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Can laterality judgment performance discriminate between people with chronic pain and healthy individuals?: a systematic review and meta-analysis

Ravat, Sadiya

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Can laterality judgment performance discriminate between people with chronic pain and healthy individuals? A systematic review and meta-analysis

Sadiya Ravat

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of MSc Physiotherapy

Johannesburg, 2017

DECLARATION

I, Sadiya Ravat, declare that the work contained in this research report is my own work, except to the extent indicated in the acknowledgements sections.

This research report is being submitted for a degree of Masters in Physiotherapy (Orthopaedic Manipulative Therapy), at the University of the Witwatersrand, Johannesburg, South Africa.

This work has not been submitted for any other degree or examination in this or any other university.

_____ 13/06/2017

Sadiya Ravat Date

ABSTRACT

Background

Chronic pain is a health problem that occurs across cultures and across the globe. Treatment of chronic pain is challenging and there is often failure of recovery, with the need to look at different approaches to understanding chronic pain. It was recently found that people with chronic pain have both central and peripheral features. Therefore, there is a need to look at central mechanisms that may be contributing to the chronicity of pain. People with chronic pain disorders experience a disturbance in body schema. Laterality judgment performance is dependent on body schema and can therefore determine the central mechanisms affected in chronic pain patients. The aim of this systematic review is to determine whether there is a difference in laterality judgment between people with chronic pain and healthy individuals.

Method

A comprehensive search was done of the following databases: MEDLINE (Pubmed), CINAHL Plus, Cochrane Controlled Trials Registered, Physiotherapy Evidence Database (PEDro), Science Direct, SCOPUS, Clinical Key and Google Scholar. Combinations of the following keywords were used: “laterality” “body schema” “motor imagery” and “pain”. The reference lists of all identified full text articles were searched for additional studies. Articles from inception up until December 2016 were considered for inclusion in this review. Outcome measures considered were reaction time (length of time taken to choose whether a pictured limb is right or left) and accuracy (correct number of responses). A total of 15 studies were included in this review. Methodological quality was assessed by two independent reviewers using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies.

Results from all the studies investigating similar conditions and using similar methodologies were analysed and pooled into statistical meta-analysis using Meta-Easy. The weighted mean differences (for continuous data) and their 95% confidence intervals were calculated for the outcome measures, namely reaction time and accuracy. The random-effects model was used, due to the variation and small sample sizes in studies. Heterogeneity was assessed by the p-value and I^2 value. Thereafter, studies were divided into sub-groups (according to condition/similar laterality tasks) and further

analysed. Statistical measures used in both meta-analyses included the probability value, mean effect size, variance effect size and maximum likelihood. Where statistical pooling was not possible the findings are presented in a narrative form.

Results

Forest plots of reaction time of five studies regardless of condition in terms of reaction time showed a positive relationship between decreased reaction time and chronic pain. Accuracy of five studies regardless of condition did not show a clear direction of effect. Due to the high heterogeneity, interpretation of this meta-analysis should be done with caution. The sub-group analysis for accuracy in lower limb conditions versus healthy individuals showed a medium statistically significant effect size (0.59) with a significant 95% CI (0.11 to 1.07). Results for low back pain and cervical pain could not be pooled into a meta-analysis, as there were different methods of reporting the results in the studies. However, results from individual studies showed that laterality judgment impairments are present in the low back pain, complex regional pain syndrome 1 and the upper limb pain population. It was not been shown to be impaired in whiplash associated disorders. There is no consensus in the literature whether laterality is affected in chronic cervical pain.

Conclusion

Laterality judgment was shown to be impaired in CPRS 1, upper limb pain, carpal tunnel syndrome, and osteoarthritis of the knee and leg pain. Due to the lack of studies, low quality of evidence and differences in results between studies there are inconsistencies with regard to back pain and therefore no conclusions can be drawn from the literature. It was not been shown to be impaired in whiplash associated disorders and there is conflicting evidence in cervical pain. It is evident that the impairment of laterality judgment cannot be assumed amongst all chronic pain conditions. This systematic review can be used as a foundation for future research. Research studies can be designed to remediate laterality recognition in affected conditions and assess the effect hereof on levels of pain and functional abilities. This could solve the missing link in understanding chronic pain syndromes and its rehabilitation. Clinicians can also gain insight on incorporating techniques (e.g. graded motor imagery) to re-train the brain's neural plasticity, and to in turn decrease chronic pain.

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DEFINITIONS OF TERMS

Pain:
"an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (http://www.iasp-pain.org/Taxonomy#Pain)

Chronic Pain:
Pain that is present after the remodelling phase of healing, after an injury. This could range from three to six months depending on the 'normal' healing time for the particular injury.

Body Schema:
Body schema refers to the way a person's body feels to themselves. The notion of body schema is unconscious. It is influenced by proprioception (decreased balance, kinaesthetic awareness and force production and discrimination), exteroception (tactile, visual, auditory, olfactory and gustation stimuli) and interoception (autonomic awareness, regulation and spatiality influences ownership and thermoregulation). It is also regulated by memory and psychosocial factors.

Laterality judgment:
The ability to determine whether a particular object is orientated to the left or right.

Laterality judgment of Body Parts:
The ability to determine if a pictured limb/body part depicts the left or right side. When presented with a stimulus (e.g. a picture of a hand), one needs to determine whether it belongs to the left or right side of the body. Unconsciously, one mentally manoeuvres one's body part to match the position of the pictured body part.

Central features of chronic pain:
These consists of neurochemical, structural and functional changes in the brain. This consists of changes in the brain activity due to a shift in the neurochemical profile as well as cortical changes in the brain's structure due to persistent pain.

Graded motor imagery:
A structured programme that starts with laterality training and progresses to mental imagery and then mirror therapy, with respect to pain. Each step in a graded motor imagery programme must be fulfilled adequately before progressing to the next.

Laterality training:
Laterality training refers to the repetition of determining whether a pictured body part belongs to the left or right hand side of the body.

Mental motor imagery:
The thinking or mental representation of a certain movement, without actually performing the movement.

Mirror therapy:
This is a form of motor imagery that uses a mirror to see the unaffected limb carry out a sequence of movements, while the affected limb is hidden. This reflective illusion conveys visual stimuli to the brain to trick it into believing that movement of the affected limb has occurred without pain.

Neuroplasticity:
The change in structure, function and organisation of the nervous system that occurs throughout one's life. In neuroplasticity the brain learns and develops new behaviours.

Cortical representation:
A neuronal network representing the homunculus, for example, the sensory homunculus in the primary somatosensory area in which the physical body is represented by neurons.

Peripheral Sensitisation:

Increased sensitivity to afferent (sensory) nerve stimuli, which was previously not painful.

Central sensitisation:

A condition whereby in the nervous system there is increased function of nociceptive pathways which results in the progression from acute to chronic pain as well as the maintenance of chronic pain. Features include pain sensitivity to non-noxious stimuli.

Speed/Accuracy Trade-off:
The ability to respond to a stimulus slowly with decreased mistakes versus the ability to respond quickly to a stimulus and make more mistakes is referred to as the speed accuracy trade-off.

LIST OF ABBREVIATIONS

ABBREVIATION	TERM
CRPS	Complex Regional Pain Syndrome
VAS	Visual Analogue Scale
CI	Confidence Interval
WAD	Whiplash Associated Disorder

CHAPTER 1: INTRODUCTION AND SCOPE OF THE RESEARCH REPORT

1.1 Introduction

Chronic pain is defined as pain that is still present after the remodelling phase of healing after an injury. This could range from three to six months depending on the 'normal' healing time for the particular injury (Apkarian et al., 2009, Merskey et al., 2011) People with chronic pain experience pain due to peripheral changes such as altered proprioception, physiological changes related to the pathology and avoidance of movement due to fear of pain (Bray and Moseley, 2011).

It was recently found that people with chronic pain have both central and peripheral features. Central features consists of neurochemical, structural and functional changes in the brain (Parker et al., 2016, Lotze and Moseley, 2007, Apkarian et al., 2011, Wand et al., 2011, Apkarian et al., 2009). Therefore, there is a need to look at central mechanisms that may be contributing to the chronicity of pain. Consequences of these brain changes could be hyperalgesia to painful stimuli, psychological and cognitive effects and disruption of body perception/ body schema (Wand et al., 2011, Apkarian et al., 2009). Research on the first two consequences are still in infancy, while it has been shown that people with chronic pain disorders experience a disturbance in body schema (Tsay et al., 2015, Haggard et al., 2013, Wand et al., 2011), which includes decreased proprioception and tactile acuity as well as decreased laterality judgment performance (Wand et al., 2011).

Body schema refers to the way a person's body feels to themselves (Lotze and Moseley, 2007). This is influenced by proprioception (decreased balance, kinaesthetic awareness and force production and discrimination), exteroception (tactile, visual, auditory, olfactory and gustation stimuli) as well as interoception (autonomic awareness, regulation and spatiality influences ownership and thermoregulation) (Tsay et al., 2015). It is also regulated by memory and psychosocial factors (Lotze and Moseley, 2007). The notion of body schema is largely an unconscious one. A disturbance in body schema can be linked to a disturbance of cortical representation of a painful body part (Tsay et al., 2015, Haggard et al., 2013, Wand et al., 2011),

i.e. a central feature of chronic pain. In chronic pain, the cortical representation of the painful body part is disturbed in posture, size or missing altogether (Tsay et al., 2015).

One of the methods of assessing the interoception part of body schema is by the use of a laterality judgment task (Jeannerod and Frak, 1999, de Lange et al., 2008). Laterality judgment refers to the ability to discern the position of one's body parts, without even looking at them. Therefore, laterality tasks require the ability to determine if a pictured limb/body part depicts the left or right side (Priganc and Stralka, 2011). Although no instruction is given, the participant mentally manoeuvres the body part (hand, foot, trunk or neck) to match position of the pictured body part, thereby activating the motor and somatosensory cortex of the brain (Pedler et al., 2013, Jeannerod and Frak, 1999, Parsons, 2001). Both imagined and executed movements have similar changes in brain activity, i.e. a similar area of the brain is activated in both movements (Moseley, 2004b). However, imagined movements, actual movements and laterality judgment abilities are dependent on an intact body schema (Lotze and Moseley, 2007, Moseley, 2004b, Parsons, 1987, Parsons and Fox, 1998)

Laterality of body parts follows an egocentric mechanism, whereby focus is only on oneself (Dalecki et al., 2012). On the other hand, laterality of letters or objects follow an allocentric mechanism, whereby focus is on other people rather than themselves (Dalecki et al., 2012). Due to this difference in mechanisms, only laterality tasks using pictured limbs can be used to test body schema.

Several individual studies investigating laterality judgment in patients with chronic pain have been done. Studies have been conducted in various populations, i.e. complex regional pain syndrome (CRPS) (Schwoebel et al., 2001, Moseley, 2004b, Reinersmann et al., 2012c, Reinersmann et al., 2010), upper limb conditions (Coslett et al., 2010b, Schmid and Coppieters, 2012, Fiorio et al., 2006), back pain (Bowering et al., 2014b, Linder et al., 2016, Bray and Moseley, 2011), cervical pain (Pedler et al., 2013, Richter et al., 2010, Elsig et al., 2014, Baarbe et al., 2016, Fiorio et al., 2007), and lower limb conditions (Coslett et al., 2010a, Stanton et al., 2012b, Stanton et al., 2013b). Various studies with a range of different findings exist in the literature, yet, to date no systematic review of the available evidence has been done and it is unclear whether laterality judgment differs in people with chronic pain syndromes compared to healthy individuals. Healthy individuals are

pain-free individuals that do not have any current pain, and have not experienced any history of long periods of constant or intermittent pain that has had an impact on their normal activity.

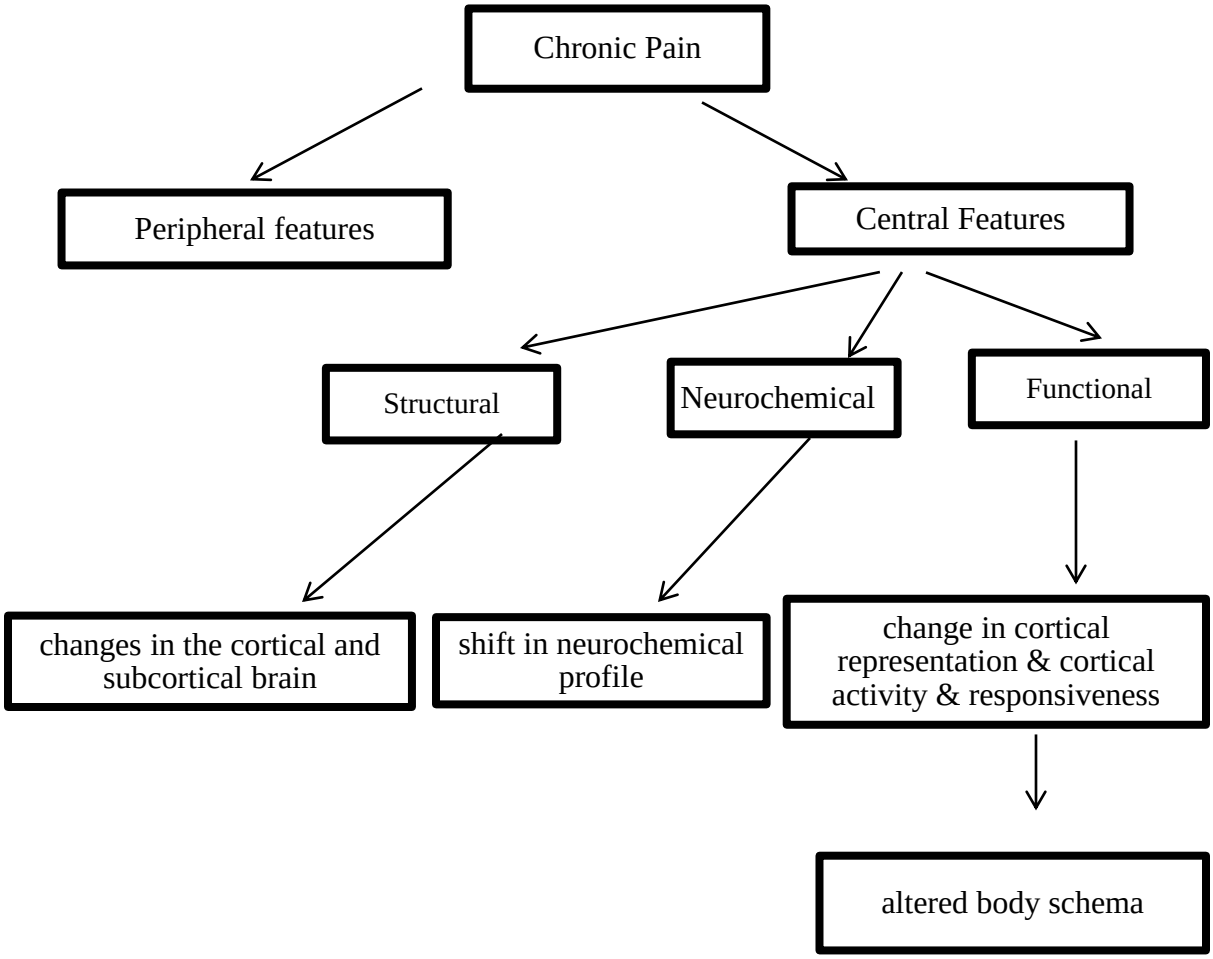

Figure 1: Diagram Illustrating Chronic Pain Features

1.2 Problem Statement

Chronic pain is a health problem that occurs across cultures and across the globe. In different parts of the world (Asia, Africa, Europe, and America) it was found that 22% of primary health care patients experience persistent pain, as well as psychological problems and activity limitations in daily life (Gureje et al., 1998) . Internationally, the prevalence of chronic pain is estimated to range between 10.8% and 53.7% (Henderson et al., 2013). A study investigating the prevalence and

impact of chronic pain in 15 European countries and Israel, found that chronic pain of moderate to severe intensity occurs in 19% of the adult population. Furthermore, it affects quality of life, activities of daily living such as sleep, household chores, walking, ability to exercise, ability to attend social events, intimacy and driving (Breivik et al., 2006). Chronic pain is also associated with psychological impact and depression (Bair et al., 2003).

Treatment of chronic pain is challenging and there is often failure of recovery, with the need to look at different approaches to understanding chronic pain. One such approach is the use of laterality judgment tasks as part of treating chronic pain syndromes (Priganc and Stralka, 2011, Bowering et al., 2013). Other treatment options for chronic pain include pharmacologic, surgical (e.g. nerve blocks) or non-pharmacological treatments. Pharmacologic treatments are centrally acting agents (anti-depressants, anticonvulsants), peripherally acting agents (acetaminophen, non-steroidal anti-inflammatory) or opioids (Reid et al., 2002). Non-pharmacologic treatments are physical therapy, cognitive behaviour therapy, exercise and relaxation (Reid et al., 2002, Hooten et al., 2013). Physiotherapy treatment can be done for many chronic pain syndromes. Each chronic pain syndrome behaves differently depending on the condition and type of physiotherapy received by the patient. On the other hand cognitive behaviour therapy utilises psychological principles to change behaviour in people with chronic pain. It's effectiveness in the treatment of chronic pain has been proven (McCracken and Turk, 2002, Alpayci et al., 2013). Exercise therapy and relaxation are used in physiotherapy treatments (Brunner et al., 2013, Taylor et al., 2007) while relaxation alone is used in cognitive behaviour therapy (Beck, 2011).

Laterality judgment performance addresses one of the central mechanisms of pain (i.e. structural changes in the brain). However, there are differences in the literature on whether laterality judgment is affected in chronic pain syndromes. Furthermore, no systematic review has been done so that the results from these studies can be pooled together and an overall difference can be established.

1.3.1 Systematic Review Question

Is there a difference in laterality judgment in people with chronic pain and healthy individuals?

1.3.2 Aim of the Study

The aim of this systematic review is to determine whether there is a difference in laterality judgment between people with chronic pain and healthy individuals.

1.4 Significance of the Study

Research has found that central features of chronic pain, such as disruption of body schema, need to be addressed as they might contribute to the chronicity of pain (Wand et al., 2011). Laterality judgment performance is dependent on body schema (Lotze and Moseley, 2007, Moseley, 2004b), and therefore can determine the central mechanisms affected in chronic pain patients.

One approach that is becoming increasingly used is laterality judgment tasks. It has been reported that laterality judgment performance activates motor and somatosensory cortices (similar to that of executed movement) and can improve neural plasticity and in turn decrease chronic pain (Priganc and Stralka, 2011).

The results from this systematic review can be used as a foundation for future research: if laterality judgment performance is found to be different in individuals with chronic pain, research studies can be designed to remediate laterality recognition and assess the effect hereof on levels of pain and functional abilities. Furthermore, if laterality judgment performance is shown to be altered in chronic pain syndromes, clinicians can gain insight on incorporating techniques (such as graded motor imagery) to re-train the brain's neural plasticity, and in turn decrease chronic pain.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Chronic pain is an increasing health problem around the world (Gureje et al., 1998). It is associated with increased health costs to the healthcare system, and decreased quality of life (Hooten et al., 2013). There are many treatment options for the treatment of chronic pain. Treatment options include pharmacologic, surgical (e.g. nerve blocks) or non-pharmacological treatments. Pharmacologic treatments are centrally acting agents (anti-depressants, anticonvulsants), peripherally acting agents (acetaminophen, non-steroidal anti-inflammatory) or opioids (Reid et al., 2002). Non-pharmacologic treatments are physical therapy, cognitive behaviour therapy, exercise and relaxation (Reid et al., 2002, Hooten et al., 2013).

Treatment of chronic pain is challenging and there is often failure of recovery (Elliott et al., 2002, Gureje et al., 2001). Treatment has focused on structural paradigms (Pelletier et al., 2015) and peripheral features of chronic pain (Snodgrass et al., 2014). However, it was recently found that in addition to peripheral features, chronic pain has central features too (Priganc and Stralka, 2011, Tsay et al., 2015). Central features of chronic pain includes neurochemical, structural and functional changes in the brain (Wand et al., 2011). Research has found that central features of chronic pain, such as disruption of body schema, need to be addressed as they might contribute to the chronicity of pain (Wand et al., 2011).

Laterality judgment tasks are used to assess body schema (Lotze and Moseley, 2007, Moseley, 2004b), which is a central feature of chronic pain. Therefore, central mechanisms of pain can be assessed in this way. Laterality judgment is the ability determine between left and right judgments of a body part (Priganc and Stralka, 2011). Laterality judgment performance activates motor and somatosensory cortices (similar to that of executed movement). This can improve neural plasticity, with the aim of decreasing chronic pain (Priganc and Stralka, 2011).

Laterality judgment studies in patients with chronic pain have been done. Therefore, the aim of this literature review is to review all the available evidence to date on studies comparing laterality judgment in people with chronic pain and healthy individuals. This will give the reader a good background on the topic of laterality judgment in chronic pain syndromes. To understand chronic

pain, this review will discuss the central features of chronic pain, as well as the concept of body schema. Furthermore, it will give a brief description of graded motor imagery as it includes laterality judgment tasks. Finally, all available evidence to date will be reviewed on laterality judgment between chronic pain syndromes and healthy individuals.

2.2 Search Strategy of Literature Review

The search process of this narrative review was done by a three-step process. Initially, a limited search of MEDLINE (Pubmed) and CINAHL Plus was searched for keywords of "laterality judgment" and "laterality in chronic pain". After analysis of keywords of the title, abstract and index terms in the articles, a comprehensive search was done of all databases. The databases searched includes: MEDLINE (Pubmed), CINAHL Plus, Cochrane Controlled Trials Registered, Physiotherapy Evidence Database (PEDro), Science Direct, SCOPUS, Clinical Key, Google Scholar. The search terms were used in various combinations and included: pain, laterality, motor imagery and body schema. Thirdly, the reference lists of all identified full text articles were searched for additional studies. All articles published from inception to December 2016 were included in this literature review.

2.3. Pain

2.3.1 Definition of Chronic Pain

Pain is considered a multifactorial issue. According to the World Health Organization and International Association for the Study of Pain, pain is defined as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (http://www.iasp-pain.org/Taxonomy#Pain). From this definition it is evident that pain, while being associated with physical damage is also a sensory and emotional experience. Focus of care in musculoskeletal pain is both on the physical as well as psychosocial and holistic management. Acute pain can be treated fairly easily by most clinicians. However, chronic pain can be more challenging. Chronic pain is defined as pain that is still present past the healing phase of an injury (Kleim and Jones, 2008). This could range from three to six months depending on the 'normal' healing time for the particular injury (Apkarian et al., 2009). Chronic pain syndromes

include conditions such as CPRS, chronic lower back pain, phantom limb pan and upper and lower limb pain.

2.3.2 Central Features of Chronic Pain

Neuroplasticity refers to a change in structure, function and organisation of the nervous system that occurs throughout one's life. In neuroplasticity the brain learns and develops new behaviours (Boudreau et al., 2010, Pascual-Leone et al., 2011, Kleim and Jones, 2008). Recent studies found neuroplastic changes within the central nervous system of people with chronic pain syndromes (Boudreau et al., 2010, Pascual-Leone et al., 2011, Kleim and Jones, 2008, Wand et al., 2011). These central features are not present in people with acute pain. Initially, these neurophysiological changes helped in healing by protecting the injured structures. However, in chronic pain these changes are secondary to the injury and as a result of altered sensory transmission from the injury (Boudreau et al., 2010, Pascual-Leone et al., 2011, Kleim and Jones, 2008, Wand et al., 2011). These changes contribute to the persistence of chronic pain. Chronic pain is also associated with a learned response due to a maladaptive memory of pain, which increases the persistence of pain (Moseley and Flor, 2012, Davis and Moayedi, 2013, Apkarian et al., 2011). This response is due to plastic changes in the meso-limbic and prefrontal areas of the brain, that are responsible for emotions such as fear, threat, attention, and motivation (Mansour et al., 2014, Ochsner et al., 2006, Seminowicz and Davis, 2006). Therefore, fear avoidance and catastrophisation is evident in chronic pain syndromes (Ochsner et al., 2006, Seminowicz and Davis, 2006).

Changes also occur in the peripheral receptors and the dorsal horn of the spinal cord, protecting from re-injury. This causes an increased response to stimuli (noxious and non-noxious) and sensory amplification. Peripheral and central sensitisation can occur (Woolf, 2011, Latremoliere and Woolf, 2009). Changes occur in the brainstem, where the descending modulation system is affected, and may contribute to the continuance of sensitisation in the spinal cord (Wang et al., 2013, Heinricher et al., 2009). Neurochemical changes also occur in the brain. This refers to shifts in the neurochemical profile in parts of the brain, a finding similar to what occurs in multiple sclerosis and Alzheimer's disease (Wand et al., 2011).

There are also structural changes in the neuronal properties, function and organisation in different cortical and sub-cortical parts of the brain, including the thalamus, primary somatosensory cortex and primary motor cortex (Parker et al., 2016, Apkarian et al., 2011). This is due to an increased amount of nociceptive stimuli entering the nervous system (Wand et al., 2011, Flor et al., 1997, Swart et al., 2009, Vartiainen et al., 2009). There is a change in cortical representation (Wand et al., 2011, Flor et al., 1997, Swart et al., 2009). Cortical representation is a neuronal network representing the homunculus, for example, the sensory homunculus in the primary somatosensory area in which the physical body is represented by neurons. In chronic pain the affected part is either shifted and expanded or decreased in size, contributing to the chronicity of pain (Wand et al., 2011). Changes in neuronal properties have been investigated in conditions such as chronic low back pain (Flor et al., 1997, Tsao et al., 2008, Tsao et al., 2011, Tsao et al., 2010, Strutton et al., 2005, Lloyd et al., 2008, Apkarian et al., 2004, Schmidt-Wilcke et al., 2006, Baliki et al., 2006), phantom limb pain (Schwenkreis et al., 2003), CRPS (Swart et al., 2009, Fukumoto et al., 1999), patellofemoral pain syndrome (On et al., 2004), rotator cuff injuries (Berth et al., 2009, Berth et al., 2010), anterior cruciate ligament injury and reconstruction (Kapreli et al., 2009, Heroux and Tremblay, 2006), dystonia (Byl et al., 2002), carpal tunnel syndrome (Tecchio et al., 2002, Tinazzi et al., 2000, Druschky et al., 2000, Maeda et al., 2013) and cervical pain and whiplash (Tinazzi et al., 2000, Falla and Farina, 2008).

The expansion of the primary somatosensory cortex results in sensory disturbances, i.e. an increased response to tactile stimuli specific to the painful limb (Flor et al., 1997, Wand et al., 2011, Tsao et al., 2011). Moreover, this relationship between the sensitivity to pain and cortical reorganisation has an effect on body schema (perceptual disturbance) (Wand et al., 2011, Priganc and Stralka, 2011). Motor disturbances (such as motor control) also occurs (Hodges and Tucker, 2011). Research suggests a relationship between injury, pain and neuroplastic changes in the primary sensory and motor cortex. Cortical reorganisation occurs when there is no pain. Treatment programs that target cortical reorganisation may improve function and decrease pain (Moseley and Flor, 2012). Therefore, new focus of research is on training the brain to reverse these changes in chronic pain.

2.4. Body Schema

Body schema is defined as "sensorimotor representations of the body that guide actions" (de Vignemont, 2010). This refers to the way a person's body feels to themselves (Lotze and Moseley, 2007). Without body schema (e.g. representation of the size and strength of ones limbs), action is not possible (de Vignemont, 2010). Body schema is influenced by proprioception (decreased balance, kinaesthetic awareness and force production and discrimination), exteroception (tactile, visual, auditory, olfactory and gustation stimuli) as well as interoception (autonomic awareness, regulation and spatiality influences ownership and thermoregulation) (Tsay et al., 2015). Psychosocial factors and memory is also an important influencing factor (Lotze and Moseley, 2007). Body schema is distinctly different from body awareness. While body schema is an unconscious notion, bodily awareness is not (de Vignemont, 2010). People with chronic pain syndromes experience a disturbance in body schema (Tsay et al., 2015, Haggard et al., 2013, Wand et al., 2011). This can be due to a disturbance of the cortical representation of the painful body part, which may be disturbed in posture, size or missing (Lewis et al., 2010, Wand et al., 2011). Some patients would describe the limb as "feeling like a dead weight" or "foreign" or "strange." Additionally, many conditions (such as CRPS) experience neglect-like symptoms of the affected limb/body part (Lewis et al., 2007, Forderreuther et al., 2004, Galer and Jensen, 1999, Frettloh et al., 2006). Patients with phantom limb pain may experience feelings of "heaviness," "floating," or "missing digit (Giummarra et al., 2007). Patients with low back pain report that they 'can't find it' when asked to sense and draw their back (Moseley and Flor, 2012). Several chronic pain syndromes such as CRPS (Moseley, 2005a, Lewis et al., 2010), chronic back pain (Bray and Moseley, 2011, Moseley, 2008) and phantom limb pain have been found to have an altered body schema (Moseley and Flor, 2012).

The interoception part (autonomic awareness, regulation and spatiality influences ownership and thermoregulation) of body schema is assessed in various ways. Initially, assessment was done using pain drawings (Tsay et al., 2015). Patients were provided with an outline of a human body (body chart), with the instruction to fill in or shade the painful area. Although this method had high test–retest reliability, there was question of what was being measured, due to the qualitative nature of the method. More recently, patients were asked to draw a picture of their body as it feels to them. This was done by providing either a blank paper or a simple outline of the body. In this method,

rather than providing a general outline of the patients pain location, they described how their body felt to themselves. However, due to a lack of standardised scoring measures this method was not feasible as there was difficulty drawing conclusions from the data. Furthermore, patient's artistic inability to draw their body image is a weakness of this method. Another method that can be used is templates, whereby pictures of different distortions are presented to the patient, and they select the image that best represents their body part (Tsay et al., 2015). Lastly, body schema can be assessed using laterality tasks (Jeannerod and Frak, 1999, de Lange et al., 2008). This is a more feasible method, with specific objective outcome measures.

In laterality judgment tasks, a picture of a stimulus is shown, and the participant needs to determine whether it is left or right (Priganc and Stralka, 2011). Laterality judgment tasks are measured by two specific outcome measures, which can be retested to determine improvements in body schema. Therefore, in this review we will be focusing only on laterality judgment as a measurement of body schema. In laterality judgment tasks participants mentally manoeuvre their limbs (i.e. imagined movement). This stimulates the motor and somatosensory cortex of the brain (Pedler et al., 2013, Jeannerod and Frak, 1999), similar to changes in brain activity with execution of movement (Moseley, 2004b). The rationale for laterality training is that the capacity to determine between left and right judgments of a body part, is based on an intact body schema (Lotze and Moseley, 2007, Moseley, 2004a), pre motor cortices are activated and it reinstates left and right concepts in the brain (Priganc and Stralka, 2011). The hypothesis is that the activation of motor and somatosensory cortices can activate cortical networks, reorganise the cortex, improve neural plasticity and in turn decrease chronic pain (Priganc and Stralka, 2011).

2.5. Graded Motor Imagery

Laterality training is a fairly new treatment technique used as part of graded motor imagery programme. A graded motor imagery programme starts with laterality training and progresses to mental imagery and then mirror therapy, with respect to pain (Priganc and Stralka, 2011). Laterality training is the first step, as it is thought that cortical training cannot take place unless a patient has a correct cortical representation of their body (Priganc and Stralka, 2011). Mental motor imagery refers to the thinking or mental representation of a certain movement, without actually performing the movement (Dickstein and Deutsch, 2007). This aspect of graded motor imagery has been well

researched. Research has been done in different scopes, i.e. in children (Gabbard, 2009), people living with stroke (Dickstein and Deutsch, 2007, Munzert et al., 2009), spinal cord injury (Dickstein and Deutsch, 2007), burn victims (Guillot et al., 2009), sports management (Lebon et al., 2012, Dickstein and Deutsch, 2007, Munzert et al., 2009) as well as chronic pain. In chronic pain, it has been shown to be effective in reducing pain in phantom limb pain (MacIver et al., 2008). In stage two shoulder impingement syndrome it has been shown to decrease pain and improve mobility (Hoyek et al., 2014). An integrative literature review (de Souza et al., 2015) has shown that in CPRS, mental imagery is shown to decrease pain and functionality that is present after a six month period. Mirror therapy has also been shown to be effective in reducing pain in phantom limb pain (Chan et al., 2007, Ramachandran and Altschuler, 2009) and CRPS (Ramachandran and Altschuler, 2009).

2.6. Laterality Performance Impairment in Chronic Pain

2.6.1 Primary Outcome Measures

Laterality performance in all studies was measured by use of pictures of healthy human body parts (with no visible marks on them). Participants were positioned in front of a computer screen and had to press either left or right arrow keys or different letters (e.g. “z” key for the left and “m” for the right or “a” key for left and “d” for right), in accordance to whether the pictured body part is left or right. In some studies participants were required to speak into a microphone. The instruction was to perform the task as fast as possible. Reaction time was measured automatically, i.e. length of time taken to choose whether a picture is right or left. Accuracy of the performance was also measured (either automatically or by an examiner), i.e. the correct number of responses. All pictures were presented in a computer generated random allocation. In one study, the letter ‘”R” was used in different orientations, instead of pictures of body parts (Baarbe et al., 2016) .

2.6.2 Secondary Outcome Measures

Many studies used outcome measures to measure pain and function. A visual analogue scale (VAS) in different forms was used in many studies (Coslett et al., 2010a, Linder et al., 2016, Reinersmann et al., 2010, Reinersmann et al., 2012a, Baarbe et al., 2016, Bray and Moseley, 2011, Coslett et al., 2010b, Pedler et al., 2013, Schwoebel et al., 2001, Schmid and Coppieters, 2012, Richter et al.,

2010, Stanton et al., 2012a, Stanton et al., 2013b). It was measured by a 5 or 11 point scale (visual), rating pain from most to least painful. In some studies VAS was also illustrated during movement (Coslett et al., 2010a, Coslett et al., 2010b). Other pain measures included were the Neuropathic Pain Scale (Moseley, 2004a), Chronic Pain Grading Scale (Baarbe et al., 2016), S-LANSS pain score (Schmid and Coppieters, 2012) and Pain Detect Questionnaire (Elsig et al., 2014). Function was measured differently between all groups, depending on the condition. General functional scales used were the McGill Pain Questionnaire (Bray and Moseley, 2011, Moseley, 2004b), Owestry Disability Index (Linder et al., 2016) and Short-Form Health Survey Questionnaire-36 (Stanton et al., 2013b). Other specific functional outcome measures used were the Disability of the Hand, Arm and Shoulder Questionnaire (Reinersmann et al., 2012c), Neck Disability Index (Elsig et al., 2014, Pedler et al., 2013), Burke-Fahn-Masden Disability scale (Fiorio et al., 2007), Neglect Scales (Reinersmann et al., 2012c, Reinersmann et al., 2010, Stanton et al., 2012a), Bonston Carpal Tunnel Questionnaire (Schmid and Coppieters, 2012) and Oxford Knee Score (Stanton et al., 2012a, Stanton et al., 2013b). Since pain measures are variable between studies, in this review, we will only be focusing on two outcome measures specific to laterality judgment, i.e. the reaction time and/or accuracy of laterality tasks. One or both of these measures of laterality judgment are used in all studies.

2.6.3 Lower Limb Pain

Laterality judgment tasks were assesed in leg pain, and knee osteoarthitis (Stanton et al., 2012a, Stanton et al., 2013b, Coslett et al., 2010a). Studies measured laterality judgment between the lower limb pain group, a pain control group and the healthy group. The addition of a pain group was beneficial to see whether decreased laterality judgment performance was not just a non-specific effect of pain. Only one study used the visual analog scale to rate their severity of pain with movement (Coslett et al., 2010a). This rating of pain is a subjective measure. However, other studies have used more functional objective outcome measures in the measurement of pain. These include the Oxford Knee Score (Stanton et al., 2012a, Stanton et al., 2013b), Neglect Scale (Stanton et al., 2012a) and the Short-Form Health Survey Questionnaire-36 (Stanton et al., 2013b). In some studies confounding factors such as age of participants were addressed (Stanton et al., 2012a), while in others it was not (Stanton et al., 2013b). For example, in Stanton et al. (2012a) healthy

individuals were significantly younger than the pain groups and therefore results of an independent sample of age and sex matched healthy individuals were used for comparisions to deretmine if there was any significant changes due to those factors. Another study in the lower limb pain population was done to determine whether there is a relationship between two-point discrimination and laterality judgment (Stanton et al., 2013b). There was no relationship found between the two. Furthermore, laterality judgment was not addressed in terms of differing angles of rotations in this study (Stanton et al., 2013b).

Two studies used pictures of the foot and not the knee in a laterality judgment task (Stanton et al., 2012a, Stanton et al., 2013b). It was proposed that in the laterality judgment of the foot, one has to mentally manoeuvre their entire lower limb to match the pictured limb. Therefore, there would be mental rotation of both the knee and foot. Proprioception of the knee is important in placement of the feet, and therefore foot and leg proproception maps should be closely related. Furthermore, determining the sidedness of a knee is difficult and therefore pictures of feet were used. However, it can be argued that using pictures of feet instead of knees is not specific to the site of pain.

2.6.4 CRPS 1 and other Upper Limb Conditions

CRPS1 has been well researched in terms of laterality judgment. Laterality judgment between people with CRPS1 was compared to healthy individuals and sometimes a pain control group (Schwoebel et al., 2001, Moseley, 2004b, Reinersmann et al., 2012a). There was also comparison to upper limb amputees with phantom limb pain (Reinersmann et al., 2010).

In one study VAS was the only measure of pain (Schwoebel et al., 2001). More objective outcomes measures on the nature of pain such as the Neuropathic Pain Scale and McGill Pain Questionnaire were used in one study (Moseley, 2004b). Functional measures were also used, such as Neglect Scales (Reinersmann et al., 2010, Reinersmann et al., 2012a) and the Disability of the Hand, Arm and Shoulder Questionnaire (Reinersmann et al., 2012a). In some studies confounding factors such as age, sex and handedness were identified and participants were matched for this (Moseley, 2004b, Reinersmann et al., 2012a, Schwoebel et al., 2001). However, in one study (Reinersmann et al., 2010) the age range was large, and this could bear consequences for the reaction time between

participants as it has shown that older adults have decreased laterality compared their younger counterparts (Saimpont et al., 2009).

Interestingly, in one study, there was a four day training program for laterality judgment in healthy individuals and people with CRPS1, which decreased the reaction time of both groups, but the healthy individuals reaction times were still significantly lower (Reinersmann et al., 2010). Another interesting study found that music therapy decreases the reaction times in people with CRPS 1 while performing a hand laterality task (Schwoebel et al., 2002).

2.6.5 Low Back Pain

There has been research done for disruption of body schema in people with low back pain (Bray and Moseley, 2011, Bowering et al., 2014b, Linder et al., 2016). Studies compared low back pain to healthy individuals (Linder et al., 2016, Bray and Moseley, 2011), as well as to people with a history of low back pain (Bowering et al., 2014b)

Some studies found a decrease in laterality judgment (Bowering et al., 2014b, Bray and Moseley, 2011), while others did not (Linder et al., 2016). Differences in results between the studies could be that in Linder et al. (2016), there was exclusion of healthy individuals who had low back pain in the last 12 months only, with no guarantee that they did not have pain previously. This is an important factor as Bowering et al. (2014b) found that in some people with a history of low back pain, their cortical networks are vulnerable and they are more prone to experiencing another episode of low back pain. If there was a sample of healthy individuals with a previous history of low back pain (more than 12 months ago), this could have affected the results. Other factors that could have contributed to the differences in results include possible pain of participants in other regions, a practice round was not done and most importantly, custom images were not used in this study like the other two studies (Bowering et al., 2014b, Bray and Moseley, 2011), but rather stock images were used (Linder et al., 2016).

A limitation of the study conducted by Bowering et al. (2014b) is that although the sample size was big, people were recruited online and put into groups according to their responses to the online questionnaires. This leaves room for mistakes in the case of completing the questionnaires inaccurately or falsifying information.

2.6.6 Cervical Pain

Studies were found regarding pain the cervical region, with regard to whiplash (Pedler et al., 2013) and chronic cervical pain (Elsig et al., 2014, Baarbe et al., 2016, Richter et al., 2010). In a study conducted by Baarbe et al. (2016), people with cervical pain and healthy individuals were assessed. Measurements were done at baseline and at four months. However, a weakness of this study was that the letter 'R' was used for the laterality judgment task. It was found that rotation of letters follow an allocentric mechanism, while rotation of body parts follow an egocentric mechanism (Dalecki et al., 2012). Therefore, due to the difference in mechanisms this study is not a true representation of body schema.

Weaknesses of the all studies were that the recognition tasks were not standardised, i.e. number of pictures and maximum reaction time were not given in all studies. Some studies had a practice run and some did not. According to Bray and Moseley (2011) a practice run of 80 pictures is essential to activate the premotor and primary motor cortex. Another weakness found in one study was that there was no assessor blinding (Elsig et al., 2014). This could introduce bias to the study results.

2.7 Conclusion

The aim of this literature review was to review all the available evidence to date on studies comparing laterality judgment in people with chronic pain and healthy individuals. This gave the reader a good background on the foundation and basis of laterality judgment in chronic pain syndromes. However, there is no systematic review to pool all the available evidence in order to draw conclusions on the impairment of laterality in chronic pain syndromes. Furthermore, many chronic pain syndromes have not been researched and further research needs to be done before making reccomendations on all chronic pain conditions. Although more research in this area is required, this new concept shows promise to the understanding and treatment of chronic pain syndromes.

CHAPTER 3: METHODOLOGY

This systematic review follows the Joanna Briggs Institute (JBI) Systematic Review methodology outlined in the Joanna Briggs Institute Reviewers' Manual (The Joanna Briggs Institute, 2014) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Group guidelines (Moher et al., 2009). The systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (reference number 42016041256).

3.1 Type of Study

This study is a systematic review and meta-analysis. The level of evidence is one.

3.2 Inclusion Criteria

3.2.1 Types of Participants

This systematic review considered studies which included participants with chronic pain as well as healthy individuals. Only chronic pain syndromes were included in this review, where pain was specifically measured. Participants experiencing chronic pain were diagnosed with CRPS 1, upper limb pain, lower limb pain, low back pain or cervical pain syndromes in the studies. Healthy individuals are pain-free individuals that do not have any current pain, and have not experienced any history of long periods of constant or intermittent pain that has had an impact on their normal activity. Only studies with adult participants (≥18 years of age) were included in this review.

3.2.2 Phenomena of interest

People with chronic pain disorders experience a disturbance in body schema (Tsay et al., 2015, Haggard et al., 2013, Wand et al., 2011), which includes decreased proprioception and tactile acuity as well as decreased laterality judgment performance (Wand et al., 2011). In this systematic review, laterality judgment performance between people with chronic pain and healthy individuals was reviewed.

3.2.3 Types of Outcomes

The main outcome measure was laterality judgment which consists of two components namely reaction time and accuracy. Laterality judgment was measured by the use of pictures of human, healthy body parts (hand, foot, trunk or neck) with no visible marks on them. Participants were positioned in front of a computer screen and had to press either left or right arrow keys or different letters (i.e. "z" key for the left and "m" for the right or "a" key for the left and "d" key for the right), in accordance to whether the pictured body part is left or right. Before performing the laterality judgment task, the instructions given was to perform the task as fast as possible. All pictures were presented in a computer-generated random allocation. Laterality judgment is commonly measured using computer software, but can also be done manually.

Reaction time is the length of time taken to choose whether a picture is right or left, and is expressed as mean response time for the correct responses. Accuracy is expressed as the correct number of responses as a percentage.

3.2.4 Types of Studies

Experimental and epidemiological study designs including randomised controlled trials, non-randomised controlled trials, quasi-experimental studies, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies were considered for inclusion. Descriptive epidemiological study designs including descriptive cross sectional studies for inclusion were also considered. Published and unpublished studies and studies in all languages were considered in this review.

3.3 Search Strategy

The search process was done in a three step process. Initially, a limited search was performed in MEDLINE (Pubmed) and CINAHL Plus using the keywords "laterality" "body schema" and "pain". After analysis of keywords found in the title, abstract and index terms in the articles found, a comprehensive search was done in all databases using the mentioned keywords as well as a combination of keywords (Figure.2). These databases were: MEDLINE via Pubmed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Controlled Trials Registered, Physiotherapy Evidence Database (PEDro), Science Direct, SCOPUS, Clinical Key and Google

Scholar. Thirdly, the reference lists of all identified full text articles were searched for additional studies. Articles from all time periods up until February 2017 were considered for inclusion in this review. Studies were performed on ‘all fields’ and the filter ‘humans’ was applied (Figure. 2)

Search	Add to builder	Query	Items found
#8	Add	Search **(((((laterality) OR ((laterality) AND judgment)) OR ((body) AND schema)) OR ((motor) AND imagery))) AND "pain"[MeSH Terms]** Filters: **Humans**	1071
#7	Add	Search **(((((laterality) OR ((laterality) AND judgment)) OR ((body) AND schema)) OR ((motor) AND imagery))) AND "pain"[MeSH Terms]**	1460
#6	Add	Search **(((laterality) OR ((laterality) AND judgment)) OR ((body) AND schema)) OR ((motor) AND imagery)**	60754
#5	Add	Search **"pain"[MeSH Terms]**	334629
#4	Add	Search **(motor) AND imagery**	2479
#3	Add	Search **(body) AND schema**	636
#2	Add	Search **(laterality) AND judgment**	720
#1	Add	Search **laterality**	58037

Figure 2. Search strategy in Pubmed using ‘laterality’, ‘’, ‘pain’, ‘body schema’, ‘motor imagery’ as keywords

3.4 Assessment of Methodological Quality

The titles, abstracts, and full texts (where indicated) of all records were screened for inclusion by the primary reviewer. Studies that met eligibility criteria were assessed by two independent reviewers for methodological quality, prior to inclusion in the review. A standardised critical appraisal instrument, namely the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross Sectional Studies (Appendix A) (http://www.joannabriggs.org/sumari. html), was used for assessment of methodological quality. This tool consists of eight items, each requiring a yes/no response. A yes answer is allocated one point while a no/unclear response is allocated no points. Methodological quality was interpreted as follows: studies scoring 1-4 (low quality), 5-6 (moderate quality) and 7-8 (high quality). In the case of any disagreements arising between the reviewers, there was a discussion between reviewers and consultation with a third reviewer if necessary.

The JBI critical appraisal tools were developed by the Joanna Briggs Institute (which has been in existence since 1996) and its collaborators. These tools have been accepted by the JBI Scientific Committee after extensive peer review. The validity of this tool has been proven and it has been

shown to be the most coherent between two other tools i.e. the critical appraisal skills program (CASP) and the evaluation tool for qualitative studies (ETQS) (Hannes et al., 2010).

3.5 Data Collection

Data was extracted from the full text articles using a table that followed the standardised data extraction tool from JBI Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix B). The data extracted included specific details about study, i.e. critical appraisal rating, study design, participants (condition/sample size/age/sex/hand or foot dominance), outcome measures and study results specific to the review question and objectives (Table 2- Results Chapter, page 25-34).

3.6 Data Synthesis

Initially, where possible, results from all the studies investigating similar conditions and using similar methodologies was analysed by meta-analysis and pooled into statistical meta-analysis using MetaEasy v1.0.5. The weighted mean differences (for continuous data) and their 95% confidence intervals were calculated for the outcome measures, namely reaction time and accuracy. The random-effects model was used due to the variation and small sample sizes in studies. This model assumes that the effects estimated in different studies follow a similar distribution, while the effects are not identical (Borenstein et al., 2010). Heterogeneity refers to the variability between studies and tests whether all studies are evaluating the same effect (Higgins et al., 2003). Heterogeneity was assessed by the p-value and I^2 value. Initially, the I^2 value was grouped into low (25%), moderate (50%) and high (75%) heterogeneity (Higgins et al., 2003), but later on it was found to not be appropriate in all situations. Recently, The Cochrane Collaboration has reported the interpretation of the I^2 value as follows: unimportant heterogeneity (0-40%), moderate (30-60%), substantial (50-90%) and considerable (75-100%) (Higgins and Green, 2011). Possible heterogeneity due to inclusion of studies of different methodological quality was investigated based on the risk of bias assessment.

Thereafter, studies were divided into sub- groups (according to condition) and further analysed. Statistical measures used in meta-analysis of all studies and meta-analysis of sub-groups included

the probability value, mean effect size, variance effect size and maximum likelihood. Where statistical pooling was not possible the findings were presented in a narrative form.

3.7 Ethical Considerations

No human participants were involved in this study. Therefore, the researchers obtained an ethical clearance waiver (Reference: W-C-J-160505-1) (Appendix C) through the University of the Witwatersrand's Human Research Ethics Committee.

3.8 Conclusion of the Methodology

In this chapter (chapter three), an outline of the methodology was described in detail. Chapter four will focus on the results of the systematic review and meta-analysis.

CHAPTER 4: RESULTS

4.1 Study Selection

The initial search yielded 4323 articles. Twenty additional records were identified through searching the reference lists. After duplicates were removed there were 560 studies. 538 studies were excluded based on the abstract (Figure. 3). After assessing the eligibility criteria of full text articles, 7 studies were excluded. Reasons for exclusion are shown in Table 1. Therefore, in total 15 studies were considered for inclusion in this systematic review (Figure. 3). All studies selected were in English. All studies that were critically appraised were included in the review. Studies included were all cross sectional studies, one with a follow up component (Reinersmann et al., 2010).

4.2 Study Characteristics

For each study, the critical appraisal rating, study design, participants (condition/sample size/age/sex/hand or foot dominance), outcome measures and study results were extracted (Table.2).

4.2.1 Conditions of Participants

Conditions assessed in the studies included all chronic pain syndromes, namely CRPS 1 (four studies) (Reinersmann et al., 2010, Reinersmann et al., 2012a, Moseley, 2004b, Schwoebel et al., 2001), arm and shoulder pain (one study) (Coslett et al., 2010b), carpal tunnel syndrome (one study) (Schmid and Coppieters, 2012), low back pain (three studies) (Bowering et al., 2014b, Bray and Moseley, 2011, Linder et al., 2016), cervical pain (three studies) (Elsig et al., 2014, Pedler et al., 2013, Richter et al., 2010), and leg and knee pain (three studies) (Coslett et al., 2010a, Stanton et al., 2012a, Stanton et al., 2013b).

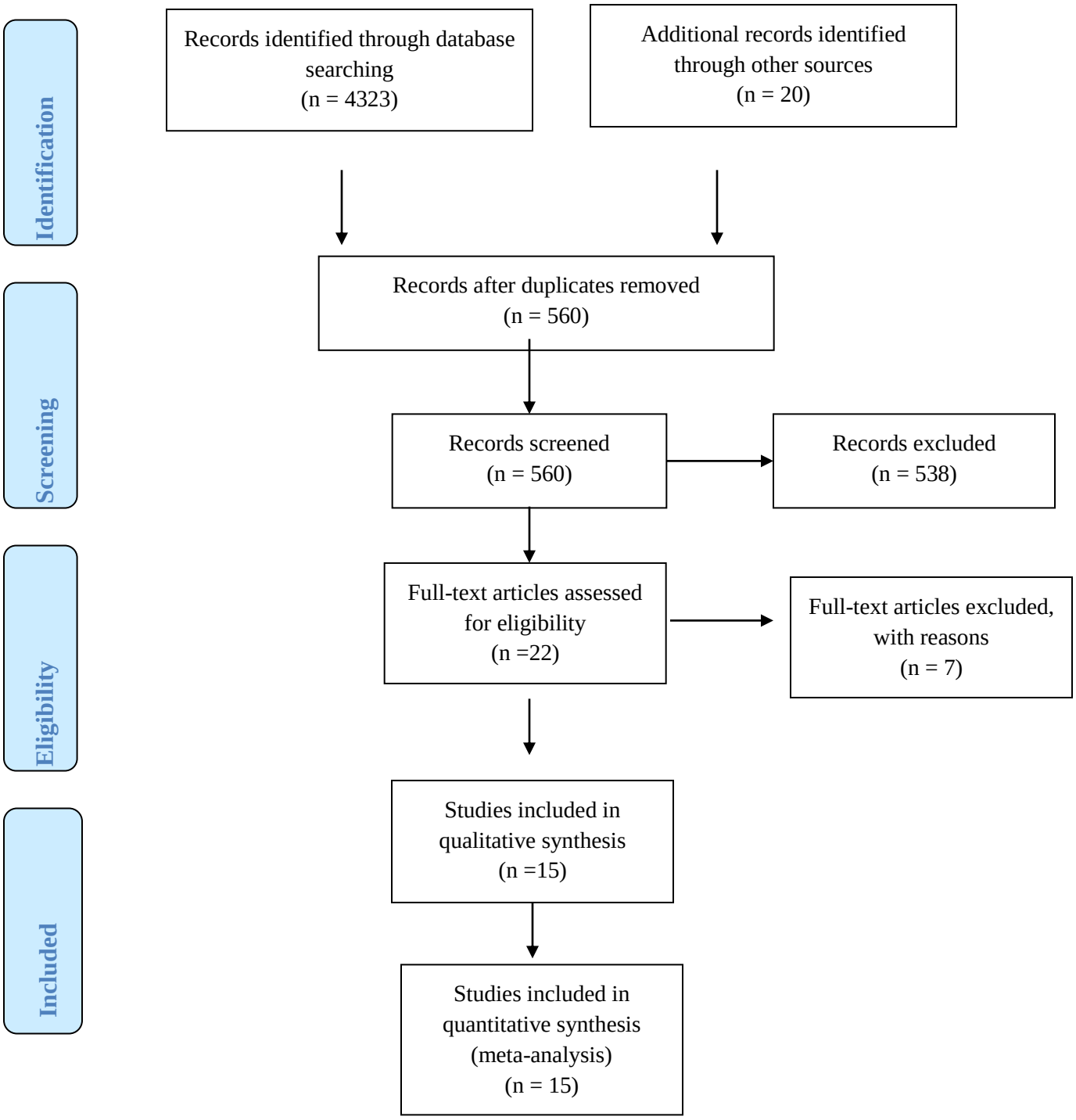

Figure 3: Flow diagram showing the processes of identification, screening, assessing eligibility and inclusion of studies

Table 1: Studies Excluded from the Review Based on Full-Text

Study	Reason/s for Exclusion
Baarbe et al. (2016)	The letter 'R' was used for the laterality judgment task. It was found that rotation of letters follow an allocentric mechanism, while rotation of body parts follw an egocentric mechanism (Dalecki et al., 2012). Therefore, due to the difference in mechanisms this study is not a true representation of body schema.
Fiorio et al. (2006)	Laterality was assessed in people with focal hand dystonia and healthy individuals. Inclusion of participants was based solely on condition and not presence of pain. Therefore, chronic pain was not specifically measured.
Fiorio et al. (2007)	Laterality was assessed in people with idiopathic cervical dystonia and healthy individuals. Inclusion of participants was based solely on condition and not presence of pain. Therefore, chronic pain was not specifically measured.
Katschnig et al. (2010)	Laterality was assessed in people with fixed dystonia and healthy individuals. Inclusion of participants was based solely on condition and not presence of pain. Therefore, chronic pain was not specifically measured.
King et al. (2015)	A single case study was done of laterality judgment for a patient with CRPS II
Reinersmann et al. (2011)	Same article as Reinersmann et al. (2010), but published in a different format
Schwoebel et al. (2002)	Laterality judgment was assessed in people with chronic unilateral arm pain, as well as assessing the severity of pain and the effect of music therapy. There was no comparison of laterality judgment with healthy individuals.

Table 2: Study Details of the Individual Studies that are included in the Systematic Review and Meta-Analysis

Study	**Critical Appraisal Rating**	**Study Design**	**Participants**	**Outcome Measures**	**Study Results**
			CRPS 1		
Moseley 2004	8/8	Analytical Cross Sectional	*Pain: No= 18 Age= 38.11 ±11.88 years Sex= 7 M; 11 F Hand dom= 15 R; 3 L *Healthy: No= 18 Age= 36 ± 10 years Sex= 7 M; 11 F Hand dom= 15 R; 3 L *During analysis added 30 healthy individuals data from previous studies (no characteristics supplied)	<u>Pain:</u> -McGill pain questionnaire -Neuropathic Pain Scale <u>Laterality:</u> -on PC -hand laterality task -1 trial x 56 images (26 right and 26 left hands) -reaction time and accuracy	Results presented in a different format compared to other studies Multivariate analysis of regression: A) Reaction time: pictured hand ($F(1,71)=29.6$; $p< 0.001$) and group ($F(1,71)= 53.2$; $p< 0.001$) B) Accuracy: Pain: Hand x group interaction ($F(1,71)- 14.6$; $p<0.001$)
Reinersmann et al., 2010	6/8	Analytical Cross Sectional	*Pain: *CRPS 1 No= 12 Age= 46.5±13.1 years Sex= 4 M; 8 F Hand dom= 12 R *PLP No= 12 Age= 51.4±10.1 years	<u>Pain:</u> -VAS -Questionnaire of neglect-like symptoms in CRPS <u>Laterality:</u> -on PC -hand laterality task -1 session each - 3 trials x 56 images each=168	A) Reaction Time: Pain: -CRPS= (2278 ms ±735.7) -PLP= (2301.3 ms ±809.3) Healthy: (1826.5 ms ±517.0)

			Sex= 10M; 2 F Hand dom= 11 R; 1 L *Healthy: No= 38 Age= 35.7±12.2 years Sex= not reported Hand dom= 38 R	images -reaction time and accuracy	
Reinersmann et al., 2012	8/8	Analytical Cross Sectional	Pain: *CRPS 1 No= 24 Age= 53.4±10.1 years Sex= 12 M; 12 F Hand dom= 24 R *upper limb pain of other origin (pain control) No= 21 Age= 51.8±11.3 years Sex= 9 M; 12 F Hand dom= 19 R; 2 L *Healthy: No= 24 Age= 52.8 years Sex=12 M; 12 F Hand dom= 24 R	<u>Pain:</u> -VAS -Questionnaire of neglect-like symptoms in CRPS - disability of the hand, arm, and shoulder (DASH) questionnaire <u>Laterality:</u> -on PC -hand laterality task -1 session each -3 trials x 56 images each=168 images - reaction time and accuracy	A) Reaction Time: Pain: -CRPS= (2235.5 ms ± 662.2) -Pain controls= (2234.0 ms ± 642.8) Healthy: (1947.9 ms ± 664.9)
Schwoebel et al., 2001	7/8	Analytical Cross Sectional	Pain: *CRPS No= 13 Age= 48±8 years Sex= 8 M; 5 F Hand dom= 11R; 2 L	<u>Pain:</u> -VAS <u>Laterality:</u> On PC -hand laterality task	B) Accuracy: Pain: (83.35% ±11.40) Healthy: (86.5% ±8.91)

			*Healthy: No= 18 Age= 47±11 years Sex= not reported Hand dom= 18 R	-8 trials x 16 images = 128 images (pain) - 4 trials x 16 images = 64 images (healthy) - reaction time and accuracy	
UPPER LIMB PAIN					
Coslett et al., 2010	7/8	Analytical Cross Sectional	Pain: 43 *unilateral arm pain No= 10 Age= 47.5±6.2 years Sex= not reported Hand dom= not reported *bilateral arm pain No= 9 Age= 55.8±8.9 years Sex= not reported Hand dom= not reported *pain control No= 24 Age= 48.6±11.1 years Sex= not reported Hand dom= not reported *Healthy: No= 41 Age= 44.4±16.8 years Sex= not reported Hand dom= not reported	<u>Pain:</u> -VAS -VAS with movement <u>Laterality:</u> -on PC - hand laterality task - 8 trials x 24 images = 192 images - reaction time and accuracy	A) Reaction Time: Pain: -bilateral arm/shoulder pain= (2956 ms ± 298) -unilateral arm/shoulder pain= (2742 ms ± 283) -pain control subjects= (2153 ms ± 187) Healthy: (1985ms ± 144)
Scmid et al., 2010	8/8	Analytical Cross	*Pain: No= 27	<u>Pain:</u> -VAS	A) Reaction Time: Pain:

		Sectional	Age= 50.3±12.0 years Sex= 12 M; 15 F Hand dom= not reported *Healthy: No= 27 Age= 49.7 ±11.7 years Sex= 12 M; 15 F Hand dom= not reported	-s-LANSS -Boston carpal tunnel questionnaire <u>Laterality:</u> -on PC -laterality task of hand, foot, head and trunk rotation -training session of 10 images - 1 trial x 48 images - reaction time and accuracy	-Hands= (2343 ms) -Neck= (1737.5 ms) -Feet= (2266.5 ms) Healthy: -Hands= (2577.2 ms) -Neck= (1634.5 ms) -Feet= (2501.5 ms) B) Accuracy: Pain: Hands= (83.95%) Neck= (91.47% ±7.34) Feet= (87.05%) Healthy: Hands= (88.75%) Neck= (94.6% ±5.0) Feet= 88.2%
LOW BACK PAIN					
Bowering et al., 2014	6/8	Analytical Cross Sectional	Complete data set (Pain+ Healthy) No= 1008 Age= 37 ±13 years Sex= 324 M; 684 F Hand dom= not reported *Pain: No= 117 (Other characteristics not reported) *Healthy:	<u>Pain:</u> none <u>Laterality:</u> -on PC- Recognise - practice trail of hand laterality - trunk laterality task - 2 trials x 40 images = 80 images - reaction time and accuracy	Results presented in a different format compared to other studies ANOVA analysis: A)Reaction time: Pain: no significant relationship: -Current pain vs healthy (p= 0.958) History of pain and healthy(p=0.149)

			No= 429 (Other characteristics not reported)		-Current pain vs history of pain (p=0.908) Healthy: (1718.75±530.41) B)Accuracy: Pain: significant relationships -Current pain (less accurate) vs healthy- ($F_{1,1003}$= 4.905, p=0.027) -History of pain (less accurate) vs healthy- ($F_{1,1003}$= 9.9966,p=0.002) -Current pain (less accurate) vs history of pain- ($F_{1,1003}$= 6.165, p=0.013) Healthy: (78.58± 38.34)
Bray and Moseley 2011	5/8	Analytical Cross Sectional	*Pain: 21 No= (9 bilateral + 12 unilateral) Age= 44±13 years Sex= 6 M, 15 F Hand dom= 17 R; 4 L *Healthy: No= 14 Age= 43±7 years Sex= 5 M, 9 F Hand dom= 14 R	<u>Pain:</u> - VAS -Short-Form McGill Pain Questionnaire -habitual physical activity questionnaire <u>Laterality:</u> -on PC - practice trial of 80 pictures -hand and trunk laterality task - 2 trials x 40 images= 80	A) Reaction Time: Pain: 2400ms Healthy: 2400ms B) Accuracy: Pain: -bilateral back pain= 53.4% (44.5% to 62.3%) -unilateral back pain= 67.2% (60.2% to 74.1%) Mean (total)= 59,3% Healthy: 87% (75% to

				images - reaction time and accuracy	98%)
Linder et al., 2015	8/8	Analytical Cross Sectional	*Pain: No= 30 Age= 44.9±11 years Sex= 10 M; 20 F Foot dom= 29 R; 1 both *Healthy: 30 No= 30 Age= 43.3±9.6 years Sex= 10 M; 20 F Foot dom= 24 R; 5 L; 1 both	<u>Pain:</u> -VAS -Oswestry Disability Index <u>Laterality:</u> -on PC= Recognise -foot and trunk laterality task - 1 trial x 60 images of each body part= 120 images - reaction time and accuracy	A) Reaction Time: Pain: -Trunk= (1910 ms ±20) -Foot= (1885 ms ±15) -Combined= (1897.5 ms ± 21.65) Healthy: -Trunk= (2010 ms ±0) -Foot= (1900 ms ±50) -Combined= (1955 ms ±65.38) B) Accuracy: Pain: -Trunk= (88.85% ± 0.15) -Foot= (93.55% ±0.75) -Combined= (91.2% ±2.41) Healthy: -Trunk= (86.9% ±0.9) -Foot= (90.55% ±0.15) -Combined= (88.73% ±1.94)
CERVICAL PAIN					
Elsig et al., 2014	8/8	Analytical Cross Sectional	*Pain: No= 30 Age= 36.9±13.62 years Sex= 5 M, 25 F Hand dom= not reported	<u>Pain:</u> -Fear Avoidance Beliefs Questionnaire -Neck Disability Index -pain Detect questionnaire	B) Accuracy: Pain: (65.71% ±17.31) Healthy: (76.61% ±13.2)

			*Healthy: No= 30 Age= 37.2± 13.5 years Sex= 5 M, 25 F Hand dom= not reported	<u>Laterality:</u> -on PC= Recognise -1 trial x 20 images -accuracy measured	
Pedler et al., 2013	8/8	Analytical Cross Sectional	*Pain: No= 64 Age= 44.7± 12.6 years Sex= 29 M, 35 F Hand dom= not reported *Healthy: No= 24 Age= 40.3± 13.4 years Sex=10 M,14 F Hand dom= not reported	<u>Pain:</u> -VAS -Neck disability index -Post-traumatic stress diagnostic scale -Cold pain thresholds -Pressure pain thresholds <u>Laterality:</u> -on PC - neck and foot laterality task -1 trial x 30 images of each body part (neck or foot)= 60 images - reaction time and accuracy	Results presented in a different format compared to other studies ANOVA analysis: A)Reaction time: Relationship between pain and healthy not significant, (p=0.32) B)Accuracy: Relationship between pain and healthy not significant, (p=0.45)
Richter et al., 2010	7/8	Analytical Cross Sectional	Pain: *neck pain (non-specific) No= 24 Age= 37± 9 years Sex= 10M; 14 F Hand dom= 24 R *neck pain (traumatic origin) No= 21 Age= 36± 5 years Sex= 10 M; 11 F Hand dom= 21 R	<u>Pain:</u> -VAS <u>Laterality:</u> -on PC -Hand laterality task -practice trail (5 pictures) - 1 trial x 80 images	Results presented in a different format compared to other studies ANOVA tests: A)Reaction time: Results explained graphically, no values given B)Accuracy: Results explained graphically, no

			*Healthy: No= 22 Age= 37 ± 9 years Sex= 9 M; 13 F Hand dom= 22 R		values given
LOWER LIMB CONDITIONS					
Coslett et al., 2010	6/8	Analytical Cross Sectional	Pain: 82 leg pain= 40: *bilateral leg pain No= 19 Age= 49.2 ± 8.8 years Sex= 10 M, 9 F Foot dom= not reported *left leg pain No= 11 Age= 53.2 ±7.3 years Sex= 4 M, 7 F Foot dom= not reported *right leg pain No= 10 Age= 49.5 ± 11.3 years Sex= 4 M, 6 F Foot dom= not reported *pain control (not involving legs) No= 42 Age= 48±12.2 years Sex= 20 M; 22 F	<u>Pain:</u> -VAS -VAS with movement <u>Laterality:</u> -on PC - foot laterality task -8 trials x 24 images = 192 images - reaction time and accuracy	A) Reaction Time: Pain: -RLP= (2271.6 ms ± 202.2) -LLP= (1846.9 ms ±192.8) - bilateral pain subjects= (1690.2 ms ± 150.7) - pain control= (1545.3 ms ± 102.4) Healthy: (1237.9 ms ± 105.1) B) Accuracy: Pain: -RLP= (88.07% ± 22.33) -LLP= (93.47% ±16.74) -BLP= (92.25% ± 16.57) Healthy: (96.59% ± 9.77)

			Foot dom= not reported *Healthy: No= 38 Age= 45.2± 18.5 years Sex= 22 M, 16 F Foot dom= not reported		
Stanton et al., 2012	8/8	Analytical Cross Sectional	Pain: *knee OA No= 20 Age= 68± 9 years Sex= 6 M; 14 F Hand dom= 18 R; 2 missing Foot dom= 18 R; 2 missing *pain control (arm pain) No= 20 Age= 64.9± 7.8 years Sex= 11M; 9 F Hand dom= 18 R; 1 L; 1 missing Foot dom= 19 R; 1 missing *Healthy: No= 20 Age= 37.3± 15.5 years Sex= 8 M; 12 F Hand dom= 20 R Foot dom= 20 R	<u>Pain:</u> -VAS -Oxford knee score -Neglect scale for the knee <u>Laterality:</u> -on PC-Recognise - foot laterality task -training session of 10 images - 1 trial x 10 images (hand and foot laterality) - reaction time and accuracy	B)Accuracy Pain: -knee OA= 60% -upper limb=75% Healthy: 100%
Stanton et al., 2013	8/8	Analytical Cross Sectional	Pain: *knee OA No= 20 Age= 68±9 years Sex= 6 M; 14 F	<u>Pain:</u> <u>Knee Group=</u> -VAS -Oxford knee score	B) Accuracy: Pain: <u>Knee</u> -Feet= (60.7% ± 20.1)

			Hand dom= 18 R; 2 missing Foot dom= 18 R; 2 missing *Healthy (knee) No= 20 Age= 37±16 years Sex= 8 M; 12 F Hand dom= 20 R Foot dom= 20 R *pain control No= 20 Age= 65±8 years Sex= 11M; 9 F Hand dom= 18 R; 1 missing Foot dom= 19 R; 1 missing *back pain No= 17 Age= 45±14 years Sex= 3 M; 14 F Hand dom= 13 R;4 L *Healthy (back pain) No= 18 Age= 41±11 years Sex= 7M; 11 F Hand dom= 18 R	<u>Back Group=</u> -VAS -Short-Form Health Survey Questionnaire (SF-36) <u>Laterality:</u> -on PC- Recognise - foot and trunk laterality task -A practice trail of 80 images - 2 trials x 40 images= 80 images (feet and trunk laterality)	<u>Back</u> -Trunk= (61.4% ± 17.6) Healthy: -Knee= (88.5% ± 21.9) -Trunk= (80.5% ± 8.7)

CRPS= Complex Regional Pain Syndrome; Hand dom= Hand dominance; PLP= phantom limb pain, VAS= visual analogue scale, PC= personal computer, Foot dom= Foot dominance; R= right; L= left; M= male; F= female

4.2.2 Sample Sizes and Recruitment of Participant's

In all, but two studies (Elsig et al., 2014, Pedler et al., 2013) the method of calculating the sample size was not discussed. The method of recruitment was discussed in some studies (Reinersmann et al., 2010, Reinersmann et al., 2012a, Coslett et al., 2010b, Bowering et al., 2014b, Linder et al., 2016, Elsig et al., 2014, Pedler et al., 2013, Richter et al., 2010, Coslett et al., 2010a, Stanton et al., 2012a), while in others it was not (Moseley, 2004b, Schwoebel et al., 2001, Schmid and Coppieters, 2012, Bray and Moseley, 2011, Stanton et al., 2013b). Sample sizes ranged from 13 to 82 participants. In one study in which participants were recruited online, there were 1008 participants.

4.2.3 Age of Participants

The ages of participants in all studies ranged between 30 and 68 years old. The majority of studies had age matched healthy individuals compared to the pain group (Moseley, 2004b, Reinersmann et al., 2012a, Schwoebel et al., 2001, Coslett et al., 2010b, Schmid and Coppieters, 2012, Bray and Moseley, 2011, Linder et al., 2016, Elsig et al., 2014, Pedler et al., 2013, Richter et al., 2010, Coslett et al., 2010a). Three studies did not match the ages of the healthy individuals to their respective pain groups (Stanton et al., 2012a, Stanton et al., 2013b, Reinersmann et al., 2010). However, Stanton et al. (2012a) performed a sensitivity analysis and used an independent sample of age matched individuals in their statistical analysis. In another study, there was a huge number of participants (1008) recruited online (Bowering et al., 2014b). There was no information reported on the age range of these participants.

4.2.4 Sex of Participants

Another confounding factor that needs to be taken into account is gender differences in the pain group compared to healthy individuals. In some studies healthy individuals were sex matched according to the pain group (Moseley, 2004b, Schmid and Coppieters, 2012, Linder et al., 2016, Elsig et al., 2014, Reinersmann et al., 2012a) but not the pain control group (Reinersmann et al., 2012a). In other studies the sample sizes were not the same but the male to female percentage ratio was similar (Pedler et al., 2013, Richter et al., 2010). Some studies had no sex matching (Bray and Moseley, 2011, Stanton et al., 2012a, Stanton et al., 2013a, Coslett et al., 2010a), while in others the sex of participants was not reported at all (Reinersmann et al., 2010, Schwoebel et al., 2001, Coslett et al., 2010b).

4.2.5 Dominance of Participants

Dominance is a possible confounding factor that was taken into account in some studies. Hand dominance, foot dominance or both were assessed in the studies. Assessment was done by the Edinburgh Handedness Inventory (Reinersmann et al., 2010, Reinersmann et al., 2012a), a questionnaire asking the participants which hand he/she uses to write with (Stanton et al., 2012a, Stanton et al., 2013b), a questionnaire asking the participants which foot he/she would use to kick a ball (Linder et al., 2016, Stanton et al., 2012a, Stanton et al., 2013b) or the measure of determining dominance was not mentioned (Bray and Moseley, 2011, Richter et al., 2010, Moseley, 2004b, Schwoebel et al., 2001).

In CRPS, participants were matched for hand dominance in two studies (Moseley, 2004a, Reinersmann et al., 2012a), with one study matching only done to the pain group and not the pain control group (Reinersmann et al., 2012a). In two CRPS studies participants were not matched for hand dominance (Reinersmann et al., 2010, Schwoebel et al., 2001). In two other studies of upper limb pain conditions, hand dominance was not reported (Coslett et al., 2010b, Schmid and Coppieters, 2012). In low back pain, one study did not report any dominance (Bowering et al., 2014b), while in one study hand dominance was assessed but not matched between the groups (Bray and Moseley, 2011). Another low back pain study assessed foot dominance but the low back pain and healthy groups were not matched (Linder et al., 2016). In cervical pain, there was no assessment of dominance done in two studies (Elsig et al., 2014, Pedler et al., 2013), while hand dominance was assessed and participants were matched in one study (Richter et al., 2010). In lower limb conditions, foot dominance was not reported in one study (Coslett et al., 2010a), while both hand and foot dominance was matched in two studies (Stanton et al., 2012a, Stanton et al., 2013b).

4.2.6 Outcome Measures for Pain

Many studies used outcome measures to measure pain and function. A visual analogue scale (VAS) in different forms was used in many studies (Coslett et al., 2010a, Linder et al., 2016, Reinersmann et al., 2010, Reinersmann et al., 2012a, Baarbe et al., 2016, Bray and Moseley, 2011, Coslett et al., 2010b, Pedler et al., 2013, Schwoebel et al., 2001, Schmid and Coppieters, 2012, Richter et al., 2010, Stanton et al., 2012a, Stanton et al., 2013b). It was measured by a 5 or 11 point scale (visual), rating pain from most to least painful. In some studies VAS was also illustrated during movement (Coslett et al., 2010a, Coslett et al., 2010b). Other pain measures included were the Neuropathic Pain

Scale (Moseley, 2004a), Chronic Pain Grading Scale (Baarbe et al., 2016), S-LANSS pain score (Schmid and Coppieters, 2012) and Pain Detect Questionnaire (Elsig et al., 2014). Function was measured differently between all groups, depending on the condition. General functional scales used were the McGill Pain Questionnaire (Bray and Moseley, 2011, Moseley, 2004b), Owestry Disability Index (Linder et al., 2016) and Short Form Health Survey-36 (Stanton et al., 2013b). Other specific functional outcome measures used were the Disability of the Hand, Arm and Shoulder Questionnaire (Reinersmann et al., 2012c), Neck Disability Index (Elsig et al., 2014, Pedler et al., 2013), Burke-Fahn-Masden Disability scale (Fiorio et al., 2007), Neglect Scales (Reinersmann et al., 2012c, Reinersmann et al., 2010, Stanton et al., 2012a), Bonston Carpal Tunnel Questionnaire (Schmid and Coppieters, 2012) and Oxford Knee Score (Stanton et al., 2012a, Stanton et al., 2013b). For laterality, both or either accuracy and reaction time was used to measure laterality judgment.

4.2.7 Method of Laterality Testing

In all studies laterality judgment was tested using a computer. Participants were positioned in front of a computer screen and a series of stimuli depicting the specific limb was presented in various orientations. The participant had to determine the laterality of the picture by pressing the left or right arrow keys or different letters (i.e. “z” key for the left and “m” for the right or “a” key for the left and “d” key for the right), in accordance to whether the pictured body part was left or right. Pictures were presented in a computer generated random allocation. However, different studies had a different amount of trials done and images presented (Table 3). In only six studies a practice trial was done (Schmid and Coppieters, 2012, Bowering et al., 2014b, Bray and Moseley, 2011, Richter et al., 2010, Stanton et al., 2012a, Stanton et al., 2013b). The images presented in the practice trial also differed. Five images (Richter et al., 2010), 10 images (Stanton et al., 2012a, Schmid and Coppieters, 2012) and 80 images (Bray and Moseley, 2011, Stanton et al., 2013b) were presented in the practice trials. One study did not specify how many images were in the practice trial (Bowering et al., 2014b). The number of trials presented to the participants was one, two, three or eight. The number of images presented in each trial ranged between 16 and 60, and therefore the total number of images ranged from 20 to 192 images. More information on the specific number of trials and images therein can be found in Table 3.

In one study that was done between people with cervical pain and healthy individuals, laterality was measured using the letter "R" in different orientations, instead of pictures of body parts (Baarbe et al., 2016). It was found that rotation of letters follow an allocentric mechanism, while rotations of body parts follow an egocentric mechanism (Dalecki et al., 2012). Due to this difference in mechanisms, this study was not used in systematic review.

4.2.8 Speed/Accuracy Trade-offs

When performing an activity, one can respond to a stimulus slowly with decreased mistakes. On the other hand, the ability to respond quickly to a stimulus and make more mistakes is referred to as the speed accuracy trade-off. Some studies specifically mentioned that there was no speed accuracy trade-offs (Moseley, 2004b, Schwoebel et al., 2001, Coslett et al., 2010b, Richter et al., 2010, Coslett et al., 2010a, Linder et al., 2016). It is assumed in all other studies that there was no speed accuracy trade-offs as decreased reaction time correlated to increased accuracy in healthy individuals (Reinersmann et al., 2010, Reinersmann et al., 2012a, Schmid and Coppieters, 2012, Pedler et al., 2013, Elsig et al., 2014, Stanton et al., 2012a, Stanton et al., 2013b, Bray and Moseley, 2011, Bowering et al., 2014b).

4.3 Assessment of Methodological Quality

The methodological quality of studies was moderate to high; with one study having a low quality design. In CRPS 1 the critical appraisal rating ranged from 5/8 to 8/8 (Moseley, 2004b, Reinersmann et al., 2010, Reinersmann et al., 2012a, Schwoebel et al., 2001), while in other upper limb conditions it was 7/8 and 8/8 respectively (Coslett et al., 2010b, Schmid and Coppieters, 2012). In low back pain the ratings ranged from 4/8 to 8/8 (Bray and Moseley, 2011, Bowering et al., 2014b, Linder et al., 2016). The low quality of evidence for one study was due to the study design being an online study, without specific inclusion and exclusion criteria, and many confounding variables (Bowering et al., 2014b). In cervical pain scores ranged from 7/8 to 8/8 (Elsig et al., 2014, Pedler et al., 2013, Richter et al., 2010). Lastly, in lower limb conditions, ratings ranged from 5/8 to 8/8 (Stanton et al., 2012a, Stanton et al., 2013b, Coslett et al., 2010a) (Table 1).

4.4 Risk of Bias within and across Studies

Risk of bias refers to a systematic error that can cause an over or underestimation of a study's true effect size (http://handbook.cochrane.org/index). The critical appraisal ratings are shown in Table 1. All studies were cross sectional studies. One study had a four day laterality training programme and

tested laterality thereafter (Reinersmann et al., 2010). Critical appraisal was completed using the standardised critical appraisal instruments from the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies (Appendix A). The mean score of critical appraisal of all 15 papers was 6.7 (SD=1,3) out of a maximum of 8. A minimum of 4/8 critical appraisal rating was obtained for one study only. Prior to discussion, there was 85% (mean) agreement between the primary and secondary reviewers. After discussion between reviewers, 100 % agreement between items was attained. The two items which showed the lowest agreement prior to discussion were items one and five. For item one ("Were the criteria for inclusion in the sample clearly defined?"), it was decided that studies will only score positively if they have both inclusion and exclsuion criteria. Many studies only stated the inclusion criteria. For item five ("Were confounding factors identified?"), the reviewers decided to consider only confounding factors that were apparent in nature (i.e. age, sex, handedness)

The greatest weakness is that in many studies the population was not clearly defined (item one), i.e. inclusion criteria were mentioned but there was no specific exclusion criteria in six studies (Reinersmann et al., 2010, Reinersmann et al., 2012a, Bowering et al., 2014b, Bray and Moseley, 2011, Coslett et al., 2010a, Stanton et al., 2013c). In two studies the study setting was described in detail, but not the patient population (item two) (Pedler et al., 2013, Coslett et al., 2010a). In one study both the sudy setting and patient population was not adequately described (Bowering et al., 2014b). In four studies only the VAS scale was used to assess pain in the population (item four) (Schwoebel et al., 2001, Coslett et al., 2010a, Bray and Moseley, 2011, Coslett et al., 2010b). The VAS scale is a subjective measure of pain. In Bowering et al. (2014b) an online questinaire was used to assess demographics, activity level, general health and current and previous back pain. There was no objective, standard criteria for measurement of low back pain used. In one study only confounding factors were not identified (item five) (Reinersmann et al., 2010). However, in four studies the confounding factors were identified but they were no strategies in place to deal with them (item six) (Reinersmann et al., 2010, Bowering et al., 2014b, Bray and Moseley, 2011, Richter et al., 2010)

A study by Bowering et al. (2014b) scored 4/8 critical appraisal rating, with items 1, 2, 4, 6 scored negatively. This study recruited participants online. Participants undertook the laterality judgment task at home on their computer. This could lead to many confounding variables that were not controlled, such as the computer specifications (processing speed, capacity and screen properties) as

well as the environment in which the task took place in (item six). The authors also acknowledged other confounding factors such as the effect of medication, education status, and this was a large study so there might be possible false positives. The inclusion and exclusion criteria were not specific (item one) and the study participants were not described in detail (item two). Standard, objective criteria were also not measured specific to the condition (item four). Due to the variability of the settings of the 1008 participants, the setting could not be described in detail (item two). There is a lack of laterality judgment studies done in the low back pain population and therefore this study will be included. However, its results should be interpreted with extreme caution, weighting all the possible confounding variables.

Table 3: Detailed Critical Appraisal Ratings of Studies

Study	Condition	1. Were the criteria for inclusion in the sample clearly defined?	2. Were the study subjects and the setting described in detail?	3. Was the exposure measured in a valid and reliable way?	4. Were objective, standard criteria used for measure-ment of the condition?	5. Were con-founding factors identified?	6. Were strategies to deal with con-founding factors stated?	7. Were the outcomes measured in a valid and reliable way?	8. Was appropriate statistical analysis used?	Total Score
Moseley (2004)	CRPS 1	Y	Y	Y	Y	Y	Y	Y	Y	8/8
Reinersmann et al. (2010)	CRPS 1	N	Y	Y	Y	N	N	Y	Y	5/8
Reinersmann et al. (2012)	CRPS 1	N	Y	Y	Y	Y	Y	Y	Y	7/8
Schwobel et al. (2001)	CRPS 1	Y	Y	Y	N	Y	Y	Y	Y	7/8
Coslett et al. (2010)	Upper Limb Pain	Y	Y	Y	N	Y	Y	Y	Y	7/8
Scmid et al. (2010)	Upper Limb Pain	Y	Y	Y	Y	Y	Y	Y	Y	8/8
Bowering et al. (2014)	Low Back Pain	N	N	Y	N	Y	N	Y	Y	4/8

Study	Condition	1. Were the criteria for inclusion in the sample clearly defined?	2. Were the study subjects and the setting described in detail?	3. Was the exposure measured in a valid and reliable way?	4. Were objective, standard criteria used for measure-ment of the condition?	5. Were con-founding factors identified?	6. Were strategies to deal with con-founding factors stated?	7. Were the outcomes measured in a valid and reliable way?	8. Was appropriate statistical analysis used?	Total Score
Bray and Moseley (2011)	Low Back Pain	N	Y	Y	N	Y	N	Y	Y	5/8
Linder et al. (2015)	Low Back Pain	Y	Y	Y	Y	Y	Y	Y	Y	8/8
Elsig et al. (2014)	Cervical Pain	Y	Y	Y	Y	Y	Y	Y	Y	8/8
Pedler et al. (2013)	Cervical Pain	Y	N	Y	Y	Y	Y	Y	Y	7/8
Richter et al. (2010)	Cervical Pain	Y	Y	Y	Y	Y	N	Y	Y	7/8
Coslett et al. (2010)	Lower Limb Pain	N	N	Y	N	Y	Y	Y	Y	5/8
Stanton et al. (2012)	Lower Limb Pain	Y	Y	Y	Y	Y	Y	Y	Y	8/8
Stanton et al. (2013)	Lower Limb Pain	N	Y	Y	Y	Y	Y	Y	Y	7/8
CRPS- Complex Regional Pain Syndrome, *N*- NO, *Y*- Yes										

4.5 Review Results

Initially, studies that had sufficient data for reaction time and accuracy were pooled together by meta-analysis. Five studies for reaction time (Reinersmann et al., 2010, Reinersmann et al., 2012b, Coslett et al., 2010a, Coslett et al., 2010b, Linder et al., 2016) and five studies for accuracy (Linder et al., 2016, Schwoebel et al., 2001, Elsig et al., 2014, Coslett et al., 2010a, Stanton et al., 2013c) were considered for meta- analysis.

Heterogeneity

Heterogeneity in the studies was assessed by the I^2 value and p-value. When pooling all studies together, regardless of the condition, into reaction time and accuracy, there was vast heterogeneity (98.01% and 87.64% respectively). This is considered to be considerable heterogeneity. Both yielded a p vale of <0.0001. This finding was expected as there is increased clinical diversity between studies, in term of differences in conditions of participants, mechanisms of chronic pain, outcomes of assessing pain, and variability of laterality judgment tasks. However, unexpectedly, when separating data into two sub-groups high heterogeneity measures were also yielded. The sub-group of CRPS and upper limb pain yielded a considerable heterogeneity measure of 97.19%, with a p-value of <0.0001. On the other hand, in the sub- group of lower limb conditions, the I^2 value was 68.35% and p-value of 0.02. This is considered substantial heterogeneity in the lower limb group.

It is important to note the source of heterogeneity in the studies. The studies do not differ much in terms of methodological heterogeneity (differences in study design and risk of bias), and statistical heterogeneity, but rather they differ with clinical heterogeneity. Differences in heterogeneity are due to differences in the conditions of participants and mechanisms of chronic pain. In sub-groups differences also include outcomes of assessing pain, and most importantly variability of laterality judgment tasks. Objective measures to investigate clinical heterogeneity are needed in research studies (Melsen et al., 2014).

There has been much debate regarding heterogeneity in meta-analysis. It is considered likely that some amount of heterogeneity exists in all meta-analysis, as it is impossible to standardise all studies in a meta-analysis (Melsen et al., 2014). However, one has to consider how much heterogeneity is acceptable in order to estimate a pooled effect. Some authors have found that continuous outcomes (as in this study), being more powerful, produce narrower confidence intervals than binary outcomes, resulting in a higher I^2 value (Alba et al., 2016, Rücker et al., 2008). This could

potentially lead to misinterpretation of results. Therefore, limitations to using the I^2 statistic do exist, in terms large sample sizes, small study variances or increased number of studies included (Alba et al., 2016, Rücker et al., 2008). However, it is the most commonly used measure of heterogeneity for the random-effects model. Although heterogeneity measures are high, it is does not mean that there is no true effect between studies (Higgins and Green, 2011). However, due to increased variability between studies one needs to interpret results with caution.

In this study, in order to visually inspect the direction of effects of laterality judgment measures, meta-analysis will be done of: 1) all five studies in terms of reaction time, 2) all five studies in terms of accuracy, 3) sub-group of CRPS 1 and other upper limb conditions and 4) sub-group of lower limb conditions. However, due to the high heterogeneity values of all five studies for accuracy (87.64%), all five studies for reaction time (98.01%) and CRPS and upper limb conditions (97.19%), these results will be interpreted cautiously, and pooled estimates will not be considered in the final analysis of results. Heterogeneity measures for lower limb conditions were 68.35%. This falls into the lower limits of substantial heterogeneity, and therefore pooled estimates for lower limb pain will be considered. CRPS 1 and upper limb pain, low back pain and cervical pain will be discussed under the narrative review.

4.5.1 Meta- analysis Across Studies

Reaction Time

The combined sample size for participants for the healthy group, pain group and pain control group (where applicable) for reaction time were 171, 117 and 87 respectively. Using the maximum likelihood method, the mean effect size was 2.59 and variance effect size was 0.34. The 95% CI for each study is shown in Figure 4. The 95% CI for the mean effect size ranged from 1.44 to 3.74. The effect sizes were classified into small (<0.2), medium (0.2–0.8), and large (>0.8), according to Cohen's interpretation of the effect size (Cohen, 1992). Therefore, reaction time in chronic pain conditions was increased compared to healthy individuals, and showed a large statistically significant effect size and significant CI (Figure 4).

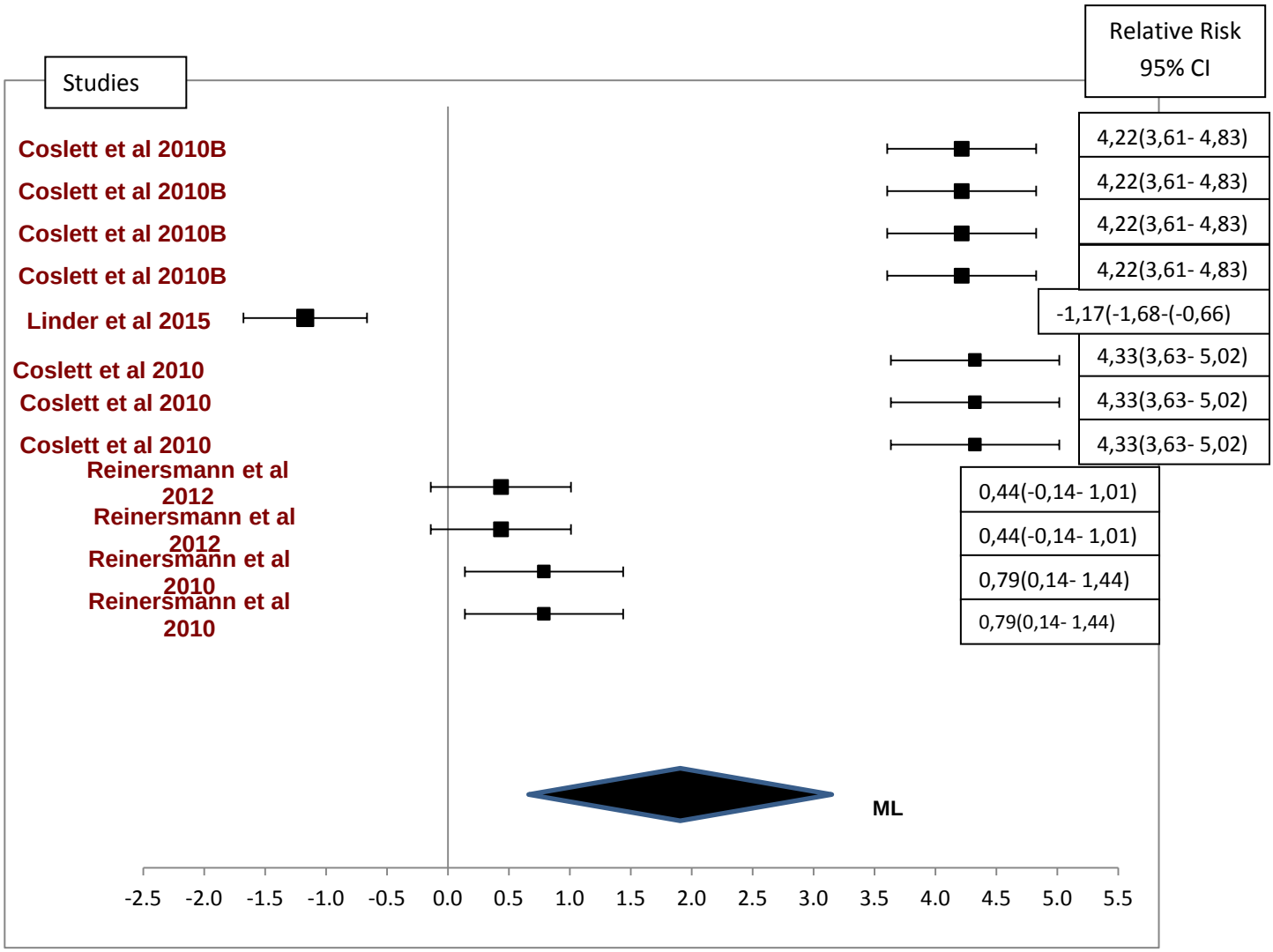

Figure 4: Forest Plot: Meta- analysis of reaction time of five studies (regardless of condition) depicting the effect sizes and confidence intervals of studies, using the maximum likelihood method.

Accuracy

The combined sample size for participants for the healthy group, pain group and pain control group (where applicable) for accuracy were 154, 150 and 62 respectively. Accuracy in chronic pain conditions was decreased compared to healthy individuals. Using the maximum likelihood method, the mean effect size was 0.42 and variance effect size was 0.07. The 95% CI for each study is shown in Figure 5. The mean effect size 95% CI ranged from 0.10 to 0.93. Although the mean effect

showed a medium statistically significant effect size (according to Cohen's interpretation of effect sizes), the CI is not statistically significant (Figure 5).

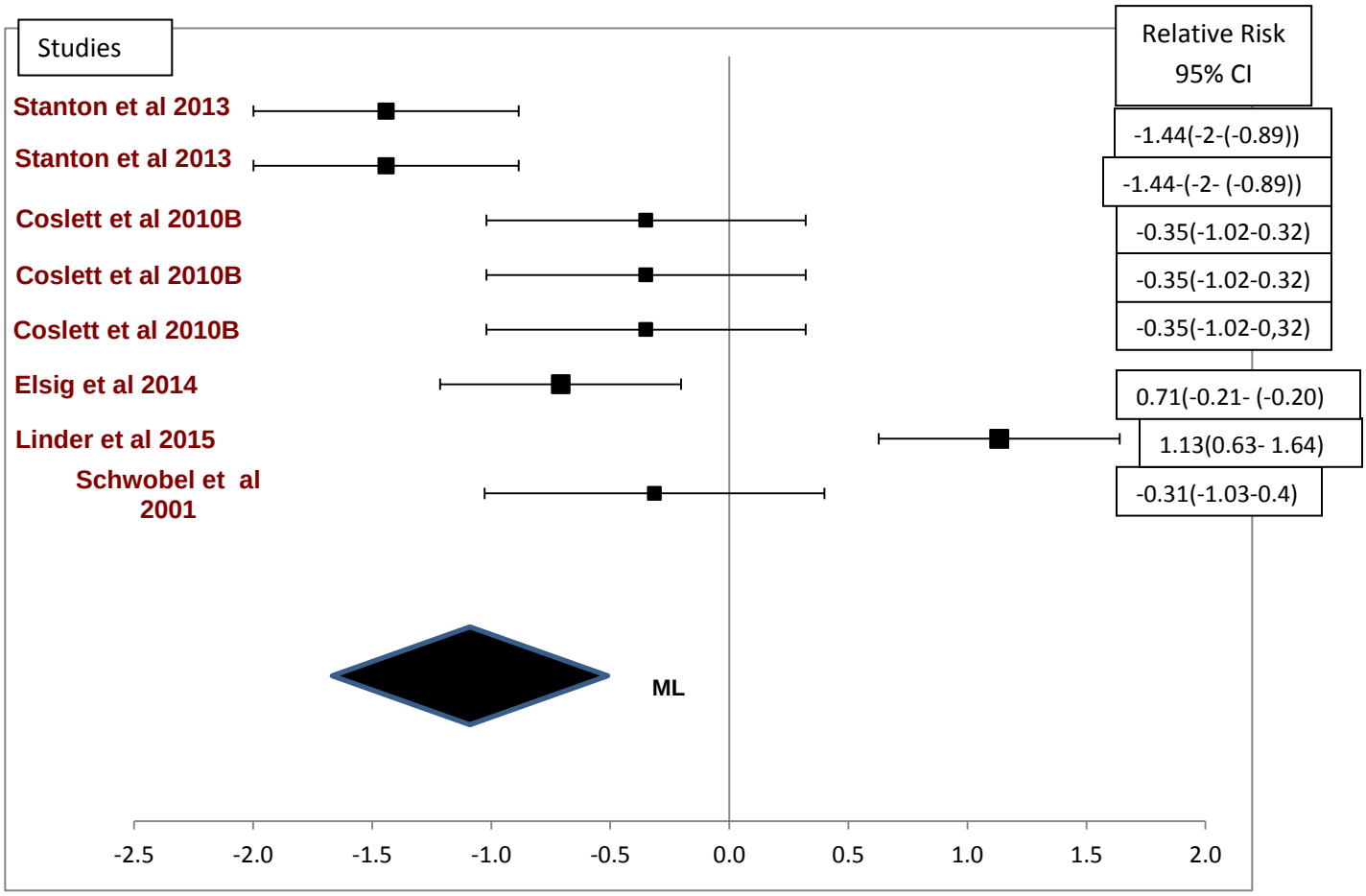

Figure 5: Forest Plot: Meta-analysis of accuracy of five studies (regardless of condition) depicting the effect sizes and confidence intervals of studies, using the maximum likelihood method.

4.5.2 Meta- analysis of Sub- groups

CRPS and Upper Limb Pain

Three studies for CRPS and upper limb pain were taken into account. Sample sizes of all three studies for the healthy group, pain group and pain control group was 80, 61 and 21 respectively. Heterogeneity results showed an I^2 value of 97.19%. Results showed a large effect size of 2.17 and variance effect size of 0.48. The 95% CI for each study is shown in Figure 6. The mean effect size 95% CI ranged from 0.83 to 3.56.

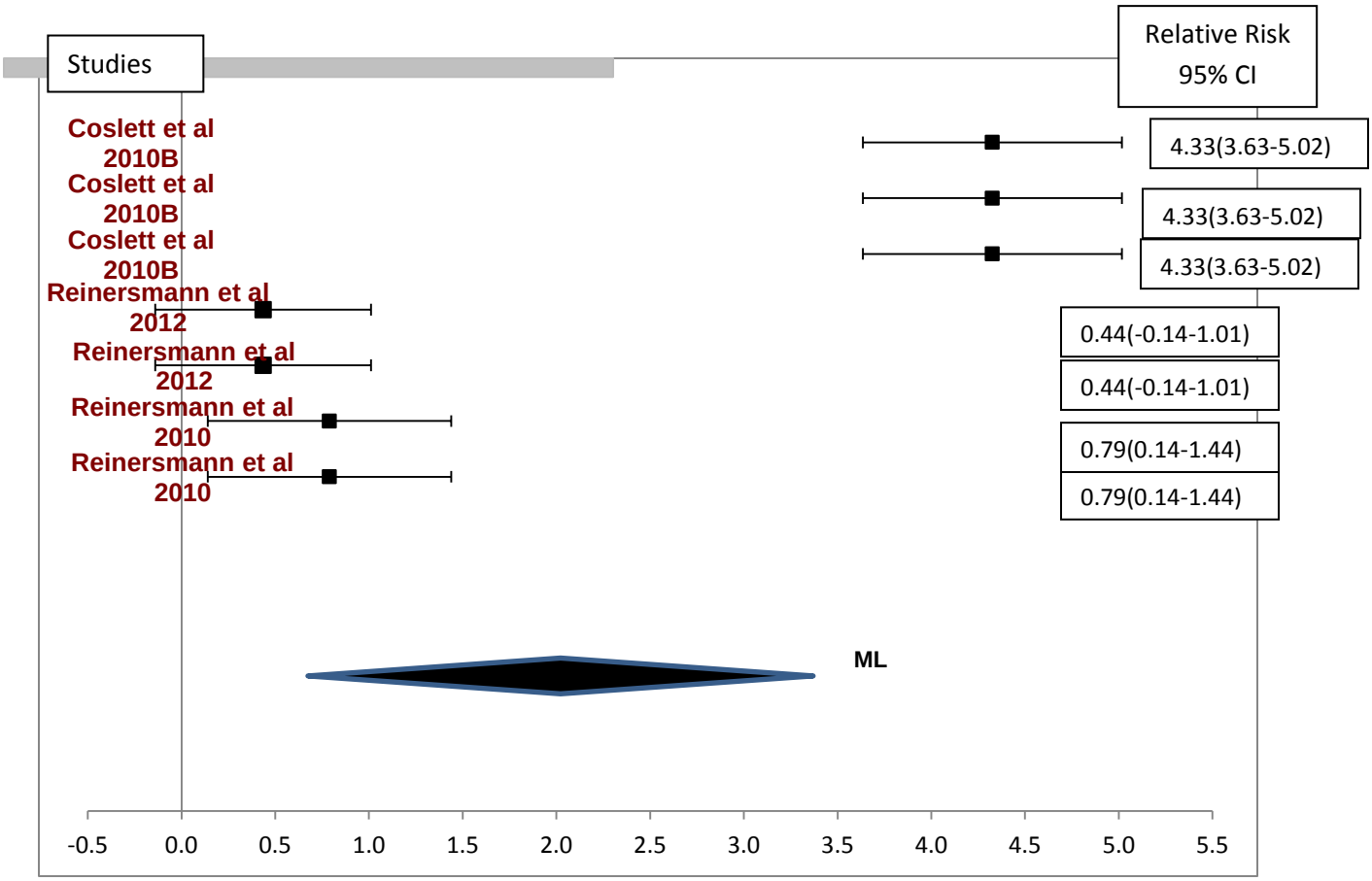

Figure 6: Forest Plot: Meta-analysis of reaction time in CRPS and upper limb pain depicting the effect sizes and confidence intervals of studies, using the maximum likelihood method.

Lower Limb Pain

Two studies measuring accuracy for foot pain and knee osteoarthritis were taken into account (Coslett et al., 2010a, Stanton et al., 2013b). Sample sizes of the two studies for the healthy group, pain group and pain control group was 77, 76 and 62 respectively. Heterogeneity results showed an I^2 value of 68.35% and a p-value of 0.02. When comparing people with lower limb pain to healthy individuals, results showed a medium statistically significant mean effect size of 0.59 of accuracy (decreased in lower limb pain) and variance effect size of 0.06. The 95% CI for each study is shown in Figure 7. The mean effect size 95% CI ranged from 0.11 to 1.07.

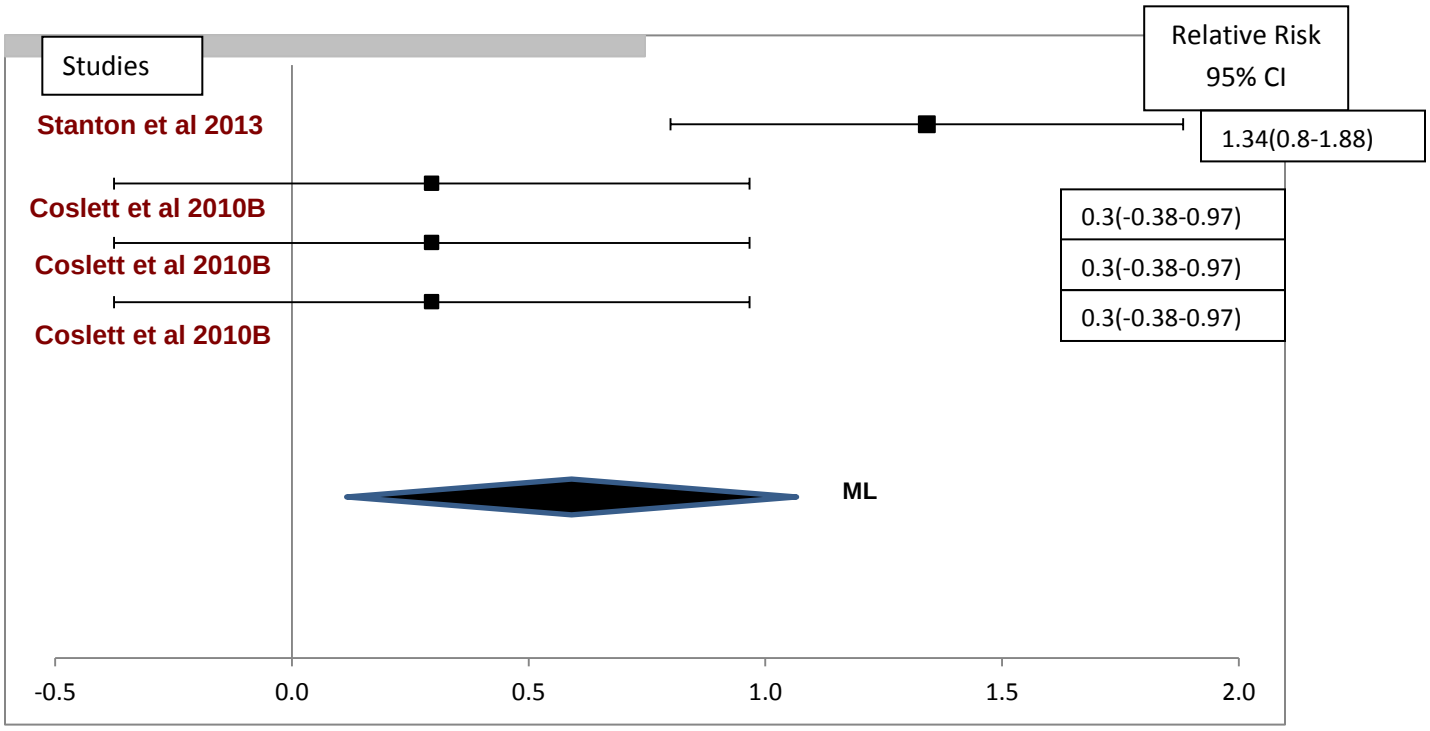

Figure 7: Forest Plot: Meta-analysis of accuracy in lower limb pain depicting the effect size and confidence intervals of studies, using the maximum likelihood method.

Reaction time was also measured in this study (Coslett et al., 2010a). Results found increased reaction times in people with leg pain compared to healthy individuals and the chronic pain control goup (Coslett et al., 2010a). One study on lower limb pain could not be pooled into meta-analysis due to insufficient data available. In a laterality judgment task by people with osteoarthitis of the knee, pain control group (people with upper limb pain) and healthy individuals, it was found that there was no significant effect on reaction time in all groups (Stanton et al., 2012a). However, healthy individuals were more accurate than both pain groups. Accuracy was also lower on the affected side in both pain groups, not associated to the site of pain.

4.5.3 Narrative Review

CRPS and Upper Limb Pain

CRPS and upper limb pain was assessed in terms of reaction time. When comparing laterality judgment between healthy individuals and people with CRPS 1 and/or phantom limb pain; reaction times of healthy individuals were significantly better (Schwoebel et al., 2001, Reinersmann et al., 2010, Moseley, 2004b). In terms of accuracy, there was no significant differences between the groups in three studies (Moseley, 2004b, Schwoebel et al., 2001, Reinersmann et al., 2012a), while one study found healthy individuals had increased accuracy compared to people with CRPS (Reinersmann et al., 2010). Furthermore, one study found no difference in both accuracy and reaction time between groups (Reinersmann et al., 2012a). Comparisons of reaction times of affected versus unaffected limbs in pain groups were mixed. Two studies (Moseley, 2004b, Schwoebel et al., 2001) found that reaction times were longer in recognising the affected compared to the unaffected hand; while two studies (Reinersmann et al., 2010, Reinersmann et al., 2012c) found that there was no significant difference in the reaction time of recognising the affected and unaffected hand.

In other upper limb conditions, in a study comparing carpal tunnel syndrome and healthy individuals, reaction time between the pain group and healthy individuals were similar (Schmid and Coppieters, 2012). Accuracy was affected by 10 percent, in that people with carpal tunnel syndrome were less accuracte than healthy individuals (Schmid and Coppieters, 2012). However, in another study consisting of people with bilateral arm/shoulder pain, people with unilateral arm/shoulder pain, people with chronic pain- not in the upper limb (pain control) and healthy individuals, there was no difference in accuracy between groups (Coslett et al., 2010b). Reaction time was increased in the bilateral and unilateral arm/shoulder pain groups, but not in the pain control group in this study.

Low Back Pain

The results of two studies could not be pooled into sub-group analysis due to inadequate data on reaction time and accuracy. Therefore, all three studies related to low back pain will be discussed (Bray and Moseley, 2011, Bowering et al., 2014b, Linder et al., 2016). Two studies compared low back pain to healthy individuals (Linder et al., 2016, Bray and Moseley, 2011), while one study compared people with low back pain, people history of low back pain and healthy individuals (Bowering et al., 2014b). In two studies (Bray and Moseley, 2011, Bowering et al., 2014a), results

were similar in that they showed that there was no significant difference is reaction time in all groups. However, accuracy was decreased in people with current low back pain (selectively) and pain-free individuals with a history of low back pain, compared to healthy individuals (Bowering et al., 2014b). This study had a critical appraisal rating on 4/8. Therefore, results of this study should be interpreted with caution. Accuracy was also decreased in unilateral low back pain, and further decreased in bilateral low back pain (Bray and Moseley, 2011). On the other hand, in one study (Linder et al., 2016), which tested trunk and foot laterality in people with back pain with/without leg pain, compared to healthy individuals, results found that there was no significant difference in healthy individuals and people with back pain both on accuracy and reaction time. This is contradictory to the other two studies (Bray and Moseley, 2011, Bowering et al., 2014a) that found decreased accuracy in people with low back pain compared to healthy individuals.

Cervical Pain

Three studies reported on laterality judgment in cervical pain. Cervical pain conditions ranged from whiplash injuries to chronic non-specific cervical pain. In a study comparing people with whiplash injuries and healthy individuals, no differences in reaction time and accuracy were found between people with whiplash injuries and healthy individuals (Pedler et al., 2013). Another study done in the whiplash population was carried out between individuals with chronic non-specific cervical pain, cervical pain of traumatic origin (whiplash associated disorder-WAD) and healthy individuals (Richter et al., 2010). It was found that people with cervical pain of traumatic orgin had faster reaction times compared to healthy individuals. The non-specific cervical pain group and control group did not differ in terms of reaction time, and accuracy was not significantly dfiiferent between all groups. In a study by Elsig et al. (2014), people with recurrent cervical pain were compared to healthy individuals. In this study only accuracy was measured and not reaction time. Results showed that people with chronic pain have a lower accuracy than healthy individuals.

4.6 Conclusion of the Results

The following differences were found in accuracy and reaction time between healthy individuals and chronic pain syndromes:

Table 4: Results of the Studies Depicting the Specific Impairments and Analysis Methods.

Chronic Pain Syndrome	**Impaired Accuracy**	**Impaired Reaction Time**	**Meta- analysis**	**Narrative Review**
Lower Limb Pain	√	√	√	X
CRPS 1	X	√	√ Results interpreted with caution due to high heterogeneity	√
Carpal Tunnel Syndrome	√	X		√
Upper Limb Pain	X	√		√
Low Back Pain	√ Results interpreted with caution	X Results interpreted with caution		√
Cervical Pain- Whiplash Associated Disorder	X	X		√
Cervical Pain- Chronic non-specific	UNCLEAR RESULTS			√

CHAPTER 5: DISCUSSION

5.1 Introduction

Chronic pain is a global healthcare issue (Gureje et al., 1998). Its pathophysiology is poorly understood and there is often failure of recovery of chronic pain syndromes. This could be due to a lack of knowledge and understanding of central mechanisms of chronic pain. In this systematic review, one of the determinants of the central features of chronic pain was explored i.e. laterality judgment. Disrupted body schema, due to distorted cortical representation of affected body parts is an important feature of chronic pain. Failure to ignore this feature might contribute to the chronicity of pain.

Forest plots of reaction time of five studies regardless of condition (figure 4) as well as the sub-group of CRPS an upper limb pain in terms of reaction time (figure 6) showed a positive relationship between decreased reaction time and the presence of chronic pain. Accuracy of five studies regardless of condition (figure 5) did not show a clear direction of effect. Specific statistical analysis of these meta-analyses will not be discussed further due to high heterogeneity between the studies.

5.2 Lower Limb Pain

In lower limb pain, accuracy was decreased in all studies (Coslett et al., 2010a, Stanton et al., 2012a, Stanton et al., 2013b). Results showed a medium statistically significant mean effect size of 0.59 and the 95% CI ranged from 0.11 to 1.07. Reaction time, on the other hand, was measured in two studies only. Results were mixed in that in one study reaction time was increased in lower limb pain (Coslett et al., 2010a), while in one study there was no significant difference in reaction time between groups (Stanton et al., 2012a)

In one study, all groups responded significantly faster to pictures of right hands, which was the dominant hand in all groups (Stanton et al., 2012a). The dominant hand has shown a faster response in many studies due to it being constantly used. In Coslett et al. (2010a) participants responded faster to right feet, but were more accurate with left feet. However, foot dominance was not established in this study. A similar theory would apply to foot dominance. Participants also responded worse to maximally rotated pictures that required an increased degree of mental rotation (Coslett et al., 2010a,

Stanton et al., 2012a, Stanton et al., 2013b). This was due to the biomechanical constraints of the specific foot. In Coslett et al. (2010a), this feature was further increased in the the bilateral and unilateral leg pain group compared to the pain control and healthy group. Therefore, the greater effect of rotation on the leg pain group versus the pain control group implies that the laterality deficits are not due to non-specific effects of pain, discomfort or medication, but rather a disruption in body schema (Coslett et al., 2010a).

The influence of the location of pain on laterality was also explored (Stanton et al., 2012a, Coslett et al., 2010a). In one study, the side of pain (left or right) was important but not the site (Stanton et al., 2012a). There was no significant difference between people with knee pain and arm pain (pain control) in terms of accuracy, except with the side of pain (left or right). Decreased accuracy in people with knee pain were not limited to pictures of feet only, but hands too (Stanton et al., 2012a). However, in another study, site of pain was affected in the laterality judgement task and not the site (Coslett et al., 2010a). People with leg pain (unilateral or bilateral) had decreased reaction time and accuracy in a foot laterality judgment task in stimuli that required a greater degree of mental rotation of the painful foot, while the pain control and healthy group did not (Coslett et al., 2010a). This proves that the results were not a non-specific effect of pain, but rather specific to the side and site tested (Coslett et al., 2010a). All corresponding studies also support this reasoning that decreased laterality judgmnet is not a non-specfic effect of chronic pain. Decrease in parameters of laterality are always related to the specific site tested. This could possibly be related to the cortical networks in the brain whereby the homunculus is depicted by certain body parts. When these cortical networks are vulnerable due to the presence of pain at a specific site, in the corresponding site of pain, laterality judgements can be affected.

Two studies measuring laterality in knee osteoarthitis used pictures of feet, instead of knees (Stanton et al., 2012a, Stanton et al., 2013b) . It was proposed that in the laterality of the foot, one has to mentally manoeuvre their entire lower limb to match the pictured limb. Therefore, there would be mental rotation of both the knee and foot. Proprioception of the knee is important in placement of the feet, and therefore foot and leg proproception maps should be closely related. Furthermore, determining the sidedness of a knee is difficult and therefore pictures of feet were used. However, it can be argued that using pictures of feet instead of knees is not specific to the site of pain.

It has been shown that aging results in a decrease in laterality judgment performance (Saimpont et al., 2009, Briggs et al., 1999). In two studies healthy individuals were significantly younger compared to their respective pain groups (Stanton et al., 2012a, Stanton et al., 2013b). In one study (Stanton et al., 2012a), healthy individuals were 37.3±15.5years, the knee pain group was 68±9years and the pain control group was 64.9±7.8years. In another study (Stanton et al., 2013b), healthy individuals were 37±16years, the knee pain group was 68±9years and the pain control group was 65±8years. However, accuracy was unaffected by age in both studies (Stanton et al., 2013b, Stanton et al., 2012a). In Stanton et al. (2012a), age was adjusted for reaction time (by sensitivity analysis). However, this adjustment had no effect on the accuracy (Stanton et al., 2012a). This could be due to a relatively easy laterality task (10 judgments) compared to other studies. However, this theory is not consistent as accuracy was not affected by age in another study that consisted of a complex task of 80 judgments (Stanton et al., 2013b). Therefore, the relationship between age and decreased laterality judgment performance is not clearly documented in the research, and needs to be further explored.

5.3 CRPS and Upper Limb Pain

All studies found in the CRPS population only recruited participants with CRPS 1. CRPS 1 is distinctly different from CRPS 2. People with CRPS 1 experience sensory loss only, while people with CRPS 2 also experience mechanical and thermal loss (Gierthmuhlen et al., 2012). This is similar to people with peripheral nerve injuries (Gierthmuhlen et al., 2012). Therefore, these results are only applicable in the CRPS 1 population and cannot be generalised to the CRPS 2 population. In three studies in CRPS 1 (Reinersmann et al., 2012c, Schwoebel et al., 2001, Reinersmann et al., 2010), healthy individuals scored better reaction times in the dominant hand compared the non-dominant hand; while in one study (Moseley, 2004b) hand dominance was not a factor. Better reaction times in the dominant hand could be as a result of consistent use of the hand daily for tasks. Comparisons of reaction time of affected versus unaffected limbs in pain groups were mixed. Two studies (Moseley, 2004b, Schwoebel et al., 2001) found that reaction times were longer in recognising the affected limb compared to the unaffected; while two studies (Reinersmann et al., 2010, Reinersmann et al., 2012c) found that there was no significant difference in the reaction times of recognising the affected and unaffected hand. Furthermore, in all studies, there were increased reaction times in all groups for increased degrees of rotations/large amplitude movements in the

affected limb, due to the biomechanical constraints of the hand. Moseley (2004b) found that reaction time to determine the laterality of a pictured hand depends on the duration of symptoms and not the intensity of pain. Interestingly, he also suggested that when pain is present in the arm, the predicted pain associated with a movement that would require the limb to rotate, is more significant than the awkwardness of the position (Moseley, 2004b).

The explanation for increased reaction time for predicated pain was given by different authors. Moseley (2004b) suggested that this was due to the guarding-type process that occurs due to the planning of a movement and subsequent prediction of the consequences thereof. It serves to avoid provocation of the painful body part. This view can be supported by the fact that laterality judgment and the execution of movement activate similar cortical networks. Furthermore, this challenges the idea that pain is as a result of excitability of the spinal motor process and primary motor cortex, to the possibility that predicted pain may occur from the primary motor cortex at a motor planning level. On the other hand, Schwoebel et al. (2001) refutes this theory on two conditions. Firstly, there was no movement of the painful limb during the laterality tasks and participants did not report any pain during the task. Secondly, reaction time was only slowed to such a degree in increased degrees of mental rotation, rather than simple orientations. If the guarding-type process was true, the reaction time would be slowed exponentially in all orientations, instead of just in increased degrees of rotation. The authors suggest that the decreased reaction time could be due to large amplitude mental rotations at both the proximal and distal joints (elbow and shoulder) that might be affected in CRPS, i.e. these movements are associated with increased pain. Furthermore, they suggest that reasons for these findings are associated with distortions in body representations that could be influenced by sensory inputs and severity of pain at the time of testing (Schwoebel et al., 2001). However, this hypothesis is still under investigation. These theories were further discussed with regard to musculoskeletal arm pain (Coslett et al., 2010b). It was also suggested that a possible cause could be neglect-like symptoms that has been reported in CRPS. However, this too can be refuted by the above explanations (Coslett et al., 2010b). The consensus is that greater mental rotations indexes pain that is associated with that particular movement (Coslett et al., 2010b, Moseley, 2004b)

Other confounding factors included speed-accuracy trade-off and age. Speed- accuracy trade off refers to the ability to respond slowly and with fewer mistakes versus the ability to respond faster with more mistakes. In all studies there were no signs of speed-accuracy trade-off. The variable of

age is one that needs to be explored in further studies. In one study (Reinersmann et al., 2010); the age of healthy individuals (35.7± 12.2years) was not matched to the CRPS group (46.5±13.1) and phantom limb pain group (51.4±10.1). This study found that there was no correlation between reaction time and age. However, this is contrary to previous findings whereby reaction time decreases with age (Saimpont et al., 2009, Briggs et al., 1999, Kosslyn et al., 1998). Another study that used age matched healthy individuals in their comparison, found slower reaction time in older adults in the healthy group (Reinersmann et al., 2012a).

The literature is not conclusive with regard to age. There has been some research indicating that older adults have an increased reaction time when compared to younger people in laterality judgment tasks (Saimpont et al., 2009, Kosslyn et al., 1998, Briggs et al., 1999). This could be due to age related changes in working memory and changes in the prefrontal cortex (Raz et al., 1999). On the other hand, some studies have shown no relationship between laterality judgment and age (Reinersmann et al., 2010, Stanton et al., 2012a, Stanton et al., 2013b). Therefore, further research needs to be done to determine the relationship of age and laterality judgment. However, due to lack of evidence, matching healthy individuals for age when comparing to the pain group should be an important consideration in the studies.

In one study, there was a four day training programme for laterality judgment in healthy individuals and people with CRPS (Reinersmann et al., 2010). There was decreased reaction time of both groups, but the healthy individual's reaction times were still significantly lower. There was no reduction in pain after the training. This is contrary to the results of improvement in pain and function when using perceptual learning programmes (Flor et al., 2001, Pleger et al., 2005) as well as laterality training as used as part of a graded motor imagery programme (Moseley et al., 2005, Moseley, 2005b). This suggests that laterality judgment training alone cannot improve body schema, but needs to be incorporated into other programmes.

Studies were done in other upper limb pain conditions, apart from CRPS, as CRPS differs from other chronic pain conditions and therefore the effects of laterality judgment cannot be assumed in all upper limb conditions. In a study by Coslett et al. (2010b), which compared people with bilateral arm pain, unilateral arm pain, a pain control group and healthy indiviuals, found that healthy individuals had a faster reaction time to people with bilateral and unilateral arm/shoulder pain but not the pain control group (chronic pain of other origin). In all groups the right hand pictures had a

faster reaction time than the left, but hand dominance was not reported. There was no significant difference in reaction time between recognising the affected and unaffected limb. This is contrary to the studies in CRPS, where participants had increased reaction time in recognising the affected limb (Moseley, 2004b, Schwoebel et al., 2001). The difference could be due to the underlying cause of CRPS compared to musculoskeletal pain. While people with CRPS are more detached and focused on the affected limb, those with musculoskeletal pain are less detached and generalise the pain over both limbs. Furthermore, images that required increased degrees of mental rotations had an increased reaction time in all groups, but substantially increased in the arm pain group (Coslett et al., 2010b). The authors have a similar viewpoint to Schwoebel et al. (2001), whereby the difference in reaction time is attributed to the association of greater degrees of mental rotation with increased pain. There was no difference in accuracy between groups (Coslett et al., 2010b)

A study comparing a less severe and less neuropathic state was done in the carpal tunnel syndrome population compared to healthy individuals (Schmid and Coppieters, 2012). Results found that there were no differences in reaction time, but differences were present in accuracy. Accuracy was selectively impaired in the laterality judgment of the affected hand and neck. Accuracy in the neck towards the affected side was decreased in increased degrees of rotation (120, 240, 300 degrees). There were no differences in the accuracy of the unaffected hands and feet. This study proved that there can be impairment of laterality judgment in less severe states. Furthermore, laterality judgment can also be impaired in conditions with prolonged low intensity pain. However, the result of decreased accuracy and normal reaction time is contrary to previous findings of normal accuracy and decreased reaction time compared to other upper limb conditions, such as chronic arm/shoulder pain (Coslett et al., 2010b) and CRPS (Moseley, 2004b, Schwoebel et al., 2001).

5.4 Low Back Pain

Since the back is not a single unit, unlike the upper and lower limb, it is difficult to categorise its laterality to a left or right judgment. Therefore, laterality judgments of the trunk require the participants to judge whether the pictured trunk is rotated or laterally flexed to the right or left from a neutral position. In the back pain population, there were no speed-accuracy trade-offs. Accuracy was affected in two studies (Bray and Moseley, 2011, Bowering et al., 2014a) and reaction time was not affected. In one study, accuracy was decreased in unilateral back pain compared to healthy individuals and further decreased in bilateral back pain (Bray and Moseley, 2011). However, all

groups scored similarly in a hand laterality task. This rules out the possibility that chronic pain mechanisms are similar in all conditions, as a result of decreased central nervous system processing (Bray and Moseley, 2011). It also refutes the theory proposed by Stanton et al. (2012b) that decreased laterality judgment is simply a non-specific effect of chronic pain and is not selective to the site of pain. Another study found that accuracy was decreased in people with current low back pain (selectively) and pain-free individuals with a history of low back pain, compared to healthy individuals (Bowering et al., 2014b). The finding of pain-free individuals having decreased accuracy proposes the theory that in some people, after the first episode of low back pain there may be some vulnerability in the cortical maps that could lead subsequent episodes of low back pain. Furthermore, in current back pain, there were contrasting results. Some found impairment in accuracy while others scored better than healthy individuals. This gave rise to a conceptual model that stated that after the first episode of low back pain, there could or could not be decreased accuracy. Those who do not have decreased accuracy recover, while those who have decreased accuracy then progress to encounter more episodes of low back pain. One of the greatest limitations of this study is that participants were self-selected online. Inclusion and exclusion criteria were only on subjective report based on an online questionnaire. There is a great possibility that false or misleading information could have been entered by participants in order to participate in the study. Furthermore, as this was completely an online study, there are technical limitations in terms of technical abilities of the user, computer processing speed and environment. These could lead to increased heterogeneity between participant data due to increased clinical diversity within the sample itself (Bowering et al., 2014b). Therefore, the results of this study will be interpreted cautiously. Due to the number of confounding variables and low quality study design, results could be skewed.

Furthermore, Bray and Moseley (2011) found no association of laterality judgment with pain intensity or duration of symptoms, while Bowering et al. (2014b) found an impairment in people with back pain and a history thereof. Linder et al. (2016) also found no association between laterality judgment with pain intensity or duration of symptoms. Differences in results between the studies could be that in Linder et al. (2016), there was exclusion of healthy individuals who had back pain in the last 12 months only, with no guarantee that they did not have pain previously. According to Bowering et al. (2014b) history of back pain is an important considerration, as it could leave cortical networks vulnerable to pain. Other factors relating to the observed differences include possible pain of participants in other regions of the body, a practice round was not done and most importantly,

custom images were not used in this study like the other two, but rather stock images (Linder et al., 2016).

A study by Rabey et al. (2015) found the need to separate lower back pain into multidimensional profiles and not pain mechanisms. However, some evidence supports the need for separation of lower back pain by pain mechanisms (Smart et al., 2011). For example, it has been found that sensory processing difficulties are found in non-mechanical back pain but not in mechanical back pain (O'Sullivan et al., 2014). This could propose that cortical reorganisation and laterality judgments could be present in people with lower back pain related to specific pain mechanisms (Linder et al., 2016). Therefore, further research should aim at classifying lower back pain according to their pain mechanisms, and determining the laterality judgment impairements thereof (Linder et al., 2016).

5.5 Cervical Pain

Laterality judgment seems largely unaffected by cervical pain. In one study there was decreased accuracy in people with cervical pain (Elsig et al., 2014). However, no data was given on specific degrees tested and correlation to healthy participants. Moreover, in this study, the assessor was not blinded to the condition of nine participants (Elsig et al., 2014). In two studies (Pedler et al., 2013, Richter et al., 2010), laterality jugement was not affected in non-specific cervical pain and whiplash associated disorders (WAD). In one study there was no difference in accuracy and reaction time between people with WAD and healthy individuals in a foot and neck laterality task (Pedler et al., 2013). People with WAD actually scored better at a neck than foot laterality task. There was also no association between laterality judgment performance and duration of symptoms (Pedler et al., 2013). This contrasted to the results found in the other study whereby reaction time in WAD was increased compared to healthy individuals (Richter et al., 2010). The non-specific cervical pain group and control group did not differ in terms of reaction time, and accuracy was not significantly dfiiferent between all groups (Richter et al., 2010). Results were comparative to other studies in that there was no speed-accuracy tradeoff, reaction time was increased in the dominant versus the non-dominant hand and there was increased reaction time for large amplitude rotations (180 degrees), due to the biomechanical constraints of the neck (Richter et al., 2010). The unusal finding of faster reaction time in the WAD can be described by various possibilities. People with WAD could not use motor imagery when performing mental rotations, but rather use an adaptive strategy that improved speed

and accurcy with time as a coping mechanism. There could also be an alteration in the visual information processing that occurs in WAD. This consists of planning, initation, coding and correction of movement. Therefore, this stategy of visuomotor processes compensates for a less functioning motor imagery ability. A limitation to this study is that there was no assessor blinding (Richter et al., 2010). Furthermore, a neck laterality task was administered, as opposed to limb (hand or foot) laterality task (Pedler et al., 2013) . There could be different processess underlying neck versus limb laterality tasks. The degrees of mental rotation required for the neck is also limited, and therefore would yeild better outcomes (Pedler et al., 2013). Findings in cervical pain studies suggest that the processes between neck laterality judgment and limb laterality judgment are different, and influenced by continuous proprioceptive input (Pedler et al., 2013). Moreover, a study was done between people with cervical pain and healthy individuals used the letter "R" in their laterality task. It was found that rotation of letters follow an allocentric mechanism, while rotation of body parts follw an egocentric mechanism (Dalecki et al., 2012). Due to this difference in mechanisms, only laterality tasks using pictured limbs can be used to test laterality judgment.

5.6 Relationship between Accuracy and Reaction Time

The laterality judgment process is based on three stages. Firstly, participants make a decision if the pictured limb belongs to the right or left side of the body (Parsons, 2001). Secondly, there is a mental rotation of the involved body part to the image of the pictured limb. Thirdly, the accuracy of the initial decision is confirmed by comparing the mental rotation to the pictured limb (Parsons, 2001). Accuracy informs one of how well they can mentally manoeuvre their limb (Bray and Moseley, 2011) and/or the personal space that they are surrounded by (Moseley et al., 2012). On the other hand, reaction time refers to the ability of the brain to process new information as well as its ability to be bias to a particular body part (Hudson et al., 2006, Moseley, 2004b). Two theories are proposed for the increased reaction time and normal accuracy and vice versa that occurs in most studies. When there is a correction in stage three (confirmation stage) to the initial decision made in stage one, this results in increased reaction time and normal accuracy (Bray and Moseley, 2011). It is described as an interpretive bias towards one limb/side over another (Pincus et al., 1994). On the other hand, decreased accuracy (with a normal reaction time) could be due to an incorrect decision in stage three (confirmation stage). It is correlated with difficulties in the proprioceptive cortical maps and incorporation with motor processes (Bowering et al., 2014b). This is indicative of a disrupted

body schema. However, one cannot assume that decreased accuracy is the only variable that indicated a disrupted body schema. Some studies yielded normal accuracy and increased reaction time, but had cortical reorganisation in the patient population (Juottonen et al., 2002, Maihofner et al., 2003, Maihofner et al., 2004). Therefore, from the research presented, it is hypothesised that both an increase in reaction time and decreased in accuracy is an abnormal finding and indicates disruption of body schema. However, further research needs to be done for the specific measures of reaction time and accuracy, and how and why they differ from each other.

Various studies found reaction time and accuracy to be affected differently. In CRPS (Schwoebel et al., 2001, Reinersmann et al., 2010, Moseley, 2004b) and upper limb musculoskeletal pain (Coslett et al., 2010b) accuracy was normal but reaction time was increased. In selective lower limb conditions studies (Stanton et al., 2012a), low back pain (Bray and Moseley, 2011, Bowering et al., 2014a) and carpal tunnel syndrome (Schmid and Coppieters, 2012), participants presented with normal reaction time, but decreased accuracy. However, accuracy was decreased in all lower limb conditions (Stanton et al., 2012a, Stanton et al., 2013b, Coslett et al., 2010a). This suggests a disrupted body schema, whereby even though the brain confirms whether a pictured limb is left or right, an incorrect decision is made (Stanton et al., 2012a). Differences between impaired reaction time in CRPS and upper limb pain compared to impaired accuracy in lower back pain could be due to the back being a single unit compared to the limbs (Bowering et al., 2014b). Furthermore, in lower back pain and carpal tunnel syndrome pictures of posture (trunk and neck), rather than an anatomical region were presented (Bowering et al., 2014b). This could possibly lead to differences in results. However, further research is needed to determine these contributing factors. Cervical pain results cannot be commented on as in one study there was no difference in reaction or accuracy between people with whiplash injury and healthy individuals (Pedler et al., 2013). Another study showed increased accuracy in people with whiplash (Richter et al., 2010), while Elsig et al. (2014) only measured accuracy (which was decreased), but not reaction time.

5.7 Implicit versus Explicit Tasks

All laterality judgment tasks included in the studies of this systematic review were implicit tasks, whereby participants were not asked to imagine the movement of the pictured limb. This is important as Moseley et al. (2008) found that an explicit task of telling participants to mentally manoeuvre their limbs and imagine themselves performing the movement actually increased pain

and swelling. Due to the implicit nature of the task, participants are merely asked whether the depicted image is left or right (Coslett et al., 2010a). However, this viewpoint is challenged in Bray and Moseley (2011). The authors propose that initially laterality is explicit, i.e. the participant is aware that they are mentally rotating their limbs to match the pictured limb. After a practice round (approximately 80 pictures), the task now becomes implicit (Bray and Moseley, 2011). This is proposed due to evidence supported by imaging studies (Moseley et al., 2003). Initially, laterality judgment activates the premotor, supplementary motor and primary motor cortices as well as the posterior parietal and sensory cortices. However, after a practice round, only the premotor and supplementary motor cortices are activated (Moseley et al., 2003). This evidence influences all studies in that a practice run was not used for all studies and well as some studies used less than 80 pictures to test laterality judgment. Therefore, it is evident that standardised protocols for laterality judgment tasks should be formulated for future studies.

Furthermore, the laterality judgment task can be used as an objective measure of pain, without expliciting asking participants for a pain rating (Coslett et al., 2010a). This would prove to be more relaible and valid, compared to subjective ratings of pain (Schwoebel et al., 2001). Subjective ratings of pain can be influenced by psychological factors such as attitudes, beliefs and emotions. It can be speculated that due to the implicit nature of the task, the influence of these psychological factors may be minimised (Coslett et al., 2010a). Other strengths of the laterality judgment task include that it can be quickly administered, on average 10-12 minutes (Coslett et al., 2010b). Laterality judgment tasks are inexpensive. They can be run without a computer (i.e. with stock images) and do not require any other equipment (Coslett et al., 2010b). Furthermore, in all studies all participants understood and could complete the task without any discomfort. However, evaluation of laterality judgment in the future needs to include assessment of other chronic pain variables such as anxiety, depression and catastrophising.

5.8.1 Limitations of the Studies

When looking at laterality judgment performance of various populations, there are certain confounding variables that need to be taken into account. The variable of age of participants has inconsistent findings in literature. It has been shown that older age people have a decreased accuracy and reaction time in laterality tasks (Wallwork et al., 2013, Saimpont et al., 2009). However, in two studies (Stanton et al., 2012a, Stanton et al., 2013b) healthy individuals were significantly younger

than the pain groups, and this did not have any effect on accuracy. Although the link between age and laterality judgment performance is unclear, it is superior to have pain and healthy participants matched in terms of age.

In two studies that looked at laterality judgment of people with knee pain (knee osteoarthitis), pictures of feet, rather than knees were used (Stanton et al., 2012a, Stanton et al., 2013b). This was done due to the difficulty of identifying pictures of other lower limb parts, other than feet. It is also based on the notion that placing the feet on the ground is a fundamental and grounding function in lower limb movements. However, it is unknown whether people with knee pain would respond better to pictures of full lower limbs (knee, lower limb and foot). On the other hand, in lower back pain and carpal tunnel syndrome pictures of posture (trunk and neck), rather than an anatomical region were presented (Bowering et al., 2014b). This could possibly lead to differences in results.

Furthermore, in all studies there is no standardisation of laterality tasks, i.e. number of trials, number of pictures used and the use of a practice run. This factor leads to high variability between studies, and could lead to conflicting results. Some studies used an instrument called "Recognise Online" while others used stock images. Recognise Online has been commonly used clinically in low back pain (Bray and Moseley, 2011, Bowering et al., 2014b, Linder et al., 2016), osteoarthritis of knee (Stanton et al., 2012a) and whiplash syndrome (Elsig et al., 2014, Pedler et al., 2013). Two studies have reported good to excellent test-retest reliability for all measures in the Recognise Online programme (Bray and Moseley, 2011, Dey et al., 2012). However, this is possibily the greatest limitation in studies in that interpretation of studies are difficult due to the great variablility in laterality tasks.

5.8.2 Limitations of the Meta-analysis

There were different methods of reporting data in the various studies. This caused great difficulty obtaining the required information for meta-analysis, and consequently many studies had to be reviewed in a narrative form.

5.9 Conclusion to the discussion

In this chapter the results of CRPS 1, upper limb pain, low back pain, cervical pain and lower limb pain were discussed in detail. In each study factors relating to laterality judgment such as hand dominance, age, study design and specific factors influencing laterality judgment were discussed.

The next chapter will synthesise the above evidence, discuss the implications of clinical practice and provide recommendations for future research.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH

6.1 Conclusion

The aim of this systematic review was to determine whether there are differences in laterality judgment between people with chronic pain and healthy individuals. Meta-analysis and a narrative review was done of all respective studies. Results showed laterality judgment impairement in some chronic pain syndromes. In CRPS, upper limb pain and carpal tunnel syndrome there is sufficient and quality evidence demonstrating laterality judgment impairment. Osteoarthitis of the knee and leg pain also showed sufficient and quality evidence that there are laterality judgment impairments in this population. In low back pain, one study was a low quality study. Although it was included in this review, one must be cautious with its results. Due to the lack of studies, low quality of evidence, and differences in results between studies; there are inconsistencies with regard to low back pain and therefore no conclusions can be drawn from the literature. Furthermore, whiplash associated disorders do not have laterality judgment impairments while there is no consensus in the literature with regard to non-specific chronic cervical pain.

This study fits into the growing body of research regarding laterality . Further studies need to be conducted in various chronic pain conditions to determine the efficacy of laterality judgment impairment in each population.

6.2 Implications for Practice

There is a need to look at central mechanisms that may be contributing to the chronicity of pain, in order to decrease chronic pain. Therefore, clinical practice should also focus on programmes that address these central mechanisms. Laterality training can aid in this aspect as well as a graded motor imagery programme. This can be used in patients with CRPS 1, upper limb pain, carpal tunnel syndrome, osteoarthritis of the knee and leg pain. Laterality training reinstates left and right concepts in the brain. The activation of motor and somatosensory cortices (similar to that of executed movement) can activate cortical networks, reorganise the cortex, improve neural plasticity and in turn decrease chronic pain. However, laterality training and graded motor imagery should not be used in isolation, but rather as a comprehensive and holistic treatment programme for chronic pain.

6.3 Recommendations for Future Research

In future studies it is recommended that authors report their data in standard formats such as mean and standard deviation of reaction time and accuracy. This will enable data to be pooled into a meta-analysis. Contacting authors can prove to be a major challenge in systematic reviews, and many authors have either destroyed their raw data or do not have the time to find them. Standardised protocols need to be formulated for the use of laterality . This would include standardised pictures, use of a practice run and number of trials. Variability of these factors leads to high heterogeneity between studies and therefore difficulty in interpretation and met-analysis.

It has been suggested that laterality measures can be used as a measure of pain, without actually asking for a pain rating. Unlike subjective ratings of pain, which are largely influenced by psychological factors due to its implicit nature, laterality judgment is not. Furthermore, it can be easily understood and quickly administered (average 10-12 minutes). Laterality judgment tasks are inexpensive. They can be run without a computer (i.e. with stock images) and do not require any other equipment (Coslett et al., 2010b). However, there has been no study conducted regarding the reliability between using a computer and manual testing. Further research needs to be conducted on this aspect.

Further research needs to be done in the field of laterality and chronic pain syndromes. It is evident that the impairment of laterality cannot be assumed amongst all chronic pain conditions. Therefore, randomised controlled trials need to be performed in different chronic pain conditions, to determine the efficacy of laterality tasks in each population. Some specific conditions such as low back pain need to be further subdivided by classifying low back pain according to their pain mechanisms, and determining the laterality judgment impairments thereof. Exploring these central features of chronic pain could be the missing link in understanding chronic pain syndromes and their rehabilitation. Research should also be done in CRPS 2, as it is distinctly different from CRPS 1 and therefore the results cannot be generalised between these syndromes. Future evaluation of laterality judgment also needs to include assessment of other chronic pain variables such as anxiety, depression and catastrophising. These variables are not assessed and are known to impact grossly on recovery. Furthermore, there are missing links in the research with regard to the relationship between reaction time and accuracy, as well as the relationship of confounders such as age. This systematic review can be used as a foundation for future research: research studies can be designed to remediate

laterality judgment in affected conditions and assess the effect hereof on levels of pain and functional abilities. Clinicians can also gain insight on incorporating techniques (e.g. graded motor imagery) to re-train the brain's neural plasticity, and in turn decrease chronic pain.

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APPENDIX

Appendix A: JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Reviewer_____ Date_____

Author_____ Year_____ Record Number _____

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	□	□	□	□
2. Were the study subjects and the setting described in detail?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were objective, standard criteria used for measurement of the condition?	□	□	□	□
5. Were confounding factors identified?	□	□	□	□
6. Were strategies to deal with confounding factors stated?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was appropriate statistical analysis used?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments (Including reason for exclusion)

_____

_____

_____

Appendix B: JBI Data Extraction Form for Experimental/Observational Studies

Reviewer _____ Date _____ Year __ Record Number __
Author _____
Journal _____

Study Method RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Ot ☐

Participant
Setting _____
Population _____
Sample size
Intervention 1_____ Intervention 2_____ Intervention 3 _____

Interventions
Intervention 1: _____
_____
Intervention 2: _____
_____

Intervention 3: _____
_____

Clinical outcome measures

Outcome Description	Scale/measure

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) mean & SD	Intervention ( ) mean & SD

Authors' conclusions: _____

_____

Comments: _____

_____

_____

Appendix C: Ethics Waiver

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: P V Tobias Health Sciences Building, 2nd floor
Tel +27 (0)11-717-2700 / 1234 / 1252 / 2656
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265
South African National Health Research Ethics Council registration: REC-250208-04
United States Office of Human Research Protections registration: FWA00000715 IRB00001223

Ref: W-CJ-160505-1 05/05/2016

TO WHOM IT MAY CONCERN:

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).

Investigator: **Sadiya Ravat (student no 358548)**

Project title: **Can laterality judgement performance discriminate between people with chronic pain and healthy controls? A systematic review.**

Reason: This is a systematic review using information in the public domain. There are no human participants.

UNIVERSITY OF THE WITWATERSRAND
PROF PE CLEATON-JONES
HREC (MEDICAL)
2016 -05- 05
JOHANNESBURG

Professor Peter Cleaton-Jones

Chair: Human Research Ethics Committee (Medical)

Copy – HREC (Medical) Secretariat: Zanele Ndlovu, Rhulani Mkansi.