalgia, low back pain, and phantom limb pain. There is also some evidence that altered sensorimotor integration is related to pain.

3.6.1. People with pathological pain should have deficits in multisensory processing

Detecting a discrepancy between motor intentions and sensory feedback requires sensorimotor integration. However, as sensorimotor integration typically relies on information from more than one sense (e.g. Holmes & Spence, 2005), multisensory processing could be considered a prerequisite of sensorimotor processing. The sensorimotor theory of pain therefor assumes that people with pathological pain are able to integrate multisensory information; otherwise they would not be able to detect a mismatch between signals. Yet deficits in multisensory processing could impair sensorimotor processing.

There is evidence to suggest that people with pathological pain are capable of multisensory processing, for instance from studies using the rubber hand illusion. In this illusion illusory ownership of a rubber limb is induced, which relies on multisensory processing of visual, tactile and proprioceptive information (Costantini & Haggard, 2007). The rubber hand illusion has been induced in people with phantom limb pain (Ehrsson et al., 2008), and CRPS (Reinersmann et al., 2013). People with fibromyalgia experienced a stronger illusion than controls (Martínez et al., 2018). In contrast, this illusion seems to be disrupted in people with focal hand dystonia (Fiorio et al., 2011). People with spinal cord injury with neuropathic pain also had a weaker effect of illusory ownership of a virtual leg, a virtual reality based variety of the rubber hand illusion, than control participants (Pozeg et al., 2017). For review, see (Christ & Reiner, 2014).

The successful induction of the illusion in pathological pain conditions such as phantom limb pain, CRPS, and fibromyalgia suggests that any disruptions in sensorimotor integration are not simply due to issues with multisensory processing, although this does not mean that subsequent sensorimotor integration is necessarily intact. In contrast, altered experiences of the rubber hand illusion in people with focal hand dystonia, and spinal cord injury might suggest altered multisensory processing, which could be detrimental to sensorimotor integration. Differences in the strength of the illusion could suggest the weighting of different types of sensory information (e.g. visual, and tactile) is altered in certain painful conditions, such as fibromyalgia.

3.6.2. People with pathological pain should have deficits in sensorimotor integration

Sensorimotor integration is required for a sensorimotor incongruence to be detected. The sensorimotor theory of pain therefore assumes that people with pathological pain are able to perform sensorimotor integration. The theory also assumes that sensorimotor adaptation does not correct for incongruent sensorimotor information (i.e. sensorimotor adaptation), which would normally be the case (Wolpert et al., 2011). Acknowledging these assumptions, the sensorimotor theory would predict that sensorimotor integration is impaired in pathological pain, as this would enable sensorimotor incongruences to arise. Evidence for this hypothesis comes from people with low back pain, Ehlers-Danlos Syndrome, fibromyalgia, CPRS, and dystonia.

Balance is an area of sensorimotor integration (Peterka, 2002) that has been studied in pathological pain conditions. Research has found that standing balance can be impaired in chronic low back pain (for review see Berenshteyn, Gibson, Hackett, Trem, & Wilhelm, 2019), and in people with Ehlers-Danlos Syndrome (Rombaut et al., 2011). Impaired balance is often found in people with fibromyalgia (Jones, King, Mist, Bennett, & Horak, 2011; Trevisan et al., 2017), but may only be detectable under conditions with reduced availability of sensory information (e.g. with eyes closed; Sempere-Rubio et al., 2018). These findings suggest that people with fibromyalgia are able to integrate sensory and motor information, but that they might have subtle deficits. When people with fibromyalgia were tasked with maintaining a steady shoulder abduction angle of 45˚ with their eyes closed, they showed a significant increase in movement variance (Bardal, Roeleveld, Ihlen, & Mork, 2016). Such differences were not observed when visual feedback was permitted, which suggest that people with fibromyalgia weight visual proprioceptive information differently to pain-free individuals. These studies demonstrate that balance can be impaired in pathological pain conditions, such as low back pain, Ehlers-Danlos Syndrome, and fibromyalgia, and could indicate that people give less weight to unreliable sensory information (e.g. in fibromyalgia).

Sensorimotor integration has been studied experimentally in people with CRPS. For instance, manipulating the auditory feedback produced by walking resulted in changes in gait for people with CRPS, thought to reflect changes in body representation (Tajadura-Jiménez et al., 2017). This suggests that people with CRPS are able to integrate auditory and motor information. Yet sensorimotor integration may be altered in CRPS, when compared to pain-free controls. During a bimanual task, people with CRPS were found to have less stable interlimb coordination compared to controls (Bank, Peper, Marinus, Van Hilten, & Beek, 2015). Furthermore, people with CRPS showed impaired voluntary force control and impaired sense of force production on a task where they had to match their precision grip force to a visual target, as indicated by greater errors (i.e. deviation from a target force), greater variability, and reduced maximum force. These effects were particularly strong for those people with abnormal hand-postures (Bank, van Rooijen, Marinus, Reilmann, & van Hilten, 2014). These findings suggest that people with CRPS can integrate sensory and motor commands, although optimal integration (Wolpert, Ghahramani, & Jordan, 1995) may still be an issue in this condition. Addressing this question, a study where people with CRPS and fixed dystonia performed a force-matching

task, which required weighting of force feedback and position sense, found that they do not integrate optimally (Mugge, van der Helm, & Schouten, 2013). That is, control participants used force feedback to scale the force that they applied to a virtual spring, whereas people with CRPS and fixed dystonia did not. These findings suggest that people with CRPS are able to perform sensorimotor integration, but that it might be less precise than controls, and that they do not integrate optimally.

Changes in sensorimotor integration are common in dystonia (for reviews see Avanzino et al., 2015; Conte et al., 2019). For instance, people with writer's cramp showed altered visuomotor tracking and force-matching compared to controls (Bleton et al., 2014). The task involved matching grip-force to a visual target, and found that people with writer's cramp showed greater error, variability, and longer release duration, with either hand, compared to controls. Altered sensorimotor integration has also been found during precision grasping (Odergren, Iwasaki, Borg, & Forssberg, 1996), during control of precision grip (Serrien, Burgunder, & Wiesendanger, 2000), and visuomotor tracking (Allgöwer, Fürholzer, & Hermsdörfer, 2018) for people with dystonia.

3.6.2.1. Sensorimotor adaptation

Sensorimotor adaption is one of the mechanisms that the sensorimotor system has to compensate for discrepant sensorimotor information (Bastian, 2008; Wolpert et al., 2011). Therefore, the sensorimotor theory of pain assumes that this process is unable to compensate for any incongruent information that it may be faced with. Hence the theory would predict that sensorimotor adaptation is impaired in pathological pain.

Impaired motor adaptation has been found for people with dystonia. For instance, during a piano task with weighted keys, pianists with focal hand dystonia showed an impaired adaptation (i.e. larger keystroke velocity errors, and lower keystroke velocities) than pianists without a focal dystonia (Furuya, Lee, Oku, & Altenmüller, 2020). Furthermore, adaptation to catching balls with a heavy load, before being exposed to a lighter load, was reduced for people with cervical dystonia with tremor, compared to those without tremor, and pain-free controls (Avanzino et al., 2018b). These findings highlight the differences that may exist in in sensorimotor adaptation within forms of dystonia.

Sensorimotor adaptation has also been studied experimentally in people with Ehlers-Danlos Syndrome. That is, they adapted to altered visual feedback during a motor task, whereby they had to guide cursor to visual targets, which was subject to a 50˚ rotation (Clayton et al., 2013). There was no difference between people with Ehlers-Danlos Syndrome and pain-free controls on the magnitude of adaptation. These findings suggest that the dynamic processes involved in sensorimotor adaptation are intact in Ehlers-Danlos Syndrome.

3.6.3. Deficits in sensorimotor integration should relate to altered cortical processing

There is limited evidence of an association between multisensory processing, sensorimotor integration, and altered cortical processing. The only studies identified looked at multisensory processing in women with fibromyalgia, showing altered cortical responses to multisensory information. That is, women with fibromyalgia reported greater

unpleasantness from multisensory stimulation (i.e. combined visual, tactile, auditory), which correlated with a reduced activation in the visual and auditory cortex, and a greater response in later stages of sensory processing (i.e. insula the anterior lingual gyrus) (Harte et al., 2016; López-Solà et al., 2014). The cortical response to nociceptive and multisensory (i.e. combined visual, tactile, auditory) stimuli can be used to distinguish people with fibromyalgia from pain-free individuals (López-Solà et al., 2017). These findings suggest that cortical activation in response to multisensory stimuli is altered in people with fibromyalgia.

3.6.4. Deficits in sensorimotor integration should relate to pain

According to the sensorimotor theory of pain, deficits in sensorimotor integration should relate to pain. There is evidence that multisensory, and sensorimotor processing can influence pain for people with fibromyalgia, CRPS, and phantom limb pain.

Altered multisensory processing is related to pain in fibromyalgia, as reviewed in the previous section (3.6.3.). Women with fibromyalgia reported increased pain in response to multisensory stimulation (López-Solà et al., 2017), and their cortical responses to this stimulation were predicted by their baseline pain (assessed during a clinical examination).

In upper limb amputees, greater phantom limb pain was associated with a smaller “bimanual coupling” effect when they were asked to imagine drawing circles with their phantom limb whilst drawing straight lines with their healthy limb (Osumi et al., 2015). This finding suggests that sensorimotor integration was altered in the presence of phantom limb pain, rather than general to amputees. For people with CRPS, altered performance was found to relate to pain on a bimanual coupling task (Bank et al., 2015). Therefore, evidence from bimanual coupling suggests that sensorimotor integration may relate to pain, which is consistent with the sensorimotor theory of pain.

3.6.5. Incongruent sensory and motor information should cause pain

Experimental evidence for the theory comes from inducing sensorimotor conflicts (e.g. using mirror visual feedback), which resulted in pain and anomalous sensations (Table 9). During incongruent mirror visual feedback participants perform anti-phase limb movements whilst looking into a mirror aligned with their body midline, which occludes one limb. This arrangement provides the participant with visual feedback of their arms moving congruently, despite performing incongruent movements. Incongruent mirror visual feedback thus creates a conflict between visual, proprioceptive, and motor information.

Table 9. Mirror visual feedback.

Summary of studies examining the responses of people with pathological pain to incongruent sensorimotor information, for instance, using incongruent mirror visual feedback (MVF).

	Population	Task	Finding
Daenen et al. (2012)	WAD, controls	MVF	Increased pain for WAD
Don et al. (2017)	WAD, controls	MVF	No influence on pain for WAD
Daenen, Roussel, Cras, and Nijs (2010)	Violinists with/without pain	MVF	No influence on pain
Don et al. (2019)	Low back pain, controls	Video feedback	No influence on pain for low back pain
Roussel et al. (2015)	Dancers with/without MSK	MVF	No influence on pain
Martínez et al. (2019)	Fibromyalgia, controls	MVF	Increased pain for fibromyalgia
McCabe, Cohen, and Blake (2007)	Fibromyalgia, controls	MVF	Increased pain for fibromyalgia
Brun et al. (2019)	CRPS, fibromyalgia, arthritis, controls	MVF	Greater sensory changes (including new pain) for CRPS, and FMS, than arthritis, and controls

CRPS = Complex Regional Pain Syndrome; MSK = musculoskeletal pain; MVF = mirror visual feedback; WAD = chronic whiplash associated disorder.

Incongruent mirror visual feedback worsened pain for people with fibromyalgia, and CRPS. There is mixed evidence that incongruent mirror visual feedback causes pain for people with chronic whiplash associated disorders, and no evidence in violinists, dancers with musculoskeletal pain, or people with low back pain (for review see Don, Voogt, Meeus, De Kooning, & Nijs, 2017). These findings suggest that people with certain pathological pain conditions are more sensitive to a sensorimotor incongruence than others, and that incongruent mirror visual feedback can influence pain.

Ambiguous visual information can cause pain in people with CRPS. When presented with bistable images people with CRPS reported increased pain, some participants also experienced a worsening of their CRPS symptoms (Cohen et al., 2012; Hall et al., 2011). None of the pain free participants, or those with rheumatology conditions reported any pain due to the bistable images. Furthermore, when people with CRPS were subjected to optokinetic stimulation, a sensory conflict used to induce motion sickness, they experienced increased limb pain (Knudsen & Drummond, 2015). This suggests that people with CRPS might be more sensitive to ambiguous sensory information than pain-free individuals, and other painful conditions. In the context of the sensorimotor theory of pain, this could suggest that they are more sensitive to a sensorimotor incongruence.

Taken together, the evidence from studies looking at induced sensorimotor incongruences therefore provides partial support for the predictions made by the sensorimotor theory of pain.

3.6.6. Interim summary

Sensorimotor integration can correct for errors in the sensorimotor system (Wolpert et al., 2011), therefore we would expect impaired sensorimotor integration in pathological pain, based on the sensorimotor theory of pain. The evidence reviewed suggests that sensorimotor integration can be altered in conditions such as CRPS, dystonia, fibromyalgia, low back pain, and phantom limb pain (Table 10). Such changes can occur both in terms of sensitivity to incongruent information, and subsequent adaptation. In some conditions, such changes were only observed in the presence of pathological pain (e.g. phantom limb pain and amputees; Osumi et al., 2015). Furthermore, there is evidence to suggest that people with pathological pain conditions do not integrate sensory and motor information optimally, which is consistent with the theoretical predictions. There is therefore evidence that aspects of sensorimotor integration are disrupted in certain pathological pain conditions, which is consistent the predictions made by the sensorimotor theory of pain.

Table 10. Sensorimotor integration.

Summary of the evidence relevant to hypotheses related to sensorimotor integration in pathological pain.

	Evidence for predictions	Mixed evidence for predictions	Evidence against predictions
People with pathological pain should have deficits in multisensory processing	Dystonia, fibromyalgia, spinal cord injury with neuropathic pain		CRPS, phantom limb pain
People with pathological pain should have deficits in sensorimotor integration	CRPS, dystonia, Ehlers-Danlos Syndrome, fibromyalgia, low back pain,		
Sensorimotor adaptation	Dystonia		Ehlers-Danlos Syndrome
Deficits in sensorimotor integration should relate to altered cortical processing	Fibromyalgia		
Deficits in sensorimotor integration should relate to pain	CRPS, fibromyalgia, phantom limb pain		Rheumatic conditions
Incongruent sensory and motor information should cause pain	CRPS, fibromyalgia	WAD	MSK

CRPS = Complex Regional Pain Syndrome; MSK = musculoskeletal pain; WAD = chronic whiplash associated disorders.

3.7. Sensorimotor treatments for pain

The efficacy of therapies targeting sensorimotor processing provides further evidence of cortical involvement in pathological pain, which includes therapies such as bodily illusions (3.7.1.1.), visual feedback (3.7.1.2.), mirror therapy (3.7.1.3.), graded motor imagery (3.7.1.4.), and prism adaptation (3.7.1.5.). The therapeutic benefit of targeting sensorimotor processing would provide support for the sensorimotor theory of pain.

3.7.1. Targeting sensation sensorimotor processing should reduce pain

3.7.1.1. Bodily illusions

Several bodily illusions have been found to reduce pain for people with conditions such as osteoarthritis, CRPS, phantom limb pain, and peripheral nerve injury (Table 11). These findings suggest that pain can be modified by bodily illusions (for reviews see Boesch, Bellan, Moseley, & Stanton, 2016; Dunn, Yeo, Moghaddampour, Chau, & Humbert, 2017; Matamala-Gomez et al., 2019; Senkowski & Heinz, 2016), and that the type of illusions that are effective for pain relief can vary between conditions. The potential therapeutic benefit of bodily illusions demonstrates the role of sensorimotor information in pathological pain, which is in agreement with theoretical predictions.

Table 11. Bodily illusions.

Summary of studies examining the effects of bodily illusions on pain, for people with pathological pain.

	Illusion type	Population	Finding
Preston, Gilpin, and Newport (2020)	Stretching, shrinking, disappearing	Hand osteoarthritis	Stretching, and shrinking led to pain reduction. Disappearing did not influence pain
Preston and Newport (2011)	Stretching, shrinking	Hand osteoarthritis	Stretching, and shrinking led to pain reduction.
Themelis and Newport (2018)	Stretching	Hand osteoarthritis	Stretching led to pain reduction.
Stanton, Gilpin, Edwards, Moseley, and Newport (2018)	Stretching, shrinking	Knee osteoarthritis	Resizing led to pain reduction
MacIntyre, Sigerseth, Pulling, Newport, and Stanton (2019)	Stretching, shrinking	Knee osteoarthritis*	Stretching had potential to reduce pain and swelling
Moseley, Parsons, and Spence (2008)	Magnification, minification	Hand pain	Magnifying increased pain and swelling, minifying decreased pain and swelling
Matamala-Gomez, Gonzalez, Slater, and Sanchez-Vives (2019)	Transparency, magnification, minification (VR)	CRPS, PNI	Increasing transparency resulted in pain relief for CRPS, but not PNI. Magnification increased pain in CRPS, but reduced it in PNI
Nishigami et al. (2019)	Muscular, reshaped, neutral	Low back pain*	Embodying a muscular back showed potential for pain reduction
Cole, Crowle, Austwick, and Henderson Slater (2009)	Virtual limb (VR)	Phantom limb pain	Reduced phantom limb pain
Mercier and Sirigu (2009)	Virtual limb (VR)	Phantom limb pain	Reduced phantom limb pain
Sano et al. (2016)	Virtual limb (VR) with/without tactile feedback	Phantom limb pain	Reduced phantom limb pain was greater when VR was combined with tactile feedback
Osumi et al. (2017)	Virtual limb (VR)	Phantom limb pain	Reduced phantom limb pain

CRPS = Complex Regional Pain Syndrome; PNI = peripheral nerve injury ; VR = virtual reality. *case study.

3.7.1.2. Visual feedback

Visual feedback of the area being moved can improve pain and movement. For instance, virtual feedback reduced pain and improved motor function in people with spinal cord injury (for review see Roosink & Mercier, 2014). Visual feedback during a movement can reduce low back pain (Diers, Löffler, Zieglgänsberger, & Trojan, 2016; Diers et al., 2013; Wand et al., 2012) (for review see Heinrich, Steiner, & Bauer, 2019), and neck pain (Beinert, Lutz, Zieglgänsberger, & Diers, 2019). The therapeutic benefit of using visual, virtual, and mirror feedback highlights the role of sensory processing in pain rehabilitation.

3.7.1.3. Mirror therapy

Mirror therapy was originally formulated for the treatment of phantom limb pain (Ramachandran & Rogers-Ramachandran, 1996), and involves performing congruent movements during mirror visual feedback (for a detailed description of mirror therapy see Ramachandran & Altschuler, 2009). Many studies report that mirror therapy reduces phantom limb pain (Barbin, Seetha, Casillas, Paysant, & Perennou, 2016). When meta-analysed, however, the evidence is not strong enough to recommend mirror therapy for phantom limb pain, although it appears to be effective for CRPS pain (Thieme, Morkisch, Rietz, Dohle, & Borgetto, 2016; Wittkopf, Lloyd, & Johnson, 2018), and post-stroke pain (Thieme et al., 2018). It should be noted that the quality of evidence for the use of mirror therapy in CRPS and phantom limb is low (Rothgangel, Braun, Beurskens, Seitz, & Wade, 2011). This suggests that there might be differences within types of pathological pain, at least in terms of responsiveness to mirror therapy.

3.7.1.4. Graded motor imagery

Graded motor imagery, which combines mirror therapy, mental hand rotation, and motor imagery (Moseley, 2004a) (Moseley, 2005b), can provide pain relief. Motor imagery is mentally rehearsing a movement, without executing it (for a detailed description see Lotze & Halsband, 2006), and can lead to pain reduction (MacIver, Lloyd, Kelly, Roberts, & Nurmikko, 2008). On average, it is more effective than physiotherapy for pain reduction (Bowering et al., 2013). Graded motor imagery appears to be particularly effective for CRPS, but less so for phantom limb pain, and post-stroke pain (for review and meta-analysis see Thieme et al., 2016). Furthermore, a recent randomised control trial found that the pain relief from graded motor imagery for phantom limb pain were retained six-months post intervention (Limakatso, Madden, Manie, & Parker, 2019). The efficacy has also been demonstrated for people with distal radial fractures (Dilek, Ayhan, Yagci, & Yakut, 2018). However, it is worth noting that not all studies find evidence of the efficacy of graded motor imagery (e.g. Johnson et al., 2012). Consistent with the evidence on mirror therapy, this suggests that some therapeutic interventions may only be beneficial to certain specific types of pathological pain. In turn, this supports the notion that the sensorimotor theory of pain is more applicable to certain types of pathological pain.

3.7.1.5. Prism adaptation

Prism adaptation has been used to treat neglect following stroke, and has shown preliminary efficacy in treating pathological pain. During prism adaptation, people perform arm movements whilst viewing their arm through lenses that induce an optical displacement

of vision, which causes a conflict between visual feedback, and proprioceptive and motor information. Initially, participants make pointing errors in the direction of the prismatic shift, but these are quickly reduced. At first, this error reduction requires a strategic recalibration (i.e. changing aim, or mentally rotating the target). After prolonged exposure and repeated movements, the sensorimotor system recalibrates (Rossetti, Rode, Pisella, & Farné, 1998), after which deliberate strategic aiming is no longer required. The application of prism adaptation to treating pathological pain is relatively recent, hence there is limited published literature evaluating its effects (for a review see Torta, Legrain, Rossetti, & Mouraux, 2016). Scientific reports of its application in pathological pain are limited to people with CRPS, perhaps because this condition is often associated with an inattention to the affected side, which resembles post-stroke neglect (Halicka et al., 2020b; Legrain, Bultitude, De Paepe, & Rossetti, 2012).

The efficacy of prism adaptation, however, could be due to improving sensorimotor integration for people with pathological pain (Bastian, 2008; Sumitani et al., 2007). That is, prism adaptation could be retraining the sensorimotor system to better deal with incongruent information, which would be inline with the sensorimotor theory of pain. However, this assumes that sensorimotor adaptation is impaired in people with CRPS, which has yet to be examined. In this case, it is possible that other conditions where sensorimotor integration is impaired could benefit from prism adaptation (3.6.2.).

Initial reports suggested that prism adaptation could provide pain relief (Bultitude & Rafal, 2010; Christophe et al., 2016a; Sumitani et al., 2007), although these studies were unblinded and lacked a control condition. In a recent randomised control trial, however, we did not observe any benefit of prism adaptation over sham treatment (Halicka et al., 2020a; Halicka, Vittersø, Proulx, & Bultitude, 2020c). This finding questions the efficacy of prism adaption for CRPS.

3.7.3. Interim summary

Although the findings are mixed, there is evidence that, in some cases, pain can be reduced by targeting sensorimotor processes. The efficacy of behavioural treatments that target components proposed to be driving pain (Table 12) provides support of the sensorimotor theory of pain. These findings provide at least partial support for the sensorimotor theory of pain, particularly for conditions where the evidence is more consistent, such as CRPS.

Table 12. Sensorimotor treatments for pain.

Summary of the evidence relevant to hypotheses related to sensorimotor treatments for pathological pain.

	Evidence for predictions	Mixed evidence for predictions	Evidence against predictions
Bodily illusion	CRPS, osteoarthritis, phantom limb pain, and peripheral nerve injury		
Visual feedback	Spinal cord injury, low back pain, neck pain		
Mirror therapy	CRPS, post-stroke pain	Phantom limb pain	
Graded motor imagery	CRPS, distal radial fractures	Phantom limb pain, post-stroke pain	
Prism adaptation		CRPS	

CRPS = Complex Regional Pain Syndrome.

4. Sensorimotor processing in CRPS

The sensorimotor theory of pain has been proposed as a possible explanation for CRPS (McCabe & Blake, 2007). Below we will discuss the evidence relevant to this claim, and consider whether CRPS is an appropriate condition to test new predictions extrapolated from the theory.

There is mixed evidence for the role of cortical changes in CRPS (3.1.). Early studies provided initial support for theoretical claims, as they found evidence of M1 reorganisation (e.g. Maihöfner et al., 2007). When meta-analysed, however, there was no consistent evidence of M1 reorganisation (Di Pietro et al., 2013a). Several studies have reported S1 reorganisation corresponding to the CRPS-affected area (Di Pietro et al., 2013b; Juottonen et al., 2002; Maihöfner, Handwerker, Neundörfer, & Birklein, 2003; Pfannmöller et al., 2019; Pleger et al., 2004; Vartiainen, Kirveskari, & Forss, 2008), although recent studies do not support these claims (Di Pietro et al., 2016; Mancini et al., 2019). There is also mixed evidence regarding the clinical relevance of S1 reorganisation, as the recent studies found no association with pain (Di Pietro et al., 2016; Mancini et al., 2019). In the context of cortical reorganisation, CRPS may not be the best condition to test the sensorimotor theory of pain. It should be noted, however, that CRPS can develop after stroke (for reviews, see Delpont et al., 2018; Harrison & Field, 2015), which suggests that, in some cases, the brain may be involved in the pathophysiology of this condition. Therefore, the cortical reorganisation of M1 and S1 might not fully capture the complexity of the central changes that can occur in CRPS. This evidence base therefore provides mixed evidence for the sensorimotor theory of pain, and suggests that CRPS may not be the most appropriate condition to test hypotheses related to cortical reorganisation of M1 and/or S1.

Motor deficits are common in CRPS (3.2.). For instance, people with CRPS have been reported to have poorer performance than controls on reach-to grasp movement (Maihöfner et al., 2007; Osumi et al., 2017), finger tapping (Schilder et al., 2012), and circle drawing (Reid et al., 2017), although such differences are not always found (Christophe et al., 2016a). Imagined movement of the affected limb has also been reported to cause an increase in swelling and pain for people with CRPS (Moseley et al., 2008). People with CRPS can present with dystonia (for reviews of dystonia in CRPS see Avanzino et al., 2015; Patel, Jankovic, & Hallett, 2014), which is associated with a poorer prognosis (Ibrahim et al., 2009; Schrag, Trimble, Quinn, & Bhatia, 2004). These findings highlight the diverse nature of motor deficits in CRPS, and demonstrate their clinical relevance, thus making CRPS a good population to test theoretical predictions related to movement. Evidence that contradicts these predictions, however, has come from studies examining the effect of pain relief on motor performance. The studies found that a ketamine infusion (Schilder et al., 2013), or a nerve blockade (Osumi et al., 2017) improved finger tapping, and reach-to-grasp movements, respectively. Although they do not rule out a bidirectional relationship, these findings contradict the assumed causality that underpins the sensorimotor theory of pain. Taken together, the broad range of motor deficits that can be present in CRPS makes the condition a good candidate for testing theoretical predictions related to motor deficits, although some studies challenge the causal effect of sensorimotor processing on pain in CRPS.

Sensory changes can occur in CRPS (3.3.). For instance, people with CRPS have been found to have reduced tactile acuity near the affected area (Pleger et al., 2006; Reiswich et al., 2012), were worse at locating touch on their affected hand (Trojan et al., 2019), and can experience referred sensations (Maihöfner et al., 2006; McCabe et al., 2003). Proprioceptive deficits have also been reported (Brun et al., 2019; Schouten et al., 2003; van de Beek et al., 2002), although these are not specific to the affected area. Proprioceptive deficits can be bilateral in unilateral CRPS (Lewis et al., 2010), which could indicate central changes. These findings suggest that the accuracy and precision of sensory information is degraded for people with CRPS, and that they can have impaired proprioception. There is some evidence that tactile deficits are related to pain (Acerra & Moseley, 2005; Maihöfner et al., 2006), and that impaired proprioception is related to motor deficits in CRPS (Bank, Peper, Marinus, Beek, & van Hilten, 2013b). The evidence for sensory changes in CRPS is compatible with the predictions made by the sensorimotor theory of pain, and suggests that this is a good condition in which to further test its predictions about sensory changes.

People with CRPS commonly have distorted representations of the shape and size of their affected area (3.4.). Altered representations of the body have been characterised through interviews (Lewis et al., 2007; Tajadura-Jiménez et al., 2017), questionnaires (e.g. Lewis & McCabe, 2010), hand mathcing tasks (Moseley, 2005; Peltz et al., 2011), or by modifying an avatar to match the experiensed shape and size of ones body (Tajadura-Jiménez et al., 2017). These studies suggest that people with CRPS have distorted representaitons of the shape and size of the affected limb, and that such distortions are common in this condition. Representations of the body are dynamic, and will update as we interact with our environment. People with CRPS are able to update their body representation (Tajadura-Jiménez et al., 2017), although we have shown that this process might differ for the CRPS-affected, and the non-affected body side (Vittersø et al., 2020). Changes in the representation of the body appear to be clinically relevant. For instance, pain reduction from multidisciplinary therapy was associated with reduced body perception distortion (Lewis et al., 2019). These findings are consistent with the theory, and provide further support for testing its predictions relevant to body representations in people with CRPS.

Less is known about spatial perception in CRPS (3.5.). Distorted spatial representations have been inferred from spatially defined motor deficits. On a circle-drawing task people with CRPS performed worse on their affected side of space than their non-affected side of space (Reid et al., 2017), although another similar study found no such bias (Christophe et al., 2016b). These findings provide mixed evidence for any distorted spatial representations, although they do not provide insight into how they may function. We addressed the latter by looking at how spatial representaitons are updated for people with CRPS following tool-use. We showed that peripersonal space representations were more flexible, and perhaps be less stable for people with CRPS, than for control participants (Vittersø et al., 2020). Due to the scarce evidence, little is known about how distorted spatial representations might relate to pain, and other CRPS symptoms. One study has provided preliminary evidence that such distortions may relate to pain (Reid et al., 2017). These findings provide preliminary support for the sensorimotor theory of pain. The limited evidence base could also be viewed as a potential avenue for future research, which would also allow for theoretical predictions related to spatial perception to be tested.

Sensorimotor integration might be altered for people with CRPS (3.6.). Although they can integrate sensory and motor information (e.g. Tajadura-Jiménez et al., 2017), they may not do so optimally. For instance, on a force-matching task that required weighting of force feedback and position sense, people with CRPS were found not to integrate optimally (Mugge, van der Helm, & Schouten, 2013). Altered sensorimotor integration can be related to pain. Poorer performance on a bimanual coupling task was associated with greater pain for people with CRPS (Bank et al., 2015). Being presented with incongruent sensorimotor information can also influence pain. Specifically, incongruent visual feedback (Brun et al., 2019), and bistable images (Cohen et al., 2012; Hall et al., 2011) have been found to increase pain for people with CRPS. Taken together, these findings suggest that people with CRPS may not integrate sensory and motor information optimally, and that impairments can relate to pain, and that sensorimotor conflict can increase pain. Altered sensorimotor integration in CRPS is consistent with theoretical predictions, as it suggests that they may be using sensory and motor information differently to those without pain, which might result in sensorimotor incongruence. However, research as yet to investigate how the nervous system adapts to incongruent sensorimotor information (i.e. sensorimotor adaptation) in CRPS. Therefore, altered sensorimotor integration in CRPS makes the condition appropriate for testing related theoretical predictions related to sensorimotor integration and/or adaptation.

The efficacy of sensorimotor treatments for CRPS (3.7.) provides further support for using this population to test predictions derived from the sensorimotor theory of pain. For instance, mirror therapy and graded motor imagery have shown efficacy in treating CRPS pain (for review and meta-analysis see Thieme et al., 2016). There is also some evidence to suggest that prism adaptation could provide pain relief (Bultitude & Rafal, 2010; Christophe et al., 2016a; Sumitani et al., 2007). Although the benefits of prism adaptation are not always found (Halicka et al., 2020c), these findings indicate that targeting sensorimotor adaptation has potential to reduce pain and CRPS symptoms. The efficacy of sensorimotor treatments for CRPS are largely in line with theoretical predictions, and further emphasise the value of using this condition as a model to examine therapies that are informed by the sensorimotor theory of pain.

To summarise, many of the changes seen in CRPS are compatible with the sensorimotor theory of pain and therefore make the condition an appropriate candidate for testing new hypotheses that can be derived from the theory. The evidence is mixed when looking at cortical reorganisation, and the causal effect of pain on motor deficits. The implications of this mixed evidence are important to bear in mind if using CRPS as a model condition to test the predictions made by the sensorimotor theory of pain, as, for instance, certain aspects of the theory may be more relevant to understanding CRPS that others. The theoretical predictions are broadly supported by research into sensory changes, body representation distortions, sensorimotor integration, and sensorimotor therapies. Therefore, CRPS can be considered an appropriate condition to test new predictions that can be derived from the sensorimotor theory of pain.

5. Conclusions

The sensorimotor theory of pain describes several components of normal movement where errors could occur, which would result in a sensorimotor incongruence, suggested to maintain pathological pain conditions (Harris, 1999). There is evidence that people with pathological pain conditions show altered performance on behavioural tasks, and from neuroimaging, which implicate altered sensorimotor processing. Specifically, cortical representations (3.1.), motor deficits (3.2.), sensory changes (3.3.), body representations (3.4.), spatial perception (3.5.), and sensorimotor integration (3.6.) can be altered in some, but not all pathological pain conditions. Consistent with theoretical predictions, there is evidence that some changes may be related pain in conditions such as carpal tunnel syndrome, CRPS, fibromyalgia, low back pain, orofacial pain, phantom limb pain, spinal cord injury, and trigeminal neuralgia. The predicted relationship between altered sensorimotor processes and pain was found most frequently in CRPS, carpal tunnel syndrome, fibromyalgia, and phantom limb pain (Table 13).

Table 13. Meta-summery table

Summary of the evidence relevant to hypotheses relating aspects of sensorimotor processing to pain, for people with pathological pain.

	Evidence for predictions	Mixed evidence for predictions	Evidence against predictions
Cortical reorganisation should relate to pain	Carpal tunnel syndrome, neuropathic pain, spinal cord injury	CRPS, phantom limb	
Motor deficits should relate to pain	Carpal tunnel syndrome, low back pain, phantom limb pain		CRPS
Sensory deficits should relate to pain	CRPS, neck pain	Low back pain	Ehlers-Danlos Syndrome
Distorted body representations should relate to pain	Orofacial pain	CRPS	Shoulder pain
Distorted spatial representations should relate to pain	Shoulder pain, trigeminal neuralgia		
Deficits in sensorimotor integration should relate to pain	CRPS, fibromyalgia, phantom limb pain		
Incongruent sensory and motor information should cause pain	CRPS, fibromyalgia	WAD	MSK

CRPS = Complex Regional Pain Syndrome; MSK = musculoskeletal pain; WAD = chronic whiplash associated disorders.

The sensorimotor theory of pain provides a useful framework within which to further our understanding of sensorimotor processing in pathological pain conditions. Although we found evidence that contradicted the theory in several instances, the sensorimotor theory of pain provides a useful framework for testable hypotheses to be generated (e.g. Table 1). Advancing our understanding of sensorimotor processing in pathological pain conditions could improve existing treatments and aid the development of new ones. For instance, there is limited research looking at sensorimotor adaptation in people with pathological pain conditions. This review highlights areas where the evidence base is consistent (e.g. distorted body representations), others where this is mixed (e.g. S1 reorganisation), and areas where the theory is contradicted (e.g. motor deficits being caused by pain in CRPS). Based on the evidence reviewed, the evidence in support of main predictions (i.e. altered sensorimotor processing should relate to pain) was most frequently found for people with CRPS, carpal tunnel syndrome, fibromyalgia, and phantom limb pain (i.e. Table 13). Furthermore, we found most support for the application of sensorimotor therapies for people with CRPS.

To conclude, there is evidence from some pathological pain conditions that matches the predictions made by the sensorimotor theory of pain, which proposes that, in the absence of clear tissue pathology, altered sensorimotor processing might be involved in the maintenance of pathological pain.

Conflict of interest

The authors have no conflicts of interest to declare.

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Chapter 1 – Conclusions

In Chapter 1 I presented a comprehensive review of different sensorimotor processes that may be altered in pathological pain conditions. The review identified many similarities across conditions, which suggest that there could be some shared mechanisms that are altered in these conditions. For instance, there was evidence suggesting that the representations of the body that correspond to the painful area are distorted, and that this is evident in many different conditions, such as CRPS, fibromyalgia, shoulder pain, osteoarthritis, orofacial pain, low back pain, phantom limb pain. The evidence that such distortions were related to pain was mixed, and had not received as much attention.

Chapter 1 highlighted several unanswered questions in the literature, and assumptions of the sensorimotor theory that have yet to be tested in people with CRPS. Of particular relevance, implicit to the theory is the assumption that sensorimotor adaptation does not correct for any incongruent information that may arise. Only a few studies had examined this idea, and found, for instance, that adaptation could be disrupted in people with dystonia. Little is known about sensorimotor adaptation in pathological pain more broadly, and this has yet to be studied in people with CRPS. Similarly, despite the distorted representations of the body being common in pathological pain conditions, little is known about their dynamic properties, as these representations will update as we interact with our environment (Martel, Cardinali, Roy, & Farnè, 2016; Medina & Coslett, 2010). Research has yet to investigate the process of updating body representations in pathological pain conditions, which I will address in Chapter 3. I will also investigate the influence of acute pain on the updating of these representations (Chapter 2).

The sensorimotor theory of pain proposes that impaired sensorimotor processing can result in pain. There was some evidence for this prediction from conditions such as CRPS, carpal tunnel syndrome, fibromyalgia, and phantom limb pain. The evidence was more mixed for other predictions, such as reorganisation of S1 in pathological pain. In some places the predictions were contradicted, as, for instance, the direction of the association between pain and motor deficits. That is, there was evidence that pain relief improved motor deficits in CRPS, which contradicts the theorised direction, unless this relationship is bidirectional. Taken together, these findings suggest that the theory might be more appropriate for certain aspects of sensorimotor processing (e.g. altered body representation) than others.

The review highlighted CRPS as one of the conditions where there was most evidence for the predictions made by the sensorimotor theory of pain. Although there was mixed evidence of cortical reorganisation, people with CRPS were commonly found to have motor deficits, sensory changes, distorted representations of their body, and altered sensorimotor integration. Furthermore, there was evidence to suggest that people with CRPS would experience pain from incongruent sensorimotor information (i.e. incongruent mirror visual feedback). Therefore, CRPS is an appropriate condition in which to study the predictions made by the sensorimotor theory of pain. I will focus on CRPS for the studies that involve clinical populations in this thesis (i.e. Chapters 3, 4, and 5).

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Chapter 2: Experimentally induced pain does not disrupt updating of peripersonal space and body representations following tool-use

Chapter 2 – Introduction

In this chapter I present a study that examines the influence of experimentally induced pain on the updating of bodily and spatial representations following tool-use. Many people with pathological pain conditions can present with distorted representation of their body and its surrounding space, as I reviewed in Chapter 1. These representations are not static, but will update as we interact with objects in our environment. This flexibility has been studied using paradigms such as tool-use. Following active tool-use, the nervous system will accommodate the tools by updating the representations of the body and its surrounding space (e.g. Maravita & Iriki, 2004; Martel et al., 2016; Serino, 2019). Having accurate and up-to-date representations of the body and its surrounding space is important for accurately predicting the outcome of a movement (Shadmehr, Smith, & Krakauer, 2010).

Any disruption of processes such as the updating of bodily and spatial representations could impair sensorimotor processing, which is theorised to cause pain. However, it is also possible that this relationship is bidirectional, or that pain disrupts sensorimotor processing, and/or the updating of bodily and spatial representations. This study addresses the latter by investigating whether the flexibility of such representations is influenced by the presence of acute pain. If acute pain disrupts the updating of bodily and spatial representations, then any differences that we might observe in people with pathological pain, relative to controls, could be due to the pain that they experience during the task. Such a finding would indicate that peripheral changes could be giving rise to any altered sensorimotor processing, rather than vice versa, and would oppose the predictions made by the sensorimotor theory of pain. Specifically, the theory assumes that pain is the consequence of a sensorimotor incongruence, and in this chapter I investigate the opposite direction of causality. Chapter 2 will therefore acts as a control experiment for Chapter 3, were the same methods will be used to investigate the updating of bodily and spatial representations in people with CRPS and control participants. Although it will not be possible to rule out a bidirectional association between pain and sensorimotor processing on the basis of this chapter, it will provide proof of concept that acute pain can, or cannot, disrupt the updating of bodily and spatial representations.

In order to assess the causal effect of pain on the updating of bodily and spatial representations, I compared pain induction to a placebo manipulation, and no manipulation. This chapter therefore contributes to the understanding of how pain may interfere with sensorimotor processing, and challenges one of the assumptions of the sensorimotor theory of pain.

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Experimentally induced pain does not disrupt updating of peripersonal space and body representations following tool-use

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Abstract

Representations of the body and peripersonal space can be distorted for people with some chronic pain conditions. Experimental pain induction can give rise to similar, but transient distortions in healthy individuals. However, spatial and bodily representations are dynamic, and constantly update as we interact with objects in our environment. It is unclear whether induced pain disrupts the mechanisms involved in updating these representations. In the present study, we sought to investigate the effect of induced pain on the updating of peripersonal space and body representations during and following tool-use. We compared performance under three conditions (pain, active placebo, neutral) on a visuotactile crossmodal congruency task and a tactile distance judgement task to measure updating of peripersonal space and body representations, respectively. Consistent with previous findings, the difference in crossmodal interference from visual distractors in the same compared to opposite visual field to the tactile target was less when tools were crossed than uncrossed. This suggests an extension of peripersonal space to incorporate the tips of the tools. Also consistent with previous findings, estimates of the felt tactile distance judgements decreased after active tool-use. In contrast to our predictions, however, we found no evidence that pain interfered with performance on either task when compared to the control conditions. Our findings suggest that the updating of peripersonal space and body representations is not disrupted by induced pain. That is, experiencing acute pain does not give rise to distorted representations of the body and peripersonal space that can be present in people with chronic pain conditions.

1. Introduction

The multisensory representations of our body and its surrounding space are constantly updated as we interact with objects in our environment. Work with macaques identified bimodal neurons that responded to both somatosensory and visual information near and on the hand, whose receptive fields were malleable as a function of active tool-use (Iriki, Tanaka, & Iwamura, 1996). When monkeys actively used a rake to retrieve food, the receptive fields of these neurons expanded to include the area near to and occupied by the rake. Subsequent research in humans has shown that responses to visual, tactile, and auditory stimuli that originate near and on tools are modulated by active tool-use. Changes that arise from active tool-use are thought to reflect that the cortical representations of the body and its surrounding space have been updated to accommodate the new properties offered by the tool (for reviews see Macaluso & Maravita, 2010; Martel, Cardinali, Roy, & Farnè, 2016; Serino, 2019; Spence, Pavani, Maravita, & Holmes, 2004a).

Active tool-use, and the changes it causes in multisensory processing, have been used to study the representations of both the body and peripersonal space. Here we define body representation as the mental model of the body, based on proprioceptive and sensory information about the body's state (Serino & Haggard, 2010), for reviews, see (De Vignemont, 2010; Medina & Coslett, 2010; Riva, 2018). This representation is flexible, and a small degree of distortion has been demonstrated in normal cognition (Longo, 2017). Peripersonal space is defined as the areas that directly surround the body that we can act upon (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997), and that can contain objects that we may need to react to (for reviews, see Bufacchi & Iannetti, 2018; Cléry & Ben Hamed, 2018; De Vignemont & Iannetti, 2015; di Pellegrino & Làdavas, 2015; Serino, 2019). The body and its representation are the centre of peripersonal space (Maravita, Spence, & Driver, 2003), hence these representations are to some degree related, and active tool-use can influence both. For instance, Canzoneri and colleagues (2013) used an audio-tactile interaction task to assess peripersonal space, and a landmark task and tactile distance perception to examine body representation, before and after participants used a tool to retrieve distant objects. The results showed that following tool-use participants perceived their arm as narrower and longer, and representations of peripersonal space surrounding the arms were extended along the axis of the tool. Therefore, active tool-use provides an opportunity to study how body and peripersonal space representations are updated.

Representations of the body and space are distorted in people with neurological disorders like asomatognosia (Baier & Karnath, 2008) and hemispatial neglect (Husain & Rorden, 2003; Vallar, 1997, 1998). Body representation is also distorted in people with certain types of chronic pain (for reviews see Haggard, Iannetti, & Longo, 2013; Senkowski & Heinz, 2016; Tsay, Allen, Proske, & Giummarra, 2015). For instance, people with chronic back pain often report a distorted sense of the size of their body near their painful area, or that parts of the body feel like they are missing (Moseley, 2008). Similarly, people with Complex Regional Pain Syndrome (CRPS) can report difficulties locating and recognising their affected limb, show a distorted perception of its size, and have difficulties locating touch on their affected hand (e.g. Förderreuther, Sailer, & Straube, 2004; Lewis, Kersten, McCabe, McPherson, & Blake, 2007; Lewis et al., 2010; Lewis & Schweinhardt, 2012; Moseley, 2004, 2005; Peltz, Seifert, Lanz, Müller, & Maihöfner, 2011; Schwoebel, Friedman, Duda, &

Coslett, 2001). Distorted spatial representations have also been reported in people with pathological pain conditions. For instance, people with unilateral hand amputations underestimate the size of near space on the side of their amputation, compared to the contralateral side (Makin, Wilf, Schwartz, & Zohary, 2010). In CRPS patients, biases in visual and tactile attention away from the affected hand have been identified by asking patients to judge the temporal order of pairs of tactile stimuli delivered to, or visual stimuli projected near to or onto, the hands (Bultitude, Walker, & Spence, 2017; Filbrich et al., 2017; Moseley, Gallace, & Spence, 2009; Reid et al., 2016). Estimates of the point in space that is straight ahead of the body midline made in complete darkness, thought to reflect the division between left and right space in an egocentric reference frame (Jeannerod & Biguer, 1987), are also deviated in people with CRPS. Such deviations in spatial perception have been reported in the direction of the affected side (Sumitani et al., 2014; Sumitani et al., 2007; Uematsu et al., 2009), and leftwards irrespectively of the affected side (Reinersmann et al., 2012), although not all studies find evidence of deviations (Christophe et al., 2016; Kolb, Lang, Seifert, & Maihöfner, 2012; Wittayer, Dimova, Birklein, & Schlereth, 2018). Furthermore, Sumitani and colleagues (2007) found that the deviation towards the CRPS-affected side was reduced following pain reduction through using a nerve block. Taken together, these studies demonstrate that bodily and spatial representations can be distorted in pathological pain conditions. What is unclear, however, is whether pain (or associated factors such as immobility and disuse) *precede*, or *follow* (e.g. Bultitude & Rafal, 2010), these altered representations.

Research has started to investigate the effect of pain on spatial perception and the representation of the body in normal cognition. Pain itself is a sensory and affective phenomenon (Merskey & Bogduk, 1994) that can be shaped by multisensory experiences (Senkowski, Höfle, & Engel, 2014) and convey spatial information about the body (Haggard et al., 2013). After participants were subjected to painful heat stimulation on one hand, their subjective body midline shifted towards the painful side, whereas vibrotactile stimulation had the opposite effect (Bouffard, Gagne, & Mercier, 2013). This suggests that pain can modify spatial perception in ways that cannot sufficiently be explained by attentional cueing effects. To date, only one study looked directly at how pain might alter the representation of the body in healthy subjects. Gandevia and Phegan (Gandevia & Phegan, 1999) found that participants reported an average of 10% increase in the perceived size of their thumb after it had been subject to painful cooling. These studies suggest that pain might alter the representations of the body and its surrounding space, however the evidence is limited. Furthermore, to our knowledge, no study has investigated the effect of pain on the updating of peripersonal space and body representation (e.g. following tool-use).

Our study aimed to investigate the effect of induced pain on the updating of peripersonal space and body representations of healthy individuals during and following tool-use. Over three separate sessions, participants completed a tool-use task while experiencing capsaicin-induced pain in their dominant arm, and in two control conditions: active placebo and neutral (i.e., no sensory manipulation). We hypothesised that inducing pain in an arm would impair participants' ability to update peripersonal space and body representations relative to the other conditions. We used a crossmodal congruency task (CCT) and tactile distance judgements (TDJs) to measure updating of peripersonal space and body representation, respectively.

The CCT has been used previously to investigate the effects of active tool-use on spatial representations (Macaluso & Maravita, 2010; Martel et al., 2016). In this task, participants make judgements about vibrotactile targets presented to the hands through the handles of the crossed or uncrossed tools while ignoring visual or auditory distractors presented at the tips of the tools. After the participants have used the tools actively, distractors on the same side of space as the targets typically have a larger effect on increasing reaction times and/or error rates when the tools are uncrossed than when the tools are crossed (Maravita, Spence, Kennett, & Driver, 2002b). In contrast, distractors on the opposite side of space as the targets have a larger effect on performance when the tools are crossed than when the tools are uncrossed. That is, after tool-use, distractors have a greater interference effect when they originate from the same *tool* as targets, rather than from the same *side of space* as the target. Maravita and colleagues (2002b) interpreted this pattern to indicate a change in peripersonal space representations (although see Holmes [2012] for an alternative interpretation), which was further suggested by the fact that this interference pattern only developed from active tool-use but did not develop when tools were held passively. We predicted that pain would interfere with the emergence of tool-specific effects of distractors on judgements made about the targets. That is, we expected to see a weaker interaction between the arrangement of the tools, the visual field in which visual distractors appear relative to vibrotactile targets, and the vertical congruence of visual distractors relative to vibrotactile targets for the pain condition, relative to the two control conditions.

TDJs have been used to measure updating of body representation following tool-use. Distances between two touched locations on the arm that are oriented parallel to the axis of the tool are perceived to be shorter after active tool-use. This is thought to indicate that body representation is altered by tool-use, such that the forearm is perceived to be longer (Canzoneri et al., 2013; Longo & Haggard, 2011; Miller, Longo, & Saygin, 2014; Miller, Longo, & Saygin, 2017; Taylor-Clarke, Jacobsen, & Haggard, 2004). We predicted that pain would interfere with the degree to which tool-use altered TDJs, such that distance estimates would have a smaller decrease when participants were in pain.

2. Methods

2.1. Design

We used a repeated-measures design with three sessions, corresponding to three sensory conditions: Pain, active placebo, and neutral (i.e. no sensory manipulation). We used a Crossmodal Congruency Task (CCT) adapted from Maravita and colleagues (2002b) to measure changes in peripersonal space and Tactile Distance judgements (TDJs) adapted from Canzoneri and colleagues (Canzoneri et al., 2013), Miller and colleagues (Miller et al., 2014; Miller et al., 2017), Longo and Haggard (Longo & Haggard, 2011), and Taylor-Clarke and colleagues (Taylor-Clarke et al., 2004) to measure changes in body representation. We wanted to know if the effects of unilateral pain induction would be specific to the stimulated arm, or global (i.e. extend to the unstimulated arm), by comparing CCT and TDJ performance between the two arms. In addition to these tasks, we also used several measures to monitor the sensory and cognitive effects of the sensory manipulations. We asked participants to give numerical ratings of pain intensity. We also used sensory testing

(Mechanical Pain Threshold, Mechanical Detection Threshold, Two Point Discrimination Threshold), and questionnaire measures (The Bath CRPS Body Perception Disturbance Scale [BPD; (Lewis & McCabe, 2010)], the Short-Form McGill Pain Questionnaire 2 [SF-MPQ-2; (Dworkin et al., 2009)]), to characterise any secondary changes caused by our sensory manipulation. The protocol was preregistered on the Open Science Framework (https://osf.io/8fduw/register/565fb3678c5e4a66b5582f67).

2.2. Participants

Thirty-one participants completed the study tasks under three sensory conditions (pain, active placebo, and neutral) in a randomized, counterbalanced order. One person was excluded because she did not report any pain (0/10 on a Numerical Rating Scale [NRS]) for 40 minutes following the application of capsaicin, even when we attempted this condition on a second occasion. One person repeated the pain condition (their session 1) due to low pain ratings in the first attempt that was completed (*M* NRS after the sensory manipulation period during the first attempt 0.6/10, *SD* = 0.97 and the second attempt 1.4/10, *SD* 0.70). One person repeated the neutral condition (their session 3) due to equipment malfunctioning during the CCT. The repeated sessions were completed in full, and took place on a different day. The mean age of the final sample was 21.6 years (*SD* = 4.3), of which 22 (73.3%) were women. Two participants were left-handed (*M* = -70.0, *SD* = 14.1), one ambidextrous (score of 30), and the remaining 27 were right-handed (*M* = 83.6, *SD* = 17.7), as indicated by the Edinburgh Handedness Inventory (Oldfield, 1971), in which extreme left and right handedness is indicated by scores of -100 and 100, and scores between 40 and -40 indicate ambidextrousness. All participants reported having normal or corrected to normal vision, and that they did not have a chronic pain condition. Participants with self-reported sensitive skin, epilepsy, high blood pressure, recent heart problems, a history of stroke, vascular problems, an allergy to capsaicin, or who were pregnant or breastfeeding were excluded to satisfy local safety guidelines for the use of capsaicin cream. Participants signed consent and safety forms prior to participating, and consented for their data to be used upon completion of the study. The study adhered to the 2013 Declaration of Helsinki, and received approval from the local ethics committee (Psychology Research Ethics Committee, Department of Psychology, University of Bath, UK. Approval Number: 16-236). Participants received £30 for their involvement.

2.3. Materials

For the pain condition, a 1cm wide band of Ungentum cream infused with a 1% concentration of capsaicin (the Specials Laboratory, United Kingdom), amounting to approximately 5g of cream, was applied to the dominant arm, just proximal to the elbow. For the ambidextrous person, the cream was applied to the right arm because this was the participant's self-reported dominant side. The cream was contained within two bands of microporous tape, and covered with cling film. This was fitted so that participants could flex and extend their elbow with ease, so as not to impede their ability to manoeuvre the tools. Applying a band of capsaicin that reaches around the arm in this location generates a burning pain that penetrates into the arm (Brun, Gagné, McCabe, & Mercier, 2017), and is accompanied by cutaneous vasodilation and hyperalgesia (Green & Shaffer, 1993). This

method has been used previously (Brun et al., 2017; Maihöfner et al., 2007). For the active placebo, a 'warm-up' gel (Elite Ozone) was used to create a non-painful warming sensation. The site and application procedures were identical to that of the capsaicin. No cream was applied in the neutral condition.

The final design of the CCT was informed by pilot research (n = 42). The materials used were based on the study by Maravita and colleagues (2002b). Two 75cm long tools (see Fig 1) that resembled golf clubs were constructed from aluminium. Two red Light Emitting Diodes (LEDs) were embedded in the distal end of each tool. Two electromagnetic solenoid-type stimulators (Tactor Minature Stimulators, Dancer Design, United Kingdom) were embedded in each of the handles to deliver vibrotactile stimulation. The LEDs and vibrotactile stimulators were controlled by a 4-channel amplifier (TactAmp 4.2, Dancer Design, United Kingdom) operated by Matlab 2014b (MathWorks). On each tool, one LED and one vibrotactile stimulator was positioned above the central axis of the tool, and one LED and one vibrotactile stimulator below it. The tools had wooden pegs attached vertically to their far ends, near the LEDs, in the 'blades' of the tools. The pegs slotted into holes in a wooden board (80 x 100 cm) that were 15 cm away from the distal end of the board, and 15 cm to the left and right from the central axis of the board. This ensured that the ends of the tools were always placed in the same position regardless of whether the tools were crossed or uncrossed. A fixation light was located at the central axis of the board, 15cm from the distal end. A 5 cm wide blue mark was placed on the handle of each tool 30 cm away from the distal end to indicate points at which participants should cross the tools. Two triple switch foot pedals (Scythe, USA) with custom software were used to collect participants' responses. White noise was played on headphones to mask any sound of the vibrotactile stimulation. A chinrest was used to ensure that participant's heads remained in a consistent position. Two webcams were positioned in line with participant's sagittal plane, at the end of and 20 cm away from the board, so that the experimenter could monitor gaze throughout the task, and record participant's movements for offline evaluation of movement quality.

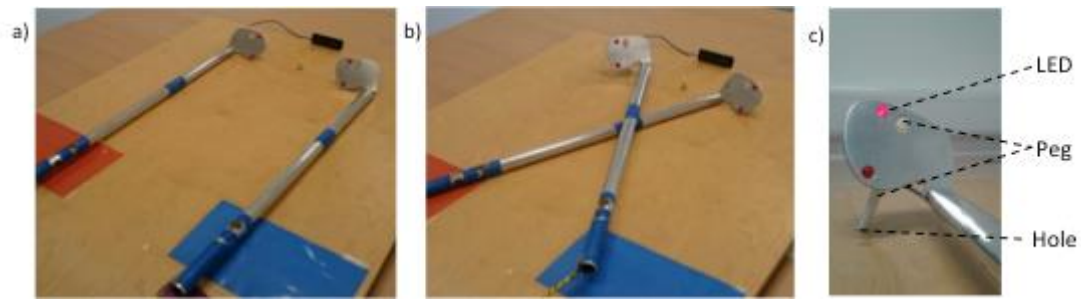

Figure 1. Tool-use materials.
From left to right, the images depict the uncrossed (A), and crossed (B) tools, and a close-up of the end of a tool (C). The tools have red Light Emitting Diodes (LEDs) embedded at the far ends of the tools, and vibrotactile stimulators embedded in the handles. A vertical peg was attached to the far ends of the tools (white oval), which slotted into holes in the wooden board to ensure the position of the tips of the tools was consistent for crossed and uncrossed trials (C). An off-white LED fixation point was positioned with equal distance to the ends of both tools. A webcam was placed in line with the fixation light and the chinrest, which were aligned with participants' sagittal plane.

Two flat-ended circular rods (1 mm diameter) were used for tactile distance judgements (TDJs). They were attached to a bow compass, so that the distance between them could be accurately adjusted. Mechanical Pain Threshold was assessed using seven pinprick stimulators (MRC Systems GmbH, Germany), ranging from 8 mN to 512 mN in force. Twenty Von Frey Filaments were used to measure Mechanical Detection Threshold (BioSeb, France), ranging from 0.008 g to 300 g in weight. Two Point Discrimination Threshold was quantified using an Exacta™ two-point discriminator (North Coast Medical, USA), ranging from distances of 2 mm to 20 mm in distance. A handheld infrared thermometer with an 8:1 distance to spot size ratio, and a red laser aim was used to measure the temperature of participants' hands.

The BPD (Lewis & McCabe, 2010) is an unvalidated 7-item questionnaire designed to characterise distorted body perception in CRPS. It includes questions about the awareness of, attention to, emotional valance of, and desire to amputate the affected area. For this study, participants were instructed to answer about the stimulated (dominant) arm. Scores can range from 0 to 57, where a higher score indicates greater distorted body perception. We included this measure because we were interested in how experimental pain induction might give rise to distortions of the body representation, and if this was similar to what is typically reported by people with pathological pain (e.g. CRPS).

The SF-MPQ-2 (Dworkin et al., 2009) is a 24-item questionnaire assessing the symptoms of neuropathic and non-neuropathic pain. Participants rate the intensity of their pain for each of 22 pain qualities (e.g. sharp, aching, hot-burning) on a scale of 0 ('none') to 10 ('worst possible'). The SF-MPQ-2 has been validated for acute pain populations (Dworkin et al., 2015). We included this measure to better characterise the different dimensions of participants' pain experiences.

2.4. Procedure

Fig 2 shows an outline of the procedure for each session. Informed written consent was obtained and self-reported handedness was recorded upon commencing the first session. Then, the first set of sensory tests (i.e. Mechanical Pain Threshold, Mechanical Detection Threshold, Two Point Discrimination) were performed on the middle finger (digit 3) of the dominant and non-dominant hands. Mechanical Pain Threshold, and Mechanical Detection Threshold were assessed following a standardised protocol (Rolke et al., 2006). Five values for each subthreshold and suprathreshold were recorded for each sensory test. That is, we recorded when touch was detected or not for the Mechanical Detection Threshold; sharp and blunt sensations for the Mechanical Pain Threshold; and the distance (mm) at which two points were perceived as one or two were recorded for the Two Point Discrimination. Then the capsaicin cream or 'warm-up' gel was applied for the pain and active placebo conditions, respectively. Pain ratings and dominant hand temperature were recorded every minute following cream application in the Pain and Active Placebo conditions, or upon completion of sensory testing in the Neutral condition. To allow the capsaicin to take effect, we waited until participants' pain ratings exceeded 5/10, or until three identical consecutive ratings >2/10 were given. Based on piloting and past research (Brun et al., 2017), we expected this to take approximately 15 minutes. Consequently, in the two control conditions,

we waited for 15 min between the first and second set of sensory tests. In all three conditions, participants viewed a nature video deemed low in arousal (Mustill, 2016) and engaged in light conversation with the experimenter during the waiting period. Then we conducted a second set of sensory tests, and participants completed the BPD and SF-MPQ-2.

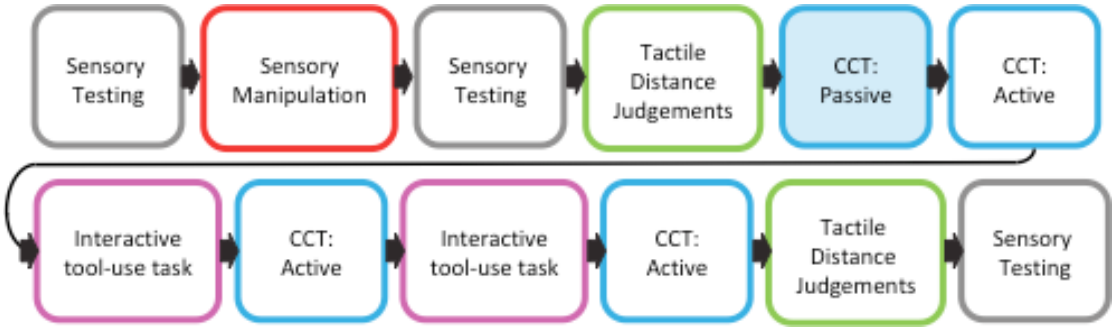

Figure 2. Procedure for each experimental session.
During the sensory manipulation phase the experimenter applied a capsaicin cream (pain condition) or warm-up gel (active placebo condition) to the participant's dominant arm, or there was no manipulation (neutral condition). During the passive stage (set 1) of the Crossmodal Congruency task (CCT) the experimenter changed the tools between the crossed and uncrossed positions. During the active stages of the CCT (sets 2-4) participants manoeuvred the tools themselves when changing position. The interactive tool-use task involved retrieving and sorting beanbags, using the same tools that were used for the CCT (see Fig 1).

We then administered the first TDJ task. The participant sat with their head in the chin rest with their eyes open and gripped the uncrossed tools. The experimenter applied the flat-ended circular rods to along the radial side of the participant's forearm (i.e. proximal-distally). Three distances (4, 6, and 8 cm) were presented on one arm in a randomised counterbalanced order, with one repetition for each distance. After the three TDJ trials were completed, the procedure was repeated for the second arm. The order in which the arms were tested was randomised and counterbalanced. Participants indicated the estimated distance between the two felt points using a diagram of 22 lines of different lengths ranging from 0.6 cm to 11.5 cm, in 0.5 cm increments, presented on an A4 sheet of paper.

After the first TDJ task, participants were instructed on how to perform the CCT. On each trial, participants identified the location of three 50 ms bursts of vibrotactile stimulation delivered to the thumb or middle finger of the left or right hand from the vibrotactile stimulators embedded in the handles of the tools. Three flashes of 50 ms from the red LEDs at the ends of the tools preceded each vibrotactile stimulation by 30ms to maximise the crossmodal interference (Spence, Pavani, Maravita, & Holmes, 2004b). Participants judged the location of the vibrotactile stimulation as either on the thumb (upper) or finger (lower), and if it was delivered to the left or right hand. Visual distractors provided no information about the location of the target vibrotactile stimulation. Participants indicated the location of the vibrotactile stimulation by pressing foot pedals using their heel (finger; "lower") or toes (thumb; "upper") of their left or right foot. Participants were instructed to respond as quickly and as accurately as possible. Incorrect responses and responses slower than 3000 ms caused all four LEDs to flash three times to provide feedback to the participants.

Participants completed four Sets of the CCT. Within each set were trials in which the tools were positioned in uncrossed or crossed positions. In the first set of the CCT (the “passive” set), the experimenter changed the position of the tools half-way through while the participants kept hold of the handles, comparable to the control experiment reported by Maravita and colleagues (2002b). The order of tool arrangements (crossed or uncrossed) was counterbalanced between participants. For the remaining three sets of the CCT (the “active” sets), participants actively changed the arrangement of the tools between crossed and uncrossed every four trials. The cue to change arrangement was all four LEDs illuminating. Before commencing the first (passive) CCT set, participants completed a practice set of 16 trials during which they held the tools still and uncrossed to ensure that they understood the CCT task. The practice set was repeated until the participant responded correctly on >80% of trials.

The CCT enabled the evaluation of the effect of the visual distractors on detection of vibrotactile stimulation depending on whether tools were uncrossed or crossed (Tool Arrangement), the distractor was in the same or the opposite side of space as the target (Visual Field), and the distractor was in the same or the opposite vertical elevation as the target (Congruence). All possible combinations of Tool Arrangement, Visual Field, and Congruence relative to the vibrotactile target (see Appendix 1 for examples) were delivered in a random order over every 32 trials. Each set was comprised of 96 trials, giving 384 trials per session. Using this procedure, we could also examine changes in the effect of the distractors over time by comparing performance in the four sets.

Actively changing the tool arrangement was the key manipulation in Maravita and colleagues’ (2002b) study to elicit the changes to CCT performance generated by active tool-use. However, following piloting, we added an additional interactive tool-use tasks in-between the second and third, and third and fourth sets of the CCT to amplify the desired effect. The task consisted of approximately 5 minutes of using the tools to sort and retrieve distant beanbags, using the same equipment as for the CCT. Participants sorted beanbags by colour, and retrieved them from the distal end of the board to coloured squares (see Fig 1) on either the left of right side of the board’s proximal end. This was inspired by comparable paradigms involving active tool-use (Farnè, Iriki, & Làdavas, 2005; Farnè & Làdavas, 2000; Maravita, Clarke, Husain, & Driver, 2002a). Upon completion of the last set of the CCT the second set of TDJs was administered, and the second set of sensory testing was conducted. Each session lasted approximately 2 hours.

In addition to the pain ratings recorded during the pain ramp-up period in the pain condition, or for 15 minutes in the active placebo and neutral conditions, participants provided an additional 12 pain ratings between different experimental tasks. They provided pain rating before each set of TDJs, and two rating for the first CCT set (passive), and then before and after each of the active CCT sets.

2.5. Analyses

We examined error rates and reaction times (RTs) from the crossmodal congruency task in separate 3x4x2x2x2x2 repeated-measures analyses of variance (ANOVAs). The

independent variables for the CCT were the Sensory Condition (pain, active placebo, neutral), Set (set 1 [passive], set 2, set 3, set 4), Side of Body on which the vibrotactile stimulation occurred (dominant, non-dominant), Tool Arrangement (uncrossed, crossed), Visual Field in which the distractor occurred relative to the target (same, opposite), and Congruence (congruent, incongruent). The median RTs and percentage of errors were calculated within level of the relevant conditions, after excluding trials with RTs <200 ms or >3000 ms. Only trials with correct responses were used to calculate the median RTs. The critical interaction that we were interested in was that between Tool Arrangement, Visual Field, and Congruence. Therefore, only interactions involving all three factors Tool Arrangement, Visual Field, and Congruence were considered relevant for addressing the aim of the study. We also considered that the three-way interaction should normally develop over time spent engaged in active tool-use (as reported by Maravita and colleagues [2002b]), which would result in interactions involving the four factors Set, Tool Arrangement, Visual Field, and Congruence. In their study (Maravita et al., 2002b), tool-use-dependent effects were only significant for RTs, not for error rates. Therefore, to be concise we will only report results from the RTs of the CCT in the main article (see S1 Text for the results of CCT error rate analyses). To aid interpretation of the results, we subtracted congruent from incongruent trials to calculate crossmodal interference for follow-up contrasts.

A mean score for the TDJs was computed for each Sensory Condition (pain, active placebo, neutral), Set (pre tool-use, post tool-use), and Side of Body (dominant, non-dominant), and analysed using a 3x2x2 repeated-measures ANOVA.

Mechanical Pain Threshold, Mechanical Detection Threshold, and Two Point Discrimination Threshold were calculated as geometric means of each value for which a participant's responses changed (e.g. from blunt to sharp for Mechanical Pain Threshold). Performance on sensory tests was analysed using ANOVAs with Sensory Condition (pain, active placebo, neutral), Set (pre manipulation, post manipulation), and Side of Body (dominant, non-dominant) as independent variables. For subsequent covariate analyses, changes on the sensory tests were calculated by subtracting pre- from post-sensory manipulation scores, within each level of Sensory Condition (pain, active placebo, neutral) for the dominant (stimulated) side of the body. The 12 pain ratings recorded after the sensory manipulation period (i.e. between sets of TDJs and CCT) were averaged across tasks, within each level of Sensory Condition, for each participant, for covariate analysis. Changes in hand temperature were calculated by subtracting the first recording (i.e. 1 minute after the sensory manipulation) from the last recording (e.g. after 15 minutes for the active placebo and neutral conditions), for each participant and within each level of Sensory Condition. To evaluate if there were any differences in participants' movements across the three sessions that could account for any difference between the effects of tool-use, movements were scored by a research assistant from video recordings taken during the first and last two minutes of the active CCT, and during the interactive tool-use task. The research assistant, who was blind to the hypotheses and task conditions, rated the speed, ease, and control of movement in each video from 0 ('worst imaginable') to 10 ('best imaginable'). A mean value was calculated from the speed, ease, and control of movement for each session, within each participant. Age, the total score for the SF-MPQ-2, BPD, change in hand temperature, average pain ratings, and changes on sensory tests from pre to post sensory manipulation were explored as covariates in analyses of covariance

(ANCOVAs) of the CCT and TDJ. Greenhouse-Geisser corrections were used when sphericity was not satisfied. Holm-Bonferroni corrections (Holm, 1979) were used for follow-up t-tests, and indicated by "$p_{adjusted}$". See preregistration (https://osf.io/8fduw/register/565fb3678c5e4a66b5582f67) for full list of planned confirmatory and exploratory analyses.

3. Results

We observed changes on both tasks that were consistent with updating bodily and spatial representations. For the crossmodal congruency task, we found a significant three-way interaction between Tool Arrangement, Visual Field, and Congruence, which is consistent with updating of peripersonal space representations. Participants perceived the distance between two tactile points (i.e. tactile distance judgments) to be smaller after active tool-use, which is consistent with updating body representations. We did not find any evidence to suggest that updating of bodily or spatial representations was influenced by acute pain, as there was no significant interaction involving Sensory Condition for either task. These findings were further supported by exploratory Bayesian analyses that showed evidence of no effect of acute pain on the updating of bodily and spatial representations.

3.1. Sensory measures

The mean duration for pain ratings to reach 5/10 or plateau after the capsaicin was administered was 16.7 minutes (*SD* = 7.62), see S2 Fig/Appendix 1 for time course. There were no differences between the changes in hand temperature as measured on the tip of digit 3 for the pain condition (*M* = -0.79°C, *SD* = 0.62), active placebo condition (*M* = -0.60°C, *SD* = 1.16), and neutral condition (*M* = -0.98°C, *SD* = 0.62) over this period $F(1.57, 44.07) = 1.24$, $p = .292$, $\eta_{2p} = .04$. There were no differences in the research assistant's ratings of the movement between the pain condition (*M* = 5.73, *SD* = 1.16), active placebo condition (*M* = 5.68, *SD* = 1.20), and neutral condition (*M* = 5.60, *SD* = 1.25), $F(2, 27) = 0.48$, $p = .627$, $\eta_{2p} = .03$. The mean pain ratings averaged across the TDJs and CCT tasks were 5.06 (*SD* = 1.88) for the pain condition, 0.27 (*SD* = 0.46) for the active placebo condition, and 0.02 (*SD* = 0.06) for the neutral condition. Pain ratings for the pain condition were significantly higher than both the active placebo, $t(29) = 14.16$, $p_{adjusted} < .001$, $d = 5.26$, and neutral conditions, $t(29) = 14.70$, $p_{adjusted} < .001$, $d = 5.46$. Participants also reported higher pain in the active placebo condition than the neutral condition, $t(29) = 2.84$, $p_{adjusted} = .030$, $d = 1.06$. Overall, these results show the capsaicin cream induced significant pain relative to the other two conditions, without influencing movement ratings or hand temperature.

There were no changes in Two Point Discrimination Threshold (*M* = 0.00 mm, *SD* = 0.25) or in Mechanical Detection Threshold (*M* = 0.00 g, *SD* = 0.01) from pre to post sensory manipulation when considered across all three sensory manipulations, or any two-way interactions of Time with Sensory Condition or Side of Body Fs ≤ 2.99, ps ≥ .094, $\eta_{2p} \leq .09$ (see S1 Table/Appendix 1). For Mechanical Pain Threshold there was an interaction between Sensory Condition x Time x Side of Body, $F(2, 28) = 4.42$, $p = .021$, $\eta_{2p} = .24$. This reflected that there was an increase in Mechanical Pain Threshold for the dominant

(stimulated) arm in the pain condition, $t(29) = 2.34$, $p_{adjusted} = .048$, $d = 0.87$, as Mechanical Pain Threshold increased from pre ($M = 178.3$ mN, $SD = 136.8$) to post ($M = 224.6$ mN, $SD = 161.5$) the application of capsaicin cream (see S3 Fig/Appendix 1). Follow-up analysis showed that there was a significant increase in Mechanical Pain Threshold for the non-dominant side of the body in the active placebo condition from pre sensory manipulation to post CCT ($M = 217$, $SD = 146.7$), $t(29) = 3.34$, $p_{adjusted} = .005$, $d = 1.24$. There were no changes in Mechanical Pain Threshold from pre to post sensory manipulation in any of the other levels of Sensory Condition by Side of Body, $ts(29) \leq 1.60$, $ps_{adjusted} \geq .214$, $ds \leq 0.59$.

Analysis of the questionnaire measures showed no difference between the neutral ($M = 9.87$, $SD = 6.35$), active placebo ($M = 12.60$, $SD = 5.60$), and pain ($M = 11.60$, $SD = 6.10$) conditions on the BPD, $F(1.64, 47.43) = 2.22$, $p = .128$, $\eta_{2p} = .07$. There was an effect of Sensory Condition on the SF-MPQ-2, $F(2, 58) = 4.46$, $p = .016$, $\eta_{2p} = .13$. Despite the pain condition ($M = 1.05$, $SD = 1.27$) scoring higher than the neutral condition ($M = 0.34$, $SD = 0.73$) and the active placebo condition ($M = 0.55$, $SD = .082$) on the SF-MPQ-2, these effects were not sufficiently large to withstand correction for multiple comparisons, $ts(29) \leq 2.58$, $ps_{adjusted} \geq .093$, $ds \leq 0.96$.

Age, SF-MPQ-2 scores, BPD scores, hand temperature, average pain ratings, and changes in sensory testing were explored as covariates for the analyses of the TDJ and CCT. When analysed within each Sensory Condition, the covariates did not consistently interact with either RTs from the CCT, error rates from the CCT, or TDJ. That is, no covariate interacted significantly across each Sensory Condition for any outcome measure. Therefore, no covariates were included for further analysis.

3.2. Crossmodal congruency task

All significant main effects and interactions for RTs are reported in S2 Table. There were main effects of Set, $F(3, 27) = 45.10$, $p < .001$, $\eta_{2p} = .83$, Side of Body, $F(1, 29) = 7.97$, $p = .009$, $\eta_{2p} = .22$, Visual Field, $F(1, 29) = 6.69$, $p = .015$, $\eta_{2p} = .19$, and Congruence $F(1, 29) = 177.18$, $p < .001$, $\eta_{2p} = .86$, on reaction times for the CCT. Reaction times became shorter for each set of the CCT (set 1 [passive]: $M = 707.9$ ms, $SD = 101.88$; set 2: $M = 694.5$ ms, $SD = 93.40$; set 3: $M = 648.4$ ms, $SD = 92.02$; set 4: $M = 629.6$ ms, $SD = 97.49$). Except for the difference between set 1 and 2 ($t(29) = 1.57$, $p_{adjusted} < .128$, $d = 0.28$), all follow-up comparisons showed a significant decrease in reaction time over time, $ts(29) \geq 3.46$, $ps_{adjusted} \leq .004$, $ds \geq 1.29$. Participants responded faster to vibrotactile stimulation on their dominant ($M = 660.3$ ms, $SD = 92.02$) than their non-dominant ($M = 679.9$ ms, $SD = 98.59$) hand. Reaction times were shorter when visual distractors appeared in the same ($M = 667.3$ ms, $SD = 93.66$) than the opposite ($M = 672.9$ ms, $SD = 93.66$) visual field relative to vibrotactile targets. Responses were slower when visual distractors were incongruent ($M = 693.3$ ms, $SD = 95.30$) than congruent ($M = 646.9$ ms, $SD = 92.57$) with vertical vibrotactile target locations.

The most important finding with regards to our hypothesis was that no interactions of interest involving Sensory Condition, Tool Arrangement, Visual Field, and Congruence were observed, indicating that pain did not interfere with the reaction times on the CCT. Most

importantly, there was no significant interaction for Sensory Condition x Tool Arrangement x Visual Field x Congruence, $F(1.66, 48.21) = 0.80$, $p = .434$, $\eta_{2p} = .03$.

The critical three-way interaction for testing the effects of tool-use on peripersonal space, between Tool Arrangement, Visual Field, and Congruence, was significant $F(1, 29) = 9.43$, $p = .005$, $\eta_{2p} = .25$ (Fig 2). The follow-up analyses showed that there was a significant difference between incongruent and congruent distractors within each level of Tool Arrangement and Visual Field (see S3 Table), $ts(29) \geq 5.29$, $ps_{adjusted} \leq .004$, $ds \geq 1.96$. Therefore, we calculated the crossmodal interference by subtracting congruent from incongruent scores, and compared this across each level of Tool Arrangement and Visual Field to evaluate what drove this interaction (Fig 3). For uncrossed tools, crossmodal interference was greater when the visual distractors appeared in the same ($M = 72.2$, $SD = 29.6$) than the opposite ($M = 27.1$, $SD = 28.1$) visual field to the vibrotactile targets, $t(29) = 6.43$, $p_{adjusted} = .004$, $d = 2.39$. When the tools were crossed, crossmodal interference was also greater when the visual distractors appeared in the same ($M = 54.2$, $SD = 35.0$) than the opposite ($M = 31.3$, $SD = 21.7$) visual field relative to the vibrotactile targets, $t(29) = 3.31$, $p_{adjusted} = .009$, $d = 0.61$, although the effect size was smaller than when tools were uncrossed. When visual distractors appeared in the same visual field as the vibrotactile targets, crossmodal interference was greater for the uncrossed than the crossed tools, $t(29) = 3.42$, $p_{adjusted} = .014$, $d = 1.27$. There was no difference in crossmodal interference when visual distractors appeared in the visual field opposite the vibrotactile targets, $t(29) = 0.80$, $p_{adjusted} = .438$, $d = 0.30$. These results suggest that peripersonal space representations were updated as a function of tool-use because the arrangement of the tools impacted on the RTs from the CCT. This is evidenced by the decreased effect size when comparing visual distractors appearing in the same or opposite side, giving rise to the critical three-way interaction. The results of the analysis of error rates (S1 Text/Appendix 1) were broadly consistent with the results of the analysis of reaction times.

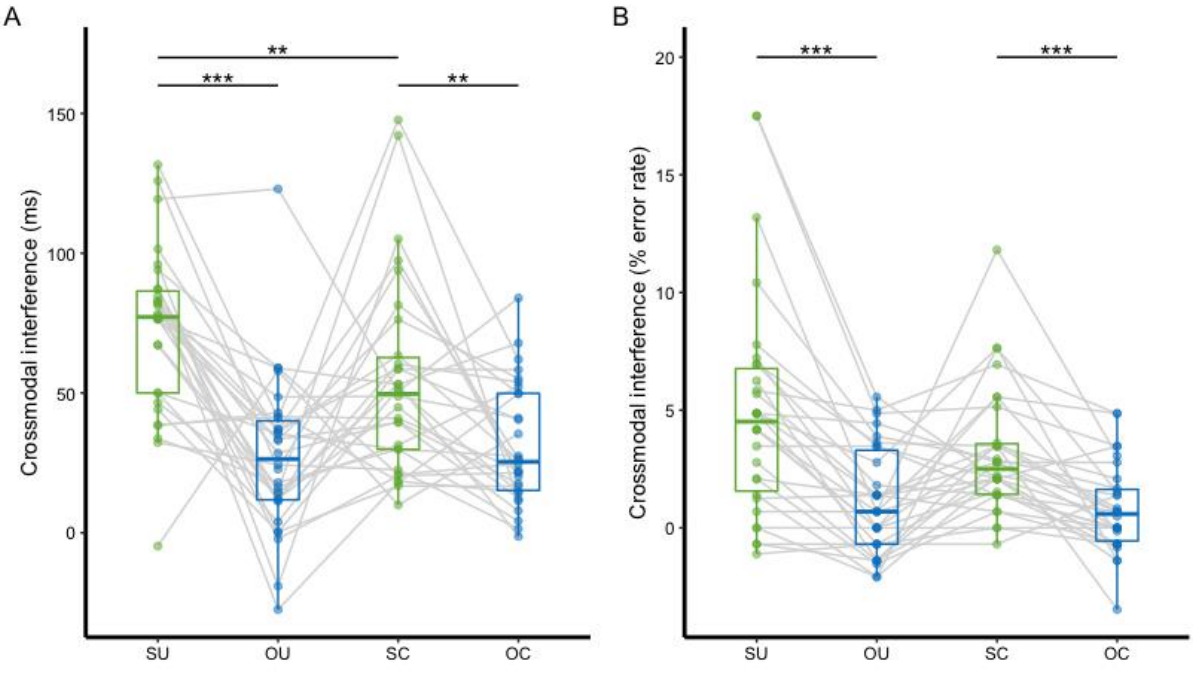

Figure 2. Crossmodal Interference – three-way interaction.
Crossmodal interference shown by Tool Arrangement (uncrossed [U], crossed [C]) and Visual Field (same [S; green], opposite [O; blue]) for reaction times (A) and percentage error rates (B), on the Crossmodal Congruency Task (CCT), for all participants (n = 30). Crossmodal interference was calculated by subtracting congruent from incongruent reaction times and error rates. Circles depict individual data points, which are connected by grey lines. Medians are depicted by the centre lines. The box limits indicate the 25th and 75th percentile. The whiskers extend 1.5 times the interquartile range from the box limits. Circles depict individual data points. ** $p < .01$, *** $p < .001$.

A four-way interaction between the factors Set, Tool Arrangement, Visual Field and Congruence on RTs for the CCT was also observed (Fig 4), $F(2.41, 70.09) = 3.28$, $p = .035$, $\eta_{2p} = .10$. Separate three-way ANOVAs of Tool Arrangement x Visual Field x Congruence for each Set revealed significant three-way interaction for only the first two sets (set 1 [passive]: $F(1, 29) = 8.89$, $p = .006$, $\eta_{2p} = .24$; set 2: $F(1, 29) = 11.09$, $p = .002$, $\eta_{2p} = .28$). This interaction was not present in set 3, $F(1, 29) = 0.39$, $p = .536$, $\eta_{2p} = .01$, or set 4, $F(1, 29) = 0.11$, $p = .748$, $\eta_{2p} < .01$. To further investigate these patterns of results we calculated the crossmodal interference and compared this across each level of Tool Arrangement and Visual Field with each set (Fig 4).

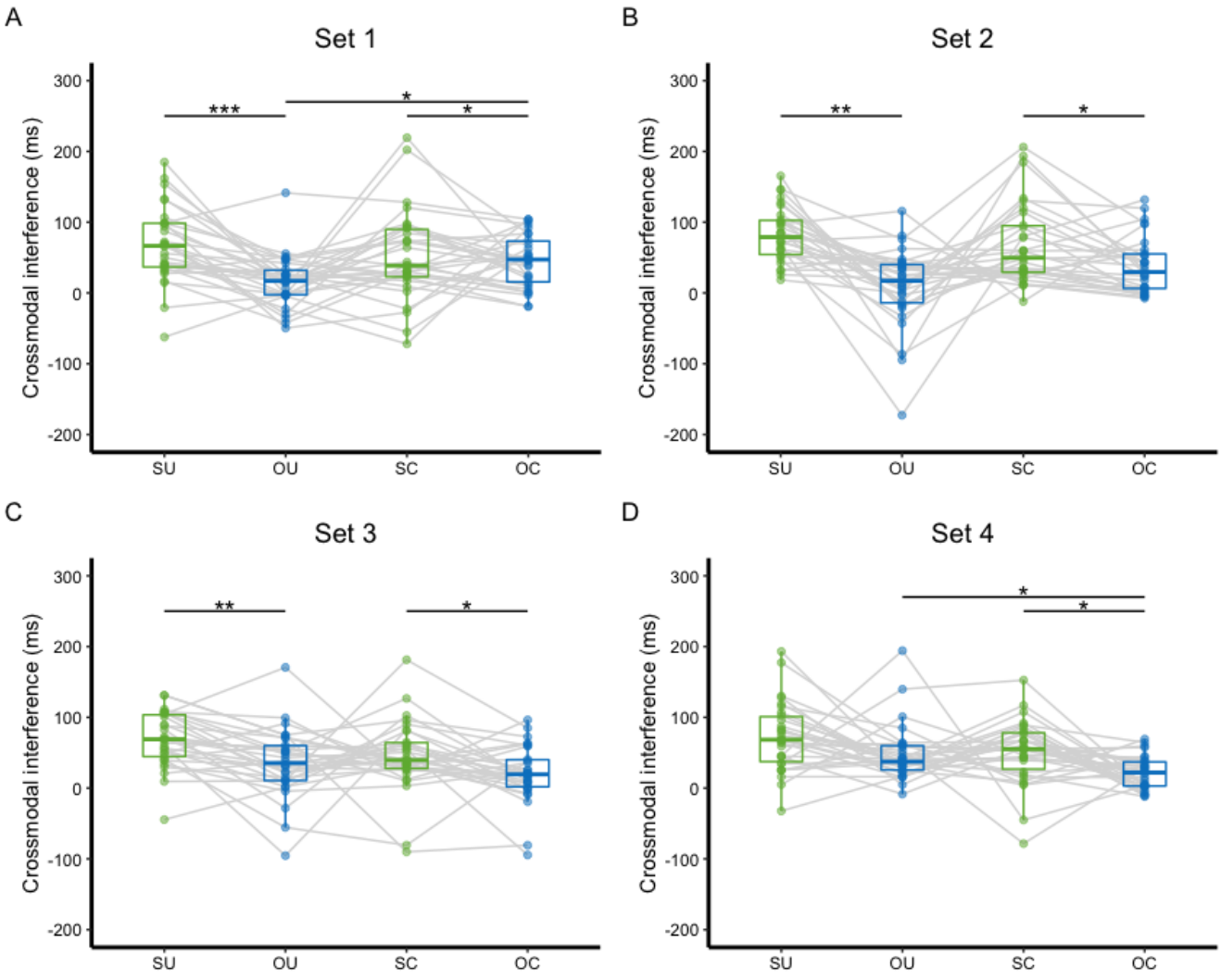

Figure 3. Crossmodal Interference - four-way interaction.
Crossmodal interference shown by Set (1 [passive], 2, 3, 4) Tool Arrangement (uncrossed, crossed) and Visual Field (same [green], opposite [blue]) for reaction times on the Crossmodal Congruency Task (CCT), for all participants (n = 30). Crossmodal interference was calculated by subtracting congruent from incongruent reaction times. Circles depict individual data points, which are connected by grey lines. Medians are depicted by the centre lines. The box limits indicate the 25ht and 75th percentile. The whiskers extend 1.5 times the interquartile range from the box limits. Circles depict individual data points * $p < .05$, ** $p < .01$, *** $p < .001$.

Follow-up analysis (see S3 Table/Appendix 1) of the crossmodal interference scores showed significantly greater interference for same side than opposite side distractors for uncrossed tools for set 1 (passive), $t(29) = 4.84$, $p_{adjusted} < .001$, $d = 1.80$, set 2, $t(29) = 5.59$, $p_{adjusted} = .004$, $d = 2.08$, and set 3, $t(29) = 3.77$, $p_{adjusted} = .004$, $d = 1.40$, but not for set 4, $t(29) = 1.98$, $p_{adjusted} = .124$, $d = 0.74$. Crossmodal interference was also greater for same side compared to opposite side distractors when tools were crossed for set 1 (passive), $t(29) = 2.76$, $p_{adjusted} = .042$, $d = 1.03$, set 2, $t(29) = 2.74$, $p_{adjusted} = .015$, $d = 1.00$, set 3, $t(29) = 2.45$, $p_{adjusted} = .048$, $d = 1.00$, and set 4, $t(29) = 2.84$, $p_{adjusted} = .012$, $d = 1.05$. For visual

distractors appearing in the opposite visual field relative to vibrotactile targets, crossmodal interference was greater for crossed than uncrossed tools for set 1, $t(29) = 2.78$, $p_{adjusted} = .042$, $d = 1.03$. There were no significant differences for opposite visual field distractors between crossed and uncrossed tools for sets 2 and 3 $ts(29) \leq 2.30$, $ps_{adjusted} \geq .058$, $ds \leq 0.85$. For set 4, however, crossmodal interference was greater for uncrossed than crossed tools, when visual distractors appeared in the opposite visual field relative to vibrotactile targets, $t(29) = 3.09$, $p_{adjusted} = .045$, $d = 1.15$. There were no significant differences for visual distractors appearing in the same visual field relative to vibrotactile targets, between crossed and uncrossed tools, $ts(29) \leq 1.71$, $ps_{adjusted} \geq .138$, $ds = 0.64$. Overall, these results show that the expected pattern of differences in interference between crossed and uncrossed conditions, reflecting that the tool tips were incorporated into peripersonal space, was evident in sets 1 (passive), 2, and 3. That is, the magnitude of crossmodal interference for distractors in the same compared to opposite visual field was smaller when tools were crossed compared to uncrossed. However, our results show that this pattern of crossmodal interference was reversed in set 4. Overall, the change in crossmodal interference across the four sets of the CCT task is not consistent with a gradual emergence of the effects of tool-use on peripersonal space over time.

3.3. Tactile distance judgements

There was a significant main effect of Set, reflecting a decrease in TDJ from pre ($M = 9.67$, $SD = 3.19$) to post active tool-use ($M = 10.09$, $SD = 3.36$), when using a one-tailed test on an *a priori* basis, $F(1, 29) = 3.20$, $p = .041$, $\eta_{2p} = .10$. There were no other main effects or interactions for the TDJ, including none involving Sensory Condition, $Fs(1, 29) \leq 2.69$, $ps \geq .111$, $\eta_{2p}s \leq .09$.

3.4. Exploratory analyses

The above results show that the pattern of interference during set 1 of the CCT is consistent with updating of peripersonal space (Fig 4a). This was unexpected, given that set 1 required only passive interaction with the tools. We considered that this could be due to the repeated-measures design of the study. That is, experience with the tool in session 1 might have primed participants to rapidly embody the tools upon grasping the handles of the tools at the beginning of sessions 2 and 3, extending peripersonal space even while passively interacting with the tools. Because the order of the study was counterbalanced, we could investigate this possibility by conducting a between groups analysis of the CCT data from only the first session, when there was no prior experience with the tools. That is, in this exploratory analysis Sensory Condition was treated as a between-subjects factor with ten participants in each of the pain, active placebo, and neutral groups. We conducted two five-way ANOVAs on the RTs and error rates from the first experimental session with Set, Side of Body, Tool Arrangement, Visual Field and Congruence as within-subjects factors; and Sensory Condition as a between-subjects factor. There was no main effect of Sensory Condition on RTs from the CCT, $F(2, 27) = 0.97$, $p = .390$, $\eta_{2p} = .07$. There was no clear effect of Sensory Condition or any interactions of interest for error rates from the CCT during session 1 (see S1 Text/Appendix 1). Furthermore, when the session order was included as a variable in the main analysis there was no change to the key interaction terms. Therefore,

it seems unlikely that the apparent extension of peripersonal space during the first set of the CCT can be attributed to familiarity with the tools due to the repeated-measures design of the study.

To test for any immediate effects of pain on peripersonal space and body representations, we also reanalysed the baseline data from the first session (i.e. prior to tool-use, and treating Sensory Condition as a between-groups factor). We also followed-up these analyses with Bayesian repeated-measures ANOVAs using JASP software (Team, 2018). To calculate the adjusted BF_{10}, we divided the posterior probability of the models, or P(M|data), from the model that included the interaction term of interest, by the model containing all other elements of the first model except from the interaction term of interest (Wagenmakers et al., 2018). For the CCT, there was no evidence of an interaction between Sensory Condition, Tool Arrangement, Visual Field, and Congruence prior to active tool-use (i.e. during Set 1) for reaction times, $F(2, 27) = 1.10$, $p = .348$, $\eta_{2p} = .08$ (adjusted $BF_{10} = 0.40$), or for error rates, $F(2, 27) = 1.50$, $p = .241$, $\eta_{2p} = .10$ (adjusted $BF_{10} = 1.45$). There was no evidence of a difference between Sensory Conditions on TDJs prior to tool-use, $F(2, 27) = 1.21$, $p = .313$, $\eta_{2p} = .08$ (adjusted $BF_{10} = 0.46$). However, as the Bayesian analysis shows, we did not find evidence of no difference between Sensory conditions at prior to tool-use on the CCT or the TDJs (Lee & Wagenmakers, 2014).

To explore the evidence for the null hypothesis, we reanalysed the main interaction terms from the CCT and TDJs that involved Sensory Condition with Bayesian ANOVAs. We found moderate evidence (Lee & Wagenmakers, 2014) of no effect of an interaction between Sensory Condition, Tool Arrangement, Visual Field, and Congruence on RTs from the CCT (adjusted $BF_{10} = 0.12$). We also found moderate evidence of no effect of an interaction between Sensory Condition and Set on TDJs (adjusted $BF_{10} = 0.24$). These findings support our interpretation that pain induction did not interfere with the updating of peripersonal space and body representations.

4. Discussion

Our study aimed to investigate the effect of induced pain on updating of peripersonal space and body representations during and following tool-use. We hypothesised that participants would be less able to update peripersonal space and body representations during pain induction to the arm, compared to the two control conditions. We used a crossmodal congruency task (CCT) and tactile distance judgements (TDJs) to measure updating of peripersonal space and body representations, respectively. The global patterns of the CCT and TDJ were consistent with previously reported effects of tool-use (e.g. Maravita et al., 2002b; Miller et al., 2017). In contrast to our predictions, we found that pain did not interfere with updating of peripersonal space and body representations following active tool-use, when compared to two control conditions (i.e. active placebo, and neutral). That is, we found evidence that the performance on the CCT and TDJ did not differ between sensory conditions. There was also no significant difference in the CCT or TDJ when we explored pain ratings as a covariate. Therefore, experimentally induced pain does not appear to influence the updating of peripersonal space and body representations during and following tool-use.

It is unlikely that the lack of an effect of pain can be attributed to failure of our protocols to induce updating in peripersonal space and body representation. For reaction times from the CCT, we found that reaction times to vibrotactile targets were slower when accompanied by visual distractors in the same visual field compared to the opposite, but this effect was weaker when tools were crossed such that the opposite side visual distractors appeared on the same tools as the vibrotactile targets. These findings are comparable to the results reported by Maravita and colleagues (2002b). We also found that estimates of the felt distance between two points (TDJs) parallel to the axis of the tool decreased in both arms after active tool-use. This is thought to reflect that the body representation has updated to incorporate the tools, and is consistent with previous findings (e.g. Miller et al., 2017). Our study thus replicated evidence of updating peripersonal space and body representations during and after tool-use, but induced pain did not modulate these effects.

It is also unlikely that the absence of a significant effect of pain on peripersonal space and body representation in this study is due to failure of our sensory manipulations or compensatory changes in movements during pain induction. Participants reported experiencing pain throughout the study in the pain condition and not for the two other conditions, indicating that our pain induction was successful. We confirmed that movement patterns were similar for all three conditions by having a condition-blind observer rate videos of participants' movements. We also found that mechanical pain threshold on the finger increased after the pain induction to the arm, and this change in Mechanical Pain Threshold remained until the end of the study. This demonstrates that our manipulation altered sensory processing relevant to the hand. However, mechanical detection thresholds remained unchanged, indicating that the ability to detect a tactile stimulation was the same across sensory conditions. Therefore, our manipulation succeeded in inducing pain, without impairing movement or tactile sensation, and so it is unlikely that our results can be attributed to methodological limitations.

Bodily and spatial representations can be influenced by pain. Previous work has demonstrated that spatial perception can be modified by experimentally induced pain. For instance, the subjective body midline deviated towards a painful thermal stimulation with a large magnitude of effect (Bouffard et al., 2013), and painful cooling can increase the felt size of the thumb (Gandevia & Phegan, 1999). Our results, however, did not show any immediate effect of pain on body and peripersonal space representations. Furthermore, they suggest that briefly-experienced acute pain does not alter the flexibility of such representations to *update* as a result of interaction with objects in our environment (e.g. during tool-use). We can only speculate as to what effect a longer pain duration would have on representations of the body and peripersonal space (i.e. beyond the ~1 hour of pain induced in our experiment), and what differences that might exist between acute and chronic pain. Nonetheless, the outcomes of the current work have ramifications for how we might conceptualise the maintained distortions in body and peripersonal space representations in people with chronic pain. Specifically, our findings could suggest that pain might not be the driving factor preventing normal body representation and peripersonal space from being restored. Therefore, future research should explore whether the plasticity of such representations could be preserved in people with chronic pain, despite their experience of distorted representations of the body and its surrounding space.

An alternative perspective on our results from the CCT, showing no effect of pain, might be offered by the distinction between goal-directed and defensive dimensions of peripersonal space, as proposed by De Vignemont and Iannetti (2015). They conceptualise goal-directed peripersonal space as the space upon which we can act, and defensive peripersonal space as the space in which we might have to react to incoming, and potentially harmful, objects. Research into tool-use largely covers goal-directed movements and tasks, and so Vignemont and Iannetti (2015) speculated that defensive space would not be modulated by tool-use. It could be that the painful stimulation used in our study altered properties of defensive peripersonal space, whereas our task measured changes in goal-directed peripersonal space representations. Although they serve separate functions, there is evidence to suggest that goal-directed and defensive peripersonal space representations can interact. Rossetti and colleagues (2015) showed that incoming painful stimuli, in this case a 4 cm long medical needle, presented both at 20 and 40 cm away from the body triggered an alerting response (as measured by skin conductance response) in healthy participants, but only after active use of a 40 cm tool. This shows that tool-use can modulate a response to an incoming painful stimulus. Our study, however, shows that acute pain does not alter the updating of goal-directed peripersonal space. More research is needed to characterise how goal-directed and defensive peripersonal space representations interact, and how different qualities of pain might influence such interactions. For instance, it could be that acute pain alters defensive peripersonal space in healthy individuals, as is the case in people with trigeminal neuralgia (Bufacchi, Sambo, Di Stefano, Cruccu, & Iannetti, 2017), or that modifications of defensive peripersonal space are limited to approaching painful stimuli (i.e. when there is the potential threat of pain).

Although our findings were qualitatively similar to Maravita and colleagues (2002b) in that we found overall less interference from opposite-side distractors when the tools were crossed compared to uncrossed, these differences were less pronounced in our study. This was despite the fact that we included additional interactive tool-use (beanbag sorting) tasks between the three active sets of the CCT task. We also did not replicate the expected effect of active tool-use on performance on the CCT over time. That is, we did not find that interference effects thought to reflect expansion of peripersonal space increased over time. Instead, we observed a decrease in this pattern as participants spent more time interacting with the tool. Furthermore, we found that participants showed interference effects consistent with expansion of peripersonal space during passive interaction with the tools. It is unclear why our results differ from those reported by Maravita and colleagues (2002b). Although our CCT task replicated that of their study in most respects, a key difference is that we asked participants to indicate the location of the vibrotactile targets using a four-alternative forced choice response (the factorial combination of up-down *and* left-right). Maravita and colleges (2002b) used a two-alternate forced choice response in which participants indicated only the up-down location of the vibrotactile stimuli regardless of the side of space upon which they were presented. We used the four-alternative forced-choice response because we sought to disentangle limb-specific effects of unilateral pain induction. That is, if we had found that pain interfered with updating of peripersonal space and body representations, we aimed to explore whether this interference was restricted to the side of the painful arm, or if pain disrupted these processes more generally. It is possible that our four-alternative forced-choice response added an additional level of spatial incongruence that prevented the emergence of a stronger effect of tool-use in this task, as the crossmodal

congruency effect is driven by the reaction time cost that arises from presenting visual distractors at spatially incongruent locations to tactile targets (Marini, Romano, & Maravita, 2017). For example, in our study spatial incongruence could be created when the tools were crossed and the distractor originated on the same tool and in the same vertical location as the vibrotactile target (i.e. the distractor and target are in opposite visual fields). In the study of Maravita and colleagues (2002b), however, no such spatial incongruence would have been present in such a trial with regards to the response required (up or down), thus making object-based effects easier to interpret. This might explain why we found an overall pattern that was comparable to Maravita and colleagues, indicative of peripersonal space updating, although the effect was less pronounced. Future studies should limit themselves to one level of spatial incongruence (e.g. up/down responses only).

To our knowledge, this was the first study testing changes in TDJs in both arms (rather than just one) following tool-use. This was partly enabled by using a simplified version of the task. Unlike previous studies (e.g. Bassolino, Finisguerra, Canzoneri, Serino, & Pozzo, 2015; Canzoneri et al., 2013; Miller et al., 2014), our TDJ task did not have a reference stimulation (typically administered to the forehead), and included fewer trials (we used one instead of at least eight trials per stimulated distance; Miller et al., 2017). This could be the reason why we found a smaller effect of tool-use on TDJs than has previously been reported. Nonetheless, we still detected the well-characterised effect of tool-use on body representation using this simplified TDJ task. Previous studies using the conventional TDJ task to investigate tool-use have tested only one arm. However, it is conceivable that there could be differences in how body representation is updated in the two arms after tool-use, for example due to differences in activity levels between arms (e.g. Bassolino et al., 2015), or in our case, due to one arm being painful. For instance, judgements about the felt distance between two stimuli are less accurate when they are nociceptive (Mancini, Steinitz, Steckelmacher, Iannetti, & Haggard, 2015) compared to tactile (i.e. a TDJ). However, our results showed no difference between the change in TDJs for the two arms, and that the experience of pain itself does not alter such judgements.

To conclude, we sought to investigate the effect of induced pain on the updating of peripersonal space and body representations during and following tool-use. Our study replicated findings showing that active tool-use updated peripersonal space and body representations. We also successfully induced pain, without impairing movement or tactile sensitivity. However, we found evidence that induced pain did not interfere with *updating* peripersonal space and body representations. When considered with previous results, these results suggest that induced pain can cause a direct change in bodily and spatial perception, but the mechanisms involved in *updating* such representations do not appear to be disrupted. This suggests that any disruption to these processes in pathological pain conditions cannot be sufficiently explained by acute pain.

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Chapter 2 – Conclusions

In this chapter I examined the influence of acute pain on the updating of bodily and spatial representations following tool-use. In agreement with previous research (e.g. Bassolino, Finisguerra, Canzoneri, Serino, & Pozzo, 2015; Canzoneri et al., 2013; Maravita, Spence, Kennett, & Driver, 2002; Marini, Romano, & Maravita, 2017; Miller, Longo, & Saygin, 2014), I found that participants updated the representations of their body and peripersonal space following active tool-use. I also found evidence that such updating did not differ between conditions (i.e. pain induction, placebo, no manipulation). Therefore, pain did not influence the updating of bodily or spatial representations following tool-use. Previous studies had found that pain induction could lead to a directional bias in visuospatial attention (Bouffard, Gagné, & Mercier, 2013), and distort representations of the body (Gandevia & Phegan, 1999). In contrast, the findings from this chapter suggest that the mechanisms involved in updating such representations are unaffected by acute pain.

In the context of the sensorimotor theory of pain, the findings suggests that the altered updating of bodily and spatial representations that can occur in pathological pain (Chapter 3, also described in Chapter 1) cannot be explained by an acute pain sensation. It is of course possible that constant exposure to pain would have a different effect on such updating, compared to the transient and voluntary experience of pain induction. However, if we had found evidence that pain interfered with updating bodily and spatial representations, this would contradict the assumptions made by the sensorimotor theory of pain. Therefore this chapter adds to our understanding of the role of pain in sensorimotor processing, and suggests that any changes in pathological pain conditions cannot be explained by the presence of acute pain.

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Chapter 3: Altered updating of bodily and spatial representations following tool-use in Complex Regional Pain Syndrome

Chapter 3 – Introduction

In this chapter I present a study that examines the updating of bodily and spatial representations in people with CRPS, and in healthy controls. In Chapter 2 I explained how tool-use is a paradigm that enables the updating of bodily and spatial representations to be studied. As I identified in Chapter 1, there is limited research that looks at how these processes may be altered in people with pathological pain conditions. Having up-to-date representations of the body and peripersonal space is important for predicting the consequences of a movement (Shadmehr et al., 2010). The sensorimotor theory of pain would therefore predict that such updating is altered in people with pathological pain conditions.

Distorted representations of the body and its surrounding space are common following immobilisation (Bassolino et al., 2015; Hall et al., 2016; Lissek et al., 2009), and they will quickly return to their normal state once movement is regained (Bassolino, Bove, Jacono, Fadiga, & Pozzo, 2012). However, it could be that the latter processes are disrupted for some people. I therefore hypothesised that the updating of such representations would be less pronounced in people with CRPS. If these representations are more rigid/less malleable, it could explain why distorted representations persist long after any initial injury has healed.

The conditions that the sensorimotor theory of pain was originally proposed to explain tend to be unilateral. Therefore, I was interested in examining whether any impairment in updating bodily and spatial representations was specific to the affected limb, specific to the affected side of the body, or general to people with CRPS. In order to address this question, I examined the updating of bodily and spatial representation in people with upper limb CRPS, and in people with lower limb CRPS. As people with upper limb CRPS can have motor deficits, a weaker or absent effect of tool-use on bodily and spatial representations could reflect that they were unable to perform the task. Therefore, having people with lower limb CRPS complete the tasks overcame some potential confounds of only testing people with an upper limb affected.

The sensorimotor theory of pain predicts that altered sensorimotor processing could result in pain and other physical symptoms. I was interested in examining the latter, as previous studies had suggested a spatial modulation of CRPS symptoms (Moseley, Gallace, Di Pietro, Spence, & Iannetti, 2013; Moseley, Gallace, & Iannetti, 2012). These studies looked at hand temperature asymmetries, which is part of the diagnostic criteria for CRPS (Harden et al., 2010; Harden, Bruehl, Stanton-Hicks, & Wilson, 2007). The studies showed that hand temperature asymmetries reduced when a CRPS-affected hand was placed in the non-affected side of space. Furthermore, by introducing an optical shift to participants' vision, they showed that this effect relied on the represented location, rather than its physical

location. Hand temperature asymmetries therefore present a potential way of assessing the influence of bodily and spatial representation on CRPS symptoms, which also addresses one of the central assumptions of the sensorimotor theory of pain. Consequently, I attempted to replicate previous findings that showed a spatially defined modulation of CRPS symptoms, and to extend them by looking at any influence of updating of bodily and spatial representations.

This chapter will add to our understanding of sensorimotor processing in CRPS. It will shed light on the updating of bodily and spatial representations in CRPS, how specific any differences are, and any relationship they may have on physical symptoms.

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Altered updating of bodily and spatial representations following tool-use in Complex Regional Pain Syndrome

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Abstract

Distorted representations of the body and peripersonal space are common in Complex Regional Pain Syndrome (CRPS), and might modulate its symptoms (e.g. asymmetric limb temperature). In pain-free people, such representations are malleable, and update when we interact with objects in our environment (e.g. during tool-use). Distortions are also common after immobilisation, but quickly normalise once movement is regained. We tested the hypothesis that people with CRPS have problems updating bodily and spatial representations, which contributes to the maintenance of their distorted representations by preventing normalization. We also explored spatially defined modulations of hand temperature asymmetries, and any influence of updating bodily and spatial representations on this effect. Thirty-six people with unilateral CRPS (18 upper limb, 18 lower limb) and 36 pain-free controls completed tool-use tasks considered to alter body and peripersonal space representations (measured using tactile distance judgements and a visuotactile crossmodal congruency task, respectively). We also tested how the arrangement (crossed, uncrossed) of the hands and tools affected hand temperature. In upper limb CRPS the non-affected arm representation updated normally, but the affected arm representation updated in the opposite to normal direction. A similar pattern was seen in lower limbs CRPS, although not significant. Furthermore, people with CRPS showed more pronounced updating of peripersonal space than the controls. We did not observe any modulation of hand temperature asymmetries by the arrangement of hands or tools. Our findings show enhanced malleability of bodily and spatial representations in CRPS, which may suggest that central mechanisms are altered in this condition.

1. Introduction

Distorted representations of the body and its surrounding (i.e. peripersonal) space are characteristic of certain neurological conditions (e.g. asomatognosia [Baier & Karnath, 2008], and hemispatial neglect [Husain & Rorden, 2003; Vallar, 1997, 1998]), and can occur during anaesthesia (Gandevia & Phegan, 1999; Paqueron et al., 2003; Silva et al., 2011), and in chronic pain (Haggard, Iannetti, & Longo, 2013; Senkowski & Heinz, 2016; Tsay, Allen, Proske, & Giummarra, 2015). For instance, aside from pain, motor deficits, and autonomic symptoms, people with Complex Regional Pain Syndrome (CRPS) can perceive their affected limb to be distorted, (partly) missing, and/or larger than its physical size (Bailey, Nelson, Lewis, & McCabe, 2013; Moseley, 2005a; Peltz, Seifert, Lanz, Müller, & Maihöfner, 2011; Schwoebel, Friedman, Duda, & Coslett, 2001). There is also evidence of attentional biases away from the CRPS-affected side of peripersonal space (Bultitude, Walker, & Spence, 2017; Filbrich et al., 2017; Halicka, Vittersø, Proulx, & Bultitude, 2020; Moseley, Gallace, & Spence, 2009; Reid et al., 2016), which are predicted by body representation distortions (Bultitude et al., 2017).

Bodily and spatial representations are use-dependent: they update if our ability to use our limbs is restricted temporarily (e.g. by casting; Hall et al., 2016) or permanently (e.g. by amputation; Canzoneri, Marzolla, Amoresano, Verni, & Serino, 2013a; Makin, Wilf, Schwartz, & Zohary, 2010), or as we interact with objects (De Vignemont & Iannetti, 2015; Macaluso & Maravita, 2010; Martel, Cardinali, Roy, & Farnè, 2016; Medina & Coslett, 2010; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997; Spence, Pavani, Maravita, & Holmes, 2004b). One paradigm that demonstrates the malleability of these representations is tool-use. Tool-use causes the multisensory representations of the body and peripersonal space to update (Cardinali et al., 2012; Martel et al., 2016; Spence et al., 2004b), whereby the nervous system changes the way it uses sensory information to enable tools to become functional and sensory extensions of the body (Miller et al., 2018). For example, using rake-like tools leads to a perceived lengthening of arm and extends peripersonal space towards the distal end of the tool (Canzoneri et al., 2013b).

Distorted representations of the body and peripersonal space might contribute to CRPS pathology by leading to conflicts between sensory and motor signals theorised to trigger pain and other symptoms (Harris, 1999; McCabe & Blake, 2007). These distortions might be due to altered sensory input (Kuttikat et al., 2016), disuse (Punt, Cooper, Hey, & Johnson, 2013), and/or cortical reorganisation of the affected limb's representation (Di Pietro et al., 2013; Juottonen et al., 2002; Maihöfner, Handwerker, Neundörfer, & Birklein, 2003; Pleger et al., 2006; Vartiainen, Kirveskari, & Forss, 2008), although the latter is challenged by recent findings (Di Pietro, Stanton, Moseley, Lotze, & McAuley, 2015; Mancini et al., 2019). Whatever the mechanism, altered body representation ("neglect-like symptoms") predicts worse pain outcomes in chronic CRPS (Wittayer, Dimova, Birklein, & Schlereth, 2018), and treatments targeting bodily and spatial representations (e.g. graded motor imagery (Moseley, 2004, 2005b, 2006), and prism adaptation (Bultitude & Rafal, 2010; Christophe et al., 2016; Sumitani et al., 2007) appear to reduce pain and other CRPS symptoms (Boesch, Bellan, Moseley, & Stanton, 2016).

Altered bodily and spatial representations are common after limb immobilisation (Bassolino, Finisguerra, Canzoneri, Serino, & Pozzo, 2015; Hall et al., 2016; Lissek et al., 2009), but

these effects typically reverse once normal movement is restored (Bassolino, Bove, Jacono, Fadiga, & Pozzo, 2012). As the distorted representations in CRPS persist, this could be due to problems with *updating* such representations. Here, we present a study investigating the updating of body and peripersonal space representations following tool-use in people with and without CRPS. We used tactile distance judgements (TDJs) (Bassolino et al., 2015; Canzoneri et al., 2013b; Miller, Longo, & Saygin, 2014; Miller, Longo, & Saygin, 2017) and a crossmodal congruence task (CCT) (Maravita, Spence, Kennett, & Driver, 2002) to examine tool-use-dependent changes in body and peripersonal space representations, respectively. We hypothesised that people with CRPS would be less able to update bodily and spatial representations than pain-free individuals, as indicated by different effects of tool-use on their TDJs and CCT responses.

Furthermore, CRPS symptoms can be spatially modulated (Moseley, Gallace, & Iannetti, 2012) depending on the *represented* location in space rather that the limb's physical position (Moseley, Gallace, Di Pietro, Spence, & Iannetti, 2013), and manipulations of bodily experience can alter skin temperature (Hohwy & Paton, 2010; Moseley et al., 2008; Salomon, Lim, Pfeiffer, Gassert, & Blanke, 2013). We therefore adapted previous protocols (Moseley et al., 2013; Moseley et al., 2012) to explore any modulation of hand temperature asymmetry by the arrangement of embodied tools. We hypothesised that hand temperature asymmetries would reduce when people with upper limb CRPS rested their hands – or the tools - in a crossed, compared to uncrossed, arrangement.

2. Method

2.1 Design

We used a mixed design with one session to measure tool-use-dependent changes in the representations of the body and peripersonal space, and hand temperature asymmetry. We compared these variables between people with upper limb CRPS, lower limb CRPS, and pain-free individuals. In line with recent recommendations for pain research (Lee et al., 2018), the study protcol and planned analyses were preregistered on the Open Science Framework (https://osf.io/pjdw9).

2.2 Participants

The inclusion criteria for all participants in the study were that they be aged over 18, have normal or corrected to normal vision, and have sufficient arm strength to manoeuvre the tools. Exclusion criteria were a history of brain injury or disorder (e.g. stroke, multiple sclerosis, Parkinson's disease), or psychiatric disorders that might be associated with pronounced perceptual changes (e.g. schizophrenia; Tseng et al., 2015). We did not exclude participants who reported a history of depression or anxiety. Additional inclusion criteria for people with CRPS were that they met the Budapest research criteria for CRPS type I or II (Harden, Bruehl, Stanton-Hicks, & Wilson, 2007) primarily affecting one upper or one lower limb. Additional exclusion criteria for the pain-free controls were that they had chronic pain (defined as having experienced pain most days for 3-months or more). Control

participants were matched to an individual with CRPS for age (± 5 years), sex, and self-reported handedness. Participants were reimbursed £10 per hour for their time, along with travel and accommodation expenses where relevant. The study adhered to the 2013 Declaration of Helsinki, and received ethical approval from the UK Health Research Authority (REC reference 12/SC/0557) and the University of Bath Psychology Department Ethics Committee (16-236).

Our sample size calculations for a 4-way repeated-measures ANOVA suggested that 17 participants would be needed in each group to detect a medium effect size (f(U) = 0.25), with an alpha of 0.05, and 80% power. We also calculated a 'safeguard power analysis' (Perugini, Gallucci, & Costantini, 2014), which overcomes some of the issues with basing sample size estimates on pilot work (Albers & Lakens, 2018). That is, we calculated an 80% confidence interval (CI) around the effect size that we obtained from our pilot data for the interaction between Tool Arrangement, Visual Field, and Congruence, on reaction times from the CCT, 80% CI = [0.32, 0.68]. Next, we calculated the sample size needed to detect the lower boundary of this effect (i.e. η_{2p} = .32) using MorePower 6.0.4 (Campbell & Thompson, 2012), which suggested that we would need 20 participants to replicate this 2x2x2 within-subject interaction. The largest number of order combinations in our counterbalancing was six. We considered the number of people with CRPS we could feasible recruit for each Group, whilst retaining even counterbalancing. Based on these estimates and considerations we decided to recruit 18 participants for each Group (i.e. lower limb CRPS, upper limb CRPS, lower limb controls, upper limb controls). One person with upper limb CRPS was not able to complete all the tasks, so we recruited an extra participant for this group (i.e. 19 people with upper limb CRPS). Therefore, 37 people with CRPS participated in the study (*M* age = 46.6, *SD* = 12.5; 27 female; 32 right-handed; see Tables 1 & 2 for clinical and demographic details). One person with left lower limb CRPS also had the left side of her torso affected. One person with CRPS in his left foot also had less severe CRPS in his left arm. One person with CRPS in her right hand also reported undiagnosed pain in her right foot, which she described as a "CRPS-like" sensation, although she did not show any signs of CRPS or experience any other symptoms of CRPS in this foot. All other participants with CRPS had only one limb affected. Sixteen of the people with CRPS also reported other pain diagnoses, such as fibromyalgia, that they considered less disabling or intrusive than their CRPS. Thirty-six pain-free individuals (*M* age = 45.8, *SD* = 13.7; 27 female; 32 right-handed) took part as control participants.

Table 1. Upper limb CRPS clinical and demographic information.

ID	Age	Sex	Self-reported hand-edness	Location & type	$CRPS_{sev}$	Duration (months)	Baseline pain (/10)	CRPS BPD (/57)	SF-MPQ-2 (/10)	Inciting event	Medication	Comorbidities
UL1	30	F	R	R-II	13	12	4	28	3.05	Crushed elbow	Gabapentin, oxycodone, nortriptyline, paracetamol, ibuprofen	
UL2	73	F	R	R-II	11	21	7	39	3.00	Carpal tunnel surgery	None	
UL3	61	M	R	L-I	12	48	4	16	1.27	Hand surgery	Paracetamol, aspirin, simvastatin, methotrexate, ramipril, bisoprolol fumarate, levothyroxine sodium, folic acid	Frozen joints
UL4	38	F	R	R-I	10	59	7	38	7.41	Minor soft tissue damage of the thumb	Amitriptyline, tramadol, naproxen, lidocaine	Pain in R foot[u]
UL5	31	F	L	L-I	12	19	8	42	7.81	Unknown	Gabapentin, naproxen, cannabidiol, buprenorphine, omeprazole	Fibromyalgia, migraines, polycystic ovaries, asthma
UL6	64	F	L	L-I	10	79	2	5	2.50	Elbow spiral fracture	Paracetamol	Fibromyalgia
UL7	32	F	R	L-I	13	27	7	30	7.77	Wrist surgery	Amitriptyline, gabapentin, codeine, tramadol, paracetamol, fluoxetine hydrochloride	Fibromyalgia, asthma

ID	Age	Sex	Self-reported hand-edness	Location & type	$CRPS_{sev}$	Duration (months)	Baseline pain (/10)	CRPS BPD (/57)	SF-MPQ-2 (/10)	Inciting event	Medication	Comorbidities
UL8	66	M	R	R-I	12	113	7	10	1.68	Soft tissue injury of the arm	Pregabalin, nortriptyline	
UL9	71	F	R	R-I	10	76	4		0.77	Soft tissue injury of the hand	Paracetamol	
UL10	51	F	R	L-I	13	57	8	28	6.32	Shoulder surgery	Gabapentin, tapentadol, paracetamol, ibuprofen, zolpidem tartrate	
UL11	57	F	R	R-I	12	60	2	13	2.05	Unknown	Amitriptyline, paracetamol, duloxetine	
UL12	30	F	R	R-I	9	73	4	25	1.55	Elbow fracture, torn ligaments in wrist	Gabapentin, meptazinol, sertraline	Chronic migraines, hypermobility, fibromyalgia
UL13	57	F	R	R-I	10	123	2	24	1.36	Multiple hand fractures	Ibuprofen	
$UL14_{T}$	53	F	R	L-I	11	2	3	37	2.23	Elbow fracture	Amitriptyline, co-codamol, paracetamol, lansoprazole	

ID	Age	Sex	Self-reported hand-edness	Location & type	$CRPS_{sev}$	Duration (months)	Baseline pain (/10)	CRPS BPD (/57)	SF-MPQ-2 (/10)	Inciting event	Medication	Comorbidities
UL15	50	F	R	L-I	12	65	6	40	5.50	Breast cyst drainage	Gabapentin, lidocaine, baclofen, rizatriptan, citalopram hydrobromide	
UL16	36	F	R	R-I	11	137	1	24	7.32	Wrist fracture	Pregabalin, co-codamol, duloxetine	
UL17	49	F	R	L-I	10	66	5	20	4.50	Wrist surgery	Tramadol, tapentadol	Arthritis, migraines
UL18	38	F	R	L-I	9	34	7	14	7.41	Surgery for dislocated shoulder	Morphine, paracetamol	Migraines, polycystic ovaries
$UL19_{noT}$	47	F	R	L-I	11	3	8	5	5.86	Arm fracture	Pregabalin, lidocaine, naproxen	
M (SD)	*48.95 (14.08)*				*10.89 (1.78)*	*46.01 (36.45)*	*5.05 (2.34)*	*23.58 (12.32)*	*4.18 (2.59)*			

CRPS BPD = Bath CRPS Body Perception Distortion scale (Lewis et al., 2007). $CRPS_{sev}$ = CRPS Severity Score (Harden et al., 2017) (/16). Duration = months since CRPS diagnosis. noT = no temperature recordings. SF-MPQ-2 = Short-form McGill Pain Questionnaire (Dworkin et al., 2009), total score. T = temperature recording only. U = undiagnosed.

Table 2. Lower limb CRPS clinical and demographic information.

ID	Age	Sex	Self-reported Hand-edness	Location & type	$CRPS_{sev}$	Duration (months)	Baseline pain (/10)	CRPS BPD (/57)	SF-MPQ-2 (/10)	Inciting event	Medication	Comorbidities
LL1	48	F	R	L-I	13	78	7	24	4.64	Unknown	Amitriptyline, pregabalin, morphine, naproxen, omeprazole, simvastatin	Tendonitis, Raynaud syndrome, sleep apnoea
LL2	42	M	R	R-I	13	8	8	56	8.59	Slipped disk	Gabapentin, epidural, paracetamol, ibuprofen	Arthritis, osteoporosis
LL3	33	M	R	L-I	13	30	8	36	5.41	Ankle fracture	Gabapentin, tramadol, levocetirizine dihydrochloride	CRPS arm (L; $CRPS_{sev}$ = 8/16), IBS
LL4	41	F	R	L-II	14	56	8	17	4.32	Spontaneous	None	Arthritis, lymphedema
LL5	50	M	R	L-I	13	43	8	21	5.64	Shin fracture	Gabapentin	Arthritis
LL6	32	F	R	L-I	11	48	7	38	4.45	Knee surgery	Paracetamol, ibuprofen	Hypermobility
LL7	56	F	L	L-I	9	13	5	30	2.05	Abdominal surgery	Codeine, naproxen, zopiclone	CRPS torso (L)
LL8	46	F	R	L-I	11	170	6	35	7.45	Abdominal surgery	Naproxen, citalopram hydrobromide	
LL9	52	F	R	L-I	14	37	10	22	8.09	Unknown[a]	None	Back pain

ID	Age	Sex	Self-reported Hand-edness	Location & type	$CRPS_{sev}$	Duration (months)	Baseline pain (/10)	CRPS BPD (/57)	SF-MPQ-2 (/10)	Inciting event	Medication	Comorbidities
LL10	57	F	R	R-II	14	349	10	17	6.36	Foot, ankle, and skull fracture	Pregabalin, morphine sulphate, paracetamol	
LL11	32	M	R	L-II	15	17	7	24	7.14	Crushed foot	Tramadol, pregabalin, lidocaine	
LL12	28	F	L	L-I	14	21	9	21	7.55	Foot surgery	Pregabalin, paracetamol	
LL13	59	M	R	L-II	13	113	7	45	5.95	Ankle compound fracture	Amitriptyline, gabapentin, paracetamol, duloxetine, atorvastatin, colecalciferol, felodipine	Knee pain (L), shoulder pain (L), type 2 diabetes
LL14	43	F	R	R-II	14	18	8	45	8.36	Foot fracture	Gabapentin, levocetirizine dihydrochloride, prednisolone, adrenaline (for allergy to nuts, latex, penicillin)	
LL15	59	F	R	L-I	12	21	7	25	7.68	Crushed ankle	Amitriptyline, lidocaine, atorvastatin, amlodipine besilate	
LL16	49	M	R	R-I	9	16	9	50	8.14	Crushed foot	Pregabalin, codeine, nortriptyline, paracetamol	Phantom pain from amputated toe (R), back and bilateral shoulder pain, type 2 diabetes, hypertension

ID	Age	Sex	Self-reported Hand-edness	Location & type	$CRPS_{sev}$	Duration (months)	Baseline pain (/10)	CRPS BPD (/57)	SF-MPQ-2 (/10)	Inciting event	Medication	Comorbidities
LL17	33	M	R	R-I	14	28	5	42	8.05	Crushed leg	Pregabalin, tramadol, nortriptyline, buprenorphine, sertraline	
LL18	41	F	R	L-I	12	35	5	41	6.91	Knee surgery	Amitriptyline, zomorph, morphine sulphate, paracetamol, citalopram hydrobromide, omeprazole	Knee pain (R), back pain
M (SD)	*44.50 (10.04)*				*12.67 (1.71)*	*61.06 (82.58)*	*7.59 (1.46)*	*32.72 (11.99)*	*6.39 (1.79)*			

a = symptoms may have been present since she had polio as a child. CRPS BPD = Bath CRPS Body Perception Distortion scale (Lewis et al., 2007). $CRPS_{sev}$ = CRPS Severity Score (Harden et al., 2017) (/16). Duration = months since CRPS diagnosis. IBS = irritable bowel syndrome. noS = no other symptoms. SF-MPQ-2 = Short-form McGill Pain Questionnaire Dworkin et al., 2009), total score.

2.3 Protocol

The protocol (see Fig. 1) was similar to that for our previous work examining the effect of experimentally induced pain on updating of bodily and spatial representations (Vittersø, Halicka, Buckingham, Proulx, & Bultitude, 2019). All participants provided informed written consent prior to undergoing a clinical assessment and completing self-report questionnaires. They then completed hand temperature recordings and TDJs before and after interacting with tools (see Fig. 2). Broadly speaking, interactive tool-use consisted of two tasks, further detailed below: the CCT and a beanbag sorting task. Participants were debriefed and given the opportunity to ask questions at the end of the study.

Figure 1. Study outline.
The study's procedure is outlined. For the first set of temperature recordings (red boxes), the participant's hand's temperature were recorded from their hands whilst the hands rested in a crossed and an uncrossed Arrangement. For the second set of temperature recordings, the temperatures were recorded with the hands uncrossed whilst holding the tools in a crossed and an uncrossed Arrangement. For the final temperature recordings we only measured hand temperature for the two tool Arrangements (tools crossed, tools uncrossed). The same counterbalancing order was used for the order of hand/tool Arrangement conditions for all the temperature recording Sets. Tactile Distance Judgements (TDJs; green boxes) were performed on the affected and non-affected arms (order counterbalanced), pre and post active tool-use. The experimenter changed the tools between the crossed and uncrossed Arrangements during the passive stage of the Crossmodal Congruency task (CCT; green boxes), in a counterbalanced order. During the active stages of the CCT (active 1, active 2, active 3), participants changed the tool Arrangement (crossed, uncrossed) by manoeuvring the tools themselves (see Fig. 2). The beanbag sorting task involved retrieving and sorting 12 beanbags, using the same tools that were used for the CCT (see Fig. 2). All tasks that involved active tool-use are depicted with shaded boxes (i.e. CCT sets 2-4, and beanbag sorting tasks). The blue vertical arrows indicate timings of pain ratings that were recorded before, during, and/or after the TDJs and CCT. In addition, participants gave 8 pain ratings for each Arrangement, during each set of temperature recording Sets.

2.3.1 Clinical assessment and self-report questionnaires

We conducted a clinical assessment of CRPS symptoms on the affected limb and contralateral non-affected limb. For control participants, we examined either their upper limbs or lower limbs, depending on where the patient that they were matched to had CRPS. When possible, we examined the same location as the person with CRPS. However, if the

control participant was tested prior to the person with CRPS (n = 11), or control participants were uncomfortable with using the CRPS-affected location for the person they were matched with (e.g. near the groin; n = 2), we used the wrist or ankle as a proxy location. We visually assessed swelling, colour differences, and/or changes in hair and nail growth, and took photos of the most painful site and wrists/ankles in case there was any need for later verification/clarification of any of the clinical features. We used the figure of eight method to measure the swelling of ankles (Petersen et al., 1999; Tatro-Adams, McGann, & Carbone, 1995) or wrists (Pellecchia, 2003). We used a goniometer to quantify inversion, eversion, flexion, and extension of the ankle; or radial, ulnar, flexion, and extension of the wrist. We used a handheld infrared thermometer with an 8:1 distance to spot size ratio to measure the temperature of participants' most painful site and equivalent location on the contralateral limb, as well as their hands (dorsal and palmar surface of the thenar muscle), or ankles (flexor digitorum brevis). Seven pinprick stimulators (MRC Systems GmbH, Germany), ranging from 8 mN to 512 mN in force, were used to measure Mechanical Pain Threshold. Mechanical Detection Threshold was measured using 20 Von Frey Filaments (BioSeb, France), ranging from 0.008 g to 300 g in force. An Exacta™ two-point discriminator (North Coast Medical, USA) with pairs of rounded tips ranging from distances of 2 mm to 20 mm apart was used to assess Two Point Discrimination Threshold. Allodynia was assessed using a paintbrush, cotton buds, and cotton wool. We assessed Mechanical Detection Threshold, Mechanical Pain Threshold, and allodynia following the procedure of the German Research Network on Neuropathic Pain (Rolke et al., 2006). We assessed Two Point Discrimination Threshold on participants' middle finger pads. For the descriptive statistics, we expressed Mechanical Detection Threshold, Mechanical Pain Threshold, allodynia, and Two Point Discrimination Threshold as the difference between the two testing locations (i.e. affected/non-dominant, non-affected/dominant), by subtracting the scores from the non-affected side from the CRPS-affected side (Rolke et al., 2006).

For all but eight participants with upper limb CRPS, the clinical assessment was performed at the beginning of the research session. For the other eight participants, the clinical assessment was conducted in conjunction with a different study (Halicka, Vittersø, Proulx, & Bultitude, 2019) in which they participated on the same day or within the 24 hours preceding the current study.

Following the clinical assessment, participants completed self-reported questionnaires. We used the Edinburgh Handedness Inventory (EHI; Oldfield, 1971) to quantify hand dominance. EHI scores range from -100 to 100, which reflect extreme left or right handedness, respectively. To characterise body perception, we used the Bath CRPS Body Perception Disturbance (BPD) scale (Lewis & McCabe, 2010). The BPD has items about awareness of, attention to, emotional valance of, and desire to amputate the affected area, with higher scores suggesting a greater distortion in body perception (range 0 - 57). We used the Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2) to assesses mean intensity of 22 pain descriptors (Dworkin et al., 2009). A higher score on the SF-MPQ-2 indicates worse pain (range 0 - 10).

Because some changes in the perception of bodily and peripersonal space appear to resemble spatial attention deficits shown by patients with hemispatial neglect following stroke (Legrain, Bultitude, De Paepe, & Rossetti, 2012), participants were screened for

visual, tactile, and motor neglect and/or extinction using confrontation tests (see supplemental digital content/Appendix 2). We used unilateral or bilateral finger movements, light taps of the knee(s), or movements of the arm(s), to test visual, tactile, and motor domains, respectively. Tactile and motor neglect and/or extinction was examined with the participant's eyes open, and eyes closed. Any omissions on the confrontation tests were recorded.

2.3.2 Hand temperature recordings

We sought to replicate spatially defined hand temperature modulations (i.e., a reduction in hand temperature asymmetries for crossed, compared to uncrossed hands) that have previously been reported for people with upper limb CRPS (Moseley et al., 2012). Our main interest in replicating this effect was that we wanted to explore whether active tool-use could result in hand temperature modulations that were dependent on the position of the tools, not just the hands. That is, we aimed to explore whether crossing the tools after active tool use (and after bodily and spatial representations were updated) would result in similar spatially defined hand temperature modulations as crossing the hands. Such a finding would further support the notion that spatially defined modulation of hand temperature is dependent on the *represented* rather than *actual* location of the limbs (Moseley et al., 2013). Participants completed three sets of temperature recordings: two prior to tool-use, and one post tool-use. For all temperature recordings, participants were seated at a table with their head resting on a chin rest. Wireless thermometers (DS1992L Thermochron iButton®, Maxim Integrated, San Jose, USA) were secured to a central point on the dorsal surface of each hand (CRPS-affected side/non-dominant, non-affected side/dominant) using microporous tape. The thermometers have been validated for skin temperature measurement (Smith, Crabtree, Bilzon, & Walsh, 2009; van Marken Lichtenbelt et al., 2006). They have also been used previously for similar research (Calzolari, Gallace, Moseley, & Vallar, 2016), and have comparable thermal resolution (0.0625˚C) to the thermal measures used to demonstrate spatially defined hand temperature modulations in CRPS (2013; 2012). The thermometers were programmed in OneWireViewer (version 0.3.19.47, Maxim Integrated, San Jose, USA). The flat, circular surface of the thermometers in contact with participants' skin had a diameter of 16 mm.

We made adjustments to the seating arrangement to accommodate people with CRPS when needed (e.g. using cushions, and/or keyboard wrist rests). During the temperature recordings, participant gave pain ratings every minute (8 per Arrangement, per Set), and were engaged in light conversation with the experimenter. The experimenter also monitored any hand movements via a computer feed from a camera placed in front of participants' hands, and he reminded participants to keep their hands still if they moved. There was no restriction on participants' gaze during the temperature recordings.

Across the entire study, hand temperature was recorded three times corresponding to three Effector Conditions [hands, t1 tools (pre tool-use), t2 tools (post tool-use)], each Condition consisting of two Arrangements (crossed, uncrossed). See supplemental digital/Appendix 2 content for a full description of the procedure.

Each hand Arrangement began with a two-minute rest period, after which we recorded the temperature from each thermometer every 12 seconds (i.e. 0.08 Hz) for seven minutes, resulting in 36 temperature recordings for each hand in each Arrangement. We expected to see smaller hand temperature asymmetries for crossed compared to uncrossed hands for people with upper limb CRPS. We did not expect to see any spatially defined modulations of hand temperature asymmetries in the other two Groups (lower limb CRPS, controls).

Once the temperature recordings for the two hand Arrangements were completed, we repeated the same procedure while manipulating the Arrangements (crossed, uncrossed) of the tools instead of the hands (i.e. the t1 tools [pre tool-use] Condition]). Participants gripped tools that were in a crossed or an uncrossed Arrangement (order counterbalanced). Participants hands remained uncrossed (i.e. they did not cross the body midline) during both Tool Arrangement conditions. In the crossed Arrangement, only the tools crossed into the opposite side of space (e.g. the distal end of the left tool extending into the right side of space, and vice versa). The tools were propped up during the temperature recordings so that participants did not have to exert any effort keep the tools in position. The experimenter moved the tools between the two Arrangements so that the participant was not required to actively use the tools. We repeated the temperature recordings for the two tool Arrangements at the end of the study (i.e. t2 tools [post tool-use] Condition). See the supplemental digital content/Appendix 2 for more details.

2.3.3 Tactile Distance Judgements

TDJs have been used to characterise changes in body representations following active tool-use (e.g. Bassolino et al., 2015; Canzoneri et al., 2013b; Miller et al., 2014; Miller et al., 2017). Participants made two Sets of TDJs for each Side of Body (affected/non-dominant, non-affected/dominant): once immediately before and once after active tool-use. TDJ tasks in previous studies typically use eight or more repetitions of each distance (Miller et al., 2017), however we used an adapted version with only one repetition of each distance. We did this because we were concerned that repeated tactile stimulation near to, or on the affected area would cause pain in people with upper limb CRPS, and potentially trigger a pain flare that would interfere with both their TDJs and their performance on the other study tasks. We also wished to keep the task as brief as possible because we were interested in comparing the judgements for the two arms, hence we needed to make this task quick enough to capture any potentially short-lived effects of tool-use (Farnè & Làdavas, 2000). In a previous study (Vittersø et al., 2019) we were able to detect tool-use dependent changes in TDJs using this shorter version of the TDJ task. We used the same materials, and procedure for the TDJs as for our previous study (Vittersø et al., 2019). Two flat-ended circular rods (1 mm diameter) were attached to a bow compass to enable the experimenter to accurately adjust the distance between the two points. We administered the TDJs by applying the flat-ended circular rods to the radial side of participants' forearms (i.e. proximal-distally) while participants gripped the tools. The distance between the two rods was 4, 6, or 8 cm. In each Set of TDJs, we applied each distance once in a randomised counterbalanced order. We blocked participants' vision of their stimulated arm with a cardboard box. Participants gave estimates of the perceived distance between the two felt points using a diagram with 22 lines of different lengths (0.5 cm to 11.5 cm, with 0.5 cm increments). We used the same diagram for all TDJ estimates. In each Set, the TDJs were

completed on both arms in a counterbalanced order. We expected that control participants would show a decrease in felt distance between two points, from pre to post tool-use, to indicate updating of body representation and a perceived reduction in arm length. We expected this effect to be smaller or absent in people with CRPS, which would indicate problems with updating.

2.3.4 Tool-use: Crossmodal Congruency and Beanbag Sorting Tasks

The Crossmodal Congruency task (CCT) was conducted with an adapted version of the materials and procedures used by Maravita and his colleagues (2002). This task introduces a conflict between visual and tactile information. The magnitude of this interference effect is thought to reflect perceptual, attentional, and response-related factors (Marini, Chelazzi, & Maravita, 2013; Marini, Romano, & Maravita, 2017). The CCT has been widely used to measure changes in peripersonal space that arise from active tool-use (Macaluso & Maravita, 2010; Martel et al., 2016), inferred from changes in interference patterns (although see Holmes [2012]) for an alternative interpretation). There were four Sets of the CCT across the entire session: passive, active 1, active 2, and active 3. In the active Sets, participants responded to vibrotactile stimuli originating from the handles of tools in the presence of visual distractors originating from the ends of the tools, crossing and uncrossing the tools every four trials. The passive Set was similar, but instead of the participants moving the tools, the experimenter moved the tools from the crossed to uncrossed Arrangement (or vice versa) half-way through the Set. The materials that we used for the CCT were from our previous study examining the effect of experimentally induced arm pain on updating of spatial and bodily representations in pain-free controls (Vittersø et al., 2019). We used two aluminium tools that resembled golf clubs (75cm long, Fig. 2), with two red Light Emitting Diodes (LEDs) embedded in the 'blade' at the distal end of each tool. The handle of each tool was embedded with two electromagnetic solenoid-type stimulators (Tactor Minature Stimulators, Dancer Design, United Kingdom). A 4-channel amplifier (TactAmp 4.2, Dancer Design, United Kingdom) operated by Matlab 2014b (MathWorks) controlled the LEDs and the vibrotactile stimulators. Each tool had one LED and one vibrotactile stimulator positioned above the central axis of the tool, and one LED and one vibrotactile stimulator below it. Each tool had a wooden peg attached vertically in the 'blade'. To ensure that the distal ends of the tools always returned to the same position (e.g. after each time the tools were crossed or uncrossed), these pegs slotted into holes in a wooden board (80 x 100 cm). The slots were 15 cm from the distal end of the board, and 15 cm left or right of the central axis of the board. Near the proximal ends of the tools there were gel wrist rests, which allowed participants to rest their hands whilst they held the tools.

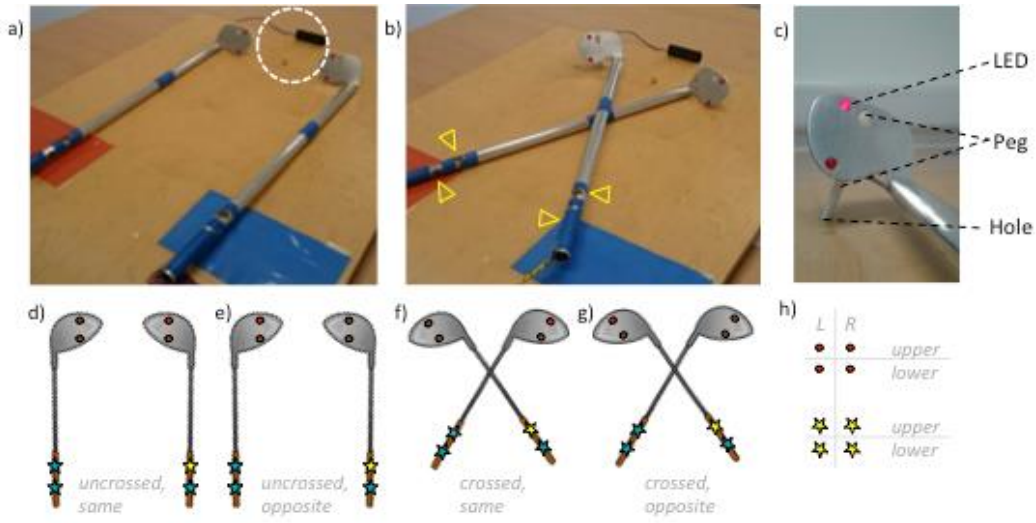

Figure 2. Equipment.
Tools used for the Crossmodal Congruency and Beanbag Sorting Tasks. The tools are depicted in their uncrossed (a, d, e), and crossed (b, f, g) Arrangements. The close-up of the distal end of a tool (c) shows the location of two red Light Emitting Diodes (LEDs) embedded in the 'blades' of the tools, which also had a vertical peg attached (white oval) that slotted into holes in the wooden board. The pegs ensured the positions of the distal ends of the tools were consistent for crossed and uncrossed trials. The blue lines midway along the tools' shaft indicated the location at which the tools should be crossed (b). Vibrotactile stimulators were embedded in the handles of the tools, indicated by yellow triangles (b), and illustrated by stars (d, e, f, g, h). A fixation light (off-white LED) was positioned mid-way between the ends of the tools, illustrated by red dots (d, e f, g, h), in line with the participant's sagittal plane. A webcam (a, b) was placed beyond the distal ends of the tools, also aligned with participant's sagittal plane. The fixation light, and webcam are highlighted with a white dotted circle (a). Visual targets were presented in the same (d, f), or opposite (e, g) Visual Field relative to vibrotactile targets (e.g. L + L, and L + R, respectively [h]). The vertical arrangement of visual targets (i.e. Congruence) was either congruent (e.g. lower + lower [h]; d, e, f, g), or incongruent (e.g. lower + upper [h]). Hence, there were four possible visual, and vibrotactile stimulus locations (h) for each tool, which were repeated for each of the Tool Arrangements (uncrossed, crossed), giving a total of 32 possible combinations. Participants completed all possible combinations of Tool Arrangement, Visual Field, and Congruence in a random order every 32 trials, three times per Set (passive, active 1, active 2, active 3), resulting in 96 trials per Set and a total of 384 trials. Fig 2. is reused with permission (CC BY 4.0) from Vittersø et al. (2019).

During the CCT participants wore headphones that played white noise to mask the sound of the vibrotactile stimulators. They also rested their head on a chin rest to ensure a consistent head position. During the CCT, participants fixated on an off-white LED located at the same distance from the participant as the ends of the two tools, equally far from both tools and in line with participants' sagittal planes. The experimenter was seated behind participants and monitored their gaze on a computer feed delivered from a camera positioned 20 cm behind the end of the board, aligned with the chinrest and fixation LED. A second webcam was positioned directly below the first one and was angled such that participants' movement could be recorded during the CCT for offline evaluation of movement quality.

Each trial consisted of three 50 ms bursts of vibrotactile stimulation delivered to the thumb ("upper" location) or middle finger ("lower" location) of the left or right hand, separated by 50 ms. We decided to use this arrangement to be consistent with Maravita and colleagues' (Maravita et al., 2002) study, although tactile processing may be more efficient when assuming a 'standard posture' of the body (i.e. fingers and thumbs in an upper and lower position, respectively; Romano, Marini, & Maravita, 2017; Romano et al., 2019a). Our arrangement was intended to make it easier for participants to grasp and manoeuvre the tools, whilst ensuring the dynamic touch needed for tool-integration (Bruggeman, Kliman-Silver, Domini, & Song, 2013; Ritchie & Carlson, 2013). However, two participants with upper limb CRPS were unable to reach the vibrotactile stimulators with the middle finger of their affected side. Instead, one used the ring finger and the other her little finger. For each trial there were also three 50 ms flashes ("distractors") from the red LEDs at the ends of the tools. To maximise crossmodal interference the distractors preceded each vibrotactile stimulation by 30 ms (Spence, Pavani, Maravita, & Holmes, 2004a). Participants were required to indicate the location of the vibrotactile stimulation as quickly and accurately as possible, while ignoring the visual distractors. Participants' responses were collected with two triple switch foot pedals (Scythe, USA) with custom software. If participants' responses were incorrect or had latencies greater than 3000 ms, all four LEDs flashed three times. Prior to starting the CCT, participants completed a practice set of 16 trials without moving the tools and in the uncrossed Arrangement. This practice set was designed to enable the participants to become accustomed to the task and its response format, and was repeated until the participant responded correctly on >80% of trials.

Participants with upper-limb CRPS and their matched controls were asked to indicate the location of the vibrotactile stimulus using four-alternate forced-choice responses - left "upper" (thumb), left "lower" (finger), right "upper" (thumb), or right "lower" (finger) – by depressing the pedal under their left toe, left heel, right toe, or right heel, respectively. This protocol was altered from the CCT of Maravita and his colleagues (Maravita et al., 2002), which used a two-alternate forced-choice response format (i.e. upper or lower, independent of body side). We added left/right judgements for people with upper-limb CRPS and their matched controls to enable us to examine for any arm-specific effects (e.g. any differences between responses for stimuli applied to the CRPS-affected/non-dominant versus non-affected/dominant arm). This was also the response format we used in a previous study (Vittersø et al., 2019). Pain and other CRPS symptoms prevented people with lower limb CRPS from using their affected limb to make foot pedal responses. Therefore, people with lower limb CRPS and their matched controls were asked to indicate the location of the vibrotactile stimulus using only two-alternate forced choice responses – "upper" (thumb) or "lower" (finger) – by depressing the pedal under the toe or heel of their non-affected foot, regardless of which hand (left or right) the stimulus had been presented to. The lower limb controls used the foot corresponding to that of the non-affected side of the person to whom they were matched.

The tools were Arranged in both crossed and uncrossed Arrangements during each Set of the CCT (passive, active 1, active 2, and active 3). The experimenter changed the Arrangement of the tools half-way through the first Set (passive), while participants kept hold of the handles. Thus, this Set did not involve any active tool-use by the participant. The order of the Tool Arrangements (crossed, uncrossed) was counterbalanced in this Set. For

the three active Sets of the CCT, participants had to manoeuvre the tools to position them in the crossed or uncrossed position, alternating between the two Tool Arrangements every four trials. Participants were signalled to change the Tool Arrangement by all four LEDs illuminating. To maintain a consistent Arrangement of the tools across trials in the crossed condition, each tool was marked with a 5 cm wide blue band of tape, 30 cm from the 'blade' of the tool (i.e. the distal end), to indicate the locations at which participants should cross the tools (see Fig. 2).

Conventionally, updating of spatial representations is inferred from the CCT by comparing the effect of visual distractors on the speed and accuracy of detecting vibrotactile stimulation depending on the Tool Arrangement (crossed, uncrossed), the Visual field (same, opposite) in which the distractor was presented relative to the target, and the Congruence (congruent, incongruent) of the vertical elevation of the distractor relative to the target (e.g. both upper/lower, or one upper and one lower). Normal updating of peripersonal space representations (Maravita et al., 2002) is considered to be indicated by 1) greater interference (i.e. longer RTs and/or higher error rates) from incongruent distractors in the same Visual Field as vibrotactile targets, compared to the opposite Visual Field, when the tools are *uncrossed*; and 2) greater interference from incongruent distractors when the distractors appear in the opposite Visual Field than the same Visual Field when the tools are *crossed* (because distractors in the opposite Visual Field appeared on the same *tool* as the vibrotactile targets). This combined pattern is taken to indicate that peripersonal space representations have been updated to incorporate the distal ends of the tools (Maravita, Spence, & Driver, 2003; Marini et al., 2017), although see Holmes (2012) for an alternative interpretation. We expected the above pattern to be less pronounced in people with CRPS compared to controls, reflecting problems with updating of peripersonal space. Because these effects should develop as a function of active tool-use, we also considered how these effects developed over time by comparing performance across the four Sets.

The changes in performance on the CCT are thought to depend on the active use of the tools. In the experiment of Maravita and his colleagues (2002), having participants actively move the tools between the crossed and the uncrossed Arrangement was sufficient to generate such effects. Following pilot testing, we decided to incorporate a beanbag sorting task between each of the active Sets of the CCT (see Fig. 1) to amplify the desired effect (e.g. by increasing dynamic touch; Bruggeman et al., 2013; Ritchie & Carlson, 2013). Thus, participants completed the beanbag sorting task twice: once between the first and second active CCT Set, and once between the second and third active CCT Set. See the supplemental digital content/Appendix 2 for more details about the beanbag sorting task.

2.3.5 Pain ratings

In addition to the pain ratings that they gave during the temperature recordings, participants provided 12 pain ratings across all the sets of TDJs and sets of the CCT (see Fig. 1) so that their pain levels could be monitored during the experiment. Pain ratings were recorded before each Set of TDJs, before each tool Arrangement in the first ("passive") Set of the CCT, and before and after each subsequent "active" set of the CCT.

2.3.6 Duration

The entire session lasted approximately 4 hours for people with CRPS, and 3 hours for the matched controls. One person with upper limb CRPS was unable to complete the second beanbag sorting task and the final CCT Set due to a pain flare, but she was able to complete all the temperature recordings. Another person with upper limb CRPS could not undertake the temperature recordings, as her affected hand was covered by a lidocaine patch, but was able to complete the CCT and TDJs. Therefore, the final sample for each task comprised 36 people with CRPS: 18 people with upper limb CRPS, and 18 people with lower limb CRPS (see Tables 1 and 2 for clinical and demographic details). One person with lower limb CRPS had to split the session over two consecutive days due to pain and time constraints. One control participant's session was split over two days due to a power failure in the laboratory. For both participants who completed the study over two days, the first session ended after recording the temperature of their hands in a crossed or uncrossed position (i.e. prior to the temperature recordings with tools and any TJDs or active tool-use tasks). Temperature recordings from two control participants were excluded; one because they experienced a headache during the temperature recordings, which resolved for later parts of the study (*M* pain during the TDJs and CCT < 1/10), and one because they fell asleep repeatedly during the temperature recordings. Both of these control participants' data were included for the CCT and TDJs, which were unaffected by headache or sleepiness. A follow-up analysis of the data from these tasks excluding the data from these participants did not substantially change the results. The final sample for the temperature recording was comprised of 18 people with upper limb CRPS, 18 people with lower limb CRPS, and 34 pain-free control participants.

2.4 Analysis plan

2.4.1 Preliminary analyses

We considered that motor impairments for people with upper limb CRPS might make it difficult to use tools, and therefore that any difficulties with updating bodily and spatial representation might be obscured by an individual's motor abilities. Therefore, we had a research assistant who was blind to the hypotheses of the study rate video recordings of participants' movement during the CCT and the beanbag sorting tasks. The research assistant gave a score from 1 (worst imaginable) to 10 (best imaginable) for the quality of the movement for each of the four recordings of each participant (i.e. CCT set 2 & set 4, beanbag sorting tasks 1 & 2). A mean score was calculated from the four ratings for each participant, which we compared with a one-way ANOVA with Group (upper limb CRPS, lower limb CRPS, control) as an independent variable. The research assistant was also asked to identify individuals who she suspected as having CRPS, and if so, which was the CRPS-affected limb (i.e. left or right upper or lower limb).

2.4.2 Tactile distance judgements analysis

For participants' TDJs, we calculated a mean distance estimate for each Set (pre tool-use, post tool-use), and Side of Body (affected/non-dominant, non-affected/dominant). The TDJ distance estimates were analysed using a 2x2x2 ANOVA with Group (upper limb CRPS, lower limb CRPS, controls) as a between groups factor.

2.4.3 Crossmodal congruency task analysis

For the CCT, we performed separate ANOVAs for the upper limb and lower limb groups due to the differences in response format. To add clarity we used crossmodal interference as the main dependent variable reported for the CCT. We calculated the median RTs and percentage of errors within each level of each condition, after excluding trials with RTs < 200 ms or > 3000 ms (1.08 % of all trials). The median RTs were calculated from trials with correct responses only. We calculated the crossmodal interference by subtracting RTs and error rates for congruent trials (i.e. where the visual distractors were vertically congruent with vibrotactile targets) from those for incongruent trials. The independent variables were Group (CRPS, controls), Set (passive, active 1, active 2, active 3), Tool Arrangement (crossed, uncrossed), and the Visual Field (same, opposite) that visual distractors appeared in relative to vibrotactile targets. For the upper limb CRPS group we also included the Side of Body (affected/non-dominant, non-affected/dominant) that received vibrotactile stimulation as an additional independent variable.

We were primarily interested in interactions that involved Tool Arrangement and Visual Field for the CCT. Therefore, we do not report or elaborate on interactions that do not included Tool Arrangement and Visual Field because these are not of theoretical interest for our study. We also followed-up the interaction of Tool Arrangement and Visual field within each Group (upper or lower limb CRPS and their matched controls) on an *a priori* basis, because this interaction is most relevant for revealing tool-use dependent changes. In the study by Maravita and his colleagues (2010), changes in performance on the CCT due to active tool-use were only seen for RTs. Therefore, we only report CCT results derived from RTs (i.e. crossmodal interference) in the main article, although we report the analyses of accuracy on the CCT in the supplemental digital content/Appendix 2).

2.4.4 Hand temperature analysis

An average hand temperature was calculated from the 36 iButton recordings for each hand, Arrangement, and effector Condition. Because CRPS symptoms can manifest as the affected limb being physically warmer *or* cooler than the non-affected limb (Harden et al., 2007), we analysed absolute temperature asymmetries between the hands of the affected and the non-affected side of the body.

The absolute hand temperature asymmetries were analysed with two separate ANOVAs. First, we conducted a 3x2 ANOVA for the 'hands only' Effector Condition, with Group (upper limb CRPS, lower limb CRPS, controls), and Arrangement (crossed, uncrossed) as independent variables. We followed-up this analysis with t-tests to compare the absolute hand temperature asymmetries for the crossed and uncrossed Arrangements in the hands only Effector Condition, within each Group. A difference in absolute hand temperature

asymmetry between the crossed and uncrossed Arrangement for people with upper limb CRPS would indicate a spatially defined modulation of CRPS symptoms similar to that reported previously (Moseley et al., 2013; Moseley et al., 2012). Second, to explore the effect of tool-use on spatially defined hand temperature modulations we conducted a 3x2x2 ANOVA, with Group (upper limb CRPS, lower limb CRPS, controls), Effector Condition (t1 tools, t2 tools), and Arrangement (crossed, uncrossed) as independent variables. We followed-up this analysis with separate 2x2 ANOVAs comparing absolute hand temperature asymmetries across Effector Condition (t1 tools, t2 tools) and tool Arrangements (crossed, uncrossed) within each Group.

2.4.5 Inference criteria

We considered a *p*-value < .05 as statistically significant. For all ANOVAs, Greenhouse-Geisser corrections were used when sphericity was not satisfied. We used Holm-Bonferroni corrections (Holm, 1979) for follow-up t-tests, which is more powerful than the original Bonferroni correction (Aickin & Gensler, 1996). The corrected *p*-values are indicated by "$p_{adjusted}$". See preregistration for a full list of planned analyses (https://osf.io/pjdw9).

3. Results

We observed changes on both the main tasks (i.e. tactile distance judgments and the crossmodal congruency task) that indicated that bodily and spatial representations had updated, but only for some of our participants. Specifically, we found a significant three-way interaction between Group, Set, and Side of Body on tactile distance judgments. This interaction appeared to be driven by a change for people with upper limb CRPS, whereby a significant difference between arms emerged after tool-use. This pattern was indicative of a perceived lengthening of the non-affected arm (i.e. the expected effect) and/or a shortening of the affected arm. For the crossmodal congruency task, we observed a significant interaction between Tool-Arrangement and Visual Field on crossmodal interference for people with CRPS, but not for control participants. This result suggests that people with CRPS updated their representations of peripersonal space, but that controls did not do so. We did not observe any influence of updating bodily and spatial representations on hand temperature asymmetries. However, this is not surprising considering we did not replicate the spatial modulation of hand temperature asymmetries that has been reported for crossing the hands such that the CRPS-affected limb is positioned in the non-affected side of space.

3.1 Sensory Testing

We found signs of hypoesthesia, hyperalgesia, allodynia, and more precise tactile discrimination ability on the affected limb, for people with upper limb, and lower limb CRPS (see supplemental digital content/Appendix 2).

There was no evidence of neglect or extinction from the confrontation testing for controls, or for people with CRPS (see supplemental digital content/Appendix 2).

3.2 Quality of movement

From the videos of participants' movements during tool-use, the research assistant correctly identified 35.3% of the people with upper limb CRPS as having an upper limb affected. They did not correctly identify any people with lower limb CRPS from their arm movements. There was a significant Group difference in the research assistant's ratings of participants' quality of movement during the CCT and beanbag sorting task, $F(2, 58) = 10.40$, $p < .001$, $\eta_{2p} = .26$. This was driven by people with upper limb CRPS ($M = 6.50$, $SD = 1.20$) being rated as having lower quality of movements than controls ($M = 7.71$, $SD = 0.68$), $t(46) = 3.84$, $p_{adjusted} = .012$, $d = 1.13$. There were no other differences in rated movement quality that were significant after correcting for multiple comparisons, $ts(42) \leq 1.35$, $ps_{adjusted} \geq .070$, $ds \leq 0.84$. These results suggest that people with upper limb CRPS had more difficulties with performing the tool-use tasks than the other two groups.

3.3 Tactile distance judgements

Participants were able tell the differences between the three Distances (small, medium, large) used for the TDJs, $F(2, 67) = 81.76$, $p < .001$, $\eta_{2p} = .71$. The small ($M = 7.09$, $SD = 4.07$) distance was rated as significantly shorter than the medium ($M = 10.41$, $SD = 4.47$), $t(70) = 9.44$, $p_{adjusted} = .003$, $d = 2.26$, and large ($M = 13.10$, $SD = 4.46$) distances, $t(70) = 13.39$, $p_{adjusted} = .003$, $d = 3.20$. The medium distance was also rated as shorter than the large distance, $t(70) = 10.19$, $p_{adjusted} = .003$, $d = 2.44$. There was no significant interaction between Group and Distance, $F(4, 136) = 0.75$, $p = .561$, $\eta_{2p} = .02$. These results suggest that participants were able to detect the difference between the three Distances, and that this performance did not significantly differ between Groups.

The typical pattern taken to indicate that the body representation has been updated to accommodate the tools is a decrease in TDJs following active tool-use, which would be indicated by a main effect of Set. We did not observe this effect, nor any other main effects on TDJs when all groups were considered together, $Fs(1, 68) \leq 1.71$, $ps \geq .196$, $\eta_{2p} \leq .03$. There was, however, a 3-way interaction between Group, Set, and Side of Body on TDJs, $F(2, 69) = 4.37$, $p = .016$, $\eta_{2p} = .11$ (Fig. 3). We followed-up this interaction with three two-way ANOVAs split by Group (i.e. controls, upper limb CRPS, and lower limb CRPS).

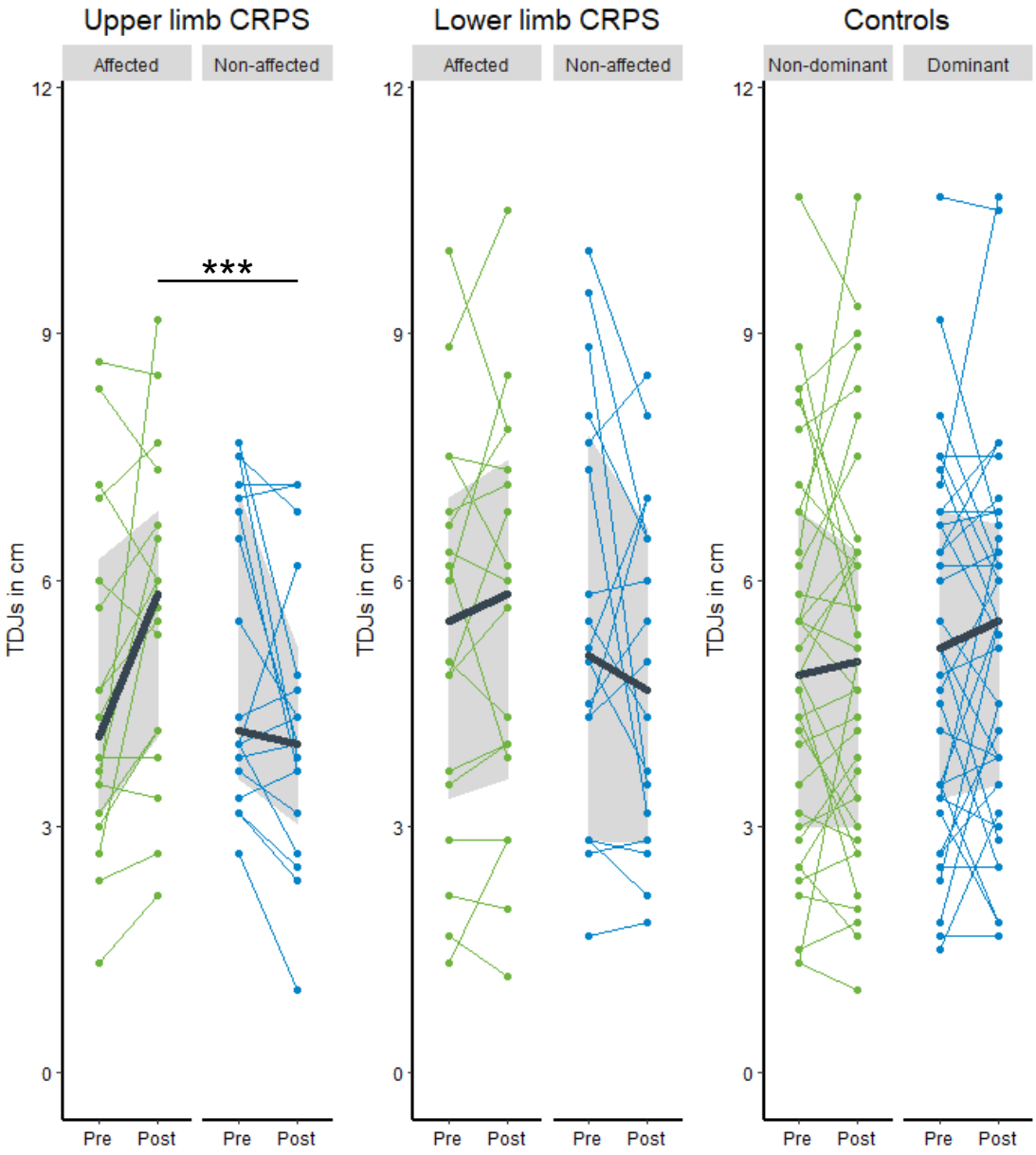

Figure 3. Tactile distance judgments.
Results for the Tactile Distance Judgement (TDJ) task. The perceived distance between two points placed on participants' forearms (TDJs) are depicted, split by Group (upper limb CRPS [n = 18], lower limb CRPS [n = 18], controls [n = 35]), Side of Body (affected/non-dominant [in green], non-affected/dominant [in blue]), and Set (pre, post). TDJs are measured by participants indicating a value on a diagram with 22 lines of different lengths (0.5 cm to 11.5 cm, with 0.5 cm increments). Individual participant's TDJs were taken as the mean indicated values for the three tested distances (4 cm, 6 cm, 8 cm) in cm. Group medians are depicted by the black lines. The limits of the grey, shaded areas indicate the 25th and 75th percentile. Individual data points are depicted by circles. *** $p_{adjusted} < .001$.

The follow-up analysis suggested that control participants did not update their body representation to facilitate tool-use, as there were no main effects or interactions for the analysis of control participants' TDJs, $Fs(1, 34) \leq 0.40$, $ps \geq .534$, $\eta_{2p} \leq .01$ (see supplemental digital content/Appendix 1 for full breakdown). In contrast, there was an

interaction between Set and Side of Body for people with upper limb CRPS, $F(1, 17) = 22.37$, $p < .001$, $\eta_{2p} = .57$. There was no significant difference in TDJs for the affected ($M = 9.28$, $SD = 4.17$) compared to non-affected ($M = 10.20$, $SD = 3.61$) Side of Body pre tool-use, $t(17) = 1.36$, $p_{adjusted} = .196$, $d = 0.66$. However, post tool-use the TDJs were significantly smaller for the non-affected Side of Body ($M = 8.48$, $SD = 3.42$) than the affected Side of Body ($M = 11.19$, $SD = 3.87$), $t(17) = 4.62$, $p_{adjusted} = .004$, $d = 2.24$. Although the direct comparisons of pre vs post tool-use TDJs within each Side of Body were not significant after correcting for multiple comparisons, $ts(17) \leq 2.47$, $ps_{adjusted} \geq .084$, $ds \leq 1.20$, the observed pattern suggests that people with upper limb CRPS tended to update their body representation in the expected direction (i.e. a perceived lengthening) for their non-affected hand, and simultaneously in the opposite direction (i.e. a perceived shortening) for their affected hand.

For people with lower limb CRPS, the pattern of TDJs observed is qualitatively similar to that seen for people with upper limb CRPS (Fig. 3). That is, there was a numerical decrease in TDJs from pre to post tool-use for the arm on the non-affected side of the body (from $M = 10.98$, $SD = 5.09$; to $M = 9.65$, $SD = 4.23$), and a numerical increase in TDJs for the arm on the affected side of the body (from $M = 10.63$, $SD = 4.90$; to $M = 10.98$, $SD = 5.02$). However, the interaction between Set and Side of Body did not reach statistical significance for this Group, $F(1, 17) = 3.23$, $p = .086$, $\eta_{2p} = .16$.

3.4 Crossmodal congruency task

3.4.1 People with upper limb CRPS and their matched controls

A main effect of Group showed that people with upper limb CRPS experienced greater overall crossmodal interference ($M = 65.23$ ms, $SD = 37.59$) than controls ($M = 38.34$ ms, $SD = 33.47$), $F(1, 34) = 5.14$, $p = .030$, $\eta_{2p} = .13$. A main effect of Visual Field indicated that visual distractors appearing in the same Visual Field ($M = 92.13$ ms, $SD = 62.88$) as vibrotactile targets resulted in greater crossmodal interference than those appearing in the opposite Visual Field ($M = 11.44$ ms, $SD = 53.64$), $F(1, 34) = 28.56$, $p < .001$, $\eta_{2p} = .46$. There were no other main effects on crossmodal interference for the analysis of upper limb patients and their matched controls, $Fs(1, 34) \leq 1.31$, $ps \geq .260$, $\eta_{2p} \leq .10$.

The critical interaction for indicating updating of peripersonal space was significant. That is, there was a significant interaction between Tool Arrangement and Visual Field, $F(1, 34) = 5.48$, $p = .025$, $\eta_{2p} = .14$. There were no significant interactions involving Group, Tool Arrangement, and Visual field on crossmodal interference, $Fs(1, 32) \leq 1.22$, $ps \geq .277$, $\eta_{2p} \leq .09$. However, we analysed the Tool Arrangement by Visual Field interactions split by Group on an *a priori* basis (Fig. 4). There was no significant Tool Arrangement by Visual Field interaction for control participants, $F(1, 17) = 0.90$, $p = .357$, $\eta_{2p} = .05$. In contrast, there was a significant two-way interaction between Tool Arrangement and Visual Field for people with upper limb CRPS, $F(1, 17) = 5.18$, $p = .036$, $\eta_{2p} = .23$. The pattern of differences between conditions was consistent with an updating of peripersonal space representations. Specifically, there was significantly greater crossmodal interference for visual distractors appearing in the same ($M = 119.18$ ms, $SD = 88.24$) compared to opposite ($M = -4.06$ ms,

SD = 54.55) Visual Field, for uncrossed tools, $t(17) = 6.54$, $p_{adjusted} = .004$, $d = 3.1$. No other contrasts were significant after correcting for multiple comparisons, $ts(17) \leq 2.17$, $ps_{adjusted} \geq .231$, $ds \leq 1.05$. The overall pattern of crossmodal interference shown by the people with upper limb CRPS is consistent with updating of peripersonal space representations, as there is only a significant effect of Visual Field on crossmodal interference when the distractors in the same visual field appear on the same tool as vibrotactile targets (i.e. for uncrossed tools). When the tools are crossed, and so the distractors in the same Visual Field appear on the opposite tool, these distractors no longer significantly interfere with the processing of the vibrotactile target. This pattern of crossmodal interference is consistent with updating of peripersonal space representations, as it shows space-based and object-based effects that would not be expected without the presence of tools. Our findings therefore suggest that people with upper limb CRPS updated their peripersonal space representations, but we did not find any evidence that their matched controls did so. There were no further interactions that involved Tool Arrangement and Visual Field (see supplemental digital content/Appendix 2).

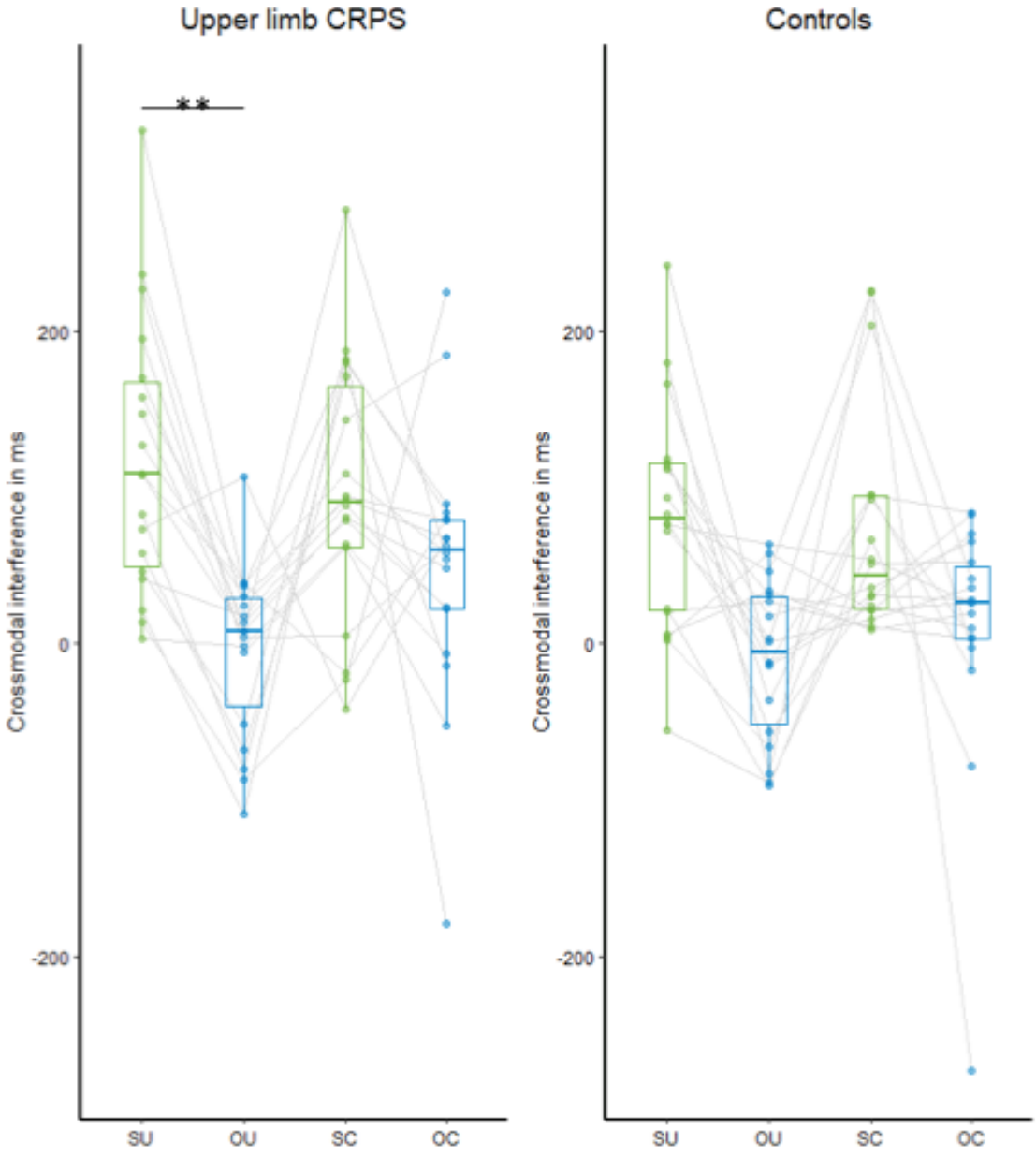

Figure 4. Crossmodal congruency task for upper limb group.
Crossmodal interference in ms on the Crossmodal Congruency Task (CCT) for people with upper limb CRPS (n = 18) and their matched controls (n = 18). Data are split by Tool Arrangement (uncrossed [U], crossed [C]) and Visual Field (same [S; in green], opposite [O; in blue]). We calculated crossmodal interference by subtracting reaction times for congruent trials from those for incongruent trials. Medians are depicted by the central lines, and box limits indicate the 25th and 75th percentile. The whiskers extend 1.5 times the interquartile range from the box limits. Individual data points are depicted by circles. ** $p_{adjusted} < .01$

3.4.2 People with lower limb CRPS and their matched controls

In the lower limb group, a main effect of Group showed that people with lower limb CRPS experienced greater overall crossmodal interference (M = 110.01 ms, SD = 60.63) than controls (M = 67.89 ms, SD = 41.07), $F(1, 34) = 5.96$, $p = .020$, $\eta_{2p} = .15$. There were no other significant main effects on crossmodal interference for the lower limb group, $Fs(1, 34) \leq 2.13$, $ps \geq .201$, $\eta_{2p} \leq .08$.

The critical interaction for indicating updating of peripersonal space was significant, as there was an interaction between Tool Arrangement and Visual Field on crossmodal interference, $F(1, 34) = 8.80$, $p = .005$, $\eta_{2p} = .21$. There were no significant interactions involving Group, Tool Arrangement, and Visual Field, $Fs(1, 32) \leq 3.81$, $ps \geq .083$, $\eta_{2p} \leq .09$. However, we analysed the Tool Arrangement by Visual Field interaction split by Group on an *a priori* basis (Fig. 5). Our findings were similar to those from the upper limb group, in that people with lower limb CRPS showed an interference pattern consistent with updating of peripersonal space representations, but their matched controls did not. There were no significant interactions involving Tool Arrangement and Visual Field on crossmodal interference for lower limb controls, $Fs(1, 32) \leq 0.81$, $ps \geq .380$, $\eta_{2p} \leq .16$. For people with lower limb CRPS, the interaction between Tool Arrangement and Visual Field on crossmodal interference was significant, $F(1, 17) = 9.93$, $p = .006$, $\eta_{2p} = .37$. There was significantly greater crossmodal interference for uncrossed (M = 144.77 ms, SD = 89.43) compared to crossed (M = 83.09 ms, SD = 93.38) tools, for visual distractors appearing in the same Visual Field as the vibrotactile target, $t(17) = 3.04$, $p_{adjusted} = .048$, $d = 1.47$. None of the other contrasts were significant after corrections for multiple comparisons, $ts(17) \leq 2.91$, $ps_{adjusted} \geq .072$, $ds \leq 1.41$. This suggests that visual distractors presented in the same Visual Field as the vibrotactile target interfered more only when they also appeared on the same *tool* as the vibrotactile target, which is consistent with updating of peripersonal space representations. Our results suggest that people with lower limb CRPS, but not their matched controls, updated their peripersonal space representations. There were no further interactions that involved Tool Arrangement and Visual Field (see supplemental digital content/Appendix 2).

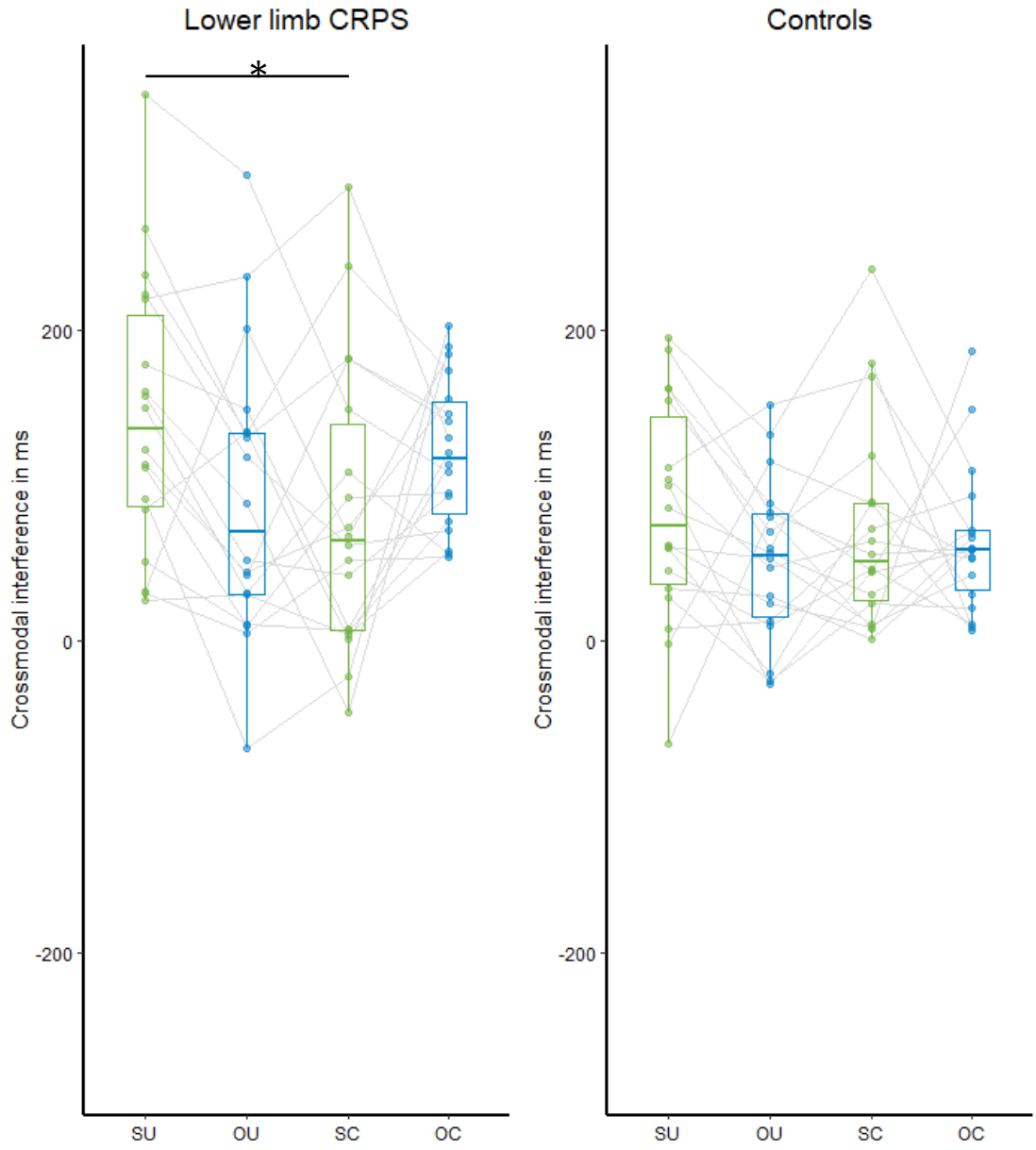

Figure 5. Crossmodal congruency task for lower limb group.
Crossmodal interference in ms on the Crossmodal Congruency Task (CCT) for people with lower limb CRPS (n = 18) and their matched controls (n = 18). Data are split by Tool Arrangement (uncrossed [U], crossed [C]) and Visual Field (same [S; in green], opposite [O; in blue]). We calculated crossmodal interference by subtracting reaction times for congruent trials from those for incongruent trials. Medians are depicted by the central lines, and box limits indicate the 25th and 75th percentile. The whiskers extend 1.5 times the interquartile range from the box limits. Individual data points are depicted by circles. * $p_{adjusted} < .05$

3.5 Hand temperature asymmetry

3.5.1 Hands Effector Condition

Previous research has demonstrated a spatially defined modulation of hand temperature in which hand temperature asymmetry normalised when the hands were crossed (Moseley et al., 2012). The analysis of hand temperature asymmetry from the first Effector Condition (i.e. hands) revealed a main effect of Group, $F(2, 67) = 7.15$, $p = .002$, $\eta_{2p} = .18$. This effect was driven by people with upper limb CRPS ($M = 1.12$ ˚C, $SD = 0.70$) having greater absolute hand temperature asymmetries than both controls ($M = 0.57$ ˚C, $SD = 0.51$), $t(45) = 2.96$, $p_{adjusted} = .027$, $d = 0.88$, and people with lower limb CRPS ($M = 0.58$ ˚C, $SD = 0.41$), $t(34) = 2.75$, $p_{adjusted} = .032$, $d = 0.94$. There was no significant difference between absolute hand temperature asymmetries of people with lower limb CRPS compared to controls, $t(45) = 0.07$, $p_{adjusted} = .995$, $d = 0.02$. There was no significant main effect of Arrangement, and no significant interaction of Group and Arrangement on hand temperature asymmetries from the hands only Condition, $Fs(2, 67) \leq 3.08$, $ps \geq .084$, $\eta_{2p} \leq .04$. However, because the previous research showing spatially defined hand temperature modulations only examined people with upper limb CRPS (Moseley et al., 2012), we followed-up the analyses of hand temperature from the hands only Condition, split by Group (upper limb CRPS, lower limb CRPS, controls; see Fig. 6).

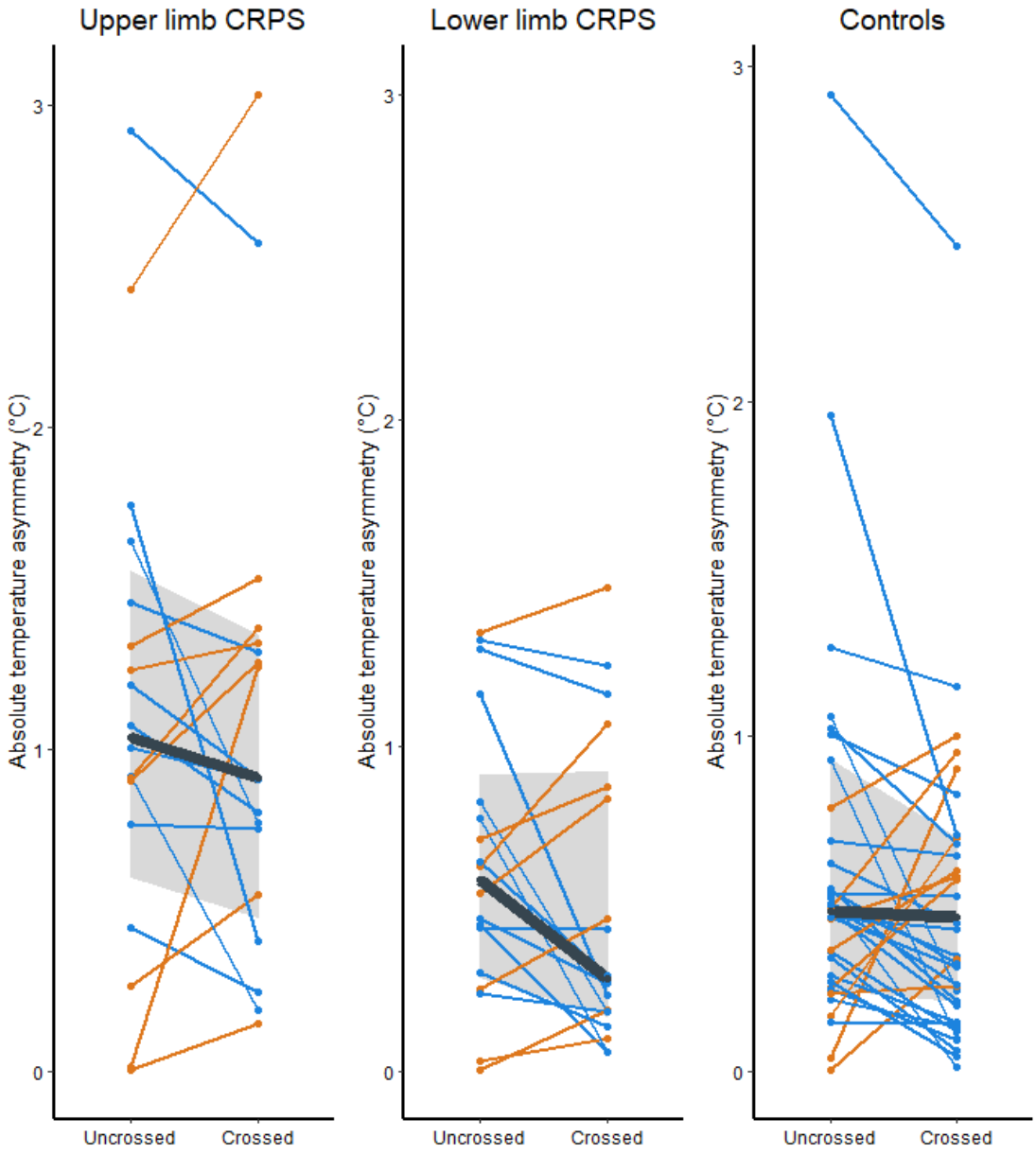

Figure 6. Hand temperature asymmetries.
Hand temperature asymmetries (absolute difference in temperature between hand of the affected and unaffected side of the body, in °C) for people with upper limb CRPS (n = 18), lower limb CRPS (n = 18), and controls (n = 34), split by hand Arrangement (uncrossed, crossed). Blue lines indicate individuals who showed a numerical decrease in absolute hand temperature asymmetry for crossed hands (i.e. the expected spatially defined reduction of CRPS symptoms for crossed hands (Moseley, Gallace, Di Pietro, Spence, & Iannetti, 2013; Moseley, Gallace, & Iannetti, 2012), compared to uncrossed hands. Orange lines indicate individuals who showed a numerical increase in hand temperature asymmetry for crossed hands compared to uncrossed hands. The black lines show the median hand-temperature asymmetries. The limits of the grey, shaded areas indicate the 25th and 75th percentile. Individual data points are depicted by circles.

We did not find any evidence of spatially defined hand-temperate modulation in any groups. That is, there was no difference in absolute hand temperature asymmetries between

crossed and uncrossed Arrangements for people with upper limb CRPS, $t(17) = 0.37$, $p_{adjusted} = .336$, $d = 0.18$, lower limb CRPS, $t(17) = 1.40$, $p_{adjusted} = .711$, $d = 0.68$, or controls, $t(28) = 1.63$, $p_{adjusted} = .327$, $d = 0.62$. Bayesian t-tests, computed using JASP software (Team, 2018), revealed moderate evidence (Wagenmakers et al., 2018) that hand Arrangement had no effect on absolute hand temperature asymmetry for people with upper limb CRPS, $BF_{10} = 0.258$, and found no evidence (i.e. anecdotal evidence; Lee & Wagenmakers, 2014) of an effect of hand Arrangement on hand temperature for people with lower limb CRPS, $BF_{10} = 0.558$, and for controls $BF_{10} = 0.766$. We considered whether these null effects for people with upper limb CRPS were because, unlike in previous studies examining spatial modulation of hand temperature (Moseley et al., 2013; Moseley et al., 2012), we did not pre-select only patients whose affected hand was at least 1 ˚C cooler than their non-affected hand. However, follow-up analyses of the data from only those people with upper limb CRPS whose affected hand was ≥1 ˚C cooler than their non-affected hand (n = 8) produced qualitatively similar results, $t(7) = 1.44$, $p = .194$, $d = 0.51$, $BF_{10} = 0.724$. Overall, our findings suggest that CRPS symptoms (i.e. hand temperature asymmetry) were not modulated by the spatial location of the hands.

3.5.2 Tools Effector Conditions

Our main interest in examining spatial modulations of hand temperature asymmetries was to assess any effects that updating spatial representations might have on spatially defined hand temperature modulations. When all groups were considered together, there were no main effects of Group, Arrangement, or Effector Condition on hand temperature asymmetries measured in the tools conditions, $Fs(1, 67) \leq 2.86$, $ps \geq .095$, $\eta_{2p} \leq .04$. There was, however, an interaction between Group and Tool Arrangement, $F(2, 67) = 3.45$, $p = .038$, $\eta_{2p} = .09$. This effects was driven by greater hand temperature asymmetries for uncrossed ($M = 0.66$ ˚C, $SD = 0.46$) than crossed ($M = 0.48$ ˚C, $SD = 0.41$) tools for people with lower limb CRPS, although it was no longer significant after correcting for multiple comparisons, $t(17) = 2.54$, $p_{adjusted} = .072$, $d = 1.23$. There were no significant effects of Arrangement on hand temperature asymmetries for people with upper limb CRPS, or controls, $ts\ (17) \leq 0.65$, $ps_{adjusted} = 1.000$, $ds \leq 0.25$. There were no other significant interactions, $Fs(2, 67) \leq 1.16$, $ps \geq .321$, $\eta_{2p} \leq .03$. In particular, there was no interaction between Group, Effector Condition, and Tool Arrangement to indicate any change in spatially defined hand temperature modulations after tool-use, $F(2, 67) = 1.16$, $p = .321$, $\eta_{2p} = .03$. Therefore, when all groups were considered, we did not find any evidence that active tool-use influenced hand temperature asymmetries. This was further supported by follow-up analyses split by group. That is, we analysed mean hand temperatures whilst holding the tools, for the two Tool Arrangements (crossed, uncrossed), before and after active tool-use (i.e. Effector Condition), split by Group (see supplemental digital content/Appendix 2 for descriptive statistics). There was no main effect of Tool Arrangement, nor were there any interactions involving Effector Condition or Tool Arrangement, on mean hand temperature asymmetry whilst holding tools for people with upper limb CRPS, $Fs(1, 17) \leq 1.40$, $ps \geq .254$, $\eta_{2p} \leq .08$, for people with lower limb CRPS $Fs(1, 17) \leq 2.62$, $ps \geq .124$, $\eta_{2p} \leq .13$, or for controls , $Fs(1, 28) \leq 2.10$, $ps \geq .158$, $\eta_{2p} \leq .07$. We therefore found no evidence suggesting that updating of spatial representations influences any spatially defined hand temperature modulation.

3.6 Exploratory analyses

In addition to the exploratory analyses reported below, we explored the influence of sensory deafferentation, as measured by differences in mechanical detection threshold, and mechanical pain thresholds between the affected and unaffected limb, on the results from the TDJs, and CCT. These results did not show any clear evidence that sensory deafferentation influenced updating of bodily or spatial representations. We also ran additional analyses of our data from the TDJs, CCT, and hand temperature asymmetry using linear mixed models, which can better account for variability between individuals than repeated measures ANOVA. The results of these analyses were consistent with those of the main repeated measures ANOVAs. These additional analyses are reported in the supplemental digital content/Appendix 2.

We explored the correlations between TDJs, CCT interference scores (for the Tool Arrangement x Visual Field interaction), hand temperature asymmetries, sensory measures, questionnaire measures, clinical information, and age (Table 3), for people with upper limb CRPS (a), and lower limb CRPS (b). There were no consistent patterns of correlations within or between tasks (i.e. TDJs, CCT, and hand temperature asymmetries) for between people with upper limb, or lower limb CRPS.

a)

	Age	Current pain	CRPS duration	CRPS severity	Movement Qual	Allodynia	MDT	MPT	Two-point discrim.	SF-MPQ-2	BPD	Δ TDJ: dom	Δ TDJ: affected	CCT: SU	CCT: OU	CCT: SC	CCT: OC	Temp asymmetry
Current pain	-.13																	
CRPS duration	0.45	-.28																
CRPS severity	-.02	-.02	.07															
Movement Qual	-.18	-.17	.26	-.15														
Allodynia	**-.50***	**.48***	-.32	.29	.09													
MDT	-.01	.07	.01	.06	-.31	-.42												
MPT	.08	-.10	.34	-.22	-.17	-.47	**.55***											
Two-point discrim.	-.01	.17	-.10	-.12	-.16	-.07	.08	.25										
SF-MPQ-2	**-.62****	**.51***	**-.60****	.02	-.03	**.63****	-.33	-.30	.04									
BPD	-.36	.49	-.29	.23	-.35	.45	-.09	-.27	.20	.48								
Δ TDJ: dom	-.17	.32	.17	-.27	.48	.14	-.18	.18	.21	.20	-.21							
Δ TDJ: affected	.04	.29	.27	.11	.15	-.06	.32	.33	.16	-.10	-.49	.47						
CCT: SU	-.23	.19	.05	.25	.39	.40	-.15	-.16	-.40	.20	-.06	.17	.16					
CCT: OU	-.19	.11	-.08	.09	.31	.29	-.24	-.30	-.26	.19	-.05	**.49***	-.06	.45				
CCT: SC	.33	.45	.12	-.43	-.16	.04	.09	.23	.22	-.13	.02	-.01	.22	.09	-.36			
CCT: OC	-.54*	-.08	-.29	-.06	.33	.23	-.07	-.29	-.45	.33	.25	-.17	-.31	-.03	-.07	-.28		
Temp asymmetry	-.30	.05	-.08	**.63****	.03	.00	**.53***	.19	-.22	.00	-.04	-.20	.38	.42	-.08	-.02	.15	
Δ Temp asymmetry	-.29	.06	**-.52***	-.29	.04	.43	-.45	-.26	-.13	.42	.31	.16	-.46	.03	.19	-.21	.27	-.37

b)

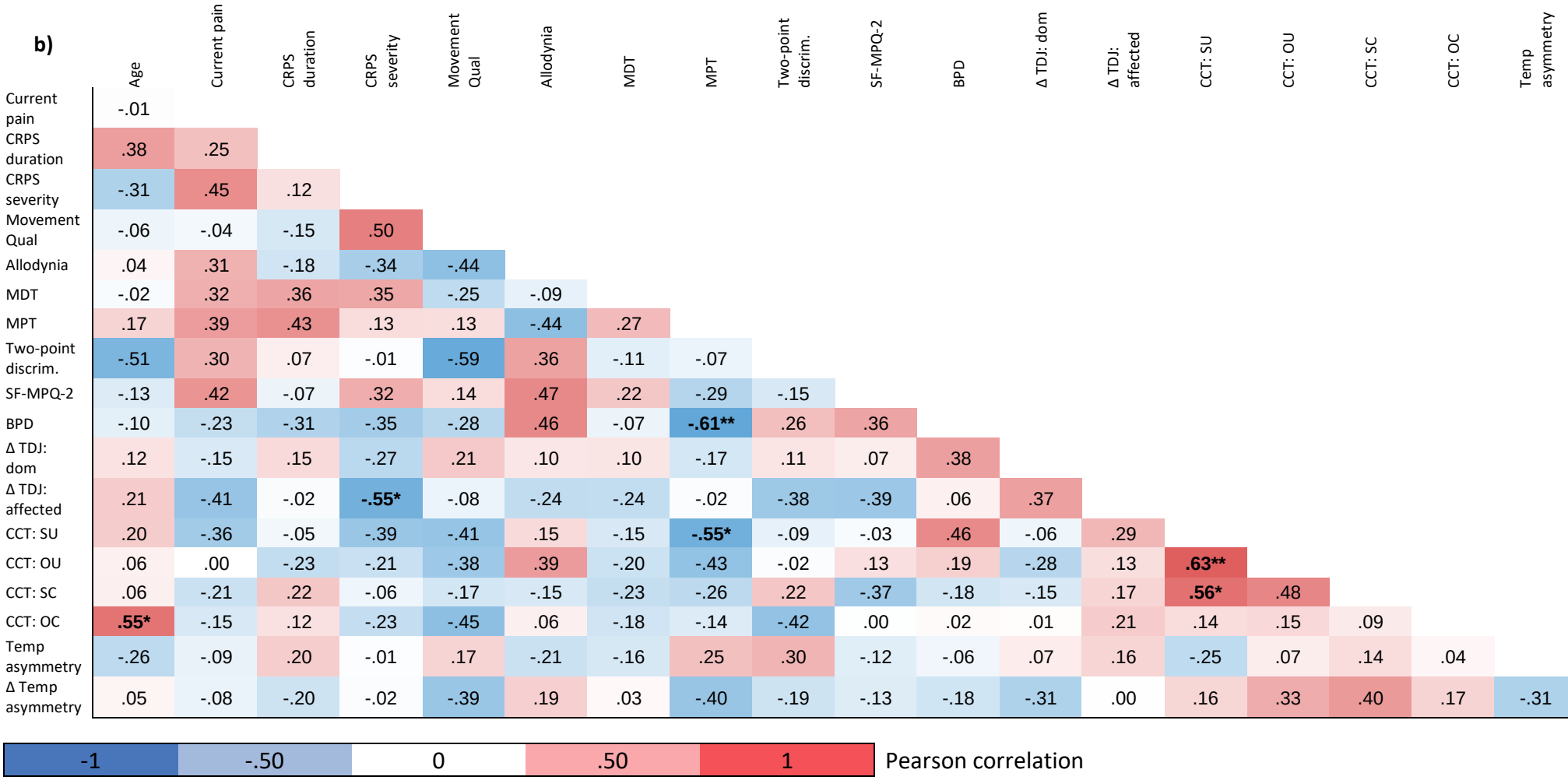
Age
Current pain
CRPS duration
CRPS severity
Movement Qual
Allodynia
MDT
MPT
Two-point discrim.
SF-MPQ-2
BPD
Δ TDJ: dom
Δ TDJ: affected
CCT: SU
CCT: OU
CCT: SC
CCT: OC
Temp asymmetry
Current pain -.01
CRPS duration .38 .25
CRPS severity -.31 .45 .12
Movement Qual -.06 -.04 -.15 .50
Allodynia .04 .31 -.18 -.34 -.44
MDT -.02 .32 .36 .35 -.25 -.09
MPT .17 .39 .43 .13 .13 -.44 .27
Two-point discrim. -.51 .30 .07 -.01 -.59 .36 -.11 -.07
SF-MPQ-2 -.13 .42 -.07 .32 .14 .47 .22 -.29 -.15
BPD -.10 -.23 -.31 -.35 -.28 .46 -.07 **-.61****** .26 .36
Δ TDJ: dom .12 -.15 .15 -.27 .21 .10 .10 -.17 .11 .07 .38
Δ TDJ: affected .21 -.41 -.02 **-.55*** -.08 -.24 -.24 -.02 -.38 -.39 .06 .37
CCT: SU .20 -.36 -.05 -.39 -.41 .15 -.15 **-.55*** -.09 -.03 .46 -.06 .29
CCT: OU .06 .00 -.23 -.21 -.38 .39 -.20 -.43 -.02 .13 .19 -.28 .13 **.63****
CCT: SC .06 -.21 .22 -.06 -.17 -.15 -.23 -.26 .22 -.37 -.18 -.15 .17 **.56*** .48
CCT: OC **.55*** -.15 .12 -.23 -.45 .06 -.18 -.14 -.42 .00 .02 .01 .21 .14 .15 .09
Temp asymmetry -.26 -.09 .20 -.01 .17 -.21 -.16 .25 .30 -.12 -.06 .07 .16 -.25 .07 .14 .04
Δ Temp asymmetry .05 -.08 -.20 -.02 -.39 .19 .03 -.40 -.19 -.13 -.18 -.31 .00 .16 .33 .40 .17 -.31
-1
-.50
0
.50
1
Pearson correlation

Figure 7. Correlation matrices.

Pearson correlation matrices presented for people with upper limb CRPS (a; n = 18), and people with lower limb CRPS (b; n = 18). Current pain intensity was reported using a numerical rating scale (0-10). CRPS severity (Harden et al., 2017) was calculated as the sum of signs, and symptoms. Movement quality was derived from a research assistant's ratings of videos of participant's movement (1 [worst imaginable] to 10 [best imaginable]) during the crossmodal congruency task (CCT), and beanbag sorting task. All quantitative sensory testing measures (i.e. allodynia, mechanical detection threshold, mechanical pain threshold), and the two-point discrimination threshold are expressed as difference scores (i.e. by subtracting the threshold for the non-affected side from the threshold of the affected side). For the Short-form McGill Pain Questionnaire 2 (SF-MPQ-2; Dworkin et al., 2009), and the Bath CRPS body perception disturbance scale (BPD; Lewis & McCabe, 2010) we used the total score. Tactile distance judgements (TDJs) are calculated by subtracting pre tool-use ratings from post tool-use ratings, for each arm (i.e. non-affected/dominant, affected/non-dominant). Interference scores from reaction time data from the CCT are presented for the sub-components of the two-way interaction between Tool Arrangement (crossed [C], uncrossed [U]), and Visual Field (same [S], opposite [O]). Absolute hand temperature asymmetries were calculated for uncrossed hands from the Hands Effector Condition. The change in hand temperature asymmetry was calculated by subtracting the absolute asymmetry for uncrossed hands from that of crossed hands. Significant correlations (i.e. $p < .05$) are presented in boldface. CRPS = Complex Regional Pain Syndrome. Movement qual = movement quality. MDT = mechanical detection threshold. MPT = mechanical pain threshold. Two-point discrim. = two-point discrimination threshold. SF-MPQ-2 = Short-form McGill Pain Questionnaire 2 (Dworkin et al., 2009). BPD = Bath CRPS body perception disturbance scale (Lewis & McCabe, 2010). TDJ = tactile distance judgements. Dom = dominant/non-affected body side. Affected = affected/non-dominant body side. CCT = crossmodal congruency task. SU = same visual field, uncrossed tools. OU = opposite visual field, uncrossed tools. SC = same visual field, crossed tools. OC = opposite visual field, crossed tools. Temp asymmetry = absolute hand temperature asymmetry. * $p < .05$, ** $p < .01$, *** $p < .001$

3.6.1 Age

There is evidence that the effects of tool-use on bodily and spatial representations can be lower for older than younger participants (Costello et al., 2015). Because our participants are on average older than those in the previous studies upon which our methods are based, we explored age as a covariate for the analyses of the CCT and TDJs. Age was not a significant covariate for the key interactions of interest. That is, there were no significant interactions involving Age and Set on TDJs, $Fs(1, 69) \leq 1.63$, $ps \geq .205$, $\eta_{2p} \leq .02$, nor any other significant interactions involving Age. For the CCT there were no interactions involving Age, Tool Arrangement, and Visual Field that reached statistical significance, $Fs(1, 69) \leq 3.35$, $ps \geq .072$, $\eta_{2p} \leq .05$. We therefore found no evidence that Age influence updating of bodily or spatial representations.

3.6.2 Movement Quality

Next, we considered that our findings from the TDJs and CCT showing that people with upper limb CRPS updated bodily and spatial representations, but their matched controls did not, might be attributed to differences in movement. That is, they might be a consequence of people with upper limb CRPS having to exert more effort than controls to manoeuvre the tools, or by having to adapt their movement strategies to perform the task (Romano, Uberti, Caggiano, Cocchini, & Maravita, 2019b). However, we did not find any evidence that the quality of movement was related to the updating of bodily or spatial representations for people with upper limb CRPS. That is, when we reanalysed the results using the research assistant's ratings of participants' quality of movement as a covariate we found that the covariate did not interact with Tool Arrangement and Visual Field in upper limb CRPS on the CCT, $Fs(1, 14) \leq 3.11$, $ps \geq .100$, $\eta_{2p} \leq .30$, nor were there any interactions with the covariate involving Set or Side of the Body on the TDJs, $F(1, 14) = 0.05$, $p = .394$, $\eta_{2p} = .05$. Due to low sample sizes we were not able to make direct comparisons between people who the research assistant correctly identified as having upper limb CRPS based on their movement (n = 6), and those who had had an upper limb affected but were not identified (n = 11). Nonetheless, this analysis provides no indication that the effort exerted or the way people moved were related to the updating of bodily and spatial representations.

4. Discussion

Our study was the first to examine the updating of body and peripersonal space representations in CRPS following tool-use. In upper limb CRPS, tactile distance judgements (TDJs) were not significantly different between arms pre tool-use, but were significantly greater for the CRPS-affected arm than the non-affected arm post tool-use. This is consistent with the perceived lengthening of the non-affected arm that is typically shown by pain-free controls, and/or a perceived shortening of the affected arm. People with lower limb CRPS showed similar (albeit non-significant) changes to the upper limb patients on TDJs. Contrary to our predictions, we found that both groups of people with CRPS showed patterns of crossmodal interference on the CCT indicative of an updating of peripersonal space that were more pronounced than the controls, who showed no evidence

of updating. Overall, our findings suggest that people with CRPS have more malleable bodily and spatial representations than controls.

Our control participants did not show the expected updating of bodily and spatial representations (e.g. Bassolino et al., 2015; Canzoneri et al., 2013b; Maravita et al., 2002; Miller et al., 2014; Miller et al., 2017; Vittersø et al., 2019). This could be because our sample was older than the typical student samples used (e.g. Canzoneri et al., 2013b; Maravita et al., 2002; Miller et al., 2017; Vittersø et al., 2019). Older age is associated with lower flexibility of such representations (e.g. following tool-use; Costello et al., 2015). The lack of change on TDJs following tool-use could be due to using a shortened version of the task (i.e. one repetition per distance instead of eight or more; Miller et al., 2017), potentially reducing the precision of our measure. Alternatively, this pattern could reflect the tool-use dependent effects decaying during the last CCT block, indicating that people with CRPS show a greater retention of this effects than controls. Therefore, our TDJ task might have been less sensitive to changes in body representation than those used in other studies. It is noteworthy that participants with CRPS showed updating of body and peripersonal space representations, although their matched controls did not.

Consistent with previous research (e.g. Bultitude et al., 2017; Lewis, Kersten, McCabe, McPherson, & Blake, 2007; Lewis & Schweinhardt, 2012; Moseley, 2005a; Turton et al., 2013) we found that participants with CRPS had distorted representations of their affected limbs. Tajadura-Jiménez and her colleagues recently showed that people with CRPS are able to update their bodily representations, because manipulating auditory feedback during walking changed the perceived dimensions of the CRPS-affected limb (Tajadura-Jiménez, Cohen, & Bianchi-Berthouze, 2017). Our study is the first to show that the ability to update bodily representations is different in people with CRPS relative to pain-free controls, and might differ for the affected and non-affected side of the body.

The difference in updating for the affected and non-affected side of the body is suggested by the changes in TDJs for the upper limb CRPS group. These were consistent with a perceived lengthening of the non-affected arm to facilitate the tools (i.e. the expected change following tool-use) and a perceived shortening of the affected arm, resulting in a significant difference in TDJs for the two arms after tool-use. A perceived shrinking of the arm, measured by forearm bisection, has been observed after pain-free participants performed tool-use tasks by using proximal body parts (i.e. shoulder), whereas using distal ones (i.e. wrist) resulted in perceived lengthening (Romano et al., 2019b). Our results might therefore be explained by people with upper limb CRPS using proximal movements in their affected arm to perform the tool-use tasks in order to protect painful distal parts of the arm. However, fewer than half of the people with upper limb CRPS had their pain and other symptoms limited to only a distal part of the arm, and we did not find any effect of the rated quality of participants' movement on the TDJs for upper limb CRPS. Alternatively, our results could reflect a tendency to avoid movement of the CRPS-affected limb in everyday life. Distorted bodily and spatial representations are common following limb immobilisation (Bassolino et al., 2015; Hall et al., 2016; Lissek et al., 2009), but quickly normalize once movement is regained (Bassolino et al., 2012). Limited movement of the affected limb has been suggested to cause distorted bodily and spatial representations in CRPS (Punt et al., 2013). Since most of our participants reported their limb as seeming larger than reality, our

findings could reflect a normalisation of the body representation for the CRPS-affected limb due to the execution of movements that are normally avoided.

We observed a body-side specific trend when testing the arms of people with lower limb CRPS, similar to the significant pattern we found in upper limb patients. Although we can only interpret this trend with caution, if it were found to be significant (e.g. in a larger sample), it would provide further support for the idea that the differences in updating that we observed cannot be attributed to peripheral changes, but instead implicate central mechanisms. Neurological assessments and neuroimaging have suggested the presence of parietal lobe dysfunction in CRPS ((Cohen et al., 2013; Maihöfner et al., 2007); for review see Kuttikat et al., 2016). For instance, motor impairments in CRPS correlate with posterior parietal cortex activation (Maihöfner et al., 2007), an area that is important for sensorimotor integration (Wolpert, Goodbody, & Husain, 1998) and maintaining a representation of the state of the body (Serino et al., 2013). The pattern of updating in upper limb patients is also consistent with altered parietal lobe functioning.

We expected people with CRPS to have less malleable spatial representations than controls, as their flexibility is use dependent (Serino, Bassolino, Farne, & Ladavas, 2007), and many people with CRPS avoid moving their affected limb (Punt et al., 2013). Yet our results from the CCT suggest more malleable representations in both upper and lower limb CRPS, or, alternatively (Holmes, 2012), more flexible spatial attention. The latter could be contributing to visuospatial attention biases in CRPS (Bultitude et al., 2017; Filbrich et al., 2017; Moseley et al., 2009; Reid et al., 2016). De Vignemont and Iannetti (2015) have proposed that peripersonal space is comprised of distinct goal-directed and defensive representations that serve to facilitate action and self-protection, respectively. Many participants with lower limb CRPS used walking aids, which might facilitate updating of goal-directed peripersonal space representations, and could potentially explain the greater flexibility that we observed (Galli, Noel, Canzoneri, Blanke, & Serino, 2015; Serino et al., 2007). However, this cannot be said for the upper limb sample, as a majority presented with motor deficits that would likely interfere with daily tool-use. It is possible that our findings instead reflect a greater activation of defensive representations by people with CRPS to avoid painful encounters. The dimensions of defensive peripersonal space representations have yet to be mapped in CRPS. However, enlarged representations, as measured by the hand-blink reflex, have been found in people with trigeminal neuralgia (Bufacchi, Sambo, Di Stefano, Cruccu, & Iannetti, 2017). Although the tool-use tasks in our study are typically considered goal-directed, it is possible that the updating seen reflects engagement of defensive peripersonal space in upper limb CRPS, as the tasks were painful. This is consistent with our finding that people with CRPS experienced greater crossmodal interference than controls, as peripersonal space representations facilitate multisensory processing (Serino, 2019). Our findings therefore highlight ways in which spatial representations might differ in CRPS.

Contrary to our predictions, we found no evidence that spatially defined hand temperature modulations were altered by active tool-use. This is not surprising given that we did not observe any spatially defined modulation of hand temperature before tool-use, when only hand Arrangement was manipulated, despite having a larger sample size than previous studies reporting such an effect (Moseley et al., 2013; Moseley et al., 2012). The equipment

that we used to measure temperature had sufficient sensitivity to detect effects of the magnitudes previously reported (Smith et al., 2009; van Marken Lichtenbelt et al., 2006), and has been used to demonstrate spatially-modulated changes in hand temperature of healthy individuals (Calzolari et al., 2016). In keeping with previous studies (Moseley et al., 2013; Moseley et al., 2012), we did not restrict participants gaze. Viewing one's hand can influence skin temperature (Sadibolova & Longo, 2014), and people with CRPS can have visuospatial attention biases away from their affected limb (Bultitude et al., 2017; Filbrich et al., 2017). Individual variability in attention bias could therefore contribute to spatially defined modulations of CRPS symptoms, when gaze is not controlled for. Our finding showing no spatially defined modulation of CRPS symptoms is therefore unlikely due to limitations of our equipment, but may relate to participants' gaze.

Distorted bodily and spatial representations could contribute to the maintenance of CRPS by distorting motor predictions. The sensorimotor theory of pain (Harris, 1999) postulates that an incongruence between motor predictions and sensory feedback could underpin some pathological pain conditions, such as CRPS (McCabe & Blake, 2007). Our findings suggest that bodily and spatial representations are more flexible and perhaps less stable in CRPS than controls. Less stable and/or reliable representations might compromise motor predictions by increasing noise in the sensorimotor system (Wolpert, Diedrichsen, & Flanagan, 2011), thereby increasing the likelihood of sensorimotor incongruence. Altered updating of bodily and spatial representations in people with CRPS is unlikely due to the acute experience of pain, as we have previously shown that capsaicin-induced pain in normally pain-free participants does not alter such updating (Vittersø et al., 2019). Although, a chronic experience of pain, and/or altered sensory processing (Bar-Shalita et al., 2018) might give rise to our results.

To conclude, our study was the first to examine how body and peripersonal space representations are updated in people with CRPS compared to controls. Our findings suggest that people with CRPS have less stable representations of the body and peripersonal space, and point toward alterations in neuropsychological processing that are specific to the affected body-side rather than selective for the CRPS-affected limb. Although we did not replicate previously reported spatially defined modulations of CRPS symptoms, our findings demonstrate that bodily and spatial processing is altered in a manner consistent with existing theories of how chronic pain might arise in the absence of clear tissue pathology.

Conflict of interest

The authors have no conflicts of interest to declare.

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Chapter 3 – Conclusions

Distorted representations of the body, and its surrounding space are common in pathological pain conditions, as I identified in Chapter 1. In the current chapter, I tested the idea that the updating of such representations might be impaired in CRPS. In contrast to my predictions, I found that body and peripersonal space representations were more flexible for people with CRPS compared to controls. As I showed in Chapter 2, these findings cannot be explained by the presence of acute pain.

The findings from this chapter are in agreement with a previous study suggesting that people with CRPS are able to update bodily representations (Tajadura-Jiménez, Cohen, & Bianchi-Berthouze, 2017). My findings, however, suggest that this process may differ depending on the side of the body that is being used.That is, the present findings suggest that people with upper limb CRPS updated the representations of their non-affected arm normally (i.e. a perceived lengthening to accommodate the tool), whereas they showed the opposite pattern for their affected arm. There was a similar pattern for people with lower limb CRPS, although this was not significant. These findings suggest that the updating of bodily representations differs between the affected and non-affected hand, and potentially the affected and non-affected side of body. I did not observe any updating for control participants, which suggests that the bodily representations are more flexible in people with CRPS.

I also found that people with CRPS showed a more pronounced updating of peripersonal space representations than controls. This effect was found for people with upper limb CRPS, and for people with lower limb CRPS. As this effect was found in both groups, and was not an influence of how people moved, it suggest that the findings are unlikely due to people with upper limb CRPS struggling to perform the tasks (e.g. due to motor deficits). Therefore, it appears that people with CRPS have more flexible representations of peripersonal space.

I observed a more pronounced updating of both bodily and spatial representations in CRPS than controls, which suggests that these representations are more flexible. If the flexibility of bodily and spatial representations relates to their stability, then this sheds light on how sensorimotor processing may be disrupted. For instance, less stable representations of the body and peripersonal space could introduce more noise into the sensorimotor system (Wolpert, Diedrichsen, & Flanagan, 2011). In turn, greater noise could make a sensorimotor incongruence more likely to occur. These findings therefore demonstrate one way in which sensorimotor processing could be altered in pathological pain, which may increase the likelihood of incongruent sensorimotor information.

I was not able to replicate findings suggesting a spatial modulation of CRPS symptoms (Moseley et al., 2013; Moseley et al., 2012). In contrast, there was evidence of no spatial modulation of hand temperature asymmetries in people with upper limb CRPS. It was therefore not surprising that I also did not find any influence of updating bodily and spatial representations on hand temperature asymmetries. These discrepant findings could be due to the fact that I did not preselect our sample on baseline hand temperature asymmetries, as previous studies did. However, when I analysed the data for only those who had a baseline asymmetry greater than 1°C, the results remain similar. The findings from this

chapter therefore oppose earlier findings that showed a spatial modulation of CRPS symptoms. The findings from Chapter 3 suggest that altered updating of bodily and spatial representations is not related to the spatial modulation of CRPS symptoms. In terms of the sensorimotor theory of pain, this finding suggests that the passive positioning of the hand is not related to symptom expression (i.e. a spatial modulation of hand temperature asymmetries). Taken together, these findings do not permit us to examine the influence of updating bodily and spatial representations on the spatially defined modulation of CRPS symptoms.

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Chapter 4: Normal manual straight ahead pointing in Complex Regional Pain Syndrome

Chapter 4 – Introduction

In this chapter I present a study that looks at manual straight ahead pointing in people with CPRS, and healthy controls. Altered representations of the body and space are common in pathological pain (Tsay, Allen, Proske, & Giummarra, 2015). Accuracy on manual straight ahead pointing depends on both bodily and spatial perception, and therefore provides us with information about their combined functioning.

Previous studies have found mixed results regarding the presence of any directional bias for people with CRPS (Christophe et al., 2016a; Christophe et al., 2016b; Jacquin-Courtois, Christophe, Chabanat, Reilly, & Rossetti, 2017; Kolb, Lang, Seifert, & Maihöfner, 2012). The current chapter will add to this debate by using a larger sample size than most previous studies, using a sensitive measure of pointing errors, and by overcoming previous task confounds. Furthermore, intra-individual variability on manual straight ahead pointing gives insight into the proprioceptive abilities, which can be altered in people with CRPS (Bank, Peper, Marinus, Beek, & van Hilten, 2013; Brun et al., 2019).

Accurate representations are needed to make predictions about the sensory outcome of a movement (Franklin & Wolpert, 2011). Therefore, in the context of the sensorimotor theory of pain, we would expect people with CRPS to show biased spatial representations, and impaired proprioception compared to controls.

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Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
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Normal manual straight ahead pointing in Complex Regional Pain Syndrome

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Abstract

Introduction: People with Complex Regional Pain Syndrome (CRPS) can present with altered bodily and spatial perception. One way of studying these alterations is through manual straight ahead (MSA) pointing, in which participants are required to point straight ahead of their perceived body midline without visual feedback of the hand. Previous MSA studies in CRPS were limited by task confounds or small sample sizes.
Objectives: To compare endpoint errors of MSA between people with CRPS versus matched controls, and according to the arm used (affected/non-dominant, non-affected/dominant).
Methods: Seventeen people with upper limb CRPS-I and 18 matched-controls performed 10 MSA pointing movements with each hand while kinematic data was recorded. Data was analysed using frequentist and Bayesian statistics.
Results: For all participants, pointing movements were biased towards the hand being used. We found moderate evidence of no difference between Groups, and no interaction with Side of Body on endpoint errors. The differences in variability between groups were non-significant/inconclusive. Correlational analyses showed no evidence of a relationships between MSA endpoint errors and clinical parameters (e.g. CRPS severity, duration, pain) or questionnaire measures (e.g. body representation, “neglect-like symptoms”, limb disability).
Conclusion: This study is the first to provide statistical evidence of no difference between people with CRPS and controls on MSA endpoint errors. Our findings suggest that clinical and self-reported measures, such as body representation distortion, and “neglect-like symptoms” are not related to any directional biases in MSA. Our findings therefore have implications for our understanding of neurocognitive changes in CRPS.

1. Introduction

Changes in spatial perception have been reported for people with Complex Regional Pain Syndrome (CRPS), which might be considered neglect-like (Halicka, Vittersø, Proulx, & Bultitude, 2020b; Legrain, Bultitude, De Paepe, & Rossetti, 2012), although see (Halicka et al., 2020a; Punt, Cooper, Hey, & Johnson, 2013). Neuropsychological changes in CRPS are evidenced through paradigms developed in the stroke literature, such as visual straight ahead (VSA) judgements, in which participants indicate when a visual target is passing directly in front of their body midline in an otherwise darkened room (i.e. absent of visual cues). VSA is thought to reflect any lateral shifts of the egocentric (i.e. anchored in the individual) reference frame and the body midline (Ferber & Karnath, 1999; Sumitani et al., 2007b). People with CRPS typically show a VSA bias away from the affected arm (Christophe et al., 2016b; Jacquin-Courtois, Christophe, Chabanat, Reilly, & Rossetti, 2017; Sumitani et al., 2014; Sumitani et al., 2007a; Sumitani et al., 2007b), or a leftward bias (Reinersmann et al., 2012) (i.e. pseudoneglect), although see (Christophe et al., 2016a; Wittayer, Dimova, Birklein, & Schlereth, 2018).

Manual straight ahead (MSA) is related to VSA, and involves pointing straight in front of one's perceived body midline without visual feedback. MSA depends on proprioceptive information and egocentric representations of space (Farnè, Ponti, & Làdavas, 1998), where deviations from zero reflect directional biases and the variability reflects proprioceptive precision. MSA has been used to quantify these effects in healthy controls (e.g. Blini, Cattaneo, & Vallar, 2013; Calzolari, Gallace, Moseley, & Vallar, 2016; Chokron et al., 2002; Colliot, Chokron, & Ohlmann, 2002; Fortis, Ronchi, Calzolari, Gallucci, & Vallar, 2013), people with post-stroke neglect (e.g. Chokron et al., 2002; Facchin, Bultitude, Mornati, Peverelli, & Daini, 2018; Farnè et al., 1998; Pisella, Rode, Farnè, Boisson, & Rossetti, 2002; Richard, Honoré, Bernati, & Rousseaux, 2004; Rossetti, Rode, Pisella, & Farné, 1998), and people with CRPS (Christophe et al., 2016a; Christophe et al., 2016b; Jacquin-Courtois et al., 2017; Kolb, Lang, Seifert, & Maihöfner, 2012).

Two case studies of the same woman with unilateral CRPS found that her MSA was biased toward the affected side when using her affected as well as her non-affected hand (Christophe et al., 2016b; Jacquin-Courtois et al., 2017), suggesting hyperattention towards (rather than "neglect" of) the affected limb. By contrast, in a group study MSA did not significantly differ from zero for either hand when averaged across seven people with CRPS (Christophe et al., 2016a). Because no control group was included, no direct conclusions can be drawn about MSA variability. In a larger study where participants were asked to extend their arm and point a laser pointer to an external point that was aligned with their body midline, no overall directional bias was found for either hand for 20 people with CRPS compared to pain-controls and pain-free controls (Kolb et al., 2012). Furthermore, people with CRPS did not show greater MSA variability (Kolb et al., 2012). However, because this version of MSA involved locating an external target, it is possible that this task involved both allocentric (i.e. object centred) and egocentric reference frames (e.g. Burgess, 2006). MSA is thought rely on egocentric representations of space (Farnè et al., 1998), hence using an external target introduces a possible confound. Egocentric reference frames are more closely related to motor control than allocentric ones (Crawford, Henriques, Medendorp, 2011), and thus they potentially offer greater insight into the sensorimotor functioning of

people with CRPS. Therefore, the evidence of MSA biases in CRPS is limited by potential task confounds, or small sample sizes without a control population.

We conducted a study of people with upper limb CRPS-I and pain-free controls using motion capture to sensitively measure MSA. We compared differences between Groups (CRPS, controls) and Side of Body (affected/non-dominant, non-affected/dominant) on MSA and its variability. We also explored the relationship between MSA, clinical data, and questionnaire measures to see if spatial biases were related to CRPS symptoms and/or disability.

2. Methods

2.1. Participants

We recruited 17 unilateral upper limb CRPS-I (M_{age} = 53.53, *SD* = 11.67; 16 female; 14 right-handed; Table 1); and 18 pain-free controls matched for age, sex, and handedness (M_{age} = 54.17, *SD* = 12.22; 17 female; 15 right-handed). Exclusion criteria for both groups were a history of brain injury, brain disorders, or psychiatric disorders. For safety reasons, we excluded people with a pacemaker, spinal cord stimulator or similar devices; or who were pregnant or breastfeeding. The study complied with the 2013 declaration of Helsinki and had ethical permission from the UK Health Research Authority (REC reference 12/SC/0557).

Table 1. Clinical information for people with upper limb CRPS.

ID	CRPS Severity (/16); B. criteria	Duration (months)	Current pain (/10)	Pain detect (/38)	CRPS BPD (/57)	DASH (/100)	TSK (/68)	NBQ (/6)	Inciting event	Medication	Comorbidities
UL1	13; R	67	8	24	20	65.9	29	3.2	Soft tissue injury of the hand	Co-codamol, etodolac, omeprazole, amitriptyline, sertraline	TMJ, FMS, IBS, migraine
UL2	5; C	64	4	15	14	29.5	29	1.8	Hand surgery	Aspirin, bisoprolol fumarate, levothyroxine sodium, ramipril, folic acid, methotrexate, statin, paracetamol	Frozen joints, arthrosis
UL3	10; R	32	8	29	43	79.5	39	4.2	None identified	Buprenorphine, gabapentin, naproxen, omeprazole, antihistamine, promethazine	FMS, migraines, PCOS, asthma
UL4	7; NOS	99	2	21	7	31.8	27	1.2	Elbow spiral fracture	Aspirin, felodipine, ramipril, paracetamol, lansoprazole	FMS
UL5	11; R	93	2	11	16	43.2	20	1.6	Soft tissue injury of the hand	Paracetamol, ibuprofen	
UL6	12; R	74	9	30	36	77.3	41	3.2	Shoulder surgery	Gabapentin, topiramate, zolmitriptan, paracetamol, ibuprofen, senna glycoside	Migraine, frozen shoulder
UL7	10; C	79	2	22	15	31.8	21	2.0	None identified	None	

ID	CRPS Severity (/16); B. criteria	Duration (months)	Current pain (/10)	Pain detect (/38)	CRPS BPD (/57)	DASH (/100)	TSK (/68)	NBQ (/6)	Inciting event	Medication	Comorbidities
UL8	6; NOS	91	1	8		11.4	29	2	Wrist fracture	Pregabalin, amitriptyline, calcium carbonate	
UL9	11; R	140	8	11	22	52.3	37	3.2	Multiple hand fractures	Bisoprolol	
UL10	11; R	39	10	19	29	63.6	41	3.6	Elbow fracture	Amitriptyline, omeprazole	
UL11	11; R	148	4	28	33	52.3	31	-	Wrist fracture	Pregabalin, amitriptyline, co-codamol, paracetamol	Low mood
UL12	10; R	16	8	12	22	38.6	40	3.0	Wrist fracture	Amitriptyline	Cartilage damage in knee (Left)
UL13	11; R	43	5	17	21	54.5	26	2.2	Surgery for dislocated shoulder	Morphine sulphate, pregabalin, propranolol	Migraines, PCOS
UL14	9; C	59	6	10	13	36.4	38	1.6	Soft tissue injury of the wrist	Co-codamol, amitriptyline, pregabalin	
UL15	14; R	39	5	24	32	77.3	40	3.4		Nortriptyline, paracetamol, aminophylline, budesonide, formoterol fumarate dihydrate, salbutamol sulphate	Asthma
UL16	12; R	14	6	26	33	59.1	52	5.6	Multiple wrist fractures	Pregabalin, paracetamol	Diabetes
UL17	8; R	138	6	16	7	-	-	1.0	Forearm fracture	Amitriptyline, tramadol, amlodipine	FMS

ID	CRPS Severity (/16); B. criteria	Duration (months)	Current pain (/10)	Pain detect (/38)	CRPS BPD (/57)	DASH (/100)	TSK (/68)	NBQ (/6)	Inciting event	Medication	Comorbidities
M (*SD*)	10.06 (2.41)	72.65 (41.62)	5.53 (2.74)	19.00 (7.1)	22.69 (10.66)	50.28 (19.74)	33.75 (8.58)	2.68 (1.22)			

B. criteria = Budapest Criteria (Harden et al., 2007,2010). BDP = Body perception disturbance score (Lewis et al., 2007). C = Clinical criteria for CRPS met (Harden et al., 2007,2010). DASH = The Disabilities of the Arm, Shoulder and Hand questionnaire (Gummesson et al., 2003). FMS = fibromyalgia syndrome. IBS = Irritable bowel syndrome. NBQ = Neurobehavioral questionnaire ("neglect-like symptoms"; Frettlöh et al., 2006; Galer & Jensen, 1999). NOS = CRPS not otherwise specified. Pain detect = Likelihood of neuropathic type pain (Freynhagen et al., 2006) PCOS = Polycystic ovary syndrome. TMJ = Temporomandibular joint syndrome. TSK = Tampa scale of kinesiophobia (Kori et al., 1990). R = Research criteria for CRPS met. - = not measured.

2.2. Procedure

After providing informed consent, participants were seated and rested their head on a chinrest. With their eyes closed, they performed 10 MSA pointing movements using their non-affected/dominant hand, followed by 10 pointing movements with their affected/non-dominant hand. We used a fixed order so that participants with CRPS could become familiar with the task before completing it with their affected hand.

To start a trial, participants placed their index finger on a raised tactile point (~1cm diameter) that was aligned with their body midline immediately in front of their trunk (the "start location"). A 200ms auditory cue (800 Hz) signalled that they should fully extend their arm and point their index finger to what felt like straight ahead of their nose. Participants could move at a comfortable speed. After holding their arm in this position for a few seconds, participants returned their finger to the start location. The experimenter then allowed the script to proceed, and once a sensor was detected within ±2cm laterally and ±3cm distally of the start location the next trial commenced.

We recorded kinematic data from a 6DOF sensor placed on the index finger with medical tape, using an electromagnetic motion capture system (trakSTAR™, 3D Guidance®, Northern Digital Incorporated). See preregistration (https://osf.io/6jpfg/) for full details about the data acquisition and pre-processing of kinematic data. We calculated angular errors (˚) at movement offset (i.e. once resultant velocity dropped below 50mm/s) from a straight line in the mid-sagittal plane for each trial. Errors made towards the affected/non-dominant side of space were coded as negative.
We adjusted for a calibration error (1.26°) causing a leftward bias in our data.

3. Results

We found evidence of no difference between Groups on endpoint errors from MSA pointing. There was also no evidence of any difference in variability between Groups, although the Bayesian analysis was inconclusive. We did not observe any correlations between MSA endpoint errors and clinical data, or questionnaire measures.

3.1 Directional errors

MSA was not different in CRPS compared to controls: we found moderate evidence of no main effect of Group, $F(1, 33) = 0.01$, $p = .971$, $\eta_{p2} < .01$, $BF_{10} = 0.288$, on endpoint errors. We found a main effect of Side of Body, $F(1, 33) = 14.11$, $p < .001$, $\eta_{p2} = .30$, $BF_{10} = 3208.531$

(Fig. 1), whereby people made errors towards their affected/non-dominant side when pointing with their affected/non-dominant arm (M = -4.16˚, SE = 1.26), and errors towards the non-affected/dominant side when using their non-affected/dominant arm (M = 3.21˚, SE = 0.96). The interaction between Group and Side of Body was not significant, $F(1, 33) = 0.06$, $p = .803$, $\eta_{p2} < .01$, with moderate evidence (Wagenmakers et al., 2018) of no effect $BF_{10} = 0.312$. The results were broadly similar when we re-expressed endpoint errors in terms of left (negative) and right (positive).

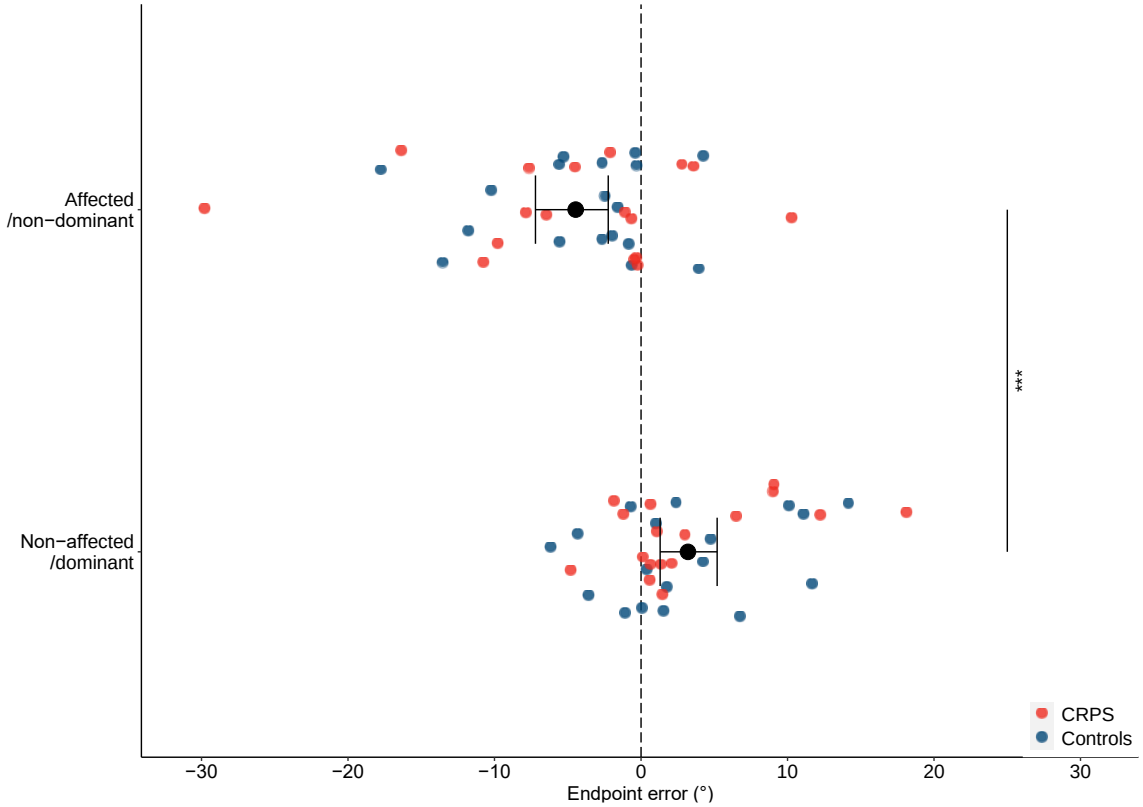

Figure 1. Manual straight ahead.
Mean endpoint errors in degrees are presented split by Side of Body (affected/non-dominant, non-affected/dominant), for participants with CRPS (orange dots, n = 17, $M_{affected}$ = -4.78˚, SD = 8.99; $M_{non\text{-}affected}$ = 3.42˚, SD = 5.77), and for control participants (blue dots, n = 18, $M_{non\text{-}dominant}$ = -4.16˚, SD = 5.85, $M_{dominant}$ = 3.01˚, SD = 5.79). Black dots show mean values, with bootstrapped 95% confidence intervals (error bars). A negative score indicates errors made towards the affected/non-dominant side. *** p < .001

3.2 Variability

When comparing the intra-individual standard deviations of endpoint errors, we found no significant main effect of Group, $F(1, 33) = 2.96$, $p = .095$, $\eta_{p2} = .08$, although this evidence was inconclusive, $BF_{10} = 1.131$. There was moderate evidence for no effect of Side of Body, $F(1, 33) = 0.12$, $p = .733$, $\eta_{p2} = .00$, $BF_{10} = 0.252$. There was no significant interaction between Group and Side of Body, $F(1, 33) = 2.43$, $p = .123$, $\eta_{p2} = .07$, although the Bayesian result was inconclusive, $BF_{10} = 0.887$.

3.3. Correlations

We explored correlations between MSA directional endpoint errors, MSA variability, clinical data (CRPS severity, duration, pain intensity), and questionnaire measures (neuropathic-type pain, body representation distortion, “neglect-like symptoms”, upper limb disability, fear of movement) for those participants with CRPS (Fig. 2). We did not observe any significant

correlations between endpoint errors or variability and clinical or questionnaire measures. The questionnaire measures were highly correlated with each other (r = .50 to .86).

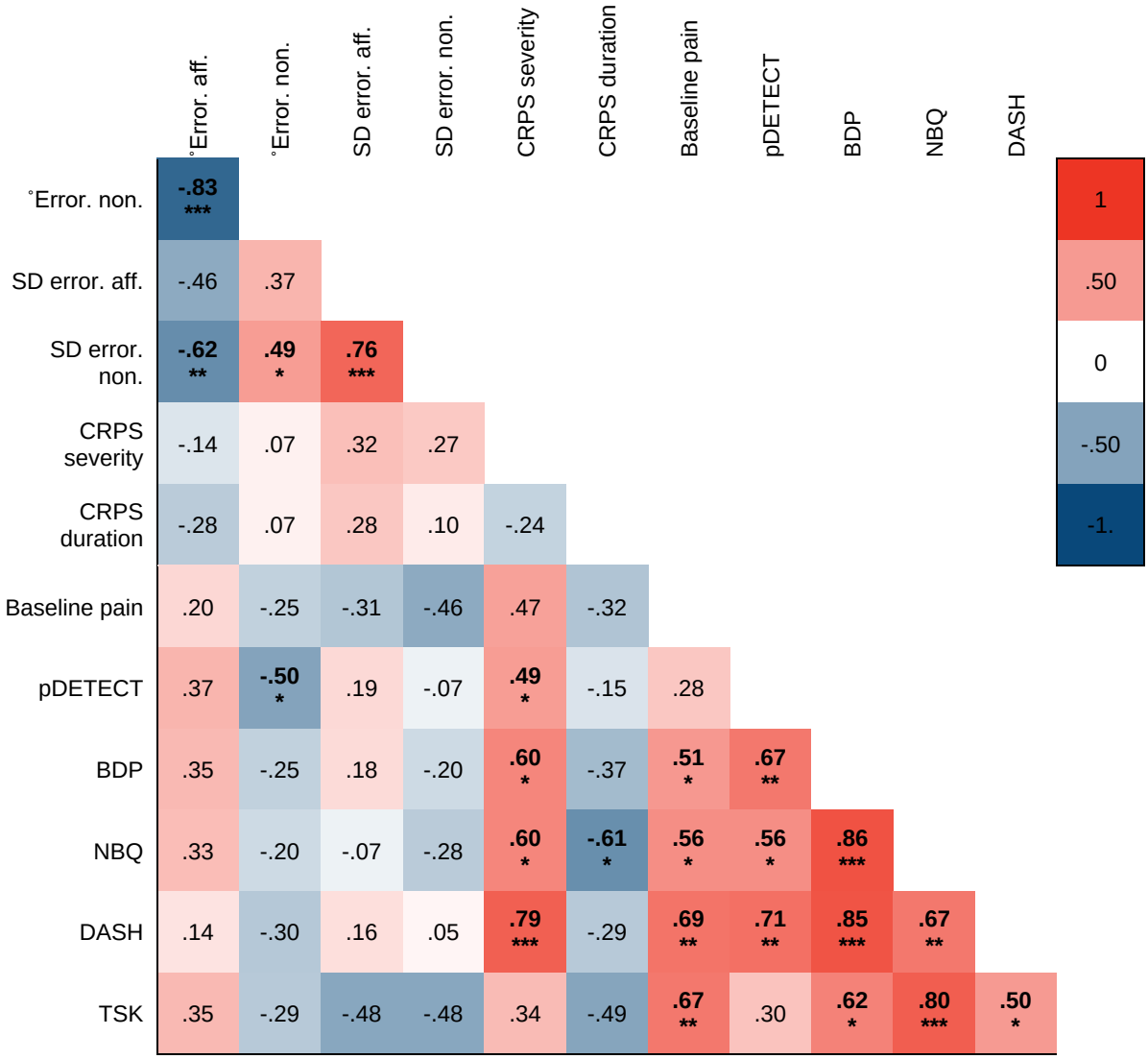

Figure 2. Correlation matrix.
Pearson correlation matrix for people with upper limb CRPS (n = 17). Significant correlations (i.e. p < .05) are presented in boldface. ˚Error aff. = endpoint error (˚) for the affected arm. ˚Error non. = endpoint error (˚) for the non-affected arm. SD error, aff. = Intra-individual variability (standard deviations) of endpoint error (˚) for the affected arm. SD error, non. = Intra-individual variability (standard deviations) of endpoint error (˚) for the non-affected arm. pDETECT = painDETECT questionnaire, a higher score reflects a greater likelihood of neuropathic pain (Freynhagen, Baron, Gockel, & Tölle, 2006). BDP = Body perception disturbance score, a higher score indicates greater disturbance (Lewis, Kersten, McCabe, McPherson, & Blake, 2007). NBQ = Neurobehavioral questionnaire (“neglect-like symptoms”), a higher score indicates a greater severity of “neglect-like” symptoms (Frettlöh, Hüppe, & Maier, 2006; Galer & Jensen, 1999). DASH = The Disabilities of the Arm, Shoulder and Hand questionnaire, a higher score indicates a more severe disability (Gummesson, Atroshi, & Ekdahl, 2003). TSK = Tampa scale of kinesiophobia where a higher score reflects greater fear of movement (Kori, 1990). *p < .05, **p < .01, ***p < .001

4. Discussion

We found no difference between people with CRPS and matched controls on MSA endpoint errors. This finding is consistent with previous research (Christophe et al., 2016a; Kolb et al., 2012), although our study is the first to use equivalence testing to show statistical evidence of no difference (Dienes, 2014; Lakens, 2017), and used a larger sample than other studies (Christophe et al., 2016a; Christophe et al., 2016b; Jacquin-Courtois et al., 2017). Regardless of Group, participants were biased towards the side corresponding to the hand used (e.g. towards the affected/non-dominant side of space when using their affected/non-dominant hand). These findings suggest that directional biases in spatial perception are not a ubiquitous feature of CRPS.

We did not find evidence of any differences in MSA variability when comparing between groups or the arm used. This is consistent with previous research on MSA variability in CRPS (Kolb et al., 2012), but contrasts with the bilateral proprioceptive deficits that have been reported in CRPS on arm position matching tasks (Brun et al., 2019; Lewis et al., 2010). These discrepancies could be due to the reference frames required, as MSA presumably relies more on an egocentric reference frame (Farnè et al., 1998), whereas arm position matching depends on a combination of egocentric and allocentric reference frames (Flanders & Soechting, 1995).

Individual MSA errors did not correlate with any clinical or questionnaire measures, suggesting that spatial biases were unrelated to CRPS symptoms. If “neglect-like symptoms” (Frettlöh, Hüppe, & Maier, 2006; Galer & Jensen, 1999) were related to spatial perception biases in CRPS, as in hemispatial neglect, they would correlate with MSA error - this was not the case in our sample. By contrast, our findings suggest that “neglect-like symptoms” were positively correlated with CRPS severity, pain, body representation distortion, upper limb disability, and fear of movement, which is in line with previous findings (Kolb et al., 2012). Therefore, “neglect-like symptoms” are of clinical relevance to CRPS (Wittayer et al., 2018), although they appear unrelated to spatial perception biases.

In contrast to biases seen with VSA pointing (Christophe et al., 2016b; Jacquin-Courtois et al., 2017; Reinersmann et al., 2012; Sumitani et al., 2014; Sumitani et al., 2007a; Sumitani et al., 2007b), our study corroborates studies suggesting that people with CRPS do not have a directional bias in MSA pointing (Christophe et al., 2016a; Kolb et al., 2012). VSA pointing is generally thought to measure shifts in egocentric reference frames (Ferber & Karnath, 1999; Sumitani et al., 2007b), and is likely to involve allocentric reference frames to a greater extent than MSA, as the latter is independent of any external cues. Discrepancies in the spatial biases in CRPS could relate to the different reference frames (egocentric, allocentric), regions of space (peripersonal, extrapersonal), and/or qualities (goal-directed, defensive) of the space being tested (Halicka et al., 2020b). Therefore, reconciling these discrepant findings is needed to further our understanding of neurocognitive changes in CRPS.

Conflict of interest
The authors have no conflicts of interest to declare.

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Chapter 4 - Conclusions

In this chapter I examined manual straight ahead pointing in people with CRPS, and healthy controls. This study builds on the idea that bodily and spatial representations can be distorted in people with pathological pain conditions (Chapter 1 & 3).

Similar to previous studies, I did not find evidence of any spatial bias (Christophe et al., 2016a; Kolb et al., 2012), when comparing people with CRPS to controls. There was, however, no evidence of any deficit in proprioception, which contrast previous findings (Brun et al., 2019; Lewis et al., 2010). The findings from the present chapter therefore suggest that both spatial representations and proprioception are intact in people with CRPS, which opposes predictions made by the sensorimotor theory of pain.

This chapter also contribute to the debate that neuropsychological changes in CRPS can be considered “neglect like” (Legrain, Bultitude, De Paepe, & Rossetti, 2012). As I found evidence of no spatial bias, this suggest that performance on manual straight ahead pointing is not “neglect-like” for people with CRPS. This finding adds to the literature suggesting that the analogy of hemispatial neglect does not capture the neuropsychological changes in CRPS (Halicka et al., 2020a; Halicka, Vittersø, Proulx, & Bultitude, 2020c).

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Chapter 5: Intact sensorimotor adaptation in Complex Regional Pain Syndrome: A kinematic analysis

Chapter 5 – introduction

In this chapter I present a study that characterised sensorimotor adaptation in people with CRPS, using prism adaptation. As I highlighted in Chapter 1, there are several sensorimotor processes that can be altered for people with CRPS, which is further evidenced by my findings in Chapter 3. However, only a few studies have examined sensorimotor integration in CRPS (Chapter 1), and none have looked at sensorimotor adaptation.

Implicit to the sensorimotor theory of pain (Harris, 1999) is the assumption that sensorimotor adaptation is impaired in pathological pain conditions. In healthy controls, the sensorimotor system will compensate for incongruent information by adapting (Bastian, 2008; Franklin & Wolpert, 2011). For people with pathological pain conditions, sensorimotor adaptation should be impaired for incongruences to result in pain; otherwise we would expect adaptation to compensate for the incongruent sensorimotor information. This chapter therefore allows us to test one of the key assumptions underpinning the sensorimotor theory of pain.

Prism adaptation has been used to study sensorimotor processing in many clinical populations, as well as in healthy people. Consequently, a lot is known about the neural mechanisms that are involved in different stages of prism adaptation (Panico, Rossetti, & Trojano, 2019). In neurological populations altered adaptation has been found for conditions such as people with cerebellar lesions (Calzolari, Bolognini, Casati, Marzoli, & Vallar, 2015; Hanajima et al., 2015; Pisella et al., 2005), and hemispatial neglect (Aimola, Rogers, Kerkhoff, Smith, & Schenk, 2012; Facchin, Bultitude, Mornati, Peverelli, & Daini, 2018). For instance, people with hemispatial neglect have been found to need more trials to adapt to the visual displacement introduced by the prisms (Facchin et al., 2018). This condition has been used as an analogy for understanding some of the neuropsychological changes that have been observed in CRPS (for reviews, see Halicka et al., 2020c; Legrain et al., 2012). Therefore, this chapter also allows for the neglect analogy to be tested in the context of sensorimotor processing for people with CRPS.

Prism adaptation has been trialled as a treatment for CRPS (Bultitude & Rafal, 2010; Christophe et al., 2016a; Halicka et al., 2020b; Sumitani et al., 2007). The pain relief was suggested to follow a normalisation of visuospatial attention biases, or improved sensorimotor integration (Sumitani et al., 2007). However, attention biases are not always found for people with CRPS (De Paepe et al., 2020; Halicka et al., 2020a), and prism adaptation has been found to reduce pain in the absence of any such biases (Christophe et al., 2016a). Therapeutic benefits might instead be due improving sensorimotor integration, although this has yet to be tested. The current chapter will therefore shed light on a potential mechanism that could be giving rise to the therapeutic benefits that have been reported for treating CRPS with prism adaptation.

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Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed		**Date**	07.05.2020

Intact sensorimotor adaptation in Complex Regional Pain Syndrome: A kinematic analysis

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Abstract
Incongruent sensorimotor information is theorised to contribute to the maintenance of pathological pain conditions, such as Complex Regional Pain Syndrome (CRPS). In a normal sensorimotor system, adaptation would typically compensate for such incongruences. Therefore, implicit to the theory is the assumption that sensorimotor adaptation is impaired, and/or unable to compensate for incongruent sensorimotor information for people with pathological pain. We tested this assumption in people with CRPS by characterising the process of adaption to lateral prismatic shifts in vision. People with unilateral upper limb CRPS-I (n = 17), and pain-free individuals (n = 18; matched for age, sex, and handedness) completed a dynamic prism adaptation paradigm with their affected/non-dominant, and non-affected/dominant hand, in a counterbalanced order. We found no evidence suggesting that strategic recalibration, which is used to correct for endpoint errors during early prism exposure, was different between people with CRPS and controls. Similarly, participants showed significant prism adaptation after-effects (i.e. endpoint errors made in the direction opposite to the prismatic shift for open-loop pointing movements), indicative of sensorimotor adaptation. The magnitude of this adaptation was not different between people with CRPS and pain-free controls, although our exploratory analysis suggested that the retention of such prism adaptation after-effect was greater for people with CRPS. Our study was the first to characterise sensorimotor adaptation in people with CRPS, and suggests that strategic recalibration, and sensorimotor adaptation to lateral prismatic shifts in vision is not impaired for people with CRPS. The latter contradicts existing theories of how pathological pain might be maintained in the absence of clear tissue pathology.

1. **Introduction**

Complex Regional Pain Syndrome (CRPS) is a pathological pain condition that is characterised by pain, motor deficits, and autonomic symptoms (Harden et al., 2010; Harden, Bruehl, Stanton-Hicks, & Wilson, 2007). Many people with CRPS also experience changes in addition to the physical characteristics of the condition. For instance, people with CRPS commonly report that the affected limb feels like it is not part of their body, and involuntary movements (Frettlöh, Hüppe, & Maier, 2006). These "neglect-like symptoms" (Galer & Jensen, 1999) predict worse pain outcomes in chronic CRPS (Wittayer, Dimova, Birklein, & Schlereth, 2018). People with CRPS typically experience their affected limb to be distorted in its shape and size (Bailey, Nelson, Lewis, & McCabe, 2013; Moseley, 2005; Peltz, Seifert, Lanz, Müller, & Maihöfner, 2011; Schwoebel, Friedman, Duda, & Coslett, 2001). Therefore, in addition to its physical manifestation, CRPS may also be accompanied by a range of neuropsychological changes (for reviews, see Halicka, Vittersø, Proulx, & Bultitude, 2020a; Kuttikat et al., 2016).

It has been suggested that neuropsychological changes contribute to the maintenance of physical symptoms in CRPS and related conditions. The sensorimotor theory of pain postulates that an incongruence between motor predictions and sensory outcomes could be driving several pathological pain conditions (Harris, 1999), such as CRPS (McCabe & Blake, 2007). This idea has been tested experimentally by having participants perform anti-phase limb movements with one limb occluded by a mirror, which is positioned such that the mirror image creates the visual illusion of synchronous arm movements (i.e. incongruent mirror visual feedback). For people with CRPS, incongruent mirror visual feedback has been found to increase pain and anomalous sensations (Brun, Mercier, et al., 2019), which are greater than those seen in pain-free controls. Compromised motor predictions and altered sensory feedback could be giving rise to incongruent sensorimotor information for people with CRPS. For instance, distorted representations of the body, and how they are updated (Vittersø, Buckingham, Halicka, Proulx, & Bultitude, 2020), might compromise motor predictions, thereby increasing the noise in the sensorimotor system. Altered sensory experiences and motor control are both part of the CRPS diagnostic criteria (Harden et al., 2010; Harden et al., 2007). Therefore, sensorimotor incongruences might arise from altered sensory feedback and/or compromised motor predictions. Under normal circumstances, however, sensorimotor adaptation occurs as a compensatory mechanism when the sensorimotor system is faced with conflicting information (Wolpert, Diedrichsen, & Flanagan, 2011). Implicit to the sensorimotor theory of pain, therefore, is the assumption that sensorimotor adaptation is disrupted in people with CRPS and related conditions, such that the sensorimotor system is not able to compensate for incongruent sensorimotor information. Understanding whether sensorimotor adaptation is altered in people with CRPS would provide further support for the sensorimotor theory of pain, and could inform new treatment approaches aimed at improving adaptation.

Sensorimotor adaptation can be studied experimentally using prism adaptation. A typical prism adaptation procedure involves performing pointing movements whilst wearing goggles fitted with prismatic lenses that create a lateral optical shift (Held & Freedman, 1963; Redding, Rossetti, & Wallace, 2005; Von Helmholtz, 1924). During prism exposure, participants initially make pointing errors in the direction of the prismatic shift. These

pointing errors will quickly reduce as movements are repeated. At first, strategic recalibration is needed to reduce pointing errors. That is, deliberately adjusting one's aim or mentally rotating the target location to correct for pointing errors (Rossetti, Koga, & Mano, 1993). However, in the longer term (e.g. over 50-100 movements) people will gradually adapt ("true adaptation") as their sensorimotor reference frames are realigned (Redding et al., 2005). That is, the spatial reference frames that coordinate visual, motor, and proprioceptive processing realign to compensate for the optical distortion introduced by the prims (Jeannerod & Rossetti, 1993). Once the prism goggles are removed, people will typically make pointing errors in the direction opposite to the optical displacement that they have been exposed to (the adaptation "after-effect"). The processes involved in prism adaptation have been studied in great detail (for reviews, see Jacquin-Courtois et al., 2013; Panico, Rossetti, & Trojano, 2019), so this paradigm enables distinct sensorimotor processes (e.g. strategic recalibration, sensorimotor realignment and its retention) to be examined in people with CRPS.

During the initial stages of prism exposure strategic recalibration is used to reduce endpoint errors. Trial-by-trial changes can be observed in movement plans, because people will update their aim (and therefore the direction in which they initiate a movement) to compensate for the error made on a previous trial (O'Shea et al., 2014). At a cortical level, strategic recalibration is thought to rely on a cerebello-parietal network, whereby the cerebellum is responsible for error detection, which then informs parietal areas involved in the strategic recalibration of movements (for review, see Panico et al., 2019). Impaired strategic recalibration has been reported for people with temporal lesions (Canavan et al., 1990), spinocerebellar ataxia type 2 (Fernandez-Ruiz et al., 2007), and hemispatial neglect (Aimola, Rogers, Kerkhoff, Smith, & Schenk, 2012; Facchin, Bultitude, Mornati, Peverelli, & Daini, 2018). The early stages of prism adaptation can therefore be used to investigate strategic recalibration, which is underpinned by cerebello-parietal processing.

With repeated movements during prism exposure, the realignment of visual and proprioceptive coordinates occurs (i.e. "true adaptation"), which takes longer to develop than strategic recalibration (Inoue et al., 2015). Sensorimotor realignment is typically indexed by the magnitude of the adaptation after-effects (i.e. the difference in endpoint errors during open-loop pointing directly after prism exposure, relative to baseline). It can also be detected in kinematic changes in the later stages of pointing movements during prism exposure (O'Shea et al., 2014). That is, the angle at which participants approach a target at peak deceleration after a prolonged period of prism exposure is predictive of the magnitude of prism after-effects. At a cortical level, sensorimotor adaptation is thought to rely on processing in the cerebellum and the primary motor cortex (Panico et al., 2019). For instance, cathodal transcranial Direct Current Stimulation (tDCS) of the cerebellum during prism exposure reduced the magnitude of the after-effects (Panico, Sagliano, Grossi, & Trojano, 2016). In contrast, anodal tDCS of the primary motor cortex during prism exposure increased the after-effects (O'Shea et al., 2017). Changes in functional connectivity between the cerebellum and the primary motor cortex have been found to correlate with the magnitude of prism after-effects (Tsujimoto et al., 2019). In clinical populations, impaired sensorimotor realignment has been reported for people with cerebellar lesions (Calzolari, Bolognini, Casati, Marzoli, & Vallar, 2015; Hanajima et al., 2015; Pisella et al., 2005). Prism adaptation therefore enables the realignment of visual and proprioceptive reference frames

to be studied, which is thought to rely on processing in and between the cerebellum and the primary motor cortex.

The realignment of visual and proprioceptive reference frames can be retained after normal movement has been regained (i.e. active retention). This retention reflects the motor system's maintenance of the adapted state (Prablanc et al., 2019), and is thought to depend on the motor cortical processing (Panico et al., 2016). Stimulating the motor cortex with anodal tDCS has been found to increase the retention of prism after-effects up to four days post exposure (O'Shea et al., 2017; Panico et al., 2017). Furthermore, a period of motor cortex stimulation one day post exposure caused a reactivation prism after-effects (Panico et al., 2017). That is, anodal tDCS of the motor cortex 24 hours after prism adaptation caused greater endpoint errors in the direction of sensorimotor after-effects (Panico et al., 2017), than prior to stimulation. Prism adaptation can therefore be used to investigate the retention of sensorimotor realignment, which depends on motor cortical processing.

Here, we present a study that aimed to characterise the process of prism adaptation in people with CRPS. During a dynamic prism adaptation paradigm, we investigated strategic recalibration; and the development, magnitude, and retention of sensorimotor realignment. We measured participants' movements using a magnetic motion capture system, which allowed us to examine several kinematic markers associated with strategic recalibration and sensorimotor realignment (O'Shea et al., 2014). People with CRPS and matched controls underwent prism adaptation once with each hand, which enabled us to compare outcomes between Groups (CRPS, controls), and the Side of Body used (affected/non-dominant, non-affected/dominant). We hypothesised that strategic recalibration and sensorimotor adaptation would be impaired for people with CRPS compared to control participants. That is, we expected that compared to pain-free controls, people with CRPS would require more trials for endpoint errors to decrease during prism exposure, and would show smaller magnitudes and less retention of after-effects. We also hypothesised that any impairments in strategic control and/or sensorimotor adaptation would be limited to, or more apparent, when people with CRPS used their affected arm, compared to their non-affected arm.

2. Materials and methods

We used a single-session mixed approach to characterise the process of prism adaptation in each individual, in which we compared the performance between people with CRPS and to that of controls.

In accordance with recent recommendations for pain research (Lee et al., 2018), the study was preregistered on the Open Science Framework (https://osf.io/6jpfg/).

2.1. Participants

Seventeen people with predominantly unilateral CRPS-I of an upper limb (M_{age} = 53.53 years, *SD* = 11.67; 16 female; 14 right-handed; Table 1) were recruited through a national CRPS registry, and from our database. The latter is an internal database of people with

CRPS consenting to participate in research who have been referred to us from the Royal United Hospitals (Bath, UK), the Oxford University Hospitals NHS Foundation Trust (Oxford, UK), Royal Stanmore (London, UK), and individuals who have contacted us directly about research participation. We decided on our sample size pragmatically, based on the maximum number of people with CRPS we could feasibly recruit within the financial and time constraints that we were faced with. All 17 participants with CRPS met the Budapest diagnostic criteria (Harden et al., 2010; Harden et al., 2007). Fourteen of the people with CRPS had previously participated in a randomised control trial of prism adaptation for pain relief (Halicka, Vittersø, McCullough, et al., 2020b; Halicka, Vittersø, Proulx, & Bultitude, 2020b). There was an average of 15.13 months (*SD* = 6.97) between participants completing the exposure phase of the randomised control trial and when they took part in the current study.

Table 14. Clinical information for people with upper limb CRPS.

ID	CRPS Severity (/16); Budapest criteria	Duration (months)	Current pain (/10)	Pain detect (/38)	CRPS BPD (/57)	DASH (/100)	TSK (/68)	NBQ (/6)	Inciting event	Medication	Comorbidities
UL1	13; R	67	8	24	20	65.9	29	3.2	Soft tissue injury of the hand	Co-codamol, etodolac, omeprazole, amitriptyline, sertraline	TMJ, FMS, IBS, migraine
UL2	5; C	64	4	15	14	29.5	29	1.8	Hand surgery	Aspirin, bisoprolol fumarate, levothyroxine sodium, ramipril, folic acid, methotrexate, statin, paracetamol	Frozen joints, arthrosis
UL3	10; R	32	8	29	43	79.5	39	4.2	None identified	Buprenorphine, gabapentin, naproxen, omeprazole, antihistamine, promethazine	FMS, migraines, PCOS, asthma
UL4	7; NOS	99	2	21	7	31.8	27	1.2	Elbow spiral fracture	Aspirin, felodipine, ramipril, paracetamol, lansoprazole	FMS
UL5	11; R	93	2	11	16	43.2	20	1.6	Soft tissue injury of the hand	Paracetamol, ibuprofen	
UL6	12; R	74	9	30	36	77.3	41	3.2	Shoulder surgery	Gabapentin, topiramate, zolmitriptan, paracetamol, ibuprofen, senna glycoside	Migraine, frozen shoulder

ID	CRPS Severity (/16); Budapest criteria	Duration (months)	Current pain (/10)	Pain detect (/38)	CRPS BPD (/57)	DASH (/100)	TSK (/68)	NBQ (/6)	Inciting event	Medication	Comorbidities
UL7	10; C	79	2	22	15	31.8	21	2.0	None identified	None	
UL8	6; NOS	91	1	8		11.4	29	2	Wrist fracture	Pregabalin, amitriptyline, calcium carbonate	
UL9	11; R	140	8	11	22	52.3	37	3.2	Multiple hand fractures	Bisoprolol	
UL10	11; R	39	10	19	29	63.6	41	3.6	Elbow fracture	Amitriptyline, omeprazole	
UL11	11; R	148	4	28	33	52.3	31	-	Wrist fracture	Pregabalin, amitriptyline, co-codamol, paracetamol	Low mood
UL12	10; R	16	8	12	22	38.6	40	3.0	Wrist fracture	Amitriptyline	Cartilage damage in knee (Left)
UL13	11; R	43	5	17	21	54.5	26	2.2	Surgery for dislocated shoulder	Morphine sulphate, pregabalin, propranolol	Migraines, PCOS
UL14	9; C	59	6	10	13	36.4	38	1.6	Soft tissue injury of the wrist	Co-codamol, amitriptyline, pregabalin	
UL15	14; R	39	5	24	32	77.3	40	3.4		Nortriptyline, paracetamol, aminophylline, budesonide, formoterol fumarate dihydrate, salbutamol sulphate	Asthma

ID	CRPS Severity (/16); Budapest criteria	Duration (months)	Current pain (/10)	Pain detect (/38)	CRPS BPD (/57)	DASH (/100)	TSK (/68)	NBQ (/6)	Inciting event	Medication	Comorbidities
UL16	12; R	14	6	26	33	59.1	52	5.6	Multiple wrist fractures	Pregabalin, paracetamol	Diabetes
UL17	8; R	138	6	16	7	-	-	1.0	Forearm fracture	Amitriptyline, tramadol, amlodipine	FMS
M (*SD*)	10.06 (2.41)	72.65 (41.62)	5.53 (2.74)	19.00 (7.1)	22.69 (10.66)	50.28 (19.74)	33.75 (8.58)	2.68 (1.22)			

BDP = Body perception disturbance score (Lewis et al., 2007). C = Clinical criteria for CRPS met (Harden et al., 2007,2010). DASH = The Disabilities of the Arm, Shoulder and Hand questionnaire (Gummesson et al., 2003). FMS = fibromyalgia syndrome. IBS = Irritable bowel syndrome. NBQ = Neurobehavioral questionnaire ("neglect-like symptoms"; Frettlöh et al., 2006; Galer & Jensen, 1999). NOS = CRPS not otherwise specified. Pain detect = Likelihood of neuropathic type pain (Freynhagen et al., 2006) PCOS = Polycystic ovary syndrome. TMJ = Temporomandibular joint syndrome. TSK = Tampa scale of kinesiophobia (Kori et al., 1990). R = Research criteria for CRPS met. - = not measured.

Eighteen pain-free control participants (M_{age} = 54.17 years, *SD* = 12.22; 17 female; 15 right-handed) matched for age (±5 years), sex, and self-reported handedness were recruited from a community sample. All participants took part in another experiment reported elsewhere (Chapter 4).

Participants were excluded if they reported a history of brain injury, brain disorders, or psychiatric disorders that can be associated with pronounced perceptual changes (e.g. schizophrenia; Tseng et al., 2015). Because the study involved exposure to a magnetic motion capture system, we also excluded people with a pacemaker, spinal cord stimulator or similar devices, and those who were pregnant or breastfeeding. All participants reported having normal or corrected to normal vision, and sufficient motor abilities to perform the movements required for the task. The study complied with the 2013 declaration of Helsinki and had ethical permission from the UK Health Research Authority (REC reference 12/SC/0557).

2.2. Stimuli and procedure

2.2.1. Questionnaire measures

After providing informed written consent, participants completed questionnaire measures. All participants completed the Edinburgh handedness questionnaire (Oldfield, 1971), in which a negative score (<-40) indicates left-handedness, and a positive score (>40) indicates right-handedness. Three people with CRPS were classed as left-handed (*M* = -83.3, *SD* = 28.9), four as ambidextrous (*M* = 19.6, *SD* = 18.0), and eight as right-handed (*M* = 87.5, *SD* = 18.3). Two control participants were classed as left-handed (*M* = -70.0, *SD* = 43.4), three as ambidextrous (*M* = 11.1, *SD* = 35.6), and 11 as right-handed (*M* = 95.0, *SD* = 11.8).

People with CRPS completed additional questionnaire measures regarding their pain, upper limb disability, fear of movement, body representation distortion, and “neglect-like symptoms” (Table 1). Neuropathic components of pain were assessed by the pain DETECT questionnaire (Freynhagen, Baron, Gockel, & Tölle, 2006), where a score above 18/38 suggests that a neuropathic component is likely (>90% probability). The QuickDASH (Gummesson, Atroshi, & Ekdahl, 2003) was used to evaluate the degree of upper limb disability, where more severe disability is indicated by a higher score (/100). The Tampa Scale of Kinesiophobia (Miller, Kori, & Todd, 1991) was used to measure pain-related fear of movement and re-injury, where scores range from 17 (no kinesiophobia) to 68 (highest possible kinesiophobia). Body representation distortion was assessed by the Bath CRPS Body Perception Disturbance Scale (Lewis & McCabe, 2010), scored from zero (no body perception disturbance) to 57 (highest possible body perception disturbance). Finally, severity of “neglect-like symptoms” were assessed by the Neurobehavioral questionnaire (Frettlöh et al., 2006; Galer & Jensen, 1999), scored from one (no “neglect-like symptoms”) to six (highest possible severity of “neglect-like symptoms”).

2.2.2. Prism adaptation

Participants performed a dynamic prism adaptation paradigm (Prablanc et al., 2019) that involved both open- and closed-loop trials. We used adaptation to optical shifts (~19°) away from the affected/non-dominant side (leftwards for 9/17 people with CRPS; leftwards for 3/18 controls) because there is some evidence that adaptation to shifts towards the affected side might exacerbate pain (Sumitani et al., 2007). Participants completed the prism adaptation protocol (Fig. 1) with each hand in a randomised and counterbalanced order. During open-loop trials participants' vision of their hand was blocked, and they performed pointing movements to a central visual target (i.e. 0°). For closed-loop trials, participants had vision of their hand when their arm was fully extended, whereas the rest of their arm from the wrist up was concealed (i.e. terminal exposure). Visual targets for closed-loop trials were 10° to the left or right of centre. For each set of 10 closed-loop trials, five left targets and five right targets were presented, in a randomised order.

	Baseline		Prism exposure											AE	Washout										
# of trials	20	15	10	2	10	2	20	2	20	2	20	2	20	15	10	2	10	2	10	2	10	2	10	2	10
Trial type	CL	OL	CL	OL	CL	OL	CL	OL	CL	OL	CL	OL	CL	OL	CL	OL	CL	OL	CL	OL	CL	OL	CL	OL	CL
Label			PC1	PO1	PA2	PO2	PC3	PO3	PC4	PO4	PC5	PO5	PC6		WC1	WO1	WC2	WO2	WC3	WO3	WC4	WO4	WC5	WO5	WC6

Figure 1. Prism adaptation protocol.
AE = Prism after-effects; CL = Closed-loop pointing; PC = closed-loop trials during prism exposure; PO = open-loop trials in-between prism exposure blocks; OL = Open-loop pointing; R = retention of prism after-effects; WC = closed-loop trials during washout; WO = open-loop trials in-between washout blocks.

The first four people with CRPS to participate performed an additional 42 trials (two open-loop trials followed by 40 washout trials) directly before the final 15 open-loop trials (i.e. the retention block). Despite their relatively good upper limb mobility, they found it difficult to complete all 287 pointing movements with their affected hand. We therefore reduced the number of washout trials (Fig. 1), and updated the preregistration accordingly (https://osf.io/6jpfg/). This resulted in a total of 245 trials per hand. As the number of washout trials can influence the retention of prism adaptation after-effects (Fernández-Ruiz & Díaz, 1999), we performed a follow-up analysis of Open-loop Blocks where we excluded the data from these four participants. Two people with CRPS were only able to perform prism adaptation with their non-affected hand. One of these participants completed the full protocol with their non-affected hand, however one person was not able to do so due to pain, and stopped after completing the third Retention Open-loop Block (R3). To include their data, we performed a separate analysis of the prism-after effects split by Side of Body (3.2.1).

Participants were seated at a custom table (Fig. 2), which had a protractor on its surface, a chin-rest affixed to the edge closest to the participant, and the magnet from the motion capture system attached to the back of the table. To avoid magnetic interference, the table was wooden, and held together by copper screws, with Velcro adjustments for the chin-rest. To start a trial, participants placed their index finger on a raised tactile point (~1cm diameter) that was aligned with their body midline and the central target, near to the trunk (i.e. the “start location”). The trial was triggered to start one second after a sensor was first detected within ±2 cm laterally and ±3 cm distally of the start location. The visual target, a red light-emitting diode (LED), appeared for 1 s, after which an audio cue (200 ms, 800 Hz) was played. Participants were instructed that upon hearing the audio cue, they should point as quickly as possible with their fully extended arm to the line leading to the visual target. The visual target stayed illuminated for a further 3 s. Participants were instructed to bring their hand back to the start location upon the target extinguishing. The experimenter then pressed a computer key to allow the script to proceed, and the next trial commenced. If interim open-loop trials (e.g. PO1, WO2) were completed incorrectly (e.g. a false start), they were repeated. No other trials were repeated.

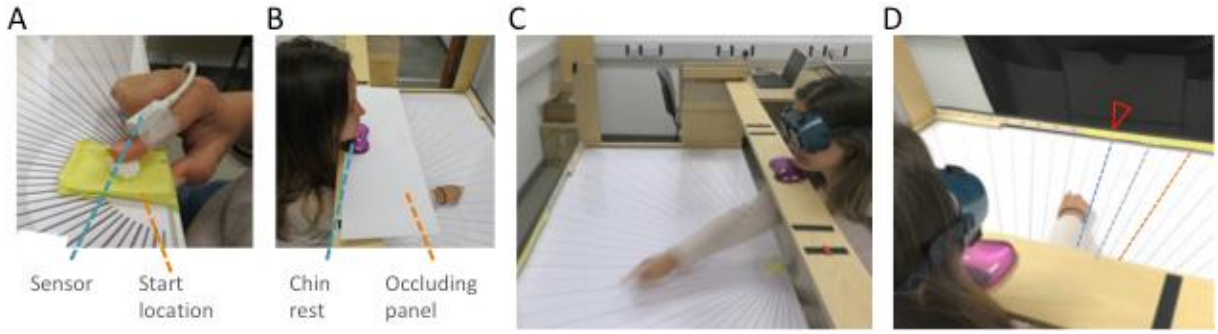


Figure 2. Prism adaptation set-up.
The prism adaptation table, chinrest, sensor (A), start location (A), and occluding panel (B). Panel B depicts an open-loop trial. Panels C and D depict closed-loop trials. The red arrow (D) indicates an example target location, with 10° left (blue), 10° right (orange), and central (i.e. 0°; grey) target axes superimposed.

We recorded kinematic data at 240 Hz from a sensor (six degrees of freedom) placed on participants' index finger with medical tape, using an electromagnetic motion capture system (trakSTAR™, 3D Guidance®, Northern Digital Incorporated). The kinematic data was low-pass filtered using a second-order dual-pass Butterworth filter at 10 Hz. We calculated instantaneous velocities and accelerations by differentiating the data with a 5-point central finite difference algorithm, twice per axis. Velocity vectors were combined to yield resultant velocity, which was used to determine movement onset, and movement offset. The threshold for movement onset was set at 50 mm/s. However, as people with CRPS can have motor impairments (e.g. spasms or arrests), we included additional criteria for movement offset. To determine movement offset, we used a threshold of 50 mm/s and the point at which the sensor returned to the same vertical location as movement onset. The later was taken as proxy of the hand being placed on the table. We visually inspected all trials, and manually adjusted movement onset and movement offsets that were identified by the above criteria when needed. We deleted trials where a false start was detected (i.e. when movements faster than 50 mm/s were detected for the first sample), which resulted in 2.52% of trials being removed.

We calculated endpoint errors (°) as the angle between a two-dimensional straight line connecting the start location and movement offset, and a straight line from the start location to the target (i.e. the target axis). We noticed a consistent leftward deviation in our data (Fig. S1). Specifically, the recorded endpoints of the baseline closed- and open-loop pointing trials were, on average, left of the target locations regardless of which hand participants were pointing with. This tendency was significantly different to zero for the controls. We deemed it unlikely that neurologically healthy participants would have any systematic leftward error in pointing with unperturbed vision prior to any sensorimotor adaptation (particularly one that would be in the same direction for each hand), therefore we assumed that this deviation was due to a calibration error. We corrected for this calibration error by subtracting the group-level mean error for control participants' baseline trials from the errors for all trials for each control and CRPS participant's data (1.18° leftwards error for closed-loop trials, 1.26° leftwards error for open-loop trials). This corrected for the presumed

calibration error, while retaining individual variability. We did not use the group-level mean baseline errors of participants with CRPS in this correction, because we would not necessarily expect their baseline pointing to be free of a directional bias. For instance, motor performance in CRPS has been reported to vary depending on the side of space in which the actions are performed (Reid et al., 2017). Therefore, the data for the participants with CRPS were corrected by the same values as used for the pain-free controls.

2.2.2.1. Exponential decay

Similar to previous studies (Facchin et al., 2018; Martin, Keating, Goodkin, Bastian, & Thach, 1996a; Nemanich & Earhart, 2015; O'Shea et al., 2014), we fitted an exponential decay function ($x = a \times e^{-b \times n} + c$) to endpoint errors from closed-loop trials for each person and each Side of Body during prism exposure and washout. We considered x as the endpoint error; a the initial error; b the decay constant; c the residual error; and n the trial number. The rate of error correction was expressed as the inverse of b (i.e. $1/b$). The inverse of b equates to the half-life of the endpoint error reduction curve, and therefore indicates half the number of trials needed for endpoint errors to reach the asymptote (i.e. the residual error c).

2.2.2.2. Trajectory orientations

We calculated kinematic markers that have previously been associated with strategic recalibration and sensorimotor realignment (see 3.5.; O'Shea et al., 2014). Specifically, we computed the tangential velocity vectors for peak acceleration (initial trajectory orientation) and peak deceleration (terminal trajectory orientation), and expressed them as the angle (in degrees) relative to the target axis. The initial trajectory orientation is related to the strategic calibration that occurs in early stages of prism exposure, whereas the terminal trajectory orientation is predictive of the magnitude of sensorimotor realignment (O'Shea et al., 2014).

2.3. Inference criteria

We processed and analysed the data in MATLAB (2014b), R (3.6.3), JAMOVI (1.1.9.0), and JASP (0.12). We considered p-values < .05 as statistically significant. We used Holm-Bonferroni corrections (Holm, 1979) for follow-up t-tests, indicated by "$p_{adjusted}$". See preregistration for full list of planned analyses (https://osf.io/6jpfg/). Analyses that were not preregistered are listed in the *Exploratory analyses* section (3.6.), or specified as exploratory.

3. Results

We did not find any difference between people with CRPS and controls on strategic recalibration, or on prism adaptation after-effects. Specifically there was no significant difference between Groups in the number of closed-loop trials needed for participants to correct for the visual displacement introduced by the prisms (3.3.). There was also no significant difference between Groups in the magnitude of endpoint errors during open-loop

pointing directly after prism exposure (3.2.). In contrast, our exploratory analysis suggested that people with CRPS showed greater retention of prism adaptation after-effects than control participants. We did not observe any differences between Groups on the kinematic markers of feedforward motor control, or sensorimotor realignment (3.5.).

3.1 Summary statistics

Descriptive statistics for clinical data and questionnaire measures for people with CRPS are presented in Table 1. As prism adaptation can be influenced by the speed of movement (Redding et al., 2005), and its main outcome measures relate to the precision of pointing movement, we compared peak velocity (3.1.1.), peak acceleration (3.1.2), and baseline endpoint errors (3.1.3) between Groups, and Side of Body.

3.1.1. Peak velocity

People with CRPS and controls performed pointing movements at a similar speed, although there was a tendency for people with CRPS to move slower when using their affected limb that did not survive correction for multiple comparisons. That is, there was no evidence of a difference between Groups (CRPS M = 1533.7 mm/s, SD = 343.9; controls M = 1575.9 mm/s, SD = 467.0), or an effect of Side of Body (affected/non-dominant M = 1545.4 mm/s, SD = 413.8; non-affected/dominant M = 1563.4 mm/s, SD = 412.4) on peak velocity averaged across all trials, Fs(1, 30) ≤ 0.60, ps ≥ .443, η_{2p} ≤ .02. There was, however, a significant interaction between Group and Side of Body, F(1, 30) = 9.05, p = .005, η_{2p} = .23. This interaction appeared to be driven by a smaller peak velocity between the affected side (M = 1472.6 mm/s, SD = 344.8) and the non-affected side (M = 1588.0 mm/s, SD = 334.0) for people with CRPS, whereas there was less of a difference between peak velocity for the non-dominant (M = 1608.2 mm/s, SD = 455.9) and dominant (M = 1543.2 mm/s, SD = 475.9) hands for controls. None of the differences between conditions was significant after correcting for multiple comparisons, t(30) ≤ 2.36, $p_{adjusted}$ ≥ .100, d ≤ 0.84.

3.1.2. Peak acceleration

Peak acceleration was comparable between people with CRPS and controls, although it was lower when people with CRPS used their affected hand. That is, there were no significant differences between Groups (CRPS M = 1058.2 mm/s^2, SD = 3995.8; controls M = 10968.1 mm/s^2, SD = 6002.6), or between the Side of Body used (affected/non-dominant M = 10437.8 mm/s^2, SD = 5046.2; non-affected/dominant M = 11111.7 mm/s^2, SD = 5212.7) on peak acceleration averaged across all trials, Fs(1, 30) ≤ 2.55, ps ≥ .121, η_{2p} ≤ .08. There was a significant interaction between Group and Side of Body, F(1, 30) = 5.99, p = .021, η_{2p} = .17. Follow-up analyses suggested that this interaction was driven by people with CRPS having lower peak acceleration when using the affected Side of Body (M = 9648.1 mm/s^2, SD = 3683.7) and the non-affected Side of Body (M = 11412.9 mm/s^2, SD = 4078.6), t(30) = 2.70, $p_{adjusted}$ = .044, d = 0.99. There were no significant difference in peak acceleration between the non-dominant (M = 11118.0 mm/s^2, SD = 5891.8) and dominant (M = 10816.5 mm/s^2, SD = 6109.6) Side of Body for controls, and or any differences

between Groups that depended on the Side of Body, ts(30) ≤ 1.10, ps$_{adjusted}$ ≥ .837, ds ≤ 0.40.

3.1.3. Baseline accuracy

Endpoint errors during closed-loop pointing were comparable between people with CRPS and controls. There were no significant main effects of Group (CRPS *M* = -0.01°, *SD* =0.43; controls *M* = -0.05°, *SD* = 0.39), or Side of Body (affected/non-dominant *M* = -0.12°, *SD* = 0.38; non-affected/dominant *M* = 0.06°, *SD* =0.41), or any interactions on endpoint errors for baseline closed-loop trials, Fs(1, 31) ≤ 2.69, ps ≥ .111, η_{2p} ≤ .08.

3.2. Open-loop endpoint errors

3.2.1. Prism adaptation after-effects

To address our main hypotheses relating to sensorimotor realignment, we analysed the effect of Group (CRPS, controls), Open-loop Block (baseline, prism after-effects, retention) on endpoint errors during open-loop pointing (Fig. 3).

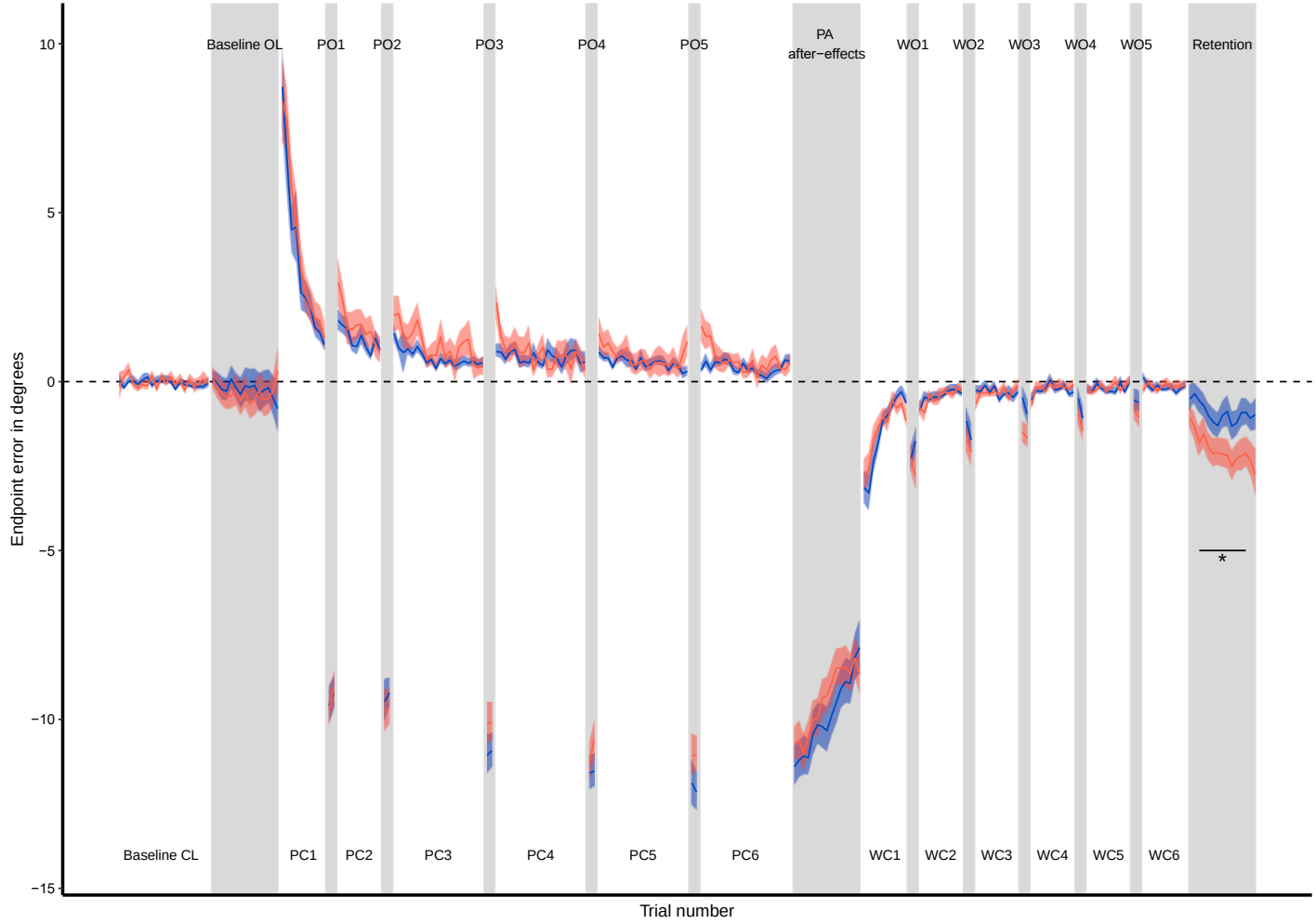


Figure 3. Endpoint errors.

Endpoint errors in degrees are presented for people with CRPS (n = 17; red) and controls (n = 18; blue). The boundaries of the coloured shaded areas show ± one standard error of the mean. The grey shaded areas indicate open loop (OL) trials (i.e. when participants performed pointing movements without vision of their hand). The white areas indicate closed-loop pointing, where participants had terminal exposure (i.e. they only had vision of their hand toward the end of a movement). Data from four participants who performed an additional two open-loop trials ("R6") and 40 closed-loop trials ("W7") at the end end of their washout phase (i.e. directly before the Retention block) were excluded from the Retention block. Their data were included for all other blocks. The black dashed lines shows the target orientation (i.e. zero degree error). Negative values indicate endpoint errors made towards the affected/non-dominant side. CL = closed-loop pointing; OL = open-loop pointing; PA = prism adaptation; PC = closed-loop trials during prism exposure; PO = open-loop trials in-between prism exposure blocks; WC = closed-loop trials during washout; WO = open-loop trials in-between washout blocks. * $p_{exploratory} < .05$

Participants adapted to the prismatic shift introduced by the goggles. There was a significant main effect of Open-loop Block, $F(2, 62) = 435.10$, $p < .001$, $\eta_{2p} = .93$. This effect was driven by errors in the open loop trials performed directly after prism exposure (i.e. the sensorimotor after-effects) that were significantly deviated in the direction opposite to the prismatic shift ($M = -9.72°$, $SD = 3.11$) compared to both baseline ($M = -0.29°$, $SD = 2.25$), and retention ($M = -1.24°$, $SD = 2.03$), ts(62) ≥ 23.95, ps$_{adjusted}$ ≤ .001, ds ≥ 6.08. Endpoint errors were also significantly deviated for the retention block compared to baseline, $t(62) = 2.95$, $p_{adjusted} = .005$, $d = 0.75$. These results suggest that adaptation to prism goggles successfully produced sensorimotor after-effects (i.e. open-loop pointing biased in the direction opposite to the prismatic shift), and that there was some retention of this effect after participants completed the washout trials.

There was also a significant main effect of Side of Body on endpoint errors, $F(1, 31) = 4.30$, $p = .047$, $\eta_{2p} = .12$, whereby participants made greater errors towards their affected/non-dominant side (i.e. in the direction opposite to the prismatic shift) when using their affected/non-dominant hand ($M = -4.21°$, $SD = 4.92$) than with their non-affected/dominant hand ($M = -3.34°$, $SD = 4.94$). These results suggest greater overall deviations in endpoint errors for the affected/non-dominant hand than the non-affected/dominant hand during open-loop pointing.

There was no evidence of a main effect of Group (CRPS $M = -3.82°$, $SD = 4.66$; controls $M = -3.71°$, SD =5.19) on endpoint errors, $F(1, 31) < 0.01$, $p = 1.000$, $\eta_{2p} < .01$. There were also no significant interactions involving Group, Side of Body, and/or Open-loop Block, Fs(1, 31) ≤ 2.35, ps ≥ .104, η_{2p} ≤ .07. This suggests that there was no difference between people with CRPS and controls on endpoint errors during open-loop pointing, and that this effect did not vary between Open-loop Blocks, and/or the Side of Body being used.

As the interaction between Group and Side of Body on endpoint errors during the prism after-effects Open-loop Block directly addressed our main hypothesis, we followed it up on an exploratory basis. We also performed a Bayesian analysis so that the strength of the evidence for the null hypothesis could be quantified. There was evidence of no main effect of Group (CRPS $M = -9.42°$, SD =2.73; controls $M = -9.98°$, $SD = 3.44$) on endpoint errors for the prism after-effects Open-loop Block, $F(1, 31) = 0.51$, $p = .480$, $\eta_{2p} = .02$ $BF_{10} = 0.38$, although the Bayesian analysis was inconclusive. There was also no significant main effect of Side of Body (affected/non-dominant $M = -10.22°$, SD =2.92; non-affected/dominant M =

-9.25°, *SD* = 3.27), $F(1, 31) = 2.20$, $p = .148$, $\eta_{2p} = .07$, $BF_{10} = 0.65$. There was no evidence of a significant interaction between Group and Side of Body, $F(1, 31) = 0.65$, $p = .426$, $\eta_{2p} = .02$, $BF_{10} = 0.45$. Therefore, we did not find any evidence to suggest a difference between people with CRPS and controls, or between the affected/non-dominant and the non-affected/dominant arm on the magnitude of endpoint errors for the prism after-effects Open-loop Block. We also found evidence of no effect for the interaction of these variables, which suggest that the magnitude of prism adaptation after-effects did not vary between levels of Group and Side of body. However, we did not find evidence of no effect of Group, Side of Body, or an interaction, on prism adaptation after-effects. Nonetheless, these findings contradict our main hypothesis as they do not provide any evidence of impaired sensorimotor integration for people with CRPS.

Two participants with CRPS were only able to complete the prism adaptation protocol with their non-affected hand, and were therefore excluded from the above analysis. However, when we included these participants and ran separate Group by Open-loop Block ANOVAs for the endpoint errors for each hand. The results were qualitatively similar to those reported above for the analysis and provided no evidence for differences in open-loop pointing error between people with CRPS and control participants.

Four participants with CRPS completed an additional 40 washout trials, and therefore had a potentially more thorough washout than the other participants. We therefore re-ran the analyses without these participants, to examine the effect of Group, Side of Body, and Open-loop Block, on endpoint errors. The overall pattern of results was similar to the analysis that included these participants. There was a main effect of Open Loop Block on endpoint errors, $F(2, 56) = 368.28$, $p < .001$, $\eta_{2p} = .93$. There were no other significant main effects, or any significant interactions, Fs$(2, 56) \leq 2.49$, ps $\geq .126$, $\eta_{2p} \leq .08$. Although the interaction between Group and Open-loop Block was not significant, we observed a qualitative difference between people with CRPS and controls for endpoint errors in the retention Open-loop Block. When we followed this analysis up on an exploratory basis, we observed a difference between Groups on the retention of sensorimotor after-effects. That is, there was a main effect of Group on endpoint errors during the retention Open-loop Block, $F(1, 28) = 4.38$, $p = .046$, $\eta_{2p} = .14$. The difference between Groups was due to a greater deviation in endpoint errors toward the affected/non-dominant side (i.e. in the direction opposite to the prismatic shift) for people with CRPS (*M* = -2.02°, *SD* =1.80) than controls (*M* = -0.93°, *SD* =2.05). This result suggests that people with CRPS had a greater retention of prism after-effects than controls. We also observed a difference in endpoint error depending on the Side of Body that was used. There was a main effect of Side of Body, $F(1, 28) = 11.03$, $p = .003$, $\eta_{2p} = .28$, which was caused by participants making endpoint errors that were more deviated towards the affected/non-dominant side (i.e. in the direction opposite to the prismatic shift) when using their affected/non-dominant hand (*M* = -2.13°, *SD* =1.82) compared to their non-affected/dominant hand (*M* = -0.61°, *SD* =1.94). There was no significant interaction between Group and Side of Body, $F(1, 28) = 0.56$, $p = .460$, $\eta_{2p} = .02$. These results therefore suggest that people with CRPS had a greater retention of prism adaptation after-effects than controls, and that both Groups retained a greater bias for their affected/non-dominant hand than their non-affected/dominant.

3.2.2. Development of prism adaptation after-effects

To examine the development of the prism after-effects we analysed the effect of Group, and Side of Body on endpoint errors during Interim Open-loop Blocks (Fig. 4; PO1, PO2, PO3, PO4, PO5).

In agreement with the analysis of prism after-effects (3.2.1), we found that participants gradually adjusted to the prismatic shift introduced by the goggles. That is, there was a main effect of Interim Open-loop Block on endpoint errors, $F(4, 124) = 21.82$, $p < .001$, $\eta_{2p} = .41$. We followed this effect up by comparing each Interim Open-loop Blocks to the first block (i.e. PO1). This effect was driven by a greater magnitude of endpoint errors made during the third (PO3; $M = -10.57°$, $SD = 3.21$), fourth (PO4; $M = -11.27°$, $SD = 3.07$), and fifth (PO5; $M = -11.57°$, $SD = 3.42$) Interim Open-loop Blocks compared to the first one (PO1; $M = -9.41°$, $SD = 2.91$), ts(124) ≥ 4.06, ps$_{adjusted}$ <.001, ds ≥ 0.73. The difference between the first and second (PO2; $M = -9.51°$, $SD = 3.18$) Interim Open-loop Blocks was not significant, $t(124) = 0.35$, $p_{adjusted} = .726$, $d = 0.06$.

The development of the after-effects was similar for people with CRPS and controls, and for the affected/non-dominant and non-affected/dominant hand. That is, there were no significant main effects of Group (CRPS $M = -10.28°$, $SD = 3.10$; controls $M = -10.66°$, SD =3.20), or Side of Body (affected/non-dominant $M = -10.69°$, SD =3.04; non-affected/dominant $M = -10.28°$, $SD = 3.26$) on endpoint errors, Fs(1, 31) ≤ 1.25, ps ≥ .272, η_{2p} ≤ .04.

There was a significant three-way interaction between Group, Side of Body, and Interim Open-loop Block (Fig. 4) on endpoint errors, $F(4, 124) = 2.59$, $p = .040$, $\eta_{2p} = .08$. The follow-up analysis split by Group suggested that this interaction was driven by a qualitatively greater effect of Interim Open-loop Block for controls than for people with CRPS. That is, for control participants, there was a main effect of Interim Open-loop Block on endpoint errors, $F(4, 68) = 17.08$, $p < .001$, $\eta_{2p} = .50$. We followed this effect up by comparing each Interim Open-loop Blocks to the first block (i.e. PO1). This effect was driven by a greater magnitude of endpoint errors made by controls participants during the third (PO3; $M = -11.00°$, $SD = 3.10$), fourth (PO4; $M = -11.56°$, $SD = 2.93$), and fifth (PO5; $M = -12.02°$, $SD = 3.61$) Interim Open-loop Blocks compared to the first one (PO1; $M = -9.41°$, $SD = 3.01$), ts(124) ≥ 3.72, ps$_{adjusted}$ <.001, ds ≥ 0.67. The difference between the first and second (PO2; $M = -9.34°$, $SD = 3.18$) Interim Open-loop Blocks was not significant, $t(124) = 0.39$, $p_{adjusted} = .694$, $d = 0.07$. There was no significant main effect of Side of Body for the control participants, $F(1, 17) = 0.71$, $p = .412$ $\eta_{2p} = .04$, and no interaction between Side of Body and Interim Open-loop Block, $F(4, 68) = 1.66$, $p = .169$, $\eta_{2p} = .09$, on endpoint errors. For people with CRPS, there was also a main effect of Interim Open-loop Block on endpoint errors, $F(4, 56) = 17.29$, $p < .001$ $\eta_{2p} = .32$. This effect was driven by the fourth (PO4; $M = -10.94°$, $SD = 3.21$), and fifth (PO5; $M = -11.06°$, $SD = 3.15$) Interim Open-loop Blocks were significantly different to the first one (PO1; $M = -9.42°$, $SD = 2.82$), ts(124) ≥ 3.52, ps$_{adjusted}$ ≤.002, ds ≥ 0.63. Endpoint errors from the second (PO2; $M = -9.70°$, $SD = 3.19$), and third (PO3; $M = -10.11°$, $SD = 3.10$) were not significantly different from the first one, ts(124) ≤ 2.10, ps$_{adjusted}$ ≥.075, ds ≤ 0.38. There was also no significant main effect of Side of Body, $F(1, 14) = 0.57$, $p = .462$, $\eta_{2p} = .04$, and no significant interaction between Side of Body and Interim Open-loop Block , $F(4, 56) = 1.27$, $p = .294$, $\eta_{2p} = .08$. The interaction between Group,

Side of Body, and Interim Open-loop Block in the overall analysis thus appeared to be driven by a more pronounced change in endpoint errors by Interim Open-loop Blocks for control participants. That is, endpoint errors were different from the first block at an earlier stage for controls (i.e. PO3) than people with CRPS (i.e. PO4). It was not clear how this varied between the Side of Body used. Taken together, the magnitude of change by Interim Open-loop Block was greater for controls, which might indicate subtle differences in the development of prism adaptation after-effects between people with CRPS and controls.

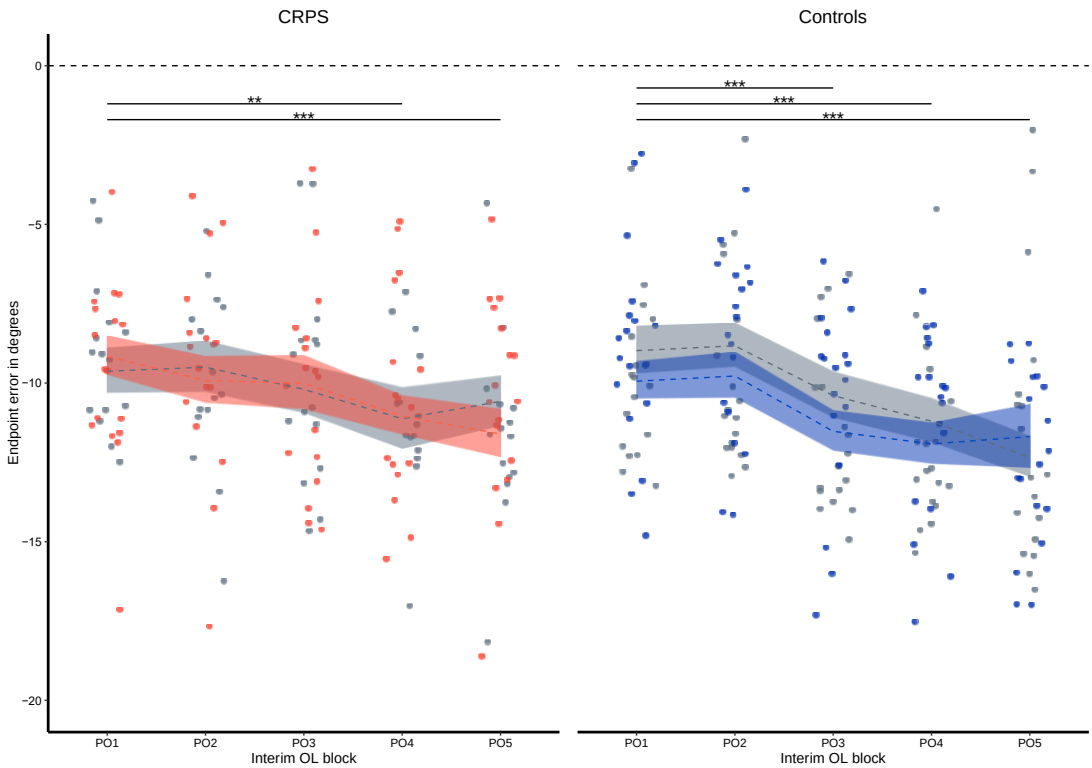


Figure 4. Development of PA after-effects.
Endpoint errors for Interim Open-loop Blocks in degrees are presented for people with CRPS (n = 17) and controls (n = 18), split by Side of Body (affected [red], non-dominant [blue], non-affected/dominant [grey]). The red, blue, and grey dashed lines show mean endpoint errors for each Interim Open-loop Block (PO1, PO2, PO3, PO4, PO5). Negative values indicate endpoint errors made towards the affected/non-dominant side. The boundaries of the shaded areas show ± one standard error of the mean. The black dashed lines shows the target location (i.e. zero degree error). ** $p_{adjusted}$ < .01, *** $p_{adjusted}$ < .001

3.2.3. Decay of sensorimotor after-effects

To examine the decay of the sensorimotor after-effects, we analysed the effect of Group, and Side of Body on endpoint errors during Washout Open-loop Blocks (Fig. 4; WO1, WO2, WO3, WO4, WO5).

The magnitude of open-loop pointing errors decreased during washout trials. That is, there was a significant main effect of Washout Open-loop Block, $F(4, 124) = 44.83$, $p < .001$, $\eta_{2p} = .59$. This main effect was driven by a decrease in the magnitude of endpoint errors from the

first (WO1; *M* = -2.25°, *SD* = 2.26) to the second (WO2; *M* = -1.66°, *SD* = 2.28) Washout Open-loop Block, $t(124) = 8.97$, $p_{adjusted} < .001$, $d = 1.61$. No other follow-up tests were significant, ts(124) ≤ 1.14, ps$_{adjusted}$ ≥.765, ds ≤ 0.20.

The decay of the after-effects did not differ between people with CRPS and controls, or between the affected/non-dominant and non-affected/dominant hand. That is, there were no significant main effects of Group (CRPS *M* = -1.65°, *SD* = 2.05; controls *M* = -1.11°, *SD* =2.02) on endpoint errors, $F(1, 31) = 0.09$, $p = .765$, $\eta_{2p} < .01$. There was also no significant effect of Side of Body (affected/non-dominant *M* = -1.98°, *SD* =2.00; non-affected/dominant *M* = -0.78°, *SD* = 1.92) on endpoint errors, $F(1, 31) = 2.75$, $p = .529$, $\eta_{2p} = .08$. Furthermore, there were no significant interactions observed involving Group, Side of Body, and/or Washout Open-loop Block, Fs(1, 124) ≤ 1.24, ps ≥ .298, η_{2p} ≤ .04. These results therefore suggest that the rate of retention of prism adaptation after-effects for open-loop trials did not vary between people with CRPS and controls, and was not related to the hand used.

3.3. Closed-loop endpoint errors during prism exposure

3.3.1. Closed-loop errors by prism exposure block

To address the research questions relating to the strategic error reduction during closed-loop prism exposure trials, we first analysed the effect of Group, and Side of Body on endpoint errors during Prism Exposure Blocks (Fig. 4; PA1, PA2, PA3, PA4, PA5, PA6).

During prism exposure participants made initial errors in the direction of the prismatic shift (i.e. towards the non-affected/dominant side), which quickly reduced. That is, there was a significant main effect of Prism Exposure Block, $F(5, 155) = 62.71$, $p < .001$, $\eta_{2p} = .67$. We followed-up this effect by comparing consecutive Prism Exposure Blocks (e.g. PA2 vs. PA3). This effect was driven by a reduction in endpoint errors between the first (PA1; *M* = 3.76°, *SD* =2.61) and second (PA2; *M* = 1.45°, *SD* =1.54) Prism Exposure Block, $t(155) = 10.72$, $p_{adjusted} < .001$, $d = 1.72$. No other follow-up tests were significant after correcting for multiple comparisons, ts(155) ≤ 2.41, ps$_{adjusted}$ ≥.068, ds ≤ 0.39.

The change in endpoint errors during closed-loop trials was not different for people with CRPS and controls, or for the affected/non-dominant and non-affected/dominant hand. That is, there were no significant main effects of Group (CRPS *M* = 1.51°, *SD* = 2.21; controls *M* = 1.25°, *SD* =1.71) on endpoint errors during prism exposure, $F(1, 31) = 0.31$, $p = .583$, $\eta_{2p} = .01$. There was also no significant effect of Side of Body (affected/non-dominant *M* = 1.19°, *SD* = 1.95; non-affected/dominant *M* = 1.50°, *SD* = 1.83) on endpoint errors, $F(1, 31) = 0.96$, $p = .335$, $\eta_{2p} = .03$. None of the interactions involving Group, Side of Body, and/or Washout Open-loop Block were significant, Fs(5, 155) ≤ 1.70, ps ≥ .138, η_{2p} ≤ .05. These results suggest that the change in endpoint errors during prism exposure trials did not vary between people with CRPS and controls, and was not related to the hand used.

3.3.2. Exponential decay of endpoint errors during prism exposure

To further examine the error reduction that occurs during prism exposure trials, we fitted the endpoint errors made during prism exposure to an exponential decay function ($x = a \times e^{-b \times n} + c$; see 2.2.2.1.). This procedure allowed us to calculate the rate at which endpoint errors decayed (i.e. 1/*b*) to reach the horizontal asymptote *c*. The latter indicates the residual endpoint error of pointing movements (i.e. their deviation from zero).

Before analysing the constants derived from the fitted models, we analysed the model fit. The model failed to converge, or there was no exponential fit for one person with CRPS (non-affected hand), and for one control (dominant hand). Next, we compared the model fit parameters between Groups and Side of Body, for those cases where the model did converge and there was an exponential decay (CRPS n = 14; controls n = 17). The results suggested that the models were not different across Groups and Side of Body (see Supplementary Text T1/Appendix 3). That is, the prediction errors (i.e. the root-mean-square error [RMSE]) which indicated the mean distance from a predicted value to an observed value, for individually fitted models was not significantly different between Groups, or Side of Body. There were also no significant differences in how much variance was explained by the models (i.e. the *adj.* R^2) between Groups, or Side of Body. Therefore, as there was no clear difference in the model fits between people with CRPS and controls, or any clear differences depending on the hand used, we proceeded to analyse the constants derived from the models (i.e. 1/*b*, and *c*; Fig. 5).

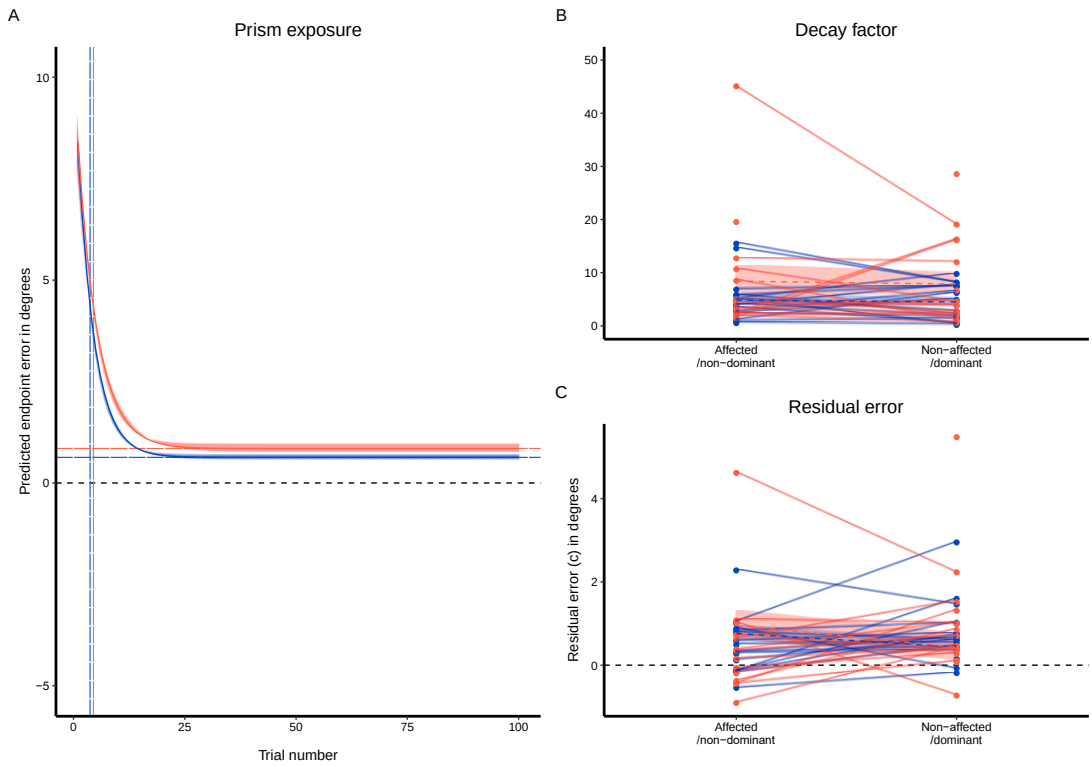


Figure 5. Decay of endpoint errors during prism exposure.
Predicted values for an exponential decay function ($x = a \times exp^{-b \times n} + c$) for endpoint errors from prism exposure at a group level (A). In figure A, solid lines indicate the predicted value, and the boundaries of the shaded areas depict the 95% confidence interval for the constants (i.e. *a*, *b*, *c*) fitted to group-level data. The black dashed lines shows the target (i.e. zero degree error) adjusted for calibration error (-1.18°). Negative values indicate endpoint errors made towards the affected/non-dominant side (A, C). The coloured dashed lines (A) indicate the decay constant (i.e. 1/*b*; vertical lines), and the residual error (i.e. *c;* horizontal lines), for people with CPRS (red), and controls (blue). Points depict individual level data is presented for the decay factor (i.e. 1/b; B) and the residual error (i.e. c; C) split by Side of Body (affected/non-dominant, non-affected/dominant), for people with CRPS (red), and controls (blue). Data points are connected for each participant, given that they had data and that we were able to fit their data to an exponential decay function. The coloured dashed lines (B, C) indicate group means, and the boundaries of the coloured shaded areas show ± one Standard Error of the Mean. Negative values (C) indicate endpoint errors made towards the affected/non-dominant side.

Endpoint errors decayed at a similar rate for people with CRPS and controls, and for the affected/non-dominant and non-affected/dominant hand. That is, there was no significant difference between people with CRPS ($M_{1/b}$ = 4.66, *SD* =3.69) and controls ($M_{1/b}$ = 8.13, *SD* = 9.65) on the decay factor (i.e. 1/*b*), $F(1, 29) = 1.23$, $p = .277$, $\eta_{2p} = .04$. There was no significant main effect of Side of Body (affected/non-dominant $M_{1/b}$ = 6.45, *SD* = 8.28; non-affected/dominant $M_{1/b}$ = 6.13, *SD* = 6.27) on the decay factor, $F(1, 29) = 0.40$, $p = .535$, $\eta_{2p} = .01$. Furthermore, there was no significant interaction between Group and Side of Body on the decay factor, $F(1, 29) = 0.07$, $p = .793$, $\eta_{2p} < .01$. These results therefore suggest that a comparable number of trials were needed by people with CPRS and controls, while using either hand, for their endpoint errors to decay during prism exposure.

The residual endpoint error during prism exposure was similar between people with CRPS and controls. That is, there was no significant difference in the residual error between people with CRPS (M_c = 0.70°, *SD* = 1.34) and controls (M_c = 0.60°, *SD* = 0.70), $F(1, 29) < 0.01$, $p = .992$, $\eta_{2p} < .01$. There was a tendency towards greater residual errors in the direction of the prismatic shift (i.e. towards the non-affected/dominant side) for the non-affected/dominant arm (M_c = 0.86°, *SD* = 1.08) compared to the affected/non-dominant arm (M_c = 0.43°, *SD* = 0.97), although not significant, $F(1, 29) = 3.10$, $p = .089$, $\eta_{2p} = .10$. There was no significant interaction between Group and Side of Body on the residual, $F(1, 29) = 0.13$, $p = .724$, $\eta_{2p} < .01$. Our results therefore suggest that the residual error during prism exposure trials was not different between people with CRPS and controls, and that there were no differences between groups that depended on the hand that was used.

3.4. Closed-loop endpoint errors during washout

3.4.1. Closed-loop errors by washout block

To address the research questions relating change in endpoint errors during closed-loop washout trials, we first analysed the effect of Group and Side of Body on endpoint errors during Washout Blocks (Fig. 4; WC1, WC2, WC3, WC4, WC5, W6).

Participants quickly deadapted during the washout phase. There was a main effect of Washout Block on endpoint errors, $F(5, 155) = 45.98$, $p < .001$, $\eta_{2p} = .60$. This effect was driven by a decrease in the magnitude of endpoint errors from the first (*M* = -1.44°, *SD* =1.22) to the second (*M* = -0.45°, *SD* =0.60) Washout Block, $t(155) = 9.58$, $p_{adjusted} < .001$, $d = 1.54$. No other follow-up tests were significant, ts(124) ≤ 1.22, ps$_{adjusted}$ ≥.896, ds ≤ 0.20.

Endpoint errors from washout trials were not significantly different between people with CRPS and controls. That is, there was no significant difference between people with CRPS (*M* = -0.45°, *SD* = 0.56) and controls (*M* = -0.49°, *SD* =0.86) on endpoint errors, $F(1, 31) = 0.08$, $p = .777$, $\eta_{2p} < .01$. There was a tendency for participants to make greater errors in the direction of the affected/non-dominant side (i.e. opposite to the induced prismatic shift) for the affected/non-dominant hand (*M* = -0.58°, *SD* = 0.72) than the non-affected/dominant hand (*M* = -0.36°, *SD* = 0.90), although not statistically significant, $F(1, 31) = 3.19$, $p = .084$, $\eta_{2p} = .09$. None of the interactions involving Group, Side of Body, and/or Washout Block were significant, Fs(5, 155) ≤ 1.14, ps ≥ .343, η_{2p} ≤ .04. These results therefore suggest that people with CRPS and controls did not differ in the magnitude of endpoint errors during closed-loop washout trials, although there was a trend for both groups to show a greater bias towards the affected/non-dominant side when using their affected/non-dominant hand.

3.4.2. Exponential decay of endpoint errors during washout

To further examine the error reduction during washout trials, we fitted the endpoint errors to an exponential decay function ($x = a \times e^{-b \times n} + c$; see 2.2.2.1. and 3.3.2.).

Prior to analysing the constants from the exponential decay function, we analysed the model fit. We were unable to fit an exponential decay function for two participants with CRPS, both

for their affected hand. For those cases where the model did converge and there was an exponential decay (CRPS n = 13; controls n = 18), we compared the model fit parameters between Groups and Side of Body. As there were no clear difference in the model fits (i.e. RMSE, *adj.* R^2; see Supplementary Text T1/Appendix 3) between people with CRPS and controls, and the tendency for the models to explain a greater proportion of the variance for the non-affected/dominant hand did not vary between groups, we proceeded to analyse the constants derived from the models (i.e. 1/*b*, and *c*; Fig. 6).

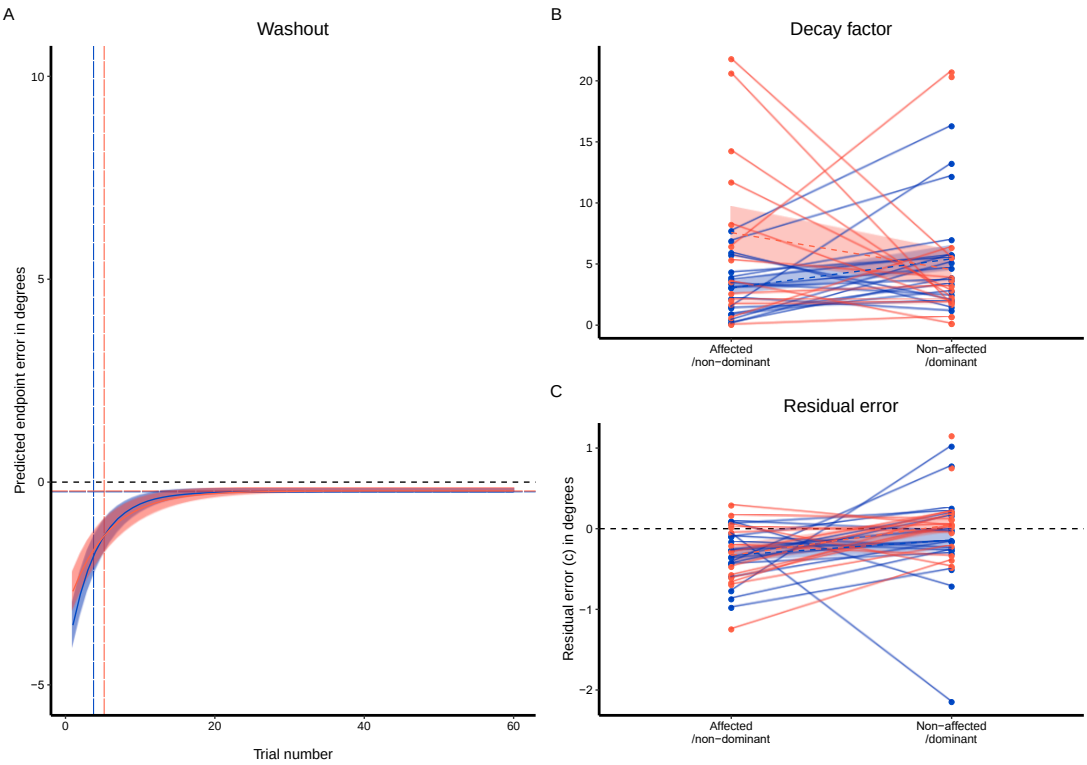


Figure 6. Decay of endpoint errors during washout.
Predicted values for an exponential decay function ($x = a \times exp^{-b \times n} + c$) for endpoint errors from washout at a group level (A). In figure A, solid lines indicate the predicted value, and the boundaries of the shaded areas depict the 95% confidence interval for the constants (i.e. *a*, *b*, *c*) fitted to group-level data. The black dashed lines shows the target (i.e. zero degree error). Negative values indicate endpoint errors made towards the affected/non-dominant side (A, C). The coloured dashed lines (A) indicate the mean decay constant (i.e. 1/*b*; vertical lines), and the mean residual error (i.e. *c;* horizontal lines), for people with CPRS (red), and controls (blue). Points depict individual level data is presented for the decay factor (i.e. 1/b; B) and the residual error (i.e. c; C) split by Side of Body (affected/non-dominant, non-affected/dominant), for people with CRPS (red), and controls (blue). Data points are connected for each participant, given that they had data and that we were able to fit their data to an exponential decay function. The coloured dashed lines (B, C) indicate group means, and the boundaries of the coloured shaded areas show ± one Standard Error of the Mean. Negative values (C) indicate endpoint errors made towards the affected/non-dominant side.

The rate at which endpoint errors reduced during washout trials was not significantly different for people with CRPS and controls, and for the affected/non-dominant and non-affected/dominant hand. That is, the decay rate did not significantly differ between people

with CRPS ($M_{1/b}$ = 5.86, SD = 6.81) and controls ($M_{1/b}$ = 4.23, SD = 3.61), F(1, 29) = 1.41, p = .244, η_{2p} = .05. There was also no significant difference in decay rate that depended on the Side of Body (affected/non-dominant $M_{1/b}$ = 4.94, SD = 5.48; non-affected/dominant $M_{1/b}$ = 4.99, SD = 5.26), F(1, 29) = 0.23, p = .635, η_{2p} = .01. There was, however, a significant interaction between Group and Side of Body on the decay rate, F(1, 29) = 6.14, p = .019, η_{2p} = .17. The interaction was driven by a difference between people with CRPS ($M_{1/b}$ = 7.57, SD = 7.38) and controls ($M_{1/b}$ = 3.04, SD = 2.35) when using their affected/non-dominant hand. Although this difference was no longer significant after correcting for multiple comparisons, t(57.32) = 2.54, $p_{adjusted}$ = .056, d = 0.67. This suggests that there was a tendency for people with CRPS to need more trials to bring their endpoint errors back to baseline during washout than controls when using their affected hand. No other follow-up comparisons between each level of Groups and Side of Body were significant, ts(57.32) ≤ 1.94, pS$_{adjusted}$ ≥.186, ds ≤ 0.39. These results therefore suggest that there was no overall difference between people with CRPS and controls in the number of trials needed to correct for endpoint errors during the washout phase. There was also no difference that depended on the hand used. However, there was a tendency for people with CRPS to need more trials for their endpoint errors to decay than controls when using their affected/non-dominant hand.

The residual endpoint error during washout trials was similar for people with CRPS and controls. That is, there was no main effect of Group (CRPS M_c = -0.12°, SD = 0.46; controls M_c = -0.23°, SD = 0.52) on residual errors (i.e. c), F(1, 29) = 0.15, p = .700, η_{2p} = .01. Although not significant, there was a tendency for participants to have a greater magnitude of residual error towards the affected/non-dominant side (i.e. the direction opposite to the prismatic shift) for their affected/non-dominant hand (M_c = -0.33°, SD = 0.36) compared to their non-affected/dominant hand (M_c = -0.05°, SD = 0.55), F(1, 29) = 3.85, p = .059, η_{2p} = .12. The interaction between Group and Side of Body on residual error was not significant, F(1, 29) = 0.12, p = .730, η_{2p} < .01. Therefore, our results suggest that the residual error during washout trials was not different between people with CRPS and controls. There was a tendency for participants to have greater error in the direction opposite to the prismatic shift for their affected/non-dominant hand, compared to their non-affected/dominant hand, which did not vary between Groups.

3.5. Kinematic changes during prism exposure

3.5.1. Feedforward motor control

To examine the strategic changes in feedforward motor control during early prism exposure trials (i.e. trials 1 to 10), we tested the relationship between the magnitude of endpoint errors on a given trial (n) and the change in movement plan on the subsequent trial (n+1). That is, we correlated endpoint errors for each early trial (n) with the change in initial trajectory orientation on the next trial (i.e. trial$_{n+1}$ - trial$_n$), on detrended data (Fig. 7). For each participant's Side of Body (affected/non-dominant, non-affected/dominant), we fitted endpoint errors and initial trajectory orientations to an exponential decay function ($x = a \times e^{-b \times n} + c$; see 2.2.2.1). We computed the residuals by subtracting the predicted values (i.e. x) from the observed endpoints for each trial. Then we calculated the change in initial trajectory orientation by subtracting the detrended values for a given trial (n) from those of

the subsequent trial (*n*+1). For each participant's Side of Body (affected/non-dominant, non-affected/dominant), we correlated the residuals of the endpoint error ($trial_n$) with the change in initial trajectory on the next trial ($trial_{n+1}$). If these two variables are unrelated then they should not show a linear relationship, because *t*-values from individual correlations should have a Gaussian distribution centred around zero. Using a one-sample t-test to compare *t*-values to zero can therefore shed light on the presence of a linear relationship between endpoint errors on a given trial (*n*) and the change in movement plan on the next trial (*n*+1). This analysis has previously been used to identify kinematic markers of early error correction during prism exposure (O'Shea et al., 2014).

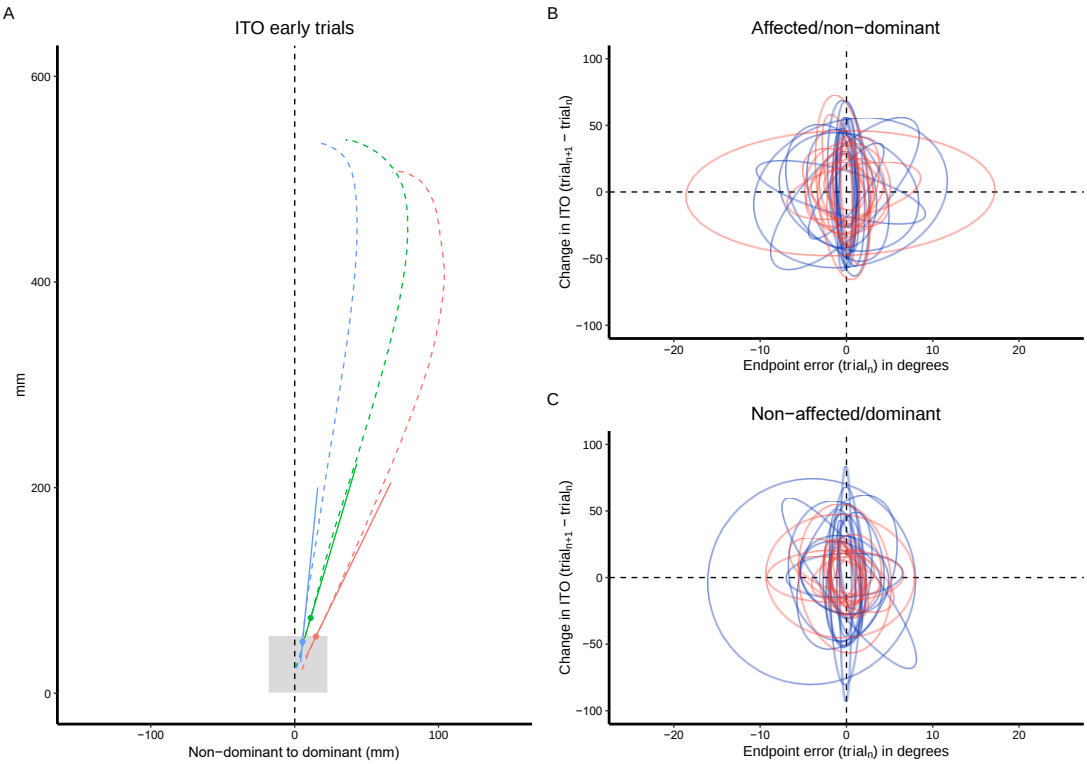


Figure 7. Initial trajectory orientations.
Illustrations of the initial trajectory orientations (ITOs) and their relationships to endpoint error for the early prism exposure trials (i.e. 1 to 10). Panel A illustrates mean trajectories (coloured dotted lines) for the control participants' dominant hands for trial 1 (red), trial 3 (green), and trial 5 (blue). Peak acceleration is indicated by coloured points. Solid lines show the initial trajectory orientations for each trial. Panels B and C indicate individual correlations between the endpoint error on $trial_n$ and the change in ITO from $trial_n$ to $trial_{n+1}$. The correlations are presented as 95% confidence ellipses for people with CPRS (red) and controls (blue). Endpoint errors and initial trajectory orientations have been fitted to an exponential decay function ($x = a \times exp^{-b \times n} + c$), and are expressed by subtracting predicted values from observed values (i.e. residuals). The black dashed lines show zero on the x and y axes, which corresponds to the target orientation (i.e. zero degree error; A), the endpoint error on $trial_n$ in degrees (B, C), or the change in ITO from trial $trial_n$ to $trial_{n+1}$ (B, C). The grey shaded rectangle (A) indicates the area within which a sensor had to be detected for a trial to start ("start location").

Prior to analysing the detrended data for initial trajectory orientations, we inspected the model fit. We were unable to fit initial trajectory orientations to the exponential decay function for one person with CRPS (non-affected hand), and two controls (one non-dominant hand, one dominant hand). For those cases where we were able to fit an exponential decay to their initial trajectory orientation, we compared the model fit parameters between Groups and Side of Body. In general, the models fitted to the initial trajectory orientations had greater prediction error (M_{RMSE} = 10.58, *SD* = 4.72) and explained less of the variance ($M_{adj.R2}$ = .02, *SD* = .06) than the models fitted to endpoint errors (M_{RMSE} = 1.09, *SD* = 0.70; $M_{adj.R2}$ = .51, *SD* = .26), which indicates that the exponential decay was a better fit for endpoint errors than for initial trajectory orientations. For initial trajectory orientations there was a tendency for the prediction error of the model to be greater for controls (M_{RMSE} = 11.80, *SD* = 5.90) than people with CRPS (M_{RMSE} = 9.24, *SD* = 2.40), although not significant, $F(1, 28) = 3.19$, $p = .085$, $\eta_{2p} = .10$. There was no significant difference in RMSE between the Side of Body used (affected/non-dominant M_{RMSE} = 10.10, *SD* = 3.42; non-affected/dominant M_{RMSE} = 11.08, *SD* = 5.83), and there was no significant interaction with Group and Side of Body, Fs(1, 28) ≤ 0.80, ps ≥ .379, η_{2p} ≤ .03. This suggests that the prediction error did not vary depending on the hand used, although there was a trend for models to make greater prediction errors for controls participants than people with CRPS. Next we analysed how much of the variance in the data was accounted for by the models (i.e. *adj.* R_2). There were no significant differences between Groups (CRPS $M_{adj.R2}$ = .04, *SD* = .08; controls $M_{adj.R2}$ = .01, *SD* = .04), or Side of Body (affected/non-dominant $M_{adj.R2}$ = .03, *SD* = .07; non-affected/dominant $M_{adj.R2}$ = .02, *SD* = .06) on *adj.* R_2, and no significant interaction, Fs(1, 28) ≤ 2.39, ps ≥ .134, η_{2p} ≤ .08. This suggests that the amount of variance explained by the models did not differ between people with CRPS and controls, or depending on the Side of Body used. However, it should be noted that the amount of variance explained by an exponential fit for initial trajectory orientations were substantially lower than that of endpoint errors.

As we anticipated the kinematic data to be noisy, we first analysed the strength of individual correlations pooling the data for each Group. That is, we compared *t*-values to zero for each Side of Body, averaged across all participants. This analysis indicated the presence of a linear relationship between endpoint errors ($trial_n$) and the subsequent change in initial trajectory orientation ($trial_{n+1}$) for participants' non-affected/dominant hand (M_t = -0.46, *SD* = 1.23), $t(32) = 2.15$, $p = .039$, $d = 0.37$. This association suggested that when participants made endpoint errors in a given direction they adjusted their movement plan in the opposite direction on the subsequent trial, relative to the exponential fit (e.g. if an endpoint error was made towards the right, the subsequent movement was angled more towards the left). We did not observe evidence of such a linear relationship when people used their affected/non-dominant hand (M_t = -0.18, *SD* = 1.24), $t(31) = 0.83$, $p = .416$, $d = 0.15$. When we analysed the data for each Side of Body, split by Group, we did not find evidence of a significant linear relationship between endpoint errors and changes in initial trajectory orientation. That is, for control participants' *t*-values for the non-dominant hand (M_t = -0.25, *SD* = 1.58) and the dominant hand (M_t = -0.52, *SD* = 1.36) did not significantly differ from zero, ts(16) ≤ 1.57, ps$_{adjusted}$ ≥ .136, ds ≤ 0.38. Similarly, the *t*-values of people with CRPS did not significantly differ from zero for their affected hand (M_t = -011, *SD* = 0.73) or their non-affected hand (M_t = -0.40, *SD* = 1.12), ts(14) ≤ 1.43, ps$_{adjusted}$ ≥ .174, ds ≤ 0.36. The data pooled across all participants provides evidence that feedforward motor control was used to reduce trial-by-trial endpoint errors relative to the previous trial for the non-affected/dominant hand - but

not the affected/non-dominant hand - during early prism exposure trials. However, when data were considered separately for each Group, we did not observe this pattern.

3.5.2. Sensorimotor realignment

To look at the sensorimotor realignment during late prism exposure trials (i.e. trials 91 to 100), we tested the relationship between trajectory modifications at peak deceleration and sensorimotor after-effects. That is, we subtracted terminal trajectory orientation from the first prism exposure trial from the median of late trials, relative to baseline. We then tested for a correlation between this change in terminal trajectory orientation and sensorimotor after-effects (i.e. median endpoint errors from open-loop trials directly after prism exposure). This analysis has previously been used to identify kinematic markers of sensorimotor realignment during prism exposure (O'Shea et al., 2014).

Despite instructions not to do so, and repeated reminders, we noticed that some participants often made corrective finger movements in the later stage of their movement when they became aware that they were about to miss the target.
The consequence of this corrective movement was that the point of peak deceleration no longer reflected a part of the arm movement. Instead, peak deceleration reflected the corrective movement, which occurred at around 95% of the movement duration. For comparison, during baseline closed-loop trials the mean peak deceleration occurred at 58.62% (*SD* = 15.18) of the movement duration. Hence, these late finger movements limited the information that could be derived from the point of peak deceleration (e.g. the terminal trajectory orientation). We therefore filtered out trials where the peak deceleration occurred after 90% of the movement was completed. To further compensate for this issue, we used median values for the analysis of the sensorimotor realignment (Fig. 8). That is, we used the median values for terminal trajectory orientations, and for endpoint errors. Due to this filtering, however, several cases were excluded from the analysis as they were missing data for the first prism exposure trial. This resulted in a reduced sample for both people with CRPS ($n_{affected} = 8$; $n_{non\text{-}affected} = 14$) and for controls ($n_{non\text{-}dominant} = 10$; $n_{dominant} = 15$). Because this substantially reduced our power for detecting differences between Groups, especially given that we expected the kinematic data to be noisy, here we focus mainly on the results of the analyses of the data pooled across Groups.

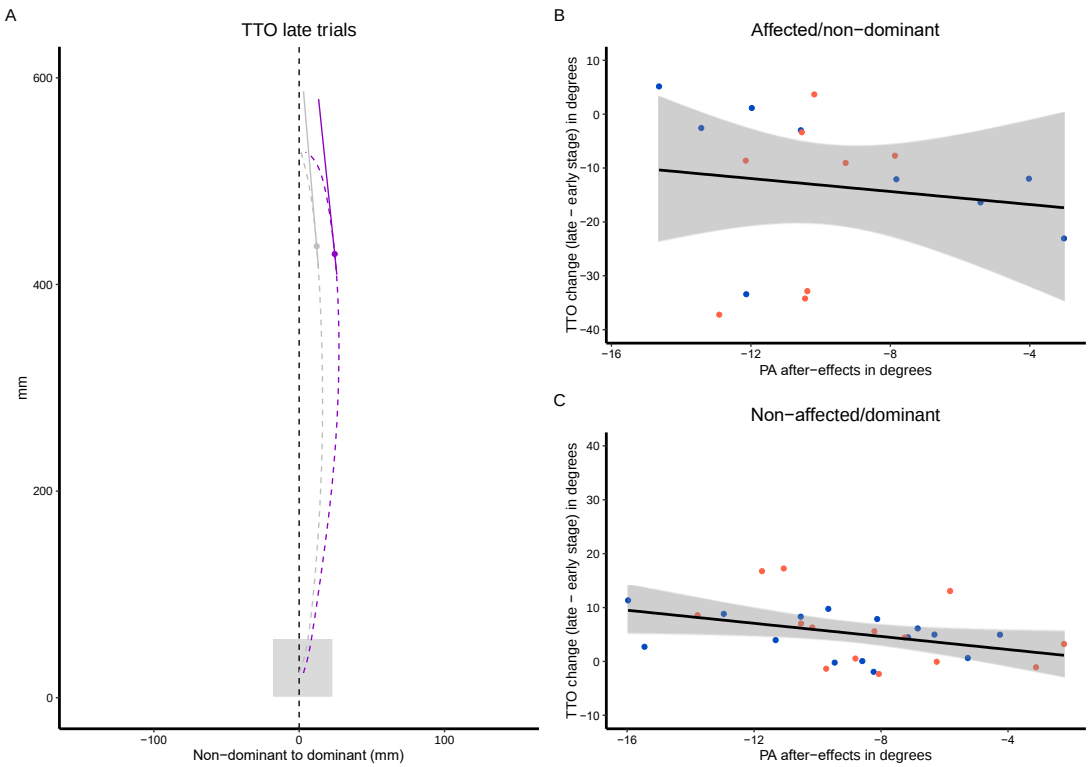


Figure 8. Terminal trajectory orientations.
Illustrations of the terminal trajectory orientations (TTOs) and their relationships to endpoint error for the early prism exposure trials (i.e. 91 to 100). In panel A, mean trajectories for control participants' dominant hand are illustrated by dotted lines for baseline (grey), and late trials (purple). Peak deceleration is indicated by points. Solid lines show the TTO for the mean trajectories. Panels B and C illustrate the associations between change in TTO and median prism adaptation after-effects (solid black lines) for group level data, split by Side of Body. The change in TTO is calculated by subtracting the TTO from trial 1 from the median TTO from late trials (i.e. 91 to 100), expressed relative to the median baseline TTO. Prism adaptation after-effects are calculated as the median endpoint error of the 15 close-loop pointing trials directly after prism exposure. Shaded grey areas (B, C) indicate 95% confidence intervals. The grey shaded rectangle (A) indicates the area within which a sensor had to be detected for a trial to start ("start location"). PA = prism adaptation.

The analysis of the association between change in terminal trajectory orientation and sensorimotor after-effects (pooled across Groups) showed that the change in terminal trajectory orientation significantly predicted sensorimotor after-effects for the non-affected/dominant hand, $F(1,27) = 4.66$, $p = .040$, $\beta = -0.38$, 95% CI [-0.75, -0.02]. This result indicates that the extent to which the late stages of movement paths of the non-affected/dominant hand were corrected during prism exposure (i.e. terminal trajectory orientations) predicted the magnitude of prism after-effects. That is, a greater change in terminal trajectory orientation was associated with more negative endpoint errors (i.e. in the direction opposite to the prismatic shift) for the non-affected/non-dominant hand. In contrast, sensorimotor after-effects were not significantly predicted by the change in terminal trajectory orientation for the affected/non-dominant hand, $F(1,16) = 0.04$, $p = .839$, $\beta = -0.05$, 95% CI [-0.58, 0.48]. When we explored the data for people with CRPS and control participants separately, the direction and magnitude of the regression coefficients remained similar, although the effects were no longer significant, $F(1,6) \leq 3.15$, $p \geq .101$, β

≥ -0.46. These results suggest that the kinematic marker of sensorimotor realignment was observed for the affected/non-dominant hand, but our analysis was only powered to detect this effect when the data was collapsed across Groups. Nonetheless, the direction of the association was the same, and of a similar magnitude for both people with CRPS and controls when using their non-affected/non-dominant hand, which suggests that this kinematic marker of sensorimotor realignment was not different between Groups.

3.6. Exploratory analyses

3.6.1. Direction of prismatic shift

We considered that the direction of the prismatic shift might have influenced our results, as this has been reported previously (Redding & Wallace, 2009). All participants were exposed to prism goggles that created an optical displacement away from their affected/non-dominant side. This meant that eight people with CRPS affecting their right side had leftward shifting goggles, whereas only three left-handed control participants had leftward shifting goggles. We therefore reanalysed endpoint errors for Open-loop Pointing Blocks using a 3-way ANOVA with Prismatic Shift, Side of Body, and Open-loop Block as independent variables. This analysis did not show any evidence that our findings were due to the direction of the prismatic shift. That is, there was no main effect of Prismatic Shift; and no interaction with Side of Body or Open-Loop Block, Fs(2, 62) ≤ 0.62, ps ≥ .544, η_{2p} ≤ .02. We did not observe any influence of the direction of the prismatic shift on our main findings, which suggests that our findings are unlikely to be due to a greater number of people with CRPS being exposed to leftward shifting prisms than controls.

3.6.2. Counterbalancing order

We considered that the counterbalancing order might influence our results, as inter-limb transfer has previously been found to be greater when the dominant hand is adapted first, compared to the non-dominant hand (Redding & Wallace, 2008, 2011). When we reanalysed the endpoint errors with Counterbalancing Order (affected/non-dominant first, non-affected/dominant first), Side of Body, and Open-loop Block as independent variables. There was no significant main effect of Counterbalancing Order on endpoint errors, and/or no significant interactions with Side of Body, or Open-loop Block, Fs(2, 62) ≤ 2.64, ps ≥ .080, η_{2p} ≤ .08. These results therefore suggest that there was no significant influence of inter-limb transfer on endpoint errors.

3.6.3. Proprioceptive accuracy

Next, we considered that the differences we observed in the retention of sensorimotor realignment (3.2.1.; Fig. 4) between Groups could be related to proprioceptive abilities, as people with unilateral CRPS have been reported to have bilateral proprioceptive deficits (Bank, Peper, Marinus, Beek, & van Hilten, 2013). In previous research, absolute pointing errors made with the unseen hand(s) has been interpreted as evidence of deficits in arm position sense in people with CRPS (Lewis et al., 2010). Therefore, we used the absolute endpoint error during the baseline Open-loop Block (“Absolute Baseline Error”) as a

measure of proprioceptive accuracy. There was no difference between Groups (CRPS, *M* = 1.88°, *SD* = 0.93; controls *M* = 1.86°, *SD* = 0.89), or between the Side of Body used (affected/non-dominant *M* = 1.92°, *SD* = 1.56; non-affected/dominant *M* = 1.82°, *SD* = 1.30), or any interaction between the two, on Absolute Baseline Error, *F*s(1, 28) ≤ 0.06, *p*s ≥ .805, η_{2p} < .01. These results suggest that there were no differences in proprioceptive accuracy between people with CRPS and controls. We then reanalysed the interaction between Group and Side of Body on endpoint errors for the retention Open-loop Block, with Absolute Baseline Error as a covariate. The main effect of Group remained significant on the retention of sensorimotor after-effects, after controlling for Absolute Baseline Error, *F*(1, 27) = 4.48, *p* = .044, η_{2p} = . 14. Absolute Baseline Error was not a significant covariate in this analysis, *F*(1, 27) = 1.32, *p* = .261, η_{2p} = .05. These results therefore suggest that proprioceptive accuracy did not influence our finding that people with CRPS showed greater retention of sensorimotor after-effects than controls.

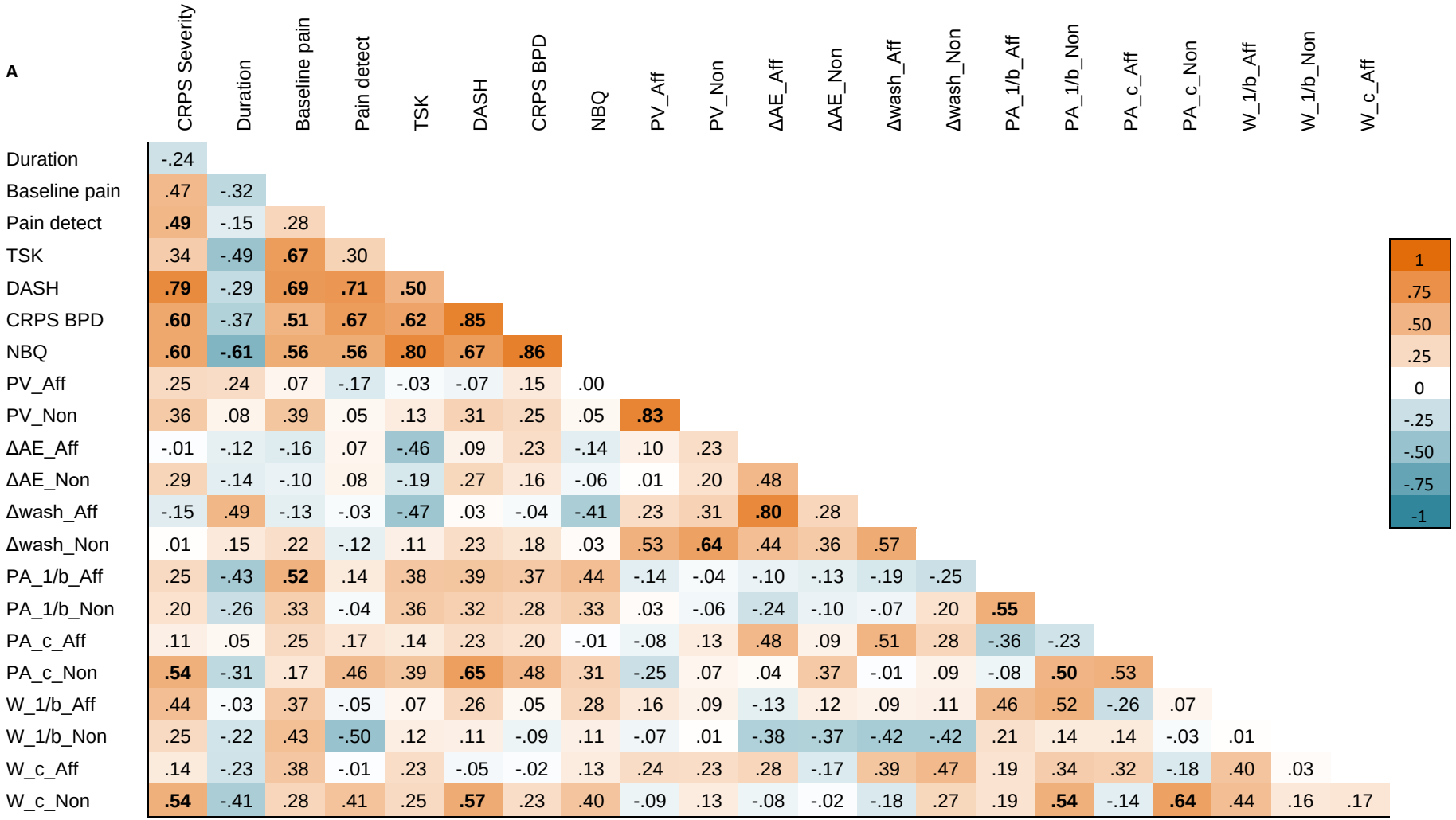
3.6.4. Speed of movement

We considered that the differences between people with CRPS and controls in the retention sensorimotor realignment (3.2.1.; Fig. 4) could be due to the speed of movement during washout trials, as motor activity influences the decay of prism adaptation after-effects (Fernández-Ruiz, Díaz, Aguilar, & Hall-Haro, 2004). Therefore, we reanalysed the interaction between Group and Side of Body on endpoint errors for the retention Open-loop Block using mean peak velocity for closed-loop washout trials as a covariate. Mean peak velocity during closed-loop washout trials was not a significant covariate for this interaction, *F*(1, 27) = 0.02, *p* = .895, η_{2p} < .01. Furthermore, the difference between people with CRPS and controls was still significant after controlling for peak velocity during washout trials, *F*(1, 27) = 4.22, *p* = .050, η_{2p} = .14. We therefore did not find any evidence to suggests that the differences between people with CRPS and controls in the retention of prism adaptation after-effects was due to the speed of movement during washout trials.

3.6.5. Correlations

To further explore the data, we analysed correlations for each Group (Fig. 9). For people with CRPS, we explored the correlations between clinical characteristics (CRPS severity, CRPS duration, baseline pain), questionnaire measures (neuropathic type pain, fear of movement, upper limb disability, body perception disturbance, “neglect-like symptoms”), basic kinematic measures (peak velocity), and prism adaptation variables (endpoint errors, decay factor, residual error). For control participants we correlated basic kinematic measures with prism adaptation variables.

A


CRPS Severity
Duration
Baseline pain
Pain detect
TSK
DASH
CRPS BPD
NBQ
PV_Aff
PV_Non
ΔAE_Aff
ΔAE_Non
Δwash_Aff
Δwash_Non
PA_1/b_Aff
PA_1/b_Non
PA_c_Aff
PA_c_Non
W_1/b_Aff
W_1/b_Non
W_c_Aff
Duration -.24
Baseline pain .47 -.32
Pain detect **.49** -.15 .28
TSK .34 -.49 **.67** .30
DASH **.79** -.29 **.69** **.71** **.50**
CRPS BPD **.60** -.37 **.51** **.67** **.62** **.85**
NBQ **.60** **-.61** **.56** **.56** **.80** **.67** **.86**
PV_Aff .25 .24 .07 -.17 -.03 -.07 .15 .00
PV_Non .36 .08 .39 .05 .13 .31 .25 .05 **.83**
ΔAE_Aff -.01 -.12 -.16 .07 -.46 .09 .23 -.14 .10 .23
ΔAE_Non .29 -.14 -.10 .08 -.19 .27 .16 -.06 .01 .20 .48
Δwash_Aff -.15 .49 -.13 -.03 -.47 .03 -.04 -.41 .23 .31 **.80** .28
Δwash_Non .01 .15 .22 -.12 .11 .23 .18 .03 .53 **.64** .44 .36 .57
PA_1/b_Aff .25 -.43 **.52** .14 .38 .39 .37 .44 -.14 -.04 -.10 -.13 -.19 -.25
PA_1/b_Non .20 -.26 .33 -.04 .36 .32 .28 .33 .03 -.06 -.24 -.10 -.07 .20 **.55**
PA_c_Aff .11 .05 .25 .17 .14 .23 .20 -.01 -.08 .13 .48 .09 .51 .28 -.36 -.23
PA_c_Non **.54** -.31 .17 .46 .39 **.65** .48 .31 -.25 .07 .04 .37 -.01 .09 -.08 **.50** .53
W_1/b_Aff .44 -.03 .37 -.05 .07 .26 .05 .28 .16 .09 -.13 .12 .09 .11 .46 .52 -.26 .07
W_1/b_Non .25 -.22 .43 -.50 .12 .11 -.09 .11 -.07 .01 -.38 -.37 -.42 -.42 .21 .14 .14 -.03 .01
W_c_Aff .14 -.23 .38 -.01 .23 -.05 -.02 .13 .24 .23 .28 -.17 .39 .47 .19 .34 .32 -.18 .40 .03
W_c_Non **.54** -.41 .28 .41 .25 **.57** .23 .40 -.09 .13 -.08 -.02 -.18 .27 .19 **.54** -.14 **.64** .44 .16 .17
1
.75
.50
.25
0
-.25
-.50
-.75
-1

B

	PV_Non	PV_Dom	ΔAE_Non	ΔAE_Dom	Δwash_Non	Δwash_Dom	PA_1/b_Non	PA_1/b_Dom	PA_c_Non	PA_c_Dom	W_1/b_Non	W_1/b_Dom	W_c_Non
PV_Dom	**.95**												
ΔAE_Non	.05	.01											
ΔAE_Dom	-.03	-.08	-.01										
Δwash_Non	-.15	-.27	.46	-.08									
Δwash_Dom	-.17	-.20	-.16	**.73**	.00								
PA_1/b_Non	.14	.10	**-.53**	-.02	-.01	.05							
PA_1/b_Dom	.20	.20	-.35	-.28	-.28	.06	**.51**						
PA_c_Non	.10	-.05	.04	.00	**.53**	-.19	.27	-.19					
PA_c_Dom	.08	-.02	-.16	-.27	.26	-.26	**.58**	.33	.41				
W_1/b_Non	.04	.05	**-.69**	-.27	-.24	-.33	.45	.23	-.05	.40			
W_1/b_Dom	.09	.06	**-.55**	.34	-.27	.20	.31	-.02	-.04	.28	.41		
W_c_Non	.16	.05	.43	-.01	**.52**	.00	.08	.01	**.66**	.04	-.40	**-.53**	
W_c_Dom	.15	.25	.17	-.27	-.32	-.04	-.04	.38	**-.70**	.04	-.04	-.24	-.24

1
.75
.5
.25
0
-.25
-.5
-.75
-1

Figure 9. Correlation matrices.

Pearson correlation matrix for people with upper limb CRPS (n = 17; A), and control participants (n = 18; B). Data from the 4 patients with 40 extra washout is excluded from the retention block (i.e. Δwash). Significant correlations (i.e. $p < .05$) are presented in boldface. Aff = CRPS affected limb; DASH = QuickDASH (Gummesson, Atroshi, & Ekdahl, 2003); ΔAE = endpoint errors from prism adaptation after-effects Open-loop Block, after subtracting baseline pointing error; Δwash = endpoint errors from retention Open-loop Block, after subtracting baseline pointing error; Duration = CRPS duration in months; CRPS BPD = Bath CRPS Body Perception Disturbance Scale (Lewis & McCabe, 2010); PV = peak velocity; TSK = Tampa Scale of Kinesiophobia (Kori et al., 1990); NBQ = Neurobehavioral questionnaire (Frettlöh et al., 2006; Galer & Jensen, 1999); Non = Non-affected limb; PA = Prism adaptation; W = Washout.

For people with CRPS, the severity of their conditions was correlated with upper limb disability, body representation disturbance, and “neglect-like symptoms”. The latter was also negatively correlated with the duration of CRPS. Furthermore, baseline pain was associated with fear of movement, upper limb disability, body representation disturbance, and “neglect-like symptoms”.

For controls, the change in open-loop pointing error during exposure significantly correlated with the change in open-loop pointing error during washout for the dominant hand, but not the non-dominant hand. For people with CRPS, the change in open-loop pointing error during exposure significantly correlated with the change in open-loop pointing error during washout for the affected hand, but not for the non-affected hand.

For people with CRPS, there were no significant correlations between any of the clinical characteristics and any endpoint error measures of after-effect and its retention (e.g. prism adaptation after-effect, retention, etc. for the affected or unaffected hand). However, clinical characteristics were correlated with certain prism adaptation variables. CRPS severity was significantly correlated with the residual error (i.e. *c*) for the non-affected hand, during both prism exposure and washout trials, rs ≥ .54, ps ≤ .030. As we would expect endpoint errors to be biased towards the non-affected side (negative values) following prism exposure (i.e. opposite direction to the prismatic displacement), a positive correlation with CRPS severity suggests that sensorimotor after-effects became more positive and approached zero as CRPS severity increased. Furthermore, greater baseline pain was correlated with a larger decay factor (i.e. 1/*b*), which suggests that those experiencing more pain also needed more trials for endpoint errors to decay during closed-loop prism exposure trials. Our exploratory correlations therefore suggest that certain clinical characteristics were related to sensorimotor processing, although they were not related to the variables involved in our key findings (e.g. prism adaptation after-effects and their retention).

4. Discussion

4.1. Summary of findings

Our study was the first to characterise sensorimotor adaptation in people with CRPS, using prism adaptation. The results did not support our main hypotheses. That is, we found no evidence for any impairment in strategic recalibration for people with CRPS, both groups were able to correct for the optical displacement introduced by the prisms. Similarly, we did not find any difference in the magnitude of prism adaptation after-effects between groups, which suggests that sensorimotor realignment was not impaired for people with CRPS. In contrast, our exploratory analysis showed that people with CRPS had greater retention of prism adaptation after-effects than controls. Below we discuss these findings (4.2.) and those related to the hand adapting used (4.3.), and consider the implications (4.4.), and limitations (4.5.) of our study.

4.2. Group differences

4.2.1. Strategic control

We found no evidence to suggest that strategic recalibration was disrupted for people with CRPS. That is, we did not observe any difference between people with CRPS and controls on endpoint errors during prism exposure, or during washout. We also did not find any group differences in the number of trials needed for endpoint errors to decay during prism exposure. Strategic recalibration is dependent on cerebello-parietal processing (Panico et al., 2019). Our findings therefore suggest that these networks are not significantly impacted in people with CRPS.

4.2.2. Sensorimotor realignment

In contrast to what we hypothesised, sensorimotor realignment was not found to be impaired for people with CRPS. We did not find any difference between groups on the magnitude of prism adaptation after-effects (i.e. endpoint errors made during open-loop pointing directly after prism exposure), or any difference in the residual errors during prism exposure or during washout. Furthermore, the kinematic marker of sensorimotor realignment was not different between groups. Sensorimotor realignment is thought to rely on processing that involves the cerebellum and the primary motor cortex (Panico et al., 2019). Our findings thus provide no evidence to suggest that sensorimotor realignment is altered in CRPS, as would be expected if cerebellar processing, motor cortical processing, and/or the connectivity between these regions (Tsujimoto et al., 2019) were disrupted.

4.2.3. Retention of prism adaptation after-effects

The decay of the prism adaptation after-effects was not different between groups during open-loop washout trials. There was also no difference in the residual error during closed-loop washout trials between groups. We did find, on an exploratory basis, that people with CRPS showed a greater retention of prism adaptation after-effects, but only after excluding four participants with CRPS who completed 40 additional washout trials.

We considered the possibility that these differences could relate to proprioceptive processing, as the retention of prism adaptation after-effects reflect the degree to which the realignment of visual and proprioceptive reference frames is maintained (Prablanc et al., 2019). People with unilateral CRPS have been found to have bilateral deficits in proprioception (Bank et al., 2013). We did not find that the magnitude of endpoint errors made during baseline open-loop pointing influenced the retention of sensorimotor after-effects, suggesting that group differences were not due to proprioceptive deficits in people with CRPS. However, baseline open-loop pointing errors did not itself differ between groups. Since proprioceptive deficits are well documented in CRPS (Bank et al., 2013; Brun, Giorgi, et al., 2019; Lewis et al., 2010), it is possible that this is not a good estimate of proprioceptive performance, possibly because there is only one target location.

Given that people with CRPS have motor deficits, we also considered that the speed of movement during washout trials, which could have differed between groups, could have underpinned the group difference in the retention of sensorimotor after-effects (Fernández-Ruiz et al., 2004). However, we did not find any influence of the speed of movement during washout trials on the retention of sensorimotor after-effects for either group. Our findings

are therefore unlikely to be due to differences in movement speed. Overall, our findings may suggest that the retention of prism after-effects differs between people with CRPS and controls, but that these differences are not due to proprioceptive deficits, or the speed of movement.

Neurostimulation studies have suggested that the motor cortex is involved in the retention of sensorimotor realignment. For instance, anodal tDCS of the motor cortex during prism exposure has been found to increase the retention of sensorimotor after-effects (O'Shea et al., 2017; Panico et al., 2017). Stimulating the motor cortex can also reactive after-effects 24 hours after prism adaptation (Panico et al., 2017), which was found to further enhance retention 48 hours post prism exposure. In people with CRPS, bilateral motor cortex disinhibition is often found (for meta-analysis, see Di Pietro et al., 2013). Cortical activation in response to movement may also be altered for people with CRPS. That is, during a finger tapping task people with CRPS showed increased bilateral motor cortex activation, assessed by functional MRI (Maihöfner et al., 2007). Therefore, it could be that the movement required by our protocol resulted in greater motor cortical activation for people with CRPS, than controls, thereby influencing the retention of sensorimotor after-effects. It should be noted, however, that M1 stimulation can increase prism-after effects (O'Shea et al., 2017). Although this effect is not always found (Panico et al., 2017), it contrasts our finding of no significant group difference for prism after-effects. Therefore, the neurostimulation studies only offer a partial explanation for our findings.

4.3. Adapting Hand

4.3.1. Endpoint errors

Several of the effects of prism adaptation differed depending on the hand used, although many did not. We did not observe any differences in prism after-effects, their development, or decay that was dependent on the hand used. We also did not see any difference between hands on endpoint errors, or their decay, for prism exposure trials, or for washout trials. In contrast, we found that participants showed a greater retention of sensorimotor after-effects for their affected/non-dominant hand, compared to their non-affected/dominant hand. This finding suggests that the retention of the after-effects was greater for the hand of the same body-side as the direction of the after-effects, than the opposite body side (e.g. leftward after-effects were greater for left hands than right hands). We also found greater residual error of pointing movements during prism exposure trials for the affected/non-dominant hand than the non-affected/dominant hand. We also observed a similar tendency for the residual error during washout-trials, although not significant.

These findings may relate to the way that movements of the dominant compared to non-dominant hands are controlled, and the direction of the prismatic shift. The motor control of the dominant hand is thought to rely more on predictive mechanisms (Sainburg, 2014), while motor control of the non-dominant hand relies more on impendence (Burdet, Osu, Franklin, Milner, & Kawato, 2001) to maintain stability during unpredictable conditions. For instance, the dominant hand was found to outperform the non-dominant during adaptation to a predictable force field, whereas better performance was seen for the non-dominant hand when the field was unpredictable (Yadav & Sainburg, 2014). Therefore, it could be

that the adaptation to the optical displacement caused by the prisms would differ between hands, with greater involvement of strategic recalibration for the dominant hand than for the non-dominant arm, which could results in the pattern of results that we observed. Therefore, the differences between the affected/non-dominant and the non-dominant/affected hand might reflect properties of the underlying motor control, which could respond differently to adaptation to prisms

Previous research in right-handed participants has found greater after-effects following 20 prism exposure trials for the right hand, compared to the left hand, when adapting to rightward shifting goggles (Redding & Wallace, 2009). We did not observe any difference between the affected/non-dominant and non-affected/dominant hand after 100 prism exposure trials. These discrepant findings could be due to our design, as we used a greater number of exposure trials and a stronger prismatic distortion than Redding & Wallace (2009). In our study, participants were exposed to 19° prismatic shifts, and completed 100 exposure trials, whereas in Redding and Wallace's (2008) study they used 11° prisms and 20 exposure trials. Both the strength of the prisms and the number of exposure trials can influence the prism adaptation after-effects (e.g. Inoue et al., 2015; McIntosh, Brown, & Young, 2019), whereby greater adaptation effects are seen with more exposure trials, and stronger prisms. Therefore, the prolonged exposure in our design might be giving rise to the results that contrast with the findings of previous research.

4.3.2. Kinematic changes

When we analysed kinematic markers of strategic feedforward motor control for early trials (O'Shea et al., 2014), we found group-level evidence suggesting that participants updated their movement plans based on the error on the previous trial, when using their non-affected/dominant hand. These correlations were not significant for the affected/non-dominant hand, or when we analysed the data separately for the two groups and according to the side of body used. Similarly, we observed the kinematic marker of sensorimotor realignment for late trials for the non-affected/dominant hand at a group level, as indicated by a change in the angle of the tangential velocity vector at peak deceleration. This analysis was not significant for the affected/non-dominant hand, or when we analysed the data separately for people with CRPS and controls.

Our findings are consistent with previous research (O'Shea et al., 2014), despite slight differences in the designs of ours and the previous study. The participants in the study of O'Shea and colleagues (2014) were all right-handed and adapted to rightward shifting goggles, hence the direction of the prismatic shift relative to hand dominance is the same as in our study. However, O'Shea and colleagues (2014) only tested the right (dominant) hand, so their results provide no insight into whether there are differences in kinematic markers of prism adaptation between the dominant and non-dominant hands. Other research has found evidence for differences between the kinematics of pointing movements made with the dominant and non-dominant hands (Sainburg, 2005, 2014). As prism adaptation can vary depending on which arm is used (Redding & Wallace, 2009), it is plausible that the kinematic changes also differ between the dominant and non-dominant arm. Therefore, our findings replicate the kinematic markers identified by (O'Shea et al.,

2014), yet suggest that they might be specific to the non-affected/dominant arm when adapting to goggles that induce a shift towards the non-affected/dominant side.

4.5. Implications

4.6.1. Theoretical implications

Sensorimotor incongruences have been theorised to contribute to the maintenance of pathological pain conditions (Harris, 1999), such as CRPS (McCabe & Blake, 2007). For people with CRPS, motor predictions might be compromised due to distorted representations of the body. In combination with sensory changes in CRPS, these distorted representations might make sensorimotor incongruence more likely, which according to the theory would cause pain. This idea has been tested by having participants perform anti-phase limb movements with one limb occluded by a mirror, which is positioned such that the mirror image creates the visual illusion of synchronous arm movements (i.e. incongruent mirror visual feedback). For people with CRPS, incongruent mirror visual feedback has been found to increase pain and anomalous sensations (Brun, Mercier, et al., 2019), which are greater than those seen in pain-free controls. This increase in pain could reflect changes in sensory sensitivity, as has been found during experimental pain induction (Brun, Gagné, McCabe, & Mercier, 2017). However, it is not clear what sensorimotor processes that this change in sensitivity is related to. Sensorimotor processing can vary between experimental paradigms (Fleury, Prablanc, & Priot, 2019), for instance, depending on whether the paradigm results in errors being internalised (e.g. prism adaptation) or attributed to the external interface (e.g. visuo-motor rotation). We speculate that the latter is more likely for incongruent mirror visual feedback, because it involves perturbation without adaptation (e.g. it does not create an after-effect; Bastian, 2008). Therefore, the influence of incongruent mirror visual feedback on pain is not necessarily related to sensorimotor adaption.

Yet one of the assumptions implicit to the sensorimotor theory of pain is that the nervous systems of people with pathological pain conditions are not able to correct for incongruent sensory and motor information. Under normal conditions, sensorimotor adaptation would occur to compensate for discrepant sensory and motor information (Wolpert et al., 2011). In contrast to theoretical predictions (Harris, 1999), we did not observe any differences between people with CRPS and controls in the magnitude of sensorimotor adaptation following exposure to a lateral visual distortion, nor in the rate at which the after-effect developed across exposure blocks. This finding suggests that people with CRPS can compensate normally for incongruent sensory and motor information. We also did not find any correlations between the magnitude of sensorimotor realignment of people with CRPS and clinical characteristics (i.e. CRPS severity, duration, pain) or questionnaire measures (i.e. neuropathic type pain, fear of movement, upper limb disability, body perception disturbances, or “neglect-like symptoms”). Therefore, our results suggest that sensorimotor integration is normal for people with CRPS, and that it is not related to pain and physical symptoms, which contradicts the predictions made by the sensorimotor theory of pain.

The dynamic properties of sensorimotor information may explain how incongruent sensorimotor information may arise in pathological pain conditions, despite normal adaptation. During prism adaptation participants are typically exposed to a stable optical

displacement, either by using one strength of prismatic lenses or by gradually increasing their strength in a multistep-exposure paradigm (Prablanc et al., 2019). This displacement is stable in the sense that it remains unchanged for a number of consecutive trials. Our findings suggest that people with CRPS are able compensate for a stable incongruence between visual and motor information. Yet the incongruent sensorimotor information that is theorised to contribute to pathological pain conditions, such as altered motor predictions, is unlikely to show such stability. For instance, motor predictions are influenced by representations of the body (Longo & Haggard, 2010; Proske & Gandevia, 2012),which are dynamic (Martel, Cardinali, Roy, & Farnè, 2016; Medina & Coslett, 2010). Motor predictions could be impaired due to less stable representations of the body in CRPS (Vittersø et al., 2020). Similar effects might also be expected as a consequence of muscle fatigue (Wolpert et al., 2011), which would be more frequent for people with CRPS and motor deficits (e.g. Harden et al., 2017). For people with CRPS, both distorted body representations, and motor deficits present dynamic challenges to the sensorimotor system. Therefore, it is possible dynamic changes in sensorimotor information give rise to sensorimotor incongruences in pathological pain conditions. This assumes, however, that sensorimotor system is less able to correct for dynamic changes, and that this may differ between people with and without pathological pain condition.

4.6.2. Clinical implications

Our findings have implications for the application of prism adaptation as a treatment for CRPS. Several studies have examined the efficacy of treating CRPS with prism adaptation (Bultitude & Rafal, 2010; Christophe et al., 2016; Halicka, Vittersø, McCullough, et al., 2020b; Sumitani et al., 2007). The first report of its application in CRPS suggested that the benefits were due to a normalisation of attention biases, or that improvements might be due to improving sensorimotor integration (Sumitani et al., 2007). However, attention biases are not always found for people with CRPS (e.g. De Paepe et al., 2020; Halicka, Vittersø, McCullough, et al., 2020a), and therapeutic benefits have been reported in the absence of any consistent biases (Christophe et al., 2016). We did not find any impairment in sensorimotor integration (i.e. prism adaptation after-effects) for people with CRPS. Although the retention of prism adaptation after-effects was greater for people with CRPS, our findings suggest that they do not have difficulties with adapting to the prism goggles. The therapeutic benefits of treating CRPS with prism adaptation are therefore unlikely to be due to correcting attention biases, or improving sensorimotor integration. However, they also suggest that any lack of an improvement is not explained by difficulties adapting to prism goggles (e.g. due to impaired sensorimotor integration). Taken together, these findings may explain why the largest trial to date found no benefit of prism adaptation compared to a sham control (Halicka, Vittersø, McCullough, et al., 2020b). Our findings are therefore compatible with recent evidence in questioning the efficacy of prism adaptation for treating CRPS.

4.6. Limitations

Several of the people with CRPS had previous experience with prism adaptation. That is, fourteen of the participants with CRPS had previously taken part in a randomised control

trial of prism adaptation (Halicka, Vittersø, McCullough, et al., 2020b; Halicka, Vittersø, Proulx, et al., 2020b), where participants either performed a prism adaptation protocol twice daily for two weeks, with prism goggles or with sham goggles (i.e. goggles fitted with neutral lenses). Therefore, half of the people who participated in both studies are likely to have had previous experience with prism adaptation, which would have been, on average, 15 months prior to participating in our study. Previous experience with prism adaptation could reduced the magnitude of adaptation (Martin, Keating, Goodkin, Bastian, & Thach, 1996b). Furthermore, when participants are given explicit instructions about what to expect from prism adaptation the magnitude of sensorimotor after-effects has been found to decrease (Jakobson & Goodale, 1989). Because the two studies took place over a year apart, it is unlikely that there were any additive effects of previous prism exposure, although we cannot rule out that participants remembered a strategy for compensating for the lateral optical distortion. In this case, our findings would underestimate the sensorimotor after-effects in CRPS, which would still contradict the hypothesised impairment in sensorimotor realignment.

5. Conclusions

Our study was the first to characterise sensorimotor adaptation in people with CRPS. Using prism adaptation, we found no evidence for any impairment in strategic recalibration and sensorimotor realignment for people with CRPS. These findings indicate that people with CRPS were able to correct for the optical displacement introduced by the prisms, and that their sensorimotor system adapted to this displacement. The latter finding opposes assumptions made by the sensorimotor theory of pain, as it would predict that people with pathological pain have impaired sensorimotor adaptation. In contrast, people with CRPS showed greater retention of prism adaptation after-effects than controls, which suggests that they retained the sensorimotor realignment for longer and to a greater extent than controls. As this difference did not relate to proprioception, or speed of movement, it could be due to greater motor cortical activity for people with CRPS than controls, which would be consistent with previous research (for meta-analysis, see Di Pietro et al., 2013). Therefore, although our findings contradict existing theories of how pain might be maintained in the absence of clear tissue pathology, they add to our understanding of neuropsychological changes in CRPS.

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Competing interests
The authors have no conflicts of interest to declare.

Chapter 5 - Conclusions

In this chapter I characterised sensorimotor adaptation in people with CRPS, using prism adaptation, which addresses a gap in the literature that I identified in Chapter 1.

Impaired sensorimotor adaptation is an implicit assumption of the sensorimotor theory of pain (Harris, 1999). However, I did not find evidence to suggest that sensorimotor adaptation to the optical displacement was different between people with CRPS and healthy controls. It is possible that adaptation may vary depending on properties of the sensorimotor information available. In the present study we introduced a stable optical distortion across a number of movements. Yet some of challenges that the sensorimotor system is faced with could vary between movements, such as muscle fatigue (Wolpert et al., 2011), which would therefore be dynamic. We therefore cannot rule out that, in people with CRPS, the sensorimotor system would adapt differently to dynamic distortions, such as the less stable body representations (Chapter 3; Vittersø, Buckingham, Halicka, Proulx, & Bultitude, 2020). However, there was no indication to suggest that this were the case. The findings rather suggest that sensorimotor adaptation is normal for people with CRPS, which contrasts the assumption that underpins the sensorimotor theory of pain. There was also no relationship between the clinical characteristics of people with CRPS and indicators of the extent of sensorimotor adaptation. This finding adds further supports to the conclusion that impaired sensorimotor adaptation is not related to CRPS. This chapter therefore provides evidence that opposes one of the underlying assumptions of the sensorimotor theory of pain.

As I highlighted in Chapter 1, there are many sensorimotor processes that can be altered for people with pathological pain conditions. The current chapter suggests that many of the processes involved in prism adaptation do not differ between people with CRPS and controls. The main difference between groups was related to the exploratory analysis of the retention of prism after-effects. This finding suggested that people with CRPS retained the sensorimotor realignment for longer and to a greater extent that controls. Proprioceptive deficits, or slower movements did not explain this difference. I therefore considered that it might relate to greater M1 activation during movements for people with CRPS, compared to controls. Stimulating M1 using anodal tDCS has been found to increase the retention of prism after-effects (O'Shea et al., 2017; Panico et al., 2017), and people with CRPS have been found to show greater M1 activation during motor tasks than controls (Maihöfner et al., 2007). If the differences in sensorimotor processing relate to altered M1 processing, it would be inline with theoretical predictions. The sensorimotor theory of pain proposed that reduced M1 inhibition and overlapping S1 representations could impair sensorimotor processing. The findings from Chapter 5 might therefore support this idea, although they challenge other assumptions that underpin the theory.

The analogy of hemispatial neglect has been used to describe the neuropsychological changes that have been observed in CRPS (for reviews, see Halicka et al., 2020c; Legrain et al., 2012). In line with recent findings (De Paepe et al., 2020; Halicka et al., 2020a), and what I found in Chapter 4, this study challenges the idea that neuropsychological changes are “neglect like” in CRPS. People with hemispatial neglect have been found to show impaired strategic recalibration (Facchin et al., 2018), which we did not find any evidence of in CRPS. Taken together, these findings suggest that the “neglect-like” analogy does not

capture the neuropsychological changes seen in people with CRPS (Halicka et al., 2020c), because, for instance, strategic recalibration was found to be normal.

The findings from this chapter also have implications for the application of prism adaptation to treat CRPS. Because people with CRPS are able to adapt to prism goggles, it suggests that the procedure itself is appropriate for this population. Pain relief from prism adaptation has been proposed to be caused by a normalisation of visuospatial attention biases, or improved sensorimotor integration (Sumitani et al., 2007). Yet, the attention biases are not always found in CRPS (De Paepe et al., 2020; Halicka et al., 2020a), and pain relief has been found in the absence of such biases (Christophe et al., 2016a). This chapter demonstrates that the there is no evidence of a deficit in sensorimotor integration. Taken together, these findings suggest that neither of the originally proposed mechanisms of action are necessarily disrupted for people with CRPS. The findings from this chapter therefore add to a recent study (Halicka et al., 2020b) in questioning the efficacy of prism adaptation for the treatment of CRPS.

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Discussion

Pain can be considered a disease of the central nervous system when it no longer provides us with any useful information about potential harm or injury. For instance, pain can persist in the absence of any clear tissue pathology. It is not well understood why pain becomes pathological. The sensorimotor theory of pain (Harris, 1999) was formulated to address this question. I have used this theory as a framework in my thesis, with the aim of furthering our understanding of the role of sensorimotor incongruence in pathological pain.

To meet this aim I have conducted a comprehensive review of the literature related to sensorimotor processing in pathological pain conditions (Chapter 1); I have examined the updating of bodily and spatial representations following tool-use in an experimental pain model (Chapter 2), and in CRPS (Chapter 3); I have investigated the symmetry of spatial representations in CRPS (Chapter 4); and I have tested sensorimotor adaptation in CRPS (Chapter 5). The research presented in this thesis has been designed to comprehensively test the sensorimotor theory of pain (Harris, 1999).

Twenty years after its formulation, there is a wealth of research that addresses questions related to the sensorimotor theory of pain (Chapter 1). The theory proposed that incongruent sensorimotor information might serve to maintain several pathological pain conditions. There is a lot of evidence to suggest that sensorimotor processes can be impaired for people with pathological pain conditions, as I identified in my literature review. The findings from my thesis add to this literature by examining sensorimotor processing in a clinical population, and using an experimental pain model. I will discuss how my results contribute to the existing understanding (1.), and consider the broader implications for pain research (2.).

1. Contribution to the existing understanding

1.1. Bodily and spatial representations

Distorted representations of the body are common in many pathological pain conditions, such as CRPS, fibromyalgia, musculoskeletal pain conditions, and phantom limb pain. These distortions tend to relate to the affected area, and have been characterized using interviews, questionnaires, and cognitive task. Similarly, altered representations of the space that surrounds the body (i.e. peripersonal) have been found for people with conditions such as CRPS, dystonia, and trigeminal neuralgia. Yet some degree of distortion is common in healthy cognition (Longo, 2017). Furthermore, the representations of the body and its surrounding space are not static, updating as one interacts with the environment (e.g. Maravita & Iriki, 2004; Martel, Cardinali, Roy, & Farnè, 2016; Serino, 2019). The existing literature therefore only provided information about the presence of a distortion, little was known about *how* bodily and spatial representations function in pathological pain.

My thesis contributes to the existing understanding on the functioning of bodily and spatial representation in the context of pain. It does so by examining how people with CRPS updated bodily and spatial representations during tool use relative to pain-free individuals (Chapter 3; Vittersø, Buckingham, Halicka, Proulx, & Bultitude, 2020), and examining the

influence of experimentally induced pain on such updating (Chapter 2; Vittersø, Halicka, Buckingham, Proulx, & Bultitude, 2019). My findings suggest that such updating is more flexible for people with CRPS than individuals without pain, which contrasts with what I hypothesized. These findings suggest that people with pathological pain might have less stable representations of the body and peripersonal space. As I demonstrated in Chapter 2, this effect cannot be explained by the presence of an acute pain sensation. My thesis therefore contributed to the literature by demonstrating another way in which sensorimotor processing can be altered in pathological pain conditions.

In the context of the sensorimotor theory of pain, these findings provide a potential mechanism through which motor predictions might be compromised for people with CRPS. More flexible, and perhaps less stable, representations of the body and peripersonal space could lead to inaccurate motor predictions. According to the theory, a mismatch between the predicted and actual outcome should result in pain and other physical symptoms. The findings from Chapter 2 suggest that this relationship is not the other way around (i.e. that sensorimotor processes are disrupted by pain), which is in agreement with the theory. Therefore, my studies looking at how bodily and spatial representations are updated are in agreement with theoretical predictions.

1.2. Multisensory processing and sensorimotor integration

Multisensory processing could be considered a prerequisite for sensorimotor integration (Chapter 1), as movement typically involves using information from more than one sense. Therefore, any deficits in sensorimotor integration could be due to an underlying deficit in multisensory processing. When I analysed visuo-tactile integration in Chapter 3, people with CRPS showed greater crossmodal interference prior to active tool-use than control participants. I interpret the larger crossmodal interference as being indicative of enlarged peripersonal space representations for people with CRPS. Nonetheless, this finding therefore provides no evidence to suggest that multisensory processing is disrupted for people with CRPS, which is comparable to the evidence from Chapter 1. Furthermore, In Chapter 5 I found no evidence to suggest that sensorimotor adaptation was impaired for people with CRPS, as their adaptation to the optical displacement introduced by wearing prism goggles was not different from that of controls. The findings in Chapter 3 and Chapter 5 are therefore in agreement with each other.

One of the assumptions underpinning the sensorimotor theory of pain, however, is that the sensorimotor system does not correct for incongruent sensorimotor information. Typically, sensorimotor adaptation would compensate for such incongruent information (Bastian, 2008; Wolpert, Diedrichsen, & Flanagan, 2011). The findings from Chapter 5 contrast this idea, demonstrating that sensorimotor realignment during prism adaptation did not differ between people with CRPS and controls. It is possible that the sensorimotor processes needed to adapt to the visual displacement introduced by prism goggles differs to those needed to correct for distorted representations of the body and/or peripersonal space. The distortion introduced by the prisms is stable (e.g. 19° in Chapter 5). Representations of the body and peripersonal space are dynamic and will update as we interact with our environment (e.g. Maravita & Iriki, 2004; Martel et al., 2016; Serino, 2019). As Chapter 3 demonstrates, these representations might be less stable for people with CRPS. Less stable representations would present an additional challenge to the sensorimotor system.

Therefore, it could be that although sensorimotor adaptation is normal in CRPS, their sensorimotor system is unable to compensate for the additional challenge that is introduced by the distorted body and peripersonal space representations. However, my findings show no evidence to suggest that sensorimotor adaptation is impaired under stable conditions for people with CRPS.

1.3. CRPS is not "neglect-like"

The findings from my thesis have implications for using hemispatial neglect as an analogy to explain the neuropsychological changes in CRPS. Some studies have reported changes in CRPS that resemble those seen in people with hemispatial neglect, e.g. in visuospatial attention biases (e.g. Bultitude, Walker, & Spence, 2017; Filbrich et al., 2017). However, such biases are not always found (De Paepe et al., 2020; Halicka et al., 2020a; Halicka, Vittersø, Proulx, & Bultitude, 2020b). The findings from Chapter 4 add to this literature by using manual straight ahead pointing to demonstrate that external space is represented symmetrically for people with CRPS. This finding is consistent with most (Christophe et al., 2016a; Kolb, Lang, Seifert, & Maihöfner, 2012), but not all previous research (Christophe et al., 2016b; Jacquin-Courtois, Christophe, Chabanat, Reilly, & Rossetti, 2017). Normal neuropsychological processing in CPRS is also consistent with the findings from Chapter 5. Prism adaptation has been used to study sensorimotor processing in people with hemispatial neglect, and typically people with this condition require more trials to reduce endpoint errors (i.e. strategic recalibration; Facchin, Bultitude, Mornati, Peverelli, & Daini, 2018). I did not find any difference between people with CRPS and controls in the number of trials needed to correct endpoint errors during prism adaptation. These findings do not support the idea that neuropsychological changes in CRPS are "neglect like". Therefore, my thesis contributes to the debate about neuropsychological changes in CRPS by suggesting that they are not "neglect-like".

The "neglect-like symptoms" questionnaire (Frettlöh, Hüppe, & Maier, 2006; Galer & Jensen, 1999) was intended to capture motor neglect symptoms in CRPS, rather than suggesting that neuropsychological changes were synonymous with those seen in hemispatial neglect (Galer, Jensen, & Butler, 2013). Hemispatial neglect can be considered a deficit in attention to sensation, movement, body representations, and/or spatial representations of the contralesional side, which is not fully explained by a sensory or motor loss (Kerkhoff, 2001). Motor neglect refers specifically to the under-utilization of a limb contralateral to a lesion, which cannot be fully accounted for by sensory or motor deficits (Laplane & Degos, 1983; Punt & Riddoch, 2006). However, this is not always the meaning that is ascribed to the "neglect-like" changes in CRPS (Punt, Cooper, Hey, & Johnson, 2013). In my thesis, this questionnaire was not related to neuropsychological changes in CRPS that would be typical in hemispatial neglect. That is, it was not related to manual straight ahead pointing (Chapter 4), or strategic recalibration during prism exposure (Chapter 5). People with CRPS completed the "neglect-like symptoms" questionnaire for the studies reported in Chapter 4 and 5. This questionnaire is predictive of pain outcomes in chronic CRPS (Wittayer, Dimova, Birklein, & Schlereth, 2018), and was related to CRPS severity and pain in my studies (Chapters 4 & 5). Understanding what this questionnaire relates to therefore has potential clinical implications. The questionnaire includes items related to difficulties with generating movement, and the affected-limb feeling dead or not part of one's body. In my thesis, I found that this questionnaire was highly correlated with

self-reported body perception disturbance, upper limb disability, and fear of movement (Chapters 4 & 5). The “neglect-like symptoms” could thus relate to immobilization of a limb, which has been suggested to give rise to many of neuropsychological symptoms seen CRPS (Punt et al., 2013), and would be more consistent with the idea of motor neglect.

2. Broader implications for pain research

2.1. The sensorimotor theory of pain

The sensorimotor theory of pain proposed that incongruent sensorimotor information could serve to maintain several pathological pain conditions. The research presented in my thesis offers partial support for the predictions derived from the theory. The findings from Chapter 3 (Vittersø et al., 2020) showing altered updating of bodily and spatial representations for people with CRPS support theoretical predictions, as they would likely impair motor predictions (Shadmehr, Smith, & Krakauer, 2010). Similarly, in Chapter 1 I identified evidence from many different pain conditions that was in agreement with the sensorimotor theory of pain, although in some cases the evidence contradicted theoretical predictions. The evidence therefore suggests that the theory provides a good framework for understanding many of the changes in sensorimotor processing that can be disrupted in pathological pain. There are, however, areas where the theory can be refined, which is highlighted by the aspects of sensorimotor processing that appear to be intact for people with pathological pain. For instance, in Chapter 5 I found that sensorimotor adaptation to prismatic shifts in vision was not impaired in CRPS, which contradicts one of the assumptions implicit to the theory. This finding therefore suggests that if sensorimotor incongruence does lead to pain, then it is not due to any impairment in sensorimotor adaptation for people with pathological pain. Nonetheless, my thesis is a testament to the utility of the sensorimotor theory of pain. For instance, in Chapter 1 I identified a number of testable hypotheses that can be derived from the theory. These hypotheses were particularly well evidenced for changes in to body representations in pathological pain, which suggests that the theory may be more applicable to certain aspects of sensorimotor processing. Therefore, the sensorimotor theory of pain provides a useful framework within which to examine such changes in pathological pain conditions, although my thesis highlights some areas where the theory could be refined.

The sensorimotor theory of pain is particularly useful for understanding abnormal body representations in pathological pain. A range of different methods have been used to study the distorted representations of the body (Chapter 1), and has been found many pathological pain conditions. For people with CRPS, distorted representation of the body can be present within days of injury (Lewis, Kersten, McCabe, McPherson, & Blake, 2007). These changes are therefore unlikely to be due to a tendency to avoid movement with the affected hand, which has been suggested as an alternative explanation for neuropsychological changes in CRPS (Punt et al., 2013). Proprioceptive deficits also do not appear to explain the distorted representations of the body seen in CRPS (Brun et al., 2019a), as proprioceptive deficits can be bilateral in unilateral CRPS (Bank, Peper, Marinus, Beek, & van Hilten, 2013), yet the distorted representations of the body typically relate to the affected area. Furthermore, distorted representations of the body were not found to correlate with proprioceptive deficits, or kinaesthesia of a CRPS-affected limb (Brun et al., 2019a). Irrespective of their origin, distorted representations of the body are related to pain

outcomes. For instance, following multidisciplinary treatment for CRPS, pain reduction was associated with a reduction in self-reported body representation disturbances (Lewis et al., 2019). In the context of the sensorimotor theory of pain, this could be understood as an improvement in motor predictions leading to a reduction in pain. These studies do not allow for causal mechanisms to be tested, and do not typically measure any changes in motor predictions, so these conclusions remain speculative. Nonetheless, they demonstrate the potential utility of the sensorimotor theory of pain, which appears to be particularly relevant for understanding changes in bodily representation and how they might relate to pathological pain conditions.

2.2. Refining the sensorimotor theory of pain

The findings from my thesis shed light on how the sensorimotor theory of pain might be refined. The findings suggest that certain aspects related to sensorimotor processing might be altered in CRPS (e.g. altered updating of bodily and spatial representations), although others are intact (e.g. sensorimotor adaptation). In Chapter 1 I demonstrated that the ways sensorimotor processes are altered can vary between pathological pain conditions. Therefore, it might be more useful to think of what aspects of sensorimotor processing are altered within conditions, rather than across pathological pain more broadly. This approach has been used in related areas of pain research. In the Quantitative Sensory Testing (QST) literature, sensory profiles for different conditions have been identified (Magerl et al., 2010; Rolke et al., 2006), which have prognostic value (Attal et al., 2013). Based on the evidence that I have presented in this thesis, we could imagine that a similar approach could be taken to identify sensorimotor profiles of pathological pain conditions. Sensorimotor profiles would provide a targeted way to test hypotheses derived from the sensorimotor theory of pain, and could inform treatments for pathological pain conditions. For instance, in this thesis I have shown that specific parts of sensorimotor processing might be altered in CRPS, whereas other parts are intact (Fig. 1). This pattern of altered processing could be considered a sensorimotor profile for CRPS, which demonstrates the areas in which the sensorimotor theory of pain is applicable. Other conditions, such as fibromyalgia, could have a distinct profile, which would allow theoretical predictions to be tailored to individual conditions.

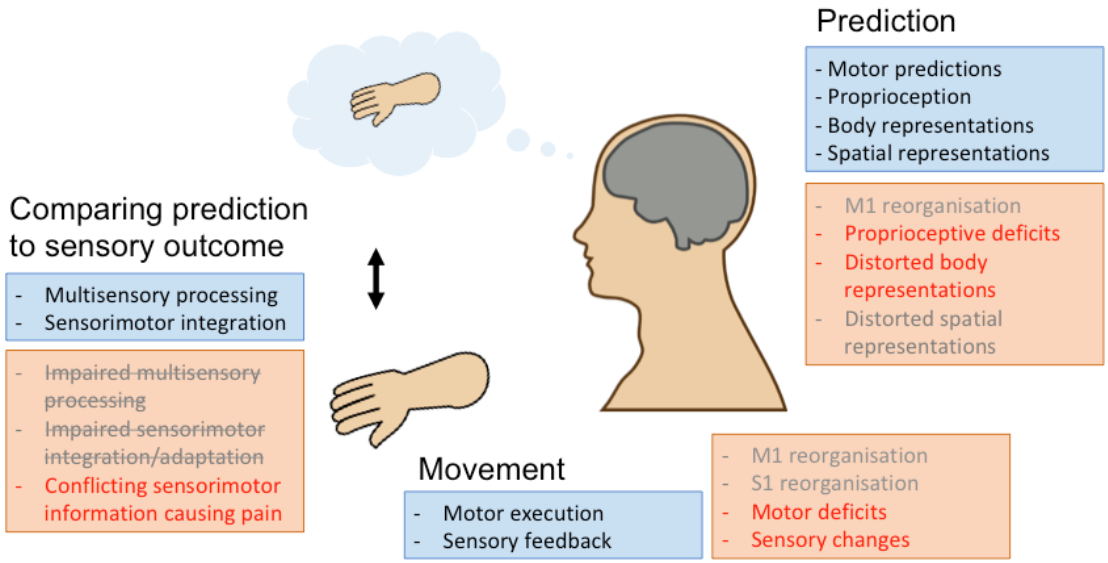

Figure 1. Sensorimotor profile of CRPS.
A speculated sensorimotor profile for people with CRPS is super imposed on the simplified model of sensorimotor processing (blue; Blakemore et al., 2000; McCabe & Blake, 2007; McCabe et al., 2005), and factors that may interfere with it (orange). The text in the oranges boxes is coloured to indicates where there is evidence (red), mixed evidence (grey), or no evidence (grey with line through) that factors influencing sensorimotor processing are altered in CRPS (i.e. a sensorimotor profile). M1 = primary motor cortex; S1 = primary somatosensory cortex.

There are several outstanding questions that would need to be addressed before sensorimotor profiles would be informative. First, the degree to which a change in sensorimotor processing would be considered clinically relevant would need to be established. Using body representations as an example, a degree of distortion is to be expected in healthy cognition (Longo, 2017), which raises the question of if/when does a distortion become problematic for sensorimotor processing? That is, at what point does a distorted representation of a body part impair predictions of the sensory outcome of moving that limb (i.e. a “clinically relevant distortion”)? In order to better address these questions, the causal relationship between altered sensorimotor processing and pain, if there is one, would need to be better understood. A second, and related question is how might such distortions (e.g. sensory, body representation, multisensory processing) interact? For instance, deficits in multisensory processing might only be problematic if they are combined with altered representations of the body, and/or sensory deficits. The processes of identifying sensorimotor profiles in pathological pain might shed light on some of these questions. Taken together, sensorimotor profiles demonstrate one way in which the sensorimotor theory of pain could be refined based on the evidence presented in this thesis.

2.3. Assuming causality

Testing the predicted causal relationship between sensorimotor processes and pain is one of the challenges by research using the sensorimotor theory of pain as a theoretical framework. Changes in sensorimotor processing can happen on the scale of milliseconds (Crevecoeur, Thonnard, & Lefevre, 2020; Hanajima et al., 2015), yet pain and physical symptoms can persist for years. Designing experiments that allow for causality to be

inferred is therefore challenging. Treatment studies demonstrate one way to start untangling this relationship, as they allow for temporal causality to be assumed. That is, that way we can observe a correlation between improvements in sensorimotor processing that may precede or follow pain reduction. For instance, pain reduction following treatment for CRPS was associated with a normalisation of digit representations in S1 (Maihöfner, Handwerker, Neundörfer, & Birklein, 2004). The causal effect of immobilisation on the shrinking of S1 representations has been demonstrated in healthy controls (Lissek et al., 2009). Therefore the correlation between pain reduction and normalisation of digit representation in CRPS could relate to regaining movement of an immobilised limb. Similar challenges arise when inferring causality from longitudinal studies. For instance, an association between neglect-like symptoms and pain outcomes six months later has been found in chronic CRPS (Wittayer et al., 2018), yet immobilisation can cause changes in bodily and spatial perception (Bassolino, Finisguerra, Canzoneri, Serino, & Pozzo, 2015; Hall et al., 2016), which might account for the changes seen in people with CRPS. The changes related to successful treatment of CRPS, and/or "neglect-like symptoms" could therefore be related to regaining movement of an otherwise immobilised limb, although this would not contradict the sensorimotor theory of pain. If, for instance, immobilisation causes a change in sensorimotor processing which then results in pain, this would still be in agreement with the theory.

Experimental studies can allow for causality to be inferred with greater certainty. A few studies have examined the effect of pain relief on sensorimotor processing. For instance motor performance has been found to improve after a ketamine infusion (Schilder et al., 2013), or a nerve blockade (Osumi, Sumitani, Kumagaya, & Morioka, 2017). Although these studies test the assumption that pain interferes with sensorimotor processing, they are able to demonstrate a causal effect. Unless the association is bidirectional, these findings oppose the direction proposed by the sensorimotor theory of pain. One of the challenges with studying pain outcomes experimentally, however, is that many experimental procedures in clinical populations are likely to cause pain (e.g. Chapter 3). Experimental studies might therefore be better suited to study other markers of pathological pain conditions. In Chapter 3 I attempted to do so by measuring the spatially defined modulation of hand-temperature asymmetries, building on previous findings from people with CRPS (Moseley, Gallace, Di Pietro, Spence, & Iannetti, 2013; Moseley, Gallace, & Iannetti, 2012). In contrast, I found evidence of no spatial modulation of hand temperature asymmetries for people with CRPS (Chapter 3; Vittersø et al., 2020). As the spatially defined modulation of CRPS symptoms did not replicate, I was unable to look at the influence of updating bodily and spatial representations on this effect. Nonetheless, hand temperature asymmetries are potentially a useful marker of fluctuations in CRPS symptoms, because they can happen on a relatively short time scale (Schilder, Niehof, Marinus, & van Hilten, 2015). This marker is useful for studying CRPS, as it relates to one of the diagnostic criteria (Harden et al., 2010; Harden, Bruehl, Stanton-Hicks, & Wilson, 2007). Different markers would be needed in different pathological pain populations, for a similar approach to be taken. Experimental paradigms have also used incongruent mirror visual feedback (Brun et al., 2019b; Don et al., 2019; McCabe, Cohen, & Blake, 2007) and optokinetic stimulation (Knudsen & Drummond, 2015) to examine the idea that incongruent sensorimotor information may cause pain. Yet a problem with these paradigms is that control participants also find the paradigm uncomfortable, so any increase in pain could relate to a general discomfort. A triangulation of methods might allow for some of these issues to be overcome. Nonetheless,

these studies highlight the challenges involved in testing the causal effect of sensorimotor incongruences on the maintenance of pathological pain.

2.4. Sensorimotor treatments for pain

Understanding how sensorimotor functioning is altered for people with pathological pain has implication for treatment. A better understanding of what types of sensorimotor processes are altered within pathological pain conditions (i.e. "sensorimotor profiles"; 2.2.) could inform what types of treatments are appropriate for people with a given condition.

If multisensory processing is impaired, and it is a prerequisite to sensorimotor integration, it might be worth targeting such processing before potentially tackling sensorimotor integration. I did not find evidence of any impairment in multisensory processing for people with CRPS (Chapter 3). However, in Chapter 1 I identified that the rubber hand illusion, which is experienced normally by people with CRPS (Reinersmann et al., 2013) and involves visuo-tactile integration (Tsakiris & Haggard, 2005), was weaker for people with focal hand dystonia (Fiorio et al., 2011), and spinal cord injury with neuropathic pain (Pozeg et al., 2017). These conditions might therefore benefit from multisensory interventions, such as perceptual, or musical training (for review, see Zhou, Cheung, & Chan, 2020), prior to any sensorimotor treatments, although this does not appear to be the case for people with CRPS.

In my thesis I have found evidence of altered updating of bodily representations for people with CRPS (Chapter 3; Vittersø et al., 2020), yet no spatial attention bias (Chapter 4), or any impairment in sensorimotor integration (Chapter 5). Each of these processes has been targeted for treatment of CRPS. For instance, prism adaptation has been trailed in CRPS. Its therapeutic benefit was thought to arise from normalising attention biases, and/or improving sensorimotor integration (Sumitani et al., 2007). The evidence, however does not necessarily support the idea of spatial attention biases in CRPS (De Paepe et al., 2020; Halicka et al., 2020a). Furthermore, as I demonstrated in Chapter 5, sensorimotor adaptation was not impaired for people with CRPS. These findings therefore question the proposed mechanisms, and therefore the efficacy, of treating CRPS with prism adaptation, and may explain why the only randomised control trial to look at prism adaptation failed to show an effect greater than sham treatment (Halicka, Vittersø, Proulx, & Bultitude, 2019).

In contrast, the findings from my thesis suggest that targeting bodily and spatial representation might be more relevant for people with CRPS. For instance, graded motor imagery combines mirror therapy, mental hand rotation, and motor imagery (Moseley, 2004, 2005), might be considered a more appropriate therapy. It is thought to improve motor predictions by targeting distorted representations of the body, and motor representations. Graded motor imagery has been found to be effective for CRPS (for review, and meta-analysis see Thieme, Morkisch, Rietz, Dohle, & Borgetto, 2016), although not all studies find evidence of its efficacy (Johnson et al., 2012). Graded motor imagery work by normalising altered body and motor representations in people with CRPS, and highlights the value of furthering our understanding of sensorimotor processing in pathological pain conditions. That is, by understanding how and what sensorimotor processes are altered within pathological pain conditions (i.e. "sensorimotor profiles"), existing treatments can be

tailored and new ones can be developed, which will hopefully improve the treatment for the many people experiencing pain.

3. Summary

To summarise, the aim of my thesis was to further our understanding of the role of sensorimotor incongruence in pathological pain. I have addressed this aim by providing a comprehensive review of the existing literature related to sensorimotor processing in pathological pain conditions, and by studying sensorimotor processing in people with CRPS, and pain-free individuals, and in experimental pain model. My research has tested the sensorimotor theory of pain, with a particular focus on processes that could interfere with predicting the outcome of a movement, and sensorimotor integration. My findings add to our understanding of sensorimotor processing in pathological pain, and how acute pain might influence such processing. The findings from my thesis provide mixed support for the theory, and oppose one of its underlying assumptions. That is, they support the idea that bodily and spatial representations may function differently for people with pathological pain, but they do not show any evidence of impaired sensorimotor integration. These findings have implications for the sensorimotor theory of pain, and for the clinical application of sensorimotor therapies. For instance, the theory could be refined by considering how changes within a given pathological pain condition might reflect an underlying sensorimotor profile. The sensorimotor theory of pain does not provide a complete explanation of the changes seen in people with pathological pain conditions. Nonetheless, the theory remains a useful framework within which to generate testable hypotheses to further our understanding of sensorimotor processing in pathological pain.

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Appendixes

Appendix 1: Chapter 2 - Supporting information

Supplementary figures

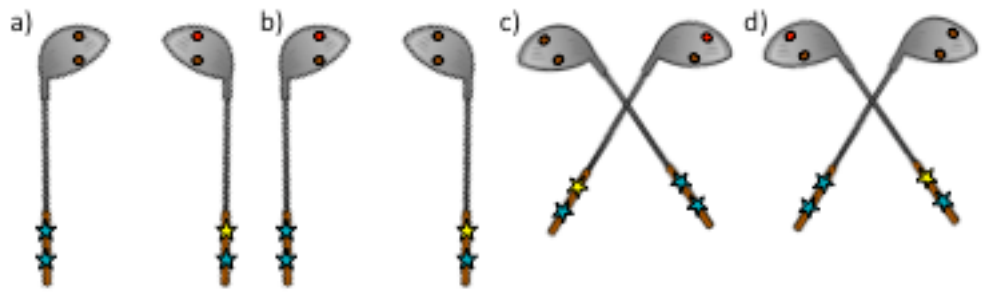

Figure S1. Example tool arrangement.
The different possible combinations for the Crossmodal Congruency task (CCT) for congruent visuotactile stimulation. The brighter red dots illustrate the location of the visual stimulation, and the yellow stars the location of the tactile stimulation for each example trial. The tools could be in the straight (A & B), or crossed (C & D) position, with light appearing in the same (A & C) or opposite (B & D) visual field as the visuotactile stimulation.

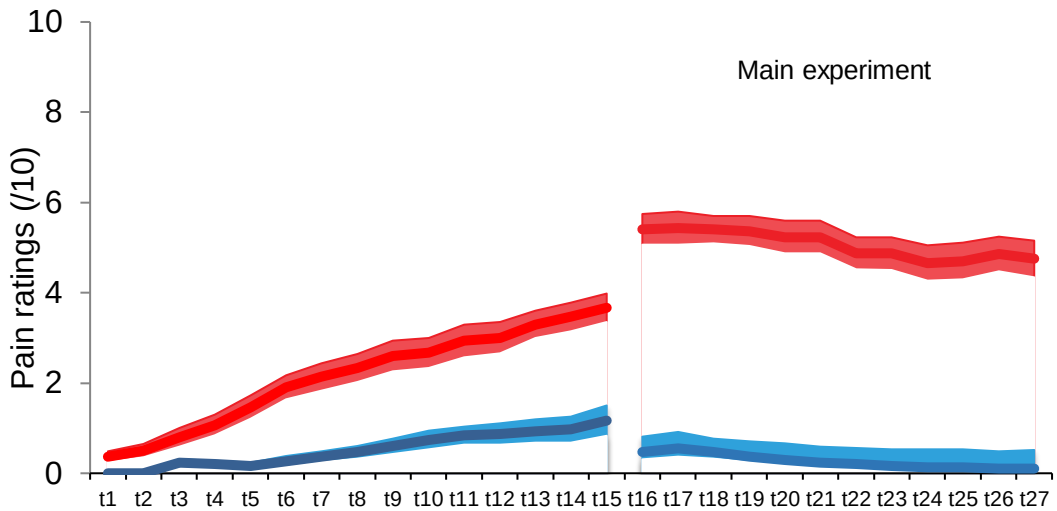

Figure S2. Pain ratings over time.
Change in pain ratings over time in the pain (red line) and active placebo (blue line) conditions. The neutral condition was omitted as mean ratings were ≈ 0. The ramp up period (t1-t15) lasted 15 min for the active placebo and neutral conditions. For the pain condition, this period lasted until pain ratings reached 5/10, or plateaued at 3/10 or higher for 3 consecutive ratings, which took on average 16.7 minutes (*SD* = 1.88). Pain ratings were recorded every minute during the ramp up period. When the ramp up period was shorter than 15 minutes, the missing ratings were adjusted to 5/10 for the purpose of this figure. *Pain ratings for ramp up periods exceeding 15 minutes are not included in this*

figure. During the main experiment (t16-t27) pain ratings were recorded between the tactile distance judgements and different set of the tool-use tasks, and so the time between pain ratings was variable.

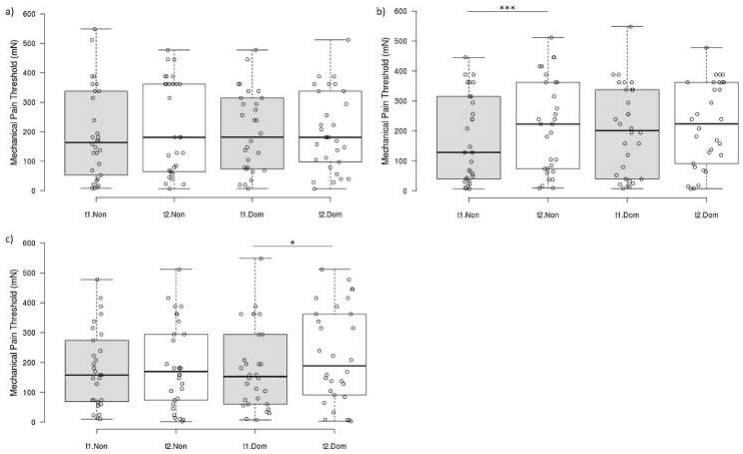

Figure S3. Change in Mechanical Pain Threshold by Sensory Condition.
Mechanical Pain Threshold (MPT) in mN on the middle finger (D3) before and after pain induction, active placebo, or no sensory manipulation (neutral), split by Side of Body for each conditions: neutral (A), active placebo (B), and pain (C). Circles depict individual data points. The dominant arm was always stimulated. (N = 30), * $p < .05$, ** $p < .01$.

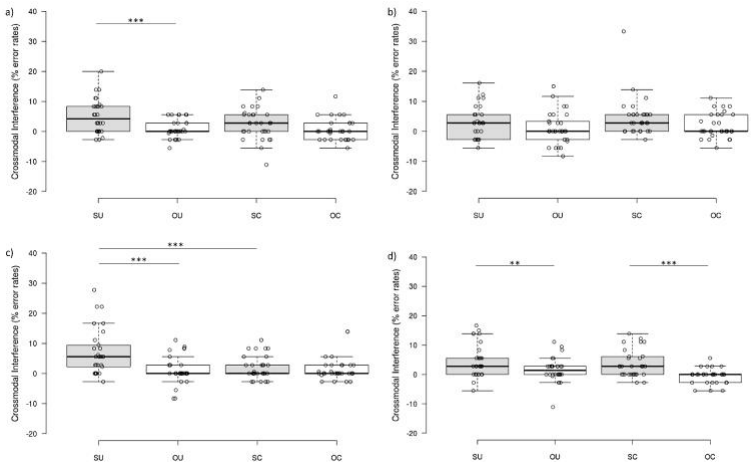

Figure S4. Crossmodal interference – four-way interaction for error rates.
Crossmodal interference shown by Set (1 [passive], 2, 3, 4), Tool Arrangement (uncrossed, crossed), and Visual Field (same, opposite) for error rates expressed in percentages on the Crossmodal Congruency Task (CCT), for all participants (n = 30). Crossmodal interference was calculated by subtracting congruent from incongruent error rates. Medians are depicted by the centre lines. The box limits indicate the 25ht and 75th percentile. The whiskers extend 1.5 times the interquartile range from the box limits. Circles depict individual data points. (N = 30). ** $p < .010$, *** $p < .001$.

Table S1. Performance on sensory tests by Sensory Condition.

Performance on sensory tests (Mechanical pain Threshold [MPT], Mechanical Detection Threshold [MDT], Two Point Discrimination [TPD]) expressed as change from pre to post Sensory Manipulation. Means and standard deviations for Sensory tests are split by Sensory Condition (Pain, Active Placebo, Natural), and Side of Body (dominant [stimulated], non-dominant).

	MPT (mN)		MDT (g)		TPD (mm)	
	M	**SD**	***M***	**SD**	***M***	**SD**
Dominant						
Pain	46.32	108.48	0.00	0.01	0.19	0.82
Active Placebo	18.58	61.03	0.00	0.01	-0.02	0.44
Neutral	1.62	48.95	0.00	0.01	0.04	0.35
Non-Dominant						
Pain	10.88	100.21	0.00	0.01	-0.13	0.47
Active Placebo	48.89	70.65	0.00	0.01	-0.06	0.37
Neutral	25.27	86.15	0.00	0.01	0.06	0.39

Table S2. CCT main effects and interactions for reaction times.

All significant main effects interactions from six-way ANOVA of Sensory Condition, Side of Body, Set, Tool Arrangement, Visual Field, and Congruence from the Crossmodal Congruency Task for reaction times.

	F	*p*	η_{2p}
Main effects			
Set	46.43	<.001	.62
Side of Body	7.97	.009	.22
Visual Field	6.69	.015	.19
Congruence	177.19	<.001	.86
Two-way			
Set x Side of Body	3.19	.039	.26
Tool Arrangement x Visual Field	10.56	.003	.27
Visual Field x Congruence			
Three-way			
Sensory Condition x Tool Arrangement x Visual Field	3.39	.048	.20
Side of Body x Tool Arrangement x Visual Field	15.5	<.001	.35
Set x Tool Arrangement x Congruence	4.36	.013	.33
Tool Arrangement x Visual Field x Congruence	9.43	.005	.25
Four-way			
Set x Tool Arrangement x Visual Field x Congruence	3.28	.035	.10

Table S3. CCT reaction times.

Descriptive statistics presented for the reaction times in ms from the crossmodal congruency task, split by Tool Arrangement (uncrossed, crossed), Side of Body (same, opposite), and Congruence (congruent, incongruent). The difference between congruent and incongruent scores are reported within each level of Tool Arrangement, and Side of Body.

	Congruent		**Incongruent**		***t***	$p_{adjusted}$
	M	***SD***	***M***	***SD***		
Uncrossed						
Same	630.11	89.92	702.85	93.04	13.45	.004
Opposite	664.73	93.63	691.89	95.26	5.29	.004
Crossed						
Same	641.03	99.28	695.21	99.63	8.47	.004
Opposite	651.73	91.50	683.07	98.30	7.91	.004

Table S4. CCT main effects and interactions for error rates.

All significant main effects interactions from six-way ANOVA of Sensory Condition, Side of Body, Set, Tool Arrangement, Visual Field, and Congruence from the Crossmodal congruency task for error rates.

	F	*p*	η_{2p}
Main effects			
Side of Body	7.38	.011	.20
Tool Arrangement	8.30	.007	.22
Visual Field	22.05	<.001	.43
Congruence	38.88	<.001	.57
Two-way			
Side of Body x Tool Arrangement	4.26	.048	.13
Side of Body x Congruence	7.12	.012	.20
Visual Field x Congruence	47.14	<.001	.62
Three-way			
Side of Body x Tool Arrangement x Visual Field	4.17	.050	.13
Four-way			
Set x Tool Arrangement x Visual Field x Congruence	4.47	.011	.33
Six-way			
Sensory Condition x Side of Body x Set x Tool Arrangement x Visual Field x Congruence	2.73	.031	.09

Supplementary text

S1 Text. Crossmodal congruency task (CCT) results – error rates.
All significant main effects and interactions are reported in S4 Table. There were main effects of Side of Body, $F(2, 29) = 7.38$, $p = .011$, $\eta_{2p} = .20$, Tool Arrangement, $F(1, 29) = 8.30$, $p = .007$, $\eta_{2p} = .22$, Visual Field, $F(1, 29) = 22.05$, $p < .001$, $\eta_{2p} = .43$, and Congruence, $F(1, 29) = 38.88$, $p < .001$, $\eta_{2p} = .57$, on error rates from the CCT. Error rates were higher for uncrossed ($M = 3.47$ %, $SD = 2.19$) than for crossed ($M = 2.71$ %, $SD = 1.64$) tools. More errors were made when visual distractors appeared in the same ($M = 3.65$ %, $SD = 2.74$) than the opposite ($M = 2.53$ %, $SD = 1.64$) visual field relative to vibrotactile targets. Participants had higher error rates for trials where the vertical locations of visual and vibrotactile stimulation were incongruent ($M = 4.35$ %, $SD = 3.29$), compared to congruent ($M = 1.84$ %, $SD = 1.10$).

The Tool Arrangement x Visual Field x Congruence interaction (Fig 3) was not significant for error rates from the CCT, $F(1, 29) = 3.68$, $p = .065$, $\eta_{2p} = .13$. There was a four-way interaction (S4 Fig) between Set, Tool Arrangement, Visual Field, and Congruence on error rates, $F(2, 28) = 4.47$, $p = .011$, $\eta_{2p} = .33$. Follow-up ANOVAs revealed a significant interaction between Tool Arrangement, Visual Field, and Congruence at set 3, $F(1, 29) = 13.28$, $p = .001$, $\eta_{2p} = .31$, but not in any other sets, $Fs(1, 29) \leq 1.68$, $ps \geq .183$, $\eta_{2ps} \leq .06$. To further investigate these patterns of results we calculated the crossmodal interference by subtracting error rates for the congruent condition from error rates for the incongruent condition, and compared this across each level of Tool Arrangement and Visual Field with each set. Follow-up tests for set 3 showed that crossmodal interference was higher for same ($M = 7.07$, $SD = 7.55$) than opposite ($M = 1.11$, $SD = 4.59$) visual field distractors relative to the vibrotactile stimulation when the tools were uncrossed, $t(29) = 4.78$, $p_{adjusted} = .004$, $d = 1.78$. For distractors appearing in the same visual field, crossmodal interference from set 3 was higher for uncrossed than crossed ($M = 1.96$, $SD = 4.59$) tools, $t(29) = 3.94$, $p_{adjusted} = .009$, $d = 1.46$. No other follow-up comparisons from set 3 were significant, $ts(29) \leq 0.73$, $ps_{adjusted} \geq .941$, $ds \leq 0.27$. The three-way interaction in set 3 for error rates from the CCT appears to be driven by greater crossmodal interference for visual distractors in the same compared to opposite visual field as tactile targets, when tools were uncrossed, but not crossed. This is consistent with a remapping of peripersonal space representations to accommodate tool-use. These findings indicate that changes in peripersonal space may have been observed in set 3. We did not observe this pattern for any other sets, as the three-way interaction Tool Arrangement x Visual Field x Congruence was only present during set 3.

There was a six way interaction between Sensory Condition, Set, Side of Body, Tool Arrangement, Visual Field, and Congruence in the analysis of error rates, $F(4.14, 120.08) = 2.73$, $p = .031$, $\eta_{2p} = .09$. Upon further analysis, however, there were no effects that were clearly driven by Sensory Condition from this interaction. We conducted four separate Set x Tool Arrangement x Visual Field x Congruence ANOVAs on the data split by Sensory Condition and Side of Body. A three-way interaction between Tool arrangement, Visual Field, and Congruence was present for error rates for tactile stimulation delivered to the non-dominant arm in the pain condition, $F(1, 29) = 5.31$, $p = .029$, $\eta_{2p} = .16$, but not in any of the other Sensory Condition by Body Side conditions, $Fs \leq 1.19$, $ps \geq .284$, $\eta_{2p}s. \leq .04$. Follow-up t-tests revealed that these results were driven by greater crossmodal interference

for distractors in the same (M = 5.78 %, SD = 7.99) than the opposite (M = 0.28 %, SD = 5.57) visual field relative to the target location for uncrossed tools, $t(29) = 2.88$, $p_{adjusted} = .016$, $d = 1.07$. However, no other follow-up tests were significant for the non-dominant arm in the pain condition, $ts(29) \leq 1.76$, $ps_{adjusted} \geq .270$, $ds \leq 0.65$. This result is consistent with peripersonal space representations being updated to accommodate the tool.

There was a four-way interaction of Set, Tool Arrangement, Visual Field, and Congruence for tactile stimulation delivered to the dominant hand in the neutral condition, $F(3, 27) = 3.99$, $p = .018$, $\eta_{2p} = .31$. Follow-up tests revealed that this was driven by significant Tool Arrangement x Visual Field x Congruence interaction in set 1 (passive), $F(1, 29) = 10.25$, $p = .003$, $\eta_{2p} = .26$, and in set 4, $F(1, 29) = 4.96$, $p = .034$, $\eta_{2p} = .15$, but not in sets 2 and 3, $Fs \leq 1.44$, $ps \geq .240$, $\eta_{2p} \leq .05$. For the dominant hand in the neutral condition, there was greater crossmodal interference for visual distractors appearing in the same (M = 8.56, SD = 11.57) than opposite (M = -0.56, SD = 8.45) visual field relative to vibrotactile targets, for uncrossed tools in set 1, $t(29) = 3.13$, $p_{adjusted} = .006$, $d = 1.16$. Crossmodal interference was greater for uncrossed than crossed (M = -1.11, SD = 10.66) tools when visual distractors appeared in the same visual field relative to vibrotactile targets, for the dominant hand in the neutral condition for set 1, $t(29) = 3.13$, $p_{adjusted} = .030$, $d = 1.26$. No other follow-up comparisons for the dominant hand in the neutral condition set 1 were significant, $ts(29) \leq 0.72$, $ps_{adjusted} \geq .994$, $ds \leq 0.27$. No follow-up test for the dominant hand in the neutral condition in set 4 withstood correction for multiple comparisons, $ts(29) \leq 3.10$, $ps_{adjusted} \geq .104$, $ds \leq 1.15$. This pattern indicates that peripersonal space representations were updated for set 1 only, for the dominant hand in the neutral condition. Therefore, there was no evidence of a change in the overall pattern of accuracy over time that would indicate emergence of updating of peripersonal space.

Our results suggest that peripersonal space extended to include the tips of the tools from as early as set 1, in which participants interacted only passively with the tools. This observation is contrary to previous findings in which extension of peripersonal space only occurred after a period of active tool use, and emerged over time with on-going tool use.

Exploratory analyses

We considered that experience with the tool in session one might have primed participants to rapidly embody the tools upon grasping the handles of the tools at the beginning of sessions 2 and 3, and extend peripersonal space even while passively interacting with them. Because the order of the study was randomised and counterbalanced, we could investigate this possibility by conducting a between groups analysis of the data from the first session. Furthermore, there were six possible orders in which participants could have completed the study. We could use this information to create a categorical variable to enable us to further explore any order effects. Thus, we conducted two five-way ANOVAs on the RTs and error rates from the first experimental session with Set, Side of Body, Tool Arrangement, Visual Field and Congruence as within-subjects factors; and Sensory Condition as a between-subjects factor with ten participants in each of the pain, active placebo, and neutral groups. There was no main effects of Sensory Condition error rates from the CCT, $F(2, 52) = 1.00$, $p = .390$, $\eta_{2p} = .07$. There was an interaction between Sensory Condition, Set, Side of Body, Tool Arrangement, Visual Field, and Congruence on error rates, $F(4.74, 64.05) = 3.17$, $p = .014$, $\eta_{2p} = .19$. We followed this analysis up with six

ANOVAs of the effects of Set, Tool Arrangement, Visual Field, and Congruence on error rates, within each level of Sensory Condition and Side of Body. However, none of the follow-up ANOVAS showed a significant interaction between Tool Arrangement, Visual Field, and Congruence, $Fs(1, 9) \leq 2.82$, $ps \geq .128$, $\eta_{2p}s \leq .24$.

Appendix 2: Chapter 3 – Supporting information

Altered updating of bodily and spatial representation following tool-use in Complex Regional Pain Syndrome: Supplementary digital content

1. Method

1.1 Protocol

1.1.1. Hand temperature recordings

Across the entire study, hand temperature was recorded three times corresponding to three Effector Conditions [hands, t1 tools (pre tool-use), t2 tools (post tool-use)], each Condition consisting of two Arrangements (crossed, uncrossed). In the first Condition (hands), participants completed the temperature recording in two Arrangements (crossed, uncrossed) in a counterbalanced order. In the uncrossed Arrangement, participants positioned their hands straight in front of them, so they were aligned with their shoulders, and did not cross the body midline (e.g. the CRPS-affected hand would be located on the CRPS-affected side of space, and vice versa). In the crossed Arrangement, each hand crossed the body midline (e.g. so that the CRPS-affected hand would be located in the non-affected side of space, and vice versa). These hand Arrangements replicated those used in previous studies to demonstrate spatially defined hand temperature changes (Moseley, Gallace, & Iannetti, 2012).

Once the temperature recordings for the two hand Arrangements were completed, we repeated the same procedure while manipulating the Arrangements (crossed, uncrossed) of the tools instead of the hands [i.e. the t1 tools (pre tool-use) Condition].

Participants completed a final temperature recording block at the end of the study (i.e. t2 tools (post tool-use) Condition) whilst holding the tools in a crossed or uncrossed Arrangement following exactly the same methods as for the t1 tools condition. The same counterbalanced order of Arrangement (crossed, uncrossed) was repeated for all three Conditions (hand arrangement, t1 tool-arrangement, t2 tool-arrangement) of temperature recording within each participant. For people with upper limb CRPS, we expected to see smaller hand temperature asymmetries for crossed compared to uncrossed tools after active tool-us (i.e. t2 tool-arrangement), if there was any influence of updating bodily and spatial representations on spatially defined modulations of CRPS symptoms. We did not expect to see any tool-use dependent effects on spatially defined modulations of hand temperature asymmetries in the other two Groups (lower limb CRPS, controls).

1.1.2 Beanbag sorting task

The task was inspired by comparable research into active tool-use (Farnè, Iriki, & Làdavas, 2005; Farnè & Làdavas, 2000; Maravita, Clarke, Husain, & Driver, 2002), and required participants to sort and retrieve 12 distant beanbags, 11 times, with the same tools that were being used for the CCT. The beanbags had to be retrieved from the distal end of the board to coloured squares (see Fig. 2) on the left or right side of the board's proximal end, sorted by colour. This task lasted approximately 5 minutes. However, for some of the people with upper limb CRPS the task took longer, breaks were needed, and/or modifications to

the task were made (e.g. placing the beanbags closer to the participants, or grasping the tools closer to their centre). If a participant required a break, they would continue to grasp the tools while the tools were supported by the gel wrist rests.

2. Results

2.1 Sensory Testing

The descriptive statistics for the sensory testing are expressed as a relative difference, calculated by subtracting thresholds, or mean ratings for the non-affected/dominant arm from the affected/non-dominant arm. For people with upper limb CRPS, the affected side relative to the non-affected side had a higher Mechanical Detection Threshold (M = 0.30 g, SD = 0.81), lower Mechanical Pain Threshold (M = -18.49 mN, SD = 79.41), more allodynia (M pain rating from 0-100 = 22.51, SD = 27.04), and a lower Two Point Discrimination Threshold (M = -0.03 mm, SD = 0.97). This is consistent with signs of hypoesthesia, hyperalgesia, allodynia, and more precise tactile discrimination ability on the affected upper limb. However, the ratings were only significantly different from zero for allodynia, $t(17) = 3.53$, $p = .015$, $d = 1.71$. There was no significant difference for any of the thresholds from the other sensory measures for people with upper limb CRPS, ts(17) ≤ 1.59, ps ≥ .188, ds ≤ 0.77. People with lower limb CRPS had a higher Mechanical Detection Threshold (M = 0.95 g, SD = 2.80), lower Mechanical Pain Threshold (M = -80.12 mN, SD = 280.33), more allodynia (M pain rating from 0-100 = 36.41, SD = 33.06), and a lower Two Point Discrimination Threshold (M = -0.09 mm, SD = 1.21) for their CRPS-affected area than the control site. This is consistent with signs of hypoesthesia, hyperalgesia, allodynia, and more precise tactile discrimination ability on the affected lower limb. However, the ratings were only significantly different from zero for allodynia, $t(14) = 4.13$, $p = .012$, $d = 2.21$, not for any of the thresholds from the other sensory measures for people with lower limb CRPS, ts(14) ≤ 1.97, ps ≥ .125, ds ≤ 1.05. The asymmetries of control participants' sensory ratings for Mechanical Detection Threshold (M = 0.04 g, SD = 0.49), Mechanical Pain Threshold (M = -6.65 mN, SD = 89.38), allodynia (M pain rating from 0-100 = 0.00, SD = 0.00), and Two Point Discrimination (M = 0.06 mm, SD = 0.95), were not significantly different from zero, ts(35) ≤ 0.46, ps ≥ .649, ds ≤ 0.16.

2.2 Confrontation testing

No control participants made any omissions on the confrontation testing. One person with upper limb CRPS made one omission during the tactile confrontation testing for a single stimulus delivered to her non-affected side, with her eyes closed. One person with upper limb CRPS made one omission during the motor neglect testing, when asked to perform a unilateral movement with their non-affected arm they instead moved their affected arm only, with their eyes open. One person with lower limb CRPS made two omissions during the motor neglect testing, when asked to perform unilateral movements with the arm of her affected side she instead moved the arm of her non-affected side only: once with her eyes open, and once with her eyes closed.

2.3 Tactile distance judgements

For our control participants, we did not find any significant main effects of Set (pre tool-use, post tool-use), $F(1, 34) = 0.31$, $p = .584$, $\eta_{2p} = .01$, or Side of Body (non-dominant, dominant),

$F(1, 34) = 0.40$, $p = .534$, $\eta_{2p} = .01$, on tactile distance judgements. We also did not observe a significant interaction between Set and Side of Body on tactile distance judgements, $F(1, 34) = 0.2$, $p = .894$, $\eta_{2p} = .00$.

2.4 Crossmodal congruency task

2.4.1 People with upper limb CRPS and their matched controls

The inferential statistics for main effects; and interactions involving Group (upper limb CRPS, controls), Tool Arrangement (crossed, uncrossed), and the Visual Field (same, opposite) on crossmodal interference (reaction times and error rates) for the upper limb group are presented in Table s1. Crossmodal interface is calculated by subtracting reaction times / error rates for congruent trials from those of incongruent trials. Other interactions are not reported because they are not relevant to the hypotheses of the study.

Table S1. Crossmodal interference – upper limb.

Inferential statistics are presented for ANOVAs of crossmodal interference (reaction times / error rates for incongruent trials minus those for congruent trials) with the factors Group (upper limb CRPS [n = 18], controls [n = 18]), Side of Body (affected/non-dominant, non-affected/dominant), Set (passive, active 1, active 2, active 3), Tool Arrangement (crossed, uncrossed), and Visual Field (same, opposite). Only those interactions involving Group, Tool Arrangement, and Visual Field are reported because other interactions are not relevant to the experimental hypotheses.

	Statistical Results	
	Reaction Times	Error Rates
Group	$F(1, 34) = 5.14$, $p = .030$, $\eta_{2p} = .13$	$F(1, 34) = 0.77$, $p = .385$, $\eta_{2p} = .02$
Side of Body	$F(1, 34) = 1.31$, $p = .260$, $\eta_{2p} = .04$	$F(1, 34) = 0.25$, $p = .783$, $\eta_{2p} = .03$
Set	$F(3, 32) = 1.14$, $p = .348$, $\eta_{2p} = .10$	$F(3, 32) = 0.79$, $p = .508$, $\eta_{2p} = .07$
Tool Arrangement	$F(1, 34) = 0.87$, $p = .359$, $\eta_{2p} = .03$	$F(1, 34) = 0.25$, $p = .620$, $\eta_{2p} = .01$
Visual Field	$F(1, 34) = 28.56$, $p < .001$, $\eta_{2p} = .46$	$F(1, 34) = 20.54$, $p < .001$, $\eta_{2p} = .38$
Group x Tool Arrangement x Visual Field	$F(1, 34) = 1.22$, $p = .277$, $\eta_{2p} = .04$	$F(1, 34) = 0.85$, $p = .363$, $\eta_{2p} = .02$
Group x Set x Tool Arrangement x Visual Field	$F(3, 32) = 0.19$, $p = .903$, $\eta_{2p} = .02$	$F(3, 32) = 3.19$, $p = .037$, $\eta_{2p} = .23$
Group x Side of Body x Tool Arrangement x Visual Field	$F(1, 34) = 0.48$, $p = .495$, $\eta_{2p} = .01$	$F(1, 34) = 0.09$, $p = .772$, $\eta_{2p} = .00$
Group x Set x Side of Body x Tool Arrangement x Visual Field	$F(3, 32) = 1.05$, $p = .383$, $\eta_{2p} = .09$	$F(3, 32) = 0.29$, $p = .829$, $\eta_{2p} = .03$

The analysis of reaction time crossmodal interference is elaborated on in the main text. A main effect of Visual Field for crossmodal interference error rates showed that visual distractors appearing in the same Visual Field ($M = 5.48$, $SD = 5.83$) as vibrotactile targets resulted in greater interference than those appearing in the opposite Visual Field ($M = 0.94$, $SD = 3.95$). There was a significant four-way interaction between Group, Set, Tool Arrangement, and Visual Field on crossmodal interference error rates (see Fig. s1, & Fig. s2). When we followed-up this interaction split by Set, there was a significant interaction between Group, Tool Arrangement, and Visual field on crossmodal error rates for the active 2 Set, $F(1, 34) = 7.85$, $p = .008$, $\eta_{2p} = .19$, but no other Sets, Fs$(1, 34) \leq 1.83$, ps $\geq .185$, $\eta_{2p} \leq .05$. Next, we followed-up the interaction from the active 2 Set split by Group, which showed no significant interaction between Tool Arrangement and Visual Field on crossmodal interference error rates for controls, $F(1, 17) = 4.25$, $p = .055$, $\eta_{2p} = .20$, $\eta_{2p} = .22$, nor for people with upper limb CRPS, $F(1, 17) = 3.60$, $p = .075$, $\eta_{2p} = .18$. Although these Tool Arrangement by Visual Field interactions were not significant, we followed them up with paired comparisons to try gain clarity on what was driving the main (four way) interaction. These comparisons showed that in the active 2 Set, control participants had greater crossmodal interference error rates from visual distractors appearing in the same Visual Field for uncrossed tools ($M = 7.31$, $SD = 7.50$) compared to crossed tools ($M = -0.37$, $SD = 6.20$), $t(17) = 3.92$, $p_{adjusted} = .004$, $d = 1.90$. No other contrasts were significant after correcting for multiple comparisons for controls, ts$(17) \leq 2.49$, ps$_{adjusted} \geq .069$, $ds \leq$

1.21, nor for people with upper limb CRPS, $ts(17) \leq 2.28$, $ps_{adjusted} \geq .144$, $ds \leq 1.11$. Therefore, overall the Group by Set by Tool Arrangement by Visual Field interaction on crossmodal interference error rates appears to be mainly driven by a reduction in crossmodal interference error rates for each Set, which occurred earlier for controls than for people with upper limb CRPS. There were no other significant interactions involving Group, Tool Arrangement, and Visual Field on crossmodal interference error rates for people with upper limb CRPS and their matched controls (Table s1).

2.4.2 People with lower limb CRPS and their matched controls

The inferential statistics for main effects; and interactions involving Group (lower limb CRPS, controls), Set (passive, active 1, active 2, active 3), Tool Arrangement (crossed, uncrossed), and Visual Field (same, opposite) on crossmodal interference (reaction times and error rates) for the lower limb group are presented in Table s2. Other interactions are not reported because they are not relevant to the hypotheses of the study.

Table S2. Crossmodal interference – lower limb

Inferential statistics are presented for ANOVAs of crossmodal interference (reaction times / error rates for incongruent trials minus those for congruent trials) with the factors Group (upper limb CRPS [n = 18], controls [n = 18]), Set (passive, active 1, active 2, active 3), Tool Arrangement (crossed, uncrossed), and Visual Field (same, opposite). Only those interactions involving Group, Tool Arrangement, and Visual Field are reported because other interactions are not relevant to the experimental hypotheses.

	Statistical Results	
	Reaction Times	Error Rates
Group	$F(1, 34) = 5.96$, $p = .020$, $\eta_{2p} = .15$	$F(1, 34) = 6.43$, $p = .016$, $\eta_{2p} = .16$
Set	$F(3, 32) = 0.94$, $p = .435$, $\eta_{2p} = .08$	$F(3, 32) = 1.83$, $p = .162$, $\eta_{2p} = .15$
Tool Arrangement	$F(1, 34) = 0.75$, $p = .393$, $\eta_{2p} = .02$	$F(1, 34) = 4.22$, $p = .048$, $\eta_{2p} = .11$
Visual Field	$F(1, 34) = 1.70$, $p = .201$, $\eta_{2p} = .05$	$F(1, 34) = 8.06$, $p = .008$, $\eta_{2p} = .19$
Group x Tool Arrangement x Visual Field	$F(1, 34) = 3.18$, $p = .083$, $\eta_{2p} = .09$	$F(1, 34) = 0.15$, $p = .705$, $\eta_{2p} = .00$
Group x Set x Tool Arrangement x Visual Field	$F(1, 32) = 0.89$, $p = .455$, $\eta_{2p} = .08$	$F(1, 32) = 1.32$, $p = .285$, $\eta_{2p} = .11$

The analysis of reaction time crossmodal interference is elaborated on in the main text. A main effect of Group for crossmodal interference error rates revealed that people with lower limb CRPS experienced greater overall interference (M = 7.27, SD = 5.52) than controls (M = 3.17, SD =4.07). A main effect of Tool Arrangement showed that crossmodal interference error rates were greater for uncrossed tools (M = 6.22, SD = 7.22) than crossed tools (M = 4.21, SD = 4.41). A main effect of Visual Field indicated that visual distractors appearing in the same Visual Field (M = 7.13, SD = 7.85) as vibrotactile targets resulted in greater crossmodal interference error rates than those appearing in the opposite Visual Field (M = 3.31, SD = 5.13). There were no significant interactions involving Group, Tool Arrangement, and Visual Field on crossmodal interference error rates for people with lower limb CRPS and their matched controls (Table s2).

2.5. Hand temperature asymmetry

The analysis of hand temperature asymmetries is elaborated on in the main text. Descriptive statistics for hand temperature asymmetries are presented in Table s3. Inferential statistics for absolute hand temperature asymmetries for the tool Effector Conditions (t1 tools, t2 tools) are presented in Table s4.

Table S3. Hand temperature asymmetries

Means and standard deviations of hand temperature asymmetries in ˚C, split by Group (upper limb CRPS [n = 18], lower limb CRPS [n = 18], controls [n = 34]), Effector Condition (hands, t1 tools, t2 tools), and Arrangement (crossed, uncrossed).

	Upper limb CRPS	Lower limb CRPS	Controls
Hands			
Crossed	1.08 (0.77)	0.52 (0.47)	0.51 (0.49)
Uncrossed	1.13 (0.76)	0.64 (0.42)	0.64 (0.60)
t1 Tools			
Crossed	1.08 (0.84)	0.47 (0.33)	0.75 (0.78)
Uncrossed	1.07 (0.89)	0.57 (0.50)	0.74 (0.78)
t2 Tools			
Crossed	1.00 (0.98)	0.48 (0.72)	0.51 (0.38)
Uncrossed	1.06 (0.95)	0.75 (0.72)	0.46 (0.52)

Table S4. Absolute hand temperature asymmetries

Inferential statistics for the ANOVA of absolute hand temperature asymmetries for the tool Effector Conditions, with the factors Group (upper limb CRPS [n = 18], lower limb CRPS [n = 18], controls [n = 34]), Set (t1 tools, t2 tools), and Arrangement (crossed, uncrossed).

	Statistical results
Group	$F(1, 67) = 2.34$, $p = .104$, $\eta_{2p} = .01$
Set	$F(1, 67) = 0.01$, $p = .943$, $\eta_{2p} = .00$
Arrangement	$F(1, 67) = 2.86$, $p = .095$, $\eta_{2p} = .04$
Group x Set	$F(2, 67) = 0.16$, $p = .857$, $\eta_{2p} = .01$
Group x Arrangement	$F(2, 67) = 3.45$, $p = .038$, $\eta_{2p} = .09$
Set x Arrangement	$F(2, 67) = 0.33$, $p = .567$, $\eta_{2p} = .01$
Group x Set x Arrangement	$F(2, 67) = 1.16$, $p = .321$, $\eta_{2p} = .03$

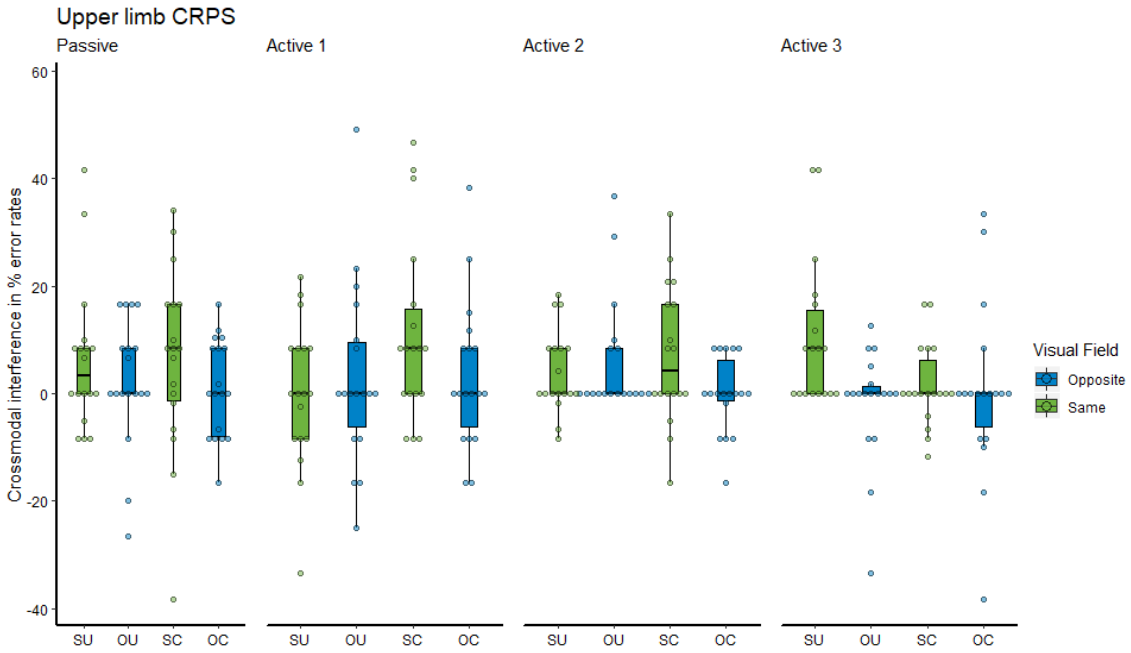

Figure S1. Crossmodal interference in error rates – upper limb

Crossmodal interference error rates in percentage on the Crossmodal Congruency Task (CCT) for people with upper limb CRPS (n = 18). Data are split by Tool Arrangement (uncrossed [U], crossed [C]) and Visual Field (same [S], opposite [O]). We calculated crossmodal interference by subtracting the percentage of error rates for congruent trials from those for incongruent trials. Medians are depicted by the central lines, and box limits indicate the 25th and 75th percentile. The whiskers extend 1.5 times the interquartile range from the box limits. Individual data points are depicted by circles.

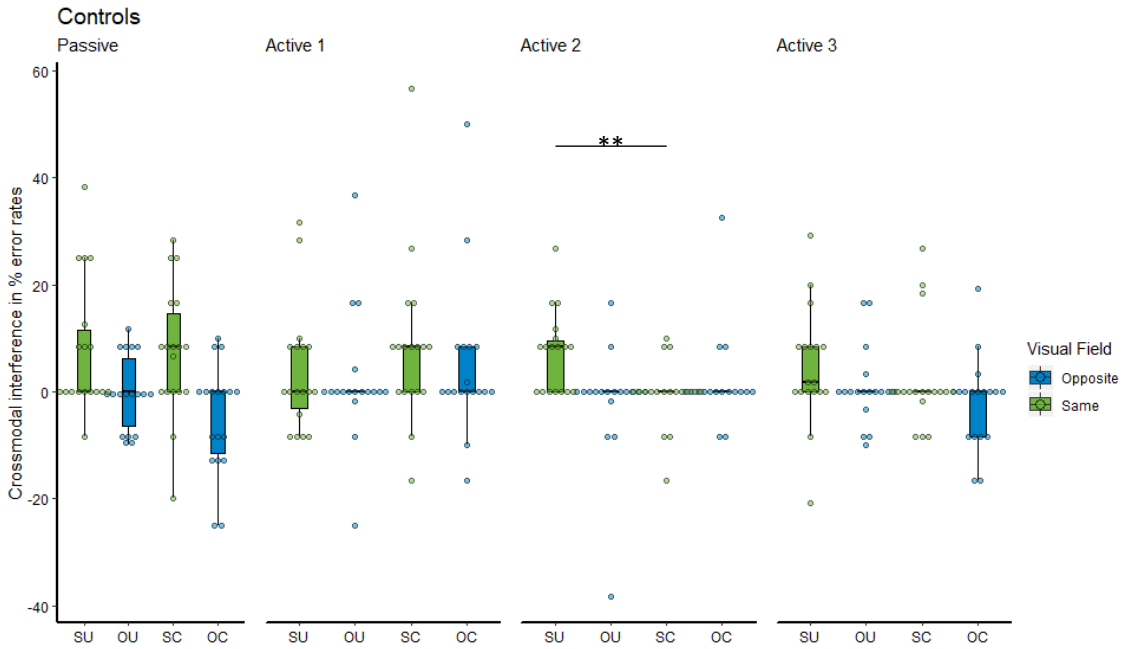

Figure S2. Crossmodal interference in error rates – lower limb

Crossmodal interference error rates in percentage on the Crossmodal Congruency Task (CCT) for upper limb controls (n = 18). Data are split by Tool Arrangement (uncrossed [U], crossed [C]) and Visual Field (same [S], opposite [O]). We calculated crossmodal interference by subtracting the percentage of error rates for congruent trials from those for incongruent trials. Medians are depicted by the central lines, and box limits indicate the 25th and 75th percentile. The whiskers extend 1.5 times the interquartile range from the box limits. Individual data points are depicted by circles. * $p_{adjusted} < .05$. ** $p_{adjusted} < .01$

2.6 Exploratory analyses

2.6.1 Sensory deafferentation

We considered that sensory deafferentation might contribute to the altered updating of bodily and spatial representations that we observed for people with CRPS. We had measures of sensory processing from the upper limbs for people with upper limb CRPS, as we had conducted quantitative sensory testing (QST) at the most painful site for all participants. We were therefore able to look at the contribution of peripheral sensory processing (i.e. from the upper limbs) to our findings, for people with upper limb CRPS. We subtracted the QST threshold from the non-affected side from that of the affected, to get a difference score for mechanical detection thresholds (MDT), and mechanical pain thresholds (MPT). We then considered these difference scores as covariates in the analyses of the tactile distance judgements (Table s5), and the CCT (Table s6). We found no clear evidence that QST difference scores influenced updating of bodily and/or spatial representation for people with upper limb CRPS. However, it is possible that such an effect would be detected with a larger sample.

We did not find any significant main effects, or interaction between Side of Body, and Set, using the QST difference scores as covariates, on TDJ estimates for people with upper limb CRPS (Table s5). Albeit non-significant, the results from the interaction (i.e. Side of Body x Set) indicate that MDT difference scores may have had some influence on the TDJ estimates. This effect would need to be tested in a larger group of people with upper limb CRPS to establish the influence of sensory deafferentation on updating bodily representations.

Table S5. Tactile distance judgements – covariate analysis.

Inferential statistics are presented for ANOVAs of tactile distance judgements, with the factors Side of Body (affected, non-affected), and Set (pre tool-use, post tool-use), with mechanical pain threshold, and mechanical detection threshold as covariates, for people with upper limb CRPS (n = 18).

	Statistical Results
Mechanical Detection Threshold (MDT)	
Side of Body x MDT	$F(1, 14) = 0.00$, $p = .949$, $\eta_{2p} = .00$
Set x MDT	$F(1, 14) = 0.08$, $p = .776$, $\eta_{2p} = .01$
Side of Body x Set x MDT	$F(1, 14) = 4.34$, $p = .056$, $\eta_{2p} = .24$
Mechanical Pain Threshold (MPT)	
Side of Body x MDT	$F(1, 14) = 3.05$, $p = .103$, $\eta_{2p} = .18$
Set x MDT	$F(1, 14) = 1.04$, $p = .325$, $\eta_{2p} = .07$
Side of Body x Set x MPT	$F(1, 14) = 0.23$, $p = .637$, $\eta_{2p} = .02$

There was a significant interaction between Side of Body, Set, Tool Arrangement, and Visual Field, with the MDT difference score as a covariate, on crossmodal interference (ms) for people with upper limb CRPS (Table s6). We followed-up this interaction within each level of Set (passive, active 1, active 2, active 3). We found a significant interaction between Side of Body, Tool Arrangement, and Visual Field, using the MDT difference score as a covariate, on crossmodal interference in ms, for the passive set, $F(1, 14) = 4.88$, $p = .044$, $\eta_{2p} = .26$, but not for any other sets (i.e. active 1, active 2, active 3), Fs$(1, 14) \leq 1.52$, ps $\geq$

.238, $\eta_{2p} \leq .10$. Next, followed up the significant interaction for the passive set split by Side of Body (affect, non-affected), which did not show any significant interaction. That is, the interaction between Tool Arrangement, and Visual Field, with MDT difference scores as a covariate, on crossmodal interference, were not significant for people with upper limb CRPS, *F*s(1, 14) ≤ 3.14, *p*s ≥ .098, $\eta_{2p} \leq .18$. We did not observe any other significant interactions with MDT, or MPT as a covariate. Therefore, as the MDT difference scores only significantly covaried with a key interaction during the passive stage of tool-use, we think it is unlikely that sensory deafferentation gave rise to our main findings from the CCT.

Table S6. Crossmodal interference – covariate analysis.

Inferential statistics are presented for ANOVAs of crossmodal interference (reaction times / error rates for incongruent trials minus those for congruent trials) with the factors Side of Body (affected, non-affected), Set (passive, active 1, active 2, active 3), Tool Arrangement (crossed, uncrossed), and Visual Field (same, opposite), with mechanical pain threshold, and mechanical detection threshold as covariates, for people with upper limb CRPS (n = 18). Only those interactions involving Tool Arrangement, and Visual Field are reported because other interactions are not relevant to the experimental hypotheses.

	Statistical Results	
	Reaction Times	Error Rates
Mechanical Detection Threshold (MDT)		
Tool Arrangement x Visual Field x MDT	$F(1, 14) = 0.05$, $p = .826$, $\eta_{2p} = .00$	$F(1, 14) = 0.29$, $p = .867$, $\eta_{2p} = .01$
Set x Tool Arrangement x Visual Field x MDT	$F(3, 12) = 1.36$, $p = .303$, $\eta_{2p} = .25$	$F(3, 12) = 0.46$, $p = .716$, $\eta_{2p} = .10$
Side of Body x Tool Arrangement x Visual Field x MDT	$F(1, 14) = 0.83$, $p = .377$, $\eta_{2p} = .07$	$F(1, 14) = 0.27$, $p = .609$, $\eta_{2p} = .02$
Side of Body x Set x Tool Arrangement x Visual Field x MDT	$F(3, 12) = 4.03$, $p = .034$, $\eta_{2p} = .50$	$F(1.58, 22.09) = 1.54$, $p = .235$, $\eta_{2p} = .10$
Mechanical Pain Threshold (MPT)		
Tool Arrangement x Visual Field x MPT	$F(1, 14) = 0.55$, $p = .470$, $\eta_{2p} = .04$	$F(1, 14) = 0.67$, $p = .427$, $\eta_{2p} = .05$
Set x Tool Arrangement x Visual Field x MPT	$F(3, 12) = 1.31$, $p = .317$, $\eta_{2p} = .25$	$F(3, 12) = 0.75$, $p = .546$, $\eta_{2p} = .16$
Side of Body x Tool Arrangement x Visual Field x MPT	$F(1, 14) = 0.06$, $p = .812$, $\eta_{2p} = .00$	$F(1, 14) = 0.07$, $p = .803$, $\eta_{2p} = .01$
Side of Body x Set x Tool Arrangement x Visual Field x MPT	$F(3, 12) = 0.83$, $p = .502$, $\eta_{2p} = .17$	$F(1.58, 22.09) = 0.16$, $p = .771$, $\eta_{2p} = .01$

2.6.2 Linear mixed models

We considered that the variance between individuals may have contributed to our main findings. We therefore analysed our data using linear mixed models, with Participant as a random effect in all our analyses (Table s7). We computed the linear mixed models in R (Team, 2013), using lme4 (Bates et al.), and lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017) packages.

Table S7. Linear mixed models

Inferential statistics are presented for the re-analysis of Tactile Distance Judgements (TDJs), the Crossmodal Congruency Task (CCT), and hand temperature asymmetries, using linear mixed models. The outcome/response variables were distance estimates, crossmodal interference, and

absolute hand temperature asymmetries, for the TDJs, CCT, and hand temperature asymmetries, respectively. Participant was entered as a random effect in all models. We used the Satterthwaite approach (Luke, 2017; Satterthwaite, 1941) to estimate degrees of freedom, and calculate *p*-values. The interaction terms are derived from Type III sums of squares. The intraclass correlations (ICC) are specified for each model. Reference conditions for fixed effects are specified in brackets.

	Interactions	Fixed effects
Tactile Distance Judgements (ICC = .73)		
Set x Arm	$F(1, 207) = 8.28$, $p = .004$	
Group x Set x Arm	$F(2, 207) = 3.57$, $p = .030$	
Lower limb CRPS (control, post, affected = 0)		$B = 1.80$, 95% CI [-0.84, 4.44], $t(207) = 1.34$, $p = .182$
Upper limb CRPS (control, post, affected = 0)		$B = 3.48$, 95% CI [0.89, 6.08], $t(207) = 2.63$, $p = .009$
Crossmodal Congruency Task		
Controls: upper limb (ICC = .02)		
Tool Arrangement x Visual Field	$F(1, 527) = 1.14$, $p = .286$	
Side of Body x Tool Arrangement x Visual Field	$F(1, 527) = 0.10$, $p = .919$	
Block x Tool Arrangement x Visual Field	$F(3, 527) = 0.62$, $p = .604$	
Side of Body x Block x Tool Arrangement x Visual Field	$F(3, 527) = 0.28$, $p = .843$	
CRPS: upper limb (ICC < .01)		
Tool Arrangement x Visual Field	$F(1, 527) = 4.92$, $p = .027$	
(crossed, opposite = 0)		$B = 160.17$, 95% CI [-31.37, 251.70], $t(527) = 1.64$, $p = .102$
Side of Body x Tool Arrangement x Visual Field	$F(1, 527) = 0.75$, $p = .387$	
Block x Tool Arrangement x Visual Field	$F(3, 527) = 0.64$, $p = .589$	
Side of Body x Block x Tool Arrangement x Visual Field	$F(3, 527) = 1.77$, $p = .150$	
Controls: lower limb (ICC = .03)		
Tool Arrangement x Visual Field	$F(1, 543) = 0.64$, $p = .423$	
Block x Tool Arrangement x Visual Field	$F(3, 543) = 0.50$, $p = .684$	
CRPS: lower limb (ICC = .08)		
Tool Arrangement x Visual Field	$F(1, 543) = 9.32$, $p = .002$	
(crossed, opposite = 0)		$B = 43.71$, 95% CI [-73.08, 160.49], $t(543) = 0.73$, $p = .464$
Block x Tool Arrangement x Visual Field	$F(3, 543) = 0.38$, $p = .769$	
Hand Temperature Asymmetry (ICC = .70)		
Group x Hand Arrangement	$F(2, 67) = 0.17$, $p = .844$	

For the TDJ, we analysed the interaction between Group (upper limb CRPS, lower limb CRPS, controls), Side of Body (affected/non-dominant, non-affected/dominant), and Set (pre tool-use, post tool-use), with Participant as a random effect, on TDJ estimates. The results were comparable to those reported in the main manuscript from ANOVAs, finding a significant interaction between Group, Side of Body, and Set, $F(2,207) = 3.57$, $p = .030$. This effect appeared to be driven by a difference between people with upper limb CRPS, and controls, which is consistent with the ANOVA findings. Therefore, we observed the same pattern of results on the TDJs, after the individual differences between participants were controlled for.

We followed up the main interactions for crossmodal interference from the CCT, split by Group (upper limb CRPS, lower limb CRPS, upper limb controls, lower limb controls), with Participant as a random effect. For the upper limb groups, we re-analysed the interaction between Side of Body (affected/non-dominant, non-affected/dominant), Block (passive, active 1, active 2, active 3), Tool Arrangement (crossed, uncrossed), Visual Field (same, opposite). We used the same factors for the two lower limb groups, bar Side of Body. The results were in agreement with the ANOVAs reported in the main manuscript, finding a significant interaction between Tool Arrangement, and Visual Field for people with upper limb CPRS, $F(1,527) = 4.92$, $p = .027$, lower limb CRPS, $F(1,543) = 9.32$, $p = .002$, but not for either control group , Fs$(1,543) \leq 1.14$, ps $\geq .286$. These interactions appeared to reflect the updating of spatial representations for people with CRPS. We did not find evidence of this effect in either control group.

These findings suggest that the results for the CCT remained comparable to those reported in the main manuscript, after individual differences between participants were controlled for.

We followed up the hand temperature asymmetry analysis for the interaction between Group (upper limb CRPS, lower limb CRPS, controls), and Hand Arrangement, with Participant as a random effect, on absolute hand-temperature asymmetries. Consistent with the ANOVAs reported in the main manuscript, this interaction was not significant, $F(2,67) = 0.17$, $p = .844$. Therefore, the results remained similar to those reported in the main manuscript.

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Appendix 3: Chapter 5 – Supporting information

1. Supplementary Figures

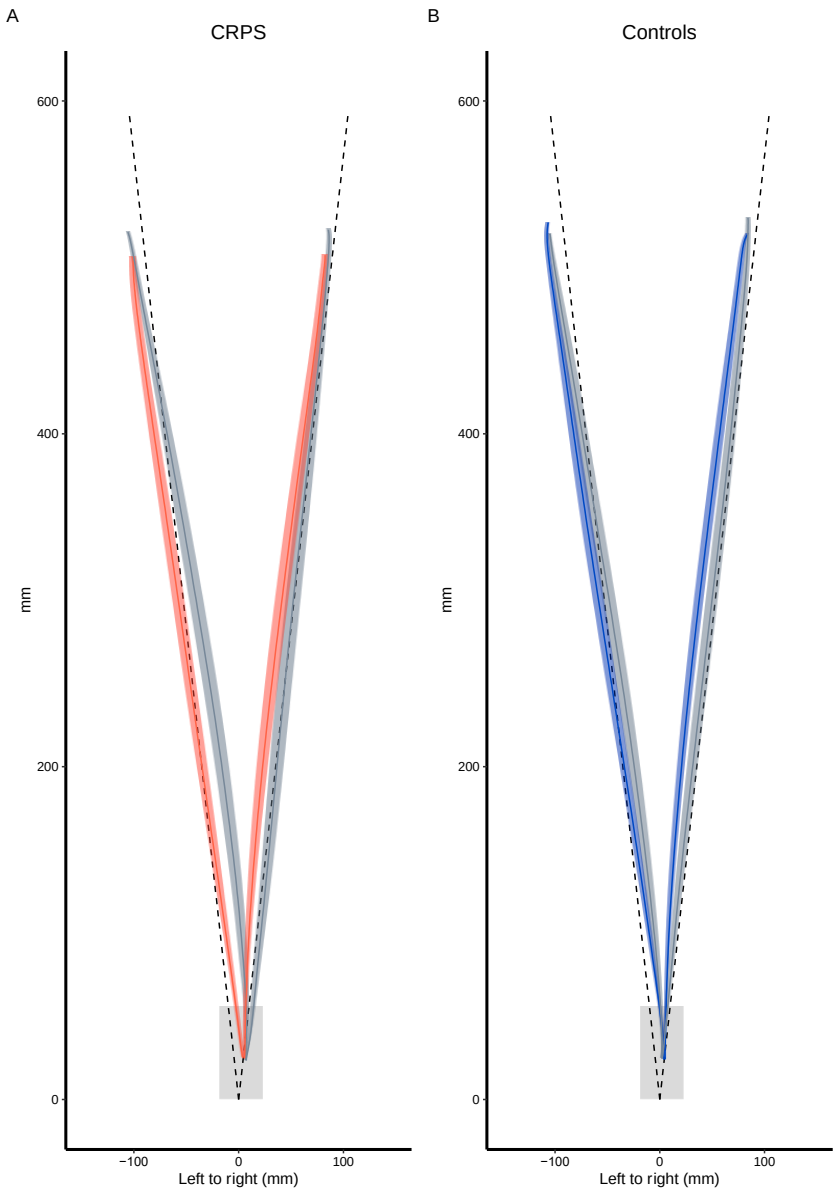

Figure S1. Calibration error
Mean hand paths for baseline closed-loop trials for people with CRPS (n = 17;A, C) and controls (n =18; B, D) split by Side of Body (affected [red], non-dominant [blue], non-affected/dominant [grey]), expressed in mm. The the boundaries of the shaded areas that surround the lines show ± one standard error of the mean. The black dashed lines shows the target axes (i.e. zero degree error) prior to adjusting for the suspected calibration error (1.18°). The grey shaded rectangle indicates the area within which a sensor had to be detected for a trial to start ("start location").

2. Supplementary Text T1: Model fit

2.1. Exponential decay of endpoint errors during prism exposure

Before analysing the constants derived from the fitted models, we analysed the model fit. The model failed to converge, or there was no exponential fit for one person with CRPS (non-affected hand), and for one control (dominant hand). Next, we compared the model fit parameters between Groups and Side of Body, for those cases where the model did converge and there was an exponential decay (CRPS n = 14; controls n = 17). The results suggested that the models were not different across Groups and Side of Body. That is, the prediction errors (i.e. the root-mean-square error [RMSE]) which indicated the mean distance from a predicted value to an observed value, for individually fitted models was not significantly different between Groups, (CRPS M_{RMSE} = 1.20, SD = 0.67; controls M_{RMSE} = 0.98, SD = 0.72), Side of Body (affected/non-dominant M_{RMSE} = 1.09, SD = 0.57; non-affected/dominant M_{RMSE} = 1.08, SD =0.82), and there was no significant interaction between the two variables, Fs(1, 29) ≤ 1.70, ps ≥ .202, η_{2p} ≤ .06. Similarly, there were no significant differences in how much variance was explained by the models (i.e. the *adj.* R_2) between Groups (CRPS $M_{adj.R2}$ = .47, SD = .26; controls $M_{adj.R2}$ = .54, SD = .26), Side of Body (affected/non-dominant $M_{adj.R2}$ = .52, SD = .25; non-affected/dominant $M_{adj.R2}$ = .50, SD = .27), and there was no significant interaction between the two variables, Fs(1, 29) ≤ 0.52, ps ≥ .475, η_{2p} ≤ .02. As there was no clear difference in the model fits between people with CRPS and controls, or any clear differences depending on the hand used, we proceeded to analyse the constants derived from the models (i.e. 1/b, and c; Fig. 5).

6.2.2. Exponential decay of endpoint errors during washout

Prior to analysing the constants from the exponential decay function, we analysed the model fit. We were unable to fit an exponential decay function for two participants with CRPS, both for their affected hand. For those cases where the model did converge and there was an exponential decay (CRPS n = 13; controls n = 18), we compared the model fit parameters between Groups and Side of Body. The prediction error (i.e. RMSE) did not differ between people with CRPS and controls, or for either hand. That is, there was no significant main effect of Group (CRPS M_{RMSE} = 0.77, SD = 0.35; controls M_{RMSE} = 0.59, SD = 0.29), Side of Body (affected/non-dominant M_{RMSE} = 0.64, SD = 0.27; non-affected/dominant M_{RMSE} = 0.69, SD = 0.37), and no significant interactions on RMSE, Fs(1, 29) ≤ 2.03, ps ≥ .165, η_{2p} ≤ .07. These results suggest that there was no difference in the prediction error between Groups or the hand used. We then analysed how much variance was explained by the models (i.e. the *adj.* R_2). There were no significant differences between Groups (CRPS $M_{adj.R2}$ = .34, SD = .23; controls $M_{adj.R2}$ = .42, SD = .30), F(1, 29) = 0.43, p = .517, η_{2p} = .01. There was a tendency for models to explain a greater proportion of the variance for models fitted to data from the non-affected/dominant hand ($M_{adj.R2}$ = .41, SD = .27) than the affected/non-dominant hand ($M_{adj.R2}$ = .35, SD = .28), although not statically significant, F(1, 29) = 3.16, p = .086, η_{2p} = .10. Neither did we find any evidence that this tendency varied between Groups, as there was no significant interaction between Group and Side of Body on *adj.* R_2, Fs(1, 29) ≤ 1.14, ps ≥ .343, η_{2p} ≤ .04. Therefore, as there was no clear difference in the model fits between people with CRPS and controls, and the tendency for the models to explain a greater proportion of the variance for the non-affected/dominant hand did not

vary between groups, we proceeded to analyse the constants derived from the models (i.e. 1/*b*, and *c*; Fig. 6).