The Effect of Chronic Pain on Human Cognitive and Sensorimotor Systems

by

Anwer Zohaib Siddiqi

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Centre for Neuroscience
University of Alberta

Abstract

Chronic pain (CP) is a debilitating disorder that has a multitude of potential etiologies as well as numerous effects on the central and peripheral nervous systems. Even though CP is highly prevalent, these etiologies and effects are often misunderstood, which has led to a lack of adequate treatments for the disorder.

In this thesis, we sought to investigate the effect that CP has on the cognitive and sensorimotor systems in the human brain. In the first project, we examined whether CP has a disruptive effect on cognition and if so, what effect this would have on quality of life and disability. We used a battery of neuropsychological as well as clinical measures to show that patients with CP do indeed have cognitive dysfunction and that this dysfunction predicts a lower quality of life and higher pain related disability. This knowledge could increase focus on therapies that target improving cognitive function and emotional health in addition to physical treatments for CP.

In the second part of this thesis, we investigated a specific CP disorder, Complex Regional Pain Syndrome (CRPS). CRPS is unique in that it has motor, as well as neurocognitive, abnormalities. Using a paired pulse protocol of Transcranial Magnetic Stimulation (TMS), we examined if participants with CRPS have changes in the excitability of inhibitory circuitry within the primary motor cortex (M1). In addition, we piloted the efficacy of an innovative therapy, known as Graded Motor Imagery (GMI), and examined its potential neuroplastic mechanisms. In our preliminary results from five participants with CRPS, there appeared to be normal recruitment of inhibitory circuitry in M1compared to sex and age-matched controls. In the two participants with CRPS that

were tested, GMI produced a reduction of pain and also an increase in the maximum amount of M1 inhibition activated by TMS. This pilot project provides introductory evidence that reductions in pain from GMI may be associated with increases in the excitability of inhibitory circuits in M1. Further research in a larger group of participants with CRPS is needed to make definitive conclusions.

The results of these studies demonstrate that CP can have widespread cortical effects, which should be taken into account in the diagnosis, treatment, and management of patients with the disorder.

Preface

This thesis is an original work by Zohaib Siddiqi. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board and Alberta's Health Research Ethics Board, Project Names "The Effect of Chronic pain on Attentional capacity and Quality of Life", No. Pro00034945, December 20, 2012 and "Sensorimotor Reorganization from Mirror Box Therapy in Patients with CRPS, No. Pro00046485, May 1 2014.

To my family.

If I have seen further than others, it is by standing upon the shoulders of giants.

-Isaac Newton

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Table of Contents

List of Tables

Chapter 2: Cognitive Disruption in Pain

Chapter 3: Sensorimotor Reorganization in Complex Regional Pain Syndrome

List of Figures

Chapter 1: Introduction and Background

Chapter 2: Cognitive Disruption in Pain

Chapter 3: Sensorimotor Reorganization in Complex Regional Pain Syndrome

Chapter 1

Introduction and Background

1.1. Forward

A five-year old boy presented to his physician with mutilated fingers and toes, a wound on his knee infected with maggots, and chronic inflammation in his ankle; the boy was diagnosed with congenital insensitivity to pain syndrome (CIP) (Rahalkar, Rahalkar, & Joshi, 2008). This is a rare disorder that results from a genetic mutation and causes the complete absence of nociception[1]. Because patients with CIP cannot detect their own injuries, the wounds refuse to heal and the patients (usually children) are frequently brought to the hospital by their parents.

A 52-year old woman presented to her physician with intense muscle spasms and diffuse pain, increasing over time (DallAgnol, Pascoal-Faria, Barros Cecilio, & Correa, 2015). She had been suffering from post-partum depression and a severe cold but had not suffered any physical injury; she was diagnosed with fibromyalgia, a devastating chronic pain (CP) disorder that can lead to pain, fatigue, depression, anxiety, and low quality of life. Almost 50% of patients at primary care centers present with chronic pain and of these up to 40% are passively or actively contemplating suicide (M. T. Smith, Edwards, Robinson, & Dworkin, 2004) .

These two case studies and the disorders they reflect illustrate complex spectrum of the phenomenon of pain; each extreme being destructive to those afflicted. For centuries, physicians, psychologists, and philosophers alike have attempted to clearly describe the perception that is "pain" but have been unsuccessful. The most commonly used definition of pain remains the one proposed by The International Association for the Study of Pain (IASP): an "unpleasant sensory and emotional experience association with actual or potential tissue

[1] Nociception if "physical/sensory" pain due to activity of receptors and nerve fibers in response to potential harmful stimulation of the body (Marchand, 2012).

damage, or described in terms of such damage" ("Pain," 2015). In the last decade, novel research has shown that the experience of pain is more complicated than this definition would suggest. While originally thought to be a physical, aversive experience following injury, it is now known that this is too simplified of an explanation, and in many cases completely inaccurate. In patients with CP, pain is present even when the physical injury has completely resolved or never existed in the first place (consider the case of the 51 year old woman). At the same time, treatments such as Cognitive Behavioral Therapy and meditation have been effective where pharmacological and invasive therapies that target nociception have failed. These observations have brought light to the fact that the experience of pain begins and ends in the brain.

This thesis will describe pain, especially CP, from this very perspective. Two projects were performed to investigate the diffuse effect of pain on cortical systems. The first study investigated whether CP can affect the human cognitive system by disrupting attention and working memory. Considering the connection between pain and cognition is not only essential in understanding the multifaceted nature of pain, but also understanding how devastating CP can be to the quality of life of individuals affected. The second project, while still preliminary, focused on one specific CP disorder: Complex Regional Pain Syndrome (CRPS). This is a devastating condition that has been misunderstood and mistreated for decades. Using an innovative protocol, the project examined the changes that have occurred in the primary motor cortex (M1) of patients with CRPS while simultaneously investigating the efficacy and mechanisms of a novel treatment. These studies will allow us to learn more about the etiology and effects of CP syndromes as well as aim to guide further treatment approaches. In addition,

they hope to elucidate further the complex nature of the experience of pain and demonstrate that the current IASP definition is insufficient.

1.2. Models of Pain

In order to understand the perception of pain, it is important to first discuss the evolution of models of pain and how they have shaped our current understanding. The first influential model of pain was proposed by Rene Descartes in the 17th century (R. K. Melzack, J., 2004). Descartes saw the human body as a machine that can be studied experimentally. He believed that the skin was attached to a central area (brain) with a "thread", much like a rope is attached to a bell; when the skin is exposed to an intense stimulus (such as fire) the rope is pulled, causing the bell to be struck and pain to be experienced **[Figure 1.1].** While this idea may seem overly simplistic, it stimulated the inception of the *Specificity Theory of Pain* in the 1950s. The basis of this theory was that pain is transferred to the brain in a specific, direct spinal pathway. Specificity theory suggested that pain is completely proportional to the size of a peripheral injury and left no room for the idea that past experiences and emotion could affect pain. This in turn led to physicians treating CP solely through the use of peripheral nerve lesions; as these treatments failed, faith in the specificity theory dropped (R. K. Melzack, J., 2004).

Arguably the most influential theory of pain was proposed by Melzack and Wall in 1965 (R. Melzack & Wall, 1965; R. K. Melzack, J., 2004). *The Gate Control Theory of Pain* stated that a "gate" in the spinal cord, specifically, the dorsal horn, modulates the nerve impulses that travel from sensory receptors to the brain. This gate is influenced by large and small diameter

fibers that close and open it respectively as well as descending impulses from the brain[2] (central control). According to the theory, all of these inputs summate when they reach the "transmission (T) cells", and if the summation reaches a certain threshold, the "action system" becomes activated and the perception known as "pain" is experienced **[Figure 1.2].** This model was the first to discuss the importance of higher order brain functioning in regards to pain. Based on his Gate Control theory, Melzack later developed the McGill Pain Questionnaire, the only measure of pain which describes it in terms of *motivational-affective* and *cognitive-evaluative* dimensions as well as the traditional *sensory-discriminative* dimension (R. Melzack, 2005).

While the Gate Control theory was a landmark development in the areas of pain and chronic pain, it still left some outstanding issues. The main threat to this theory was the clinical observation that amputees experience "phantom limbs", limbs that have been removed but feel as though they are still attached and under the control of the amputee (R. Melzack, 1990; Ramachandran & Hirstein, 1998; Ramachandran & Rogers-Ramachandran, 2000). Interestingly, many of these patients experience excruciating, inexorable pain in these phantom limbs, termed "phantom limb pain", that does not respond to pharmacotherapy or even surgical interventions (R. Melzack, 1990). The Gate Control Theory could not effectively describe a phenomenon that did not result from input to the dorsal horn (R. Melzack, 1999; R. K. Melzack, J., 2004).

The issue of phantom limbs led to a more brain-based approach to pain (R. Melzack, 1990, 1999). It became clear that widespread cortical and sub-cortical regions were relevant in

[2] Central factors that may affect the gate include but are not limited to: previous experience, attention, and affect (R. K. Melzack, J., 2004).

the experience of pain. Melzack proposed that there are neural processes that exist in our brain that are activated and modified by inputs, but do not need these inputs to function. For example, the right arm is represented by a certain cortical network, one that functions with or without the arm's attachment to the body. Even after the right arm has been amputated, it is experienced and endures as a phantom limb because the cortical network for its representation still exists. Pain also exists as a neural network and can be experienced with or without an input (R. Melzack, 1990, 2001; R. K. Melzack, J., 2004). Melzack also suggested that humans conceptualize their body as a "self" which is distinct from the external environment and other humans. This feeling of "self" cannot arise from neural processes in the peripheral nervous system or spinal cord and must exist in the cortex. The "body-self" is ingrained due to genetics and therefore cannot be ignored; however, it can and is modified by experience. It is these conclusions that led to the advent of the *Neuromatrix Model of pain* (R. Melzack, 1999, 2001; R. K. Melzack, J., 2004).

The "body-self" is centered in widespread, cyclical neural circuits that travel around the cortex, thalamus, and limbic system. The **neuromatrix** is the name given to the anatomical substrate of the body-self, an entire network of circuits and synaptic links that is genetically ingrained and modified by experience **[Figure 1.3]**. Cyclical divergent and converging processing through the circuits in the neuromatrix gives rise to a characteristic pattern of activity, the **neurosignature**. This neurosignature is genetically predetermined, varies from person to person, and is structurally plastic over time. Take the example of the neurosignature of the arm. The brain has certain circuits that represent the arms somatosensory and motor function (that is to say, the arms "identity") which were originally determined by the individual's genetic code. This neurosignature changes over time depending on what

environmental conditions the arm is in, how the arm is used, etc. After amputation, the neurosignature has not yet been altered in the brain, giving the illusion that the limb still exists. Inputs from the body give rise to and modify a plethora of different neurosignatures. In the case of Pain Neuromatrix, there exists a network of neuroanatomical regions that become active during an individuals perception of pain, with or without a peripheral stimulus. Each facet of pain is coded for by different neurosignatures, which vary between individuals and are highly malleable (R. Melzack, 1999, 2001; R. K. Melzack, J., 2004). The neuromatrix model of pain will be especially relevant when discussing the cortical plasticity that occurs in Complex Regional Pain Syndrome and how this plasticity can be reversed.

1.3. Chronic Pain (CP)

Recall the case of the 51-year old woman described in the forward; this woman was in constant, persistent agony, despite not having any clear injury (DallAgnol et al., 2015).

The IASP defines CP as "current continuous or intermittent pain or discomfort which has persisted for more than three months, with recent or frequent seeking of treatment or use of analgesic medication" (B. H. Smith, Hopton, & Chambers, 1999). Estimates of the prevalence of CP (using the IASP definition) range from 11.5% to 55.2% of the population (Harstall & Ospina, 2003). The most common forms of CP are those that affect the limbs and joints but the back, neck, and head are also common sites. Diagnosis of CP can be difficult because many patients present with pain at different sites as well as have co-morbidities. Further, because pain cannot be measured except from individual reports, patients are often misdiagnosed as malingering or drug seeking. CP is devastating not just because of the noxious physical experience that an individual is forced to live with but also for psychological and social factors.

Many patients experience social withdrawal and isolation and develop problems in interpersonal relationships (B. H. Smith et al., 1999). The total cost of CP in the United States in 2010 ranged from $261 to $300 billion; this was greater than the cost of heart disease, cancer, or diabetes (Gaskin & Richard, 2012). Because CP syndromes are not clearly understood, they are often dealt with from a dualistic approach; that is to say, physicians attempt to separate "psychogenic" from "somatic" pain thereby creating a distinction between the mind and the body (B. H. Smith et al., 1999) . This leads to lack of comprehensive, adequate treatment approaches for a disorder that involves physical, emotional, as well as cognitive factors. Pharmacotherapy is the most common treatment for CP and involves typical analgesics such as opioids as well as atypical ones that include antidepressants and anticonvulsants (B. H. Smith et al., 1999). While opioids are the most effective analgesics for post-surgery pain, they are accompanied by rapid dependence and tolerance as well as potent adverse effects (Ballantyne, 2015). There is evidence that suggests that antidepressant and anticonvulsants are effective for CP and may have fewer side effects. Invasive therapies such as nerve blocks have also been used but they often have a short-term effect and are accompanied with greater risks (B. H. Smith et al., 1999). Physiotherapy is often used for CP but the evidence for efficacy is conflicting with some studies showing that it is no better than placebo (B. H. Smith et al., 1999). Cognitive therapies have also been used and interestingly, seem to have the most therapeutic potential. These strategies aim to address the negative thoughts and beliefs that accompany CP and train patients to develop positive coping styles (Morley, Eccleston, & Williams, 1999; B. H. Smith et al., 1999). Even though it is not completely understood why cognitive therapies tend to be effective, it is evident that there is a clear connection between pain and cognition. In order to understand this relationship as well as its

importance, it is crucial to first analyze mechanisms of cognition and how they can be disrupted in CP.

1.4. Cognition

The most general way of describing cognition is as a group of mental processes that allow "external or internal inputs to be transformed, reduced, elaborated, stored, recovered, and used" (Brandimonte, Bruno, & Collina, 2006). Cognition involves a variety of higher-level functions such as attention, memory, reasoning, problem solving, and planning that are necessary for our formation of conscious experience. This section will specifically focus on the processes of *attention* and *working memory* as well as their potential mechanisms and neural correlates.

1.4.1. Models of Attention

In the 19th century, William James defined attention as the "the taking of possession by the mind in clear and vivid form, of one out of what seem several simultaneous objects or trains of thoughts" (J. H. S. Eric R. Kandel, Thomas M. Jessel, Steven A. Siegelbaum, A.J. Hudspeth, 2013). It was not until 1958 that the first influential theory of attention was proposed by Donald Broadbent (Driver, 2001). Broadbent's Filter Theory explained attention in two sequential steps. The first step involves the brain receiving information about a stimulus' physical properties (for example, hearing the pitch of a certain sound). The second stage involves the brain processing these properties and extracting more meaningful information (for example, recognizing a sound in a certain song). The first stage functions in parallel but has a selective filter that decides which properties will enter the second stage (Driver, 2001). The second stage

functions in a serial manner and is limited by the first. Broadbent used the metaphor of a Y-shaped tube to describe these two processes; **[Figure 1.4]** information enters through the Y portion in the shape of two balls, but if both balls enter at the same time, they will not be able to pass through the narrow opening, the filter (Broadbent, 1957). Broadbent's theory was effective at explaining the Cocktail Party Phenomenon[3], a major cognitive problem at the time, but was overly simplistic (Driver, 2001). The theory did not account for unattended information that enters below the level of consciousness. For example, in a dichotic listening task[4] in which certain words were conditioned with electric shocks, participants had an elevated galvanic skin response[5] to the conditioned words, even when they were not consciously attended. Further, an elevated galvanic skin response was even seen to synonyms of the paired words, which is evidence of higher level processing. Participants did not make a conscious response to these synonymous words (Driver, 2001) showing that information can enter as well as be processed without an individual's conscious awareness. Treisman modified Broadbent's theory to suggest that the perception of unattended stimuli is not completely filtered out, but attenuated (Treisman, 1969). Thus, unattended stimuli would enter the second stage but to less of a degree than the attended stimuli. Further, a stimulus that has personal significance (such as an individual's name or shock-paired word) is more likely to be attended to and perceived (Driver, 2001). The above models assume a channel-based capacity of attention (i.e. serial and parallel processing channels create bottlenecks on what is perceived). However, the limits on attention may be due to the capacity of a central processor (Kahneman, 1973). In this model, the central

[3] The problem of how a person can have a single, selective conversation with another while there are many conversations in the background (Driver, 2001). The selective conversation has more meaningful information.

[4] Two different sounds are played in each ear and participant has to respond to one (Gadea, Alino, Garijo, Espert, & Salvador, 2015)

[5] Measure of sympathetic activity (Driver, 2001) .

processor (brain) has a limited capacity but it can mobilize different networks and allocate different resources depending on the task. For example, in the Cocktail Party scenario, more central processing capacity is being devoted to the individual conversation versus those happening around.

1.4.1.1 Posner and Petersen Model

The model first proposed by Posner and Petersen in 1990 is the most recent model that looks at the specific attributes of attention (Petersen & Posner, 2012; Posner, 2014; Posner & Petersen, 1990). The model states that the attention system, while interacting with other systems in the brain, is still anatomically separate and is its own identity. It suggests that attention is the product of the function of various neural networks. Much like the Pain Neuromatrix (mentioned above), the neural networks of the attention system work in conjunction to integrate both top-down and bottom-up mechanisms[6]; deficits in one of the hubs of the system can cause the entire system to become disrupted. The Posner and Petersen model addresses three specific subsystems of attention: *orienting, alerting,* and *detecting/executive* (Petersen & Posner, 2012; Posner, 2014; Posner & Petersen, 1990).

1.4.1.1.1 Orientation

During visual **orientation**, *saccades* (eye movements) ensure that a target is brought into focus on the *fovea* to increase its acuity (Posner, 2014). However, it is also possible to shift attention toward a stimulus without changing eye position (covert shift). Orientation is crucial to vision as demonstrated by *change blindness* experiments. In these experiments, participants

[6] Top-down processing involves the use of previous knowledge and experiences in perceptual analysis whereas bottom-up processing is just the transfer of information from sensory input to motor output (Corbetta & Shulman, 2002).

watch a video of a scene; at some point in the video a drastic change (such as the entrance of a new character) occurs but without any cues (such as motion). Many participants do not report these changes showing the importance of visual cues to orienting as well as the importance of attention to vision (Posner, 2014).

There appears to be a dorsal and ventral neural network relevant in attentional orienting. The former involves shifting attention voluntarily (*top-down*) and is composed of the superior **parietal lobe** and **frontal eye fields**[7]. The latter is important in automatic shifting (*bottom-up*), specifically to salient and unexpected stimuli, and is strongly right lateralized, including the **temporo-parietal** and **inferior frontal** cortices; lesions to the ventral area are most often associated with *hemi-spatial neglect*[8] (Corbetta & Shulman, 2002; Posner, 2014). As will be discussed later, patients who have certain types of pain syndromes show symptoms of hemi-spatial neglect even though they have not had any clear neurological injury (Lotze & Moseley, 2007; G. L. Moseley, 2004b). Other areas relevant in orienting are the **superior colliculus** as well as **thalamus**, damage to which impairs selective attention (Posner & Petersen, 1990).

1.4.1.1.2 Alerting

The second component of the Posner and Peterson's model of attention is **alerting** or, the ability to maintain an alert/vigilant state. The process of alerting has been shown to be strongly dependent on the right hemisphere (Petersen & Posner, 2012). Lesions to this area cause hemi-spatial neglect, poorer performance on tasks that require vigilance, and decreased change in heart rate in response to warning signals (Posner & Petersen, 1990). The **norepinephrine**

[7] Frontal lobe region that receives input from visual centers and controls movement of the eyes (Corbetta & Shulman, 2002).
[8] A syndrome, often resulting from damage to the right parietal lobe, in which patients fail to respond to information from the contralesional visual field (Corbetta & Shulman, 2002).

pathway, which contains nodes in the **frontal** and **parietal** cortices, is crucial in processing warning signals, and therefore, in maintaining alertness (Petersen & Posner, 2012; Posner & Petersen, 1990). Norepinephrine has also been shown to be involved in the top-down control mechanisms of pain (Pertovaara, 2006).

1.4.1.1.3 Executive Control (originally called Target Detection (Posner & Petersen, 1990))

The third attentional network, the **executive**, is the system that is involved in the voluntary, controlled aspects of attention, that is to say, top-down processing (Fernandez-Duque, Baird, & Posner, 2000; Petersen & Posner, 2012; Rueda, Posner, & Rothbart, 2005). It brings an object into conscious awareness despite interference from other targets, thoughts, or feelings. In addition, it is responsible for inhibiting responses that are not valid in the particular circumstance, allowing the attention system to focus on the relevant task. The executive system is also important in conflict resolution, that is to say, choosing one response when another is present such as in the Stroop Task[9] (Rueda et al., 2005).

The Anterior Cingulate Cortex (ACC) seems to be the central hub of the executive system (Petersen & Posner, 2012; Posner & Petersen, 1990; Rueda et al., 2005). The ACC becomes active when a participant performs the Stroop task and event related potentials (ERPs)[10] originating from the ACC are larger during tasks involving more conflict (Rueda et al., 2005). Further, the greater the number of targets to be detected in a task, the greater the blood flow to the ACC (Posner & Petersen, 1990). It has been suggested that two separate

[9] A task that involves reciting different color names written in different colors (the word RED written in GREEN ink) (Petersen & Posner, 2012).
[10] Event-related potentials are small deflections in an electroencephalogram in response to certain stimuli (Sur & Sinha, 2009).

networks of top-down control exist: the 'fronto-parietal' and 'cingulo-opercular' (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Petersen & Posner, 2012). The **fronto-parietal** network is composed of the dorsolateral prefrontal cortex, intraparietal sulcus, and dorsal frontal cortex. These regions become active during task onset and are important in initiating and adjusting control over attention. The fronto-parietal network also includes the dorsal attentional system (Corbetta & Shulman, 2002) mentioned earlier (Dosenbach et al., 2008). The **cingulo-opercular** network is composed of the anterior prefrontal cortex, anterior insula, dorsal ACC, and thalamus. These regions are relevant in maintaining attention during the entire task **[Figure 1.5].** Together, these networks create a complex system of executive control (Dosenbach et al., 2008; Petersen & Posner, 2012). Dopamine and D1 receptors in the ventral tegmental area are the most likely neurochemical candidates relevant in executive attention (Rueda et al., 2005).

The executive system has now been broadened to encompass all forms of self-regulation/self-control (Fernandez-Duque et al., 2000; Petersen & Posner, 2012). This includes the avoidance of arousal to sexual stimuli, prevention of fear to frightening stimuli, and control of cravings during drug withdrawal (Petersen & Posner, 2012). All of the above neuroanatomical regions have been implicated in pain, especially in the emotional and cognitive aspects of its top-down control. Further, these regions have also often shown to be dysfunctional in chronic pain syndromes (Bushnell, Ceko, & Low, 2013).

The process of attention is further complicated by the existence of numerous sub-divisions, each of which can be disrupted by pain. In order to discover how disabling pain really is, it is important to look at each of these sub-divisions in turn, analyzing what they are, how they are tested, and why they are so crucial in maintaining our survival.

1.4.2 Types of Attention

1.4.2.1 Sustained Attention

According to DeGangi and Porges (1990), **sustained attention** is "the ability to direct and focus cognitive activity on specific stimuli" (DeGangi & Porges., 1990). There are two components to sustained attention: the duration of time over which performance can be maintained and how constant the performance is during that time. Lapses of attention may occur when performance on a task alternates between poor and normal (Sohlberg & Mateer, 1989). Sustained attention becomes relevant in everyday life during any long, tedious task such as driving for hours on a long, straight road or performing repetitive calculations while analyzing taxes. There are three stages to sustained attention: attention getting, attention holding, and attention releasing (DeGangi & Porges., 1990). Attention getting is the process by which an individual first *orients* as well as *alerts* to a stimulus. It is a top-down as well as bottom up process as it is dependent not on only on the salience of the stimulus but also on the individual's prior experience with the stimulus. For example, even though a car alarm might be louder, a song might get more attention from an individual due to its emotional significance. The next phase, attention holding, is the process through which attention is *maintained* on a novel stimulus; a measure of attention holding is the length of time that the stimulus is attended to. The final stage, attention releasing, is the "turning off" of attention to a stimulus. It could occur for a variety of reasons such as fatigue or a decrease in arousal levels. Sustained attention is important because it guides learning as well as allows individuals to respond to changing environmental demands (DeGangi & Porges., 1990).

An example of a test of sustained attention is the *continuous performance task*. Participants attend to a screen where 800 digits are sequentially presented to them for approximately 750 ms (Moore, Keogh, & Eccleston, 2012). They must respond with a key press if they see three odd or three even digits in order. Another example is the lottery task in the Test of Everyday Attention (TEA), which will be discussed later.

1.4.2.2 Selective Attention

As sustained attention is a measure of how long an individual can focus on a specific stimulus **selective attention** is a measure of how well an individual is able to select relevant information for conscious processing in the midst of distracting, non-relevant stimuli (Sohlberg & Mateer, 1989). An everyday activity that involves selective attention is reading a map and marking relevant locations while ignoring irrelevant ones. As discussed above, there are different theories on how the cognitive system selects for relevant information. Broadbent proposed a filter model that suggested that the process of attention is composed of "channels" that limit the amount of stimulus information that enters our conscious awareness, much like a bottleneck. Treisman's attenuation model suggested that the information about stimuli that enters awareness is differentiated based on the specific features of the stimuli; for example, an individual looking for a friend at a restaurant will attend to those features of individuals that are similar to his friends, such as black hair and red shirt (Sohlberg & Mateer, 1989; Treisman, 1969; Treisman & Gelade, 1980). The capacity model claims that there exists a central processor, the capacity of which is differentially allocated to different stimuli depending on their features or significance to the individual. The higher the arousal of an individual, the greater the capacity of the central processer (Kahneman, 1973). Because selective attention determines which information enters awareness and therefore memory, it guides learning and

development, especially during adolescence. Selective attention also decides which information is relevant in performing a specific task and thus guides how well a task is performed. Deficits of selective attention will not only lead to problems in learning new tasks but also performing old ones (Leong, 2013).

The most famous selective attention test is the Stroop Task (discussed above). Patients with head injury are mildly impaired on this task and have longer response times (Sohlberg & Mateer, 1989). A more complicated test of selective attention is the Flanker Task in which participants are presented with a fixation cross which is replaced by a target number surrounded ("flanked") by another number. The participant must indicate which is the target number as quickly as possible. When the "flanking" number is different from the target, the response time is larger (Moore et al., 2012).

1.4.2.3 Divided Attention

Divided attention measures an individual's ability to perform two or more tasks simultaneously (Sohlberg & Mateer, 1989). In this process, each task is attended to imperfectly, that is to say, with loss of information. This is due to the fact that both tasks compete for limited attentional resources. When there are more tasks to be performed, more capacity of the attentional system is taken up resulting in more task errors (Kahneman, 1973). Whenever more tasks need to be attended to, there is a cost of reaction time, accuracy, or both. The decline in performance when another task is added is measured by a value called dual-task interference (E.E. Smith & Kosslyn, 2006a). This interference is especially present when the two tasks involve the same modalities; for example, hearing words will hinder one's ability to remember numbers and scanning a map will hinder one's ability to remember a picture. One test that

examines divided attention is the Mills and Bisgrove task in which a person has to press a key when three consecutive odd or even digits are displayed. At the same time, the participant must indicate whether two lines that are in the periphery have different orientations (Moore et al., 2012).

A strong real-world example of divided attention is the task that air traffic controllers need to perform, namely, tracking multiple aircraft simultaneously (E.E. Smith & Kosslyn, 2006a). Tasks that measure divided attention are often the most complicated and can be most difficult for head injury patients (Sohlberg & Mateer, 1989). Deficits in divided attention cause significant impairments in quality of life as patients cannot do everyday activities such as cooking while listening to music. The syndrome of hemineglect (see above) is also a potential deficit in divided attention. Patients are unable to focus on both sides of space and attend only to one. They will ignore food on one side of their plate, only dress one side of their body, and even ignore sounds that are coming from a certain area in space. The example of hemineglect patients is a clear example of the importance of the ability to divide one's attention and the severe handicaps that can be caused by its disappearance (E.E. Smith & Kosslyn, 2006a)

1.4.2.4 Alternating Attention/ Attentional Switching

Alternating attention, also known as, **attentional switching**, measures an individual's flexibility in switching from one task to a different one that involves different mental resources (Sohlberg & Mateer, 1989). There is a clear difference between divided and alternating attention. In divided attention, resources are split between the different tasks that are being performed. For example, if a person is listening to music, doing an assignment, and smelling their lunch at the same time, part of their attention will be on music, part of it on their

assignment, and part of it on their lunch simultaneously. However, in alternating attention, a person will switch between devoting *all* of their attention to one task and then to another task. An example of this would be a person working on an assignment, then messaging a friend, then going back to their assignment (Sohlberg & Mateer, 1989).

Generally individuals take longer to perform experiment blocks in which tasks are constantly switching than when the task remains constant; this additional time is referred to as the *switching cost* (E.E. Smith & Kosslyn, 2006b). One model suggests that there are two levels of processing involved in attentional switching, task processing and executive processing; the latter influences the former (E.E. Smith & Kosslyn, 2006b). Take the example of an individual who must alternate between sorting his socks into a white and colored pile and then switch the task to sorting them based on size. In the task processing level, the individual recognizes the color/size of the sock and then decides which pile to put it in. In the executive processing level, the individual sets the goal of the task (sort by color or sort by size) and then sets rules to complete this goal (focus on color or focus on size). If the individual must constantly switch between the "sort color" and "sort size" tasks, he will be constantly changing the goal and rules of the task, leading to increased recruitment of the executive processing level and an eventual decrement in performance (E.E. Smith & Kosslyn, 2006b).

A famous task that is often used to assess attentional switching as well as executive functioning is the Windes Task (Eccleston, 1994, 1995). In this test, a participant is given cards with a certain number of digits on them. The participant must first say the digit that is on the card as quickly as possible. In the second part of the test, the rules are changed and the person must say the number of digits on the card; there is a switching cost here because the participant has a tendency to want to report the stronger stimulus (the digits instead of number of digits)

[Figure 1.6]. On the third part of the test, the participant must alternate between reporting the value of digits and reporting the number of digits without any prior cue. It is this third part of the Windes task that is especially difficult for patients with CP.

1.4.3 Working Memory

1.4.3.1 Baddeley's Model of Working Memory

Alan Baddeley describes working memory as "the systems that are assumed to be necessary in order to keep things in mind while performing complex tasks such as reasoning, comprehension, and learning" (Baddeley, 2010). The understanding of working memory is crucial in neuropsychology as it has shown to be highly correlated with reasoning skill as well as a good predictor of technical learning capacity, general intelligence as measured by IQ tests, and SAT scores (Baddeley, 1992; E.E. Smith & Kosslyn, 2006c). The model of working memory most relevant to this paper will be that proposed by Baddeley and Hitch in 1974 (Baddeley, 1992), which posits that even though storage is a function of working memory, it is only one of the functions of the system, the main one being the coordination of cognitive resources (Baddeley, 1992). According to the model, working memory is composed of two subsystems, the *phonological loop* and *visuospatial sketchpad*, controlled by a central executive. Recently, another component, the *episodic buffer*, was added (Baddeley, 2010) **[Figure 1.7].**

1.4.3.1.1 The Visuospatial Sketchpad

The function of the **visuospatial sketchpad** (Baddeley, 1998a) is to store information about an object's visual appearance and features as well as its spatial location (although there

may be a double dissociation between the areas of the brain that control these functions, the former controlled by the occipital lobes and the latter being controlled by the parietal (Goodale, Milner, Jakobson, & Carey, 1991)). This system is a measure of non-verbal intelligence and can be a predictor of success in fields requiring visuospatial manipulation such as architecture and engineering (Baddeley, 2003b). Further, the visuospatial sketchpad allows us to engage in visual imagery of written representations (recalling the verbal description of a room by keeping an image of the room in one's mind), a strategy which allows higher storage of information (Baddeley, 2003b). However, asking a participant to track a spot of light on a screen or engage in another visuospatial task can disrupt this imagery while keeping verbal working memory intact (Baddeley, 1992). The visuospatial sketchpad has a limited capacity, only being able to store and process three to four objects at once; this limitation has been proposed to be the cause of the change blindness phenomenon discussed earlier (Baddeley, 2003). It has also been shown to be strongly lateralized to the **right hemisphere** (E. E. Smith, Jonides, & Koeppe, 1996), specifically in the premotor, occipital, parietal, and prefrontal regions (Jonides et al., 1993).

1.4.3.1.2 The Phonological Loop

The **phonological loop** component of Baddeley and Hitch's model is responsible for verbal working memory; that is to say, it stores and manipulates speech-based information such as words in sentences or digits in the digit span task[11] (Baddeley, 1992, 1998a). The system has two main functions, the first, to store phonological (auditory) information for two to three seconds, and the second, to engage in an articulatory rehearsal process based on subvocal speech (Baddeley, 1992, 1998a, 1998b, 2003b). For example, when trying to learn a phone

[11] In this task, the participant repeats a sequence of numbers (Baddeley, 1998a).

number, an individual repeats the number several times in their mind, the process of articulatory rehearsal. The information is kept temporarily in the phonological store, constantly being refreshed by articulatory rehearsal, until it can be transferred to the individuals long term memory store (E.E. Smith & Kosslyn, 2006c)

Evidence of this system comes from the acoustic similarity affect, where recall of words is worse when they sound similar, the irrelevant speech affect, where recall of items is poor when task irrelevant words are heard, the world length affect, where recall of words decreases as the length of the words increases, and articulatory suppression, where recall is worse when a participant is told to repeat a task irrelevant word to prevent them from rehearsing the target word (Baddeley, 1992, 1998b, 2003b). The system is intimately linked to the language systems in the brain and has been proposed to be crucial in developing language in childhood as well as learning a foreign language (Baddeley, 1998a, 2003b). Children who perform better at the digit span task tend have better language development later (Baddeley, 1998a). There is much evidence to suggest that the phonological store component of this system is based in **Wernicke's Area** and that the sub-vocal speech component is based in **Broca's area**[12].

1.4.3.1.3 The Central Executive

The **central executive** component, already discussed earlier, is responsible for attentional control (Baddeley & Della Sala, 1996) and therefore control of the other two subsystems of the Baddeley and Hitch Model (Baddeley, 1992, 1998a, 2003b). The executive system seems especially important in dual-task performance, specifically those that involve use of the

[12] Wernicke's and Broca's areas are the major language centers in the brain the former being important in speech comprehension and centered in the tempero-parietal junction and the latter being relevant in speech articulation and centered in the frontal cortex (J. H. S. Eric R. Kandel, Thomas M. Jessel, Steven A. Siegelbaum, A.J. Hudspeth & 2013).

phonological loop and visuospatial sketchpad. Evidence from functional MRI suggests that the prefrontal cortex is relevant in performing these dual tasks (D'Esposito et al., 1995). Patients with Alzheimer Disease (AD) were asked to perform a motor tracking task (visuospatial) with a digit recall task (phonological). These patients perform much more poorly on this type of dual task compared to healthy aging participants. In a follow up study, it was found that the performance of patients with AD on dual tasks declined much more quickly compared to their performance on each task alone (Baddeley, 1998b; Baddeley & Della Sala, 1996). Patients with chronic pain show a similar profile; they can perform simple single tasks just as well as controls, but in difficult dual tasks that require alternating attention, performance falls drastically (Eccleston, 1995). Further, patients with CP also show grey matter degeneration in areas responsible for attention and working memory and this degeneration correlates with the length of time the patient has had pain for (Apkarian et al., 2004; Kuchinad et al., 2007; Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2009)

1.4.3.1.4 The Episodic Buffer

The **episodic buffer** was a recent addition to the Baddeley three-component model (Baddeley, 2000, 2003b). The episodic buffer is responsible for temporarily storing and integrating information from other systems as well as provides a temporary connection between the phonological loop and visuospatial sketchpad, allowing it to integrate verbal and spatial information. It is controlled by the central executive, which can decide which information enters through the mediums of attention and conscious awareness. It has been proposed that patients with long-term memory deficits still have the episodic buffer intact; therefore, the episodic buffer might be a temporary stage until information can be stored in long-term memory. This system can not only access new information in the environment but also create

novel cognitive representations, and therefore be crucial in problem solving (Baddeley, 2000, 2003b).

The addition of the episodic buffer provides a link between working memory, long-term memory, and conscious awareness. The neurobiological correlates of the episodic buffer are not clear, but the **right frontal cortex** seems a likely candidate as it becomes active during integration of verbal and spatial information (Baddeley, 2000).

1.4.3.2 Verbal and Spatial Working Memory

There is an important distinction between verbal and visuospatial working memory (Shah & Miyake, 1996). As described above, verbal working memory is responsible for storing and rehearsing phonological information such as words and digits (Baddeley, 2003a) . While tasks such as the digit span were traditionally used to assess verbal working memory, these do not correlate well with reading ability (Meredyth Daneman & Carpenter, 1980). Reading comprehension involves a more complex form of verbal working memory as the reader must store previous information to understand and integrate subsequent text. Verbal information can "decay" if it is not sufficiently rehearsed in a certain amount of time and can "displace" if other information is stored in the verbal working system to reach capacity. Verbal working memory is essential to the development of language. As children get older, a strong verbal working memory allows them to acquire new vocabulary as well as improve at repeating unfamiliar non-words (Acheson & MacDonald, 2009). One study found that children who have Duchenne's Muscular Dystrophy have impaired verbal working memory, which may limit their verbal IQ and consequently, performance in school (Hinton, De Vivo, Nereo, Goldstein, & Stern, 2001).

Visuospatial working memory, on the other hand, is responsible for storing information about the features ("where" pathway/dorsal stream) and location ("what pathway"/ ventral stream) of an object (Goodale et al., 1991; McAfoose & Baune, 2009; Zimmer, 2008). This system may also be able to store verbal information that was originally encoded in visual form. The visuospatial system is intimately linked to the executive function system (potentially even more than the verbal working memory system), which may be crucial in the active rehearsal process. Typically, four items can be stored but each item can have any number of features (McAfoose & Baune, 2009; Zimmer, 2008). The neuroanatomical correlates of spatial working memory overlap with those of spatial attention (frontal and parietal cortices) and lesions in these areas can interrupt both processes (Striemer, Ferber, & Danckert, 2013). Deficits in spatial working memory may contribute to the symptoms seen in patients with hemispatial neglect (see above). When patients have poor spatial memory, they are more likely to forget stimuli in the right side of space leading to a repetitive search strategy and inability to disengage attention (Malhotra et al., 2005).

Both the verbal and spatial working memory systems are assumed to have a finite storage capacity and structures compete for this limited storage (M. Daneman & Merikle, 1996). However, it has been found that there is no significant correlation between performance on reading tasks and performance on spatial tasks (Shah & Miyake, 1996). Tasks that disrupt visual information can affect performance on spatial tasks but not on verbal ones and irrelevant speech can disrupt performance on reading tasks but not spatial ones (McAfoose & Baune, 2009). In addition, there is a double dissociation between neural structures implicated in verbal working memory and those implicated in spatial working memory. Verbal working memory is strongly lateralized to the left hemisphere (E. E. Smith et al., 1996) with the storage portion

being localized in the left supramarginal gyrus and the rehearsal component in Broca's area (inferior frontal gyrus) (Paulesu, Frith, & Frackowiak, 1993). However, the spatial working memory system is more diffuse, being localized in the prefrontal, occipital, parietal, and premotor cortices. Recognizing object location is probably more centered in the parietal lobe (dorsal stream) whereas recognizing object features probably more in the temporal and occipital lobes (ventral stream) (Goodale & Humphrey, 1998).

Both verbal and visuospatial working memory relate to Kahneman's capacity model. If a task is more complicated and requires more processing, it will take up more storage space (Kahneman, 1973). Kahneman's capacity model suggests that the cognitive system is analogous to a toaster containing a slide of bread. When the bread (information) is inserted into the toaster (brain/cognitive system), there is an increased load on the electrical supply (cognitive resources). To compensate for this change, a "governer system" exists that increases power to maintain voltage. The greater the capacity of the toaster, the more the power supplied. However, the toaster can only supply so much power, and when the capacity increases beyond the limit, there is no longer any electrical input. The "capacity" of the cognitive system is equivalent to the "mental effort" exerted by an individual. The more difficult the task to be performed, the more effort is required by the individual. However, the amount of effort that can be exerted is limited; increasing task difficulty is accompanied by a decreasing increase in mental effort. The higher the demands of the task, the greater the difference between the effort the task requires and the effort actually provided by the system. Further, the greater the mental effort required of the system, the greater the chance that interference will occur between information (Kahneman, 1973). Because working memory is important in processing as well as

storing, individuals who have inefficient processing have smaller storage capacities because they are allocating more resources to processing (M. Daneman & Merikle, 1996).

1.5 Attention and Pain

As discussed above, the attentional system has a limited capacity and increasing cognitive load (by increasing the number of stimuli, task difficulty, etc.) steadily exhausts the resources available to process all of the information equally (Broadbent, 1957; Kahneman, 1973). When an individual is experiencing pain and performing a task at the same time, attention will be divided and/or switched between the two. If an individual is performing a task while experiencing low amounts of pain, the intensity of pain experienced will decrease due to attention shifting away from pain (distraction). However, if the individual performs the same task while experiencing intense, chronic pain, attention will be maintained on the pain and performance on the task will be decrease (Eccleston, 1994; McCaul & Malott, 1984).

1.5.1 Attentional Control of Pain

For centuries, there have been accounts of individuals forgetting an injury during an emotionally engaging event. Soldiers can often ignore grievous injuries on the battlefield when there are more salient stimuli to focus on but can react to relatively small surgical procedures after battle. Conversely, focusing on pain can increase the perceived intensity of the pain and experiencing negative emotions can increase its unpleasantness (Bushnell et al., 2013), hence showing the importance of attention to the perception of pain. Using the Windes Task, Eccleston showed that patients with CP who have low levels of pain can attain ‘distractional analgesia’ when performing a task of low difficulty (Eccleston, 1995). Another study showed

that patients with CP experience less pain even while completing a simple mechanical grip task (Schreiber et al., 2014). A systematic review of 11 studies has shown that virtual reality mechanisms of distraction, those that create artificial 3 dimensional visual environments, can not only reduce experimentally induced pain, but also that induced by burn injuries (Malloy & Milling, 2010). This is not just a change in subjective reporting of a decreased level of pain but a modulation of endogenous pain mechanisms. In one study, thermal pain was induced in healthy participants using a laser stimulator and ERPs were recorded (Friederich et al., 2001). Patients in the distraction group heard a short crime story while they were being stimulated. Amplitudes of the N200 and P320, electroencephalographic (ERP) measures of physical pain intensity, were much smaller in the distraction condition compared to the control one **[Figure 1.8].** Further, healthy pain-free individuals who distract themselves while receiving painful heat stimulation have significantly more activation in the periaqueductal gray (Tracey et al., 2002) and decreased activation in the thalamus, insula, and anterior cingulate cortex[13] (Bantick et al., 2002) as measured by functional magnetic resonance imaging (fMRI).

A review by McCaul and Mallot in 1984 discussed the effect that distraction has on pain and looked at the evidence supporting it. They concluded that the attention capacity model could explain the mitigation of pain through distraction if certain assumptions are met. The first assumption is that pain is a controlled process rather than an automatic one (that is to say, pain requires attention). The second assumption is that the distraction task must also be a controlled and not automatic process (for example, a when a person gets up from bed and brushes their teeth, while in pain, the pain will not be mitigated because the task is automatic, and will take up few attentional resources. The authors then go on to discuss four principles regarding the

[13] Areas that are part of the pain neuromatrix (Bantick et al., 2002; R. Melzack, 2001).

effect of distraction on pain (if the assumptions are met). Firstly, when an individual in pain performs a task, the experience of pain will be mitigated. Secondly, more difficult tasks (that use more attentional capacity) will have a greater effect on this mitigation. It is important to note that selective attention will always be imperfect; two stimuli will compete for attentional resources but one will never completely diminish another. This leads to the third principle, when experiencing pain and performing a task simultaneously, the processing of each will be mitigated. However, as the intensity of the pain increases, the effectiveness of the distraction decreases because more resources are being used to process the pain stimuli. The last principle suggests that at low pain intensities, distraction will be more effective than redefinition[14] for pain but at high pain intensities, the opposite will be true (McCaul & Malott, 1984).While these principles give a good outline of the relationship between the attentional capacity model and the experience of pain, McCaul and Mallot do not discuss what happens during a high pain and high difficulty task, which is what will be discussed next.

1.5.2 Cognitive Disruption in Pain

1.5.2.1 Attention Deficits

There are numerous studies suggesting that cognitive ability can be disrupted during an experience of pain. Some studies have used healthy controls who are exposed to painful stimuli while others have used patients with CP who are in pain at the time of the experiments.

[14] During a redefinition strategy, individuals experiencing pain are asked to attend to painful sensations from a non-emotional perspective. For example, they are asked to describe them using non-emotional words such as “strong pressure”, “throbbing”, or “cold” instead of “wretched”, “miserable”, or “unbearable” (McCaul & Malott, 1984).

One of the first studies to look at the effect of pain on skilled tasks was performed by Walker in 1971. She found that distraction did not decrease experimentally induced pain in participants but the pain did harm performance on a neuromuscular skilled task (Walker, 1971). In another study, thermal pain was induced in healthy participants when they performed a battery of tasks: continuous performance task (measures sustained attention), flanker task (measures selective attention), endogenous precueing task (measures ability to shift attention), n-back task (measures attention span/working memory), attention inhibition task (measures ability to stop a task given stimulus), attentional switching task (measures ability to switch attention between tasks), and divided attention task (measures ability to attend to two concurrent tasks). Compared to the control condition, participants experiencing pain performed worse on the n-back, attentional switching, and divided attention tasks but not on the others, suggesting that disability is task specific, and is especially present in complex tasks (Moore et al., 2012). In another study, participants performed significantly worse on an auditory discrimination task when exposed to an electrical pain stimulus (Crombez, Eccleston, Baeyens, & Eelen, 1996). When participants told that they will receive a high intensity stimulus, they perform more poorly on this auditory discrimination task compared to controls who are not, even though both groups are given the same intensity stimulus (Crombez, Eccleston, Baeyens, & Eelen, 1998). This is evidence that threat of a pain stimulus has an effect on cognitive function. In a similar experiment, authors showed that the cognitive disruption caused by the pain stimulus was somewhat mitigated when participants had habituated to the stimulus (Crombez, Eccleston, Baeyens, & Eelen, 1997). Cognitive disruption due to pain is especially evident during complex tasks that require goal-directed planning and executive function (Keogh, Moore, Duggan, Payne, & Eccleston, 2013). Collectively, these studies show that

induced acute/tonic pain disrupts cognition but other factors determine the extent to which this disruption occurs.

Studies have also found significant cognitive disruption in patients with CP. In one study, patients with CP and patients with traumatic brain injury both received scores well below the mean on tests involving motor speed, coordination, and immediate recall (Grigsby, Rosenberg, & Busenbark, 1995). However, patients with CP performed worse on tasks involving processing speed. In a landmark study, Eccleston asked participants with high pain, low pain, and no pain to perform different protocols of the Windes Task. The participants were first asked to perform consecutive trials of naming the value of digits on the cards, then take a one-minute break, then perform consecutive trials reporting the number of digits on the cards. All groups performed equally well on this version of the task **[Figure 1.9A].** However, in the second version of the task, participants were given two cards and asked to choose which card has the higher number or value. This task was of a greater difficulty and the performance of high pain participants greatly dropped **[Figure 1.9B]** (Eccleston, 1994). This is due to the fact that individuals with low pain have focus shifted away from their pain (distractional analgesia) but individuals with high pain have focus shifted away from the task, thereby decreasing performance (Eccleston, 1995). A study which used a version of the Stroop Test (measures selective attention) composed of different subtasks of varying difficulty found that response times were positively correlated with the difficulty of the task (J. M. Grisart & Plaghki, 1999). However, only patients with pain of high intensity had significantly higher response times. Even though participants with higher pain reported higher anxiety, this did not correlate with task performance. Another study found that only those patients who have high pain and high somatic awareness (more frequently report perception of bodily sensations) performed poorly

on tasks that demand attention (Eccleston, Crombez, Aldrich, & Stannard, 1997). This experiment shows that those individuals who are more likely to focus on their pain are more likely to perform poorly on tasks. These results are not just limited to the laboratory setting. Pain intensity correlated with attentional disability even when participants were completing a cognitive experiment from the comfort of their home (Attridge, Noonan, Eccleston, & Keogh, 2015). When participants with CP experienced headache, there is a general performance drop in performance on the n-back task, the flanker task, as well as the attentional switching task, rather than specific deficits (such as increased attentional switching cost) (Moore, Keogh, & Eccleston, 2013). Women experiencing menstrual cramps show a slower reaction time and worse performance on a range of tasks instead of a specific attentional deficit (Keogh, Cavill, Moore, & Eccleston, 2014). This is evidence that, in patients with CP, there is evidence of a general impairment compared to the deficit in specific attention processes that is seen when pain is induced experimentally.

It is possible that the patients with CP have an attentional bias to their pain that prevents them from focusing on the relevant task. When experimental pain is induced in participants, those with increased bias toward the pain (that is to say, an increased focus on pain-related words and pictures) benefit less from distractional analgesia (Van Ryckeghem, Crombez, Van Hulle, & Van Damme, 2012). At the same time, studies of attentional bias in pain have been conflicting and a meta-analysis showed that even though patients with CP may experience attentional bias toward pain, this bias has a small effect size. However, this effect size is larger for bias toward experimental pain (Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013). Some research has also shown that patients with CP have an attentional bias away from

pain and therefore, more research is needed to clarify this phenomenon (Crombez, Heathcote, & Fox, 2015).

1.5.2.2 Working Memory Deficits

As previously discussed, there are overlaps between the neuroanatomical regions underlying attention and memory (e.g. frontal cortex and executive system). Further, attention is needed for information to enter conscious awareness and therefore, to be held in working memory (Baddeley & Della Sala, 1996; Broadbent, 1957; Heuer & Schubo, 2016; Kahneman, 1973). Patients with CP often present with working memory deficits in addition to the attentional deficits described above. When patients with fibromyalgia were tested using the Wechsler Memory Scale (looks at verbal, visual, immediate, and delayed aspects of working memory), they performed significantly worse on the verbal and delayed components compared to healthy controls (Grace, Nielson, Hopkins, & Berg, 1999). Further, there was a significant negative relationship between pain severity and general memory scores. As mentioned before, it has been predicted that individuals with CP will perform worse on tests that involve controlled processes compared to automatic ones because the former involve more attention (McCaul & Malott, 1984). When individuals with fibromyalgia were asked to perform tests involving controlled (conscious recollection) and automatic processes of working memory, they performed worse on controlled processes compared to those who had localized pain as well as healthy controls (J. Grisart, Van der Linden, & Masquelier, 2002). In addition, fibromyalgia patients show much more impairment on working memory tasks when additional distractors, which compete for attentional resources are added (Leavitt & Katz, 2006). Deficits in working memory function occur irrespective of the pain condition and are not just confined to fibromyalgia; however, it is unclear if these deficits are present due to the pain itself

(Schnurr & MacDonald, 1995), or the depression associated with the pain (Landro, Stiles, & Sletvold, 1997).

1.5.2.3 Cortical Reorganization

While attentional bias may be a one of the causes of performance deficits on cognitive tests, there is much evidence to suggest that there may be a reorganization of the cortical cognitive system. In a study investigating the functional connectivity of the attention-pain network, participants who experienced pain while completing a cognitively demanding task had increased activation in their inferior frontal, superior parietal, premotor, and anterior insula regions compared to controls, even though their performance was the same (Seminowicz & Davis, 2007). This may suggest that pain causes recruitment of additional resources to compensate for the additional load on the cognitive system. In a fMRI study, it was found that, in patients with chronic low back pain, intensity of pain correlates with activity in the medial prefrontal cortex and duration of pain correlates with activity in the right insula **[Figure 1.10]** (Baliki et al., 2006). Another fMRI study found that chronic back pain patients have altered activity in their default-mode network[15] (Baliki, Geha, Apkarian, & Chialvo, 2008). Both patients and healthy controls performed a line-tracking task (involves attention) while lying down in an MRI machine. During the task, the fMRI signal was more deactivated in healthy controls compared to chronic back pain patients, even though both groups performed equally well on the task (Baliki et al., 2008). These results show that there has been a change in the functional connectivity (discussed in detail in *Chapter 4*) of a region that is important in memory and decision making (Euston, Gruber, & McNaughton, 2012). Another study showed

[15] Regions in the brain that have been shown to be active at rest and decrease their activity during task performance. Investigating the default-mode networks has revealed much about the functional connectivity of the human brain (Fox & Raichle, 2007).

that patients who have chronic pain due to hip osteoarthritis have a decrease in grey matter compared to healthy controls in the anterior cingulate cortex and dorsolateral prefrontal cortex (DLPFC) (Rodriguez-Raecke et al., 2009). The ACC has been implicated in executive functioning (Petersen & Posner, 2012; Posner & Petersen, 1990; Rueda et al., 2005) and the DLPFC is important in working memory (Barbey, Koenigs, & Grafman, 2013). Six weeks after a hip replacement surgery and consequent decrease in pain, grey matter volume went up in the same regions. A similar study was performed with fibromyalgia that showed the same grey matter loss but also included grey matter loss in the medial prefrontal cortex (Kuchinad et al., 2007). The authors found that the longer the patients were afflicted with fibromyalgia, the higher the decrease in grey matter. Further, patients had an accelerated grey matter loss, approximately 9.5 times faster than normal aging. Patients with chronic back pain show a similar profile with degeneration of grey matter specifically in the DLPFC (Apkarian et al., 2004). However, in another study, when mood disorders were controlled for, there were no differences in grey matter volume between fibromyalgia patients and healthy controls (Hsu et al., 2009). Together, these studies show that cognitive disruption in chronic pain may be due to cortical changes and potentially, subtle neurodegeneration.

1.5.2.4 Effects of Medication

While pain can reduce cognitive functioning, analgesia can possibly restore it. A nerve block procedure decreased pain and increased the amplitude of the mismatch negativity (MMN)[16] ERP when patients with CP were performing two difficult cognitive tasks (B. D. Dick et al., 2003). One study found that morphine induced analgesia decreased the amplitude of

[16] A negative deflection in the EEG elicited in response to a recognizable change in an auditory stimulus. It is a measure of auditory attention (Sur & Sinha, 2009).

laser evoked potentials, measures of nociceptive stimulation, as expected (Lorenz, Beck, & Bromm, 1997). However, it also improved performance on an auditory oddball task as well as increased the amplitude of the auditory P2 and P300[17], which are measures of selective and sustained attention **[Figure 1.11].** Evidence for the reversal of cognitive disruption by opioid treatment is conflicting. In some studies, treatment by opioids such as fentanyl and oxycodone has been linked to worse attention, working memory, and psychomotor speeds. However, in others pain relief due to opioid treatment is significantly correlated with improvement in cognitive performance (Kendall, Sjogren, Pimenta, Hojsted, & Kurita, 2010). In a cross-sectional study, 37 patients with chronic back pain who underwent long-term opioid therapy were compared to 33 patients with chronic back pain who did not undergo long-term opioid therapy as well as healthy controls (Schiltenwolf et al., 2014). As predicted, both pain groups performed worse on tasks examining working memory, attention, and executive functioning[18]. However, patients undergoing long-term opioid therapy performed significantly worse on tasks examining spatial memory capacity, working memory, and concept change. Further, this disability was correlated with pain intensity, depression, as well as use of medication. Therefore, more research is needed on the effects of opioid treatment as well as other medications on cognitive performance.

It is evident that there is a strong interrelationship between pain, attention, and working memory. However, the cognitive system does not stand alone in its relationship to pain and CP.

[17] The P300 is a positive ERP that is elicited between 250-400 ms, usually in response to auditory stimuli (Sur & Sinha, 2009).
[18] Mean intelligence in groups was not significantly different.

As evidenced by Complex Regional Pain Syndrome, CP can drastically affect the sensorimotor system as well, disrupting motor function and drastically increasing disability.

1.6 Complex Regional Pain Syndrome (CRPS)

CRPS, formerly known as Reflex Sympathetic Dystrophy, is a potentially debilitating condition that presents with several possible signs and symptoms. In many cases, the condition outlasts the original tissue injury. Many believe CRPS to be a form of neuropathic pain. The affliction is often localized in the upper or lower limbs and is divided into two subtypes: CRPS I, in which a nerve lesion cannot be identified and CRPS II, in which it can (Li, Smith, Smith, & Koman, 2005). In the acute stage, a limb affected by CRPS is often red, swollen, and painful **[Figure. 1.12A]** and can be markedly warmer or colder than the unaffected limb**.** After a few months, in the chronic stage, the limb can also become chronically warmer or colder with the limb presenting with mottled colouring, skin sloughing, and abnormal hair and nail growth **[Figure. 1.12B]**. Motor abnormalities, such as dystonia and tremor, can also develop in chronic patients **[Figure. 1.12C].** CRPS occurs after a variety of medical events including, but not limited to, fractures, bone injuries, stroke, or even myocardial infarction and can leave the patient severely disabled (Marinus et al., 2011). Many of these patients develop co-morbid psychological problems subsequent to the disease onset such as depression and anxiety, which can be related to increased disability (Huge et al., 2011). In Minnesota, USA, the prevalence of CRPS is 20.57 cases per 100,000 people with an incidence rate of 5.46 new cases per year. This would correspond to 58,000 existing cases and 15,000 new cases across the country every year (Bennett & Harden, 2003). Further, the upper limb is more likely to be affected than the lower limb (de Mos et al., 2007). Clearly defining the etiology of CRPS has confounded researchers

for decades, complicating diagnosis and treatment. CRPS was originally thought by many to be a result of a malfunctioning sympathetic nervous system, but when sympatholytic drugs are used, the pain does not recede in many patients (Drummond, 2010). Further, this pain can result from several events including stroke and myocardial infarction where the sympathetic nerves to the limb are initially untouched (Marinus et al., 2011).

1.6.1 Cortical Reorganization in CRPS

1.6.1.1 Evidence from Functional Imaging

Using fMRI and electrophysiological techniques, several studies have implicated central nervous system anomaly as a key factor in the development of CRPS. The phenomenon where regions in the brain have formed new connections and change in size, shift, or become hyperactive is called cortical reorganization (Ramachandran, Brang, & McGeoch, 2010; Ramachandran & Hirstein, 1998). In patients, representations of the affected, as well as non-affected, limbs in the primary somatosensory (S1) cortex have been noted to become re-organized which is associated with the amount of pain experienced (Swart, Stins, & Beek, 2009). When the fingers of patients with upper limb CRPS undergo tactile stimulation, magnetoencephalography has shown that the distance between the regions representing the thumb and little finger is shorter in the S1 contralateral to the affected limb compared to the ipsilateral one (Juottonen et al., 2002). Further, the area representing the affected hand is shifted toward the area representing the lip. There is a positive correlation between this reorganization in the affected cortex and the mechanical hyperalgesia and pain intensity experienced by patients (Maihofner, Handwerker, Neundorfer, & Birklein, 2003). Following recovery from CRPS, there is a positive correlation between increase in distance between the

regions representing the thumb and little finger and decrease in pain (Maihofner, Handwerker, Neundorfer, & Birklein, 2004). In a fMRI study where the fingers of the affected limb were mechanically stimulated, the regions representing the fingers in the contralateral S1 and secondary somatosensory cortex (SII) were shrunken compared to the ipsilateral representation (Pleger et al., 2005). Further, following behavioural therapy, pain intensity decreased and was associated with a restoration of contralateral S1 size.

In the primary motor cortex (M1), the region representing the affected limb has, in some reports, not shifted topographically but has become hyperexcitable. In one study, when patients performed a finger tapping task while undergoing fMRI, they were found to have increased activation in the M1 and supplementary motor cortex (SMA) representing the fingers of the affected limb compared to healthy controls (Maihofner et al., 2007). In addition, unlike controls, this activation was present in both hemispheres, suggesting that there may also be a change in transcallosal connections associated with this disease. When kinematic analysis was used to measure motor impairment, patients with CRPS took much longer to perform reaching movements with their affected limb than their unaffected limb, as well as the limbs of healthy controls. In addition, the degree of this motor impairment was positively correlated with activation in the posterior parietal cortex, M1, and SMA (Maihofner et al., 2007).

Transcranial Magnetic Stimulation (TMS), a technique that uses a changing magnetic field to stimulate focal regions of the cortex, has been useful at elucidating the excitability of cortical circuits in patients with CRPS. When the M1 of patients with CRPS is stimulated using paired-pulse TMS (*Chapter 3*), the excitability of GABAa-ergic inhibitory neurons is reduced in the M1 contralateral to the affected limb (Eisenberg et al., 2005) or even in the M1 of both hemispheres (Schwenkreis, Maier, & Tegenthoff, 2005). Further, the motor threshold is lower

in the affected limb of those who have allodynia compared to those who do not (Schwenkreis et al., 2005). Therefore, there is increased excitability in the M1 of patients with CRPS and this increase may be associated with the pain symptoms experienced.

1.6.1.2 Evidence from Clinical Testing

In patients with CRPS, functional imaging studies have shown the change in size of S1 and its association with pain and the hyper-activation in M1 and its association with motor dysfunction (Swart et al., 2009). Many of these patients also suffer from altered sensations, which, in some cases, can be evidence of cortical reorganization. In one study, using pinprick, body regions of patients with CRPS were stimulated. Patients experienced sensations not only in the area that was stimulated, but also in areas represented adjacently in S1. For example, if the finger was pricked, sensations would also be experienced on the cheek and if the foot was pricked, sensations would also be experienced on the knee (McCabe, Haigh, Halligan, & Blake, 2003).

CRPS is a condition that not only involves S1 and M1 but diffuse regions of the cortex. When patients looked at the reflection of their unaffected limb in a mirror, stimulation of an area on the unaffected limb that corresponded to a *painful region* on the affected limb caused pain in the affected limb. However, pain was not experienced when an area of the unaffected limb was stimulated that corresponded to a *normal region* on the affected limb. This phenomenon has been described as 'dysynchiria' [**Figure. 1.13**; (Acerra & Moseley, 2005)].

Some patients with CRPS also take longer to recognize their affected limb (G. L. Moseley, 2004b) and have their visual subjective body-midline (i.e., what a person perceives as the center of their visual field) shifted toward the affected side (Reinersmann et al., 2012),

suggesting that they may suffer from a phenomenon that, to some extent, resembles hemi-neglect (Lotze & Moseley, 2007). Together, this evidence suggests that higher visual cortical areas and the parietal lobe may be involved in the brain dysfunction that contributes to CRPS pathology (Cohen et al., 2013; Maihofner & Peltz, 2011). The interaction between these areas, M1, and S1 is not known. One hypothesis is that visual input can modulate sensitivity to tactile stimulation and modulate the activity of cells in the posterior parietal cortex (Ro, Wallace, Hagedorn, Farne, & Pienkos, 2004). Modulation of these cells may lead to activation of inhibitory neurons in S1 and even the thalamus, leading to decreased excitability in the S1 and M1 and visual input dominating tactile input [(G. L. Moseley, Gallace, & Spence, 2008)**; Fig. 1.14**].

1.6.1.3 Changes in the Pain Neuromatrix

The findings listed above relate to the concept of a *pain neuromatrix* (R. Melzack, 1990; G. L. Moseley, 2003). As discussed in *Chapter 1.2*, the neuromatrix is a network of cells that produces constant perceptual or motor output, with or without an input. In regards to the pain neuromatrix (includes the S1, Anterior Cingulate Cortex, Anterior Insula, Thalamus, and Posterior Parietal Cortex; (G. L. Moseley, 2003)), the entire network can become activated from a single stimulus. For example, the single stimulus of a needle pricking a finger would cause diffuse activation in the entire matrix. In the case of chronic pain, it is posited that the neuromatrix becomes highly sensitized and can become activated to increasingly irrelevant stimuli; a non-noxious touch, thinking about the limb, or even watching someone in pain (G. L. Moseley, 2004b; G. L. Moseley et al., 2008).

1.6.2 Graded Motor Imagery

Graded Motor Imagery (GMI), an innovative form of "training the brain" capitalizes on the pain neuromatrix theory. This therapy aims to retrain the motor circuits that activate the neuromatrix so that they become less sensitive to irrelevant stimuli. GMI uses exercises that activate these motor circuits, but does so in a way that is non-triggering to the pain neuromatrix (G. L. Moseley, 2003; G. L. Moseley, Butler, D.S., Beams, T.B. & Giles, T. J. , 2012). GMI is composed of three sequential stages, each of which progressively puts more load on the motor system, much like physiotherapy would on muscles. In the first stage, the participant looks at photographs of hands making different postures and must decide if they are photos of the left or right hand **[Figure. 1.15A].** An online program records the response time, accuracy, and amount of performance **[Figure. 1.15B].** This *implicit* (unconscious) motor imagery presumably activates regions in the premotor cortex, and is less likely to activate the pain neuromatrix compared to *explicit* (conscious) motor imagery (G. L. Moseley, Butler, D.S., Beams, T.B. & Giles, T. J. , 2012; G. L. Moseley et al., 2008). After the patient feels comfortable with the laterality recognition, they begin to imagine forming a posture with their affected hand in the same way as in the laterality photographs. In this second stage, using *explicit* motor imagery, there is activation of M1 circuits (G. L. Moseley, Butler, D.S., Beams, T.B. & Giles, T. J. , 2012). When the patient is ready, they move on to actually making movements with their limbs that mimic the limb postures observed. Therefore, in the third and final stage, the patient inserts the affected limb in the mirror box **[Figure. 1.16]**, so that it is hidden, and makes postures with the *unaffected* limb while focusing their visual attention on the reflection of the unaffected limb in the mirror. This creates the appearance to the brain of the affected limb moving without pain. The postures that will be adopted are the same as in the

photographs given in stage 1. When the patient feels comfortable, s/he can begin to move *both* limbs. During the third stage, there can be recruitment of a multitude of cortical areas including motor, visual, and parietal (G. L. Moseley, Butler, D.S., Beams, T.B. & Giles, T. J. , 2012)

To prevent exacerbations in pain and swelling, it is essential for the patient to begin each stage with as simple an exercise as possible and progress gradually from there. Further, the order of the stages is relevant to the recovery from the disease, suggesting that recovery may be due to sequential activation of cortical networks (G. L. Moseley, 2005). This step-by-step increase in the complexity of the exercises, as well as ordered activation of circuits, is the origin of the term *graded* motor imagery. As a consequence of the clinical trials that have been performed with GMI, there is Level II evidence (Daley & Bialocerkowksi, 2009) to suggest that it should be the treatment of choice for CRPS. GMI produced a 23.4% decrease in pain at the end of the 6 week program and this increased to 32.1% at the 6 month follow up as measured using the visual analogue scale [see **Appendix B:3]**. Patients who were receiving standard physical therapy had an 11.1% decrease at the end of 6 weeks and this did not change at 6 months (G. L. Moseley, 2005). A systematic review of 11 studies, including five clinical trials, showed that GMI had the highest significant clinical benefit for patients with upper and lower limb CRPS compared to physiotherapy or medical management (Daly & Bialocerkowski, 2009).

It is evident that pain is interrelated with both the cognitive as well as sensorimotor systems. When pain becomes maladaptive, in the form of CP, both of these systems can potentially become disrupted. Individuals who have CP present with deficits in working

memory and attention, which may be linked to altered structue or activity of gray matter. In CRPS, a specific type of CP syndrome, M1 and S1 can become reorganized and this correlates with the amount of pain experienced.

However, much remains unknown about the effect that CP can have on the cognitive and sensorimotor systems. It is still unclear to what extent pain intensity can predict cognitive deficits as well as what affect this can have on disability and quality of life. Further, few studies have been performed which look at the effect that GMI therapy may have on the brains of individuals with CRPS. This thesis sought to tackle these issues and by doing so, further elucidate the complex and debilitating nature of CP.

1.7 Figures

Figure 1.1: Descartes' Model of Pain. Pain is the result of a direct pathway between the skin (receptors) and a central area (brain).

Taken from *(R. K. Melzack, J., 2004)*

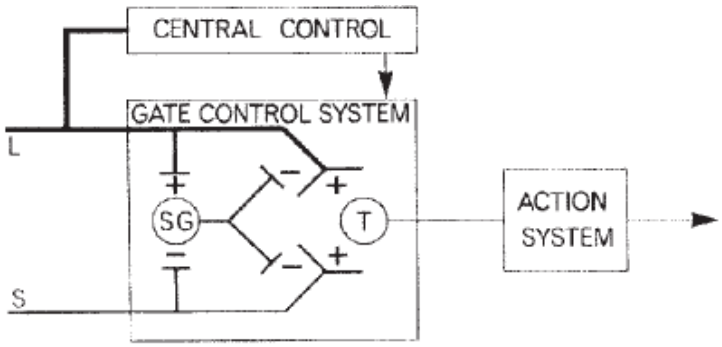


Figure 1.2: Gate Control Theory (R. Melzack & Wall, 1965). Large and small fibers synapse on the Substantia Gelatinosa in the dorsal horn of the spinal cord as well as the transmission (T) cells. Large fibers (-) close the gate and small fibers (+) open the gate. Large fibers can also modulate central control mechanisms, which in turn modulate the gate control system through descending inputs. The characteristic response of pain is experienced when output of the T cells exceeds a critical threshold.

Taken from *(R. K. Melzack, J., 2004)*

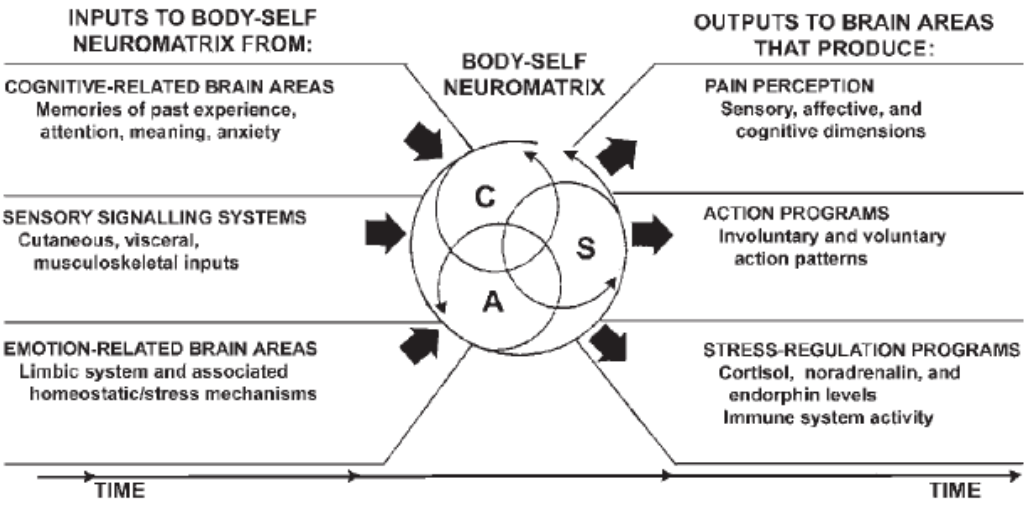


Figure 1.3: The Pain Neuromatrix Theory. Patterns of activity in the neuromatrix are created from cognitive, sensory, and emotional modules. The output of the neuromatrix creates different facets of the pain experience as well as homeostatic and behavioural responses.

Taken from *(R. K. Melzack, J., 2004)*

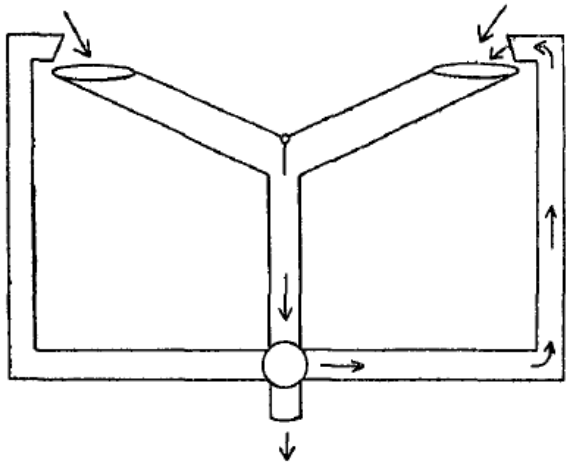


Figure 1.4: Broadbent's model of (selective) attention. Stimulus information can enter from the Y portion but if two stimuli enter at the same time, both cannot pass through the narrow opening, the filter.

Taken from *(Broadbent, 1957)*

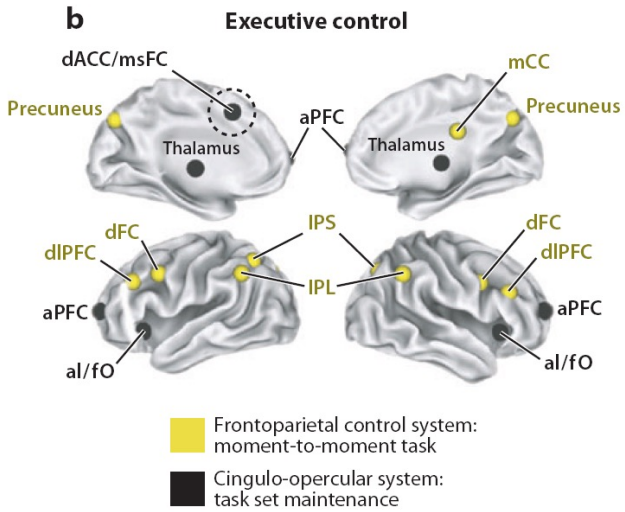


Figure 1.5: The executive control network described by Petersen and Posner. The fronto-parietal network (dorsolateral prefrontal cortex, intraparietal sulcus, and dorsal frontal cortex) becomes active during task onset and includes the dorsal attentional system (Corbetta & Shulman, 2002). The cingulo-opercular network (anterior prefrontal cortex, anterior insula, dorsal ACC, and thalamus) is relevant in maintaining attention during the entire task (Dosenbach, et al., 2008).

Taken from *(Petersen & Posner, 2012)*

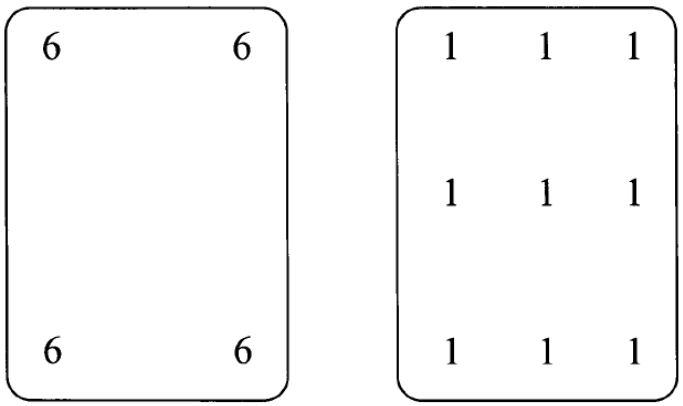


Figure 1.6: The Windes Task. The participant must first say the digit that is on the card as quickly as possible (6, 1 respectively). Later, the rules are changed and the person must say the number of digits on the card (4, 9 respectively).

Taken from *(Eccleston, 1994)*

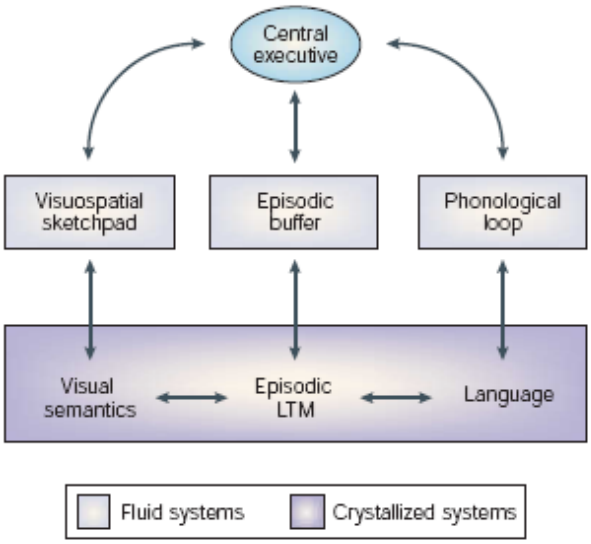


Figure 1.7: Baddeley's multi-component model of working memory. The grey areas represent components of working memory that are being manipulated. The dark purple areas describe areas that have been consolidated and are being stored in long-term memory.

Taken from *(Baddeley, 2003b)*

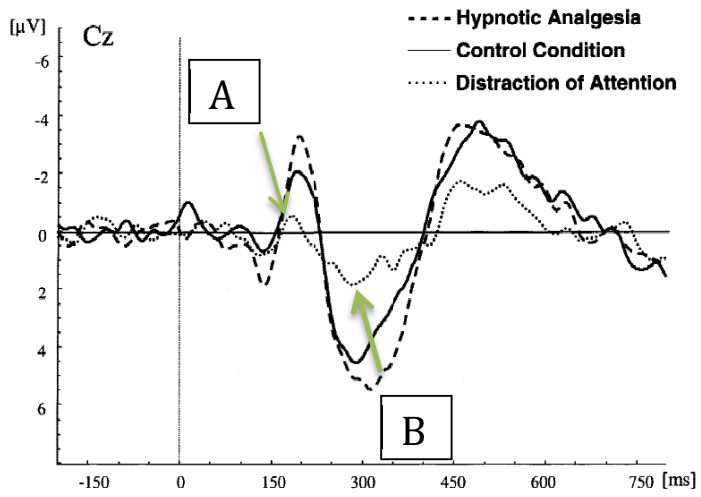


Figure 1.8: Evoked potentials in participants receiving thermal pain under hypnosis (dashed), distraction (dotted), and control (solid) conditions. When participants were told a story that distracted them from the pain, there was a significant decrease in the amplitude of the N200 (A) and P320 (B) ERPs.

Taken from *(Friederich et al., 2001)*

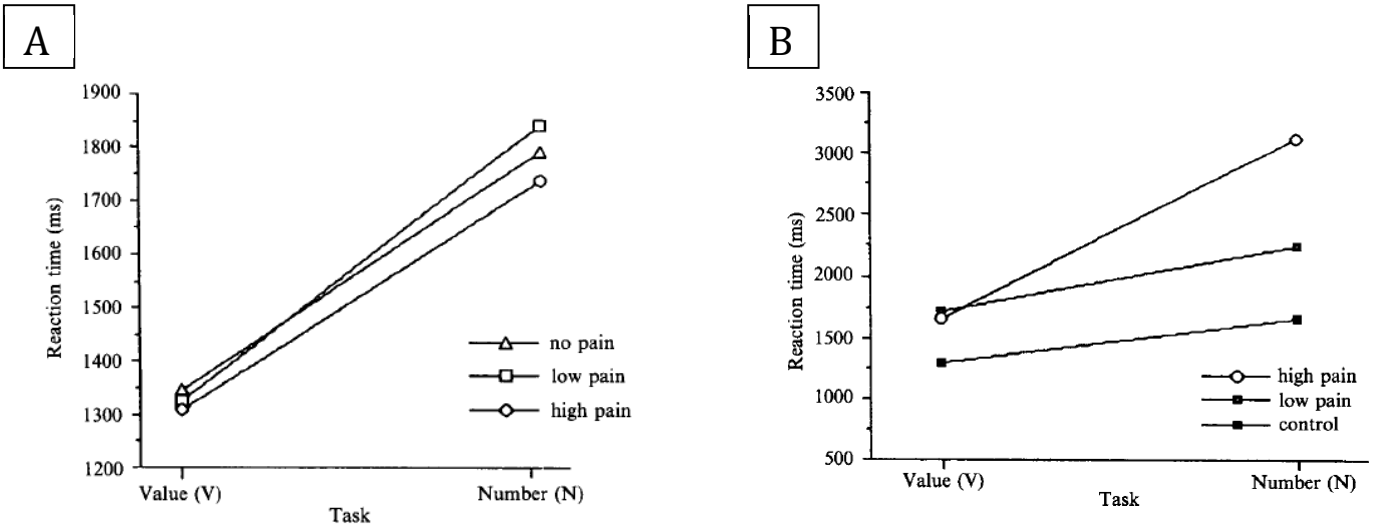


Figure 1.9: Participants performing an easier (A) and harder (B) version of the Windes Task. When the task difficulty is increased, a significant drop in performance and increase in reaction time is seen in high pain participants.

Taken from *(Eccleston, 1994)*

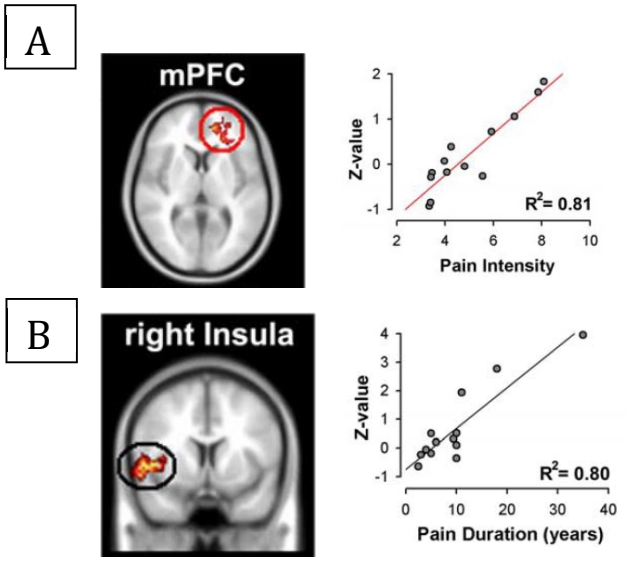


Figure 1.10: Activity in certain brain areas is correlated with the intensity and duration of pain in patients with chronic back pain. There is a strong correlation between the intensity of pain experienced and activity in the medial prefrontal cortex (mPFC; ***A***) and a strong correlation between pain duration and activity in the right insula (***B***).

Taken from *(Baliki et al., 2006)*

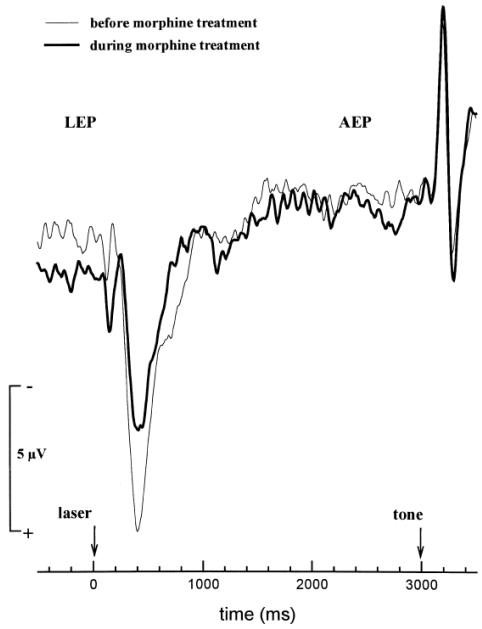


Figure 1.11: Laser (LEP) and auditory (AEP) evoked potentials in patients with CP before (grey) and during (black) morphine treatment. Participants were asked to perform an auditory task in which they have to detect an odd frequency tone from a series of tones. As expected, the amplitude LEP was attenuated during morphine treatment demonstrating a decrease in sensory stimulation. However, the amplitude of the AEP increased following morphine administration demonstrating higher cognitive activity.

Taken from *(Lorenz et al., 1997)*

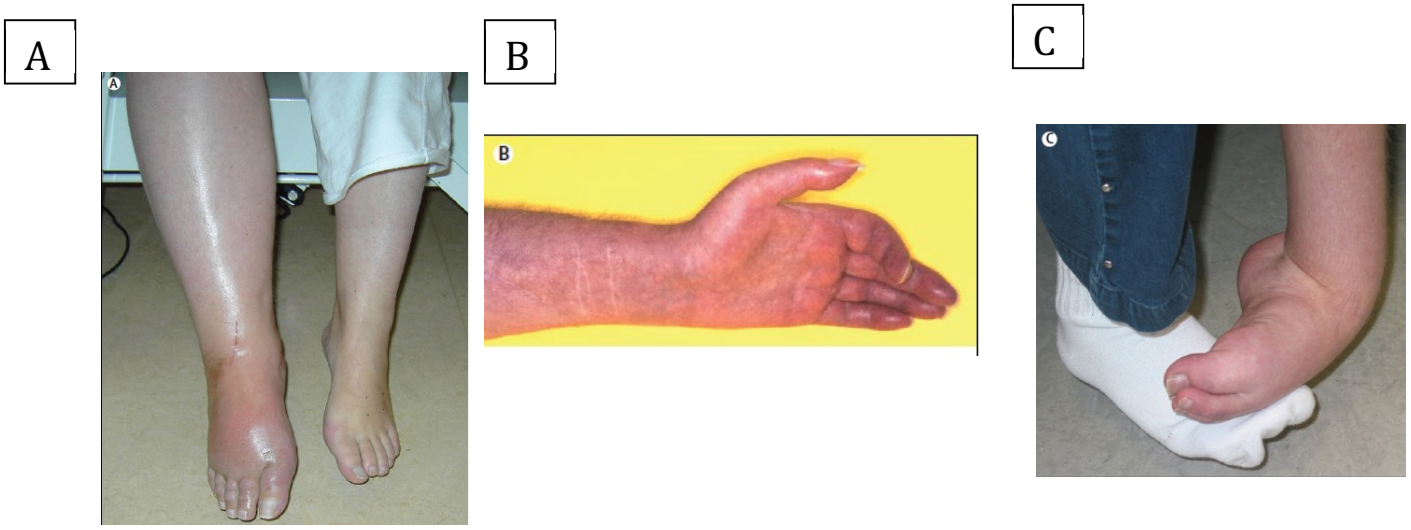


Figure 1.12: CRPS affected limbs. *A* acute stage CRPS with much swelling and glossy skin. *B* Chronic CRPS with less swelling, increased redness, and increased hair and fingernail growth. *C* CRPS dystonia with foot and toes curling inward due to hyperactivity of muscles.

Taken from *(Marinus et al., 2011)*

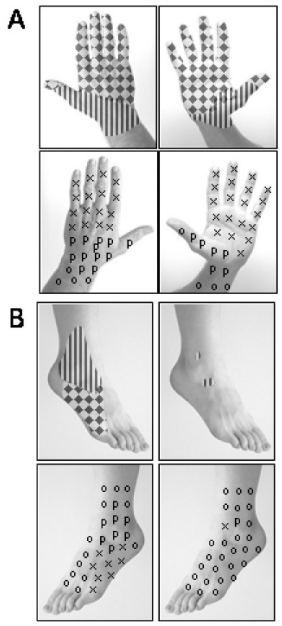


Figure 1.13: The phenomenon of dysynchiria. Patients with CRPS were staring at the reflection of their un-affected limb in the mirror while it was being stimulated. Sensations in the affected limb were recorded. When an area on the un-affected limb that corresponded to a painful region on the affected limb was stimulated, pain was experienced. When an area on the un-affected limb was stimulated that corresponded to a normal region on the affected limb, there was no pain. A_{top}: Area of hand with dysynchiria in affected patient A_{bottom}: Type of dysynchiria in patient. B_{top}: Area of foot affected before (left) and after (right) training. B_{bottom}: Type of dysynchiria before and after training. Checks= paresthesias, vertical lines=allodynia, *p*=pain, *x*=odd sensation, *o*=normal/no sensation.

Taken from *(Acerra & Moseley, 2005)*

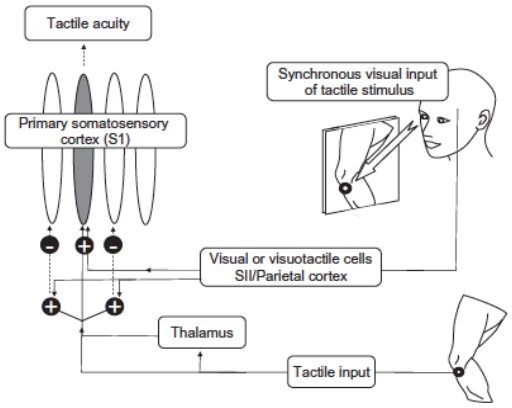
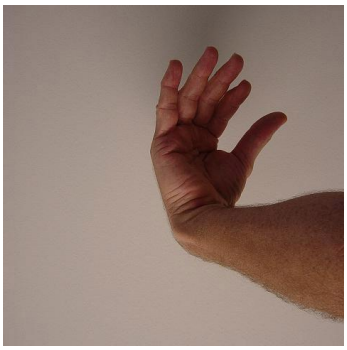


Figure 1.14: Possible mechanisms by which visual input may override the input by tactile stimulation. Seeing the mirror image of touch may stimulate visuotactile cells in the secondary somatosensory cortex (SII) or parietal cortex. These in turn activate inhibitory neurons in S1 and even the thalamus.

Taken from *(G. L. Moseley et al., 2008)*

A



B

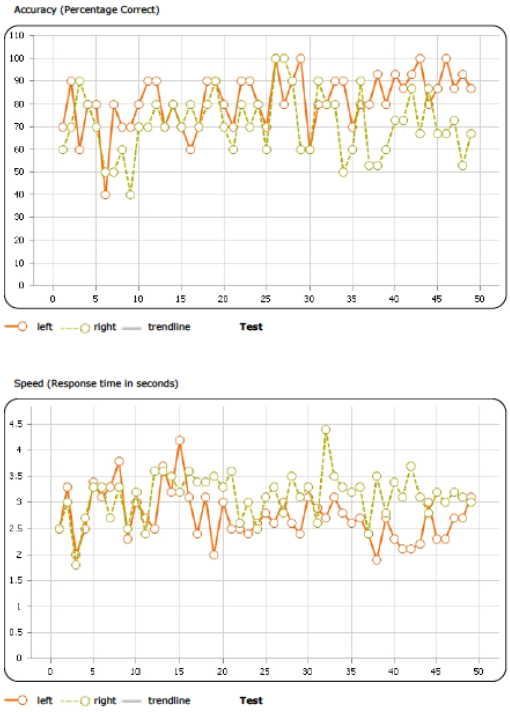


Figure 1.15: Stage 1 (Laterality Recognition) of Graded Motor Imagery therapy. *A:* Example of an image used in the online *Recognize* tests. The patient must decide if the image is of the left or right hand in a specified amount of time. *B:* Example of electronic sheet detailing the results from 3 Recognize tests (*Top*=average accuracy vs test number *Bottom*=Average response time vs test number).

Taken from *Neuroorthopedic Institute Website*

Figure 1.16: Stage 3 (Mirror Therapy) of Graded Motor Imagery. Patient inserts affected limb into box and focuses on reflection of non-affected limb. In the beginning, patient only moves the non-affected limb but as pain decreases in CRPS limb, patient moves both limbs simultaneously.

Taken from *Neuroorthopedic Institute Website*

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Chapter 2

Cognitive Disruption in Pain

2.1. Introduction and Rationale

Patients with chronic pain (CP) report significant depression, anxiety, disability, and sleep disruption (B. Dick, Eccleston, & Crombez, 2002) and all of these factors have been shown to be correlated with cognitive dysfunction (Alfarra, Fins, Chayo, & Tartar, 2015; Grace et al., 1999; Priyamvada, Ranjan, & Chaudhury, 2015). However, one study showed that, in patients with CP, when the above factors are used as co-variates, the only correlate of attentional disability is pain intensity (B. Dick et al., 2002). Another showed that memory deficits are correlated with pain as well as anxiety but not depression or sleep (Grace et al., 1999). Therefore, it is still unclear whether the link between CP and cognitive dysfunction is a direct one, or due to co-morbid psychological disorders. In a previous study (B. D. Dick & Rashiq, 2007), it was shown that participants with CP have worse performance on tasks of attention and working memory, especially those that are challenging. The study was unique in that it used an array of cognitive tests that measured different types of attention as well as verbal and visuospatial working memory. In addition, it used co-factors such as demographic history, catastrophizing, mental health, and sleep quality to determine to what extent cognitive disruption was predicted by pain intensity and chronicity. However, the study was underpowered (only 24 participants) and did not take into consideration the effect of medication regimens nor the quality of life and disability of participants.

2.2. Objectives

1. To examine if the severity of chronic pain (intensity and chronicity) can predict a patient's performance on attention and working memory tasks.

2. To examine if other factors (mood, sleep, medication) can predict a patient's performance on attention and working memory tasks.
3. To examine if deficits in attention, working memory and other factors (pain, mood, sleep, medication) predict a patients' quality of life and disability.

2.3. Hypotheses

1. Pain intensity as well as the duration of the CP will be the strongest predictors of cognitive disruption, specifically in attention and, primarily, working memory.
2. Those with greater pain will perform significantly worse on more difficult tasks such as the Spatial Span Test
3. Cognitive disruption will be the strongest predictor of higher disability and lower quality of life.

2.4. Methods

2.4.1 Participants

Written informed consent was obtained from all participants in accordance with the University of Alberta's Health Research Ethics Board requirements before study inclusion. We recruited 50 participants (21 females; 29 males) from the Multidisciplinary Pain Centre at the University of Alberta.

2.4.1.1 Inclusion Criteria:

- Participant was at or over the age of 18
- Participant could read and write English

- Participant had normal or corrected to normal vision
- Participants had consistent pain in some region of their body for at least six months.

2.4.1.2 Exclusion Criteria:

- Participant could not be suffering from severe mental health disorders (severe anxiety and depression, bipolar disorder, psychoses)
- Participant could not have severe (followed by loss of consciousness) head injury or any other disorders that could affect cognition (such as epilepsy, multiple sclerosis, Parkinson's disease, chronic migraine/chronic daily headache)

2.4.2. Cognitive Measures

2.4.2.1 Attentional Functioning

The Test of Everyday Attention (TEA) is a standardized test of neuropsychological functioning (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996). The reliability of the TEA ranges from 0.59 to 0.86 in healthy controls and 0.41[19] to 0.90 in stroke patients. Precautions were taken as a part of the standardization process in the construction of this test as per industry standards to ensure that the TEA is valid in studying attention and not sensory modalities such as vision and hearing or verbal intelligence[20]. The TEA correlates with other measures of attention, and can discriminate between a range of neurological conditions. When applied to stroke patients, results on many of the subtests correlated with measures of the patients'

[19] The lowest reliability is of the dual-task decrement score of the dual task. This may be due to the fact that there is a high learning effect which allows participants to perform better the second time they take the test (Robertson et al., 1996).
[20] Scores on the subtests of the TEA correlate minimally with verbal intelligence scores (Robertson et al., 1996). The participants in our study were ensured to have normal or corrected-to-normal vision and hearing so as to not create potential confounds.

mobility, food preparation, domestic work, and leisure. In addition, certain subtests of the TEA can discriminate between mild and moderate signs of Alzheimer disease and can also discriminate progressive supranuclear palsy patients from healthy controls. It can also test different forms of attention such as: selective, sustained, divided, and attentional switching as well as verbal working memory. Other benefits to the TEA include its high face validity as well as the short time taken for its administration (45-60 minutes). The person is told that they are on a road trip to Pittsburgh and will be given multiple tasks.

There are Eight Subtests of TEA (Crawford, Sommerville, & Robertson, 1997; Robertson et al., 1996):

Map Search: In this subtest, participants search for a fork and knife symbol in a colored map of the city of Philadelphia. The participant must find as many symbols as they can in one, and then two minutes. (Assesses **visual selective attention and speed**)

Elevator Counting: The participant must count and report the number of tones presented. (Assesses **sustained attention**)

Elevator Counting with Distraction: The participant counts middle-pitched tones while ignoring interspersed high-pitched tones. (Assesses **auditory-verbal working memory**)

Visual Elevator: The participant counts pictures of elevators and reverses count when they see an arrow pointing up or down. (Assesses **attentional switching**)

Elevator Counting with Reversal: The participant must count middle pitch tones and reverses account if they hear a high pitched or low pitched tone. (Assesses **auditory-verbal working memory**)

Telephone Search: The participant searches for plumber symbols in an imitation telephone directory. (Assesses **visual selective attention and speed**)

Telephone Search Dual Task: Participants search for a different set of symbols in a different imitation telephone directory but also must count and report tones heard (such as the ones presented in the *Elevator task*). (Assesses **visual selective attention and speed**, **sustained attention,** and **divided attention**)

Lottery: The participant listens to a 10 minute recording of "lottery numbers" in the form of 'BC143' and must write down the letters of those lottery numbers that end in '55'. (Assesses **sustained attention**)

The TEA has been standardized from a population of healthy controls as well as a population of patients with brain injury; a score of "10" signifies the scaled mean(Robertson et al., 1996). The scaled score of each subtest was added to form a *sum score,* which was compared across participants. An individual score in the "clinically impaired range" signifies that less than 7% of the individuals in that age group would receive a scaled score that low.

2.4.2.2 Attentional/Working Memory Capacity

Spatial working memory and verbal working memory are separable (Shah & Miyake, 1996) and were assessed using different tests.

The **Reading Span Test (RST)** is effective at assessing *verbal* attention and working memory as well as linguistic and non-linguistic capabilities (Lobley, Baddeley, & Gathercole, 2005)). The participant is told to read a list of sentences out loud and say "yes" if the sentences do make sense or "no" if the sentences do not make sense. After each series of sentences is

complete, the participant must remember and say the last word in each of the sentences presented. Patients with early Parkinson's disease (PD) perform more poorly on the RST compared to healthy controls and patients with mild Alzheimer disease (AD) perform even worse (Kensinger, Shearer, Locascio, Growdon, & Corkin, 2003). In both groups of patients, scores on the RST correlated with scores on other working memory tasks (such as digit span).

The **Spatial Span Test** (SST) was used to investigate *spatial* attention and working memory because it correlates well with other spatial ability tests (Shah & Miyake, 1996). In this task, the participant must make a mental rotation while also keeping track of spatial information. The participant determines if a letter presented on screen is in a normal or mirrored configuration after which he must decide which way the top of letter was pointing **[Figure 2.1].** Therefore, this task involves interference, much like the more challenging attention task used by (Eccleston, 1994).

The RST and SST each approximately take 20 minutes to complete.

The order in which the cognitive tests were performed was randomized for each individual participant. This was done in order to control for the effect that a participant's fatigue may have on the performance of a test.

2.4.3 Self-report Measures

The following measures were used to assess variables of interest:

Demographic: Age, sex, number of years of education, employment history (**Appendix A 1**).

Medical and pain history: Diagnosis, etiology of pain (if known), age at onset of pain, chronicity of pain, location of pain, a detailed list of medications being taken at the time of testing (**Appendix A 1**).

Pain:

Pain intensity was assessed using the McGill Pain Questionnaire (MPQ; **Appendix; A 3**) specifically, the Pain Rating Index score (PRI). A *higher* PRI indicates higher pain intensity. The MPQ consists of a list of adjectives ("burning", "cutting", "throbbing") and the participant is told to check off words that they feel describe their pain (R. Melzack, 1975). This questionnaire assesses the sensory, affective, and evaluative aspects of pain. The MPQ is sensitive to differences in pain levels as well as variations in the different qualities of an individual's pain. It has a reliability of approximately 0.70, can detect mild pain due to its multidimensional nature, and correlates with the VAS as well as measures of anxiety and depression (Hawker et al., 2011).

Quality of life: Health-related quality of life (HrQOL) was measured using the 15D (Sintonen, 2001). The 15D (**Appendix A 4**) is a questionnaire that tests: breathing, mentality, communication, vision, mobility, day-to-day activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort, sexual activities, and depression; each of these aspects is further divided into five different levels. The maximum score in a section is 1 (perfect HrQOL) and the minimum score is 0 (no signs of life). The questionnaire has a reliability between 0.92 and 1 and is more comprehensive and sensitive compared to other measures (Sintonen, 2001). Individuals living with Parkinson Disease, a neurodegenerative disease that causes tremor,

rigidity, and severe slowness of movement had a score of 0.77 on the 15D (Haapaniemi, Sotaniemi, Sintonen, & Taimela, 2004).

Functional disability: Difficulty and disability in everyday functioning due to pain was measured with the Pain Disability Index (PDI; **Appendix A 5**). The PDI examines respondents' levels of perceived disability due to pain in seven domains of daily living (Pollard, 1984). Each section rates from 0 to 10 with a *higher* score indicating more disability. The reliability of the PDI is 0.76 and the validity with pain intensity is 0.69 (Soer et al., 2013).

Mental health (anxiety and depression): The Hospital Anxiety and Depression Scale (HADS; **Appendix A 6**) (Zigmond & Snaith, 1983) is a brief (14-item) measure that was used to assess current levels of depression and anxiety. There is a list of comments such as "I feel tense or wound up" and the participant checks off a box indicating how often the comment applies to them. A *higher* score indicates more severe anxiety and/or depression. The internal consistency of the depression portion of the HADS varies between 0.67 and 0.90 and the anxiety portion of the HADS varies between 0.68 to 0.93. For both portions, the values for sensitivity and specificity are 0.80 (Bjelland, Dahl, Haug, & Neckelmann, 2002).

Sleep: The quality of sleep was measured using the Pittsburgh Sleep Quality Index (PSQI; **Appendix A 7**). This test is currently the most reliable and valid measure of sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI consists of 19 questions, which address issues such as sleep duration, latency, and problems and are scored from 1-3. The overall score an individual will receive will be from 0-21 with a higher score indicating worse sleep. The test-retest reliability of the PSQI is 0.83, its sensitivity is 0.90 and specificity

is 0.87. It is a quantitative measure which is quite effective at distinguishing good from bad sleepers (Buysse et al., 1989).

Medication Regimen: The Medication Quantification Scale III (MQS; **Appendix A 8**) is a method to objectively quantify the medication regiment the patient is receiving at a point in time (Harden et al., 2005). Each medication is assigned a **detriment weight**, a value between 1.1 and 4.5 that indicates the potential of the medication to produce adverse effects. A medication such as acetaminophen, which does not have a high potential, would be given a score of 2.2, whereas steroid medications, which can be much more toxic, are given a score of 4.4. Next, the **dosage level** is calculated; it is a score between 1 and 4 which indicates if the individual is on a sub-therapeutic dose (1), lower 50% of the therapeutic dose range (2), upper 50% of the therapeutic dose range (3), or in the supratherapeutic dose range (4). Opioid medications are different because the dose has to be converted to a "morphine equivalent", that is to say, be converted to the dose of morphine that would have the same therapeutic effect as the opioid medication of interest. The final score of each medication is obtained by multiplying the detriment weight by the dosage level; a higher score indicates a stronger medication regimen.

The clinical measures took approximately 30 minutes to complete and were always done before the cognitive testing.

2.4.4 Statistical Analyses

Scores on clinical measures as well as the TEA were first assessed *qualitatively*. *Correlations* were then performed to examine key relationships between cognitive, clinical, and

demographic factors, with all factors being included in analysis. The Pearson correlation coefficient, *r*, which is a value between -1 and +1, is a measure of the strength and direction of a correlation (Howell, 2012). A higher value indicates a stronger correlation and the sign indicates whether the relationship is a positive or negative one. For example, if two variables (X and Y) have an r value of 0.900, it would be possible to state that there is a strong linear relationship between X and Y. However, it would be impossible to state that X predicts Y or vice versa; to make a prediction of Y based on knowledge about X, a regression analysis must be performed (Howell, 2012).

In the present study, *stepwise multiple linear regression* techniques were used to investigate which factors best predict cognitive function and other key outcomes such as disability in this patient population (Howell, 2012). Demographic and medical history factors were entered including pain level, sleep, mood, and medication. In a *multiple* regression, the goal is to determine the relationship between one dependent variable and several independent variables (Howell, 2012). In a *stepwise* multiple regression, the goal is to determine what the best combination of independent variables would be to predict a specific dependent variable. In this type of multiple regression, not all independent variables end up in the equation, just those that significantly predict the dependent variable (Howell, 2012).

The *B coefficient* is a measure of the strength of the relationship between the independent and dependent variable; in the scatterplot graph of the independent variable vs the dependent variable, the B coefficient is the slope of the line of best fit (Howell, 2012). Similar to r, B coefficients can have a positive or negative value indicating whether the dependent variable varies in the same or opposite direction, respectively, as the independent variable. The standard error of the coefficient (*B SE*) is the difference between the actual score and predicted score.

For example, if the line of best fit states that the value of the dependent variable will be (X) when the independent variable is (Y) and the true value of the dependent variable is (X'), the B SE would be X-X'. In other words, it is a measure of how much a value on the line of best fit differs from the actual point on the scatterplot. If a coefficient is large compared to the standard error, it most likely differs from 0. In a multiple regression, often the variables included in analysis have different units, for example when comparing the age (years) of a participant to a score that they may attain on the PDI (points). A *Beta* coefficient is similar to a b coefficient but is standardized. It's a measure of how many standard deviations the dependent variable will change per standard deviation change in the independent variable. The Beta coefficient allows determination of which independent variable has a stronger effect on the dependent variable when the units of measurement are no longer relevant. Finally, the *t score* is a measure of how much the coefficients differ from 0 (the null hypothesis). If the coefficient is smaller than the hypothesized value (0) the t score will be negative and if it is larger, it will be positive. The greater the absolute value of the t score, the greater the results deviate from the null hypothesis. The t score is used to calculate the *p-value* (Howell, 2012).

2.5. Results

2.5.1. Descriptive Statistics

The descriptive statistics for the demographic and pain history, types of pain, clinical measures, and cognitive measures are shown in **Tables 2.1, 2.2, 2.3 and 2.4** respectively. As can be seen in **Table 2.1**, our population did have a wide age range but the majority was of middle age. There was a large range for the number of years an individual was suffering from

chronic pain (i.e., pain chronicity). However, a mean of 15.4 years suggests that the majority of the population had been suffering from pain for a significant portion of their adult lives. This is not surprising given that participants were recruited from a tertiary care chronic pain centre with a very large catchment area that specializes in complex chronic pain management. Considering this high mean amount of pain chronicity, the pattern of results noted in the clinical measures is not unexpected. The majority of our pain population was afflicted by musculoskeletal pain, followed by fibromyalgia and neuropathic, and arthritic **[Table 2.2].**

The mean PDI score (max/worst score =10) of our participants was 6.9 **[Table 2.3 row 2].** The HRQoL of our participants, as measured by the mean score on 15D, was found to be very low [0.55; **Table 2.3 row 3**]. As stated above, patients with PD have a score much higher at 0.77 and this comparison is suggestive of how disabled our population was and the effects of that disability on individuals' quality of life. In addition, our population was moderately anxious and depressed [mean score of 11.2 and 10.4 respectively; **Table 2.3 rows 4 and 5**]. Given that a mean score of 5 on the PSQI suggests poor sleep quality, much of our population (mean score of 14.4) endured exceptionally poor sleep quality as well **[Table 2.3 row 6].**

2.5.2. Correlations

Our correlation analyses revealed associations that suggest strong face validity in that data patterns related to demographic, medical, and psychological factors are in line with patterns of results in previously published studies.

These correlation findings suggests that our population, categorized by significant disability, poor sleep and marked mood issues and very poor quality of life follows the pattern of results that one would expect given broader findings in the scientific literature. It is

important to recognize that correlations merely reflect statistical associations between factors and cannot imply causation or direct statistical patterns.

2.5.2.1 Demographic and Clinical Factor Correlations

Anxiety was positively correlated with depression ($r=0.54$, $p\leq0.01$) and PSQI ($r=0.358$, $p\leq0.05$) scores and negatively correlated with the 15 D (quality of life) ($r=-0.43$, $p\leq0.01$). As patients become more anxious, their depression increases, sleep worsens, and predictably, quality of life decreases. Depression was also positively correlated with PSQI scores (0.48, $p\leq0.01$) and negatively correlated with 15D scores ($r=-0.63$, $p\leq0.01$). Increased depression in patients is associated with worse sleep and lower quality of life. Pain intensity (MPQ) was positively correlated with anxiety ($r=0.42$, $p\leq0.01$), depression ($r=0.48$, $p\leq0.01$), and pain-related disability scores ($r=0.455$, $p\leq0.01$) and strongly negatively correlated with the 15D (quality of life) score ($r=-0.69$, $p\leq0.01$). High levels of participant pain are associated with more anxiety, depression, and disability and poorer quality of life. Pain-related disability was correlated with depression ($r=0.42$, $p\leq0.01$) and PSQI score ($r=0.33$, $p\leq0.05$) and negatively correlated with 15D score ($r=-0.55$, $p\leq0.01$). People with higher levels of depression and poorer quality of life tend to report higher levels of disability. Finally, the 15D score was also negatively correlated with the PSQI (-0.423, $p\leq0.01$). Predictably, as sleep worsens, people are more likely to report lower quality of life.

2.5.2.2 Cognitive Factor Correlations

Correlations of note are shown in **Table 2.5.**

With respect to correlation associations related to cognitive outcome measures, the only test employed in this study that has been specifically developed for clinical use with (brain-

injured) patient populations is the TEA. Other cognitive measures in this study have been widely used to study human cognitive performance but no clinical norms exist for comparison to our participant population. TEA scores from almost half of our population suggested some form of clinically significant cognitive impairment **[Figure 2.2A].** Ten of our participants had one score in the clinically significant range, six had two such scores, and five had three or more significantly impaired scores **[Figure 2.2B].** This represents a high level of cognitive impairment in a population that has been carefully screened for previous brain trauma and injury, neurological disorders, and diseases known to impair cognitive function. Further, our participant population's high mean education level suggests that there is little reason to suppose that this level of cognitive impairment is a result of general cognitive deficiency.

The TEA sum score was negatively correlated with the MPQ pain intensity score ($r=-0.30$, $p\leq0.05$). As a patient's pain increases, their attentional function tended to be poorer. Age was negatively correlated with SST Mirror image scores ($r=-0.29$, $p\leq0.05$). Older participants were slightly more likely to have more difficulty with this complex spatial working memory task. Education level had a slightly higher positive correlation with the RST words recalled score ($r=0.31$ $p\leq0.05$). People with higher levels of education showed somewhat stronger verbal working memory scores. The RST words recalled score positively correlated with TEA sum score ($r=0.39$, $p\leq0.01$) and negatively correlated with pain related disability ($r=-0.26$, $p\leq0.05$) and PSQI score ($r=-0.36$, $p\leq0.05$). Verbal working memory scores were positively associated with an index of general attentional function. Stronger verbal working memory is also associated with less disability. As expected, individuals with poorer sleep tend to perform worse on measures of verbal working memory. The SST orientation ($r=0.39$, $p\leq0.01$) and SST mirror score ($r=0.36$, $p\leq0.05$) were positively correlated with the TEA sum score. Thus, spatial

working memory scores were associated, as expected, with a general index of attentional function. As well, SST orientation was negatively correlated with pain-related disability (r=-0.37, p≤0.01). Patients whose spatial working memory is worse were more likely to experience higher levels of pain-related disability. The correlations above are weak and are not a robust measure of the cause of disability and cognitive dysfunction in CP patients. While they do replicate previous studies that show relationships between, age, education, sleep, working memory, attention, and disability, they do not describe which factor predicts another. To determine this, we performed regression analyses.

2.5.3. Regression Analyses

Multiple regression analyses were performed into order to explore predictors of key outcomes. Scores of the PDI, 15D, TEA Sum, SST, and RST were used as dependent variables in different models and important predictors of pain-related disability, working memory, attention, and quality of life were found. When scores on the PDI were inserted as the dependent variable, scores on the 15D (B=-0.56, p=0.000) as well as spatial span orientation task (B=-0.34, p=0.005) were significant predictors **[Table 2.6]**. Specifically, poorer working memory and lower health-related quality of life predicted greater pain-related disability. In another model, when the 15D was inserted as the dependent variable, the MPQ PRI pain score (B=-0.51, p=0.000), HADS depression score (B=-0.33, p=0.003), and the RST words-recalled score (B=0.26, p=0.007) **[Table 2.7]** were significant predictors. Thus, individuals who experience higher levels of pain and more depression together with poorer working memory have a much lower quality of life. The only predictor of the SST mirror image score was the TEA sum score (B=0.37, p=0.014) **[Table 2.8]**, showing that general attentional function predicted spatial working memory performance. Lower TEA sum scores (B=0.39, p=0.005)

and higher PSQI scores (B=-0.33, p=0.016) significantly predicted lower RST words recalled scores **[Table 2.9]**. Not surprisingly, individuals with better general attentional function and those who report better sleep quality experience better verbal working memory performance. Better working memory capacity also predicted better attentional function as the words-recalled portion of the RST, mirror image portion of the SST, and orientation portion of the SST, all predict the TEA Sum Score (B=0.34, p=0.011; B=0.30, p=0.023; B=0.31, p=0.018 respectively) **[Table 2.10]**. Given the tremendous amounts of previous knowledge that suggests that attention and working memory are interrelated (Heuer & Schubo, 2016; Lepsien & Nobre, 2006), in addition to the important findings related to cognitive and other predictors of pain-related disability and health-related quality of life, the above results also suggest that our data show strong construct validity.

2.6. Discussion

The aim of this study was to determine the predictors of cognitive function, disability, and quality of life in individuals with CP. We used a series of neuropsychological and cognitive performance tests as well as clinical questionnaires to examine these factors using rigorous statistical analyses. To our knowledge, no study has performed such an extensive analysis with a sufficient sample size. Overall, our findings suggest that marked cognitive impairment was present in many participants that are afflicted with CP and that this dysfunction can strongly predict disability and quality of life. However, unlike previous studies (B. D. Dick & Rashiq, 2007; B. D. Dick, Verrier, Harker, & Rashiq, 2008), we did not find that pain intensity predicted cognitive dysfunction. Some potential reasons for the data patterns discovered will be discussed below.

Our study provided further evidence of the marked physical and psychological difficulties, including cognitive deficits that contribute to the disability of people with CP. The average participant in this study had been suffering from CP for a duration of 15 years as well as a high intensity of pain at the time of the experiment. Participants also suffered from moderate to high levels of anxiety, depression, poor sleep, and very low health-related quality of life (much worse than those with PD). Compared to a similarly designed previous study (B. D. Dick & Rashiq, 2007), the clinical population in the current study had higher mean scores on the HADS for both anxiety and depression as well as higher average pain rating on the MPQ (PRI Score). In a previous study investigating the PDI, the high-disability group was found to have a mean score of 6.98[21] (Pollard, 1984), a score only slightly higher than our mean score of 6.92 in this study. Thus, our results are reflective of a highly disabled patient population.

Previous studies have shown the high prevalence of depression and anxiety in patients with CP. It is not clear how many patients are afflicted with co-morbid depression but estimates range from 20-60% (Licciardone, Gatchel, Kearns, & Minotti, 2012; Surah, Baranidharan, & Morley, 2013). In one study of chronic and acute headache, 22.8% of patients with episodic headache and 43.6% of patients with chronic headache were afflicted with depression (Zebenholzer et al., 2016). Anxiety disorders are also quite prevalent in patients with CP. In patients with episodic headache, anxiety is 34.1% prevalent and in patients with chronic headache, this number is 53.9% (Zebenholzer et al., 2016). Twenty percent of chronic back pain patients report high anxiety sensitivity[22], which is correlated with high somatic anxiety, avoidance behaviors, and negative affect (Asmundson & Norton, 1995). Both depression and

[21] In the study, total scores on the PDI were calculated. The total score of highly disabled was participants was 48.89. This score divided by seven (categories) yielded the score of 6.98.
[22] A personality trait that describes an individual's likelihood of developing a conditioned fear response (Asmundson & Norton, 1995).

anxiety can significantly increase the disability experienced by patients with CP. In a study that looked at 5808 CP patients in primary care, 41% of participants with depression reported disabling chronic pain whereas this number was 10% in those without depression. Individuals afflicted with both depression and chronic pain had a poorer quality of life and higher prevalence of panic disorder (Arnow et al., 2006). Chronic headache co-morbid with anxiety and depression can lead to a higher unemployment rate, lower earnings, and feelings of isolation (Zebenholzer et al., 2016).

In regards to cognition, almost half of our population at least one score in the impaired range on the TEA and several participants had more than four scores in this range[23]. The TEA was designed for use in a clinical populations with marked brain impairment including brain injury and is a relatively easy neuropsychological test for most healthy individuals. One clinically significant score is evidence of a significant neurological deficit, several clinically significant scores is suggestive of considerable impairment. This may be particularly relevant given that our participant population was a fairly educated sample that had been carefully screened for organic and traumatic brain pathology. It is not surprising that individuals who demonstrate this level of disability both cognitively and physically and who experience such considerable challenges with respect to sleep and mood disruption report tremendously poor health-related quality of life.

Our correlation analyses, while not capable of pointing to causal statistical relationships, shed light on some interesting and important associations between factors measured in this study. They also suggest that our results show strong face/ecological and content validity (i.e.

[23] This is a lower percentage than that attained in a previous study (B. D. Dick & Rashiq, 2007). However, the sample size of the current study was twice as large.

the study evaluated the actual target constructs of interest and that conceptually related factors varied in relation to each other in patterns that are in line with previous studies). Indeed, previous studies have shown to varying degrees associations between chronic pain, depression, anxiety, and sleep dysfunction as well as the effect of this co-morbidity on disability and quality of life (Outcalt et al., 2015). Of some note, we did find that lower overall scores of attention were correlated with higher pain scores. This association was not strong enough in our sample to result in this factor being a significant predictor in regression analysis as will be discussed later.

2.6.1 Factors Associated With Cognitive Dysfunction

It is difficult to establish what the precise cause of the cognitive disruption experienced by patients with CP is. As discussed above, CP is often co-morbid with depression, anxiety, as well as sleep abnormalities. Previous studies have shown that all of these are also associated with cognitive dysfunction (Alfarra et al., 2015; Disner, Beevers, Haigh, & Beck, 2011; Eysenck, Derakshan, Santos, & Calvo, 2007), which makes it difficult to specifically ascertain what causes cognitive disruption in patients with CP. It is still possible that pain alone may cause cognitive impairment through a plethora of mechanisms. In Kahneman's capacity model, the more difficult the task, the greater the difference between the effort needed to successfully complete the task and the effort actually exerted by the attentional system. Further, the greater the mental effort required of the system to complete the task, the greater the chance that interference between information will occur (Kahneman, 1973). When experiencing pain and performing a task simultaneously, there is greater mental effort required to perform the task due to a salient and powerful competing stimulus. After a certain threshold of pain, more resources are being used to process the pain stimulus, the effort exerted by the system cannot adequately

compensate, and performance on the cognitive task declines (Kahneman, 1973; McCaul & Malott, 1984). Many of our participants experienced high levels of pain during neuropsychological testing and it is highly possible that this pain could have been interfering with performance on the cognitive tasks, among other factors.

However, often when patients with CP are not in pain, they still perform poorly on cognitive tasks. Dick and Rashiq performed neuropsychological tests in participants with CP before and after they received analgesia (B. D. Dick & Rashiq, 2007). While the participants did report a decrease in pain, their cognitive function was still impaired and, in both conditions was markedly impaired compared to healthy controls' cognitive function. This is suggestive of long-term structural and functional changes in neurocognitive regions and relates to the idea of a "dynamic pain connectome" (Kucyi & Davis, 2015), which will be discussed in more detail in *Chapter 4*.

2.6.2 Pain, Pain-Related Disability, Cognitive Dysfunction, and Quality of Life

Our regression analyses found that low HrQOL and poor spatial working memory significantly predicted greater pain-related disability. This is important as, to the best of our knowledge, it is the first time that cognitive deficits have been directly linked to pain-related disability. Patients have been arguing that this is the case for years but little research has been designed to explore this relationship. In addition, our study found that individuals who have higher pain levels and depression together with worse verbal working memory have a much lower HrQOL. As mentioned in *Chapter 1*, pain is most disruptive to a task when the task involves controlled processes versus automatic ones (J. Grisart et al., 2002; McCaul & Malott, 1984). When more sentences are added to trials in the RST, the individual must make a more

conscious and controlled effort to encode as well as recall end-of-sentence words. As the task becomes increasingly difficult more interference between pain and task-relevant stimuli occurs and performance drops. A congruent effect occurs on the SST when more letters are added to trials. A deficit in the ability to perform controlled processes would cause significant disruption in everyday tasks and cause a significant decrease in quality of life as well as increased disability. Therefore, the results from our regression analyses are indeed in agreement with our hypotheses.

Previous studies have shown that cognitive impairment can severely increase disability and decrease HrQOL in other conditions such as schizophrenia (Sigaudo et al., 2014) and acute respiratory distress syndrome (Rothenhausler, Ehrentraut, Stoll, Schelling, & Kapfhammer, 2001). However, few studies have looked at the effect of cognitive dysfunction related to CP on HrQOL. One study investigated patients with chronic rhinositus and found that higher pain and worse HrQOL were associated with greater cognitive dysfunction (Tarasidis et al., 2015). However, that study also only used a retrospective questionnaire to assess cognitive dysfunction instead of standardized neuropsychological examination. Further, the study failed to account for factors such as depression, anxiety, and poor sleep, which are also associated with cognitive dysfunction (Alfarra et al., 2015; Grace et al., 1999; Priyamvada et al., 2015).

2.6.3 Linking Pain and Cognitive Dysfunction

For the present study, given previous findings (B. D. Dick & Rashiq, 2007; B. D. Dick et al., 2008), it was predicted that pain intensity would predict cognitive function. We also hypothesized that pain chronicity would predict cognitive disruption, specifically, attentional

function and working memory. While there was a significant negative correlation between the pain intensity and performance on the TEA, this was modelled out when the regression analysis was performed. It was also expected that individuals with intense pain would perform significantly worse on more difficult tasks such as the SST. Interestingly, no relationship was found between the SST and pain chronicity or intensity. There is much evidence that memory impairment occurs in patients with CP but the exact connection is still uncertain (Liu, Li, Tang, Wu, & Hu, 2014). This may be due to differences in sample size as well as an effect of co-morbid anxiety, depression, emotional distress, and sleep disruption. Etherton and others investigated 49 individuals with CP but found no significant connection between working memory and CP (Etherton, Bianchini, Ciota, Heinly, & Greve, 2006). In another study, cognitive disruption was found in patients with CP but the dysfunction was not linked to pain intensity or chronicity (Jorge, Gerard, & Revel, 2009). The previously described studies performed by Eccleston (1994, 1996) did find that cognitive disruption and pain were correlated but had a small sample size of 24 participants and did not analyze the effects of depression, anxiety and sleep. Similarly, Sjogren et al., had a large sample size of 91 patients with CP and found that there was a significant association between high pain scores as well as scores on tests of working memory and attention but did not include depression, anxiety, or sleep in their analysis (Sjogren, Christrup, Petersen, & Hojsted, 2005). In another study by Munoz et al., retrospective recall of self-described memory impairment was explored with no objective measurement data (Munoz & Esteve, 2005). That study found evidence of memory impairment in individuals with CP but the regression analysis showed that this impairment was mainly correlated with depression and anxiety and not pain duration.

Our results did support previous literature, which has reported a strong connection between attention and working memory (Heuer & Schubo, 2016; Lepsien & Nobre, 2006). In Baddeley's model, there exist two working memory systems, the phonological loop and visuospatial sketchpad, which are controlled by a central executive (Baddeley, 1992; Baddeley & Della Sala, 1996). In our experiment, the RST investigated the phonological loop, the SST investigated the visuospatial sketchpad, and the TEA *best*[24] examined executive function. Given that our regression analyses found all three of these tests to be mutually predictive, they are supported Baddeley's model.

2.6.4 Possible Limitations

It is important to remember that the current study did not have a healthy control group with which to compare the pain population. Our study aimed to compare those with high and low pain. While we used a consecutive sampling method, it is possible that our population was not heterogeneous enough in terms of pain duration and intensity to find meaningful differences between those with high levels of pain and those with low levels of pain in our sample[25]. This may be due to the high level of medical complexity in the tertiary care clinic where recruitment took place, the high level of pain reported by participants, and/or the lack of variability in pain ratings across participants. Most of the individuals were affected by a high intensity and long duration of pain chronicity and, therefore, the model was not able to adequately compare "high pain" and "low pain" groups.

[24] Of course, all three tests examined executive function but given that the TEA required individuals to perform numerous tasks involving divided attention and well as attentional switching, it is the best measure of executive function in the present study.
[25] While the MPQ-PRI mean score was high, the distribution was still found to be normal as well as linear.

2.6.5 Future Directions

In future projects, it would be important to examine the effects of specific treatments on cognitive function in individuals with CP. As previously mentioned, morphine induced analgesia can potentially improve cognitive function evidenced by an increase in the amplitude of P2 and P300 evoked potentials, which are measures of attention (Lorenz et al., 1997). In patients who are depressed, CBT can normalize the hypoactivation of the dorsolateral PFC that occurs. There has been much evidence to suggest that meditative exercises are effective at reducing pain (Grant, 2014). One case study showed that a meditator experiencing pain had activation in primary and secondary somatosensory cortices, dorsal anterior cingulate cortex, insula, and thalamus but after meditation, activation in these regions had almost completely disappeared. In another study, meditators had reduced activation in the amygdala, hippocampus, and prefrontal regions compared to controls during pain. Long-term studies have even shown that training in mindfulness meditation can increase cold-pain tolerance. Imaging and other assessment methods have the potential to help us to better understand how treatments of a variety of modalities may be associated with improvement in pain, cognitive function, mood, sleep, and quality of life.

2.7 Figures

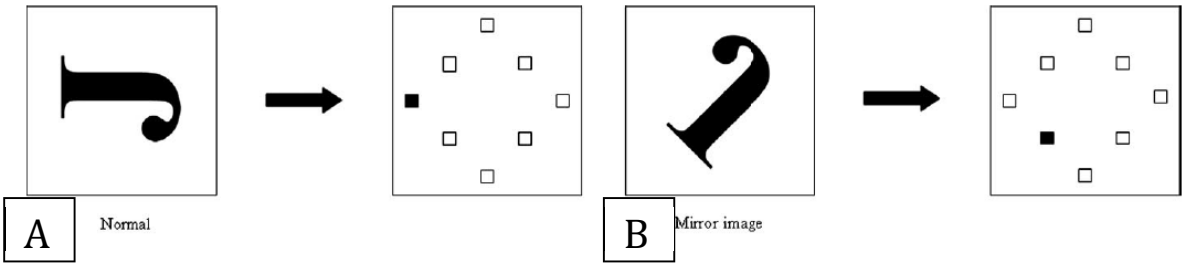

Figure 2.1: The spatial span test. Participants must first decide if a letter is in the normal (***A***) or mirrored (***B***) orientation. After they do this for a certain number of consecutive letters (1-5), they must indicate on a grid which direction the top of each letter was pointing.
Taken from (B. D. Dick & Rashiq, 2007)

Variable	Mean	SD	Max	Min	N
Age in Years	50.7	10.5	71	21	50
Amount of education in years	14.5	3.63	22	8	48
Pain Chronicity in years	15.4	15.1	59	1	49

Table 2.1: Descriptive Statistics for Demographics

Arthritic	Musculoskeletal	Fibromyalgia	Neuropathic
5	25	10	10

Table 2.2: Number of patients with Arthritic, Musculoskeletal, Fibromyalgia, and Neuropathic pain

Clinical Measure	Possible Score Range	Mean	SD	Max	Min	N
MPQ-PRI Score	0-78 (0.00)*	43.3	14.6	78	18	50
PDI-Mean Score	0-10	6.92	1.89	9.43	1.71	50
15D	0-1 (0.96)*	0.59	0.12	0.87	0.32	50
HAD-Anxiety	0-21 (2.97)*	11.2	4.7	20	1	50
HAD Depression	0-21 (0.80)*	10.4	4.64	19	1	50
PSQI-Global Score	0-21 (2.67)*	14.4	3.94	21	5	50

*** Normative Control Values (Buysse et al., 1989; B. D. Dick et al., 2008)**

Table 2.4: Descriptive Statistics for Clinical Measures

Cognitive Measure	Mean	SD	Max	Min	N
RST Grammar (% correct)	94.9	4.51	100	82	49
RST Words Recalled (% correct)	41.5	11.1	71	25	49
SST Mirror Image (% correct)	38.8	16.2	95.6	2	48
SST Orientation (% correct)	70.3	18.4	88.9	8.4	48
TEA-Sum Score	93.9	17.6	136	36	50

Table 2.4: Descriptive Statistics for Cognitive Measures

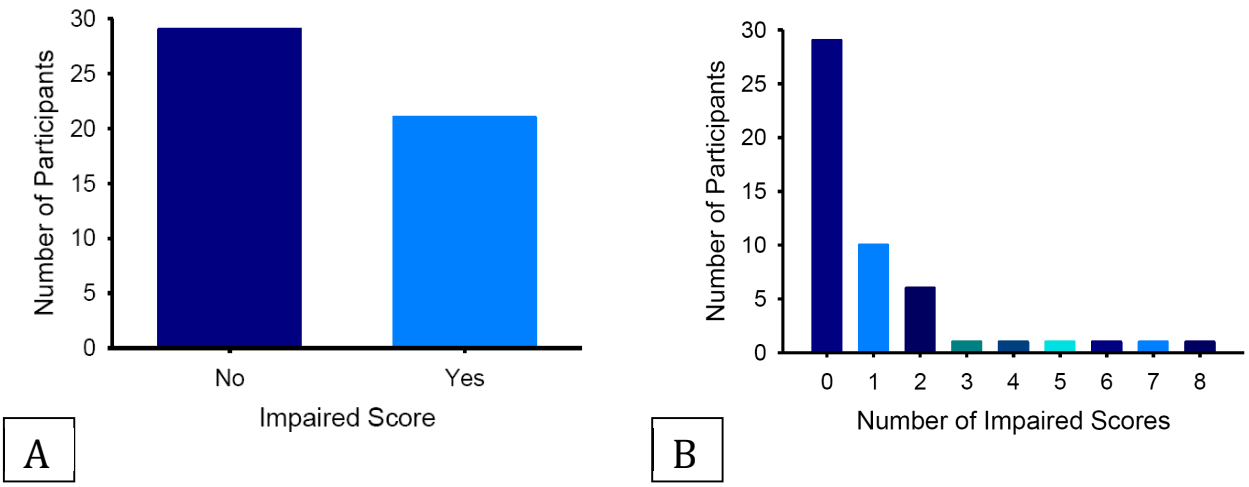

Figure 2.2: Number of Scores in the impaired range on TEA. ***A*** shows whether the number of participants who had scores in the impaired range (*1* is no impairment and *2* is impairment) and ***B*** shows the number of impaired scores per participant.

Variable	PDI Mean	HADS Anxiety	HADS Depression	15D	PSQI	TEA Sum	SST Mirror Image	SST Orientation	RST Words Recalled
Age	-	-		-	-	-	-0.29§	-	-
Education	-	-		-	-	-	0.31§	-	-
McGill PRI	0.46✣	0.42✣	0.48✣	-0.69✣	-	-0.30✣	-	-	-
PDI Mean	-	-	0.42✣	-0.55✣	-	0.33✣	-	-0.37§	-0.28✣
RST Words Recalled	-	-0.31§		0.42✣	-0.36§	-0.39✣	-	-	-
SST Mirror Image	-	-		-	-	-0.39✣	-	-	-
SST Orientation	-	-		-	-	-0.36✣	-	-	

Table 2.5: Significant Correlations. HADS=Hospital Anxiety and Depression Scale; SST=Spatial Span Test; RST= Reading Span Test

§ $P < 0.05$

✣ $P < 0.01$

Measure	B	SE B	Beta	t score	Significance
15D Score	-8.648	1.147	-0.56	-4.92	0.000
SST-Orientation Score	-0.04	0.013	-0.336	-2.953	0.005

Table 2.6: Predictors of Pain Related Disability

Measure	B	SE B	Beta	t score	Significance
MPQ Score	-0.004	0.001	-0.508	-4.999	0.000
HAD-Depression	-0.009	0.003	-0.325	-3.119	0.003
RST-Words Recalled	0.003	0.001	262	2.818	0.007

Table 2.7: Predictors of 15D HrQoL

Measure	B	SE B	Beta	t score	Significance
TEA-Sum Score	0.375	0.146	0.365	2.568	0.014

Table 2.8: Predictor of Spatial Span Test - Mirror Image % Correct

Measure	B	SE B	Beta	t score	Significance
TEA-Sum Score	0.229	0.077	0.390	2.982	0.005
PSQI-Global Score	-0.864	0.346	-0.327	-2.500	0.016

Table 2.9: Predictors of Reading Span Test - Words Correctly Recalled

Measure	B	SE B	Beta	t score	Significance
RST - Words Recalled	0.577	0.217	0.339	2.664	0.011
SST-Orientation	0.342	0.139	0.309	2.468	0.018
SST-Mirror Image	0.288	0.122	0.296	2.37	0.023

Table 2.10: Predictors of TEA Sum Score

2.8 References for Chapter 2

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Chapter 3

Sensorimotor Reorganization in Complex Regional Pain Syndrome

3.1. Introduction and Rationale

Complex Regional Pain Syndrome (CRPS) is believed to be a disease of the central nervous system caused by a reorganization and hyper-excitability of cortical networks. A study using magneto-encephalograpy has suggested that there may be shrinkage of the affected primary somatosensory cortex (S1) of patients with CRPS, in addition to a shift of the representation of the affected hand to adjacent, non-affected areas (i.e., lip) (Maihofner et al., 2003). Interestingly, the amount of shrinkage and shift of the affected hand representation in S1 was correlated with the amount of pain and hyperalgesia experienced by patients with CRPS. In addition to S1, hyperexitability in the primary motor cortex (M1) has also been suggested as shown by reduced short-interval intracortical inhibition [SICI; (Eisenberg et al., 2005; Schwenkreis et al., 2005)] and excessive activation of the affected and non-affected M1 during movement of the affected hand (Maihofner et al., 2007). Moreover, focal dystonia in patients with CRPS is associated with decreased activation in S1, as well as the premotor cortex (Gieteling et al., 2008), regions that may have inhibitory inputs to M1 (Duque, Labruna, Verset, Olivier, & Ivry, 2012). Although these studies are promising, a recent meta-analysis of functional studies in CRPS (Di Pietro et al., 2013a, 2013b) concluded that there are not enough studies to convincingly demonstrate S1 and M1 reorganization and/or hyper-excitability in CRPS and none to show how sensory and motor processing are integrated.

As mentioned above, the excitability of inhibitory circuits in M1 can be investigated using a paired-pulse TMS protocol known as SICI in which a sub-threshold *pre-pulse* to the motor cortex that does not elicit a motor evoked potential (MEP) is followed by a supra-threshold *test* pulse that does (Chen et al., 1998; Ni & Chen, 2008; Roshan, Paradiso, & Chen,

2003; Rothwell, Day, Thompson, & Kujirai, 2009). The pre-pulse specifically activates low-threshold GABAergic inhibitory interneurons that inhibit pyramidal neurons activated by the test pulse (Di Lazzaro, Ziemann, & Lemon, 2008; Roshan et al., 2003). An example of a pre-pulse inhibiting a test MEP is depicted in **Figure 3.1** whereby the test MEP (black trace) is suppressed to ~37% of its original value (red trace) [SICI = (conditioned MEP/test MEP) * 100%) = 37%]. As such, the amount that the test MEP is reduced to by the sub-threshold pre-pulse has been used as a measure of the excitability of GABAa-ergic inhibitory interneurons in M1 (i.e., SICI). In this Chapter, the excitability of SICI circuits in the affected M1 of patients with CRPS was examined using an incremental range of pre-pulse intensities (to produce a SICI recruitment curve) and was compared to age and sex matched control participants.

To specifically examine how sensory inputs from the hand interact with these inhibitory circuits in M1, a technique of S*ensoriMotor Organization (SMO)* has been used in musicians with dystonia. In this protocol, the effects of muscle vibration on SICI were compared when vibration was applied to the tested muscle and to surrounding muscles and results were obtained akin to the phenomenon of "surround inhibition" (Rosenkranz, Butler, Williamon, & Rothwell, 2009; Rosenkranz, Kacar, & Rothwell, 2007). For example, in healthy subjects (HS), when the APB (thumb abductor) was vibrated, SICI measured in the APB muscle decreased (white bar: SICIvib/SICIno vib >100%) while increasing (< 100%) when the FDI (index finger abductor, black bar) and ADM (pinky abductor, gray bar) muscles were vibrated [**Figure 3.2left, before condition**]. In healthy musicians (HM), a similar organization occurred except that when the adjacent FDI muscle was vibrated, SICI in the APB muscle decreased (> 100%), likely because these two muscles were activated congruently and rapidly when playing the piano [**Figure 3.2centre, before**]. In musicians with dystonia (MD) where there was a

premature contraction of the fourth (ring) finger when the other fingers were being used, this reorganization had become maladaptive. That is, when *all* surrounding muscles were vibrated (adjacent FDI and distant ADM), SICI in the APB muscle was decreased (all > 100%) [**Figure 3.2right, before**]. This lack of surround inhibition is thought to underlie the observed dystonia in these patients.

When musicians with dystonia received proprioceptive training where all three muscles were vibrated in random order, the SMO profile of the dystonic musicians returned to that of healthy musicians [compare after conditions in **Figure 3.2centre** and **3.2right**; (Rosenkranz et al., 2007)] and interestingly, the dystonia was also reduced. By extension, retraining the manner through which inputs from the sensory cortex activate the motor cortex in CRPS might reorganize sensorimotor integration and by doing so, reduce pain. In CRPS, it has been posited that Graded Motor Imagery reverses maladaptive sensorimotor reorganization by sequentially activating motor and sensory areas in a non-noxious manner. This might involve retraining of how sensory inputs activate the motor cortex. Thus, it is important to examine the effect that GMI has on sensorimotor integration, specifically using the measures of SMO described above. Elucidating these changes may not only increase our understanding about the etiology of the sensorimotor signs and symptoms that accompany CRPS, but also give rise to more treatment modalities.

3.2. Objectives

1. To determine if there is a reduction in the excitability of inhibitory networks in M1 of participants with CRPS.

2. To determine if *SMO in M1* in patients with CRPS is altered as it is in musicians with dystonia, specifically for the representation of the FDI muscle (Rosenkranz et al., 2007).
3. To examine if there are *changes in the SMO* of patients with CRPS after GMI therapy.
4. To assess *associations between changes* in SMO organization and changes in CRPS symptoms such as pain and motor function.

3.3. Methods

3.3.1 Participants

3.3.1.1. Inclusion Criteria:

Participants ≥18 years with upper-limb CRPS must fit the ***clinical*** Budapest Diagnostic Criteria [Harden et al., 2007, **Figure 3.3**]. A total of 16 participants with CRPS were needed based on calculation using previous differences in maxiumum SICI (Eisenberg et al., 2005; Schwenkreis et al., 2005) at a power level of 0.8 and alpha level of 0.05 to give n = 16 participants; 16 age/gender matched controls were also included for comparison.

3.3.1.2. Exclusion Criteria:

Previous neurological disorders, psychiatric disorders such as severe depression (≥18 on Hospital Anxiety and Depression Scale-see below), and confounds to TMS.

3.3.2. Protocol

Before participants underwent GMI treatment, two baseline TMS experiments, separated by at least 1 week, were performed to establish reproducibility of the measures. In controls, only a single TMS experiment was performed as there is good normative data in this group (Rosenkranz et al., 2007). In each TMS experiment, a SICI recruitment curve followed by a SMO protocol was obtained.

3.3.2.1. SICI

SICI was measured at incrementing intensities of conditioning (pre-pulse) stimulation to obtain a SICI recruitment curve. The intensity of the conditioning pulse was set as a percentage of the active motor threshold (aMT), which was the minimum TMS intensity that produced a distinguishable MEP in 50% of the trials during an active muscle contraction. In order to find the optimal location for stimulation, the coil was moved around the head to find a location where the largest MEPs could be evoked in the FDI muscle. The test pulse intensity was adjusted until a 1 mV MEP was elicited in the FDI muscle and was kept constant throughout the experiment. The intensity of the conditioning pulse was incremented by 5 or 10% of aMT, ranging from 40 to 140% aMT, until a U-shaped SICI recruitment curve was obtained. The maximum amount of SICI, i.e., the deepest part of the U-shaped SICI recruitment curve, was measured for participants with CRPS and age/sex matched controls.

3.3.2.2. SMO

Participants underwent a SMO protocol using an intensity of the conditioning pulse that produced a SICI value of 50% (i.e., a 50% reduction of the test MEP) as determined from the

SICI recruitment curve. Vibration was applied to the FDI, APB, or ADM muscles while measuring SICI in the FDI muscle. The vibration lasted 1.5 seconds with the TMS pulse(s) timed to occur at the 1 second mark. In order to ensure that there was no voluntary contraction or a tonic vibration reflex during TMS [a tonic contraction in the muscle due to activation of 1a afferent fibres (Marsden, Meadows, & Hodgson, 1969)], the EMG was monitored throughout the experiment. A trial was excluded from analysis if there was a background contraction in the EMG recording. For every participant, 10 test alone trials, 10 SICI trials and 10 SICI trials with vibration of either the FDI, APB or ADM muscle were performed (30 trials total). To confirm that we could replicate the SMO findings of the Rosenkrantz (2009) study, experiments were performed on 9 non-age matched controls before they were performed on the participants with CRPS.

3.3.2.3. GMI

After the second baseline TMS experiment, participants with CRPS were trained in GMI and completed the therapy at their homes. They were asked to complete 60 minutes of GMI daily (7x's per week)[26] and their performance was monitored through electronic reports **[Figure 1.15B]** and journals **[Appendix B: 1]**. Following the 6 weeks of GMI, a final TMS experiment was performed.

3.3.3. Clinical measures

In addition to the TMS, questionnaires were used before and after GMI treatment to quantitatively determine improvements in the affected limb [**Appendix A**]. These

[26] In previous studies that have found GMI to be efficacious (G. L. Moseley, 2004a, 2006), participants were asked to perform the therapy for 60 minutes per day.

questionnaires included a *demographics and pain history questionnaire* [**Appendix B: 1**] and the *Hospital Anxiety and Depression Scale* (Zigmond and Snaith, 1983; **Appendix B: 6**) to determine exclusion criteria, the visual analogue scale [**Appendix B: 2**] and *McGill Pain Questionnaire (MPQ)* (Melzack, 2005; **Appendix B:3**) to assess pain, the *15D Questionnaire (15D)* (Sintonen, 2001; **Appendix B: 4**) to assess health-related quality of life, the *Pain Disability Index (PDI)* (Crighton et al., 2014; **Appendix B: 5**) to determine disability related to pain, the *Motor Activity Log (MAL)* ((Uswatte, Taub, Morris, Light, & Thompson, 2006); **Appendix B: 10**), to assess the quality of movement in the affected limb, and the *Activity Numerical Rating Scale (NRS)* ((Moseley, 2006); **Appendix B: 11**) to assess functionality in performing everyday tasks.

3.3.4. Data analysis

The SICI recruitment curves for the participants with CRPS (baseline values) and the age/sex matched controls were compared to determine if they both followed a U-shaped profile. The maximum SICI was compared between the two groups via an unpaired Student's t-test. The two baseline measures of SICI in the participants with CRPS (when available) were averaged together. In addition, the maximum SICI was compared before and after GMI treatment. The average pattern of SMO was qualitatively compared between the participants with CRPS and non-age/sex matched controls. Changes in clinical measures after GMI were also qualitatively assessed.

3.4. Hypotheses

1. Maximum SICI in participants with CRPS is lower compared to age/sex-matched controls due to the hyper-excitability of M1.
2. In participants with CRPS, prior to GMI therapy, there is an altered SMO profile compared to controls. This will be evidenced by a decrease in FDI SICI when the surrounding muscles (ABP and ADM) are vibrated (all SMO values > 100%), similar to musicians with dystonia.
3. Following GMI training, the SMO profile in participants with CRPS reverts to that of controls and the inhibition in M1 (SICI) is restored. This will be evidenced by an increase in FDI SICI when the surrounding muscles are vibrated (values < 100%) and by an increase in maximum SICI values (larger suppression of test MEP).
4. Following GMI training in participants with CRPS, the normalization of SMO and increase in M1 inhibition (SICI) will parallel the decrease in pain and increase in motor function.

3.5. Results

Only a small number of participants with CRPS were recruited to perform baseline measures of SICI and SMO [n = 4 SICI (CRPS 002, 003, 004 and 005) and n = 5 SMO (CRPS 001, 002, 003, 004, and 005)]. Further, it was only possible to provide GMI to two participants, and thus, only two post-GMI TMS experiments were performed [n = 2 GMI (CRPS 002 and 003)]. Therefore, this Chapter is presented as a pilot study on these initial measures. All of the participants with CRPS were women; this is not surprising given that CRPS is three times more common in women compared to men (de Mos et al., 2007). Some of the participants with

CRPS have missing data in the SMO experiments (CRPS 002 post-GMI and CRPS 003 pre and post-GMI) because the muscle vibration started to become painful.

3.5.1. Baseline SICI

3.5.1.1. Participants with CRPS

A single baseline SICI recruitment curve was obtained for CRPS 004 and 005 and two baseline measures were obtained for CRPS 002 and 003 as they also completed the GMI training. The data shown in **Figure 3.4** is the single or first baseline experiment for each participant. In each graph, the percent suppression of the test MEP is plotted against each conditioning (pre-pulse) intensity to demonstrate the SICI recruitment curve. The SICI recruitment curves displayed a U-shaped profile with a maximum amplitude of SICI (Max SICI, see values in each graph) at conditioning stimulation intensities of 85 to 95% of aMT, except for CRPS 004 at 65% aMT. There was good to fair reproducibility of Max SICI between the two baselines sessions for CRPS 002 (20.8% and 16.7%) and CRPS 003 (15.9% and 25.4%). The average Max SICI for the 4 participants with CRPS was **33.9 ± 17.1%** (the 2 baseline values for CRPS 002 and 003 were first averaged together). The mean test MEP amplitude used was **1.2 ± 0.6 mV.**

3.5.1.2. Age/Sex Matched Controls

The SICI recruitment curves for the 3 age/sex matched controls are presented in **Figure 3.5.** Like for the participants with CRPS, the SICI recruitment curves followed a U-shaped profile with maximum SICI occurring at a conditioning stimulation intensity of around 85%

aMT. The average maximum SICI in the control participants was **26.5 ±12.4%** and appeared not to be significantly different than the participants with CRPS (P = 0.55)**.** The mean test MEP amplitude used was **1.1 ± 0.4 mV**, similar to the participants with CRPS**.**

3.5.2 SMO

3.5.2.1. Non Age/Sex Matched Controls

Data from the 9 control participants that were *not* age/sex-matched to the CRPS participants is presented in **Figure 3.6**. The raw FDI MEPs for three different conditions: no vibration, vibrate FDI, and vibrate APB, is shown for a single participant in **Figure 3.6A**. It is evident that when the FDI muscle is vibrated (middle panel), the amplitude of the MEP during SICI (green trace) is larger compared with the no vibration condition (red trace, left panel), indicating that SICI measured in the FDI muscle decreased when the FDI muscle was vibrated. However, when a surrounding muscle, such as the APB was vibrated, the amplitude of the MEP measured during SICI decreased (blue line, right panel), indicating that SICI had increased. Similar to the Rosenkrantz (2009) data of **Figure 3.2**, there was a surround inhibition in the M1 region representing the FDI muscle in the group average of the data **[Figure 3.6B].** For example, when the FDI was vibrated (red bar), SICI in the M1 region supplying the FDI decreased, as represented by %SICI values > 100%. However, when the surrounding muscles were vibrated (APB black bar, ADM green bar), SICI in the M1 region supplying the FDI increased, as marked by %SICI values < 100%. Note that 2 of the 9 control participants did not display this exact pattern of surround inhibition.

3.5.2.2 Participants with CRPS

SMO data for the five participants with CRPS is presented in **Figure 3.7.** Two of the five participants with CRPS showed a similar SMO profile to the *non*-age/sex matched controls (CRPS 002 and 005). In the remainder of participants, there was an altered profile whereby SICI was either increased in the FDI muscle when the FDI was vibrated (e.g., CRPS 001) or decreased when a surrounding muscle was vibrated (e.g., CRPS 003 ADM). Compared to controls, the averaged SMO graph of the five participants with CRPS (**Figure 3.7F**) shows a much reduced modulation of SICI when the FDI and ADM muscles were vibrated. In addition, there was a decrease in SICI when the APB muscle was vibrated but this was likely dominated by data from CRPS 001. Not enough age/sex-matched control SMO profiles (n = 2) were obtained to make any reasonable comparisons.

3.5.3 GMI Clinical Data

Six weeks of GMI therapy were provided for CRPS 002 and CRPS 003. For Stage 1 (laterality recognition), accuracy and response time data for both participants was obtained **[Figure 3.8].** For CRPS 002, it is evident that her accuracy and response time **[Figure 3.8A and 3.8C]** improved for the left hand more than the right. Given that her left hand/right cortex was unaffected, this result was to be expected (G. L. Moseley, Butler, D.S., Beams, T.B. & Giles, T. J. , 2012). CRPS 003 initially had less pain and disability in her affected (left) hand compared to CRPS 002 **(Table 3.1).** She improved in both hands but to a lesser extent compared to CRPS 002 **[Figure 3.8B and D]**.

Pain levels were measured during the first two stages for CRPS 002 and for all three stages for CRPS 003 **[Fig. 9].** In both participants, the greatest pain decrease was during stage 1

[Figure 3.9A and C]; this change in pain stabilized during the latter stages **[Figure 3.9B, D]** or increased slightly **[Figure 3.9E].**

The amount of time spent doing GMI for each stage is shown in **Figure 3.10**, (data for CRPS 002 Stage 3 missing). While participants were asked to perform GMI for 60 minutes per day, they did not come close to accomplishing this goal. For CRPS 002, the average time spent per day over two weeks was 6.4 minutes during stage 1 and 3.5 minutes for stage 2. CRPS 003 put in more time and had averages of 9.7 minutes, 10.7 minutes, and 7.14 minutes for stage 1, 2, and 3 respectively.

Results of the questionnaires to examine motor function **(NRS and MAL),** disability due to pain **(PDI),** pain **(MPQ),** quality of life **(15D),** and number of flare-ups are presented for CRPS 002 and 003 in the **Table 3.1.** The normal scores for each questionnaire are shown below each heading. Both participants improved in response to GMI therapy. CRPS 002 was not receiving any other treatment during the time of the study and started with a very high pain level (MPQ = 41). Even though she did not achieve a large decrease in pain, her pain related disability (PDI mean score=4.14) and flare ups (1) greatly decreased and activity level went up (1.4). However, her quality of life improved only slightly (0.57). While CRPS 003 began at a lower pain level than CRPS 002 (MPQ = 19), her motor dysfunction was significantly higher (MAL = 1.62/1.64). She acquired a marked improvement in her motor function as measured by the MAL (3.89/4.10) and NRS (8.4). Further, while her flare-ups were constant before she began the therapy, she reported that they had completed disappeared after the therapy. Her improvement in motor function as well as decrease in flare-ups may be why her quality of life increased significantly more than CRPS 002 (0.88). It is important to note that, unlike CRPS 002, CRPS 003 was also taking narcotic medications as well as receiving physiotherapy.

3.5.4. Post-GMI SICI

SICI curves were obtained for both CRPS 002 and 003 post-therapy **[Figure 3.11]** and showed an increase in Max SICI post-GMI that occurred at similar intensities of conditioning stimulation (~95% aMT)**.** Following 6 weeks of GMI, CRPS 002's Max SICI increased from 20.8% to **6.79%** of the test amplitude **[Figure 3.11A].** For CRPS 003, Max SICI reached a value of **10.8%** of test amplitude from a baseline value of 15.9% **[Figure 3.11B].**

Reliable SMO data was not obtained post-GMI.

3.6. Discussion

The primary goal of this study was to determine if there is sensorimotor reorganization in patients with CRPS, using the innovative protocol developed by Rosenkrantz et al., 2009. In addition, the study aimed to investigate the excitability of the inhibitory circuits in M1 and compare it to that of healthy controls. Finally, the project sought to confirm the clinical efficacy of GMI therapy as well as uncover its potential mechanisms. We obtained preliminary measures of the excitability of inhibitory circuits (SICI) in M1 of participants with CRPS as well as their activation by sensory inputs (SMO). Contrary to other studies of CRPS (Eisenberg et al., 2005; Schwenkreis et al., 2005), we did not find differences in SICI between participants with CRPS and age and sex-matched controls when measuring maximum SICI from the recruitment curve. There were some differences in SMO; however, the small number of participants, as well as the pain induced by the vibration in some of these participants, precludes forming any firm conclusions of SMO in CRPS. In addition, we examined the effect of GMI in 2 participants with CRPS and found similar improvements in pain, motor function,

and disability as shown previously (G. L. Moseley, 2004a, 2006). Even though there were increases in maximum SICI after GMI, no conclusions can be made due to the small sample size and the poor adherence to the GMI protocol.

3.6.1. SICI

In our study, there was no difference in maximum SICI between CRPS and age and sex-matched control participants even though test MEP sizes were well matched between the groups and similar intensities of conditioning intensity were used. Previous literature has shown that, when the conditioning intensity is between 85% -95% of active motor threshold, SICI in the FDI can range between 20-30% in healthy controls (Peurala, Muller-Dahlhaus, Arai, & Ziemann, 2008; Ridding, Taylor, & Rothwell, 1995; Wagle-Shukla, Ni, Gunraj, Bahl, & Chen, 2009). We were able to replicate this value in the current study. However, we did not find a decrease in inhibition in participants with CRPS compared to age and sex-matched controls. SICI in M1 of patients with CRPS has been shown to be decreased compared to healthy controls but the results are conflicting. In one study, patients with CRPS had facilitation of the test MEP instead of inhibition, but this disinhibition was only found in the affected cortex (Eisenberg et al., 2005). In another, inhibition was still present in M1 of participants with CRPS (albeit much less than healthy controls) and both cortices seemed to be affected (Schwenkreis et al., 2005). The difference between these studies and ours may be due to our limited sample size or due to the difference in protocols. In our study, we performed an entire SICI recruitment curve for each participant. This allowed us to determine maximum SICI values from a large range of conditioning stimulation intensities. Since the two studies mentioned above did not acquire these curves, it is possible that they may have used conditioning stimulation intensities that were not optimal to produce maximum SICI. This

would lead to variations in mean SICI values between all three studies. It is also possible that the participants in our study were in greater pain during testing compared to participants in other studies, which may have led to an increase in inhibition. Painful heat stimulation to the hand causes MEPs in the FDI to be smaller, showing that pain may increase inhibition in M1 (Valeriani et al., 1999).

While it is still possible that there is a change in excitability, the nature and cause of this change remains unclear. One possibility is that less activity of GABAergic interneurons predisposes an individual to develop chronic pain and motor dysfunction following injury. Another possibility is that immobilizing the CRPS affected limb for a long period of time causes a change in M1 circuitry. Participants who had wrist immobilization following fractures exhibited greater intracortical facilitation (an increase in the test response following a conditioning stimulus) in the APB muscle of the immobilized hand compared to the contralateral one (Zanette, Manganotti, Fiaschi, & Tamburin, 2004). Further research is required to truly elucidate the complexities of M1 circuitry in patients with CRPS.

3.6.2. SMO

In the first 9 non-age matched controls, we replicated results from previous literature (Rosenkranz et al., 2008; Rosenkranz et al., 2009; Rosenkranz & Rothwell, 2003; Rosenkranz et al., 2005) in that there was a decrease in inhibition in the FDI when the FDI muscle was vibrated, but an increase when the surrounding muscles (ABP and ADM) were vibrated. Uniquely, our study performed an SMO protocol in participants with CRPS in order to test for altered sensory input to M1. In these individuals, we expected the results to resemble those found in dystonic musicians, i.e., a decrease in FDI SICI when the surrounding muscles were

vibrated (Rosenkranz et al., 2009; Rosenkranz et al., 2007). The patient average showed that FDI SICI was modulated in a similar manner when the FDI and ADM were vibrated but the extent of modulation was smaller. Moreover, there was a large decrease in FDI SICI when the APB was vibrated, unlike in controls. Only two of the five participants with CRPS followed a similar SMO profile to the average profile measured in the nine healthy controls. The variation in the results acquired may be due to the difference in pain and and motor dysfunction across participants. Without a larger sample size, this variability makes it difficult to make a definitive conclusion about SMO in participants with CRPS. While the profile of these participants is not the same as that found in musicians with dystonia, these preliminary results suggest that there may be a change in the sensorimotor organization of patients with CRPS.

The phenomenon of surround inhibition in the M1 is considered to be the sensorimotor analogue to the visual system's center-surround inhibition. It is believed that muscle vibration activates muscle spindles and Ia afferents, which then primarily activate neurons in area 4 of M1. These neurons in turn have reciprocal inhibitory and excitatory connections with each other, the balance of which determines whether vibration of one muscle has an inhibitory or excitatory effect on the activation of another (Belvisi et al., 2014). This leads to SICI decreasing in the vibrated muscle while increasing in adjacent ones. One major confound with performing the SMO protocol in participants with CRPS is that vibrating their hand can elicit pain. As mentioned before, a painful stimulation can decrease the size of MEPs (Valeriani et al., 1999). This phenomenon is thought to be due to modulation of neurons in the M1 by inhibitory inputs from the secondary somatosensory cortex (SII). Since vibration was delivered before the TMS pulses, it is difficult to know if the results that we obtained are indeed due to a

lack of surround inhibition or due to M1 modulation by nociceptive pathways in SII (Valeriani et al., 1999).

3.6.3. GMI

We were only able to recruit two participants with CRPS to undergo the three stage GMI therapy and the participants unfortunately did not complete nearly as much time in doing their average daily GMI exercises as called for in the protocol. In stage 1, CRPS 002 was much worse at recognizing her affected (right) hand compared to her un-affected hand and performed more poorly than CRPS 003. This is not surprising as CRPS 002 began with more pain and it has been previously reported that higher pain is associated with worse performance on laterality recognition tasks, particularly in trials involving the affected hand (G. L. Moseley, Butler, D.S., Beams, T.B. & Giles, T. J. , 2012). While the pain decreased greatly for both participants during stage 1, this change became almost non-existent toward the latter two stages. For CRPS 002, this could be due to the fact that she did not spend the necessary amount of time to obtain the full clinical benefits, especially given her high pain level. CRPS 003 did spend more time than 002 but was also on other concurrent therapies. Her pain reduced to a minimal amount during the latter two stages thereby possible creating a ceiling effect on potential improvement. If GMI therapy becomes too repetitive to patients, clinical improvement can slow down (G. L. Moseley, Butler, D.S., Beams, T.B. & Giles, T. J. , 2012). While this is a possibility with either of our participants, it is unlikely due to the fact that neither of our participants spent adequate amounts of time performing GMI.

At the end of the six-week therapy, both participants had improvements on clinical measures. It is important to note that CRPS 002's improvements are more relevant to this study as she was not on other therapies during this time. In previous literature, activity level, according to the NRS, improved by 20% and pain, measured by the VAS, improved by 23.4% (G. L. Moseley, 2006). Both of our participants showed similar improvements even though we used a more accurate measure of pain [MPQ; (R. Melzack, 2005)]. In addition, we noticed improvements in quality of life as well as disability, measures that were not investigated in previous studies. Preliminary evidence shows that GMI may indeed have clinical benefit for patients with CRPS as previous research has suggested (G. L. Moseley, 2004a, 2006). However, future studies are required that control for concurrent treatments that participants are receiving as well as have larger sample sizes. Further, objective measures such as swelling and limb temperature must also be obtained in order to determine if patients still meet Budapest Criteria post-therapy.

Following GMI therapy, the shape of both participants' SICI curve changed and max SICI values decreased. It is possible that recovery from CRPS is associated with a reversal of M1 reorganization that has occurred as well as a decrease in disinhibition. As mentioned earlier, the goal of GMI is to sequentially activate motor circuits in a graded manner (G. L. Moseley, Butler, D.S., Beams, T.B. & Giles, T. J. , 2012). Stage 1 of GMI involves making hand laterality judgements which increases activation in the intraparietal sulcus and premotor cortex (PMC) contralateral to the hand that is presented (de Lange, Helmich, & Toni, 2006). In stage 2, participants must imagine making movements with the affected and unaffected limbs; this causes an increase in activation in the supplementary motor area (SMA), PMC and M1, albeit, not as much as actually executing movements (Park et al., 2015). Finally, in stage 3 of

GMI, participants place their affected limb in the mirror box and make movements with the unaffected limb. Interestingly, this leads to activation in both the ipsilateral and contralateral cortices, specifically in the SMA, PMC, SII, and M1 (Milde et al., 2015). Since the PMC and prefrontal cortex have inhibitory inputs to M1 (Duque et al., 2012), one possibility is that activating these regions using GMI increases inhibition in M1. However, in a previous TMS study with healthy controls, mirror visual feedback improved performance on a motor task that was correlated with increased excitation in M1 of both hemispheres even when only one hand was moving; however, mirror visual feedback did not affect SICI (Nojima et al., 2012). Therefore, it is still unclear whether CRPS is associated with disinhibition and if so, whether GMI can reverse this disinhibition. Our preliminary results show that GMI may affect excitability in M1 of patients with CRPS but more research needs to be performed if this effect is to be further explained.

3.7. Figures

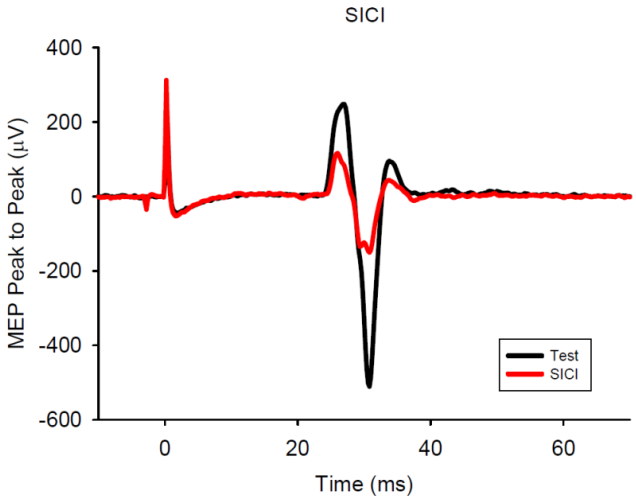

Figure 3.1: Mean MEP of a control participant with (red) and without (black) SICI. The hand region of the participant's left M1 was stimulated and the resulting MEPs were recorded in the FDI muscle. During SICI, two pulses were given, the first below threshold and the second above. The two pulses were separated by an interstimulus interval of 3 ms.

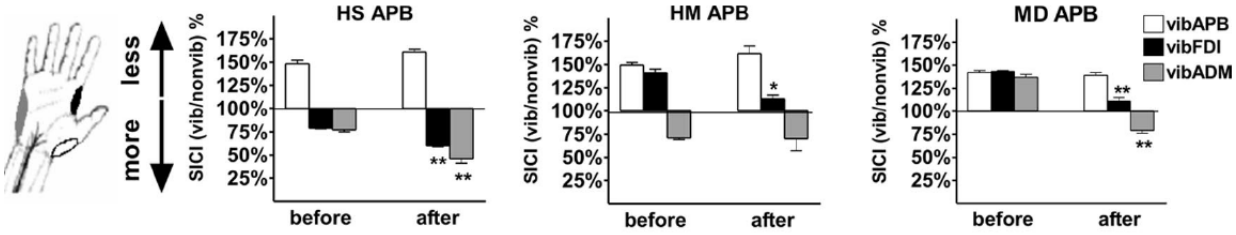

Figure 3.2: SICI recorded in the APB (thumb) muscle during vibration (vib) as a percentage of SICI without vibration (novib): SMO = (SICI vib/SICIno vib) x 100%. Note that a decrease in SICI (less) is marked by the bar going above >100% and an increase in SICI by values < 100%. The FDI, APB, and ADM muscles were vibrated sequentially in Healthy Controls (*HC*), Healthy Musicians (*HM*), and Musicians with dystonia (*MD*).

Taken from *(Rosenkranz et al., 2009)*

To make the *clinical* diagnosis, the following criteria must be met:

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

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For *research* purposes, diagnostic decision rule should be at least one symptom ***in all four*** symptom categories and at least one sign (observed at evaluation) in two or more sign categories.

Figure 3.3: Budapest Diagnostic Criteria for Complex Regional Pain Syndrome. The *clinical* criteria have a sensitivity of 0.99 and a specificity of 0.68 (minimizes false negatives). For the *research* criteria, the sensitivity is 0.94 and specificity is 0.70 (minimizes false positives).

Taken from *(Harden, Bruehl, Stanton-Hicks, & Wilson, 2007)*

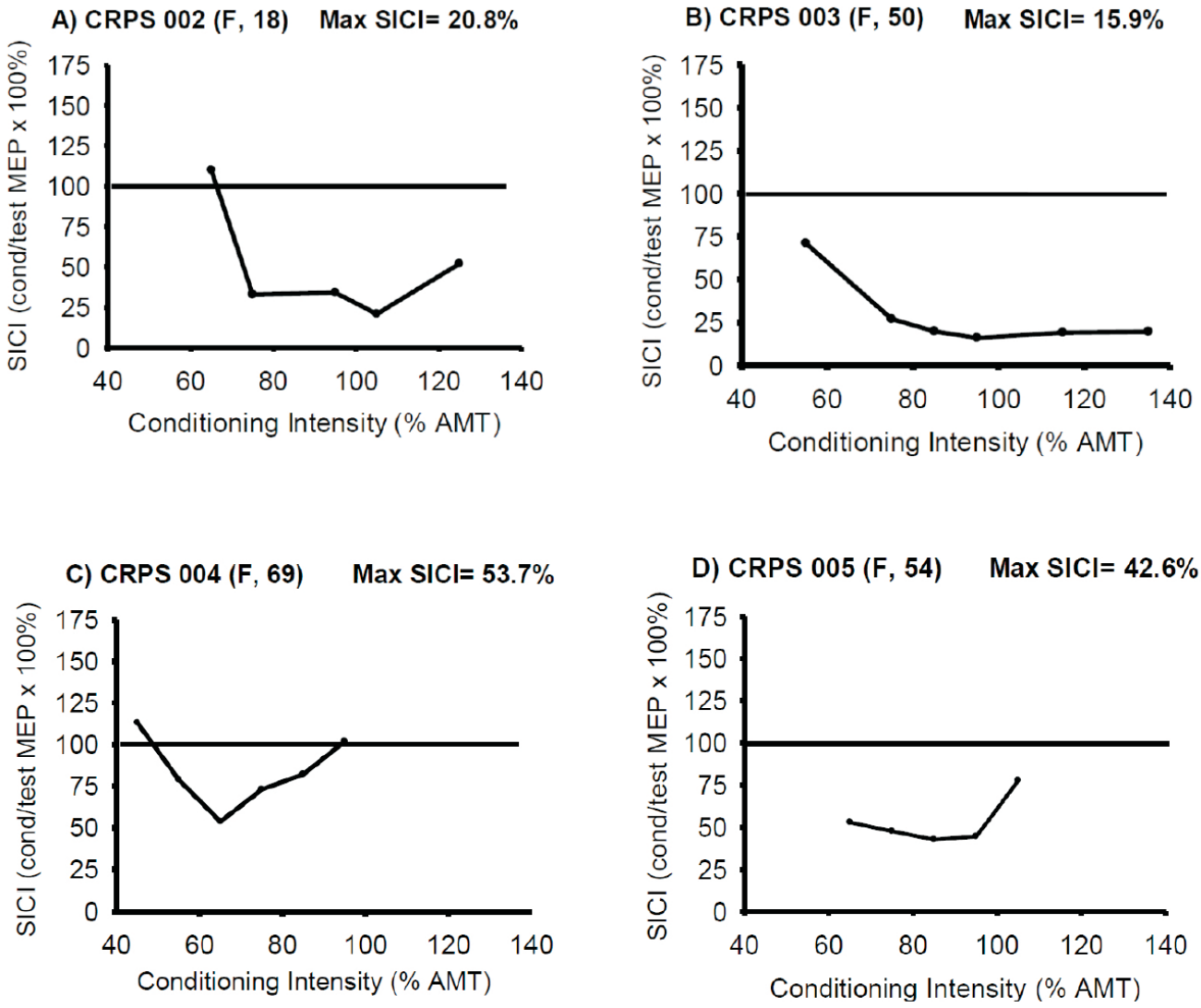
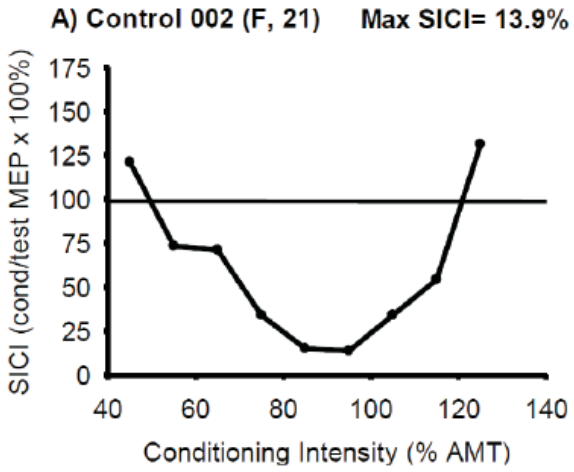
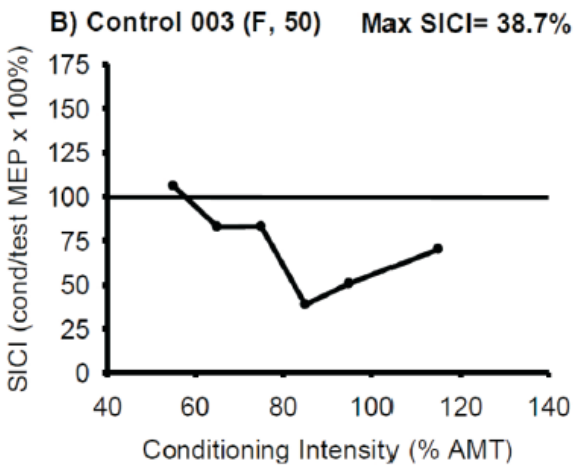


Figure 3.4: Participants with CRPS SICI Curves. SICI recruitment curves were obtained for ***A)*** CRPS 002 ***B)*** CRPS 003 ***C)*** CRPS 004 and ***D)*** CRPS 005. We were not able to obtain a curve for CRPS 001. The sex and age respectively of each participant is written to the right of the participant number. The maximum amount of inhibition (percent of test) is described above each figure. The line indicates the point at which no SICI occurs.





C)

N/A

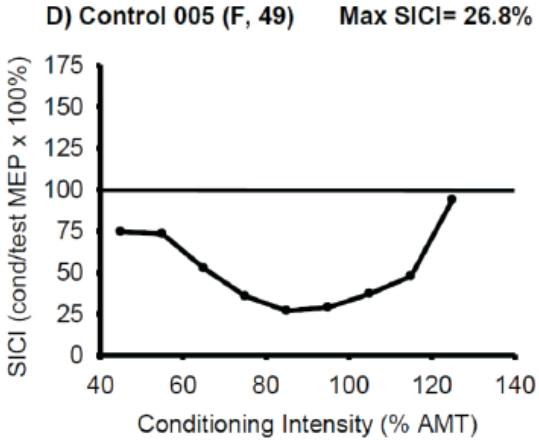


Figure 3.5: Age Matched Control SICI Curves. SICI recruitment curves were obtained for age matched controls for ***A)*** CRPS 002 ***B)*** CRPS 003 ***C)*** CRPS 004. The maximum amount of inhibition (percent of test) is described above each figure. The line indicates the point at which no SICI occurs.

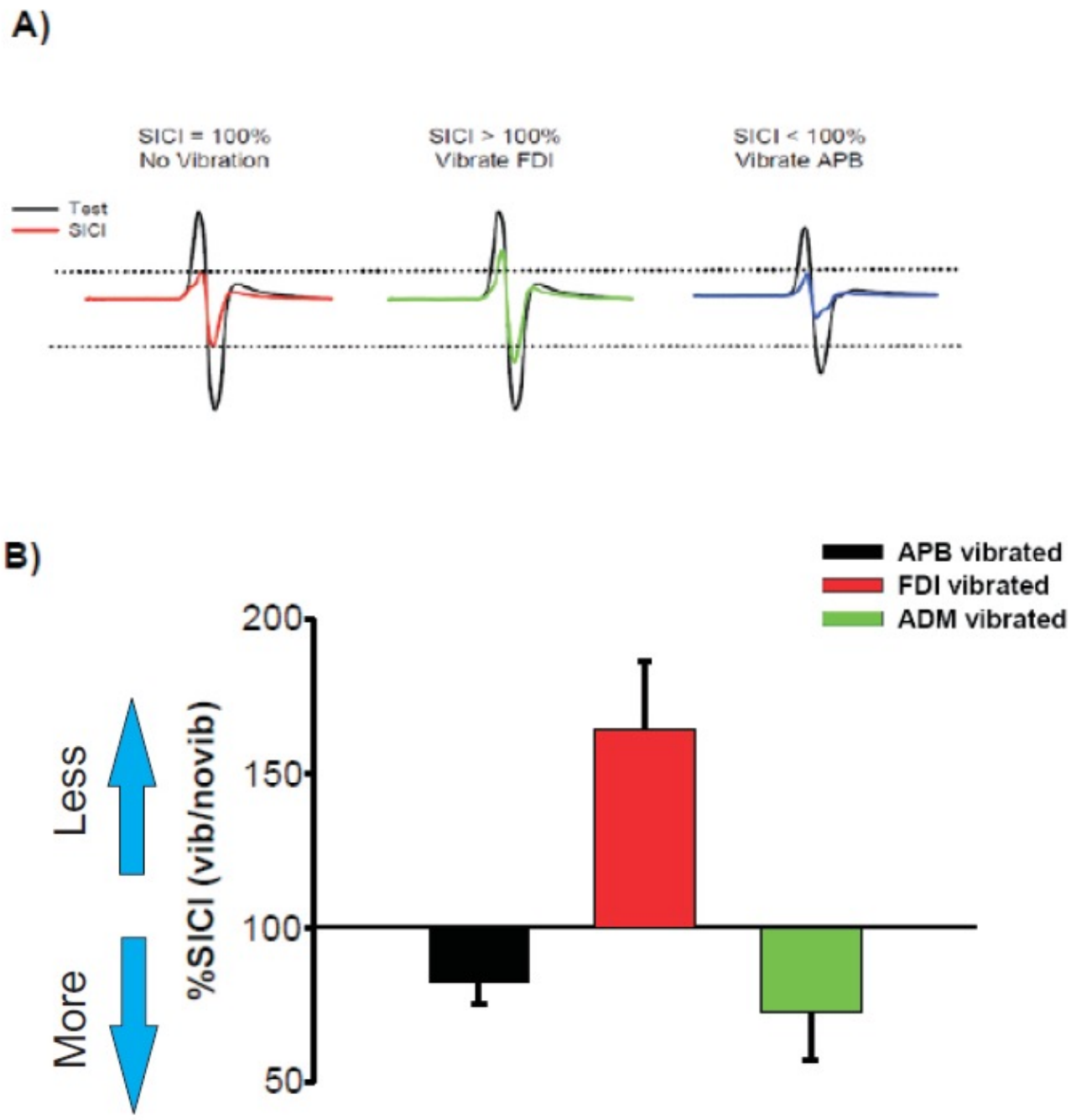


Figure 3.6: SMO Raw Data of *A)* one *B)* average percentage graphs of non-age matched controls when the FDI muscle is recorded.

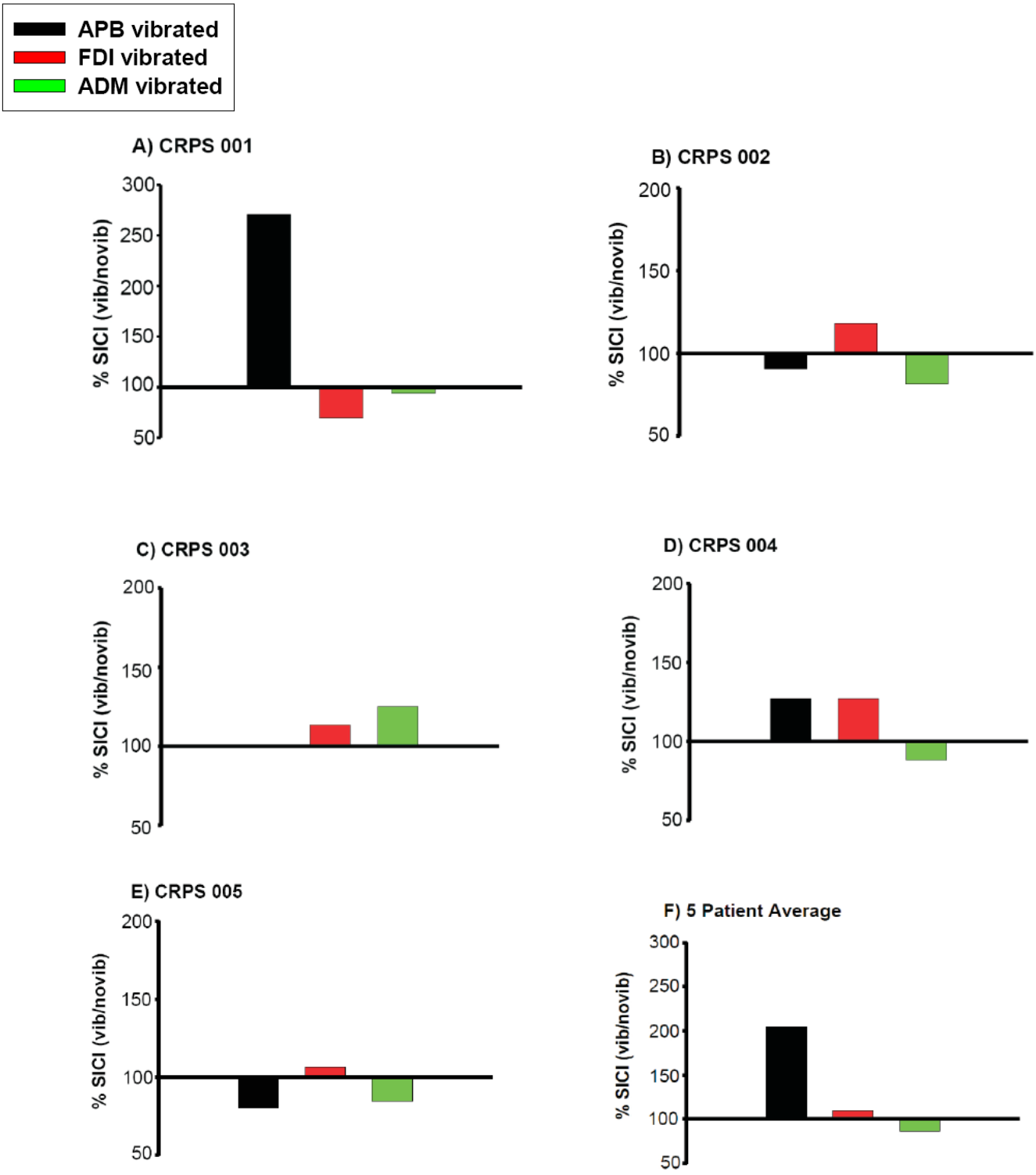


Figure 3.7: SMO Data for Participants with CRPS. SMO graphs were obtained for ***A)*** CRPS 001 ***B)*** CRPS 002 ***C)*** CRPS 003 and ***D)*** CRPS 004 ***E)*** CRPS 005. A decrease in inhibition is shown by a bar going above the axis.

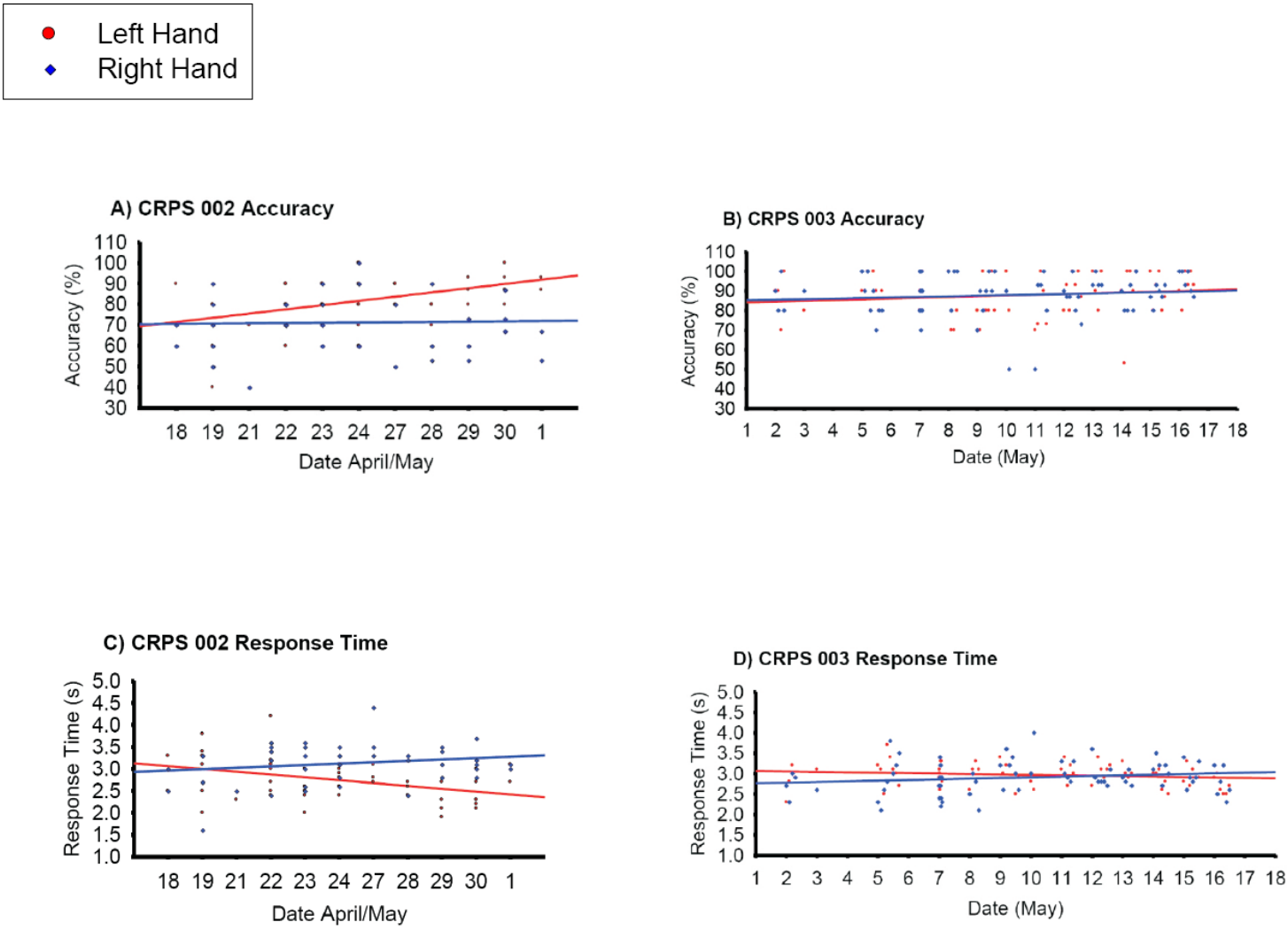


Figure 3.8: GMI Stage 1 Graphs for CRPS 002 and CRPS 003. ***A)*** CRPS 002 Accuracy Graph ***B)*** CRPS 003 Accuracy Graph ***C)*** CRPS 002 Response Time Graph ***D)*** CRPS 003 Response Time Graph

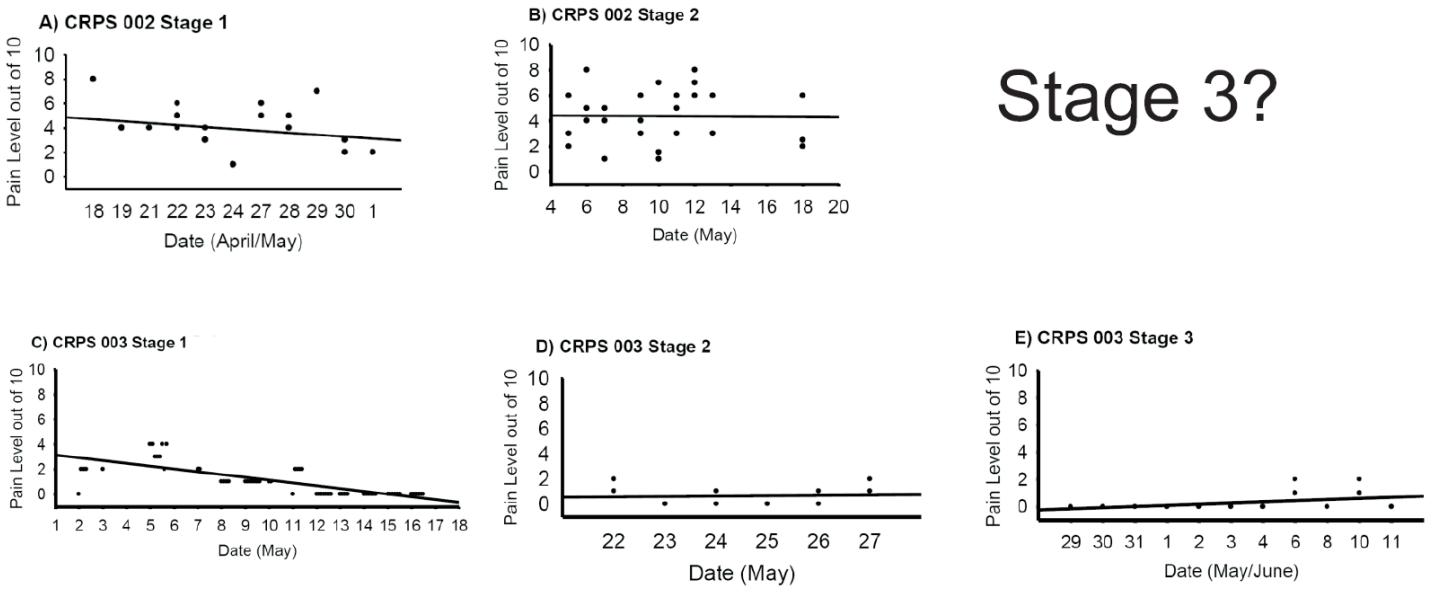


Figure 3.9: GMI Pain Graphs. ***A)*** CRPS 002 Stage 1 pain ***B)*** CRPS 002 Stage 2 Pain Graph ***C)*** CRPS 003 Stage 1 Pain ***D)*** CRPS 003 Stage 2 Pain ***E)*** CRPS 003 Stage 3 Pain. Stage 3 pain data for CRPS 002 was not obtained.

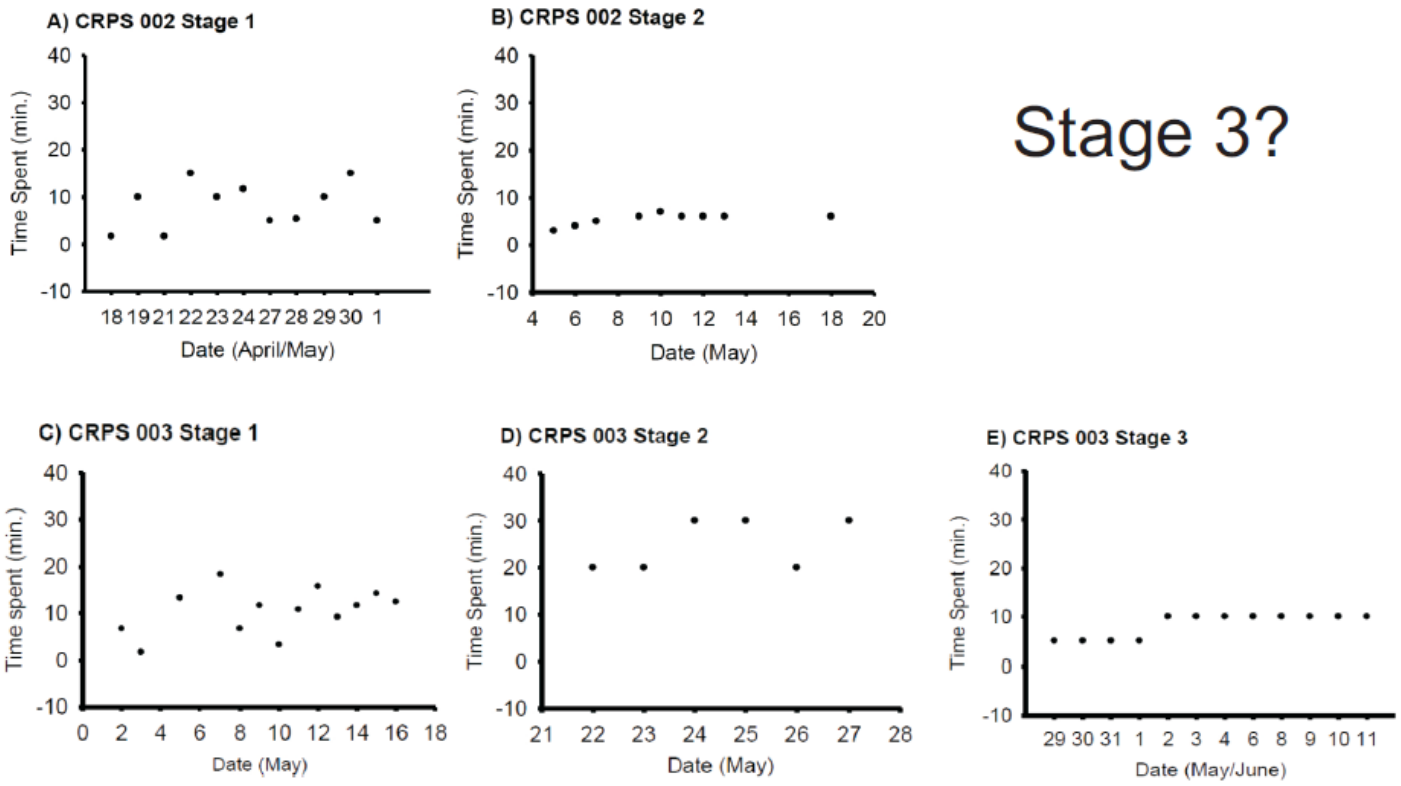


Figure 3.10: GMI Amount of time spent. ***A)*** CRPS 002 Stage 1 time spent ***B)*** CRPS 002 Stage 2 time spent ***C)*** CRPS 003 Stage 1 time spent ***D)*** CRPS 003 Stage 2 time spent ***E)*** CRPS 003 Stage 3 time spent. Stage 3 time spent data for CRPS 002 was not obtained.

	NRS (10)	MAL (Amount/ How well; 5)	PDI (0)	MPQ (0)	15D (1)	Flare Ups
CRPS002						
Before	3.6	3.23/3.13	5.57	41	0.55	4
After	5.0	3.33/3.30	4.14	38	0.57	1
Difference	**+1.4**	**+0.10/0.17**	**-1.43**	**-3**	**+0.02**	**-3**
CRPS003						
Before	3.2	1.62/1.64	3.86	19	0.69	constant
After	8.4	3.89/4.10	2.00	15	0.88	0
Difference	**+5.2**	**+2.27/2.46**	**-1.86**	**-4**	**0.19**	**Complete Improvement**

Table 3.1: Questionnaire Data. NRS=Numerical Response Scale; MAL= Motor Activity Log; Pain Disability Index (PDI);MPQ= McGill Pain Questionnaire; 15D= 15D Quality of Life; best score in brackets

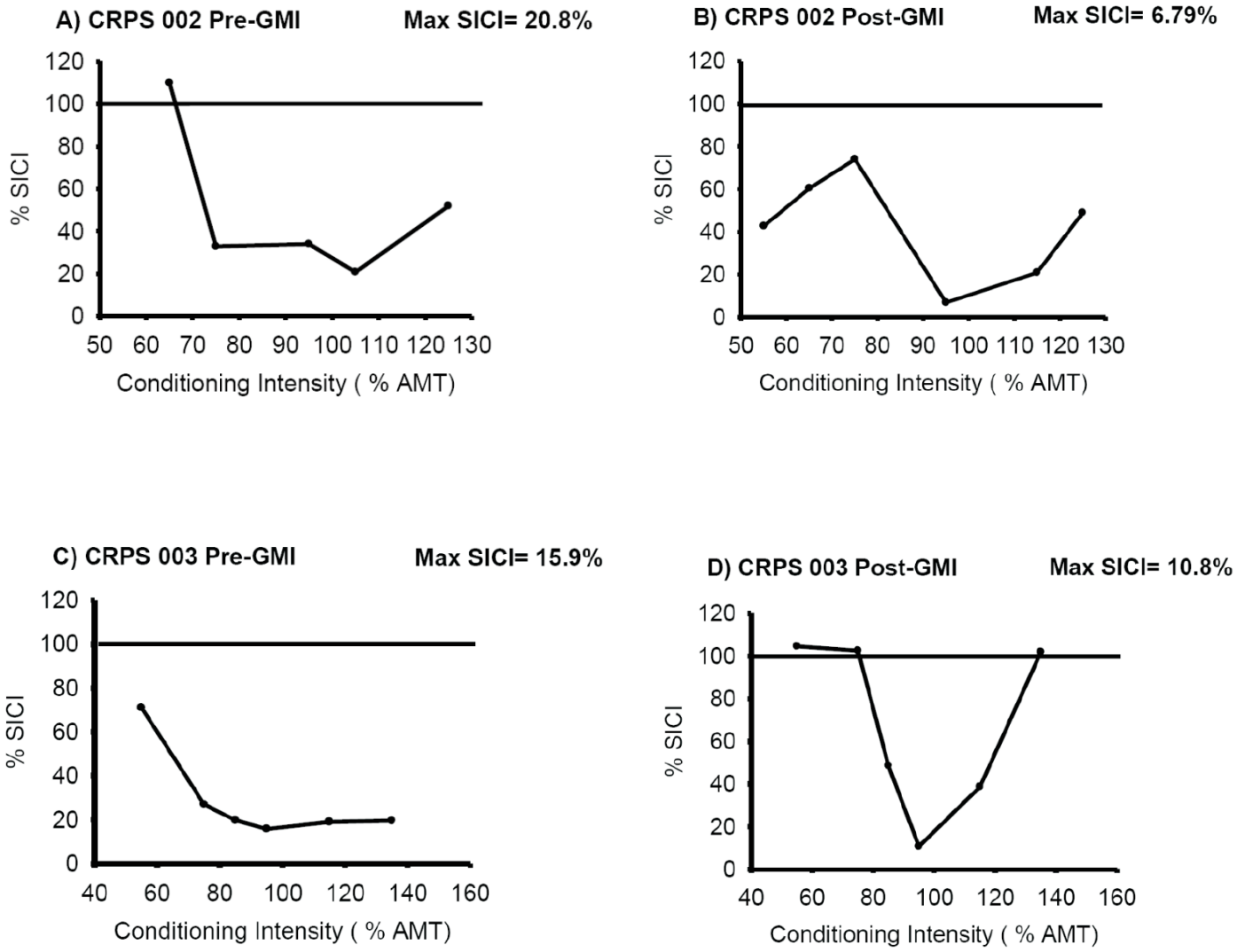


Figure 3.11: SICI Recruitment Curves before and after GMI Therapy. ***A)*** CRPS 002 Pre-GMI SICI ***B)*** CRPS 002 Post GMI SICI ***C)*** CRPS 003 Pre-GMI SICI ***D)*** CRPS 003 Post-GMI SICI. Line indicates no SICI.

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Chapter 4

General discussion

4.1. Summary of Thesis

Pain is one of the most useful perceptions adapted by humans for survival. Individuals afflicted with congenital insensitivity to pain do not have access to this adaptation and consistently present to the emergency room with injuries due to accidental self-harm (Rahalkar et al., 2008). However, the perception of pain is a double-edged sword, one that needs to be kept balanced between optimizing the utility of the response while preventing pathology. Chronic pain (CP) can be a severely debilitating disorder that leaves patients in constant agony. It can lead to depression, anxiety, and increased risk of suicide. Unfortunately, treatments for these individuals are limited which may, in part, be due to the fact that the pathophysiology of CP is still not properly understood.

This thesis aimed to investigate the diffuse changes that may occur in the brains of individuals with CP. In *Chapter 2*, we replicated previous studies (B. D. Dick et al., 2008; Eccleston, 1994, 1995; Moore et al., 2012) and showed that cognitive dysfunction is indeed present in individuals with CP but went further in showing that this dysfunction is associated with increased pain related disability and decreased quality of life. This study was the first to assess cognitive function in a large sample of individuals with CP to explore predictors of pain-related disability through objective, reliable neuropsychological tests as well as gather information on pain, depression, anxiety, sleep quality, medication regimen, disability, quality of life, and even demographics. For the first time in a CP population, we showed that working memory and quality of life are predictors of disability and that pain, depression, and working memory together are predictors of quality of life. In addition, almost half of our participants had at least one score in the clinically significant range on the Test of Everyday Attention and many had several scores in this range. This is strong evidence of a significant cognitive

disability, especially considering our population had a high mean education level. While CP was traditionally thought to be a disorder due to changes in the peripheral nerves as well as spinal cord, cognitive abnormalities are suggestive of potential neuroplastic changes in the brain.

In *Chapter 3*, we investigated neuroplasticity in individuals with Complex Regional Pain Syndrome (CRPS). Using a short-interval intracortical inhibition (SICI) procedure, we investigated the excitability of primary motor cortex (M1) circuits in healthy controls as well as participants with CPRS. Uniquely, we investigated sensorimotor organization (SMO) in these patients using a novel and innovative protocol, which allows the ability to examine sensory inputs to M1 (Rosenkranz et al., 2009). We then went a step further and looked at the effects of Graded Motor Imagery (GMI) therapy on SICI as well as SMO. We recruited five participants with CRPS and five age- and sex- matched controls. Unlike previous studies, in our very small sample size, we did not find a significant difference in max SICI between groups. For the SMO procedure, we first replicated results of previous studies (Rosenkranz et al., 2008; Rosenkranz et al., 2009; Rosenkranz et al., 2005) on nine healthy controls and then proceeded to investigate the five participants with CRPS. There was a difference between the average SMO profile of participants with CRPS and that of the nine healthy controls. We were only able to look at GMI in two participants but found that it does indeed have therapeutic efficacy and a potential to change maximum SICI. We concluded that this study provides preliminary evidence of changes in SMO in patients with CRPS as well as the neuroplastic effects of GMI but because of several confounds (low numbers, low adherence to GMI therapy and vibration producing pain) future studies are needed to get a clearer picture.

4.2 A Unified Approach

There is a tremendous of amount of evidence showing that pain, and specifically CP[27], is the result of a diffuse cortical phenomenon involving the interplay between sensory, motor, and especially, cognitive systems. When an individual is distracted while experiencing pain, there is a decrease in activity in their pain neuromatrix, specifically the insula, thalamus, and anterior cingulate cortex (ACC) (Bantick et al., 2002), and greater activity in analgesic regions such as the periaqueductal gray (PAG) (Tracey et al., 2002). At the same time, CP can cause performance deficits in tasks involving attention and working memory (see *Chapter 2*), diminish evoked potentials which are markers of attentional function (Lorenz et al., 1997), and reduce gray matter in regions involved in the attentional system (e.g. prefrontal cortex and ACC) (Kuchinad et al., 2007; Rodriguez-Raecke et al., 2009). Further, individuals with CRPS experience what some have proposed is a hemi-neglect-like syndrome in which they take longer to recognize the affected limb (G. L. Moseley, 2004b); interestingly, when an individual crosses their arms, the neglect is transferred to the healthy hand (G. L. Moseley, Gallace, & Spence, 2009). Individuals with CRPS also have hyperactivation in the posterior parietal area during a finger tapping task, a region shown to be involved in spatial attention as well as integrating sensory input (Maihofner et al., 2007). The extent of parietal lobe dysfunction in CRPS is correlated with motor dysfunction (Maihofner et al., 2007) as well as allodynia (Cohen et al., 2013). Therapies such as GMI, which increase attention to the affected limb can decrease the amount of pain experienced, increase motor function, and improve functional

[27] While CRPS is a form of CP, at times the two will be distinguished in this section. This is due to the fact that CRPS is a rare CP disorder that requires a very specific diagnosis, presents with unique signs and symptoms, and has an etiology that is not completely understood. In order to discuss both Chapters 2 and 3, it is essential to provide a unified explanation that includes CRPS as well as all other CP disorders.

outcomes (G. L. Moseley, 2004a, 2006; G. L. Moseley, Butler, D.S., Beams, T.B. & Giles, T. J. , 2012), possibly though reversing sensorimotor organization that has occurred (*Chapter 3*).

The multi-factorial nature of pain may be necessary for its goal of promoting survival and may be due to the interaction of complex intrinsic sensory, motor, and cognitive neural networks. A somewhat unified model was proposed recently that suggests the concept of a "dynamic pain connectome"(Kucyi & Davis, 2015). An extension to the idea of a "pain matrix", the pain connectome is a spatial and temporal neural signature that represents the integration of the processing of the different facets of pain. The pain experienced after a nociceptive stimulus is dependent on "pre-stimulus activity" in the signature. This activity in turn is determined by an individual's attentional state towards the stimulus, which fluctuates over time. The model posits that three general brain systems exist that are involved in attentional shifts related to nociceptive stimuli, evidence of which comes from functional connectivity studies [28]. The salience network (SN) is comprised of the dorsal ACC, anterior insula, mid-cingulate cortex, temporoparietal junction, and dorsolateral prefrontal cortex (PFC). This network is responsible for determining to what extent external stimuli intrinsically capture attention (Downar, Crawley, Mikulis, & Davis, 2000; Kucyi & Davis, 2015; Seeley et al., 2007). There is greater activity in this region when attention is maintained on pain. This is understandable given the high salience of pain as a survival-related stimulus (Eccleston & Crombez, 1999). An opposing network, known as the default mode network (DMN), is comprised of the posterior cingulate cortex, medial PFC, and lateral parietal lobe among other regions. The DMN is known to become active when an individual is performing no task in

[28] Functional connectivity is the existence of correlation between signal fluctuations in distinct brain areas during resting state functional MRI (van den Heuvel & Hulshoff Pol, 2010). Regions that become active together during task performance also show strong functional connectivity.

particular - in other words, during a "resting state". In healthy participants, the experience of pain causes deactivation in the DMN; the opposite occurs when a person's focus shifts away from pain (Kucyi, Salomons, & Davis, 2013). The third network is the PAG descending pain modulatory system described in *Chapter 1*. It is has been implicated in analgesia as well as pain modulating attentional processes. For example, functional and structural connectivity between the DMN and PAG in healthy participants experiencing pain has been associated with an increase in attention away from pain (Kucyi et al., 2013). Davis suggests that each individual has variation in the above systems, which leads to a unique "intrinsic attention to pain (IAP)". The IAP may be disrupted in various CP conditions, including CRPS, as evidenced by abnormal functional connectivity in the DMN, SN, and PAG systems (Becerra et al., 2014; Bolwerk, Seifert, & Maihofner, 2013; Kucyi & Davis, 2015). The 'dynamic pain connectome' theory proposed by Davis can explain the constant perception of pain as well as cognitive disruption experienced by individuals with CP (*Chapter 2*). However, the theory has yet to be fully developed, remains overly simplistic and fails to account for many of the signs and symptoms experienced by individuals with CRPS. For example, Davis fails to account for the SN's role in interoceptive awareness and modulating autonomic reactivity (Seeley et al., 2007). Given that functional connectivity of the SN is abnormal in CRPS (Becerra et al., 2014), this function may be crucial in understanding the central (and possibly peripheral) autonomic disruption that accompanies this disorder. Further, Davis' theory omits other relevant intrinsic brain networks such as the fronto-parietal (FP; includes PFC and posterior parietal cortex) and sensorimotor (SM) networks. There has been evidence that the functional connectivity of these networks has also been altered in a variety of pain conditions, especially CRPS (Becerra et al., 2014). Altered functional connectivity in the FP network in individuals with CRPS may explain

the abnormal parietal function as well as hemi-sensory neglect experienced by these patients. Further, individuals with CRPS have altered FC within the M1 and primary somatosensory (S1) portions of the SM network. This is in line with previous studies, which have shown aberrant activation in M1 and S1 in individuals with CRPS (Eisenberg et al., 2005; Maihofner et al., 2007; Maihofner, Forster, Birklein, Neundorfer, & Handwerker, 2005; Schwenkreis et al., 2005; Swart et al., 2009)

A diffuse interface of distinct, intrinsic neural networks gives rise to the phenomenon that humans experience as "pain". During CP, communication breaks down within each individual network as well as within the entire interface. Cognitive, autonomic, motor, executive, and affective abnormalities are the result of malfunction of each individual network but chronic pain may be the result of malfunction of the entire interface. Damage of tissue is merely an input to this complex system, one that is not necessary to maintain or even initiate pain. Therefore, it is evident that the current IASP definition of pain, which insists on pain being described only in terms of tissue damage, is unsatisfactory. A new description is to be created if pain is to be properly investigated as well as effectively treated.

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Appendix A: Clinical Measures

1. Demographic and Pain History

Background Information

Please answer the following background questions.

1) How old are you? _____ years

2) Gender Male Female

3) Education (please circle all that apply):

Some high school (no diploma)	Yes	No	How many years? _____
High school diploma	Yes	No	
Post-secondary	Yes	No	How many years? _____
Other education (specify below)	Yes	No	How many years? _____

_____

6) Please indicate your current employment status.

 Employed full time Unemployed Student

 Employed part time On sick leave or medical leave Retired

The following questions are about the pain related to the problem you are attending the pain clinic for.

1) Please describe your current problem in a few words (e.g., low back pain, headaches, arthritis, joint pain, injury-related pain). _____

2) How long have you had CRPS?

_____

4) How long have you had pain from CRPS?

_____

5) How did your current pain problem begin?

- Motor vehicle accident
- Pain just began (without injury)
- Accident at home
- After an illness
- Accident at work
- Other *(please specify):* _____
- Other accident

6) Are you participating in a Workers Compensation Board (WCB) program or another return to work program? No Yes

7) Do you have other sources of (chronic) pain? No Yes

8) If YES how long have you had this pain?

_____

9) What is the diagnosis of for the source of this pain (Please Explain)

_____

10) Where do you experience the **most** pain? **Please check only one**. If you cannot decide which location has the most pain, please select the area in which your pain first occurred.

- Head, face, mouth
- Neck (cervical) region
- Shoulders
- Arms, hands
- Chest
- Abdominal Region
- Upper back
- Lower back, lumbar spine
- Legs, feet
- Pelvic region
- Hips
- Genital region
- Other *(please specify):* _____

11) If you have pain in other areas as well, **please check all that apply**.

- Head, face, mouth
- Neck (cervical) region
- Shoulders
- Arms, hands
- Chest
- Abdominal Region
- Upper back
- Lower back, lumbar spine
- Legs, feet
- Pelvic region
- Hips
- Genital region
- Other *(please specify):* _____

9) Which statement best describes your pain experience?

- Always present - Always the same intensity.
- Always present - Intensity varies.
- Often present - Have short periods without pain.
- Often present - Have pain-free periods lasting 1 to 6 hours.
- Often present - Have pain-free periods lasting more than 6 hours.
- Occasionally present - Have pain daily, lasting a few minutes to an hour.
- Occasionally present - Have pain daily, lasting a few seconds to a few minutes.
- Infrequently present - Have pain every few days or weeks.

10) Do you have difficulty reading or understanding what you read? No Yes

11) Do you have difficulty reading or understanding written English? No Yes

12) Have you ever been treated by a psychiatrist or psychologist? No Yes
If yes, please state when and your diagnosis: _____

13) Are you afraid of tight and/or closed spaces (claustrophobic)? No Yes

If YES, how would you rate this fear from 1-10 (10 being the worst imaginable fear)

_____

14) Have you ever had a serious head injury? No Yes

If yes, please describe this injury: _____

_

Did you lose consciousness with that injury? No Yes

15) Do you have any neurological conditions? No Yes

If yes, please list: _____

_

2. Visual Analogue Scale

Pain Rating Scale

Please draw a vertical line on the line below that shows your **current** pain level.

0
No pain

10
Worst pain
Imaginable

3. McGill Pain Questionnaire

McGILL PAIN QUESTIONNAIRE

Please place a check mark (√) beside each word that describes the pain you experienced during your pain.

1
- FLICKERING
- QUIVERING
- PULSING
- THROBBING
- BEATING
- POUNDING

2
- JUMPING
- FLASHING
- SHOOTING

3
- PRICKING
- BORING
- DRILLING
- STABBING
- LANCINATING

4
- SHARP
- CUTTING
- LACERATING

5
- PINCHING
- PRESSING
- GNAWING
- CRAMPING
- CRUSHING

6
- TUGGING
- PULLING
- WRENCHING

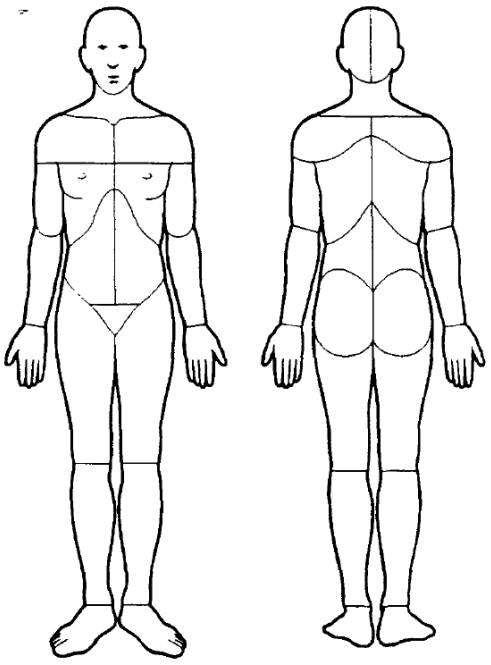
7
- HOT
- BURNING
- SCALDING
- SEARING

8
- TINGLING
- ITCHY
- SMARTING
- STINGING

9
- DULL
- SORE
- HURTING
- ACHING
- HEAVY

10
- TENDER
- TAUT
- RASPING
- SPLITTING

IN THE DRAWING BELOW, PLEASE 'SHADE IN' THE AREAS THAT CORRESPOND TO WHERE YOU FEEL PAIN.



Comments:

PPI PLEASE CIRCLE A NUMBER TO INDICATE HOW MUCH PAIN YOU ARE EXPERIENCING PRESENTLY

0 1 2 3 4 5 6 7 8 9 10

NO PAIN MILD DISCOMFORTING DISTRESSING HORRIBLE EXCRUCIATING

11
- TIRING
- EXHAUSTING

12
- SICKENING
- SUFFOCATING

13
- FEARFUL
- FRIGHTFUL
- TERRIFYING

14
- PUNISHING
- GRUELLING
- CRUEL
- VICIOUS
- KILLING

15
- WRETCHED
- BLINDING

16
- ANNOYING
- TROUBLESOME
- MISERABLE
- INTENSE
- UNBEARABLE

17
- SPREADING
- RADIATING
- PENETRATING
- PIERCING

18
- TIGHT
- NUMB
- DRAWING
- SQUEEZING
- TEARING

19
- COOL
- COLD
- FREEZING

20
- NAGGING
- NAUSEATING
- AGONIZING
- DREADFUL
- TORTURING

CURRENT MEDICATION FOR PAIN

- _____
- _____
- _____

PATIENT'S NAME _____ DATE _____ TIME _____am /pm

PRI: S_____ A _____ E _____ M _____ PRI (T) _____ PPI _____

{1-10} {11-15} {16} {17-20} {1-20}

4. 15 D Quality of Life

QUALITY OF LIFE QUESTIONNAIRE (15D©)

Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes **your present health status**. Continue through all 15 questions in this manner, giving only **one** answer to each.

QUESTION 1. MOBILITY

1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION

1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING

1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING

1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING

1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING

1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH

1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

QUESTION 8. ELIMINATION

1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES

1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION

1 ( ) I am able to think clearly and logically, and my memory functions well
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS

1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

QUESTION 12. DEPRESSION

1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS

1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.

QUESTION 14. VITALITY

1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY

1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.

5. Pain Disability Index

Pain Disability Index

Pain Disability Index: The rating scales below are designed to measure the degree to which aspects of your life are disrupted by chronic pain. In other words, we would like to know how much pain is preventing you from doing what you would normally do or from doing it as well as you normally would. Respond to each category indicating the overall impact of pain in your life, not just when pain is at its worst.

For each of the 7 categories of life activity listed, please circle the number on the scale that describes the level of disability you typically experience. A score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your pain.

Family/Home Responsibilities: This category refers to activities of the home or family. It includes chores or duties performed around the house (e.g. yard work) and errands or favors for other family members (e.g. driving the children to school).
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Recreation: This disability includes hobbies, sports, and other similar leisure time activities.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Social Activity: This category refers to activities, which involve participation with friends and acquaintances other than family members. It includes parties, theater, concerts, dining out, and other social functions.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Occupation: This category refers to activities that are part of or directly related to one's job. This includes non-paying jobs as well, such as that of a housewife or volunteer.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Sexual Behavior: This category refers to the frequency and quality of one's sex life.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Self Care: This category includes activities, which involve personal maintenance and independent daily living (e.g. taking a shower, driving, getting dressed, etc.)
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Life-Support Activities: This category refers to basic life supporting behaviors such as eating, sleeping and breathing.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

6. Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

7. Pittsburgh Sleep Quality Index

Name:_____ Date: _____

Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

1. During the past month, what time have you usually gone to bed at night? _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? _____
3. During the past month, what time have you usually gotten up in the morning? _____
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

8. Medication Quantification Scale Detriment Weights

Table 1. Pain Medication Class Detriment Weights

Medication Class	*Mean (SD)*	*Median*	*2003 Weight*	*1998 Weight*	*1992 Weight*
Topical/transdermal anesthetics, capsaicin	1.1 (0.8)	1	1.1	1*	—
Antidepressants — serotonin reuptake inhibitors	1.7 (0.9)	2	1.7	2*	2*
Antidepressants — other	1.9 (0.9)	2	1.9	2*	2*
Anticonvulsants — GABAergic	1.9 (1.0)	2	1.9	3*	
Antihypertensives	2.0 (1.0)	2	2.0	—	—
Anti-anxiety — miscellaneous	2.1 (1.2)	2	2.1	2*	—
Muscle relaxants — non–dependency producing	2.2 (1.1)	2	2.2	3*	3*
Acetaminophen	2.2 (1.4)	2	2.2	1	1
Cyclooxygenase-2 inhibitors	2.3 (1.1)	2	2.3	—	—
Antidepressants — tricyclics/tetracyclics	2.3 (1.1)	2	2.3	2*	2*
Analgesic — miscellaneous (ie, tramadol)	2.3 (1.1)	2	2.3	2	—
Anticonvulsants — sodium channel blockers	2.8 (1.1)	3	2.8	3*	—
Sedative hypnotics	3.1 (1.3)	3	3.1	4*	—
Opioids — Schedule II	3.4 (1.4)	3	3.4	5	6
Nonsteroidal anti-inflamatories	3.4 (1.2)	3	3.4	2	2
Antipsychotics	3.6 (1.2)	4	3.6	—	—
Opioids — Schedule IV	3.7 (1.3)	4	3.7	4	4
Opioids — Schedule III	3.7 (1.2)	4	3.7	4	4
Muscle relaxants — dependency producing	3.8 (1.3)	4	3.8	3*	3*
Benzodiazepines	3.9 (1.2)	4	3.9	5	4
Steroids	4.4 (1.3)	5	4.4	—	—
Barbiturates	4.5 (1.2)	5	4.5	5*	5*

Abbreviation: SD, standard deviation.

*Indicates medication classes combined in previous rankings.

9. Graded Motor Imagery Home Journal

Graded Motor Imagery Home Journal

Date	Time Started	Time Ended	Type of Exercise	Comments

10. Motor Activity Log

UAB Training for CI Therapy

SID_____ Name _____ Date _____ Visit _____ Examiner _____

Motor Activity Log (UE MAL) Score Sheet

Amount Scale How Well Scale

1. Turn on a light with a light switch ____ ____ if no, why? (use code) _____ Comments _____
2. Open drawer ____ ____ if no, why? (use code) _____ Comments _____
3. Remove an item of clothing from a drawer ____ ____ if no, why? (use code) _____ Comments _____
4. Pick up phone ____ ____ if no, why? (use code) _____ Comments _____
5. Wipe off a kitchen counter or other surface ____ ____ if no, why? (use code) _____ Comments _____
6. Get out of a car *(includes only the movement needed to get body from sitting to standing outside of the car, once the door is open).* ____ ____ if no, why? (use code) _____ Comments _____
7. Open refrigerator ____ ____ if no, why? (use code) _____ Comments _____
8. Open a door by turning a door knob/ handle ____ ____ if no, why? (use code) _____ Comments _____
9. Use a TV remote control ____ ____ if no, why? (use code) _____ Comments _____
10. Wash your hands *(includes lathering and rinsing hands; does not include turning water on and off with a faucet handle).* ____ ____ if no, why? (use code) _____ Comments _____

Codes for recording "no" responses:

1. "I used the unaffected arm entirely." (assign "0").
2. "Someone else did it for me." (assign "0").
3. "I never do that activity, with or without help from someone else because it is impossible." For example, combing hair for people who are bald. (assign "N/A" and drop from list of items).
4. "I sometimes do that activity, but did not have the opportunity since the last time I answered these questions." (carry-over last assigned number for that activity).
5. Non-dominant hand hemiparesis. (only applicable to #24; assign "N/A" and drop from list of items).

UAB Training for CI Therapy

SID_____ Name _____ Date _____ Visit _____ Examiner _____

Amount Scale How Well Scale

11. Turning water on/off with knob/lever on faucet	____	____	if no, why? (use code) _____ Comments _____
12. Dry your hands	____	____	if no, why? (use code) _____ Comments _____
13. Put on your socks	____	____	if no, why? (use code) _____ Comments _____
14. Take off your socks	____	____	if no, why? (use code) _____ Comments _____
15. Put on your shoes *(includes tying shoestrings and fastening straps)*	____	____	if no, why? (use code) _____ Comments _____
16. Take off your shoes *(includes untying shoestrings and unfastening straps)*	____	____	if no, why? (use code) _____ Comments _____
17. Get up from a chair with armrests	____	____	if no, why? (use code) _____ Comments _____
18. Pull chair away from table before sitting down	____	____	if no, why? (use code) _____ Comments _____
19. Pull chair toward table after sitting down	____	____	if no, why? (use code) _____ Comments _____
20. Pick up a glass, bottle, drinking cup, or can *(does not need to include drinking)*	____	____	if no, why? (use code) _____ Comments _____

Codes for recording "no" responses:

1. "I used the unaffected arm entirely." (assign "0").
2. "Someone else did it for me." (assign "0").
3. "I never do that activity, with or without help from someone else because it is impossible." For example, combing hair for people who are bald. (assign "N/A" and drop from list of items).
4. "I sometimes do that activity, but did not have the opportunity since the last time I answered these questions." (carry-over last assigned number for that activity).
5. Non-dominant hand hemiparesis. (only applicable to #24; assign "N/A" and drop from list of items).

UAB Training for CI Therapy

SID_____ Name _____ Date _____ Visit _____ Examiner _____

Amount Scale How Well Scale

21. Brush your teeth *(does not include preparation of toothbrush or brushing dentures unless the dentures are brushed while left in the mouth)*	____	____	if no, why? (use code) _____ Comments _____
22. Put on makeup base, lotion, or shaving cream on face	____	____	if no, why? (use code) _____ Comments _____
23. Use a key to unlock a door	____	____	if no, why? (use code) _____ Comments _____
24. Write on paper *(If hand used to write pre-stroke is more affected, score item; if non-writing hand pre-stroke is more affected, drop item and assign N/A)*	____	____	if no, why? (use code) _____ Comments _____
25. Carry an object in your hand *(draping an item over the arm is not acceptable)*	____	____	if no, why? (use code) _____ Comments _____
26. Use a fork or spoon for eating *(refers to the action of bringing food to the mouth with fork or spoon)*	____	____	if no, why? (use code) _____ Comments _____
27. Comb your hair	____	____	if no, why? (use code) _____ Comments _____
28. Pick up a cup by a handle	____	____	if no, why? (use code) _____ Comments _____
29. Button a shirt	____	____	if no, why? (use code) _____ Comments _____
30. Eat half a sandwich or finger foods	____	____	if no, why? (use code) _____ Comments _____

Codes for recording "no" responses:

1. "I used the unaffected arm entirely." (assign "0").
2. "Someone else did it for me." (assign "0").
3. "I never do that activity, with or without help from someone else because it is impossible." For example, combing hair for people who are bald. (assign "N/A" and drop from list of items).
4. "I sometimes do that activity, but did not have the opportunity since the last time I answered these questions." (carry-over last assigned number for that activity).
5. Non-dominant hand hemiparesis. (only applicable to #24; assign "N/A" and drop from list of items).

How Well Scale (HW)

0 - The weaker arm was not used at all for that activity **(never).**

.5

1 - The weaker arm was moved during that activity but was not helpful **(very poor).**

1.5

2 - The weaker arm was of some use during that activity but needed some help from the stronger arm or moved very slowly or with difficulty **(poor).**

2.5

3 - The weaker arm was used for the purpose indicated but movements were slow or were made with only some effort **(fair).**

3.5

4 - The movements made by the weaker arm were almost normal, but were not quite as fast or accurate as normal **(almost normal).**

4.5

5 - The ability to use the weaker arm for that activity was as good as before the stroke **(normal).**

Possible Reasons for Not Using the Weaker Arm for the Activity:

Reason A. "I used the unaffected arm entirely."

Reason B. "Someone else did it for me.".

Reason C. "I never do that activity, with or without help from someone else because it is impossible." For example, combing hair for people who are bald.

Reason D. "I sometimes do that activity, but did not have the opportunity since the last time I answered these questions."

Reason E. "That is an activity that I normally did only with my dominant hand before the stroke, and continue to do with my dominant hand now."

11. Activity Numerical Rating Scale

Activity Numerical Rating Scale

Please list five activities that you performed prior to your CRPS injury but now find difficult due to pain, limited range of motion, etc.

Activity Number 1:_____

How well can you do this activity now?

_____

0 10

(completely UNABLE to perform) (completely ABLE to perform)

Activity Number 2:_____

How well can you do this activity now?

_____

0 10

(completely UNABLE to perform) (completely ABLE to perform)

Activity Number 3:_____

How well can you do this activity now?

_____

0 10

(completely UNABLE to perform) (completely ABLE to perform)